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The effect of herbal medicines for induction of labour on maternal outcomes: a systematic review and meta-analysis

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ABSTRACT

Objective

The use of herbal medicines for induction of labour (ILO) is common globally and yet its impact on pregnancy outcomes is poorly understood. We conducted a systematic review of published literature to address this issue.

Data sources

We searched for studies in the MEDLINE, AMED, CIHAHL and bibliographies of relevant papers, using the following terms: herbal medicines, labour and pregnancy outcomes. We considered both experimental and observational studies that compared relevant maternal outcomes between users and non-user of herbal medicines for IOL. Two authors independently assessed the quality of the studies and extracted the data.

Planned outcome measures

The occurrence of haemorrhage, sepsis, caesarean section, uterine rupture, assisted vaginal delivery and maternal death.

Results

We found 1,418 papers after the initial search, but only six papers were retained following eligibility and quality assessment. The papers were from high and upper-middle income countries and no data were found on sepsis, maternal death and uterine rupture. The occurrence of caesarean section (RR=1.30; 95% CI=0.90-1.88), vaginal assisted delivery (RR= 0.86; CI= 0.60-1.22) and haemorrhage (RR= 0.81; 95% CI= 0.40-1.62) were not significantly different

between users and non-users of herbal medicines for IOL. None of the included studies addressed the outcomes of sepsis, maternal death and uterine rupture.

Conclusion

We found no evidence on the benefits or harm associated with herbal medicine use for IOL. This was mostly due to insufficient number of studies and lack of statistical power and non-representative studies in terms of location. Therefore, a definite conclusion concerning the impact of herbal medicines for IOL cannot be made based on the current data. Larger studies with sufficient statistical power and of high methodological quality are recommended.

Keywords: Herbal medicines, medicinal plants, pregnant women, labour, pregnancy outcomes

Strengths and limitations of this study

- Induction of labour is one of the most common motives for the use of herbal medicines during pregnancy and yet its effects on pregnancy outcomes remain underexplored. This systematic review is an effort to addresses this gap.
- We searched in three major databases (MEDLINE, CINAHL and AMED) relevant to the topic and no restrictions were applied on date of publications, location and study design
- Our analysis may not have sufficient statistical power due to inadequate number of studies and relatively small sample sizes

INTRODUCTION

Across the world, the use of unconventional or traditional medical therapies is very high [1-4]. These non-biomedical remedies are together referred to as complementary and alternative medicines (CAM). The World Health Organisation (WHO) recognises the role of CAM, of verified quality, safety and efficacy in ensuring universal access to health care [5]. As such, for the period between 2014 and 2023, the WHO traditional medicine strategy focused on harnessing the potential contribution of CAM in health care and promoting its safe and effective use [5]. Although this requires rigorous evidence on safety and efficacy of CAM, research in this area remains limited [5]. Herbal medicine or medicinal plant, is one of the well-known CAM therapies that involves the use of plants or plant extracts for therapeutic motives [6]. As in the general population, the use of herbal medicines is common among pregnant women globally [7-10]. The estimated prevalence varies between regions and countries but ranges from 10% to 80% [11 12]. One of the common indications for herbal medicine use during pregnancy is prolonged labour or merely the desire to induce or augment labour for different reasons [13 14]. This practice is well-documented and transcends cultural and generational boundaries [14].

From a medical perspective, induction of labour (IOL) changes the physiological processes associated with childbirth in ways that may increase the risk of adverse pregnancy outcomes such as infection, neonatal mortality, foetal distress, premature birth, haemorrhage, uterine rupture and caesarean section [15-17]. Because of this, the WHO recommends that labour should only be induced in health facilities with the capacity for continual monitoring and emergency obstetric care, in case of complications [18]. The emphasis on facility-based IOL and close monitoring of pregnant women demonstrates the risks associated with the procedure.

Nonetheless, with herbal medicine-induced labour, monitoring of women is often out of the question due to self-prescription [2 19]. So, the use of herbal medicines for IOL is likely to be even more risky and it is plausibly an important factor influencing adverse pregnancy outcomes in settings where herbal medicine use for IOL is common.

Despite scarcity of population-level data concerning the efficacy of herbal medicines for IOL, in vitro studies have confirmed that some of the herbal medicines have oxytocic properties [13 20]. For instance, a study in Nigeria found that several plants that are used to facilitate childbirth in the country significantly induced muscle cell contractility [13]. However, safety is the main concern as many of the herbal medicines are believed to be poisonous and may contribute to maternal and neonatal mortality as well as morbidity [21 22]. So far, there is mixed evidence from population-based studies regarding the safety of herbal medicines for IOL [23-25] and yet data from these studies have not been systematically evaluated and synthesised to provide rigorous evidence necessary to inform decisions. As such, there is a lack of high quality and consistent data, which makes recommendations and regulations challenging [5]. Consequently, we conducted a systematic review to examine the relationship between the use of herbal medicines for IOL and pregnancy-related complications. This review is important to inform the development of guidelines relating to the use of herbal medicines among pregnant women.

METHODS

Data sources and searches

To identify the papers for this review, we searched in MEDLINE, AMED and CINAHL databases using key terms such as herbal medicine, labour and pregnancy outcomes, which were

modified in accordance with each database (see additional file 1 for full electronic search strategy). More papers were identified through scanning the reference list of studies found in the initial search and direct searches in relevant journals such as the Journal for Herbal Medicine, BMC Complementary and Alternative Medicine, Journal of Alternative and Complementary Medicine and Journal of Integrative Medicine.

Inclusion/exclusion criteria

We considered studies that included pregnant or postpartum women as its participants irrespective of any social or demographic factor. The intervention or exposure of interest was herbal medicines for induction or shortening of labour. For studies that did not explicitly indicate the reasons for use, the name of the medicine was used to determine if IOL could have been a possible motive. There was no restriction on dosage, but the route of administration was oral. The plants could be either processed or crude and used alone or alongside conventional medicines. An appropriate comparison group comprised either pregnant women who did not use the herbal medicine under consideration or used biomedical drugs exclusively. The outcomes of interest were haemorrhage, sepsis, caesarean section, uterine rupture, assisted vaginal delivery and maternal death. Both experimental and observational study designs, including randomised controlled trials (RCT), quasi-experimental, cohort, case-control and cross sectional were eligible for selection. We only included studies published in English or with a detailed English abstract and no restrictions were applied on the date of publication.

Quality/risk of bias assessment

A standardised critical appraisal tool (Johns Hopkins Nursing Evidence-Based Practice Rating Scale) developed by Newhouse et al [26] was used to assess the quality of all studies that met the inclusion criteria (see additional file 2). Since the review includes studies of different designs, this tool was preferred because it is not design specific and it has been used by comparable reviews [27 28]. The tool divides the strength of research evidence into five levels based on the study design. The RCTs occupy the top level (level I) followed by quasi-experimental studies (level II) and non-experimental studies (level III). The last two levels are for opinion-related papers either based on research evidence (level IV) or individual expertise (level V) [26]. The quality of evidence for each level of strength is further graded as high (A), good (B) and low quality or major flaws (C) depending on the risk of bias and scientific basis for the conclusions. In this review, studies that were deemed to be of unsatisfactory quality (i.e. grade C) were excluded regardless of level of strength. CZ (Collins Zamawe) performed the initial screening and CM (Chrispin Mandiwa) independently cross-checked.

Data extraction and analysis

A data extraction form (see additional file 3) was developed specifically for this review based on the templates developed by the Joanna Briggs Institute and the Cochrane Pregnancy and Childbirth Group [29 30]. The form included specific details about the study design, participants, setting, intervention/exposure, control and outcomes. CZ extracted all the data from the papers and this was validated by CM. Any differences were resolved by discussion.

Meta-analyses were performed to compare the incidence of adverse pregnancy outcomes between users and non-users of herbal medicines for IOL. A random-effects model was used as variations were expected between studies due to the differences in setting and design [31]. Subject to the availability of sufficient studies, subgroup analyses were planned based on type of exposure. Heterogeneity was explored through the I^2 statistic and meta-analysis was considered viable only when less than 50% of the variability in the estimated effect was attributed to heterogeneity [32]. The potential publication bias was assessed using Egger's test as all the analysis had less than the minimum number of ten studies to use a funnel plot technique [32 33]. Summary effects were measured using risk ratios (RR).

Patient and public involvement

As this was a review of existing literature, we did not involve any patient and the public in the design and conduct of the study. However, the development of the review question was informed by the experiences of pregnant women observed in the literature.

RESULTS

Study selection process

Searches in the three electronic databases returned a total of 1,418 papers (CINAHL=419, AMED=278 and MEDLINE=721). After removal of duplicates (n=539), the titles and or abstracts of 879 publications were screened against the inclusion criteria and 801 studies were dropped at this stage for various reasons (see figure 1). Full text articles were retrieved for 78 studies for further eligibility assessment and 73 papers failed to meet the inclusion criteria and were thus excluded. Additional potential relevant papers (n=2) were identified after a direct

search in journals and reference lists. Seven papers were appraised in the final stage and one was dropped due to poor methodological quality (i.e. grade C). Thus, six studies were included in this review. Figure 1 is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection. The results have also been reported in accordance with the PRISMA 2009 guidelines [34] (see additional file 4).

Figure 1: A PRISMA flow diagram summarising the study selection process

An overview of the included studies

Table 1 presents the characteristics of the studies, such as location, exposure, outcomes and ratings. In brief, of the six studies, a pair was conducted in Australia [35 36] and one each in South Africa [37], Israel [38], Thailand [39], and USA [40]. In relation to the World Bank's classification of countries by income, four studies were conducted in high income countries (HIC) and the remaining two in upper middle-income countries (UMIC). No study from low income countries (LIC) or lower middle-income countries (LMIC) was included.

Three types of exposures were reported by the studies. The two studies from Australia were concerned with exposure to raspberry leaf [35 36]. This is one of the common herbal remedies used during pregnancy that is believed to prepare the uterus for childbirth and thereby effectively reduce the length of labour [14]. In both studies, exposure was self-reported by the participants. However, the difference was that in one study [36] pregnant women were given raspberry pills by the nurses to take at home while in the other [35] they were merely asked if they had used it. Therefore, the actual amount of raspberry taken by the participants in these studies could not be

ascertained. Three studies examined exposure to castor oil [38-40]. The oil is derived from the castor plant's bean and is widely thought to have oxytocic properties [40 41]. In all the studies, pregnant women consumed 60ml of castor oil, but in one study [39] the treatment was repeated in women who did not deliver within one week after the first dose. One study [37] did not measure exposure to a specific type of herbal medicine.

The designs of the included studies are cohort (3), RCT (2) and quasi-experimental (1) and this implies that the strength of evidence ranged from I to III. The quality of the evidence was not that high as only one study received a Grade of A and the rest were B's (Table 1). In total, three pregnancy outcomes were examined by the included studies in relation to the use of herbal medicines for IOL. These were caesarean section, haemorrhage and vaginal assisted delivery. No data were found on the following outcomes: sepsis, maternal death and uterine rupture.

Table 1: Characteristics of studies in the systematic review on the safety of herbal medicines for induction of labour

Outcome 1: Incidence of caesarean section

Six studies [35-40] examined this outcome and five of them found no significant difference between users and non-users of herbal medicines for IOL. However, Mabina et al found a significant increase in risk of caesarean section among users of herbal medicines. Overall, there was no significant difference between the groups (RR=1.30; 95% CI=0.90-1.88) (figure 2). Heterogeneity was reasonable (I^2=18.5%; p=0.28) and publication bias was not significant (Bias= -0.60; 95% CI= -3.66-2.46).

Figure 2: The use of herbal medicines for induction of labour and the risk of caesarean section

Incidence of assisted vaginal delivery

In this review, assisted vaginal delivery was defined as the use of medical interventions such as forceps and episiotomy to aid delivery. This outcome was reported by five studies [35-39]. As shown in figure 3, no significant difference was observed between the groups (RR= 0.86; CI= 0.60-1.22). The level of heterogeneity was not high enough to affect the outcomes (I^2=44%; p=0.13) and neither was the publication bias (Bias= -1.87; 95% CI= -6.12-2.38).

Figure 3: The use of herbal medicines for induction of labour and the risk of vaginal assisted delivery

Outcome 3: Incidence of haemorrhage

Two studies [36 39] evaluated this outcome and neither of them found a significant difference between the groups (figure 4). Collectively, there was no significant difference between the groups (RR= 0.81; 95% CI= 0.40-1.62). Heterogeneity was almost non-existent (I^2= 0.0%; p=0.73) and publication bias was not assessed due to inadequate number of studies.

Figure 4: The use of herbal medicines for induction of labour and the risk of haemorrhage

DISCUSSION

Overall, we found weak evidence to determine the safety of herbal medicines for IOL, with none of the included studies addressing the outcomes of sepsis, maternal death and uterine rupture. Data on the three outcomes that could be examined showed no evidence of effect. The findings indicate that the incidence of caesarean section, vaginal assisted delivery and haemorrhage were not significantly different between users and non-users of herbal remedies for IOL. The implication is that the herbal medicines were neither detrimental nor helpful to pregnant women. A closer look at the data reveals that more users of herbal medicines tended to deliver through caesarean section, whereas more non-users had haemorrhage and assisted vaginal delivery. These inconsistencies suggest there is little that can be said about the safety of herbal medicines for IOL based on the current data. Nonetheless, to be on the safe side, herbal medicines for IOL should be avoided until there is substantial evidence of safety.

Our findings lend support to previous studies on similar topics [28 39 42 43]. For instance, Ernst [44] observed in his review that the use of different herbal medicines during pregnancy could have no effect or result in adverse events or lead to improved outcomes. However, the findings may not be reliable as the quality of the included papers was not assessed, it was not focussed on specific outcomes and above all, it is now outdated. Another related review recently found that some herbal medicines were neither harmful nor effective in pregnancy, whereas others appeared to be associated with adverse effects [28]. Together, the data on the safety of herbal medicines during pregnancy is inconclusive. As such, more rigorous studies are recommended to improve the evidence-base.

Several factors or limitation could have influenced the results obtained. To begin with, crude or unadjusted data were used in all meta-analyses. Even though the baseline characteristics of the study groups were similar in most of the included studies, there were still differences in some covariates and for that reason the results do not rule out the influence of other factors. In addition, the sample size of some studies was very small and so was the number of studies included in each meta-analysis. Therefore, some of the analyses in this review did not have adequate statistical power. In some studies, the use of herbal medicines was self-reported by the respondents; hence, it is important to bear in mind the possible recall and social desirability biases that may have affected the assessment of exposure. As pregnancy outcomes were retrieved from the hospital archives, the researchers had no control over the quality of data and there could be some variations in the definition of outcomes between health facilities and countries. These limitations strongly suggest that the results of this review need to be interpreted with caution.

A few observations from this review are worth mentioning. First, in almost all the studies, herbal remedies were provided at the health facility and pregnant women were somewhat monitored by clinical staff. In this way, many potential adverse events, if any, may have been averted or the damage lessened. Nevertheless, this approach does not represent the reality of the usual context in which herbal medicines are taken and thus the results of these studies may be misleading. In sub Saharan Africa, for instance, herbal medicines are more likely to be taken outside the health facility and often without the knowledge and support of health care providers [12 37 45]. In such circumstances, the risk of adverse events associated with herbal medicines for IOL could be higher than reported by the studies in this review.

Secondly, as mentioned earlier, all included studies are from higher and upper-middle income countries. No study from low or lower middle-income countries were included. This probably suggests lack of impact studies on this subject in limited resource settings. Hence, the findings of this review cannot be extrapolated beyond higher and upper-middle income countries. Bearing in mind that the issue of the safety of herbal medicines in pregnancy relates to maternal as well as neonatal morbidity and mortality [22 37 46-48], which are predominantly low-income problems [49 50], high-quality studies that include a range of maternal morbidity and mortality outcomes in LIC are urgently needed [22 51].

CONCLUSIONS AND IMPLICATIONS

We found comparable occurrences of adverse pregnancy outcomes among the users and non-users of herbal medicines for IOL. Hence, there is insufficient evidence on the benefit or harm of herbal medicines for IOL. Our findings are limited by an inadequate number of studies, non-representative studies in terms of location, lack of statistical power and the inclusion of unadjusted data from observational studies. As such, a definite conclusion regarding the safety of herbal medicines for IOL cannot be made based on these results. Since there are possibilities that some herbal remedies could lead to pregnancy complications, larger studies with sufficient statistical power and of high methodological quality are recommended. This is particularly important in sub Saharan Africa, where both the use of herbal medicines among pregnant women and adverse pregnancy outcomes are high. In the meantime, the use of herbal medicines of unproven safety should be avoided during pregnancy.

Contributors

CZ, CK, HJ and EF conceived the review. CZ and CM conducted the literature search, appraised the papers and extracted the data. CZ performed the analysis and drafted the manuscript. CK and EF commented on drafts and provided technical input at all stages. All authors have read and approved the final manuscript.

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Competing interests

None

Data sharing statement

All data used in this review can be accessed from the corresponding author

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Table 1: Characteristics of studies in the systematic review on the safety of herbal medicines for induction of labour

Study	Design and Sample	Setting	Exposure	Outcomes	Limitations/comments	Ratings
Lamadah 2014 [23]	A hospital-based quasi-experimental study involving 100 pregnant women who went to the facility to give birth. Only those with cephalic presentation and no contraindication to vaginal delivery were included	Egypt, North Africa	Castor oil (unknown dosage) for induction of labour (IOL) vs no treatment taken prior to attending the hospital	Haemorrhage, Caesarean section	Some baseline characteristics are different between groups; possible confounders not accounted for. Very few details regarding the intervention and how the outcomes were obtained has been provided. However, it seems exposure was self-reported prior to childbirth. Hence it may be cohort study not quasi-experimental.	II C (Excluded)
Gilad 2012 [38]	A randomised double blind controlled study involving 80 singleton and post-date (40-42 weeks) pregnant women. Other inclusion criteria were Bishop score ≤7, no uterine contraction or caesarean section.	Israel, Middle-East	60ml of castor oil for IOL vs placebo	Caesarean section, assisted vaginal delivery	Only conference abstract available, so there aren't many details on how the treatment was administered as well as outcome measurement. The sample size is small, which may limit generalisation of the results.	I B
Boel 2009 [39]	A historical cohort study that used hospital maternity records (2005-2007) of 612 outpatient pregnant women with a gestation at birth of ≥ 40 weeks.	Thailand, Asia	At least 60ml of castor oil for IOL vs no treatment	Haemorrhage, caesarean section, vaginal assisted delivery,	Baseline characteristics similar between groups, small sample size for a historical cohort, different places of delivery mean different treatment; there was no standard measure of outcomes; possible confounders not controlled; retrospective analysis.	III B
Mabina 1997 [37]	A hospital-based prospective cohort of 229 women who went to the facility for delivery. Outcomes were retrieved from hospital records.	South Africa	Any herbal medicine, but most likely Isihlambezo, which is used for IOL	Caesarean section, assisted vaginal delivery	Recorded baseline characteristics similar between groups, but some key confounders were not measured. Confounders were not controlled; recall bias due to self-reported exposure; unknown dosage.	III B
Simpson 2001 [36]	A double-blind hospital-based randomised controlled trial involving 192 pregnant women who booked to deliver at a study facility. Criteria for inclusion included being nulliparous with low-risk, healthy pregnancy, fluent in English and a doctor's approval.	Australia	2.4g of Raspberry leaf per day from gestation week 26-30 until delivery (to shorten labour) vs placebo.	Caesarean section, haemorrhage, vaginal assisted delivery	Rigorous recruitment process; reasonable statistical power; study groups were comparable; consumption of the tablet was self-reported. Generalisation limited to low-risk nulliparous. It is not known how many were excluded because of language as it was one of the inclusion criteria.	I A

Garry 2000 [40]	A hospital-based quasi-experimental study involving 103 pregnant women with the following characteristics: singleton, gestational age between 40 and 42weeks, Bishop score ≤4 and no uterine contractions.	USA	60ml castor oil for IOL vs no treatment. Eligible pregnant women (i.e. >40-week gestation) were alternately assigned to one of the two study groups.	Caesarean section.	Measured covariates equally distributed in two groups, but the study lacks adequate statistical power as the sample size was small. Not all possible confounders were considered. Timing of treatment and how it was administered not indicated and the follow-up details are not clear.	II B
Parsons 1999 [35]	A hospital-based retrospective cohort study involving a convenience sample of 108 women who had given birth at the facility. Outcome data and all the data for the control group was retrieved from hospital records.	Australia	Raspberry leaf vs no raspberry leaf	Vaginal assisted delivery, caesarean section	The study and control groups were somewhat different; data collection methods were different between the study and control groups; confounders not accounted for; convenience sample; response rate unclear; inconsistent dosage and timing; no details on how the outcomes were measured; women delivered with different providers (private/public) and this was not accounted for. Relatively small sample size.	III B

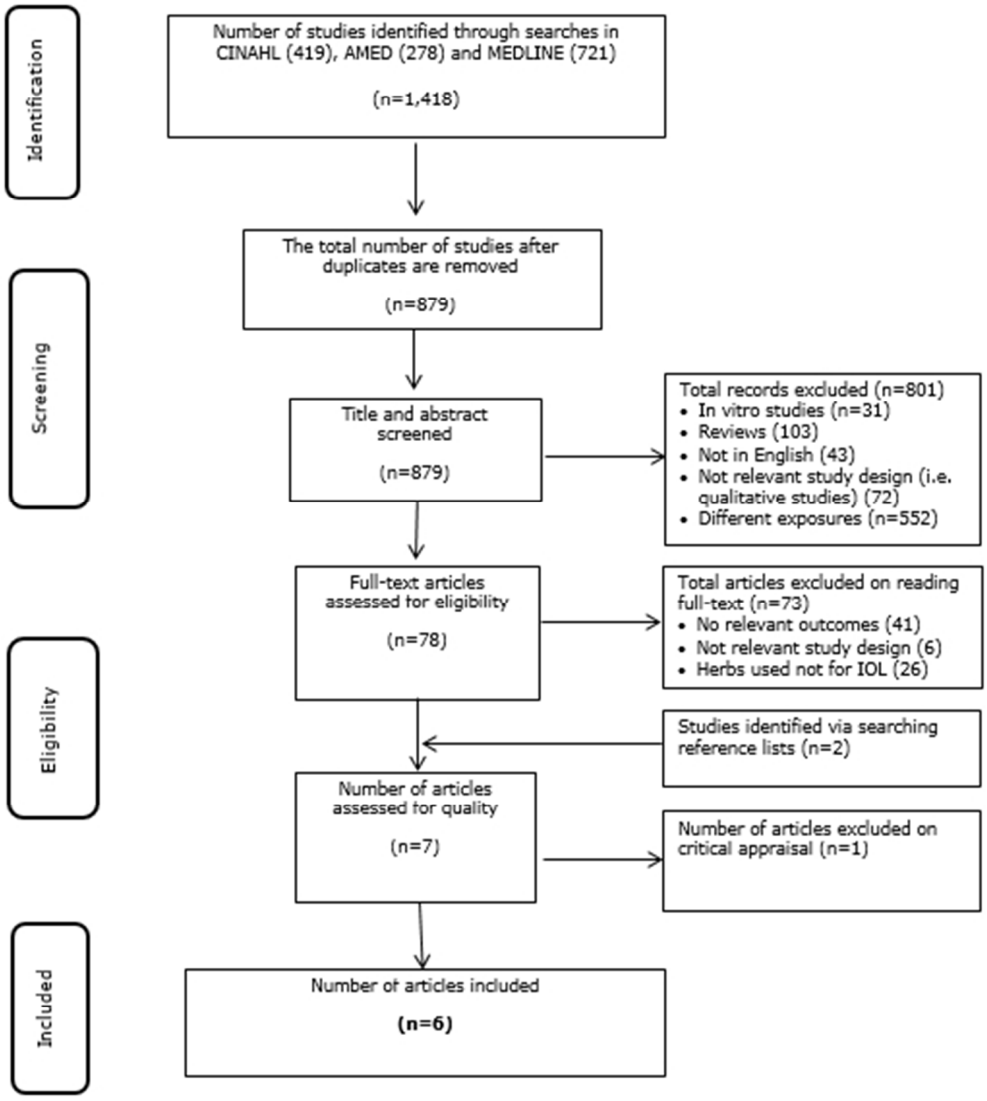

Figure 1: A PRISMA flow diagram summarising the study selection process

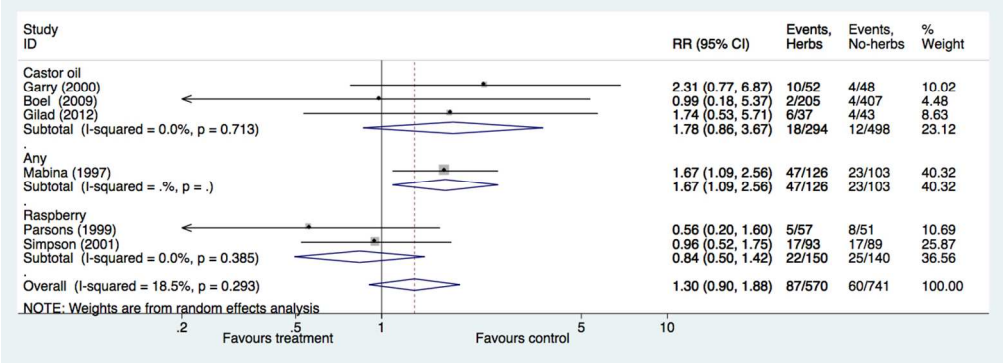

Figure 2: The use of herbal medicines for induction of labour and the risk of caesarean section

232x84mm (144 x 144 DPI)

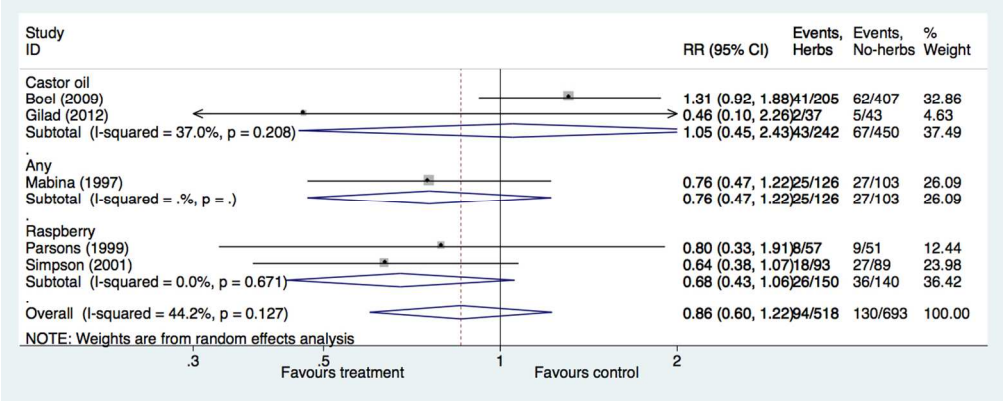

Figure 3: The use of herbal medicines for induction of labour and the risk of vaginal assisted delivery

232x93mm (144 x 144 DPI)

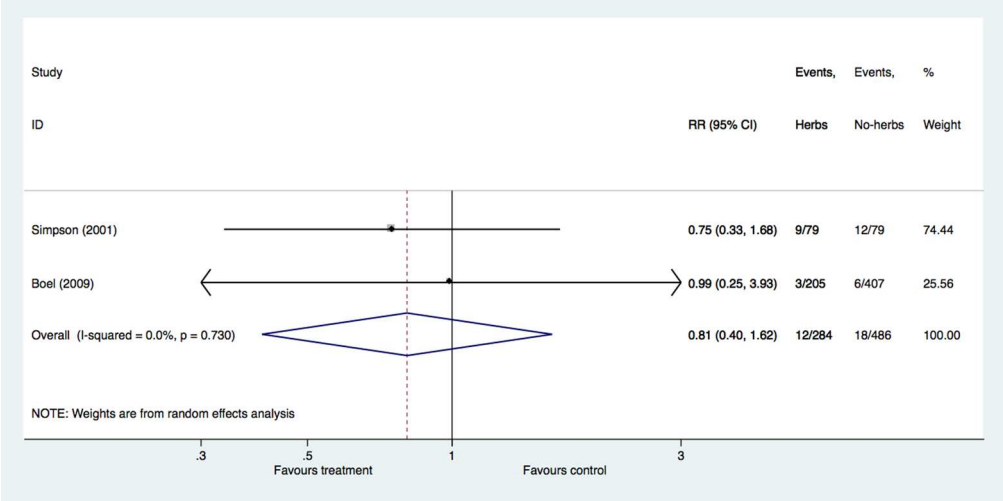

Figure 4: The use of herbal medicines for induction of labour and the risk of haemorrhage

232x116mm (144 x 144 DPI)

Full electronic search strategy

Search ID	Search terms
	S9 AND S22
S22	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S21
S21	"labour"
S20	(MM "Labor+") OR "labor" OR (MM "Labor Stage, Third") OR (MM "Labor Stage, Second") OR (MM "Labor Stage, First") OR (MM "Labor, Premature") OR (MM "Labor, Induced+") OR (MM "Labor Complications+") OR "labor"
S19	(MM "Childbirth+") OR "childbirth"
S18	(MM "Delivery, Obstetric+") OR "delivery, obstetric" OR (MM "Obstetrical Forceps") OR (MM "Vacuum Extraction, Obstetrical") OR (MM "Surgery, Obstetrical+")
S17	(MM "Abnormalities+") OR "birth defect*"
S16	"birth outcome*"
S15	(MM "Maternal Mortality") OR (MM "Child Mortality") OR (MM "Infant Mortality") OR "mortality"
S14	"neonatal complication*"
S13	(MM "Pregnancy Outcomes") OR "pregnancy outcome*"
S12	(MM "Pregnancy Complications") OR "pregnancy complications"
S11	(MM "Expectant Mothers") OR "pregnant women"
S10	(MM "Pregnancy+") OR "pregnancy" OR (MM "Pregnancy Outcomes")
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S8	ginseng OR echinacea OR cranberry OR raspberry OR blue cohosh OR black cohosh OR castor oil OR evening primrose oil OR chamomile OR licorice OR ginger
S7	"chinese herbal medicine"
S6	"herb*"
S5	"herbal product*"
S4	(MM "Medicine, Herbal+") OR (MM "Drugs, Chinese Herbal") OR (MM "Herbs, Seasoning") OR "herbal remed*"
S3	(MM "Plants, Medicinal+") OR "medicinal plant*"
S2	(MM "Medicine, Traditional+") OR "traditional medicine"
S1	(MM "Medicine, Herbal+") OR (MM "Medicine, Oriental Traditional+") OR (MM "Medicine, Native American") OR (MM "Medicine, African Traditional") OR "herbal medicine" OR (MM "Medicine, Latin American Traditional") OR (MM "Medicine, Arabic") OR (MM "Plants, Medicinal+")

JHNEBP Evidence Rating Scales

Strength of the Evidence	
Level I	Experimental study/randomized controlled trial (RCT) or meta analysis of RCT
Level II	Quasi-experimental study
Level III	Non-experimental study, qualitative study, or meta-synthesis.
Level IV	Opinion of nationally recognized experts based on research evidence or expert consensus panel (systematic review, clinical practice guidelines)
Level V	Opinion of individual expert based on non-research evidence. (Includes case studies; literature review; organizational experience e.g., quality improvement and financial data; clinical expertise, or personal experience)

Quality of the Evidence		
A High	Research	consistent results with sufficient sample size, adequate control, and definitive conclusions; consistent recommendations based on extensive literature review that includes thoughtful reference to scientific evidence.
	Summative reviews	well-defined, reproducible search strategies; consistent results with sufficient numbers of well defined studies; criteria-based evaluation of overall scientific strength and quality of included studies; definitive conclusions.
	Organizational	well-defined methods using a rigorous approach; consistent results with sufficient sample size; use of reliable **and** valid measures
	Expert Opinion	expertise is clearly evident
B Good	Research	reasonably consistent results, sufficient sample size, some control, with fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence
	Summative reviews	reasonably thorough and appropriate search; reasonably consistent results with sufficient numbers of well defined studies; evaluation of strengths and limitations of included studies; fairly definitive conclusions.
	Organizational	Well-defined methods; reasonably consistent results with sufficient numbers; use of **reliable and valid** measures; reasonably consistent recommendations
	Expert Opinion	expertise appears to be credible.
C Low quality or major flaws	Research	little evidence with inconsistent results, insufficient sample size, conclusions cannot be drawn
	Summative reviews	undefined, poorly defined, or limited search strategies; insufficient evidence with inconsistent results; conclusions cannot be drawn
	Organizational	Undefined, **or** poorly defined methods; insufficient sample size; inconsistent results; undefined, poorly defined or measures that lack adequate reliability or validity
	Expert Opinion	expertise is not discernable or is dubious.

**A study rated an A would be of high quality, whereas, a study rated a C would have major flaws that raise serious questions about the believability of the findings and should be automatically eliminated from consideration.*

Newhouse R, Dearholt S, Poe S, Pugh LC, White K. The Johns Hopkins Nursing Evidence-based Practice Rating Scale. 2005. Baltimore, MD, The Johns Hopkins Hospital; Johns Hopkins University School of Nursing.

Data Extraction Form for Experimental/Observational Studies

Details of the study

	Description	Location in text
First author		
Year		
Publication type		
Study period		
Aim of the study		

Methods

	Description	Location in text
Study design		
Population		
Setting		
Country		
Inclusion criteria		
Exclusion criteria		
Recruitments		
Sample size		
Exposure type:		
Pattern and frequency		

Results – continuous

Outcome	Intervention/after			Control/before			
	Mean	SD	Sample size	Mean	SD	Sample size	Location in the text

Results – dichotomous

Outcome	Intervention/after		Control/before		
	No. of events	Sample size	No. events	Sample size	Location in the text

Authors' conclusions:

Comments/observations:

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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 registration number.	NA
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 rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7, 9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
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.	9, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
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).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 2-4
DISCUSSION			
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., healthcare providers, users, and policy makers).	13-14
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).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

BMJ Open

The effectiveness and safety of herbal medicines for induction of labour: a systematic review and meta-analysis

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Reproductive medicine, Pharmacology and therapeutics, Obstetrics and gynaecology, Complementary medicine
Keywords:	Herbal medicine < THERAPEUTICS, Induction of labour, Pregnancy outcomes, Complementary and alternative medicine

The effectiveness and safety of herbal medicines for induction of labour: a systematic review and meta-analysis

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Word count: 3609

ABSTRACT

Objective

The use of herbal medicines for induction of labour (ILO) is common globally and yet its effects are not well understood. We assessed the efficacy and safety of herbal medicines for IOL.

Design

Systematic review and meta-analysis of published literature.

Data sources

We searched in MEDLINE, AMED and CIHAHL in April 2017, updated in June 2018.

Eligibility criteria

We considered experimental and non-experimental studies that compared relevant pregnancy outcomes between users and non-user of herbal medicines for IOL.

Data extraction and synthesis

Data were extracted by two reviewers using a standardised form. A random-effects model was used to synthesise effects sizes and heterogeneity was explored through I^2 statistic. The risk of bias was assessed using 'John Hopkins Nursing School Critical Appraisal Tool' and 'Cochrane Risk of Bias Tool'.

Results

A total of 1,421 papers were identified through the searches, but only 10 were retained after eligibility and risk of bias assessments. The users of herbal medicine for IOL were significantly more likely to give birth within 24 hours than non-users (RR = 4.48; CI = 1.75 – 11.44). No significant difference in the incidence of caesarean section (RR = 1.19; 95% CI=0.76 - 1.86), vaginal assisted delivery (RR = 0.73; CI = 0.47 - 1.14), haemorrhage (RR = 0.84; CI = 0.44 – 1.60), meconium-stained liquor (RR = 1.20; CI = 0.65 – 2.23) and admission to nursery (RR = 1.08; CI = 0.49 – 2.38) was found between users and non-users of herbal medicines for IOL.

Conclusions

The findings suggest that herbal medicines for IOL are effective, but there is inconclusive evidence of safety due to lack of good quality data. Thus, the use of herbal medicines for IOL should be avoided until safety issues are sorted. More studies are recommended to establish the safety of herbal medicines.

Keywords: Herbal medicine, complementary and alternative medicine, induction of labour, pregnancy outcomes

Strengths and limitations of this study

- Due to safety and ethical reasons, herbal medicines for pregnant women are rarely evaluated through randomised controlled/clinical trials (RCTs). Nonetheless, most of the reviews of herbal medicines during pregnancy are restricted to RCTs. The present review included non-experimental studies to assess a wider evidence base.

- No restrictions were applied on the date of publication, location, study design and types of treatment (herbal medicine used).
- There is lack of data on key outcomes (e.g. maternal death and sepsis) and from low-income countries.
- Some analyses did not have sufficient statistical power due to the inadequate number of studies and small sample sizes

INTRODUCTION

Across the world, the use of unconventional or traditional medical therapies is very high [1-4]. These non-biomedical remedies are together referred to as complementary and alternative medicines (CAM). The World Health Organisation (WHO) recognises the role of CAM of verified quality, safety and efficacy in ensuring universal access to health care [5]. As such, for the period between 2014 and 2023, the WHO traditional medicine strategy focused on harnessing the potential contribution of CAM in health care and promoting its safe and effective use [5]. Although this requires rigorous evidence on safety and efficacy of CAM, research in this area remains limited [5]. Herbal medicine or medicinal plant is one of the well-known CAM therapies that involve the use of plants or plant extracts for therapeutic motives [6]. As in the general population, the use of herbal medicines is common among pregnant women globally [7-10]. The estimated prevalence varies between regions and countries but ranges from 10% to 80% [11 12]. One of the common indications for herbal medicine use during pregnancy is prolonged labour or merely the desire to induce or augment labour for different reasons [13 14]. This practice is well-documented and transcends cultural and generational boundaries [14].

From a medical perspective, induction of labour (IOL) changes the physiological processes associated with childbirth in ways that may increase the risk of adverse pregnancy outcomes such as neonatal mortality, foetal distress, premature birth, haemorrhage, uterine rupture and caesarean section [15-17]. Because of this, WHO recommends that labour should only be induced in health facilities with the capacity for continual monitoring and emergency obstetric care [18]. The emphasis on facility-based IOL and close monitoring of pregnant women demonstrates the risks associated with the procedure. Nonetheless, with herbal medicine-induced labour, monitoring of

women is often out of the question due to self-prescription [2 19]. So, the use of herbal medicines for IOL is likely to be riskier and it is plausibly an important factor influencing adverse pregnancy outcomes in settings where its use is common.

In vitro studies have confirmed that some of the herbal medicines used during pregnancy have oxytocic properties [13 20]. For instance, a study in Nigeria found that several plants that are used to facilitate childbirth in the country significantly induced muscle cell contractility [13]. However, safety is the main concern as many of the herbal medicines are believed to be poisonous and may contribute to maternal and neonatal mortality as well as morbidity [21 22]. To date, there is mixed evidence from population-based studies regarding the efficacy and safety of herbal medicines for IOL [23-25] and yet available data have not been systematically evaluated and synthesised to provide the rigorous evidence necessary to inform decisions. Lack of high quality and consistent data on efficacy and safety of herbal medicines makes recommendations and regulations challenging [5]. Consequently, we conducted a systematic review to explore the effectiveness and safety of herbal medicines for IOL. This review is important to inform the development of guidelines relating to the use of herbal medicines among pregnant women.

METHODS

Design

This is a systematic review and meta-analysis of published literature on effectiveness and safety of herbal medicines for IOL. The reporting of the abstract (Supplementary file S1) and results

(Supplementary file S2) are guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [26].

Data sources and searches

We searched in MEDLINE, AMED and CINAHL from 13 February to 22 April 2017 and repeated this on 22 June 2018 using key terms such as herbal medicine, labour and pregnancy outcomes, which were modified in accordance with each database (Supplementary file S3). More papers were identified through scanning the reference list of studies found through the initial search as well as direct searches in the following journals: African Journals Online (AJOL), Journal for Herbal Medicine, BMC Complementary and Alternative Medicine, Journal of Alternative and Complementary Medicine and Journal of Integrative Medicine.

Inclusion/exclusion criteria

The inclusion criteria were based on PICOS (participant, intervention, control, outcomes and studies). We considered studies with pregnant or postpartum women as participants. The treatment or exposure was herbal medicines for induction or shortening of labour. For studies that did not explicitly indicate the reasons for use, the name of the medicine was used to determine if IOL was the possible motive. There was no restriction on dosage, but the route of administration was oral. The plants could be either processed or crude and used alone or alongside conventional medicines. An appropriate comparison group comprised either pregnant women who did not use the herbal medicine under consideration or used biomedical drugs exclusively. The maternal outcomes were haemorrhage, sepsis, caesarean section, uterine rupture, assisted vaginal delivery and maternal death; while the neonatal outcomes were,

stillbirth, premature birth, neonatal mortality, meconium-stained liquor/foetal distress, birth defects and referral to neonatal intensive care unit (also known as nursery).

Due to ethical, safety and methodological issues, pregnant women are often excluded from randomised clinical trials (RCTs) and herbal medicines may not be evaluated through RCTs [27-29]. Thus, observational studies are a common source of literature for efficacy and safety of herbal medicines in pregnancy. Accordingly, we considered both experimental and non-experimental study designs. In particular, the following study designs were eligible for inclusion: randomised controlled/clinical trials (RCTs), quasi-experimental, cohort, case-control and cross-sectional. We only considered studies published in English or in other languages, but with a detailed English abstract. No restrictions were applied on the date of publication and study setting.

Data extraction

A data extraction form (Supplementary file S4) was developed specifically for this review based on templates developed by the Joanna Briggs Institute and the Cochrane Pregnancy and Childbirth Group [30 31]. The form included specific details about the study design, participants, setting, intervention/exposure, control and outcomes. Owing to the focus of our study (i.e. efficacy and safety), 'per protocol' treatment effects were preferred in RCTs [32]. As none of the observational studies reported adjusted effect estimates, crude data were extracted and used in this review. Two reviewers – Collins Zamawe (CZ) and Chrispin Mandiwa (CZ) – separately extracted the data and any differences were resolved by discussion.

Quality/risk of bias assessment

Two different tools were used to assess the risk of bias in experimental and non-experimental studies that met the inclusion criteria. CZ and CM independently performed the risk of bias assessment and any disagreements were resolved by discussion. For experimental studies, Cochrane Risk of Bias tool for the RCTs [33] was used and the following domains were assessed: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases (Supplementary file S5). Only abstracts were available in English for two studies [25 34] and hence their risk of bias is largely unclear. The overall risk of bias for the other RCTs is low.

The risk of bias for non-experimental studies was assessed using a standardised critical appraisal tool developed by 'John Hopkins Nursing School' [35]. This tool divides the strength of research evidence into five levels based on the study design. The RCTs occupy the top level (level I) followed by quasi-experimental studies (level II) and other non-experimental studies (level III). The last two levels are for opinion-related papers either based on research evidence (level IV) or individual expertise (level V). The quality of evidence is further graded as high (A), good (B) and low quality or major flaws (C) depending on the risk of bias and scientific basis for the conclusions. Based on this tool, a list of 10 questions (or domains) was developed to guide the assessment (Supplementary file S6). Since the review used crude data, the need to control extraneous variables and whether this was done (if required) were key factors in determining the study grade. For instance, grade C was given to studies in which the treatment and control groups were not comparable and confounders were not adjusted for. Two studies [23 36] received a grade of C and were eventually excluded from the review.

Data analysis

Meta-analyses were performed to compare the onset of labour (effectiveness) and the incidence of adverse pregnancy outcomes (safety) between the users and non-users of herbal medicines for IOL. As variations were expected between studies due to the differences in setting, design and types of herbal medicines, a random-effects model was used to synthesise effects sizes of the studies [37]. Heterogeneity was explored through the I^2 statistic and meta-analysis was conducted regardless of the outcome as random-effects model accommodates statistical heterogeneity [38]. Subject to availability of the sufficient number of studies, subgroup analyses were conducted based on the type of treatment/exposure or study design to explain observed heterogeneity. Potential publication bias was assessed using Egger's test since all analyses had less than 10 studies to use a funnel plot method [39 40]. Summary effects were measured using risk ratios (RR) and all analyses were performed using Stata/SE 13.1 software.

Patient and public involvement

As this was a review of existing literature, we did not involve any patient and the public in the design and conduct of the study. However, the development of the review question was informed by the experiences of pregnant women as observed in the literature.

RESULTS

Study selection process

Searches in the three databases returned a total of 1,421 papers (CINAHL=420, AMED=279 and MEDLINE=723). After removal of duplicates (n=539), the titles and or abstracts of 882

publications were screened and 802 studies were dropped at this stage for various reasons (see Figure 1). Full-text articles were retrieved for 80 studies for further eligibility assessment and 71 of them failed to meet the inclusion criteria. Additional potential relevant papers (n=3) were identified through direct searches in journals and reference lists. Twelve papers were appraised in the final stage and two were excluded due to poor methodological quality (see Supplementary file S6). Thus, 10 studies were included in this review.

Figure 1: A PRISMA flow diagram summarising the study selection process

An overview of the included studies

Supplementary file S7 presents the characteristics of the studies, such as location, exposure, outcomes and ratings. In brief, of the 10 studies in the review, three were conducted in Iran, two in the USA and one each in South Africa, Israel, Thailand, Australia and Italy. In relation to the World Bank's classification of countries by income, half of the studies were conducted in high-income countries (HIC) and the other half in upper-middle-income countries (UMIC). No study from low-income countries (LIC) or lower-middle-income countries (LMIC) was included.

Three types of exposures were reported by the studies. An Australian study was concerned with exposure to raspberry leaf [41]. This is one of the common herbal remedies used during pregnancy that is believed to prepare the uterus for childbirth and thereby effectively reduce the length of labour [14]. In this study, exposure was self-reported by the participants as they were given raspberry pills by the nurses to take at home. Eight studies examined exposure to castor oil [25 34 42-47]. The oil is derived from the castor plant's bean and is widely thought to have oxytocic

properties [44 45]. In all the studies, pregnant women consumed 60ml of castor oil, but in one study [43] the treatment was repeated in women who did not deliver within one week after the first dose. One study [48] assessed general exposure to herbal medicines, but there are indications in the report that they were for IOL.

Five of the included studies are RCTs and the remaining five are non-experimental, including cohort (3), case-control (1) and quasi-experimental (2) designs. The following pregnancy outcomes were reported by the included studies: onset of labour within 24 hours, caesarean section, haemorrhage, neonatal referral to nursey care, meconium stained liquor, vaginal assisted delivery, stillbirth, neonatal death, maternal death and uterus rupture.

Outcome 1: Onset of labour within 24 hours

Eight studies explored the onset of labour within 24 hours after the use of herbal medicine for IOL. Castor oil was the exposure or intervention in all the studies. As shown in figure 2, herbal medicine users were significantly more likely to give birth within 24 hours than non-users (RR = 3.46; CI = 1.58 – 7.55). In the subgroup analysis by study design, similar results were observed among experimental studies, but there was no significant difference in onset of labour between users and non-users among the non-experimental studies (Supplementary file S8). Publication bias was not an issue (Bias = 3.23; CI = 0.48 - 5.97), but heterogeneity was significant (I^2 = 90.2%, P=<0.001) and this was likely due to variations in study design and or setting.

Figure 2: The use of herbal medicines for induction of labour and onset of labour

Outcome 2: Incidence of caesarean section

The association between herbal medicine use and occurrence of caesarean section was examined by six studies. A meta-analysis (Figure 3) found no significant difference in the rate of caesarean section between the users and non-users of herbal medicines (RR = 1.19; 95% CI=0.76 - 1.86). Similar results were observed in subgroup analysis by type of treatment (Supplementary file S9) and study design (Supplementary file S10), except that Mabina [48] (e.g. any exposure), found a significant difference in the incidence of caesarean section between the study groups. Both heterogeneity (I^2 = 45.6%; p = 0.102) and publication bias were not significant (Bias = -0.39; 95% CI= -4.47 - 3.70).

Figure 3: The use of herbal medicines for induction of labour and the incidence of caesarean section

Outcome 3: Incidence of assisted vaginal delivery

In this review, assisted vaginal delivery was defined as the use of medical interventions such as forceps and episiotomy to aid delivery. This outcome was reported by five studies and a meta-analysis (Figure 4) found no significant difference between the users and non-users of herbal medicines (RR = 0.73; CI = 0.47 - 1.14). Heterogeneity was significant (I^2 = 74.4%; p = 0.004), but publication bias was not (Bias= -1.87; 95% CI= -6.12-2.38). Subgroup analyses by type of treatment (Supplementary file S11) and study design (Supplementary file S12) did not substantially change the results.

Figure 4: The use of herbal medicines for induction of labour and the incidence of vaginal assisted delivery

Outcome 4: Incidence of haemorrhage

The occurrence of haemorrhage among users and non-users of herbal medicines for IOL was assessed by four studies and a meta-analysis (Figure 5) shows no significant difference between the two groups (RR = 0.84; CI = 0.44 – 1.60). These results were consistent with those in subgroup analyses by type of treatment (Supplementary file S13) as well as study design (Supplementary file S14). Heterogeneity was almost non-existent (I^2= 0.0%; p = 0.802) and publication bias was not significant (Bias = 0.49; CI = -2.73 – 3.70).

Figure 5: The use of herbal medicines for induction of labour and the incidence of haemorrhage

Outcome 5: Incidence of meconium-stained liquor

The occurrence of meconium-stained liquor (MSL), a strong indicator of foetal distress [49], was reported by five studies. Overall, there is no significant difference in the rate of MSL between users and non-users of herbal medicines (RR = 1.20; CI = 0.65 – 2.23) (Figure 6). Comparable results were observed in subgroup analysis by type of treatment (Supplementary file S15). However, in subgroup analysis by study design, the experimental studies tended to favour treatment while the non-experimental inclined towards control, but both results were not statistically significant (Supplementary file S16). Publication bias was not significant (Bias = -2.38; CI = -6.76 – 2.00), but heterogeneity was high (I^2= 77.9%; p= 0.001) probably due to variations across studies.

Figure 6: The use of herbal medicines for induction of labour and the incidence of meconium-stained liquor

Outcome 6: Neonates' admission to nursery

Whether a newborn child is referred to neonatal intensive care unit (also known as nursery) or not is often used as an indicator for wellbeing [41]. This outcome was reported by three studies and none of them individually found a significant difference in admission to nursery between users and non-users of herbal medicines for IOL. A meta-analysis (Figure 7) found no significant difference between the two groups (RR = 1.08; CI = 0.49 – 2.38). Both publication bias (Bias = -1.51; -7.66 – 4.64) and heterogeneity (I^2= 0.0%; p= 0.482) were not significant. Subgroup analysis was not performed due to the inadequate number of studies.

Figure 7: The use of herbal medicines for induction of labour and neonatal admission to nursery

Other outcomes

The following outcomes were either reported by a single study or there was insufficient data and hence meta-analyses were not performed: maternal death, stillbirth and uterine rupture. A single study assessed maternal death and stillbirth outcomes among users (n=205) and non-users (n=407) of castor oil to induce labour [43]. No maternal death occurred in either group, but one case of stillbirth (0.3%) was reported in the control group. Uterine rupture was reported by two studies in relation to castor oil and only one case was reported among exposed women in one of

the studies [43 47]. Overall, no study found a significant difference in any of the three outcomes between users and non-users of herbal medicines for IOL.

DISCUSSION

The findings of this review indicate that herbal medicines for IOL are effective and safe. On efficacy, we have found that women who used the herbal medicines were significantly more likely to give birth within 24 hours than their counterparts who did not use. This corroborates many in-vitro studies around the world that have shown that some herbal medicines effectively induce uterine contractions [13 20 50]. For instance, studies in Malawi and Nigeria have established that some medicinal plants commonly prescribed by traditional healers to induce childbirth have oxytocic properties [13 20]. Previous reviews, however, found insufficient evidence for the effectiveness of herbal medicines for IOL [51 52]. This contradiction could be as a result of the differences in inclusion criteria. Most of the related reviews excluded non-experimental studies [51 52], which are a common source of efficacy data due to safety issues surrounding RCTs for herbal medicines or pregnant women [27 28 53]. Whereas this allowed us to assess a wider evidence base than the previous reviews, we are also mindful of the biases inherent in observational studies. Therefore, a definite conclusion about the efficacy of herbal remedies for IOL cannot be put forward based on the present review [54-56].

On safety, we did not find any statistically significant difference in the rate of haemorrhage, caesarean section, assisted vaginal delivery, referral to neonatal intensive care unit, meconium-stained liquor, maternal death, stillborn and uterine rupture between participants in treated and control groups. The implication is that herbal medicines for IOL may not be harmful to women

or neonates. This observation is consistent with the results that have been reported by other reviews on a related topic [51 52]. Notwithstanding, caution must be exercised in the interpretation of this data because in some outcomes (e.g. caesarean section) the difference in the number of cases between treated and control groups was very high. This was also noted by Boltman-Binkowski [51] in her review. Despite lack of statistical significance, she argues that a higher number of adverse outcomes among women who ingested castor oil implies that the link between the two cannot be entirely dismissed. The finding may also be inconclusive owing to lack of data on key outcomes, such as maternal death, sepsis and neonatal death.

The results of this review should be considered in the context of the following limitations and biases. First, although the baseline characteristics of the observational studies were similar across study groups, not all potential confounders were measured. Likewise, of the five RCTs in this review, three were unclear on selection, performance and detection biases while two had unclear attrition, reporting and other biases. Thus, the risk of bias may have been introduced as a result of these poor methodologies. In addition, some analyses lacked adequate statistical power because of small sample sizes or the insufficient number of studies. These issues strongly suggest that the outcomes of this review be treated with considerable caution.

Secondly, in almost all the studies, herbal remedies were provided at the health facility and pregnant women were somewhat monitored by clinical staff. In this way, many potential adverse events may have been averted or lessened. Nevertheless, this does not entirely represent the reality of the context in which herbal medicines are taken and thus the results of these studies may be misleading. In sub-Saharan Africa, for instance, herbal medicines are often taken outside

the health facility without the knowledge and support of health care providers [12 48 57]. In such situations, the risk of adverse events could be higher than reported by these studies.

Lastly, all studies in this review are from higher and upper-middle income countries. No study from a low or lower middle-income country was included. This probably suggests lack of studies on this subject in limited resource settings. Hence, the findings of this review cannot be extrapolated beyond higher and upper-middle income countries. Since the issue of safety of herbal medicines in pregnancy relates to maternal as well as neonatal morbidity and mortality [22 48 58-60], which are principally the problems of LIC [61 62], high-quality studies that include a range of maternal morbidity and mortality outcomes in LIC are urgently needed [22 63].

CONCLUSIONS AND IMPLICATIONS

The evidence from this review suggests that herbal medicines for IOL are effective, but their safety among women and neonates require further exploration. Therefore, we would not recommend the use of these medicines until all the safety concerns are adequately addressed. In the meantime, larger safety and efficacy studies with sufficient statistical power and of high methodological quality should be conducted to improve the evidence base.

Contributors

CZ, CK, HMJ and EF conceived the review. CZ and CM conducted the literature search, appraised the papers and extracted the data. CZ performed the analysis and drafted the manuscript. CK and EF commented on drafts and provided technical input at all stages. All authors have read and approved the final manuscript.

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Competing interests

None

Data sharing statement

All data used in this review can be accessed from the corresponding author

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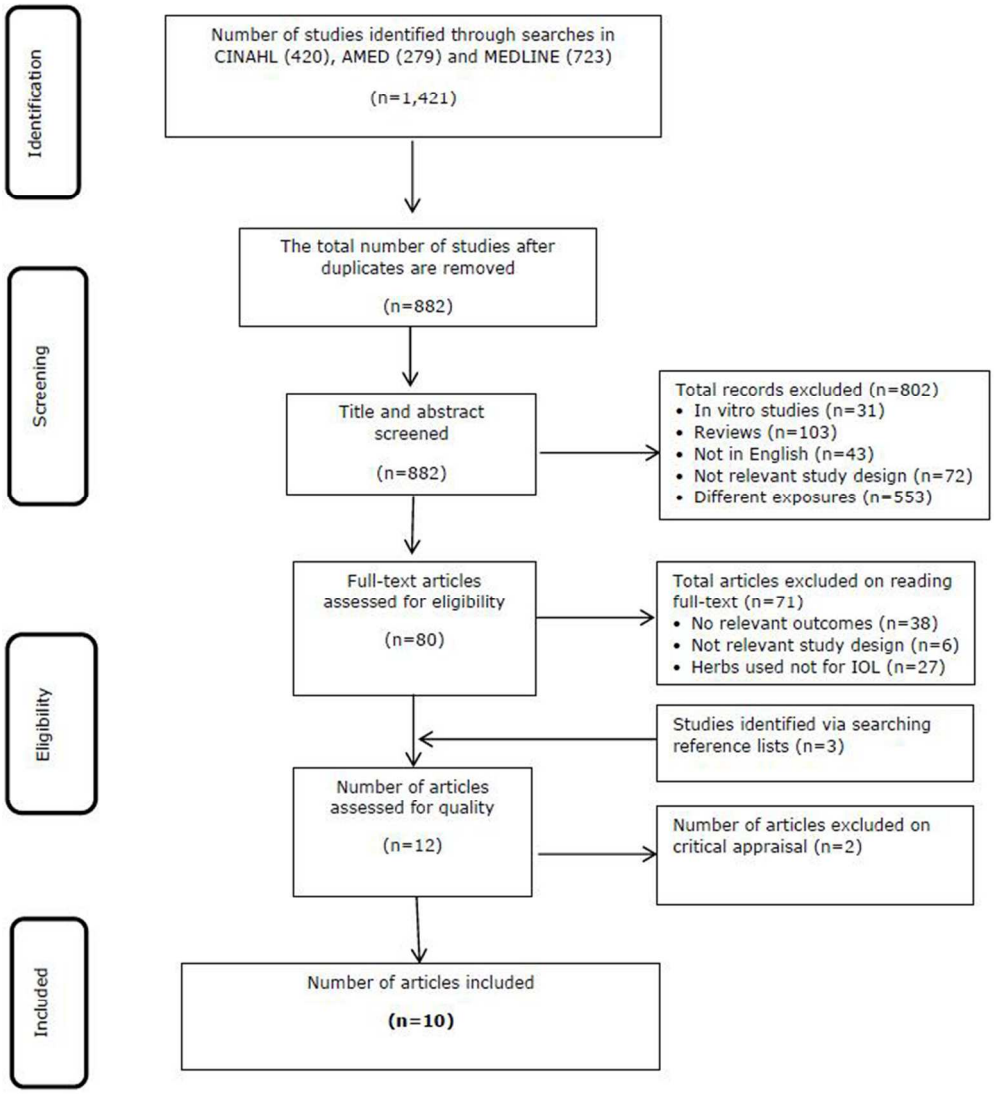

Figure 1: A PRISMA flow diagram summarising the study selection process

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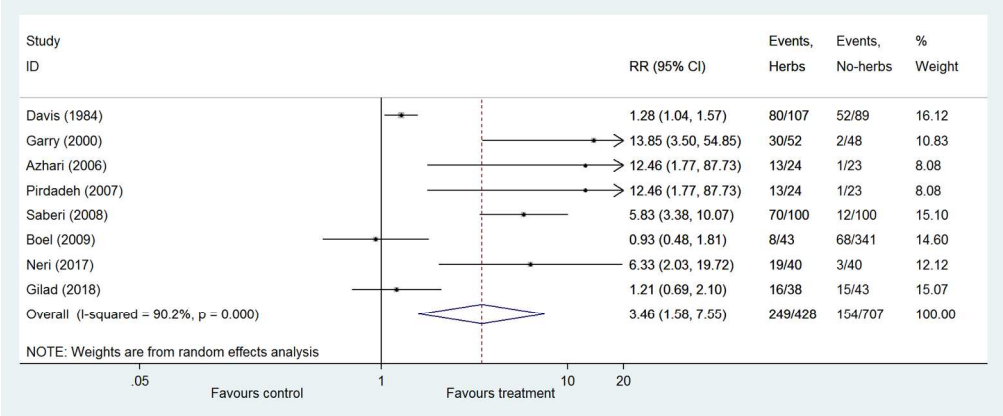

Figure 2: The use of herbal medicines for induction of labour and onset of labour

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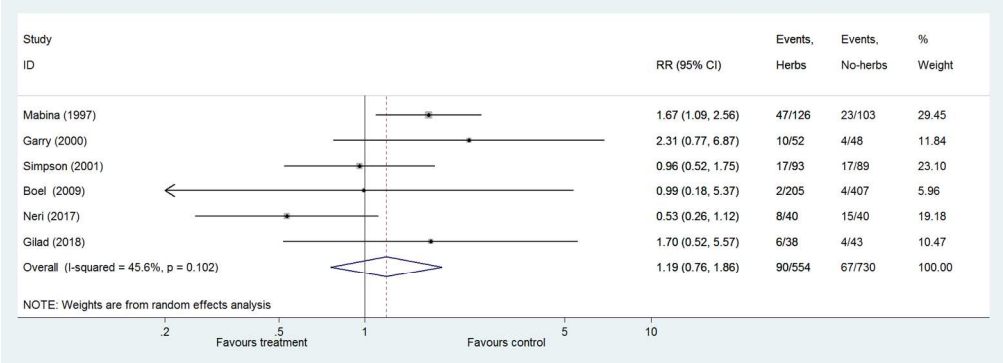

Figure 3: The use of herbal medicines for induction of labour and the incidence of caesarean section

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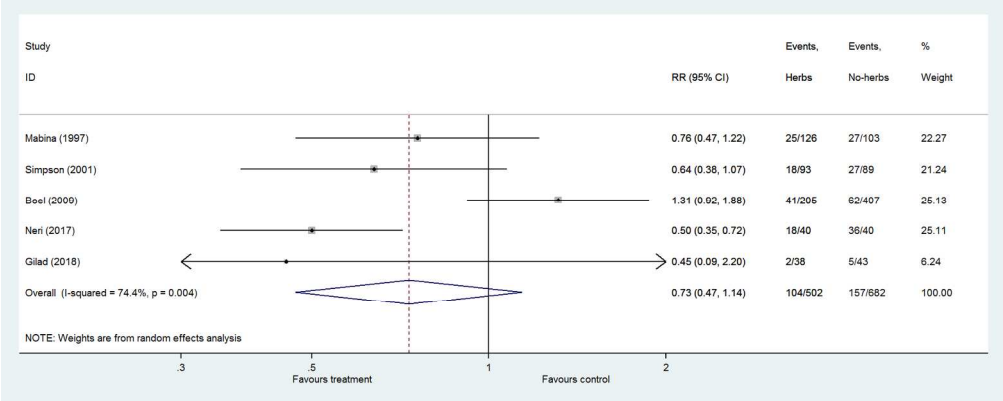

Figure 4: The use of herbal medicines for induction of labour and the incidence of vaginal assisted delivery

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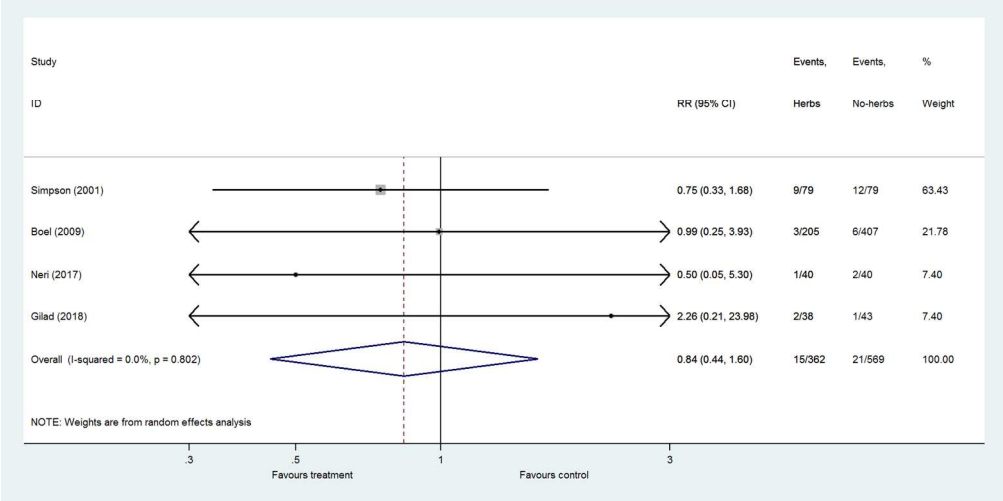

Figure 5: The use of herbal medicines for induction of labour and the incidence of haemorrhage

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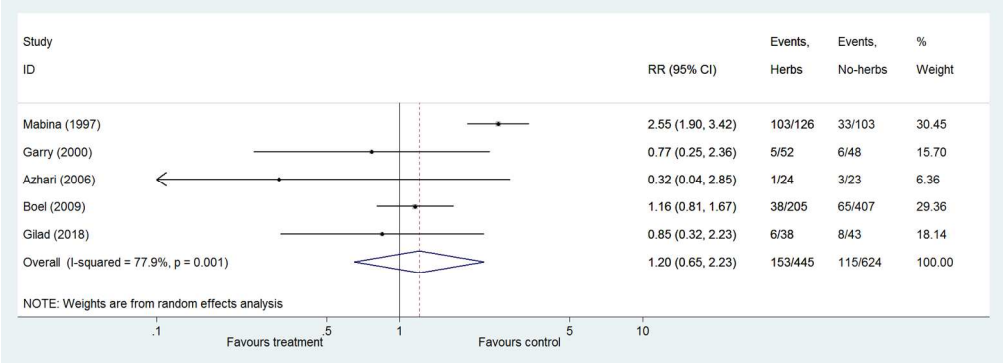


Figure 6: The use of herbal medicines for induction of labour and the incidence of meconium-stained liquor

270x98mm (300 x 300 DPI)

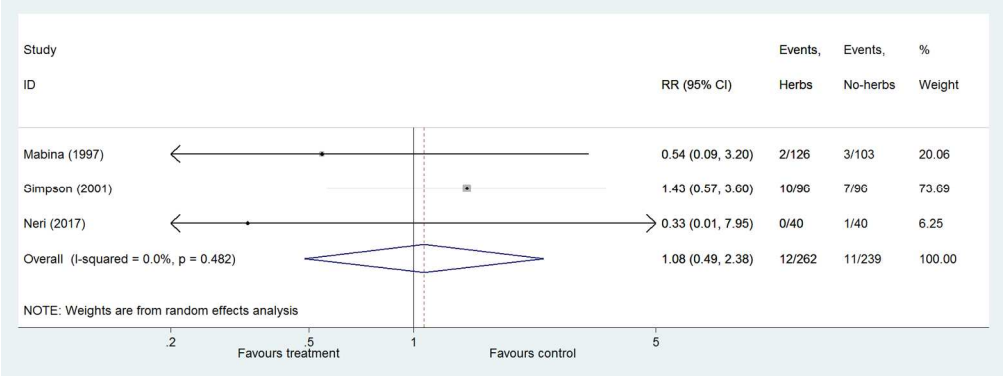


Figure 7: The use of herbal medicines for induction of labour and neonatal admission to nursery

270x101mm (300 x 300 DPI)

The PRISMA for Abstracts Checklist

TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	2
BACKGROUND		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	2
METHODS		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	2
4. Information sources:	Key databases searched and search dates.	
5. Risk of bias:	Methods of assessing risk of bias.	
RESULTS		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	3
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	
DISCUSSION		
9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	3
10. Interpretation:	General interpretation of the results and important implications	
OTHER		
11. Funding:	Primary source of funding for the review.	None
12. Registration:	Registration number and registry name.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
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 registration number.	Not done
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 rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9-8, 10-11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	9-10
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
RESULTS			
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.	10-11, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	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).	17, S5, S6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 3-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 3-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	17,S5,S6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	S8-S16
DISCUSSION			
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., healthcare providers, users, and policy makers).	16-17
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).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Full electronic search strategy for CINAHL (Same search terms were used in others databases)
Last search date: 22 June 2018

Search ID	Search terms
	S9 AND S22
S22	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S21
S21	"labour"
S20	(MM "Labor+") OR "labor" OR (MM "Labor Stage, Third") OR (MM "Labor Stage, Second") OR (MM "Labor Stage, First") OR (MM "Labor, Premature") OR (MM "Labor, Induced+") OR (MM "Labor Complications+") OR "labor"
S19	(MM "Childbirth+") OR "childbirth"
S18	(MM "Delivery, Obstetric+") OR "delivery, obstetric" OR (MM "Obstetrical Forceps") OR (MM "Vacuum Extraction, Obstetrical") OR (MM "Surgery, Obstetrical+")
S17	(MM "Abnormalities+") OR "birth defect*"
S16	"birth outcome*"
S15	(MM "Maternal Mortality") OR (MM "Child Mortality") OR (MM "Infant Mortality") OR "mortality"
S14	"neonatal complication*"
S13	(MM "Pregnancy Outcomes") OR "pregnancy outcome*"
S12	(MM "Pregnancy Complications") OR "pregnancy complications"
S11	(MM "Expectant Mothers") OR "pregnant women"
S10	(MM "Pregnancy+") OR "pregnancy" OR (MM "Pregnancy Outcomes")
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S8	ginseng OR echinacea OR cranberry OR raspberry OR blue cohosh OR black cohosh OR castor oil OR evening primrose oil OR chamomile OR licorice OR ginger
S7	"chinese herbal medicine"
S6	"herb*"
S5	"herbal product*"
S4	(MM "Medicine, Herbal+") OR (MM "Drugs, Chinese Herbal") OR (MM "Herbs, Seasoning") OR "herbal remed*"
S3	(MM "Plants, Medicinal+") OR "medicinal plant*"
S2	(MM "Medicine, Traditional+") OR "traditional medicine"
S1	(MM "Medicine, Herbal+") OR (MM "Medicine, Oriental Traditional+") OR (MM "Medicine, Native American") OR (MM "Medicine, African Traditional") OR "herbal medicine" OR (MM "Medicine, Latin American Traditional") OR (MM "Medicine, Arabic") OR (MM "Plants, Medicinal+")

Data Extraction Form for Experimental/Observational Studies

Details of the study

	Description	Location in text
First author		
Year		
Publication type		
Study period		
Aim of the study		

Methods

	Description	Location in text
Study design		
Population		
Setting		
Country		
Inclusion criteria		
Exclusion criteria		
Recruitments		
Sample size		
Exposure type:		
Pattern and frequency		

Results – continuous

Outcome	Intervention/after			Control/before			
	Mean	SD	Sample size	Mean	SD	Sample size	Location in the text

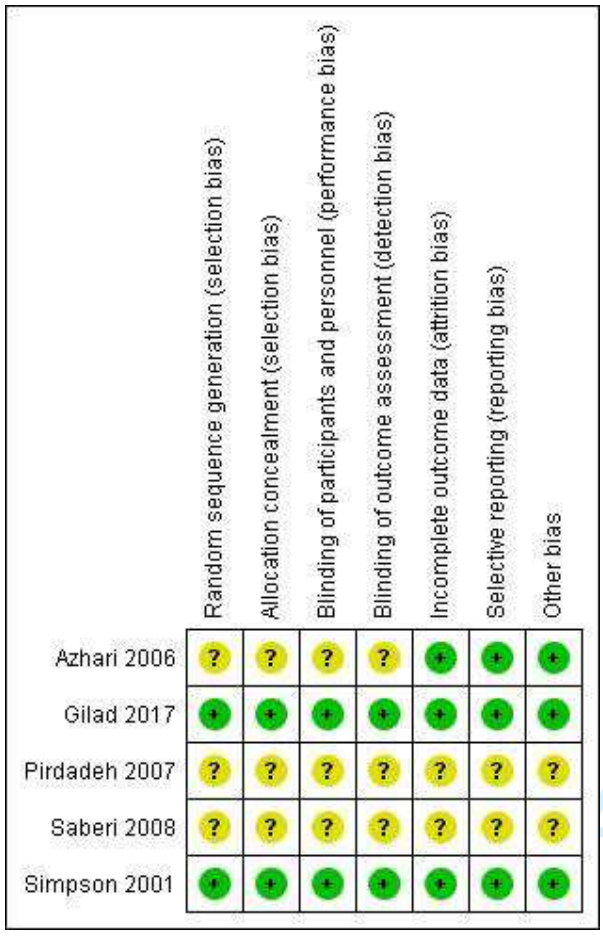
Results – dichotomous

Outcome	Intervention/after		Control/before		
	No. of events	Sample size	No. events	Sample size	Location in the text

Authors' conclusions:

Comments/observations:

Risk of bias summary: review authors' judgements about each risk of bias item for each included randomised controlled/clinical trial.



Risk of Bias for non-experimental studies

	Assessment questions	Non-experimental studies						
		Lamadah 2014	**Boel 2009**	**Mabina 1997**	**Garry 2000**	**Parsons 1999**	**Neri 2017**	**Davis 1984**
1	Is sample size justified?	No	No	No	No	No	No	No
2	Is there good response rate?	Not reported	Yes	Yes	Yes	Not reported	Yes	Yes
3	Is selection bias present?	Yes	No	No	No	Yes	No	No
4	Adequate control group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Is there need to control extraneous variables? (Based on comparability of cases and controls)	Yes	No	No	No	Yes	No	No
6	Were extraneous variables controlled?	No	Yes	No	No	No	No	No
7	Is there social desirability bias?	Yes	No	Yes	No	Yes	Yes	No
8	Is exposure self-reported?	Yes	No	Yes	No	Yes	Yes	No
9	Are outcomes self-reported?	No	No	No	No	No	No	No
10	Is the conclusion definite?	No	Yes	Yes	Yes	No	Yes	Yes
	Authors' judgement on risk of bias	II C	III B	III B	III B	III C	III B	III B

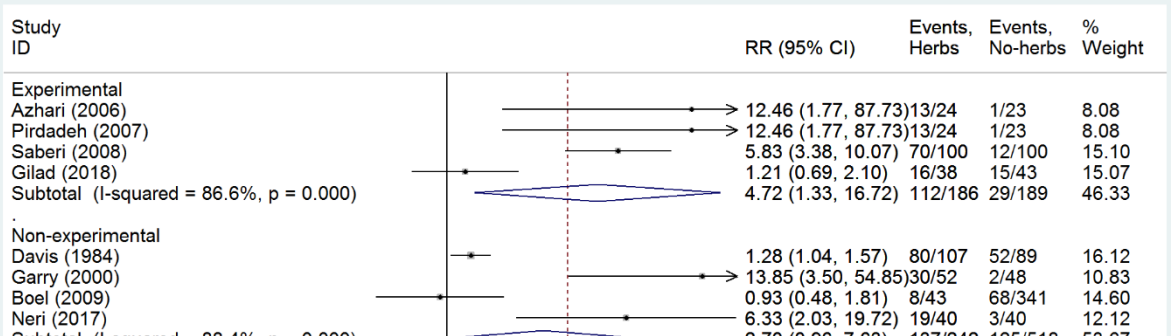
Characteristics of studies in the systematic review, including those excluded during risk of bias assessment

Study	Design and Sample	Setting	Exposure	Outcomes of interest	Limitations/comments	Ratings
Lamadah 2014	A hospital-based quasi-experimental study involving 100 pregnant women who went to the facility to give birth. Only those with cephalic presentation and no contraindication to vaginal delivery were included	Egypt, North Africa	Castor oil vs no treatment taken prior to attending the hospital	Meconium-stained liquor, haemorrhage, Caesarean section, onset of labour in 24 hours	Relatively small sample size; some baseline characteristics are different between groups; possible confounders not accounted for. Very few details regarding the intervention and how the outcomes were obtained has been provided. However, it seems exposure was assessed retrospectively. Unknown dosage.	II C (Excluded)
Gilad 2018	A randomised double blind controlled study involving 80 singleton and post-date (40-42 weeks) pregnant women. Other inclusion criteria were Bishop score ≤7, no uterine contraction or caesarean section.	Israel, Middle-East	60ml of castor oil vs placebo	Caesarean section; meconium-stained liquor, assisted vaginal delivery, onset of labour in 24 hours	Baseline characteristics of the study groups similar, except for age. Modest sample size and involvement of only low-risk population may limit generalization.	Low Risk of Bias
Boel 2009	A historical cohort study that used hospital maternity records (2005-2007) of 612 outpatient pregnant women with a gestation at birth of ≥ 40 weeks.	Thailand, Asia	At least 60ml of castor oil vs no treatment	Haemorrhage, caesarean section, vaginal assisted delivery, onset of labour in 24 hours	Baseline characteristics similar between groups, different places of delivery means different types of delivery care were received; there was no standard measure of outcomes; other possible confounders not controlled; retrospective analysis.	III B
Saberi 2008	A randomised clinical trial conducted with 200 pregnant women with gestational age ≥ 40 weeks.	Iran, Middle-East	60ml of castor oil vs no treatment	Onset of labour in 24 hours	Only abstract available in English, so details of exposure and outcome measurement not available. However, the abstract reports it was an RCT, with a reasonable sample size and strict recruitment criteria.	Not clear
Mabina 1997	A hospital-based prospective cohort of 229 women who went to the facility for delivery. Outcomes were retrieved from hospital records	South Africa	Any herbal medicine, but likely Isihlambezo	Caesarean section, meconium-stained liquor, assisted vaginal delivery, neonatal referral to special care	Recorded baseline characteristics similar between groups, but some key confounders were not measured. Confounders were not controlled; recall bias due to self-reported exposure; unknown dosage.	III B

Azhari 2006	A hospital-based randomised clinical trial of 47 pregnant women with the following characteristics: 19-35 years old, 40-42 gestational weeks, singleton pregnancy, cephalic presentation, Bishop score ≤4, intact membrane regular foetal heart rate, normal foetal movement and estimated foetal weigh of 2.5 to 4kgs	Iran, Middle-East	60cc/ml of castor oil vs no treatment	Onset of labour in 24 hours, meconium-stained liquor,	Baseline characteristics similar between groups; rigorous recruitment process; small sample size; bias due to self-reporting of some outcomes. No clears details of blinding, randomisation and allocation concealment have been provided.	Low Risk of Bias
Simpson 2001	A double-blind hospital-based randomised controlled trial involving 192 pregnant women who booked to birth at a study facility. Criteria for inclusion included being nulliparous with low-risk, healthy pregnancy, fluent in English and a doctor's approval.	Australia	2.4g of Raspberry leaf per day from gestation week 26-30 until delivery.	Caesarean section, haemorrhage, vaginal assisted delivery, neonatal referral to nursey care	Rigorous recruitment process; reasonable statistical power; study groups were comparable; consumption of the tablet was self-reported. Generalisation limited to low-risk nulliparous. It is not known how many were excluded because of language as it was one of the inclusion criteria.	Low Risk of Bias
Garry 2000	A hospital-based quasi-experimental study involving 103 pregnant women with the following characteristics: singleton, gestational age between 40 and 42weeks, Bishop score ≤4 and no uterine contractions.	USA	60ml castor oil vs no treatment	Onset of labour in 24 hours, meconium-stained liquor, caesarean section.	Measured covariates equally distributed in two groups though not all possible confounders were measured. Timing of treatment and how it was administered not indicated and the follow-up details are not clear. Small sample size.	II B
Davis 1984	Retrospective review of records of 196 low-risk pregnant women with uncomplicated medical and obstetric history at an out-of-hospital birthing centre. All women had premature rupture of membrane before the onset of labour.	USA	2oz (60ml) of castor oil vs no treatment	Onset of labour in 24hrs	The baseline characteristics of the two study groups were similar; women who chose to deliver at the birthing centre may be different to those who delivered at the hospital; side effects or safety not assessed; retrospective design, reasonable sample size.	III B

Parsons 1999	A hospital-based retrospective cohort study involving a convenience sample of 108 women who had given birth at the facility. Outcome data and all the data for the control group was retrieved from hospital records.	Australia	Raspberry vs no raspberry	Vaginal assisted delivery, caesarean section	The study and control groups were somehow different; data collection methods were different between the study and control groups; confounders not accounted for; convenience sample; response rate unclear; inconsistent dosage and timing; no details on how the outcomes were measured; women delivered with different providers (private/public) and this was not accounted for. Small sample size.	III C (Excluded)
Neri 2017	A hospital-based case-control study of 80 low-risk pregnant women with the gestational age of 40-41 weeks. The study was implemented over a five-year period (2009-2014)	Italy	60 ml castor oil dissolved in 200 ml of warm water	Caesarean section, neonatal referral to nursey care, haemorrhage, vaginal assisted delivery and onset of labour in 24hrs	Study groups were comparable. Women delivered at different facilities, which may imply different types of care. Small sample size; confounders not adjusted for. Exposure to castor oil self-reported and hence prone to social desirability bias.	III B
Pirdadeh 2007	A randomized controlled clinical trial involving 47 pregnant women with gestational age of 40-42 weeks and no regular uterine contractions.	Iran, Middle-East	60cc of Castor oil	Onset of labour in 24hrs	Only abstract is in English, so limited information could be accessed. Exposure and outcomes were not self-reported. The sample size is small.	Not clear

The use of herbal medicines for induction of labour and onset of labour (by study design)



The use of herbal medicines for induction of labour and the incidence of caesarean section (by type of treatment)

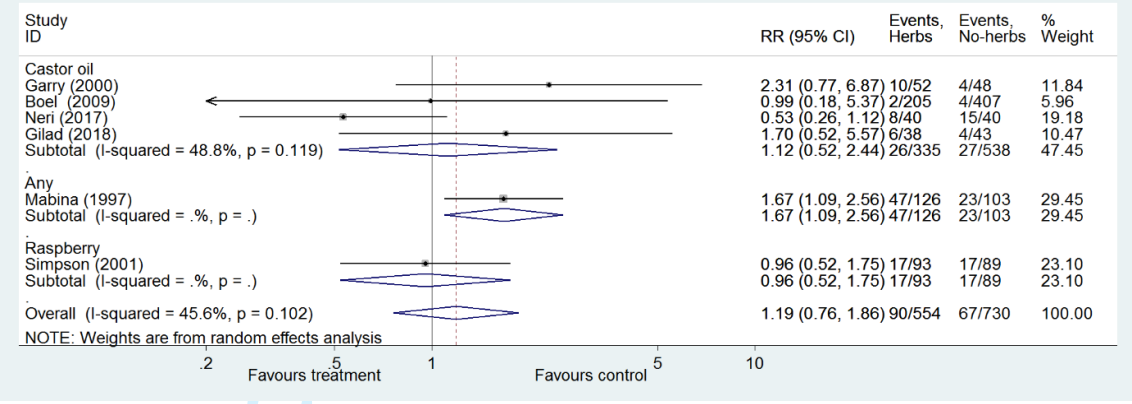
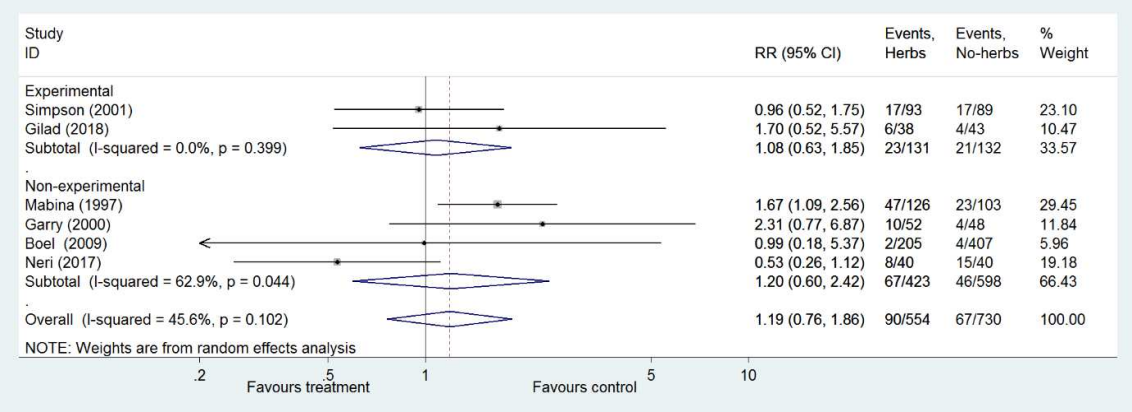
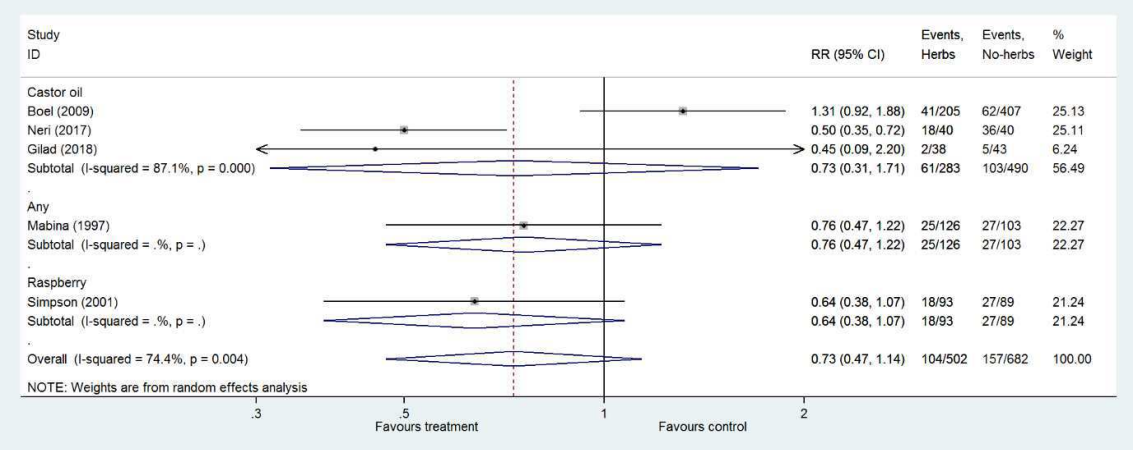


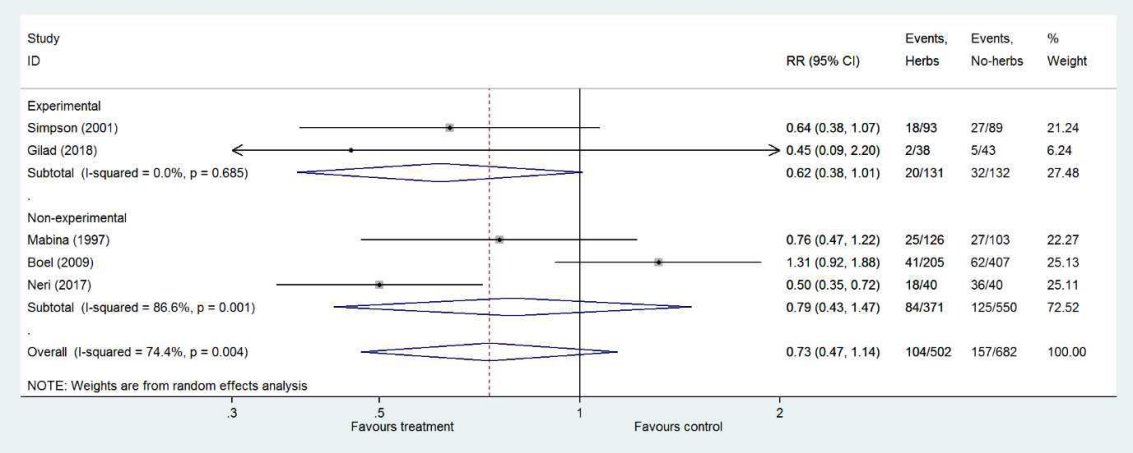
Figure 3: The use of herbal medicines for induction of labour and the incidence of caesarean section (by study design)



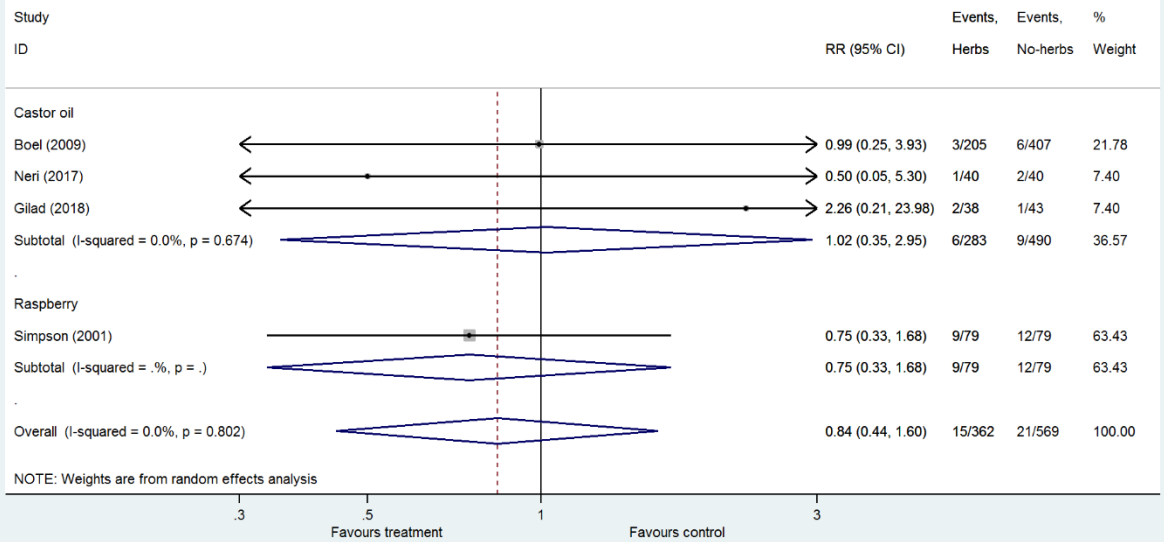
The use of herbal medicines for induction of labour and the incidence of vaginal assisted delivery (by type of treatment)



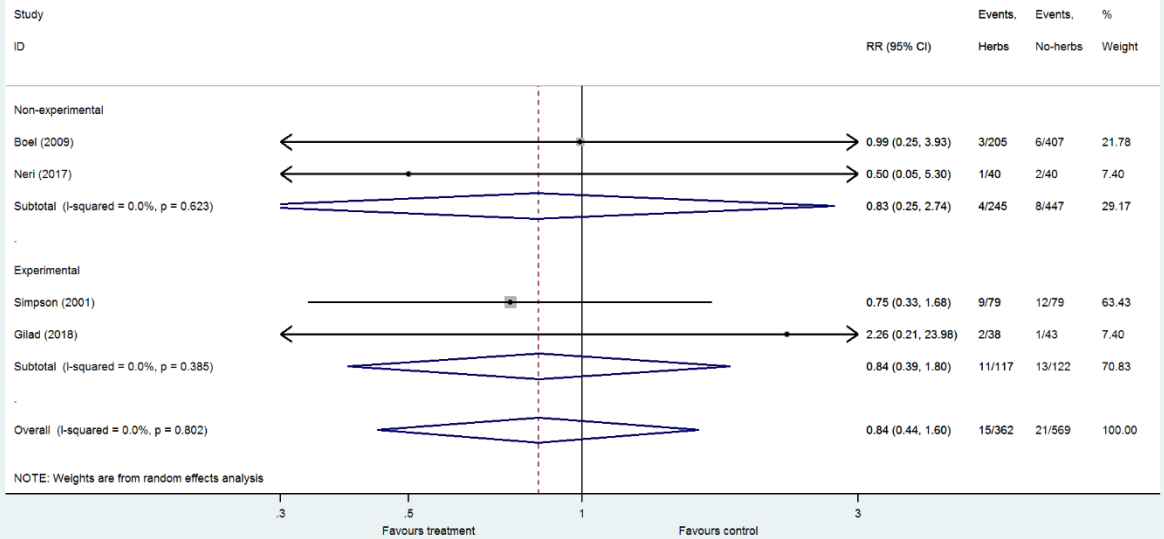
The use of herbal medicines for induction of labour and the incidence of vaginal assisted delivery (by study design)



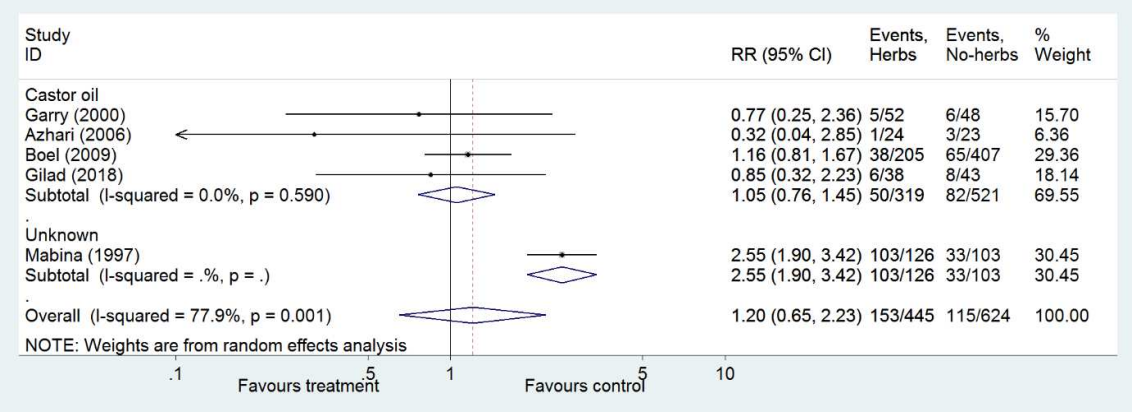
The use of herbal medicines for induction of labour and the incidence of haemorrhage (by type of treatment)



The use of herbal medicines for induction of labour and the incidence of haemorrhage (by study design)



The use of herbal medicines for induction of labour and the incidence of meconium-stained liquor (by type of treatment)



The use of herbal medicines for induction of labour and the incidence of meconium-stained liquor (by study design)