BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023729
Article Type:	Research
Date Submitted by the Author:	25-Apr-2018
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Keywords:	Herbal medicine < THERAPEUTICS, Systematic review, Cardiac surgery < SURGERY, GYNAECOLOGY, Laparoscopy, Maternal medicine < OBSTETRICS

Herbal medications for surgical patients: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: To summarize the effects of herbal medications for the treatment and prevention of anxiety, depression, pain, and postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic, obstetric/gynecologic, or cardiovascular surgical procedures.

Methods: Searches of MEDLINE, EMBASE, CENTRAL and LILACS to January 2018 were performed to identify randomized controlled trials. The inclusion criteria were: Randomized controlled trials, adults undergoing laparoscopic, obstetric/gynecological or cardiac surgeries and that used any herbal medicines. The primary outcomes were anxiety, depression, pain, and PONV. We used the GRADE approach to rate overall certainty of the evidence by outcome.

Results: Twelve trials including 738 patients were eligible. Results from three RCTs suggested a statistically significant reduction in vomiting (Risk relative (RR) 0.57, 95% Confidential Interval (CI) 0.38, 0.86; p = 0.008; I^2=0%, p=0.67) and nausea (Risk relative (RR) 0.69, 95% Confidential Interval (CI) 0.50, 0.96; p = 0.03; I^2=0%, p=0.39) with the use of *Zingiber officinale* compared to placebo in both laparoscopic and obstetric/gynecological surgeries. Also results suggested a non statistically significantly reduction in the need for rescue medication for pain (Risk relative (RR) 0.52, 95% Confidential Interval (CI) 0.13, 2.13; p = 0.36; I^2=92%, p=0.00001) with *Rosa damascena* (Damask rose) and *Zingiber officinale* (Ginger) compared to placebo in laparoscopic and obstetric/gynecological surgery.

Conclusions: There is low-certainty evidence regarding the efficacy of herbal medication in reducing vomiting (200 fewer per 1000; 288 fewer to 205 fewer), nausea (207 fewer per 1000; 333 fewer to 27 fewer) and, need for rescue medication for pain (666 fewer per 1000; 580 fewer to 752 more) in patients undergoing either laparoscopic

or obstetric/gynecological surgeries. This systematic review was registered in the PROSPERO (International Prospective Register of Systematic Reviews) data base under the number CRD 42016042838, and the protocol was also published where else.

Keywords: herbal, laparoscopy, gynecologic surgery, obstetrical surgery, cardiac surgery, GRADE; systematic review.

Strengths and limitations of this study

- This systematic review included a broad search;
- The evaluation of eligibility, risk of bias, and data abstraction were made independently and in duplicate;
- The GRADE approach was used in rating the quality of evidence; and focus on both absolute and relative effects of the intervention on patient-important outcomes.
- Trials analyzed in this systematic review often had outcomes reported incompletely, inadequate random sequence, a fail of blinding due to the nature of the intervention, and for some studies also avoidable lack of blinding (outcome adjudication).
- This review included only four trials with 364 patients, making difficult to find statistical power in some of the pre-defined outcomes.

Word count: 3.371

1. 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 as high as 80%[2,3]. In addition to decreased quality of life, PONV has also been associated with increased hospital length of stay and systemic costs[4]. While recommendations for pharmacological prophylaxis and treatment for PONV exist, these medications may be associated with notable side-effects[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 to 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]. Depression and anxiety disorders have been associated with increased rates of readmission[11], morbidity[12] and mortality[13] in surgical patients.

Evidence from the United States 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 hospitalized 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].

Conventional medications are the general treatment for this set of symptoms. Pre-medication with anxiolytic and sedative drugs may reduce preoperative anxiety[18]. On the other hand, the role of anxiolytic pre-medication for surgical patients remains unclear and postoperative side effects may result from routine pre-medication[19]. Recently, new generations of antiemetic and shorter-acting anesthetic drugs have been used in PONV[20]. Opioid agonists are the current mainstay of pain treatment after surgery, but opioid therapy is severely limited by side-effects at effective doses[21]. Preoperative cognitive behavioral therapy (CBT) has been associated with less post-day surgery pain and a lower risk of chronic postoperative pain[22]. Postoperative CBT has also been associated with decreased postoperative depression rates relative to conventional medications[23].

Use of herbal medications by surgical patients is quite common worldwide for a number of these indications as well, though geographic variability exists. A study of hospitalized patients in a public medical center in Israel found that 44% reported using herbal remedies in the last year; 89 different remedies were reportedly used[24]. In comparison, the estimated prevalence of herbal medicine use for patients undergoing surgery in the United States has been reported to range from 32 to 51%[25]. Eighty-five percent of the Brazilian population has been reported to use medicines involving plants or plant-based preparations as part of their healthcare[26]. Reported prevalence rates for herbal medicine use in the European range from 5.9 to 48.3% across the United Kingdom, Germany, Turkey, Switzerland, Sweden, Norway, Denmark, Italy, Israel, Finland and Spain[27].

While herbal medications have been associated with positive effects on postoperative pain, anxiety and PONV[28-30], 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[31-37]. 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[38].

The American Society of Anesthesiology (ASA) recommends discontinuing herbal remedies consumption two weeks prior to surgery[39]. Nevertheless, a recent study showed that only around 23% of preoperative surgical patients discontinue their herbal medication regimens prior to surgery[40].

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 summarizing the efficacy and safety of herbal medications for the treatment and prevention of anxiety, depression, pain, and PONV in patients undergoing laparoscopic, obstetric/gynecologic and cardiovascular surgical procedures.

2. Methods

The Cochrane Handbook for Intervention Reviews[41] guided our choice of methods. This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[42] and also the PRISMA checklist[42] were used when writing this report. This systematic review was registered in the PROSPERO (International Prospective Register of Systematic Reviews) data base under the number CRD42016042838, and the protocol was also published where else[43].

2.1 Eligibility criteria

The inclusion criteria were:

- Study design: Randomized controlled trials (RCTs).
- Patients: Adults (≥ 18 years of age) undergoing laparoscopic, obstetric/gynecological, or cardiac surgeries.
- Interventions: Any herbal medicines from any of the following plant preparations (whole, powder, extract, crude drug, standardized mixture, drug extract ratio and solvent) which were compared against conventional treatment, placebo, no intervention, other type of complementary and alternative therapy (e.g. acupuncture, homeopathy), or another herbal medication. The following routes of administration were considered: oral (e.g. dropping pills, aqueous decocts), topical and intravenous.

The patient-important outcomes (primary outcomes) that we were interested were: anxiety (Spilberger Anxiety Inventory – Trait Anxiety Inventory (STAI) and other validated instruments); depression (Depression Scale – Hospital Anxiety and Depression Scale (HADS-D) 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, hospitalization, 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);

- Others.

The exclusion criteria were:

- Patients: Studies where the majority of participants were HIV-positive or transplant patients were not considered eligible for inclusion.
- 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.

2.2 Data source and searches

We searched Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid EMBASE, LILACS, ISI Web of Science and CINAHL, from their initial dates to January 30, 2018. Search terms describing laparoscopic, obstetrical/gynecological, cardiovascular surgeries, and herbal medication interventions were combined (Appendix Table 1). The search strategy was designed with the assistance of a trained librarian. No restrictions were placed on language, year of publication or publication status.

2.3 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, data extraction and risk of bias assessments were established by discussion and adjudication by a third reviewer as necessary.

2.4 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-standardized 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[44,45].

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

2.5 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[45]. Detailed GRADE guidance was used to assess overall risk of bias[46], imprecision[47], inconsistency[48], indirectness[49] and publication bias[50]. Consensus was established by discussion and adjudication by a third reviewer as necessary, and final results were summarized in an evidence profile.

2.6 Data synthesis and statistical analysis

Pooled risk ratios (RRs) were calculated for dichotomous outcomes and standardized mean differences (SMD) for continuous variables with the associated confidential interval (CI)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 in the meta-analysis[51].

Variability was addressed in results across studies by using I^2 statistic and the p-value obtained from the Cochran chi square test. Our primary analyses were based on eligible patients who had reported outcomes 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 used Review Manager (*RevMan*) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses[52].

2.7 Patient and public involvement

No patients or public were involved in the present study.

3. Results

3.1 Search selection

The initial searches identified 7,210 titles from the electronic searches. After the duplicates titles were removed, 6,775 potentially relevant articles were retained for further assessment (Figure 1). Subsequent to reading titles and abstracts, 6,715 of these

articles were excluded because they evaluated were off-topic or in vitro and animal studies. Sixty articles were retrieved for further assessment. After screening the full texts, 12 randomized controlled trials (RCTs) and quasi-RCT[53-64] were included in the qualitative synthesis (Figure 1).

Six[54,55,57,61,62,64] of the included trials were published in Chinese. Authors of all included studies were contacted, but none of them supplied us with the requested information.

3.2 Study characteristics

Table 1 describes study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up. Eleven[54-64] were RCTs, and one[53] were quasi-RCT. Ten[53-59,61-63] trials employed a parallel two-arm design. Six trials[54,55,57,61,62,64] were conducted in China, three[56,60,63] in Iran, two[53,58] in Thailand, and a further one[59] in France. The trials sample size ranged from 20[59] to 120[58] patients. Participants were adults with an average mean age of 22.3[56] to 63.0 years old[59].

The majority of the included studies among the cardiovascular surgical procedures presented as an inclusion criteria patients with rheumatic heart disease of ASA grade II - III[54,55,61,64]. For those included studies among the obstetric/gynecologic procedures the most common inclusion criteria were pregnant patients[56,63] and ASA grade I or II[58] while for the laparoscopic procedures were non-cancer gynecologic conditions[53]. Studies followed participants from two hours[60] to 15days[59] (Table 1).

Table 2 describes study characteristics related to type surgery, intervention and control groups, and assessed outcomes. In relation to the type of surgery, eight[54,55,57,59-62,64] included studies evaluated patients undergoing cardiovascular surgical (mostly were

heart valve replacement), three[56,58,63] obstetric/gynecologic and, one[53] laparoscopic procedure.

Among the cardiovascular surgery[54,55,57,59-62,64] studies, *Ginkgo biloba* was used in three[54,55,59] studies and *Astragalus* in two[61,64], and herbal medications were mostly used in the form of mixture[57,59,61,62,64] or standardized extract[54,55]. Six of these studies reported the use of herbal medication via intravenous[54,55,57,61,62,64], with as control group intravenous normal saline[54,55,57,61,62,64]. The measured outcome was biochemical analysis[54,55,57,59-62,64] (Table 2).

The obstetric/gynecologic surgery procedures studies used *Zingiber officinale* (Ginger)[58,63] and in other *Rosa damascena* (damask rose)[56], in the form of powder[56,58] and administered via oral[56,58,63]. Placebo was used as the control group[56,58,63]. The measured outcomes evaluated were pain[56], nausea[58,63] and vomiting[58,63] (Table 2).

The only included study[53] that evaluated laparoscopic procedure used *Zingiber officinale*, in the form of powder by oral route (capsules), and placebo was used as the control group. The measured outcomes were nausea and vomiting (Table 2).

3.3 Risk of bias assessment

Figure 2 and table 3 describe the risk of bias assessment. Only the domain blinding of statistician was rated as high risk of bias in all studies[53-64]. However, other domains such as blinding of caregivers[53-55,57,61,62,64], blinding of data collectors[53-55,57,59,61,62,64] and blinding of outcome assessment[53-55,57,59,61-64] were rated mostly as high risk of bias due to the lack of information in the included studies.

3.4 Outcomes

3.4.1 Vomiting

Results from three RCTs[53,58,63] with a total of 272 participants suggested a statistically significantly reduction in vomiting with the use of *Zingiber officinale* compared to placebo in both laparoscopic and obstetric / gynecological surgery (RR 0.57, 95% CI 0.38, 0.86; p = 0.008; I^2=0%, p=0.67) (Figure 3). Certainty in evidence was rated down to low because of risk of bias, due to allocation concealment[53], lack of blinding of caregivers[53], data collectors[53], statistician[53,58,63] and outcome assessment[53,63] and, indirectness in both studies (Table 4).

3.4.2 Nausea

Results from two RCT[58,63] with a total of 212 participants suggested a statistically significantly reduction in nausea with the use of *Zingiber officinale* compared to placebo in obstetric/gynecological surgery (RR 0.69, 95% CI0.50, 0.96; p = 0.03; I^2=0%, p=0.39) (Figure 4). Certainty in evidence was rated down to low because of risk of bias, due to lack of blinding of statistician[58,63] and outcome assessment[63], selective outcome reporting[58] and, indirectness in both studies (Table 4).

3.4.3 Pain

Results from one RCT[56] with a total of 92 participants suggested a statistically significantly reduction in pain with the use of *Rosa damascena* powder capsules compared to placebo in obstetric/gynecological surgery (RR 0.14, 95% CI 0.07, 0.30; p = 0.00001;I^2=not applicable) (Appendix Figure 1). Certainty in evidence was rated low because of risk of bias, due to random generation, allocation concealment, lack of blinding of statistician, selective outcome reporting, and indirectness (Table 4).

3.4.4 Need for rescue medication for pain

Results from three RCTs[53,56,58] 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 to placebo in laparoscopic and obstetric/gynecological surgery (RR 0.52, 95% CI 0.13, 2.13; p=0.36; I^2=92%, p=0.00001) (Figure 5, panel A). A plausible worse case sensitivity analysis excluding Gharabaghi[56] study yielded results that were consistent with the primary analysis and fail to show a difference in the effects of herbal medicine compared to placebo (RR 0.87, 95%CI 0.66, 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 randomization[56], allocation concealment[53,56], lack of blinding of caregivers[53], data collectors[53], statistician[53,56,58], and outcomes assessment[53], selective outcome reporting[56,58], indirectness, imprecision, and inconsistency (Table 4).

4. Discussion

4.1 Main findings

According to GRADE approach, meta-analysis of low to very low certainty evidence from four eligible placebo randomized clinical trials[53,56,58,63], including 364 surgical patients from laparoscopic and obstetric/gynecological surgeries, suggested a significantly reduction in vomiting and nausea favoring herbal medicine (*Zingiber officinale*) and a reduction in the need for rescue medication for pain favoring herbal medicine (i.e., *Rosa damascena* and *Zingiber officinale*). Other evaluated result such as pain[56] on obstetric/gynecological surgery, were also presented favorable for herbal medication (*Rosa damascena*, *Zingiber officinale*) with certainty in evidence rated very low (Table 4).

Regarding the herbal medication *Zingiber officinale*, it is widely used around the world and the most common ailments treated are nausea, vomiting and motion sickness[53,58,63]. In a systematic review[65], *Zingiber officinale* was evaluated for nausea and vomiting and six RCTs were reviewed. Were identified three on postoperative nausea and vomiting and two of these suggested that *Zingiber officinale* was superior to placebo and equally effective as metoclopramide (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) and placebo groups taken before operation (absolute risk reduction 0.052 (95% confidence interval -0.082 to 0.186). These studies collectively favored *Zingiber officinale* over placebo.

In another systematic review[66] which evaluated *Zingiber officinale* in the treatment of pregnancy-associated nausea and vomiting, twelve RCTs involving 1278 pregnant women were included. *Zingiber officinale* was compared to placebo and significantly improved the symptoms of nausea (MD 1.20, 95% CI 0.56-1.84, p = 0.0002, I^2 = 0%). *Zingiber officinale* did not significantly reduce the number of vomiting episodes, when compared to placebo, although there was a trend towards improvement (MD 0.72, 95% CI −0.03-1.46, p = 0.06, I^2 = 71%). An additional indication which support this potential is about its properties. *Zingiber officinale* acts peripherally, within the gastrointestinal tract, increasing the gastric tone and motility due to anticholinenergic and antiserotonergic actions[67] and it is also reported that this herbal medication increase gastric emptying[68]. These activities can 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[68]. Regarding the findings of the present systematic review as well as the results of other systematic

reviews [65,66], *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.

In relation to the pain evaluated, *Rosa Damascena* which has been tested already in pre-clinical studies[69,70] for anti-inflammatory and analgesic properties, and in clinical studies for analgesic and antinociceptive effects[71,72]. Also a systematic review[73] showed promising evidences for its effectiveness and safety in pain relief. Although these positive findings[69-73], and due to limitations such as heterogeneity and low quality methodology in the present systematic review, these results must be cautiously interpreted. *Rosa damascena* presents promising indication for the effectiveness in pain relief but more studies are also needed.

Regarding the need for rescue medication for pain, these herbal medications, as described above, have been reported for abdominal pain[68] (*Zingiber officinale*) and for anti-inflammatory and analgesic properties[71,72] (*Rosa damascena*), however, in this meta-analysis were found a high risk of selection bias and certainty in evidence was rated low to very low.

4.2 Implications for clinical practice and for research

There is low-certainty evidence showing that *Zingiber officinale* is more effective compared to placebo for the reduction of vomiting (laparoscopic and obstetric/gynecological surgery) and nausea (obstetric/gynecological surgery) in patients. There is also low-certainty evidence showing that *Rosa damascena* is more effective compared to placebo for the reduction of pain in patients undergoing obstetric/gynecologic surgery. However, there is very low-certainty evidence showing that *Rosa damascena* and *Zingiber officinale* are more effective compared to placebo for

the reduction of the need for rescue medication for pain in laparoscopic and obstetric/gynecologic surgeries.

Author Contributions. APNA is the guarantor, led the writing of the manuscript, and participated in data extraction. RED and LCL were the project managers, co-investigators, contributed to the writing and revision of this systematic review. APA was the Trial Search Coordinator responsible for the search strategy. CCB was co-investigator, helped to revise the protocol, and participated in data extraction. YZ, AA, HAG, CG, MDG, LARR, SBF, LDO, LPR and BJ contributed to the writing and revision of the manuscript and participated in data extraction. All authors read and approved the final manuscript.

Funding. R. El Dib was supported by Brazilian Research Council (CNPq) scholarship grant number (CNPq 310953/2015-4).

Competing interests None declared.

Patient consent. Not required.

Data sharing statement. No additional data are available.

REFERENCES

1. Kable AK, Gibberd RW, Spigelman AD. Adverse events in surgical patients in Australia. *Int J Qual Health Care.* 2002 Aug;14(4):269-76.
2. Farhadi K, Choubsaz M, Setayeshi K, et al. The effectiveness of dry-cupping in preventing post-operative nausea and vomiting by P6 acupoint stimulation: A randomized controlled trial. Lauche. R, ed. *Medicine*. 2016;95(38):e4770.
3. Youssef N, Orlov D, Alie T, et al. What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery?: a meta-analysis of randomized controlled trials. *Anesth Analg.* 2014; 119:965–977.
4. Palazzo MG, Strunin L. Anaesthesia and emesis: 1. Etiology. *Can Anaesth Soc J*. 1984;31:178–87.
5. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014; 118:85–113.
6. Underwood M, Firmin RK, Jehu D. Aspects of psychological and social morbidity in patients awaiting coronary artery bypass grafting. *Br Heart J.* 1993; 69(5):382-384.
7. Marcolino J, Suzuki F, Cunha L, et al. Medida de ansiedade e da depressão em pacientes no pré-operatório: Estudo comparativo. *Rev Bras Anestesiol.* 2007;57(2):157-166.
8. Kil HK, Kim WO, Chung WY, et al. Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia. *Br J Anaesth.* 2012; 108:119-25.
9. Shoar S, Naderan M, Aghajani M, et al. Prevalence and Determinants of Depression and Anxiety Symptoms in Surgical Patients. *Oman Med J.* 2016;31(3):176-181.
10. Yohannes AM, Willgoss TG, Baldwin RC, et al. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psychiatry*. 2010;25:1209–1221.
11. Daratha KB, Barbosa-Leiker C, Burley HM et al. Co-occurring mood disorders among hospitalized patients and risk for subsequent medical hospitalization. *Gen Hosp Psychiatry*. 2012 Sep-Oct;34(5):500-505.
12. Gasse C, Laursen TM, Baune BT. Major depression and first-time hospitalization with ischemic heart disease, cardiac procedures and mortality in the general population: A retrospective Danish population-based cohort study. *Eur J Prev Cardiol*. 2014May;21(5):532-540.
13. Fan VS, Ramsey SD, Giardino ND, et al. National Emphysema Treatment Trial (NETT) Research Group. Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease. *Arch Intern Med*. 2007 Nov;167(21):2345-2353.
14. Svensson I, Sjostrom B, Haljamae H. Assessment of pain experiences after elective surgery. *J Pain Symptom Manage*. 2000; 20: 193–201.
15. Boisseau N, Rabary O, Padovani B, et al. Improvement of dynamic analgesia does not decrease atelectasias after thoracotomy. *Br J Anaesth*. 2001; 87:564-9.
16. Brattwall M, Warren Stomberg M, Rawal N, et al. "Patients' assessment of 4-week recovery after ambulatory surgery. *Acta Anaesthesiologica Scandinavica*, 2011; 55,1: 92–98.
17. Campagna S, D'olx MDA, Paradiso R, et al. Postoperative Pain, an Unmet Problem in Day or Overnight Italian Surgery Patients: A Prospective Study. *Pain Res Manag*. 2016;2016:6104383.

18. Iizawa A, Oshima T, Kasuya Y, et al. Oral tandospirone and clonidine provide similar relief of preoperative anxiety. *Can J Anaesth*. 2004;51:668-671.
19. Ng EH, Miao B, Ho PC. Anxiolytic premedication reduces preoperative anxiety and pain during oocyte retrieval. A randomized double blinded placebo-controlled trial. *Hum Reprod.* 2002;17:1233-1238.
20. Papadimitriou L, Pourgezi T, Petropoulos G, et al. Tropisetron or ondansetron for the prevention of post-operative nausea and vomiting (PONV). *Eur J Anaesthesiol.*1999; 16: 736.
21. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth*. 2002; 89: 409–23.
22. Burns JW, Moric M. Psychosocial factors appear to predict postoperative pain: interesting, but how can such information be used to reduce risk? *Tech Reg Anesth Pain Management.* 2011;15:90–9.
23. Freedland KE, Skala JA, Carney RM, et al. Treatment of Depression After Coronary Artery Bypass Surgery: A Randomized Controlled Trial. *Arch Gen Psychiatry*. 2009;66(4):387-396.
24. Levy I, Attias S, Ben-Arye E, et al. Adverse events associated with interactions with dietary and herbal supplements among inpatients. *Br J Clin Pharmacol*. 2016 Oct 19.
25. Kaye AD, Clarke RC, Sabar R, et al. Herbal medications: current trends in anesthesiology practice—a hospital survey. *J Clin Anesth*. 2000;12:468–471.
26. BRASIL. Política Nacional de Plantas Medicinais e Fitoterápicos. Série B Textos Básicos de Saúde. 2006. http://bvsms.saude.gov.br/bvs/publicacoes/-politica_nacional_fitoterapicos.pdf.
27. Eardley S, Bishop FL, Prescott P, et al. A systematic literature review of complementary and alternative medicine prevalence in EU. *Forsch Komplement med*. 2012;19 Suppl 2:18-28.
28. Gharabagy PM, Zamany P, Delazar A, et al. Efficacy of Eremostachys laciniata herbal extract on mitigation of pain after hysterectomy surgery. *Pak J Biol Sci.* 2013Sep1;16(17):891-4.
29. Nanthakomon T, Pongrojpaw D. The efficacy of ginger in prevention of postoperative nausea and vomiting after major gynecologic/obstetric surgery. *J Med Assoc Thai.* 2006 Oct;89Suppl 4:S130-6.
30. Akhlaghi M, Shabanian G, Rafieian-Kopaei M, et al. Citrus aurantium blossom and preoperative anxiety. *Rev Bras Anestesiol.* 2011 Nov-Dec;61(6):702-12.
31. Ang-Lee M, Moss J, Yuan C-S. Herbal medicines and perioperative care. *JAMA* 2001;286:208–16.
32. Norred C, Finlayson C. Hemorrhage after the preoperative used of complementary and alternative medicine. *AANA J*. 2000;68: 217–20.
33. Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. *J Am Coll Cardiol.* 2010;55:515–25.
34. Hodges PJ, Kam PC. The perioperative implications of herbal medicines. *Anaesthesia.* 2002 Sep;57(9):889-99.
35. Cotterill J. Severe phototoxic reaction to laser treatment in a patient taking St John's Wort. *J Cosmet Laser Ther*. 2001;3:159–60.
36. Rose KD, Croissant PD, Parliament CF, et al. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: A case report. *Neurosurgery*. 1990;26:880–82.
37. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med.* 1996;125:940–41.
38. Levy I, Attias S, Ben-Arye E, et al. Perioperative Risks of Dietary and Herbal Supplements. *World J Surg*. 2016 Nov 22.

39. American Society of Anesthesiologists [Internet]. What you should know about your patients' use of herbal medicines. [update 2003, cited 2017 fev12]. Available in: http://www.wehealny.org/services/BI_Anesthesiology/herb-Patient.pdf
40. Franco Ruiz S, Gonzalez Maldonado P. Dietary supplements and the anesthesiologist: research results and state of the art. *Rev Colomb Anesthesiol*. 2014; 42:90–99
41. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.Available from http://handbook.cochrane.org/(accessed august 2016).
42. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ.* 2009;339:b2535.
43. Arruda APN, Ayala AP, Lopes LC et al. Herbal medications for surgical patients: a systematic review protocol. *BMJ Open* 2017;7:e014290.
44. Guyatt GH, Busse JW. Modification of Cochrane Tool to assess risk of bias in randomized trials. http://distillercer.com/resources/(accessed august 2016).
45. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6.
46. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6.
47. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol.* 2011;64:407-15.
48. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol.* 2011b;64:1283-93.
49. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol.* 2011c;64:1294-302.
50. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol.* 2011d;64:1303-10.
51. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol.* 2011e;64:1277-82.
52. The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.
53. Apariman S, Ratchanon S, Wiriyasirivej B. Effectiveness of ginger for prevention of nausea and vomiting after gynecological laparoscopy. *J Med Assoc Thai.* 2006 Dec;89(12):2003-9.
54. Deng, YK, Wei F, Zhang DG. Brain protective effects of ginkgo biloba leaf extract (ginaton) in patients undergoing hypothermic cardiopulmonary bypass. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2006 Sep;26(9):795-8.
55. Deng YK, Wei F, Zhang DG. Erythrocyte protective effects of ginaton in patients undergoing hypothermic cardiopulmonary bypass. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2010 Apr;30(4):365-8
56. Gharabaghi PM, Tabatabei F, Fard SA et al. Evaluation Of The Effect Of Preemptive Administration Of *Rosa Damascena* Extract On Post-Operative Pain In Elective Cesarean Sections. *Afr. J. Pharm. Pharmacol.* 2011 Oct; 5(16):1950-55.
57. Huang ZY, Liao CX, Chen DZ. Effect of radix *Salviae miltiorrhizae* on production of free radical products from lung during cardiopulmonary bypass operation. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 1996 Aug;16(8):451-3.

58. Nanthakomon T, Pongrojpaw D. The efficacy of ginger in prevention of postoperative nausea and vomiting after major gynecologic surgery. *J Med Assoc Thai.* 2006 Oct;89 Suppl 4:S130-6.
59. Pietri S, Séguin JR, d'Arbigny P, Drieu K, Culcasi M. Ginkgo biloba extract (EGb 761) pretreatment limits free radical oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther.* 1997 Apr;11(2):121-31.
60. Safaei N, Babaei H, Azarfarin R, Jodati A-R, Yaghoubi A, Sheikhalizadeh M-A. Comparative Effect of Grape Seed Extract (*Vitis Vinifera*) and Ascorbic Acid in Oxidative Stress Induced by On-pump Coronary Artery Bypass Surgery. *Ann Card Anaesth.* 2017 Jan-Mar;20(1):45-51.
61. Wang F, Xiao MD, Liao B. Effect of Astragalus on cytokines in patients undergoing heart valve replacement. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2008 Jun;28(6):495-8.
62. Xie RQ, Du J, Hao YM. Myocardial protection and mechanism of Puerarin Injection on patients of coronary heart disease with ischemia/reperfusion. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2003 Dec;23(12):895-7.
63. Zeraati H, Shahinfar J, Imani Hesari S, Masrorniya M, Nasimi F. The Effect of Ginger Extract on the Incidence and Severity of Nausea and Vomiting After Cesarean Section Under Spinal Anesthesia. *Anesth Pain Med.* 2016 Aug 15;6(5):e38943.
64. Zhou S, Shao W, Zhang W. Clinical study of Astragalus injection plus ligustrazine in protecting myocardial ischemia reperfusion injury. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2000 Jul;20(7):504-7.
65. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth.* 2000 Mar;84(3):367-71.
66. Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutr J.* 2014 Mar 19;13:20.
67. Adbel-Aziz H, Windeck T, Ploch M, Verspohl EJ. Mode of action of gingerols and shogaols on 5-HT3 receptors: binding studies, cation uptake by the receptor channel and contraction of isolated guinea-pig ileum. *Eur J Pharmacol.* 2006 Jan 13;530(1-2):136-43.
68. Hu ML, Rayner CK, Wu KL et al. Effect of ginger on gastric motility and symptoms of functional dyspepsia. *World J Gastroenterol.* 2011 Jan 7;17(1):105-10.
69. Hajhashemi V, Ghannadi A, Hajiloo M. Analgesic and anti-inflammatory effects of *Rosa damascena* hydroalcoholic extract and its essential oil in animal models. *Iran J Pharm Res.* 2010 Spring;9(2):163-8.
70. Latifi G, Ghannadi A, Minaiyan M. Anti-inflammatory effect of volatile oil and hydroalcoholic extract of *Rosa damascena* Mill. on acetic acid-induced colitis in rats. *Res Pharm Sci.* 2015 Nov-Dec;10(6):514-22.
71. Shirazi M, Mohebitabar S, Bioos S et al. The effect of topical *Rosa damascena* (Rose) oil on pregnancy-related low back pain a randomized controlled clinical trial. *J Evid Based Complementary Altern Med.* 2017 Jan;22(1):120-126.
72. Bani S, Hasanpour S, Mousavi Z, Mostafa GP, Gojazadeh M. The effect of *Rosa damascena* extract on primary dysmenorrhea: a double-blind cross-over clinical trial. *Iran Red Crescent Med J.* 2014 Jan;16(1):e14643.
73. Nayebi N, Khalili N, Kamalinejad M, Emtiazy M. A systematic review of the efficacy and safety of *Rosa damascena* Mill. with an overview on its phytopharmacological properties. *Complement Ther Med.* 2017 Oct;34:129-140.

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

#	Searches	Results
1	gynecology/ or obstetrics/ or thoracic surgery/ or Minimally Invasive Surgical Procedures/	61687
2	laparoscopy/ or hand-assisted laparoscopy/	69622
3	thoracic surgical procedures/ or exp cardiac surgical procedures/	195024
4	expGynecologic/obstetric Surgical Procedures/	72904
5	Cholecystectomy, Laparoscopic/	10733
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.	153069
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.	101339
9	(herbalism or botany or herbology).tw,kf.	1255
10	Phytotherapy/	33568
11	(phyto-therap* or phytotherap*).tw,kf.	1680
12	exp Plant Preparations/pd, tu, ad, st [Pharmacology, Therapeutic Use, Administration & Dosage, Standards]	103896
13	or/1-6 [Surgery]	457564
14	or/7-12 [Herbal medicine]	194482
15	13 and 14	1296
16	adult.mp. or middle aged.sh. or age:.tw.	7608507
17	15 and 16	470

Table 1. 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.*partici-pants	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria	Follow-up
Apariman, 2006[53]	Quasi-RCT	Thailand, Asian	I: 30 C:30	I: 34.37 C: 34.93	I:0 C:0	Non-cancer gynecologic 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 orany medications that might have side effects of nauseaor vomiting within 24 hours before surgery, or had ahistory of ginger allergy. Patients who would undergolaparoscopic hysterectomy were also excluded.	6 hours
Deng, 2006[54]	RCT	China, Asian	I: 30 C:30	I: 45.2 C: 46.1	I:56.7 C:60	Patients with rheumatic heart disease of ASA grade II - III who were scheduled for mitral valve replacement with intravenous anesthesia	Any cerebrovascular, neurological or metabolic diseases prior to surgery, any organ failure.	3 hours
Deng, 2010[55]	RCT	China, Asian	I: 15 C:30	I: 45.2 C: 46.1	I:56.7 C:60	Patients with rheumatic heart disease of ASA grade II - III who were scheduled for mitral valve replacement with intravenous anesthesia	High cholesterolemia, hematological disease, repiratory illnesses, pulmonary hypertension, abnormal liver or renal function	3 hours
Gharabaghi, 2011[56]	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 to 40 years having term pregnancy, without the history of hypersensitivity to local anesthetics (Lidocaine, Marcaine) and with the body mass index of 9.24 to 5.18 who were supposed to undergo cesarean section for different reasons.	Emergency cesarean sections, need to general anesthesia, history of psychological disorder, history of hypersensitivity to local anesthetics and R.damascena extract, prolongation of surgery more than one 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[57]	RCT	China, Asian	I: 15 C:15	I: 37 C: 35.8	I:40 C:47	Patients undergoing heart valve replacement	Not reported/none	6 hours
Nanthakomon, 2006[58]	RCT	Thailand, Asian	I: 60 C:60	I: not reported C: not reported	I:0 C:0	All patients were ASA (American Society of Anesthesia) 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[59]	RCT	France, Europe	I: 10 C:10	I: 63.0 C: 63.0	I:75 C:57.14	(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 antiischemic, antiin_ammatory, vasoactive, or Antioxidant medications for at least 5 days before surgery.	Not reported/none	15 days
Safaei, 2017[60]	RCT	Iran, Europe	I: 29 IVC: 29 C:29	I: 56.3 IVC: 56.7 C:58.2	I: 75.8 IVC: 72.4 C:82.7	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 ischemic time exceeded 120 min.	2 hours
Wang, 2008[61]	RCT	China, Asian	I: 15 C:15	I: 39.4 C: 41.1	I:33.3 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, WBC>10^9/L, positive Antistreptolysin O Test; abnormal liver or renal function	1 day

Xie, 2003[62]	RCT	China, Asian	I: 39 C:39	I: 55.6 C: 54.1	I:51.3 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
Zeraati, 2016[63]	RCT	Iran, Europe	I: 46 C: 46	I: not reported C: not reported	I: 0 C: 0	Pregnant women who had elective cesarean section with spinal anesthesia.	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 anesthesia, 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[64]	RCT	China, Asian	HM1: 6 HM2: 6 HM3: 6 C: 6	HM1: 40 HM2: 33.8 HM3: 37.8 C: 39.5	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

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

Table 2. 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[53]	Laparosco-pic	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[54]	Cardiovascu-lar surgical procedures	Ginkgo biloba extract (trade name: Ginaton)	Standardized extract containing 24% ginkgo biloba flavonoid glycoside, 3.1% ginkgolide, 2.9% bilobalide	Intravenous	Intravenous normal saline	Blood gas, lactatic acid concentration, acitivity of superoxide dismutase, malonaldehyde content, arterial oxygen content, jugular venous oxygen content, arterial to venous oxygen content difference, cerebral oxygen extraction ratio, arteriojugular lactate difference
Deng, 2010[55]	Cardiovascu-lar surgical procedures	Ginkgo biloba extract (trade name: Ginaton)	Standardized extract containing 24% ginkgo biloba flavonoid glycoside, 3.1% ginkgolide, 2.9% bilobalide	Intravenous	Intravenous normal saline	Plasma malondialdehyde and superoxide dismutase; erythrocyte malondialdehyde and superoxide dismutase; erythrocyte activity of Na K ATPase and Ca Mg ATPase
Gharabaghi, 2011[56]	Obstetric/ gynecologic	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 five minutes. The collected extract was completely dried under low pressure by rotary evaporator.	Oral	Placebo capsules containing starch	Pain

Huang, 1996[57]	Cardiovascu -lar surgical procedures	*Radix Salviae Miltiorrhizae* injection	Standardized mixture available commercially, exact formulation not published	Intravenous	Intravenous normal saline	Difference in level of peroxidation product and leukocyte count in arterial blood between left and right ventricles
Nanthakomon, 2006[58]	Obstetric/ gynecologic	Ginger 2 capsules (one capsule contains 0.5 g)	Powder	Oral	2 capsules of placebo (each capsule contains 0.5 g of lactose)	Nausea and vomiting
Pietri et al., 1997[59]	Cardiovascu -lar surgical procedures	GingoBiloba extract - EGB 761(Tanakan®, IPSEN, 320 mg/day)	Standardized mixture	Oral	Placebo	Malondialdehyde, ascorbyl free radical, myoglobin, myosin, pressure, heart rate, pulmonary capillary wedge pressure, and cardiac output
Safaei, 2017[60]	Cardiovascu -lar surgical procedures	Grape seed extract (GSE), 24 h before operation, 100mg every 6h.	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 F et al., 2008[61]	Cardiovascu -lar surgical procedures	Astragalus injection	Standardized 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 RQ et al., 2003[62]	Cardiovascu -lar surgical procedures	Puerarin injection	Standardized mixture available commercially, exact formulation not published	Intravenous	Intravenous normal saline	Angina attacks in balloon dilatatory stage of ercutaneoustransluminal 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[63]	Obstetric/ gynecologic	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 S et al., 2000[64]	Cardiovascu -lar surgical procedures	HM1: Astragalus injection HM2: Ligustrazine injection HM3:Astralagus plus ligustrazine injection	HM1 = HM2 = HM3 commercially available standardized 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)

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

Table 3. Risk of bias assessment.

Author, year	Was the randomization 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 statistician?	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[53]	Definitely yes	Probably no	Definitely yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably yes
Deng, 2006[54]	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably yes
Deng, 2010[55]	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably yes
Gharabaghi, 2011[56]	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Probably no	Probably yes	Definitely yes	Probably no	Definitely yes
Huang, 1996[57]	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Definitely no
Nanthakomon, 2006[58]	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Probably no	Probably yes	Definitely yes	Probably no	Probably yes
Pietri, 1997[59]	Probably yes	Probably no	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no
Safaei, 2017[60]	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Probably no	Definitely yes	Definitely yes	Probably yes	Definitely yes
Wang, 2008[61]	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably no
Xie, 2003[62]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely yes	Probably yes	Definitely no
Zeraati, 2016[63]	Definitely yes	Probably yes	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Probably yes	Definitely yes
Zhou, 2000[64]	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).

Table 4. GRADE evidence profile for RCTs: Herbal compared to placebo.

Quality assessment						Summary of findings					Certainty in estimates
						Study event rates		Relative risk	Anticipated absolute effects Over 24 hours		OR
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Placebo*	Herbal	(95% CI)	Placebo*	Herbal	Quality of evidence
Vomiting											
272 (3) 4-24 h	Serious limitation[1]	No serious limitations	Serious limitations[3]	No serious limitations	Undetected	42/136	24/136	**0.57** (0.38-0.56)	466 per 1000	200 fewer per 1000 (288 fewer to 205 fewer)	⊕⊕OO LOW
Nausea											
212 (2) 4-24 h	Serious limitations[1]	No serious limitations	Serious limitations[3]	No serious limitations	Undetected	42/106	29/106	**0.69** (0.50-0.96)	666 per 1000	207 fewer per 1000 (333 fewer to 27 fewer)	⊕⊕OO LOW
Pain											
92 (1) 24 h	Serious limitations[1]	Undetected	Serious limitations[3]	No serious limitations	Undetected	42/46	6/46	**0.14** (0.07-0.30)	913 per 1000	785 fewer per 1000 (849 fewer to 639 fewer)	⊕⊕OO LOW
Need for rescue medication for pain											
136 (3) 6-24 h	Serious limitations[1]	Serious limitations[2]	Serious limitations[3]	Serious imprecision[4]	Undetected	86/136	45/136	**0.52** (0.13-2.13)	666 per 1000	320 fewer per 1000 (580 fewer to 752 more)	⊕OOO VERY LOW

h.: hours

[1]Serious limitation related to randomization[56], allocation concealment[53,56], lack of blinding of caregivers[53], data collectors[53], statistician[53,56,58,63], and outcomes assessment[53,63], and selective outcome reporting[56,58].

[2]Serious limitation related to Heterogeneity, $I^2 = 92\%$
[3] Serious limitation related to surgery where the results are not applicable for cardiac surgery.
[4]95% CI for absolute effects include clinically important benefit and no benefit.

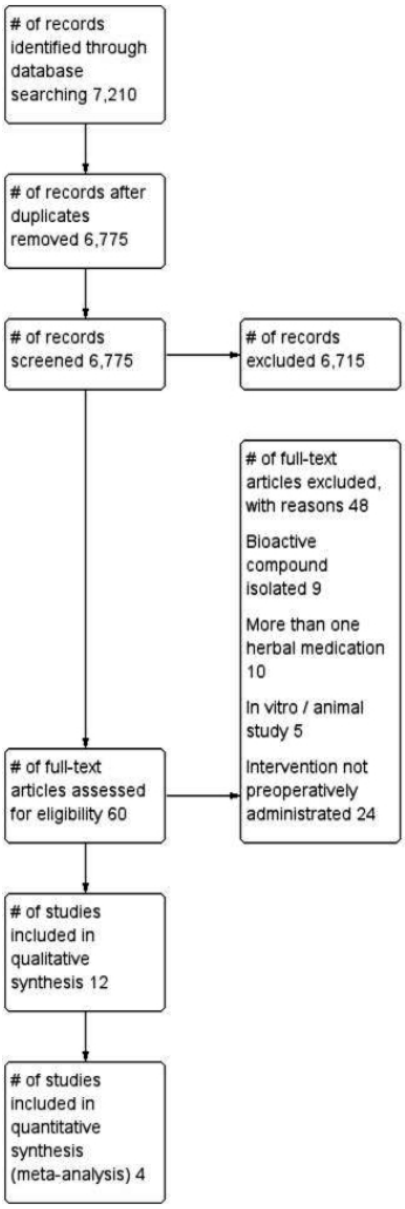


Figure 1. PRISMA flow diagram.tif

29x86mm (300 x 300 DPI)

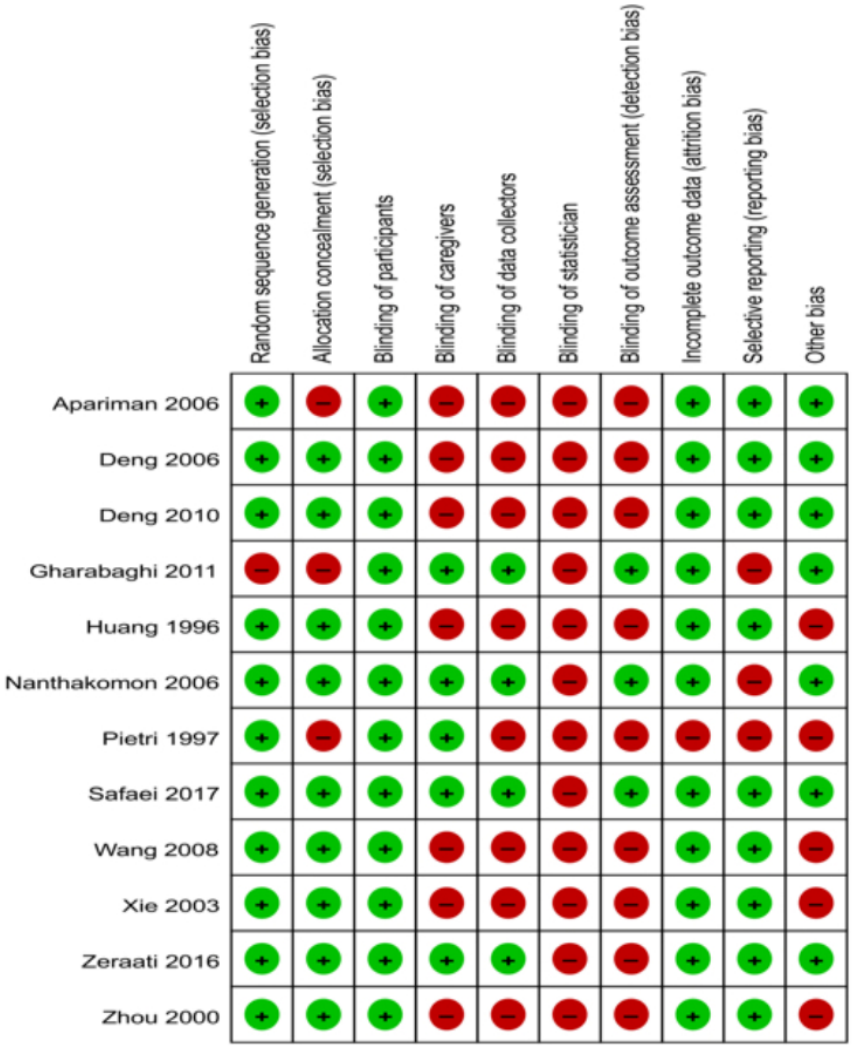


Figure 2. Risk of bias.tif

62x86mm (300 x 300 DPI)

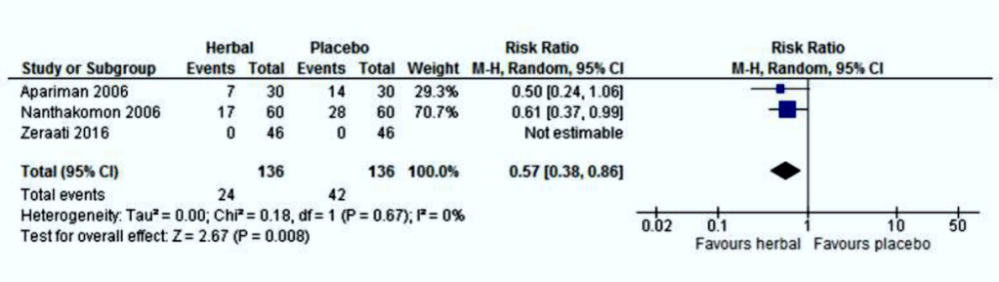


Figure 3. Meta-analysis comparing herbal versus placebo on vomiting for laparoscopic or obstetric_gynecologic.tif

86x24mm (300 x 300 DPI)

Figure 4. Meta-analysis comparing herbal versus placebo on nausea for obstetric_gynecologic.tif

86x18mm (300 x 300 DPI)

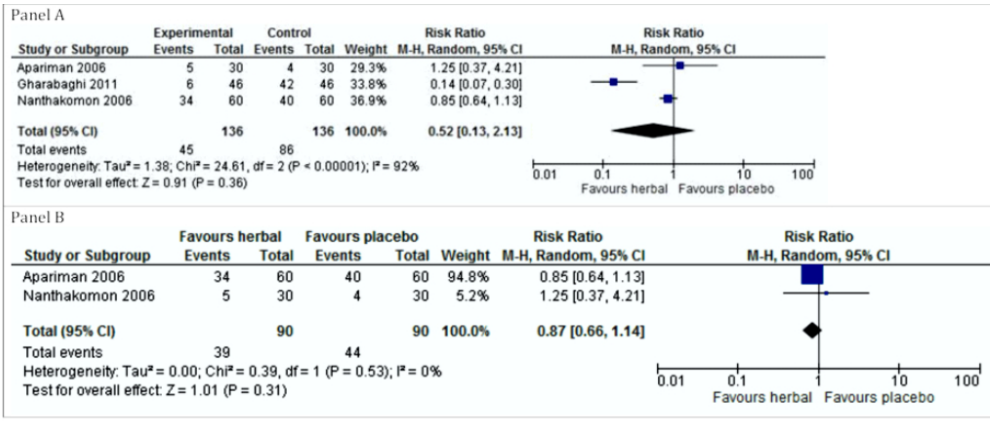
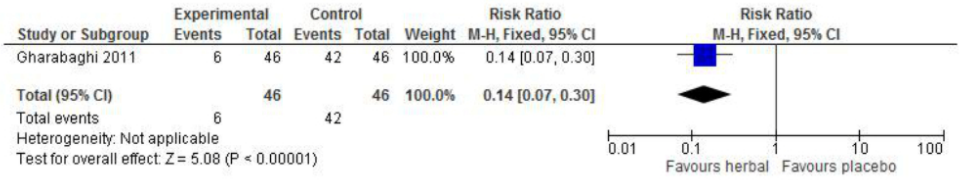


Figure 5. Meta-analysis comparing herbal versus placebo on need for rescue medication for pain.tif

86x37mm (300 x 300 DPI)



Appendix Figure 1. Representention of meta-analysis comparing herbal versus placebo on pain.tif

86x17mm (300 x 300 DPI)

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2,3
Rationale	#3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	6

Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6-8
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	8
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See note 1
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	8
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	9
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	9,10
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	9
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	10
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9,10
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and	See note

		included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	2
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	11, 12
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	See note 3
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	13, 14
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	13, 14
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	See note 4
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 5
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	14
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	3
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	17

Author notes

1. Appendix Table 1

2. 10, Figure 1. PRISMA flow diagram

3. 12, Figure 2 and table 3

4. Table 4. GRADE assessment

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023729.R1
Article Type:	Research
Date Submitted by the Author:	23-Nov-2018
Complete List of Authors:	Arruda, Ana Paula; Universidade Estadual Paulista Julio de Mesquita Filho Faculdade de Medicina Campus de Botucatu, Department of Surgery and Orthopedics Zhang, Yuchen; University of Toronto Faculty of Medicine Gomaa, Huda; Tanta Chest Hospital, Department of Pharmacy Bergamaschi, Cristiane; Universidade de Sorocaba, Pharmaceutical Sciences Guimaraes, Caio; Faculdade Sao Leopoldo Mandic, Terapeutica Righesso, Leonardo; University Medical Center Mainz, Mainz, Germany, Dept. of Oral & Maxillofacial Surgery, Moura, Mariana ; University of Sorocaba, Pharmaceutical Sciences Barberato-Filho, Silvio; Universidade de Sorocaba, Pharmaceutical Sciences Lopes, Luciane; UNISO, Pharmacie Science Ayala Melendez, Ana Patricia; University of Toronto, Gerstein Science Information Centre de Oliveira, Luciane ; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, São José dos Campos - SP - Brazil, Department of Biosciences and Oral Diagnosis Paula-Ramos, Lucas ; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, Department of Biosciences and Oral Diagnosis Johnston, Bradley; Dalhousie University Faculty of Medicine, Community Health and Epidemiology El Dib, Regina; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, Department of Biosciences and Oral Diagnosis; McMaster University, Institute of Urology, St. Joseph's Healthcare
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Surgery
Keywords:	Herbal medicine < THERAPEUTICS, Systematic review, Cardiac surgery < SURGERY, GYNAECOLOGY, Laparoscopy, Maternal medicine < OBSTETRICS

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

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ABSTRACT

Objective: To summarize the effects of herbal medications for the treatment and prevention of anxiety, depression, pain, and postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic, obstetric/gynecologic, or cardiovascular surgical procedures.

Methods: Searches of MEDLINE, EMBASE, CENTRAL and LILACS up until January 2018 were performed to identify randomized controlled trials (RCTs). We included RCTs or quasi-RCTs evaluating any herbal medication among adults undergoing laparoscopic, obstetric/gynecologic or cardiovascular surgeries. The primary outcomes were anxiety, depression, pain, and PONV. We used the GRADE approach to rate overall certainty of the evidence by outcome.

Results: Twelve trials including 738 patients were eligible. Results from three RCTs suggested a statistically significant reduction in vomiting (Risk Relative (RR) 0.57; 95% Confidential Interval (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 to placebo in both laparoscopic and obstetric/gynecologic surgeries. Results suggested a non-statistically significantly reduction in the need for rescue medication for pain (RR 0.52; 95% CI 0.13 to2.13) with *Rosa damascena* (damask rose) and ginger compared to placebo in laparoscopic and obstetric/gynecologic surgery.

Conclusions: There is low certainty evidence regarding the efficacy of herbal medication 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 obstetric/gynecologic surgeries. This systematic review was registered a priori with the International Prospective Register of Systematic

Reviews (CRD42016042838).

Keywords: herbal, laparoscopy, gynecologic surgery, obstetrical surgery, cardiovascular surgery, GRADE; systematic review.

Strengths and limitations of this study

- We included RCTs or quasi-RCTs evaluating any herbal medication among adults undergoing laparoscopic, obstetric/gynecologic 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 GRADE approach was used in rating the certainty of evidence; and we present both absolute and relative effects of the interventions on patient-important outcomes.

Word count: 3.772

1. 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 as high as 80%[2,3]. In addition to decreased quality of life, PONV has also been associated with increased hospital length of stay and systemic costs[4]. While recommendations for pharmacological prophylaxis and treatment for PONV exist, these medications may be associated with notable side-effects[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 to 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]. Depression and anxiety disorders have been associated with increased rates of readmission[11], morbidity[12] and mortality[13] in surgical patients.

Evidence from the United States 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 hospitalized 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 a number of these indications as well, though geographic variability exists. A study of hospitalized patients in a public medical center 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 United States 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 medications consumption two weeks prior tosurgery[31]. Nevertheless, a recent study 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 summarizing the efficacy and safety of herbal medications for the treatment and prevention of anxiety, depression, pain, and PONV in patients undergoing laparoscopic, obstetric/gynecologic and cardiovascular surgical procedures.

2. 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 the PROSPERO (International Prospective Register of Systematic Reviews) database under the number CRD42016042838, and the protocol was also published elsewhere[35].

2.1 Eligibility criteria

The inclusion criteria were:

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

The patient-important outcomes (primary outcomes) that we were interested were: anxiety (Spilberger Anxiety Inventory – Trait Anxiety Inventory (STAI) and other validated instruments); depression (Depression Scale – Hospital Anxiety and Depression Scale (HADS-D) 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, hospitalization, 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);
- Others.

The exclusion criteria were:

- Patients: Studies where the majority of participants were HIV-positive or transplant patients were not considered eligible for inclusion.
- 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.

2.2 Data source and searches

We searched Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid EMBASE, LILACS, ISI Web of Science and CINAHL, from their initial dates to January 30, 2018. Search terms describing laparoscopic, obstetrical/gynecological, cardiovascular surgeries, and herbal medication interventions were combined (Table 1). The search strategy was designed with the assistance of a trained librarian. No restrictions were placed on language, year of publication or

publication status.

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

#	Searches	Results
1	gynecology/ or obstetrics/ or thoracic surgery/ or Minimally Invasive Surgical Procedures/	61687
2	laparoscopy/ or hand-assisted laparoscopy/	69622
3	thoracic surgical procedures/ or exp cardiac surgical procedures/	195024
4	exp Gynecologic/obstetric Surgical Procedures/	72904
5	Cholecystectomy, Laparoscopic/	10733
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.	153069
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.	101339
9	(herbalism or botany or herbology).tw,kf.	1255
10	Phytotherapy/	33568
11	(phyto-therap* or phytotherap*).tw,kf.	1680
12	exp Plant Preparations/pd, tu, ad, st [Pharmacology, Therapeutic Use, Administration & Dosage, Standards]	103896
13	or/1-6 [Surgery]	457564
14	or/7-12 [Herbal medicine]	194482
15	13 and 14	1296
16	adult.mp. or middle aged.sh. or age:.tw.	7608507
17	15 and 16	470

2.3 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 and/or the pharmaceutical companies leading eligible trials were contacted for additional data and information that could be potentially included.

2.4 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, data extraction and risk of bias assessments were established by discussion and adjudication by a third reviewer as necessary.

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

2.6 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 summarized in an evidence profile.

2.7 Data synthesis and statistical analysis

Pooled risk ratios (RRs) were calculated for dichotomous outcomes and standardized mean differences (SMD) for continuous variables with the associated confidential interval (CI) 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 in the meta-analysis.

Variability was addressed in results across studies by using I^2 statistic and the p-value obtained from the Cochran chi square test. Our primary analyses were based on eligible patients who had reported outcomes 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 used Review Manager (*RevMan*) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses[43].

2.8 Patient and public involvement

No patients or public were involved in the present study.

3.1 Search selection

The initial searches identified 7,210 titles from the electronic searches. After the duplicates, titles were removed, 6,775 potentially relevant articles were retained for further assessment (Figure 1). Subsequent to reading titles and abstracts, 6,715 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, 12 randomized controlled trials (RCTs) and quasi-RCT[44-55] were included in the qualitative synthesis (Figure 1).

Six[45,46,48,52,53,55] of the included trials were published in Chinese. Authors of all included studies were contacted, but none of them supplied us with the requested information.

3.2 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. Eleven[45-55] were RCTs, and one[44] were quasi-RCT. Ten[44-50,52-54] trials employed a parallel two-arm design. Six trials[45,46,48,52,53,55] were conducted in China, three[47,51,54] in Iran, two[44,49] in Thailand, and a another one[50] in France. The trials sample size ranged from 20[50] to 120[49] patients. Participants were adults with an average mean age of 22.30[47] to 63.00 years old[50].

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 gynecologic 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]	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 anesthesia	Any cerebrovascular, neurological or metabolic diseases prior to surgery, any organ failure.	3 hours
Deng, 2010[46]	RCT	China, Asian	I: 15 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 anesthesia	High cholesterolemia, hematological 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 to 40 years having term pregnancy, without the history of hypersensitivity to local anesthetics (Lidocaine, Marcaine) and with the body mass index of 9.24 to 5.18 who were supposed to undergo cesarean section for different reasons.	Emergency cesarean sections, need to general anesthesia, history of psychological disorder, history of hypersensitivity to local anesthetics and Rosa damascena extract, prolongation of surgery more than one 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
Nanthako-mon, 2006[49]	RCT	Thailand, Asian	I: 60 C:60	I: not reported C: not reported	I:0 C:0	All patients were ASA (American Society of Anesthesia) 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 antiischemic, antiinflammatory, 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 ischemic 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, WBC>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
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 cesarean section with spinal anesthesia.	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 anesthesia, 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

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

The majority of the included studies among the cardiovascular surgical procedures presented as an inclusion criteria patients with rheumatic heart disease of ASA grade II - III[45,46,52,55]. For the included studies among the obstetric/gynecologic procedures the most common inclusion criteria were pregnant patients[47,54] and ASA grade I or II[49] while for the laparoscopic procedures were non-cancer gynecologic conditions[44]. Studies followed participants from two 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, eight[45,46,48,50-53,55] included studies evaluated patients undergoing cardiovascular surgical (mostly were heart valve replacement), three[47,49,54] obstetric/gynecologic and, one[44] laparoscopic procedure.

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]	Cardiovascular surgical procedures	Ginkgo biloba extract (trade name: Ginaton)	Standardized extract containing 24% ginkgo biloba flavonoid glycoside, 3.1% ginkgolide, 2.9% bilobalide	Intravenous	Intravenous normal saline	Blood gas, lactic acid concentration, activity of superoxide dismutase, malonaldehyde content, arterial oxygen content, jugular venous oxygen content, arterial to venous oxygen content difference, cerebral oxygen extraction ratio, arterio-jugular lactate difference
Deng, 2010[46]	Cardiovascular surgical procedures	Ginkgo biloba extract (trade name: Ginaton)	Standardized extract containing 24% ginkgo biloba flavonoid glycoside, 3.1% ginkgolide, 2.9% bilobalide	Intravenous	Intravenous normal saline	Plasma malondialdehyde and superoxide dismutase; erythrocyte malondialdehyde and superoxide dismutase; erythrocyte activity of Na K ATPase and Ca Mg ATPase
Gharabaghi, 2011[47]	Obstetric/ gynecologic	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 five minutes. The collected extract was completely dried under	Oral	Placebo capsules containing starch	Pain

			low pressure by rotary evaporator.			
Huang, 1996[48]	Cardiovas-cular surgical procedures	*Radix Salviae Miltiorrhizae* injection	Standardized mixture available commercially, exact formulation not published	Intravenous	Intravenous normal saline	Difference in level of peroxidation product and leukocyte count in arterial blood between left and right ventricles
Nanthakomon, 2006[49]	Obstetric/ gynecologic	Ginger 2 capsules (one capsule contains 0.5 g)	Powder	Oral	2 capsules of placebo (each capsule contains 0.5 g of lactose)	Nausea and vomiting
Pietri et al., 1997[50]	Cardiovas-cular surgical procedures	Gingo Biloba extract - EGB 761(Tanakan®, IPSEN, 320 mg/day)	Standardized mixture	Oral	Placebo	Malondialdehyde, ascorbyl free radical, myoglobin, myosin, pressure, heart rate, pulmonary capillary wedge pressure, and cardiac output
Safaei, 2017[51]	Cardiovas-cular surgical procedures	Grape seed extract (GSE), 24 h before operation, 100 mg every 6h.	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 F et al., 2008[52]	Cardiovas-cular surgical procedures	Astragalus injection	Standardized 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 RQ et al., 2003[53]	Cardiovas-cular surgical procedures	Puerarin injection	Standardized 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]	Obstetric/ gynecologic	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 S et al., 2000[55]	Cardiovas-cular surgical procedures	HM1: Astragalus injection HM2: Ligustrazine injection HM3:Astralagus plus ligustrazine injection	HM1 = HM2 = HM3 commercially available standardized mixture	Intra- venous	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)

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

Among cardiovascular surgery[45,46,48,50-53,55] studies, *Ginkgo biloba* was used in three[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 standardized extract[45,46]. Six 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 obstetric/gynecologic surgery procedures studies used *Zingiber officinale* (ginger)[49,54] and in other *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]. 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).

The only two herbal medications found in the literature were the ones described above.

3.3 Risk of bias assessment

Figure 2 and table 4 describe the risk of bias assessment. Only the domain blinding of statistician 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.

Table 4. Risk of bias assessment.

Author, year	Was the randomization 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 statistician?	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]	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably yes
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).

3.4 Primary Outcomes

3.4.1 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 to placebo in both laparoscopic and obstetric/gynecological 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 low because of risk of bias, due to allocation concealment[44], lack of blinding of caregivers[44], data collectors[44], statistician[44,49,54], outcome assessment[44,54] and indirectness (Table 5).

Table 5. GRADE evidence profile for RCTs: Herbal compared to placebo.

Quality assessment						Summary of findings				
						Study event rates		Relative risk (95% CI)	Anticipated absolute effects Over 24 hours		Certainty in estimates OR Quality of evidence
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Placebo	Herbal		Placebo	Herbal	
Vomiting											
272 (3) 4-24 h	Serious limitation[1]	No serious limitations	Serious limitations[6]	No serious limitations	Undetected	42/136	24/136	0.57 (0.38 to 0.86)	466 per 1000	200 fewer per 1000 (288 fewer to 205 fewer)	⊕⊕OO LOW
Nausea											
212 (2) 4-24 h	Serious limitations[2]	No serious limitations	Serious limitations[6]	No serious limitations	Undetected	42/106	29/106	0.59 (0.50 to 0.96)	666 per 1000	207 fewer per 1000 (333 fewer to 27 fewer)	⊕⊕OO LOW
Pain											
92 (1) 24 h	Serious limitations[3]	Undetected	Serious limitations[6]	No serious limitations	Undetected	42/46	6/46	0.14 (0.07 to 0.30)	913 per 1000	785 fewer per 1000 (849 fewer to 639 fewer)	⊕⊕OO LOW
Need for rescue medication for pain											
272 (3) 6-24 h	Serious limitations[4]	Serious limitations[5]	Serious limitations[6]	Serious imprecision[7]	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

h.: hours

[1]Serious limitation related to allocation concealment[44], lack of blinding of caregivers[44], data collectors[44], statistician[44,49,54], and outcomes assessment[44,54].

[2]Serious limitation related to lack of blinding of statistician[49,54], and outcomes assessment[54], and selective outcome reporting[49].

[3]Serious limitation related to random generation, allocation concealment, lack of blinding of statistician, and selective outcome reporting[47].

[4]Serious limitation related 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]
[5]Serious limitation related to Heterogeneity, $I^2 = 92\%$
[6] Serious limitation related to surgery where the results are not applicable for cardiac surgery.
[7]95% CI for absolute effects include clinically important benefit and no benefit.

3.4.2 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 to placebo in obstetric/gynecologic 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 low because of risk of bias, due to lack of blinding of statistician[49,54] and outcome assessment[54], selective outcome reporting[49] and, indirectness in both studies (Table 5).

3.4.3 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 to placebo in obstetric/gynecologic 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 low because of risk of bias, due to random generation, allocation concealment, lack of blinding of statistician, selective outcome reporting, and indirectness (Table 5).

3.4.4 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 to placebo in laparoscopic and obstetric/gynecologic 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[47] study yielded results that were consistent with the primary analysis and fail to show a difference in the effects of herbal medications compared to

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, and inconsistency (Table 5).

3.4.5Anxiety and depression

None of the included studies reported on these outcomes.

3.5 *Secondary Outcomes*

3.5.1 Adverse events

None of the included studies reported on this outcome.

3.5.2 Number of patients reporting adverse events

None of the included studies reported on this outcome.

3.5.3 Quality of life

None of the included studies reported on this outcome.

3.5.4 Satisfaction with herbal medications

None of the included studies reported on this outcome.

3.5.5 Need for rescue medication

None of the included studies reported on this outcome.

3.5.6 Duration of symptoms

None of the included studies reported on this outcome.

4. Discussion

4.1 Main findings

From laparoscopic and obstetric/gynecologic surgeries, 212 surgical patients suggested a significantly reduction in both vomiting and nausea favoring herbal medication (*Zingiber officinale*) and in the need for rescue medication for pain favoring herbal medications (i.e., *Rosa damascena* and *Zingiber officinale*). Other evaluated result such as pain[47] on obstetric/gynecologic surgery, were also presented favorable for herbal medication (*Rosa damascena*, *Zingiber officinale*) with certainty in evidence rated very low (Table 5).

Regarding the herbal medication *Zingiber officinale*, it is widely used around the world and the most common ailments treated are nausea, vomiting and motion sickness[44,49,54]. In a systematic review[56], *Zingiber officinale* was evaluated for nausea and vomiting, and six RCTs were reviewed. Three of these RCTs evaluated the PONV, with two of them suggesting that *Zingiber officinale* was superior to placebo and equally effective as metoclopramide (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) and placebo groups taken before operation (absolute risk reduction 0.05 (95% confidence interval 0.08 to 0.18). These studies collectively favored *Zingiber officinale* over placebo.

In another systematic review[57] which evaluated *Zingiber officinale* in the treatment of pregnancy-associated nausea and vomiting, twelve RCTs involving 1278 pregnant women were included. *Zingiber officinale* was compared to placebo and

significantly improved the symptoms of nausea (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 to placebo, although there was a trend towards improvement (MD 0.72, 95% CI 0.03 to 1.46, p = 0.06, I^2 = 71%). An additional indication which support this potential is about its properties. *Zingiber officinale* acts peripherally, within the gastrointestinal tract, increasing the gastric tone and motility due to anticholinenergic and antiserotonergic actions[58] and it is also reported that this herbal medication increase gastric emptying[59]. These activities can 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 not much published information on adverse effects of *Zingiber officinale*, the data found comment that some of its components may be mutagenic[60,61].

Regarding the findings of the present systematic review 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.

In relation to pain, *Rosa damascena* which has been tested in pre-clinical studies[62,63] for anti-inflammatory and analgesic properties, and in clinical studies for analgesic and antinociceptive effects[64,65]. Also a systematic review[66] showed promising evidences for its effectiveness and safety in pain relief. Although these positive findings[62-66],and due to limitations such as heterogeneity and low quality methodology in the present systematic review, these results must be cautiously interpreted. *Rosa damascena* presents promising indication for the effectiveness in pain relief but more studies are also needed. *Rosa damascena*[67] petals infusion has been tested for toxicity

and it was well tolerated, showing minimal nephrotoxic or hepatotoxic effects, unless it is used at unusually extreme doses.

These herbal medications, as described above, have been reported for abdominal pain[59] (*Zingiber officinale*) and for anti-inflammatory and analgesic properties[64,65] (*Rosa damascena*), however, this meta-analysis has found a high risk of selection bias and a certainty in evidence rated low to very low.

Another focus of this manuscript was to assess the adverse events with the use of herbal medication, but none of the evaluated clinical trials reported that information. Considering all the data evaluated in the present study, it is reiterated the importance of patients continuing to follow the guidance provided by ASA[31], which was previously described in the introduction, which is to stop using herbal medications two 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 is untrue and 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 some of which are capable of causing serious injuries, poisoning, and even potential life-threatening conditions[68-71].

4.2 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 random

sequence, and a fail of blinding due to the nature of the intervention, but for some studies also avoidable lack of blinding (outcome adjudication). Another limitation of this review is the fact that we were able to include only four trials including 364 patients, making difficult to find statistical power in some of our pre-defined outcomes.

Other 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[44] used 1.5 g of powder capsules; Nanthakomon[49] used 1.0 g of powder capsules and Zeraati[54] used 25 drops of liquid extract.

Another limitation of this review that one might also consider is the possibility that a gastric content may have played a role in the occurrence of vomiting between Apariman[44] and Zeraati[54] studies.

4.3 Implications for clinical practice and for research

There is low-certainty evidence showing that *Zingiber officinale* is more effective compared to placebo for the reduction of vomiting (laparoscopic and obstetric/gynecologic surgery) and nausea (obstetric/gynecologic surgery) in patients. There is also low-certainty evidence showing that *Rosa damascena* is more effective compared to placebo for the reduction of pain in patients undergoing obstetric/gynecologic surgery. However, there is very low-certainty evidence showing that *Rosa damascena* and *Zingiber officinale* are more effective compared to placebo for the reduction of the need for rescue medication for pain in laparoscopic and obstetric/gynecologic surgeries.

Author Contributions. APNA is the guarantor, led the writing of the manuscript, and participated in data extraction. RED and LCL were the project managers, co-investigators, contributed to the writing and revision of this systematic review. APA was the Trial Search Coordinator responsible for the search strategy. CCB was co-investigator, helped to revise the protocol, and participated in data extraction. YZ, HG, CCG, LARR, MDGM, SBF, LDO, LPR and BJ contributed to the writing and revision of the manuscript and participated in data extraction. All authors read and approved the final manuscript.

Funding. R. El Dib was supported by Brazilian Research Council (CNPq) scholarship grant number (CNPq 310953/2015-4).

Competing interests. None declared.

Patient consent. Not required.

Data sharing statement. No additional data are available.

Acknowledgments. We are thankful to Arnav Agarwal for English language editing.

REFERENCES

1. Kable AK, Gibberd RW, Spigelman AD. Adverse events in surgical patients in Australia. *Int J Qual Health Care*. 2002 Aug;14(4):269-76.
2. Farhadi K, Choubsaz M, Setayeshi K, et al. The effectiveness of dry-cupping in preventing post-operative nausea and vomiting by P6 acupoint stimulation: A randomized controlled trial. Lauche. R, ed. *Medicine*. 2016;95(38):e4770.
3. Youssef N, Orlov D, Alie T, et al. What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery?: a meta-analysis of randomized controlled trials. *Anesth Analg.* 2014; 119:965–977.
4. Palazzo MG, Strunin L. Anaesthesia and emesis: 1. Etiology. *Can Anaesth Soc J*. 1984;31:178–87.
5. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2014; 118:85–113.
6. Underwood M, Firmin RK, Jehu D. Aspects of psychological and social morbidity in patients awaiting coronary artery bypass grafting. *Br Heart J.* 1993; 69(5):382-384.
7. Marcolino J, Suzuki F, Cunha L, et al. Medida de ansiedade e da depressão em pacientes no pré-operatório: Estudo comparativo. *Rev Bras Anestesiol.* 2007;57(2):157-166.
8. Kil HK, Kim WO, Chung WY, et al. Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia. *Br J Anaesth.* 2012; 108:119-25.
9. Shoar S, Naderan M, Aghajani M, et al. Prevalence and Determinants of Depression and Anxiety Symptoms in Surgical Patients. *Oman Med J.* 2016;31(3):176-181.
10. Yohannes AM, Willgoss TG, Baldwin RC, et al. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psychiatry*. 2010;25:1209–1221.
11. Daratha KB, Barbosa-Leiker C, Burley HM et al. Co-occurring mood disorders among hospitalized patients and risk for subsequent medical hospitalization. *Gen Hosp Psychiatry*. 2012 Sep-Oct;34(5):500-505.
12. Gasse C, Laursen TM, Baune BT. Major depression and first-time hospitalization with ischemic heart disease, cardiac procedures and mortality in the general population: A retrospective Danish population-based cohort study. *Eur J Prev Cardiol*. 2014May;21(5):532-540.
13. Fan VS, Ramsey SD, Giardino ND, et al. National Emphysema Treatment Trial (NETT) Research Group. Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease. *Arch Intern Med*. 2007 Nov;167(21):2345-2353.
14. Svensson I, Sjostrom B, Haljamae H. Assessment of pain experiences after elective surgery. *J Pain Symptom Manage*. 2000; 20: 193–201.
15. Boisseau N, Rabary O, Padovani B, et al. Improvement of dynamic analgesia does not decrease atelectasias after thoracotomy. *Br J Anaesth*. 2001; 87:564-9.
16. Brattwall M, Warren Stomberg M, Rawal N, et al. "Patients' assessment of 4-week recovery after ambulatory surgery. *Acta Anaesthesiologica Scandinavica*, 2011; 55,1: 92–98.
17. Campagna S, D'olx MDA, Paradiso R, et al. Postoperative Pain, an Unmet Problem in Day or Overnight Italian Surgery Patients: A Prospective Study. *Pain Res Manag*. 2016;2016:6104383.
18. Levy I, Attias S, Ben-Arye E, et al. Adverse events associated with interactions with dietary and herbal supplements among inpatients. *Br J Clin Pharmacol*. 2016 Oct 19.
19. Kaye AD, Clarke RC, Sabar R, et al. Herbal medications: current trends in anesthesiology practice—a hospital survey. *J Clin Anesth*. 2000;12:468–471.
20. Gharabagy PM, Zamany P, Delazar A, et al. Efficacy of Eremostachys laciniata herbal extract on mitigation of pain after hysterectomy surgery. *Pak J Biol Sci.* 2013Sep1;16(17):891-4.

21. Ozgoli G, Saei Ghare Naz M. Effects of Complementary Medicine on Nausea and Vomiting in Pregnancy: A Systematic Review. *Int J Prev Med.* 2018 Aug 30;9:75
22. Akhlaghi M, Shabanian G, Rafieian-Kopaei M, et al. Citrus aurantium blossom and preoperative anxiety. *Rev Bras Anestesiol.* 2011 Nov-Dec;61(6):702-12.
23. Ang-Lee M, Moss J, Yuan C-S. Herbal medicines and perioperative care. *JAMA* 2001;286:208–16.
24. Norred C, Finlayson C. Hemorrhage after the preoperative used of complementary and alternative medicine. *AANA J*. 2000;68: 217–20.
25. Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. *J Am Coll Cardiol.* 2010;55:515–25.
26. Hodges PJ, Kam PC. The perioperative implications of herbal medicines. *Anaesthesia.* 2002 Sep;57(9):889-99.
27. Cotterill J. Severe phototoxic reaction to laser treatment in a patient taking St John's Wort. *J Cosmet Laser Ther*. 2001;3:159–60.
28. Rose KD, Croissant PD, Parliament CF, et al. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: A case report. *Neurosurgery*. 1990;26:880–82.
29. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med.* 1996;125:940–41.
30. Levy I, Attias S, Ben-Arye E, et al. Perioperative Risks of Dietary and Herbal Supplements. *World J Surg*. 2016 Nov 22.
31. American Society of Anesthesiologists [Internet]. What you should know about your patients' use of herbal medicines. [update 2003, cited 2017 fev12]. Available in: http://www.wehealny.org/services/BI_Anesthesiology/herbPatient.pdf
32. Franco Ruiz S, Gonzalez Maldonado P. Dietary supplements and the anesthesiologist: research results and state of the art. *Rev Colomb Anesthesiol*. 2014; 42:90–99
33. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.Available from http://handbook.cochrane.org/(accessed august 2016).
34. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ.* 2009;339:b2535.
35. Arruda APN, Ayala AP, Lopes LC, et al. Herbal medications for surgical patients: a systematic review protocol. *BMJ Open* 2017;7:e014290.
36. Guyatt GH, Busse JW. Modification of Cochrane Tool to assess risk of bias in randomized trials. http://distillercer.com/resources/(accessed august 2016).
37. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6.
38. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol*. 2011;64:407-15.
39. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol.* 2011b;64:1283-93.
40. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol.* 2011c;64:1294-302.
41. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol.* 2011d;64:1303-10.
42. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol.* 2011e;64:1277-82.
43. The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.
44. Apariman S, Ratchanon S, Wiriyasirivej B. Effectiveness of ginger for prevention of nausea and vomiting after gynecological laparoscopy. *J Med Assoc Thai.* 2006;89:2003-9.

45. Deng, YK, Wei F, Zhang DG. Brain protective effects of ginkgo biloba leaf extract (ginaton) in patients undergoing hypothermic cardiopulmonary bypass. *Chin J Integr Med*. 2006; 26:795-8.
46. Deng YK, Wei F, Zhang DG. Erythrocyte protective effects of ginaton in patients undergoing hypothermic cardiopulmonary bypass. *Chin J Integr Med*. 2010;30:365-8.
47. Gharabaghi PM, Tabatabei F, Fard SA et al. Evaluation Of The Effect Of Preemptive Administration Of Rosa Damascena Extract On Post-Operative Pain In Elective Cesarean Sections. *Afr J Pharm Pharmacol.* 2011;5:1950-55.
48. Huang ZY, Liao CX, Chen DZ. Effect of radix *Salviae miltiorrhizae* on production of free radical products from lung during cardiopulmonary bypass operation. *Chin J Integr Med*. 1996;16:451-3.
49. Nanthakomon T, Pongrojpaw D. The efficacy of ginger in prevention of postoperative nausea and vomiting after major gynecologic/obstetric surgery. *J Med Assoc Thai.* 2006 Oct;89(4):S130-6.
50. Pietri S, Séguin JR, d'Arbigny P, et al. Ginkgo biloba extract (EGb 761) pretreatment limits free radical oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther.* 1997;11:121-31.
51. Safaei N, Babaei H, Azarfarin R, et al. Comparative Effect of Grape Seed Extract (*Vitis Vinifera*) and Ascorbic Acid in Oxidative Stress Induced by On-pump Coronary Artery Bypass Surgery. *Ann Card Anaesth.* 2017;20:45-51.
52. Wang F, Xiao MD, Liao B. Effect of Astragalus on cytokines in patients undergoing heart valve replacement. *Chin J Integr Med*. 2008;28:495-8.
53. Xie RQ, Du J, Hao YM. Myocardial protection and mechanism of Puerarin Injection on patients of coronary heart disease with ischemia/reperfusion. *Chin J Integr Med*. 2003;23:895-7.
54. Zeraati H, Shahinfar J, Imani Hesari S, et al. The Effect of Ginger Extract on the Incidence and Severity of Nausea and Vomiting After Cesarean Section Under Spinal Anesthesia. *Anesth Pain Med.* 2016;6:e38943.
55. Zhou S, Shao W, Zhang W. Clinical study of Astragalus injection plus ligustrazine in protecting myocardial ischemia reperfusion injury. *Chin J Integr Med*. 2000;20:504-7.
56. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth.* 2000;84:367-71.
57. Viljoen E, Visser J, Koen N, et al. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutr J*. 2014;13: 1-14.
58. Adbel-Aziz H, Windeck T, Ploch M, et al. Mode of action of gingerols and shogaols on 5-HT3 receptors: binding studies, cation uptake by the receptor channel and contraction of isolated guinea-pig ileum. *Eur J Pharmacol.* 2006;530:136–43.
59. Hu ML, Rayner CK, Wu KL et al. Effect of ginger on gastric motility and symptoms of functional dyspepsia. *World J Gastroenterol.* 2011;17:105–10.
60. Abraham S, Abraham SK, Radhamony G. Mutagenic potential of the condiments, ginger and turmeric. *Cytologia* 1976; 41: 591–5 30
61. Nagabhushan M, Amonkar AJ, Bhide SV. Mutagenicity of gingerol and shogaol and antimutagenicity of zingerone in salmonella/ microsome assay. *Cancer Lett* 1987; 36: 221–33
62. Hajhashemi V, Ghannadi A, Hajiloo M. Analgesic and anti-inflammatory effects of Rosa damascena hydroalcoholic extract and its essential oil in animal models. *Iran J Pharm Res.* 2010;16:3–8.
63. Latifi G, Ghannadi A, Minaiyan M. Anti-inflammatory effect of volatile oil and hydroalcoholic extract of Rosa damascena Mill. on acetic acid-induced colitis in rats. *Res Pharm Sci.* 2015; 10:514-22.
64. Shirazi M, Mohebitabar S, Bioos S et al. The effect of topical Rosa damascena (Rose) oil on pregnancy-related low back pain a randomized controlled clinical trial. *J Evid Based Complementary Altern Med.* 2016; 22: 120-26.

65. Bani S, Hasanpour S, Mousavi Z, et al. The effect of rosa damascena extract on primary dysmenorrhea: a double-blind cross-over clinical trial. *Iran Red Crescent Med J.* 2014;16: e14643.
66. Nayebia N, Khalilib N, Kamalinejadc M, et al. A systematic review of the efficacy and safety of Rosa damascena Mill. with an overview on its phytopharmacological properties. *Complement Ther Med.* 2017; 34: 129–140
67. Akbari M, Kazerani HR, Kamrani A et al. A preliminary study on some potential toxic effects of Rosa damascena Mill. Iran J Vet Res. 2013;14(3): 232-36.
68. Ernst E. Toxic heavy metals and undeclared drugs in Asian herbal medicines. *Trends Pharmacol Sci.* 2002; 23: 136–139.
69. Ekor M, Osonuga OA, Odewabi AO, et al. Toxicity evaluation of Yoyo 'cleanser' bitters and fields Swedish bitters herbal preparations following sub-chronic administration in rats. *Am J Pharmo &Toxicol.* 2010;5,159–166.
70. Auerbach BJ, Reynolds SJ, Lamorde M, et al. Traditional herbal medicine use associated with liver fibrosis in rural Rakai, Uganda. *PLoS ONE* 2012;7, e41737.
71. Ekor, M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol.* 2014; 4:177.

FIGURE LEGENDS

Figure 1. PRISMA flow diagram.

Figure 2. Risk of bias.

Figure 3. Meta-analysis comparing herbal versus placebo on vomiting for laparoscopic or obstetric-gynecologic.

Figure 4. Meta-analysis comparing herbal versus placebo on nausea for obstetric-gynecologic.

Figure 5. Meta-analysis comparing herbal versus placebo on need for rescue medication for pain. Panel A: primary analysis considering laparoscopic or obstetric/gynecologic surgeries. Panel B: sensitivity analysis excluding Gharabaghi 2011 study considering laparoscopic or obstetric/gynecologic surgeries.

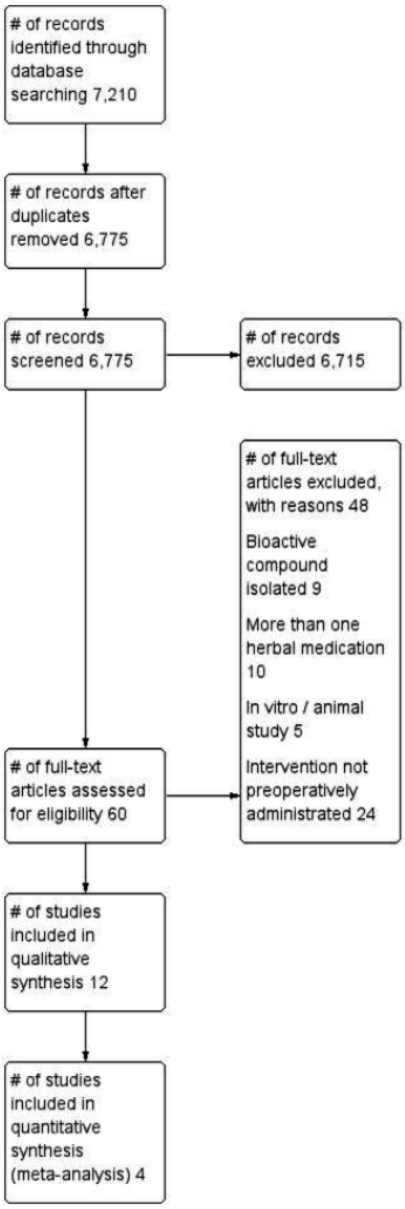

Figure 1. PRISMA flow diagram.tif

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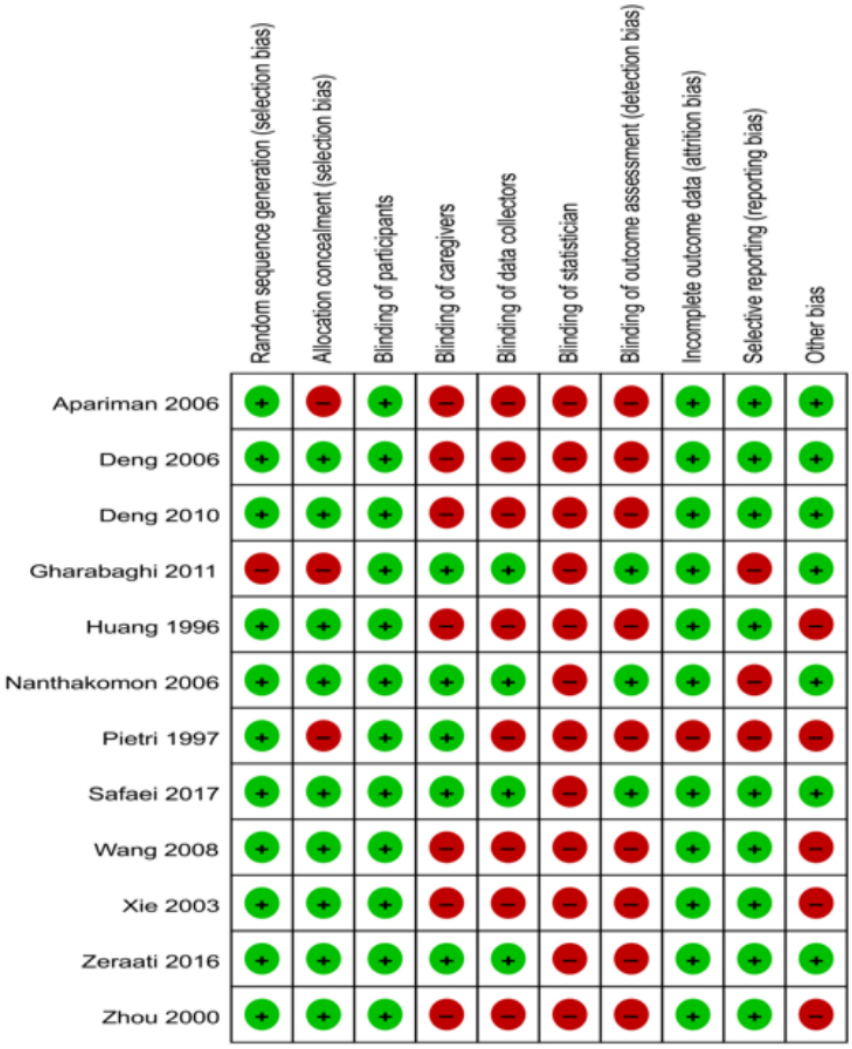

Figure 2. Risk of bias.tif

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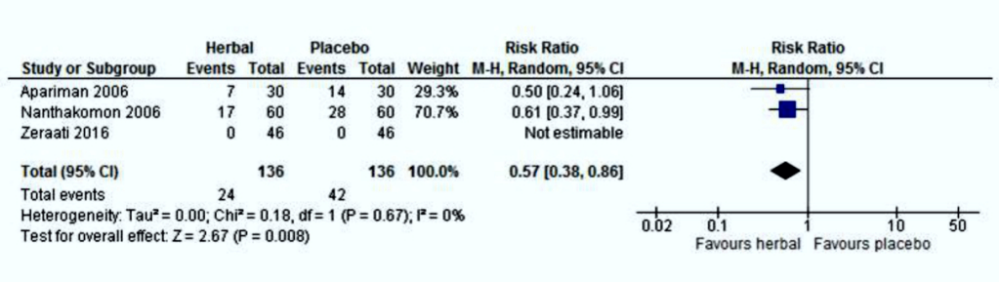

Figure 3. Meta-analysis comparing herbal versus placebo on vomiting for laparoscopic or obstetric_gynecologic.tif

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Figure 4. Meta-analysis comparing herbal versus placebo on nausea for obstetric_gynecologic.tif

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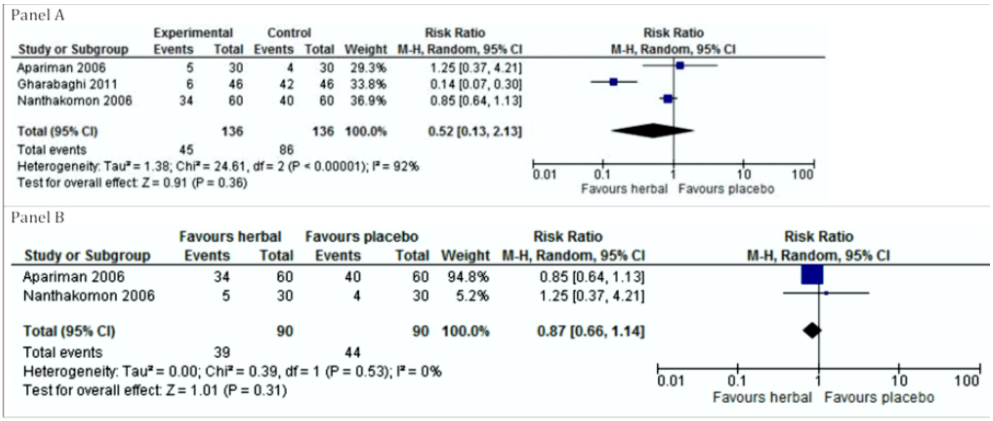

Figure 5. Meta-analysis comparing herbal versus placebo on need for rescue medication for pain.tif

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Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis	2,3

		methods; results; limitations; conclusions and implications of key findings; systematic review registration number	
Rationale	#3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	6
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6,7
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	7,8
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	8,9
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any	9

		processes for obtaining and confirming data from investigators.	
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	8
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	9
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	10
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9,10
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study	#18	For each study, present characteristics for which data were	Tables

characteristics		extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	2,3, pag 11
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Table 4, fig. 2
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	21-26
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	26-28
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4, figure 2
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	----
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	28,29
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	28,29
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	29

Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	30

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023729.R2
Article Type:	Research
Date Submitted by the Author:	29-Mar-2019
Complete List of Authors:	Arruda, Ana Paula; Universidade Estadual Paulista Julio de Mesquita Filho Faculdade de Medicina Campus de Botucatu, Department of Surgery and Orthopedics Zhang, Yuchen; University of Toronto Faculty of Medicine Gomaa, Huda; Tanta Chest Hospital, Department of Pharmacy Bergamaschi, Cristiane; Universidade de Sorocaba, Pharmaceutical Sciences Guimaraes, Caio; Faculdade Sao Leopoldo Mandic, Terapeutica Righesso, Leonardo; University Medical Center Mainz, Mainz, Germany, Dept. of Oral & Maxillofacial Surgery, Moura, Mariana ; University of Sorocaba, Pharmaceutical Sciences Barberato-Filho, Silvio; Universidade de Sorocaba, Pharmaceutical Sciences Lopes, Luciane; UNISO, Pharmacie Science Ayala Melendez, Ana Patricia; University of Toronto, Gerstein Science Information Centre de Oliveira, Luciane ; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, São José dos Campos - SP - Brazil, Department of Biosciences and Oral Diagnosis Paula-Ramos, Lucas ; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, Department of Biosciences and Oral Diagnosis Johnston, Bradley; Dalhousie University Faculty of Medicine, Community Health and Epidemiology El Dib, Regina; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, Department of Biosciences and Oral Diagnosis; McMaster University, Institute of Urology, St. Joseph's Healthcare
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Surgery
Keywords:	Herbal medicine < THERAPEUTICS, Systematic review, Cardiac surgery < SURGERY, GYNAECOLOGY, Laparoscopy, Maternal medicine < OBSTETRICS

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

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ABSTRACT

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

Methods: Searches of MEDLINE, EMBASE, CENTRAL and LILACS up until January 2018 were performed to identify randomized controlled trials (RCTs). We included RCTs or quasi-RCTs evaluating any herbal medication among adults undergoing laparoscopic, obstetric/gynecologic or cardiovascular surgeries. The primary outcomes were anxiety, depression, pain, and PONV. We used the GRADE 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% Confidence Interval (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 to placebo in both laparoscopic and obstetric/gynecologic 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 to placebo in laparoscopic and obstetric/gynecologic 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 obstetric/gynecologic surgeries. Among our eligible studies, there was no reported evidence on AEs. This

systematic review was registered a priori with the International Prospective Register of Systematic Reviews (CRD42016042838).

Keywords: herbal, laparoscopy, gynecologic surgery, obstetrical surgery, cardiovascular surgery, GRADE; systematic review.

Strengths and limitations of this study

- We included RCTs or quasi-RCTs evaluating any herbal medication among adults undergoing laparoscopic, obstetric/gynecologic 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 GRADE approach was used in rating the certainty of evidence; and we present both absolute and relative effects of the interventions for patient-important outcomes.

Word count: 4.060

1. 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, gastro-intestinal 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 United States 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 hospitalized 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 hospitalized patients in a public medical center 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 United States 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[20,21,22], 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[23,24,25,26,27,28,29]. 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 medications consumption two weeks prior tosurgery[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 summarizing the efficacy and safety of herbal medications for the prevention of anxiety, depression, pain, and PONV in patients undergoing laparoscopic, obstetric/gynecologic and cardiovascular surgical procedures.

2. 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 the PROSPERO (International Prospective Register of Systematic Reviews) database under the number CRD42016042838, and the protocol was also published elsewhere[35].

2.1 Eligibility criteria

The inclusion criteria were:

- Study design: Randomized controlled trials (RCTs) and quasi-RCT.
- Patients: Adults (≥ 18 years of age) undergoing laparoscopic, obstetric/gynecologic, 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, standardized mixture, drug extract ratio and solvent) which were compared against conventional treatment, placebo, no intervention, other type of complementary and alternative therapy (e.g. acupuncture, homeopathy), or another herbal medication. The following routes of administration were considered: oral (e.g. 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 (STAI) and other validated instruments); depression (Depression Scale – Hospital Anxiety and Depression Scale (HADS-D) 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, hospitalization, 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.

2.2 Data source and searches

We searched Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid EMBASE, LILACS, ISI Web of Science and CINAHL, from their initial inception dates to January 30, 2018. Search terms describing laparoscopic, obstetrical/gynecological, cardiovascular surgeries, and herbal medication interventions were combined (Table 1). The search strategy was designed with the assistance of a trained librarian. No restrictions were placed on language, year of publication or publication status.

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

#	Searches	Results
1	gynecology/ or obstetrics/ or thoracic surgery/ or Minimally Invasive Surgical Procedures/	61687
2	laparoscopy/ or hand-assisted laparoscopy/	69622
3	thoracic surgical procedures/ or exp cardiac surgical procedures/	195024
4	exp Gynecologic/obstetric Surgical Procedures/	72904
5	Cholecystectomy, Laparoscopic/	10733
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.	153069
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.	101339
9	(herbalism or botany or herbology).tw,kf.	1255
10	Phytotherapy/	33568
11	(phyto-therap* or phytotherap*).tw,kf.	1680
12	exp Plant Preparations/pd, tu, ad, st [Pharmacology, Therapeutic Use, Administration & Dosage, Standards]	103896
13	or/1-6 [Surgery]	457564
14	or/7-12 [Herbal medicine]	194482
15	13 and 14	1296
16	adult.mp. or middle aged.sh. or age:.tw.	7608507
17	15 and 16	470

2.3 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.

2.4 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.

2.5 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-standardized 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.

2.6 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 summarized in an evidence profile table.

2.7 Data synthesis and statistical analysis

Pooled risk ratios (RRs) were calculated for dichotomous outcomes and standardized mean differences (SMD) for continuous variables with the associated confidential interval (CI) 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 (chi square) 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 used Review Manager (*RevMan*) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses[43].

2.8 Patient and public involvement

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

3.1 Search selection

The initial searches identified 7,210 titles from the electronic searches. After the duplicates, titles were removed, 6,775 potentially relevant articles were retained for further assessment (Figure 1). Subsequent to reading titles and abstracts, 6,715 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) randomized controlled trials (RCTs) or quasi-RCT[44,45,46,47,48,49,50,51,52,53,54,55] 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.

3.2 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 ranged from 22.30[47] to 63.00 years old[50].

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 gynecologic 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 anesthesia	Any cerebrovascular, neurological or metabolic diseases prior to surgery, any organ failure; hematological 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 to 40 years having term pregnancy, without the history of hypersensitivity to local anesthetics (Lidocaine, Marcaine) and with the body mass index of 9.24 to 5.18 who were supposed to undergo cesarean section for different reasons.	Emergency cesarean sections, need to general anesthesia, history of psychological disorder, history of hypersensitivity to local anesthetics and Rosa damascena extract, prolongation of surgery more than one 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 (American Society of Anesthesia) 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 antiischemic, antiinflammatory, 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 ischemic 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, WBC 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	No angina 48 hours prior to surgery	7 days

						transluminal coronary angioplasty and stenting		
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 cesarean section with spinal anesthesia.	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 anesthesia, 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

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

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 obstetric/gynecologic 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 gynecologic conditions[44]. Studies followed participants from two 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] obstetric/gynecologic and, one[44] laparoscopic procedure.

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)	Standardized 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]	Obstetric/ gynecologic	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 five minutes. 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	Standardized mixture available commercially, exact formulation not published	Intravenous	Intravenous normal saline	Difference in level of peroxidation product and leukocyte count in arterial blood between left and right ventricles

Nanthakomon, 2006[49]	Obstetric/ gynecologic	Ginger 2 capsules (one capsule contains 0.5 g)	Powder	Oral	2 capsules of placebo (each capsule contains 0.5 g of lactose)	Nausea and vomiting
Pietri, 1997[50]	Cardiovascular surgical procedures	Gingo Biloba extract - EGB 761(Tanakan ®, IPSEN, 320 mg/day)	Standardized mixture	Oral	Placebo	Malondialdehyde, ascorbyl free radical, myoglobin, myosin, pressure, heart rate, pulmonary capillary wedge pressure, and cardiac output
Safaei, 2017[51]	Cardiovascular surgical procedures	Grape seed extract (GSE), 24 h before operation, 100 mg every 6h.	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	Standardized mixture available commercially, exact formulation not published	Intravenous	Intravenous normal saline	Tumour necrosis factor alpha, interleukin 6 (IL6), IL8, IL1 from radial blood samples
Xie, 2003[53]	Cardiovascular surgical procedures	Puerarin injection	Standardized 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]	Obstetric/ gynecologic	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 standardized 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)

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

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 standardized 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 obstetric/gynecologic surgery procedures studies used *Zingiber officinale* (ginger)[49,54] and in other *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).

3.3 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.

Table 4. Risk of bias assessment.

Author, year	Was the randomization 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).

3.4 Primary Outcomes

3.4.1 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 to the control group (i.e., placebo and tap water) in both laparoscopic and obstetric/gynecological 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).

Table 5. GRADE evidence profile for RCTs: Herbal compared to placebo.

Quality assessment						Summary of findings				
						Study event rates		Relative risk (95% CI)	Anticipated absolute effects Over 24 hours		Certainty in estimates OR Quality of evidence
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Placebo	Herbal		Placebo	Herbal	
Vomiting											
272 (3) 4-24 h	Serious limitation[1]	No serious limitations	Serious limitations[2]	Serious imprecision[3]	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 h	Serious limitations[4]	No serious limitations	Serious limitations[2]	Serious imprecision[3]	Undetected	42/106	29/106	0.59 (0.50 to 0.96)	666 per 1000	207 fewer per 1000 (333 fewer to 27 fewer)	⊕OOO VERY LOW
Pain											
92 (1) 24 h	Serious limitations[5]	Undetected	Serious limitations[2]	Serious imprecision[3]	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 h	Serious limitations[6]	Serious limitations[7]	Serious limitations[2]	Serious imprecision[3]	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

h.: hours

[1]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].

[2] Serious limitations related to surgery where the results are not applicable for cardiac surgery.

[3] Serious imprecision related to outcome (fewer than 300 to 400 events).
[4] Serious limitations related to lack of blinding of data analyst[49,54], and outcomes assessment[54], and selective outcome reporting[49].
[5]Serious limitations related to random generation, allocation concealment, lack of blinding of data analyst, and selective outcome reporting[47].
[6]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].
[7] Serious limitation related to inconsistency ($I^2 = 92\%$).

3.4.2 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 to the control group (i.e., placebo and tap water) in obstetric/gynecologic 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).

3.4.3 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 to placebo in obstetric/gynecologic 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 of blinding of data analyst, selective outcome reporting), imprecision (fewer than 300 to 400 events), and indirectness (Table 5).

3.4.4 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 to placebo in laparoscopic and obstetric/gynecologic 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[47] study yielded results that were consistent with the primary analysis and fail to show a difference in the effects of herbal medications compared to 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).

3.4.5Anxiety and depression

None of the included studies reported on these outcomes.

3.5 *Secondary Outcomes*

3.5.1 Adverse events

None of the included studies reported on this outcome.

3.5.2 Number of patients reporting adverse events

None of the included studies reported on this outcome.

3.5.3 Quality of life

None of the included studies reported on this outcome.

3.5.4 Satisfaction with herbal medications

None of the included studies reported on this outcome.

3.5.5 Need for rescue medication

None of the included studies reported on this outcome.

3.5.6 Duration of symptoms

None of the included studies reported on this outcome.

3.5.7 Qualitative analysis of non patient-important outcomes

Seven trials[45,46,48,50,51,52,53,55] from the qualitative analysis assessed different types of biochemical analyzes during cardiovascular surgical procedures. Two[45,46,50] of them analyzing *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 analyzing *Astragalus* found that it may decrease the inflammation cytokine promoting factors and increase the level of antiinflammatory 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[48] evaluated *Radix Salviae Miltiorrhizae* and found effects towards the prevention of lung leukocyte aggregation and a reduction in the production of lung free radical products while the study of Safaei[51] tested the effect of *Vitis vinifera* and found an antioxidative effect during coronary artery bypass grafting surgery. Lastly, Xie[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 ischemia reperfusion.

4. Discussion

4.1 Main findings

From laparoscopic and obstetric/gynecologic surgeries, based on 212 surgical patients evidence suggests a statistically significant reduction in both vomiting and nausea favoring *Zingiber officinale* and in the need for rescue medication for pain favoring both *Rosa damascena* and *Zingiber officinale*. We also found favorable results for *Rosa damascena* and *Zingiber officinale* for pain[47] associated with obstetric/gynecologic 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% confidence interval 0.08 to 0.18). These studies collectively favored *Zingiber officinale* over placebo.

In another systematic review[57] that evaluated *Zingiber officinale* in the treatment of pregnancy-associated nausea and vomiting, twelve RCTs involving 1278 pregnant women were included. *Zingiber officinale* was compared to placebo and significantly improved the symptoms of nausea (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 to 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 standardized 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 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 two 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]..

4.2 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[44] used 1.5 g of powder capsules; Nanthakomon[49] used 1.0 g of powder capsules and Zeraati[54] used 25 drops of liquid extract. A fourth limitation was the inconsistent standardization 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[44] and Zeraati[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 minimize the potential interaction with the postoperative medications (e.g., anti-emetics, painkillers) on the predefined outcomes.

4.3 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 obstetric/gynecologic surgery) and nausea (obstetric/gynecologic 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 obstetric/gynecologic 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 obstetric/gynecologic surgeries.

Author Contributions. APNA: Conceived the review, undertook the searches, screened search results, extracted data from papers, wrote to authors of papers for additional information, contributed in analyzing RevMan statistical data, contributed in making statistical inferences, interpreted the data, wrote the review, and revised the

manuscript. RED: conceived the review, supervise the whole manuscript, contributed in analyzing RevMan statistical data, contributed in making statistical inferences, interpreted the data, wrote the review, and revised the manuscript. APA was the Trial Search Coordinator responsible for the search strategy. CCB, YZ, HG, CCG, LARR, MDGM, SBF, LDO, LPR, and LCL screened search results and extracted data from papers. BCJ: interpreted and analyzed the data and revised the manuscript. All authors read and approved the final manuscript.

Funding. R. El Dib was supported by Brazilian Research Council (CNPq) scholarship grant number (CNPq 310953/2015-4).

Competing interests. None declared.

Patient consent. Not required.

Data sharing statement. No additional data are available.

Acknowledgments. We are thankful to Arnav Agarwal for English language editing.

REFERENCES

1. Kable AK, Gibberd RW, Spigelman AD. Adverse events in surgical patients in Australia. *Int J Qual Health Care.* 2002 Aug;14(4):269-76.
2. Farhadi K, Choubsaz M, Setayeshi K, et al. The effectiveness of dry-cupping in preventing post-operative nausea and vomiting by P6 acupoint stimulation: A randomized controlled trial. Lauche. R, ed. *Medicine*. 2016;95(38):e4770.
3. Youssef N, Orlov D, Alie T, et al. What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery?: a meta-analysis of randomized controlled trials. *Anesth Analg.* 2014; 119:965–977.
4. Palazzo MG, Strunin L. Anaesthesia and emesis: 1. Etiology. *Can Anaesth Soc J.* 1984;31:178–87.

5. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2014; 118:85–113.
6. Underwood M, Firmin RK, Jehu D. Aspects of psychological and social morbidity in patients awaiting coronary artery bypass grafting. *Br Heart J.* 1993; 69(5):382-384.
7. Marcolino J, Suzuki F, Cunha L, et al. Medida de ansiedade e da depressão em pacientes no pré-operatório: Estudo comparativo. *Rev Bras Anestesiol.* 2007;57(2):157-166.
8. Kil HK, Kim WO, Chung WY, et al. Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia. *Br J Anaesth.* 2012; 108:119-25.
9. Shoar S, Naderan M, Aghajani M, et al. Prevalence and Determinants of Depression and Anxiety Symptoms in Surgical Patients. *Oman Med J.* 2016;31(3):176-181.
10. Yohannes AM, Willgoss TG, Baldwin RC, et al. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psychiatry*. 2010;25:1209–1221.
11. Daratha KB, Barbosa-Leiker C, Burley HM et al. Co-occurring mood disorders among hospitalized patients and risk for subsequent medical hospitalization. *Gen Hosp Psychiatry*. 2012 Sep-Oct;34(5):500-505.
12. Gasse C, Laursen TM, Baune BT. Major depression and first-time hospitalization with ischemic heart disease, cardiac procedures and mortality in the general population: A retrospective Danish population-based cohort study. *Eur J Prev Cardiol*. 2014May;21(5):532-540.
13. Fan VS, Ramsey SD, Giardino ND, et al. National Emphysema Treatment Trial (NETT) Research Group. Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease. *Arch Intern Med*. 2007 Nov;167(21):2345-2353.
14. Svensson I, Sjostrom B, Haljamae H. Assessment of pain experiences after elective surgery. *J Pain Symptom Manage*. 2000; 20: 193–201.
15. Boisseau N, Rabary O, Padovani B, et al. Improvement of dynamic analgesia does not decrease atelectasias after thoracotomy. *Br J Anaesth*. 2001; 87:564-9.
16. Brattwall M, Warren Stomberg M, Rawal N, et al. "Patients' assessment of 4-week recovery after ambulatory surgery. *Acta Anaesthesiologica Scandinavica*, 2011; 55,1: 92–98.
17. Campagna S, D'olx MDA, Paradiso R, et al. Postoperative Pain, an Unmet Problem in Day or Overnight Italian Surgery Patients: A Prospective Study. *Pain Res Manag*. 2016;2016:6104383.
18. Levy I, Attias S, Ben-Arye E, et al. Adverse events associated with interactions with dietary and herbal supplements among inpatients. *Br J Clin Pharmacol*. 2016 Oct 19.
19. Kaye AD, Clarke RC, Sabar R, et al. Herbal medications: current trends in anesthesiology practice—a hospital survey. *J Clin Anesth*. 2000;12:468–471.
20. Gharabagy PM, Zamany P, Delazar A, et al. Efficacy of Eremostachys laciniata herbal extract on mitigation of pain after hysterectomy surgery. *Pak J Biol Sci.* 2013Sep1;16(17):891-4.
21. Ozgoli G, Saei Ghare Naz M. Effects of Complementary Medicine on Nausea and Vomiting in Pregnancy: A Systematic Review. *Int J Prev Med.* 2018 Aug 30;9:75
22. Akhlaghi M, Shabanian G, Rafieian-Kopaei M, et al. Citrus aurantium blossom and preoperative anxiety. *Rev Bras Anestesiol.* 2011 Nov-Dec;61(6):702-12.
23. Ang-Lee M, Moss J, Yuan C-S. Herbal medicines and perioperative care. *JAMA* 2001;286:208–16.
24. Norred C, Finlayson C. Hemorrhage after the preoperative used of complementary and alternative medicine. *AANA J*. 2000;68: 217–20.
25. Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. *J Am Coll Cardiol.* 2010;55:515–25.
26. Hodges PJ, Kam PC. The perioperative implications of herbal medicines. *Anaesthesia.* 2002 Sep;57(9):889-99.

27. Cotterill J. Severe phototoxic reaction to laser treatment in a patient taking St John's Wort. *J Cosmet Laser Ther*. 2001;3:159–60.
28. Rose KD, Croissant PD, Parliament CF, et al. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: A case report. *Neurosurgery*. 1990;26:880–82.
29. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med.* 1996;125:940–41.
30. Levy I, Attias S, Ben-Arye E, et al. Perioperative Risks of Dietary and Herbal Supplements. *World J Surg*. 2016 Nov 22.
31. American Society of Anesthesiologists [Internet]. What you should know about your patients' use of herbal medicines. [update 2003, cited 2017 fev12]. Available in: http://www.wehealny.org/services/BI_Anesthesiology/herbPatient.pdf
32. Franco Ruiz S, Gonzalez Maldonado P. Dietary supplements and the anesthesiologist: research results and state of the art. *Rev Colomb Anesthesiol*. 2014; 42:90–99
33. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.Available from http://handbook.cochrane.org/(accessed august 2016).
34. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ.* 2009;339:b2535.
35. Arruda APN, Ayala AP, Lopes LC, et al. Herbal medications for surgical patients: a systematic review protocol. *BMJ Open* 2017;7:e014290.
36. Guyatt GH, Busse JW. Modification of Cochrane Tool to assess risk of bias in randomized trials. http://distillercer.com/resources/(accessed august 2016).
37. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6.
38. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol.* 2011;64:407-15.
39. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol.* 2011b;64:1283-93.
40. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol.* 2011c;64:1294-302.
41. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol.* 2011d;64:1303-10.
42. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol.* 2011e;64:1277-82.
43. The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.
44. Apariman S, Ratchanon S, Wiriyasirivej B. Effectiveness of ginger for prevention of nausea and vomiting after gynecological laparoscopy. *J Med Assoc Thai.* 2006;89:2003-9.
45. Deng, YK, Wei F, Zhang DG. Brain protective effects of ginkgo biloba leaf extract (ginaton) in patients undergoing hypothermic cardiopulmonary bypass. *Chin J Integr Med*. 2006; 26:795-8.
46. Deng YK, Wei F, Zhang DG. Erythrocyte protective effects of ginaton in patients undergoing hypothermic cardiopulmonary bypass. *Chin J Integr Med*. 2010;30:365-8.
47. Gharabaghi PM, Tabatabei F, Fard SA et al. Evaluation Of The Effect Of Preemptive Administration Of Rosa Damascena Extract On Post-Operative Pain In Elective Cesarean Sections. *Afr J Pharm Pharmacol.* 2011;5:1950-55.
48. Huang ZY, Liao CX, Chen DZ. Effect of radix *Salviae miltiorrhizae* on production of free radical products from lung during cardiopulmonary bypass operation. *Chin J Integr Med*. 1996;16:451-3.

49. Nanthakomon T, Pongrojpaw D. The efficacy of ginger in prevention of postoperative nausea and vomiting after major gynecologic/obstetric surgery. *J Med Assoc Thai.* 2006 Oct;89(4):S130-6.
50. Pietri S, Séguin JR, d'Arbigny P, et al. Ginkgo biloba extract (EGb 761) pretreatment limits free radical oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther.* 1997;11:121-31.
51. Safaei N, Babaei H, Azarfarin R, et al. Comparative Effect of Grape Seed Extract (*Vitis Vinifera*) and Ascorbic Acid in Oxidative Stress Induced by On-pump Coronary Artery Bypass Surgery. *Ann Card Anaesth.* 2017;20:45-51.
52. Wang F, Xiao MD, Liao B. Effect of Astragalus on cytokines in patients undergoing heart valve replacement. *Chin J Integr Med*. 2008;28:495-8.
53. Xie RQ, Du J, Hao YM. Myocardial protection and mechanism of Puerarin Injection on patients of coronary heart disease with ischemia/reperfusion. *Chin J Integr Med*. 2003;23:895-7.
54. Zeraati H, Shahinfar J, Imani Hesari S, et al. The Effect of Ginger Extract on the Incidence and Severity of Nausea and Vomiting After Cesarean Section Under Spinal Anesthesia. *Anesth Pain Med.* 2016;6:e38943.
55. Zhou S, Shao W, Zhang W. Clinical study of Astragalus injection plus ligustrazine in protecting myocardial ischemia reperfusion injury. *Chin J Integr Med*. 2000;20:504-7.
56. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth.* 2000;84:367-71.
57. Viljoen E, Visser J, Koen N, et al. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutr J*. 2014;13: 1-14.
58. Adbel-Aziz H, Windeck T, Ploch M, et al. Mode of action of gingerols and shogaols on 5-HT3 receptors: binding studies, cation uptake by the receptor channel and contraction of isolated guinea-pig ileum. *Eur J Pharmacol.* 2006;530:136–43.
59. Hu ML, Rayner CK, Wu KL et al. Effect of ginger on gastric motility and symptoms of functional dyspepsia. *World J Gastroenterol.* 2011;17:105–10.
60. Abraham S, Abraham SK, Radhamony G. Mutagenic potential of the condiments, ginger and turmeric. *Cytologia* 1976; 41: 591–5 30
61. Nagabhushan M, Amonkar AJ, Bhide SV. Mutagenicity of gingerol and shogaol and antimutagenicity of zingerone in salmonella/ microsome assay. *Cancer Lett* 1987; 36: 221–33
62. Dugasani, S., Pichika, M. R., Nadarajah, V. D., Balijepalli, M. K., Tandra, S., and Korlakunta, J. N. (2010). Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol
63. Hajhashemi V, Ghannadi A, Hajiloo M. Analgesic and anti-inflammatory effects of Rosa damascena hydroalcoholic extract and its essential oil in animal models. *Iran J Pharm Res.* 2010;16:3–8.
64. Latifi G, Ghannadi A, Minaiyan M. Anti-inflammatory effect of volatile oil and hydroalcoholic extract of Rosa damascena Mill. on acetic acid-induced colitis in rats. *Res Pharm Sci.* 2015; 10:514-22.
65. Shirazi M, Mohebitabar S, Bioos S et al. The effect of topical Rosa damascena (Rose) oil on pregnancy-related low back pain a randomized controlled clinical trial. *J Evid Based Complementary Altern Med.* 2016; 22: 120-26.
66. Bani S, Hasanpour S, Mousavi Z, et al. The effect of rosa damascena extract on primary dysmenorrhea: a double-blind cross-over clinical trial. *Iran Red Crescent Med J.* 2014;16: e14643.
67. Nayebia N, Khalilib N, Kamalinejadc M, et al. A systematic review of the efficacy and safety of Rosa damascena Mill. with an overview on its phytopharmacological properties. *Complement Ther Med.* 2017; 34: 129–140
68. Akbari M, Kazerani HR, Kamrani A et al. A preliminary study on some potential toxic effects of Rosa damascena Mill. Iran J Vet Res. 2013;14(3): 232-36.

69. Mills E, Wu P, Johnston BC, et al. Natural health product-drug interactions: a systematic review of clinical trials. Ther Drug Monit. 2005 Oct; 27(5):549-57.
70. Awortwe C, Bruckmueller H, Cascorbi I. Interaction of herbal products with prescribed medications: A systematic review and meta-analysis. Pharmacol Res. 2019 Mar;141:397-408.
71. Zhou X, Li CG, Chang D, et al.Current status and major challenges to the safety and efficacy presented by chinese herbal medicine. Medicines 2019, 6, 14.

FIGURE LEGENDS

Figure 1. PRISMA flow diagram.

Figure 2. Risk of bias.

Figure 3. Meta-analysis comparing herbal versus placebo on vomiting for laparoscopic or obstetric-gynecologic.

Figure 4. Meta-analysis comparing herbal versus placebo on nausea for obstetric-gynecologic.

Figure 5. Meta-analysis comparing herbal versus placebo on need for rescue medication for pain. Panel A: primary analysis considering laparoscopic or obstetric/gynecologic surgeries. Panel B: sensitivity analysis excluding Gharabaghi 2011 study considering laparoscopic or obstetric/gynecologic surgeries.

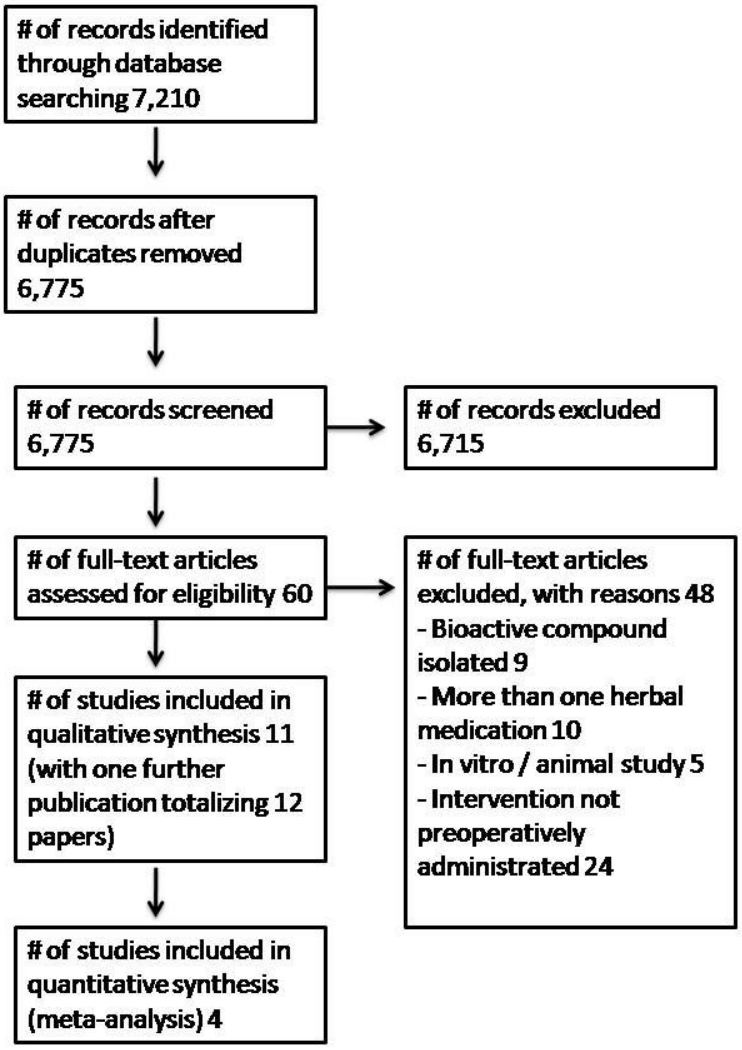

Figure 1. PRISMA flow diagram.

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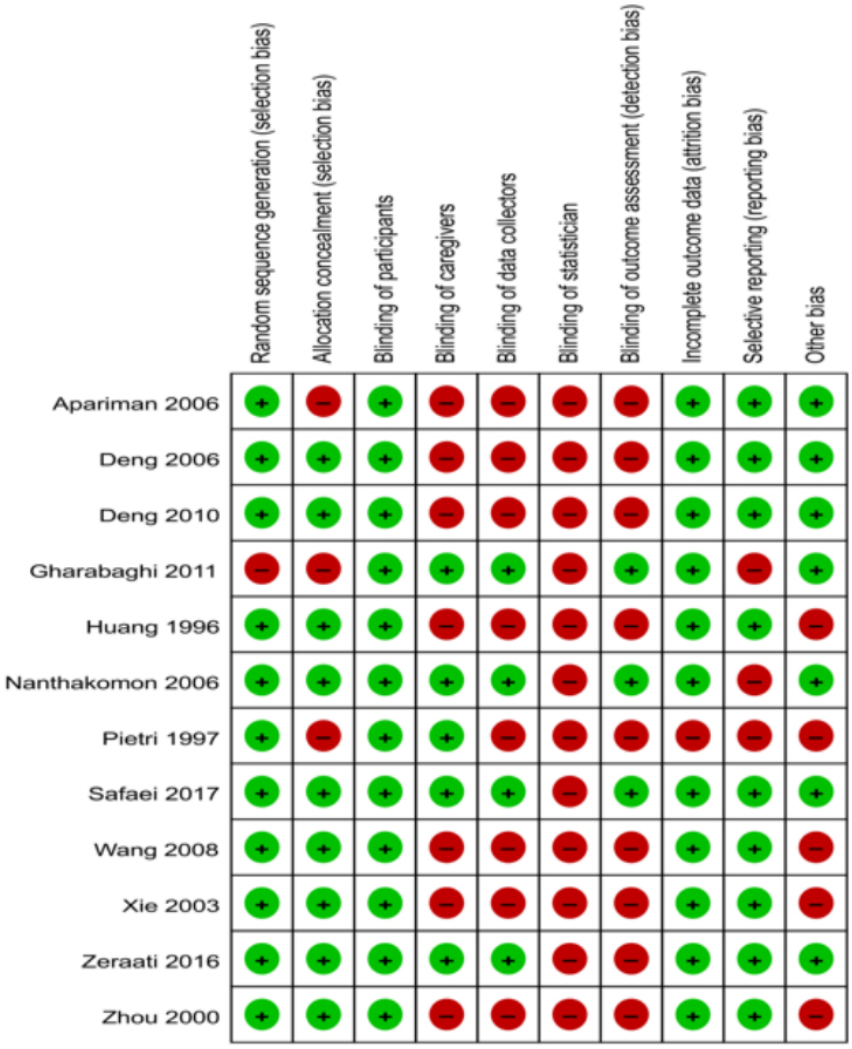

Figure 2. Risk of bias.tif

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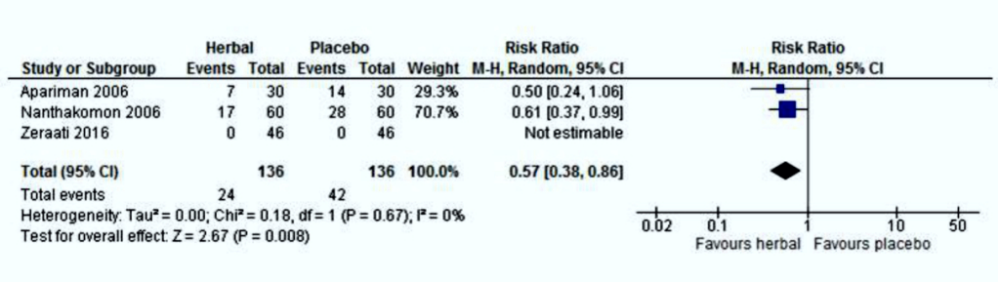

Figure 3. Meta-analysis comparing herbal versus placebo on vomiting for laparoscopic or obstetric_gynecologic.tif

86x24mm (300 x 300 DPI)

Figure 4. Meta-analysis comparing herbal versus placebo on nausea for obstetric_gynecologic.tif

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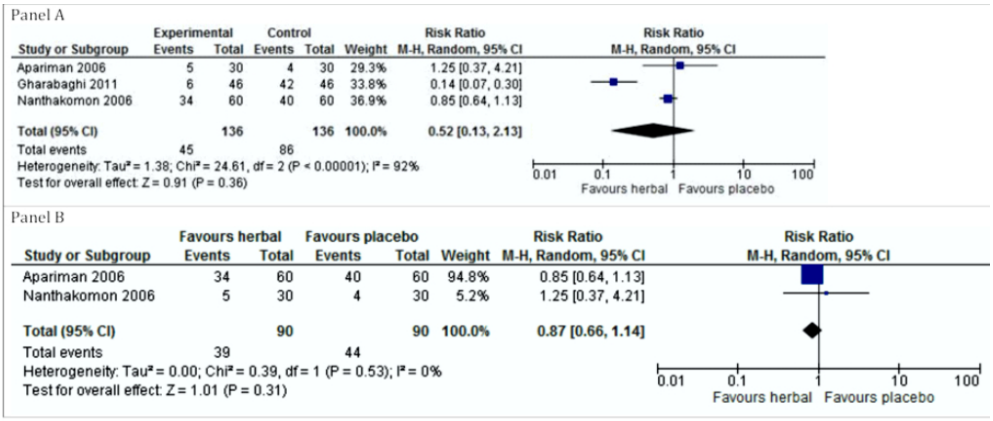

Figure 5. Meta-analysis comparing herbal versus placebo on need for rescue medication for pain.tif

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Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2,3
Rationale	#3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	6
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6,7
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	7,8
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8

Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	9
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	9
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	8
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	9
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	10
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9,10
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1, 11
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	12-14
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	20 and fig. 2
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	21, 24-26
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	27-29
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	20, fig. 2
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-	----

		regression [see Item 16]).	
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	29,30
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	29
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	30
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	31

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023729.R3
Article Type:	Research
Date Submitted by the Author:	15-Apr-2019
Complete List of Authors:	Arruda, Ana Paula; Universidade Estadual Paulista Julio de Mesquita Filho Faculdade de Medicina Campus de Botucatu, Department of Surgery and Orthopedics Zhang, Yuchen; University of Toronto Faculty of Medicine Gomaa, Huda; Tanta Chest Hospital, Department of Pharmacy Bergamaschi, Cristiane; Universidade de Sorocaba, Pharmaceutical Sciences Guimaraes, Caio; Faculdade Sao Leopoldo Mandic, Terapeutica Righesso, Leonardo; University Medical Center Mainz, Mainz, Germany, Dept. of Oral & Maxillofacial Surgery, Moura, Mariana ; University of Sorocaba, Pharmaceutical Sciences Barberato-Filho, Silvio; Universidade de Sorocaba, Pharmaceutical Sciences Lopes, Luciane; UNISO, Pharmacie Science Ayala Melendez, Ana Patricia; University of Toronto, Gerstein Science Information Centre de Oliveira, Luciane ; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, São José dos Campos - SP - Brazil, Department of Biosciences and Oral Diagnosis Paula-Ramos, Lucas ; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, Department of Biosciences and Oral Diagnosis Johnston, Bradley; Dalhousie University Faculty of Medicine, Community Health and Epidemiology El Dib, Regina; UNESP – Universidade Estadual Paulista, Institute of Science and Technology, Department of Biosciences and Oral Diagnosis; McMaster University, Institute of Urology, St. Joseph's Healthcare
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Surgery
Keywords:	Herbal medicine < THERAPEUTICS, Systematic review, Cardiac surgery < SURGERY, GYNAECOLOGY, Laparoscopy, Maternal medicine < OBSTETRICS

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

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ABSTRACT

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

Methods: Searches of MEDLINE, EMBASE, CENTRAL and LILACS up until January 2018 were performed to identify randomized controlled trials (RCTs). We included RCTs or quasi-RCTs evaluating any herbal medication among adults undergoing laparoscopic, obstetric/gynecologic or cardiovascular surgeries. The primary outcomes were anxiety, depression, pain, and PONV. We used the GRADE 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% Confidence Interval (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 to placebo in both laparoscopic and obstetric/gynecologic 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 to placebo in laparoscopic and obstetric/gynecologic 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 obstetric/gynecologic surgeries. Among our eligible studies, there was no reported evidence on AEs. This

systematic review was registered a priori with the International Prospective Register of Systematic Reviews (CRD42016042838).

Keywords: herbal, laparoscopy, gynecologic surgery, obstetrical surgery, cardiovascular surgery, GRADE; systematic review.

Strengths and limitations of this study

- We included RCTs or quasi-RCTs evaluating any herbal medication among adults undergoing laparoscopic, obstetric/gynecologic 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 GRADE approach was used in rating the certainty of evidence; and we present both absolute and relative effects of the interventions for patient-important outcomes.

Word count: 4.119

1. 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, gastro-intestinal 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 United States 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 hospitalized 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 hospitalized patients in a public medical center 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 United States 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[20,21,22], 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[23,24,25,26,27,28,29]. 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 medications consumption two weeks prior tosurgery[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 summarizing the efficacy and safety of herbal medications for the prevention of anxiety, depression, pain, and PONV in patients undergoing laparoscopic, obstetric/gynecologic and cardiovascular surgical procedures.

2. 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 the PROSPERO (International Prospective Register of Systematic Reviews) database under the number CRD42016042838, and the protocol was also published elsewhere[35].

2.1 Eligibility criteria

The inclusion criteria were:

- Study design: Randomized controlled trials (RCTs) and quasi-RCT.
- Patients: Adults (≥ 18 years of age) undergoing laparoscopic, obstetric/gynecologic, 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, standardized mixture, drug extract ratio and solvent) which were compared against conventional treatment, placebo, no intervention, other type of complementary and alternative therapy (e.g. acupuncture, homeopathy), or another herbal medication. The following routes of administration were considered: oral (e.g. 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 (STAI) and other validated instruments); depression (Depression Scale – Hospital Anxiety and Depression Scale (HADS-D) 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, hospitalization, 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.

2.2 Data source and searches

We searched Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid EMBASE, LILACS, ISI Web of Science and CINAHL, from their initial inception dates to January 30, 2018. Search terms describing laparoscopic, obstetrical/gynecological, cardiovascular surgeries, and herbal medication interventions were combined (Table 1). The search strategy was designed with the assistance of a trained librarian. No restrictions were placed on language, year of publication or publication status.

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

#	Searches	Results
1	gynecology/ or obstetrics/ or thoracic surgery/ or Minimally Invasive Surgical Procedures/	61687
2	laparoscopy/ or hand-assisted laparoscopy/	69622
3	thoracic surgical procedures/ or exp cardiac surgical procedures/	195024
4	exp Gynecologic/obstetric Surgical Procedures/	72904
5	Cholecystectomy, Laparoscopic/	10733
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.	153069
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.	101339
9	(herbalism or botany or herbology).tw,kf.	1255
10	Phytotherapy/	33568
11	(phyto-therap* or phytotherap*).tw,kf.	1680
12	exp Plant Preparations/pd, tu, ad, st [Pharmacology, Therapeutic Use, Administration & Dosage, Standards]	103896
13	or/1-6 [Surgery]	457564
14	or/7-12 [Herbal medicine]	194482
15	13 and 14	1296
16	adult.mp. or middle aged.sh. or age:.tw.	7608507
17	15 and 16	470

2.3 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.

2.4 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.

2.5 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-standardized 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.

2.6 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 summarized in an evidence profile table.

2.7 Data synthesis and statistical analysis

Pooled risk ratios (RRs) were calculated for dichotomous outcomes and standardized mean differences (SMD) for continuous variables with the associated confidential interval (CI) 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 (chi square) 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 analyzed 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*) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses[43].

2.8 Patient and public involvement

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

3.1 Search selection

The initial searches identified 7,210 titles from the electronic searches. After the duplicates, titles were removed, 6,775 potentially relevant articles were retained for further assessment (Figure 1). Subsequent to reading titles and abstracts, 6,715 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) randomized controlled trials (RCTs) or quasi-RCT[44,45,46,47,48,49,50,51,52,53,54,55] 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.

3.2 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 ranged from 22.30[47] to 63.00 years old[50].

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 gynecologic 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 anesthesia	Any cerebrovascular, neurological or metabolic diseases prior to surgery, any organ failure; hematological 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 to 40 years having term pregnancy, without the history of hypersensitivity to local anesthetics (Lidocaine, Marcaine) and with the body mass index of 9.24 to 5.18 who were supposed to undergo cesarean section for different reasons.	Emergency cesarean sections, need to general anesthesia, history of psychological disorder, history of hypersensitivity to local anesthetics and Rosa damascena extract, prolongation of surgery more than one 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 (American Society of Anesthesia) 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 antiischemic, antiinflammatory, 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 ischemic 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, WBC 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	No angina 48 hours prior to surgery	7 days

						transluminal coronary angioplasty and stenting		
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 cesarean section with spinal anesthesia.	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 anesthesia, 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

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

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 obstetric/gynecologic 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 gynecologic conditions[44]. Studies followed participants from two 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] obstetric/gynecologic and, one[44] laparoscopic procedure.

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)	Standardized 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]	Obstetric/ gynecologic	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 five minutes. 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	Standardized mixture available commercially, exact formulation not published	Intravenous	Intravenous normal saline	Difference in level of peroxidation product and leukocyte count in arterial blood between left and right ventricles

Nanthakomon, 2006[49]	Obstetric/ gynecologic	Ginger 2 capsules (one capsule contains 0.5 g)	Powder	Oral	2 capsules of placebo (each capsule contains 0.5 g of lactose)	Nausea and vomiting
Pietri, 1997[50]	Cardiovascular surgical procedures	Gingo Biloba extract - EGB 761(Tanakan ®, IPSEN, 320 mg/day)	Standardized mixture	Oral	Placebo	Malondialdehyde, ascorbyl free radical, myoglobin, myosin, pressure, heart rate, pulmonary capillary wedge pressure, and cardiac output
Safaei, 2017[51]	Cardiovascular surgical procedures	Grape seed extract (GSE), 24 h before operation, 100 mg every 6h.	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	Standardized mixture available commercially, exact formulation not published	Intravenous	Intravenous normal saline	Tumour necrosis factor alpha, interleukin 6 (IL6), IL8, IL1 from radial blood samples
Xie, 2003[53]	Cardiovascular surgical procedures	Puerarin injection	Standardized 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]	Obstetric/ gynecologic	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 standardized 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)

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

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 standardized 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 obstetric/gynecologic surgery procedures studies used *Zingiber officinale* (ginger)[49,54] and in other *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).

3.3 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.

Table 4. Risk of bias assessment.

Author, year	Was the randomization 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).

3.4 Primary Outcomes

3.4.1 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 to the control group (i.e., placebo and tap water) in both laparoscopic and obstetric/gynecological 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).

Table 5. GRADE evidence profile for RCTs: Herbal compared to placebo.

Quality assessment						Summary of findings				
						Study event rates		Relative risk (95% CI)	Anticipated absolute effects Over 24 hours		Certainty in estimates OR Quality of evidence
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Placebo	Herbal		Placebo	Herbal	
Vomiting											
272 (3) 4-24 h	Serious limitation[1]	No serious limitations	Serious limitations[2]	Serious imprecision[3]	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 h	Serious limitations[4]	No serious limitations	Serious limitations[2]	Serious imprecision[3]	Undetected	42/106	29/106	0.59 (0.50 to 0.96)	666 per 1000	207 fewer per 1000 (333 fewer to 27 fewer)	⊕OOO VERY LOW
Pain											
92 (1) 24 h	Serious limitations[5]	Undetected	Serious limitations[2]	Serious imprecision[3]	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 h	Serious limitations[6]	Serious limitations[7]	Serious limitations[2]	Serious imprecision[3]	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

h.: hours

[1]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].

[2] Serious limitations related to surgery where the results are not applicable for cardiac surgery.

[3] Serious imprecision related to outcome (fewer than 300 to 400 events).
[4] Serious limitations related to lack of blinding of data analyst[49,54], and outcomes assessment[54], and selective outcome reporting[49].
[5]Serious limitations related to random generation, allocation concealment, lack of blinding of data analyst, and selective outcome reporting[47].
[6]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].
[7] Serious limitation related to inconsistency ($I^2 = 92\%$).

3.4.2 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 to the control group (i.e., placebo and tap water) in obstetric/gynecologic 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).

3.4.3 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 to placebo in obstetric/gynecologic 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 of blinding of data analyst, selective outcome reporting), imprecision (fewer than 300 to 400 events), and indirectness (Table 5).

3.4.4 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 to placebo in laparoscopic and obstetric/gynecologic 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[47] study yielded results that were consistent with the primary analysis and fail to show a difference in the effects of herbal medications compared to 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).

3.4.5Anxiety and depression

None of the included studies reported on these outcomes.

3.5 *Secondary Outcomes*

3.5.1 Adverse events

None of the included studies reported on this outcome.

3.5.2 Number of patients reporting adverse events

None of the included studies reported on this outcome.

3.5.3 Quality of life

None of the included studies reported on this outcome.

3.5.4 Satisfaction with herbal medications

None of the included studies reported on this outcome.

3.5.5 Need for rescue medication

None of the included studies reported on this outcome.

3.5.6 Duration of symptoms

None of the included studies reported on this outcome.

3.5.7 Qualitative analysis of non patient-important outcomes

Seven trials[45,46,48,50,51,52,53,55] from the qualitative analysis assessed different types of biochemical analyzes during cardiovascular surgical procedures. Two[45,46,50] of them analyzing *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 analyzing *Astragalus* found that it may decrease the inflammation cytokine promoting factors and increase the level of antiinflammatory 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[48] evaluated *Radix Salviae Miltiorrhizae* and found effects towards the prevention of lung leukocyte aggregation and a reduction in the production of lung free radical products while the study of Safaei[51] tested the effect of *Vitis vinifera* and found an antioxidative effect during coronary artery bypass grafting surgery. Lastly, Xie[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 ischemia reperfusion.

4. Discussion

4.1 Main findings

From laparoscopic and obstetric/gynecologic surgeries, based on 212 surgical patients evidence suggests a statistically significant reduction in both vomiting and nausea favoring *Zingiber officinale* and in the need for rescue medication for pain favoring both *Rosa damascena* and *Zingiber officinale*. We also found favorable results for *Rosa damascena* and *Zingiber officinale* for pain[47] associated with obstetric/gynecologic 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% confidence interval 0.08 to 0.18). These studies collectively favored *Zingiber officinale* over placebo.

In another systematic review[57] that evaluated *Zingiber officinale* in the treatment of pregnancy-associated nausea and vomiting, twelve RCTs involving 1278 pregnant women were included. *Zingiber officinale* was compared to placebo and significantly improved the symptoms of nausea (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 to 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 standardized 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 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 two 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]..

4.2 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[44] used 1.5 g of powder capsules; Nanthakomon[49] used 1.0 g of powder capsules and Zeraati[54] used 25 drops of liquid extract. A fourth limitation was the inconsistent standardization 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[44] and Zeraati[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 minimize the potential interaction with the postoperative medications (e.g., anti-emetics, painkillers) on the predefined outcomes.

4.3 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 obstetric/gynecologic surgery) and nausea (obstetric/gynecologic 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 obstetric/gynecologic 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 obstetric/gynecologic surgeries.

Author Contributions. APNA: Conceived the review, undertook the searches, screened search results, extracted data from papers, wrote to authors of papers for additional information, contributed in analyzing RevMan statistical data, contributed in making statistical inferences, interpreted the data, wrote the review, and revised the

manuscript. RED: conceived the review, supervise the whole manuscript, contributed in analyzing RevMan statistical data, contributed in making statistical inferences, interpreted the data, wrote the review, and revised the manuscript. APA was the Trial Search Coordinator responsible for the search strategy. CCB, YZ, HG, CCG, LARR, MDGM, SBF, LDO, LPR, and LCL screened search results and extracted data from papers. BCJ: interpreted and analyzed the data and revised the manuscript. All authors read and approved the final manuscript.

Funding. R. El Dib was supported by Brazilian Research Council (CNPq) scholarship grant number (CNPq 310953/2015-4).

Competing interests. None declared.

Patient consent. Not required.

Data sharing statement. No additional data are available.

Acknowledgments. We are thankful to Arnav Agarwal for English language editing.

REFERENCES

1. Kable AK, Gibberd RW, Spigelman AD. Adverse events in surgical patients in Australia. *Int J Qual Health Care.* 2002 Aug;14(4):269-76.
2. Farhadi K, Choubsaz M, Setayeshi K, et al. The effectiveness of dry-cupping in preventing post-operative nausea and vomiting by P6 acupoint stimulation: A randomized controlled trial. Lauche. R, ed. *Medicine*. 2016;95(38):e4770.
3. Youssef N, Orlov D, Alie T, et al. What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery?: a meta-analysis of randomized controlled trials. *Anesth Analg.* 2014; 119:965–977.
4. Palazzo MG, Strunin L. Anaesthesia and emesis: 1. Etiology. *Can Anaesth Soc J.* 1984;31:178–87.

5. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2014; 118:85–113.
6. Underwood M, Firmin RK, Jehu D. Aspects of psychological and social morbidity in patients awaiting coronary artery bypass grafting. *Br Heart J.* 1993; 69(5):382-384.
7. Marcolino J, Suzuki F, Cunha L, et al. Medida de ansiedade e da depressão em pacientes no pré-operatório: Estudo comparativo. *Rev Bras Anestesiol.* 2007;57(2):157-166.
8. Kil HK, Kim WO, Chung WY, et al. Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia. *Br J Anaesth.* 2012; 108:119-25.
9. Shoar S, Naderan M, Aghajani M, et al. Prevalence and Determinants of Depression and Anxiety Symptoms in Surgical Patients. *Oman Med J.* 2016;31(3):176-181.
10. Yohannes AM, Willgoss TG, Baldwin RC, et al. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psychiatry*. 2010;25:1209–1221.
11. Daratha KB, Barbosa-Leiker C, Burley HM et al. Co-occurring mood disorders among hospitalized patients and risk for subsequent medical hospitalization. *Gen Hosp Psychiatry*. 2012 Sep-Oct;34(5):500-505.
12. Gasse C, Laursen TM, Baune BT. Major depression and first-time hospitalization with ischemic heart disease, cardiac procedures and mortality in the general population: A retrospective Danish population-based cohort study. *Eur J Prev Cardiol*. 2014May;21(5):532-540.
13. Fan VS, Ramsey SD, Giardino ND, et al. National Emphysema Treatment Trial (NETT) Research Group. Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease. *Arch Intern Med*. 2007 Nov;167(21):2345-2353.
14. Svensson I, Sjostrom B, Haljamae H. Assessment of pain experiences after elective surgery. *J Pain Symptom Manage*. 2000; 20: 193–201.
15. Boisseau N, Rabary O, Padovani B, et al. Improvement of dynamic analgesia does not decrease atelectasias after thoracotomy. *Br J Anaesth*. 2001; 87:564-9.
16. Brattwall M, Warren Stomberg M, Rawal N, et al. "Patients' assessment of 4-week recovery after ambulatory surgery. *Acta Anaesthesiologica Scandinavica*, 2011; 55,1: 92–98.
17. Campagna S, D'olx MDA, Paradiso R, et al. Postoperative Pain, an Unmet Problem in Day or Overnight Italian Surgery Patients: A Prospective Study. *Pain Res Manag*. 2016;2016:6104383.
18. Levy I, Attias S, Ben-Arye E, et al. Adverse events associated with interactions with dietary and herbal supplements among inpatients. *Br J Clin Pharmacol*. 2016 Oct 19.
19. Kaye AD, Clarke RC, Sabar R, et al. Herbal medications: current trends in anesthesiology practice—a hospital survey. *J Clin Anesth*. 2000;12:468–471.
20. Gharabagy PM, Zamany P, Delazar A, et al. Efficacy of Eremostachys laciniata herbal extract on mitigation of pain after hysterectomy surgery. *Pak J Biol Sci.* 2013Sep1;16(17):891-4.
21. Ozgoli G, Saei Ghare Naz M. Effects of Complementary Medicine on Nausea and Vomiting in Pregnancy: A Systematic Review. *Int J Prev Med.* 2018 Aug 30;9:75
22. Akhlaghi M, Shabanian G, Rafieian-Kopaei M, et al. Citrus aurantium blossom and preoperative anxiety. *Rev Bras Anestesiol.* 2011 Nov-Dec;61(6):702-12.
23. Ang-Lee M, Moss J, Yuan C-S. Herbal medicines and perioperative care. *JAMA* 2001;286:208–16.
24. Norred C, Finlayson C. Hemorrhage after the preoperative used of complementary and alternative medicine. *AANA J*. 2000;68: 217–20.
25. Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. *J Am Coll Cardiol.* 2010;55:515–25.
26. Hodges PJ, Kam PC. The perioperative implications of herbal medicines. *Anaesthesia.* 2002 Sep;57(9):889-99.

27. Cotterill J. Severe phototoxic reaction to laser treatment in a patient taking St John's Wort. *J Cosmet Laser Ther*. 2001;3:159–60.
28. Rose KD, Croissant PD, Parliament CF, et al. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: A case report. *Neurosurgery*. 1990;26:880–82.
29. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med.* 1996;125:940–41.
30. Levy I, Attias S, Ben-Arye E, et al. Perioperative Risks of Dietary and Herbal Supplements. *World J Surg*. 2016 Nov 22.
31. American Society of Anesthesiologists [Internet]. What you should know about your patients' use of herbal medicines. [update 2003, cited 2017 fev12]. Available in: http://www.wehealny.org/services/BI_Anesthesiology/herbPatient.pdf
32. Franco Ruiz S, Gonzalez Maldonado P. Dietary supplements and the anesthesiologist: research results and state of the art. *Rev Colomb Anesthesiol*. 2014; 42:90–99
33. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.Available from http://handbook.cochrane.org/(accessed august 2016).
34. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ.* 2009;339:b2535.
35. Arruda APN, Ayala AP, Lopes LC, et al. Herbal medications for surgical patients: a systematic review protocol. *BMJ Open* 2017;7:e014290.
36. Guyatt GH, Busse JW. Modification of Cochrane Tool to assess risk of bias in randomized trials. http://distillercer.com/resources/(accessed august 2016).
37. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6.
38. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol.* 2011;64:407-15.
39. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol.* 2011b;64:1283-93.
40. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol.* 2011c;64:1294-302.
41. Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol.* 2011d;64:1303-10.
42. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol.* 2011e;64:1277-82.
43. The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.
44. Apariman S, Ratchanon S, Wiriyasirivej B. Effectiveness of ginger for prevention of nausea and vomiting after gynecological laparoscopy. *J Med Assoc Thai.* 2006;89:2003-9.
45. Deng, YK, Wei F, Zhang DG. Brain protective effects of ginkgo biloba leaf extract (ginaton) in patients undergoing hypothermic cardiopulmonary bypass. *Chin J Integr Med*. 2006; 26:795-8.
46. Deng YK, Wei F, Zhang DG. Erythrocyte protective effects of ginaton in patients undergoing hypothermic cardiopulmonary bypass. *Chin J Integr Med*. 2010;30:365-8.
47. Gharabaghi PM, Tabatabei F, Fard SA et al. Evaluation Of The Effect Of Preemptive Administration Of Rosa Damascena Extract On Post-Operative Pain In Elective Cesarean Sections. *Afr J Pharm Pharmacol.* 2011;5:1950-55.
48. Huang ZY, Liao CX, Chen DZ. Effect of radix *Salviae miltiorrhizae* on production of free radical products from lung during cardiopulmonary bypass operation. *Chin J Integr Med*. 1996;16:451-3.

49. Nanthakomon T, Pongrojpaw D. The efficacy of ginger in prevention of postoperative nausea and vomiting after major gynecologic/obstetric surgery. *J Med Assoc Thai.* 2006 Oct;89(4):S130-6.
50. Pietri S, Séguin JR, d'Arbigny P, et al. Ginkgo biloba extract (EGb 761) pretreatment limits free radical oxidative stress in patients undergoing coronary bypass surgery. *Cardiovasc Drugs Ther.* 1997;11:121-31.
51. Safaei N, Babaei H, Azarfarin R, et al. Comparative Effect of Grape Seed Extract (*Vitis Vinifera*) and Ascorbic Acid in Oxidative Stress Induced by On-pump Coronary Artery Bypass Surgery. *Ann Card Anaesth.* 2017;20:45-51.
52. Wang F, Xiao MD, Liao B. Effect of Astragalus on cytokines in patients undergoing heart valve replacement. *Chin J Integr Med*. 2008;28:495-8.
53. Xie RQ, Du J, Hao YM. Myocardial protection and mechanism of Puerarin Injection on patients of coronary heart disease with ischemia/reperfusion. *Chin J Integr Med*. 2003;23:895-7.
54. Zeraati H, Shahinfar J, Imani Hesari S, et al. The Effect of Ginger Extract on the Incidence and Severity of Nausea and Vomiting After Cesarean Section Under Spinal Anesthesia. *Anesth Pain Med.* 2016;6:e38943.
55. Zhou S, Shao W, Zhang W. Clinical study of Astragalus injection plus ligustrazine in protecting myocardial ischemia reperfusion injury. *Chin J Integr Med*. 2000;20:504-7.
56. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth.* 2000;84:367-71.
57. Viljoen E, Visser J, Koen N, et al. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutr J*. 2014;13: 1-14.
58. Adbel-Aziz H, Windeck T, Ploch M, et al. Mode of action of gingerols and shogaols on 5-HT3 receptors: binding studies, cation uptake by the receptor channel and contraction of isolated guinea-pig ileum. *Eur J Pharmacol.* 2006;530:136–43.
59. Hu ML, Rayner CK, Wu KL et al. Effect of ginger on gastric motility and symptoms of functional dyspepsia. *World J Gastroenterol.* 2011;17:105–10.
60. Abraham S, Abraham SK, Radhamony G. Mutagenic potential of the condiments, ginger and turmeric. *Cytologia* 1976; 41: 591–5 30
61. Nagabhushan M, Amonkar AJ, Bhide SV. Mutagenicity of gingerol and shogaol and antimutagenicity of zingerone in salmonella/ microsome assay. *Cancer Lett* 1987; 36: 221–33
62. Dugasani, S., Pichika, M. R., Nadarajah, V. D., Balijepalli, M. K., Tandra, S., and Korlakunta, J. N. (2010). Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol
63. Hajhashemi V, Ghannadi A, Hajiloo M. Analgesic and anti-inflammatory effects of Rosa damascena hydroalcoholic extract and its essential oil in animal models. *Iran J Pharm Res.* 2010;16:3–8.
64. Latifi G, Ghannadi A, Minaiyan M. Anti-inflammatory effect of volatile oil and hydroalcoholic extract of Rosa damascena Mill. on acetic acid-induced colitis in rats. *Res Pharm Sci.* 2015; 10:514-22.
65. Shirazi M, Mohebitabar S, Bioos S et al. The effect of topical Rosa damascena (Rose) oil on pregnancy-related low back pain a randomized controlled clinical trial. *J Evid Based Complementary Altern Med.* 2016; 22: 120-26.
66. Bani S, Hasanpour S, Mousavi Z, et al. The effect of rosa damascena extract on primary dysmenorrhea: a double-blind cross-over clinical trial. *Iran Red Crescent Med J.* 2014;16: e14643.
67. Nayebia N, Khalilib N, Kamalinejadc M, et al. A systematic review of the efficacy and safety of Rosa damascena Mill. with an overview on its phytopharmacological properties. *Complement Ther Med.* 2017; 34: 129–140
68. Akbari M, Kazerani HR, Kamrani A et al. A preliminary study on some potential toxic effects of Rosa damascena Mill. Iran J Vet Res. 2013;14(3): 232-36.

69. Mills E, Wu P, Johnston BC, et al. Natural health product-drug interactions: a systematic review of clinical trials. Ther Drug Monit. 2005 Oct; 27(5):549-57.
70. Awortwe C, Bruckmueller H, Cascorbi I. Interaction of herbal products with prescribed medications: A systematic review and meta-analysis. Pharmacol Res. 2019 Mar;141:397-408.
71. Zhou X, Li CG, Chang D, et al.Current status and major challenges to the safety and efficacy presented by chinese herbal medicine. Medicines 2019, 6, 14.

FIGURE LEGENDS

Figure 1. PRISMA flow diagram.

Figure 2. Risk of bias.

Figure 3. Meta-analysis comparing herbal versus placebo on vomiting for laparoscopic or obstetric-gynecologic.

Figure 4. Meta-analysis comparing herbal versus placebo on nausea for obstetric-gynecologic.

Figure 5. Meta-analysis comparing herbal versus placebo on need for rescue medication for pain. Panel A: primary analysis considering laparoscopic or obstetric/gynecologic surgeries. Panel B: sensitivity analysis excluding Gharabaghi 2011 study considering laparoscopic or obstetric/gynecologic surgeries.

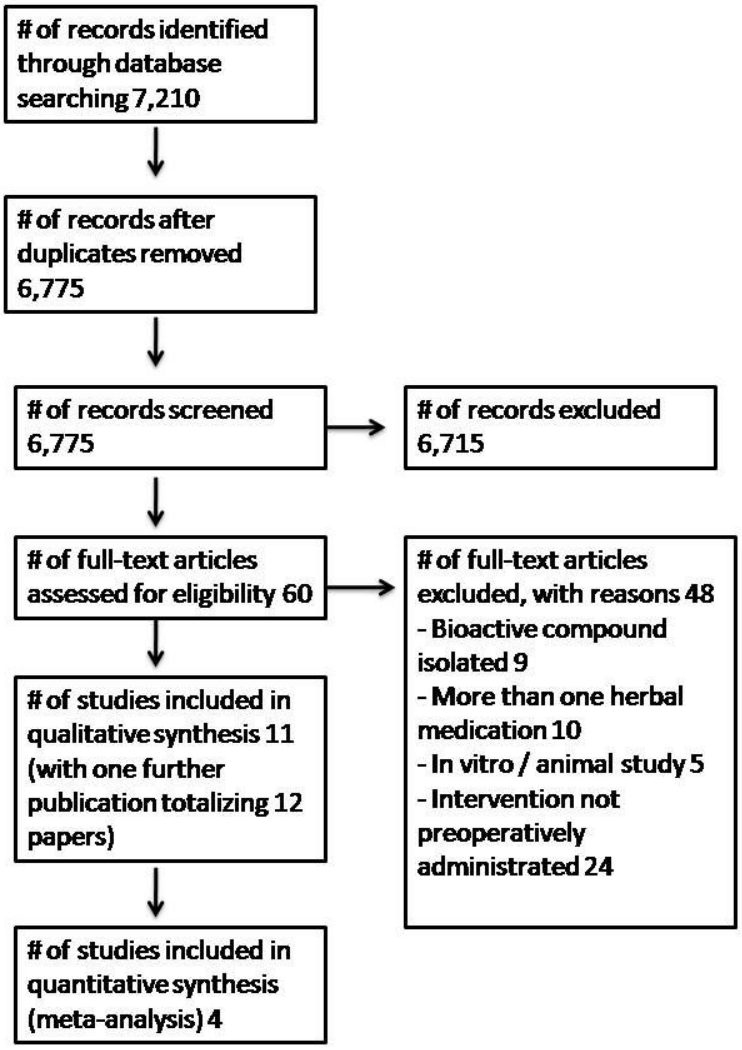

Figure 1. PRISMA flow diagram.

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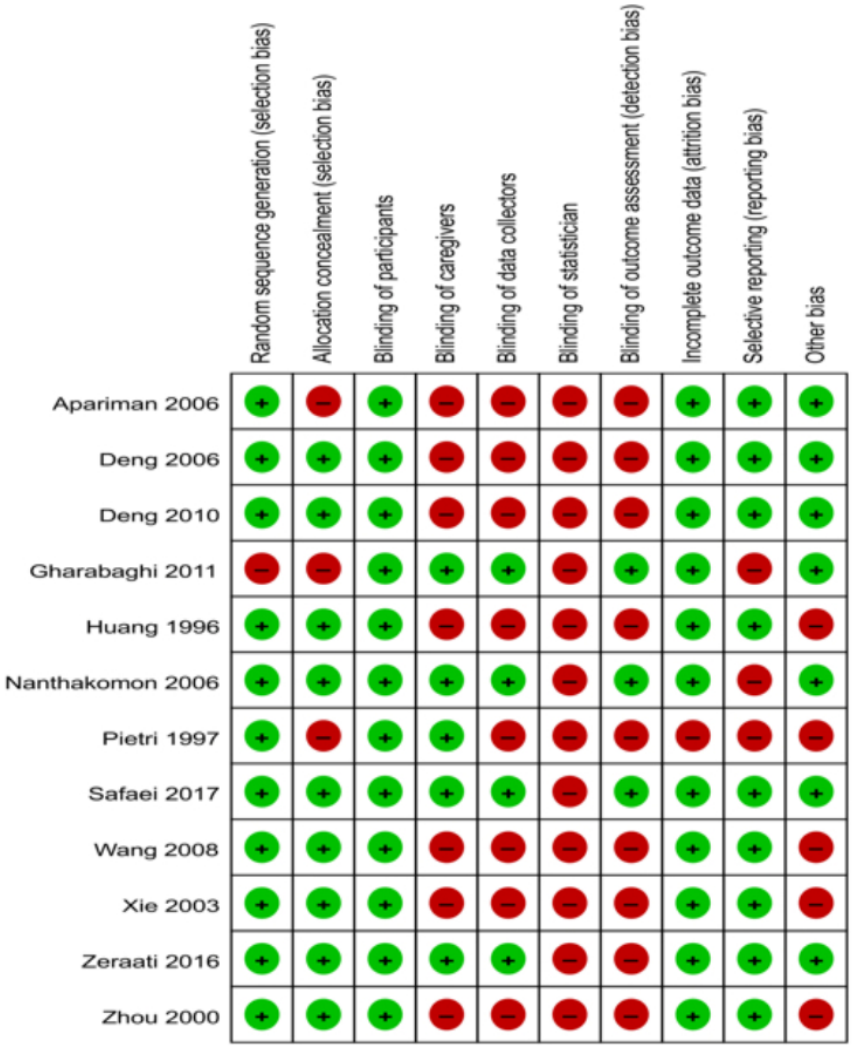

Figure 2. Risk of bias.tif

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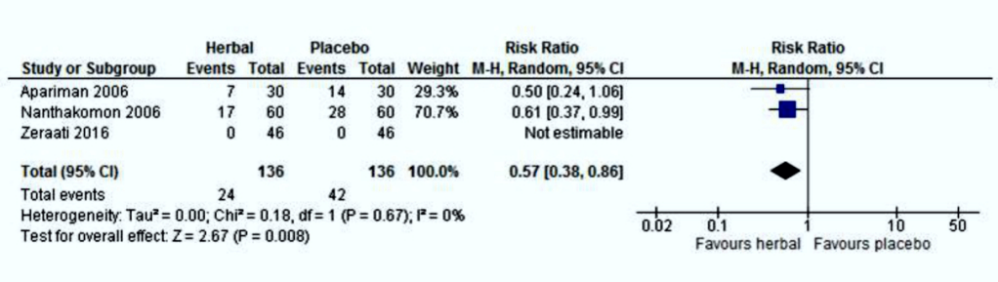

Figure 3. Meta-analysis comparing herbal versus placebo on vomiting for laparoscopic or obstetric_gynecologic.tif

86x24mm (300 x 300 DPI)

Figure 4. Meta-analysis comparing herbal versus placebo on nausea for obstetric_gynecologic.tif

86x18mm (300 x 300 DPI)

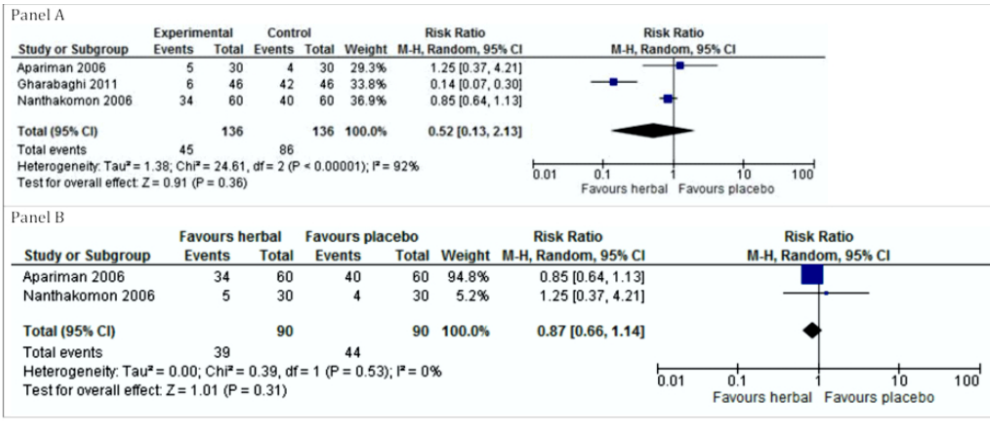

Figure 5. Meta-analysis comparing herbal versus placebo on need for rescue medication for pain.tif

86x37mm (300 x 300 DPI)

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2,3
Rationale	#3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	6
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6,7
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	7,8
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8

Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	9
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	9
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	8
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	9
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	10
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9,10
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1, 11
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	12-14
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	20 and fig. 2
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	21, 24-26
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	27-29
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	20, fig. 2
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-	----

		regression [see Item 16]).	
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	29,30
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	29
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	30
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	31