Vitex agnus-castus in premenstrual syndrome: A meta-analysis of double-blind randomised controlled trials

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ABSTRACT

Although chasteberry (Vitex agnus-castus, VAC) has been studied in several clinical trials and available as medicine for the alleviation of premenstrual syndrome (PMS) symptoms, the efficacy of properly characterised preparations has not been assessed in meta-analyses. The aim of our work was to evaluate the efficacy of VAC in PMS.

The meta-analysis was performed following the PRISMA guidelines using the PICOS format, taking into account the CONSORT recommendations. PubMed, Embase, the Cochrane Central Register of Controlled Trials and Web of Science were searched for studies on VAC. The analysis assessed the efficacy of properly characterised products VAC compared to a placebo for the alleviation of PMS symptoms in terms of responder rate, considering the decrease of Total Symptom Score or PMS Diary score. The random effects model was used to calculate summary relative risk (RR) and 95% confidence interval (CI). Only those randomised, double-blind, placebo-controlled trials were included that fulfilled the criteria of the CONSORT recommendations aiming at the proper characterization of herbal products.

Out of the 21 clinical trials, three studies (520 females) fulfilled the inclusion criteria, comparing the efficacy of special extracts Ze 440 and BNO 1095 to a placebo for the treatment of PMS. VAC preparations were confirmed to be effective in the reduction of PMS symptoms: women taking VAC were 2.57 (95% CI 1.52–4.35) times more likely to experience a remission in their symptoms compared to those taking the placebo. Although several clinical trials have been carried out with VAC, the majority of the studies cannot be used as evidence for efficacy due to incomplete reporting, especially concerning the description of the used medication. More trials following the CONSORT recommendations are needed to assess the efficacy of VAC extracts.

1. Background

Premenstrual syndrome (PMS), characterised by significant distress or impaired functioning, includes behavioural, mood and physical symptoms that occur in the luteal phase of the menstrual cycle and remit with the menstrual flow. [1] Although PMS is related to and similar to premenstrual dysphoric disorder (PMDD), there are well-defined differences between these two states. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), characterises PMDD by mood lability, irritability, dysphoria, and anxiety symptoms that occur during the premenstrual phase of the cycle and remit around the onset of menses or shortly thereafter. [2] According to the diagnostic criteria of DSM-5, in the majority of menstrual cycles, at least five symptoms must be present, including at least one of the following axial symptoms:

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marked affective lability; marked irritability or anger or increased interpersonal conflicts; marked depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension, and/or feelings of being keyed up or on edge. In case of PMS, a minimum of five symptoms is not required, and there is no stipulation for affective symptoms. [2] PMS is considered to be less severe than PMDD. While twelve-month prevalence of PMDD is 1.8–5.8% within the population of menstruating women, PMS affects approximately 20–25% of women. Moreover, based on epidemiological surveys, it is estimated that 75% of women with regular menstrual cycles experience some PMS symptoms. [3] PMS is marked by mild physical symptoms and minor mood changes (e.g: abdominal bloating, swelling of the extremities, weight gain, breast pain, joint or muscle pain, sleep disturbances, changes in appetite, depressed mood, anger, irritability, confusion, loss of control, and difficulty in concentrating). [4]

The aetiology of PMS is still unexplored. The great diversity of symptoms corresponds with the wide variety of medicines used to relieve subjective complaints. The most frequently prescribed pharmacotherapies for PMS are selective serotonin reuptake inhibitors, hormones (oestradiol and progesterone) or hormone analogues (GnRH analogues). [5] However, apart from these, there are other approved medicines used in treating of PMS. One of these is the extract of fruits of *Vitex agnus-castus* L., Lamiaceae (VAC).

Although the pharmacology of VAC has been studied extensively, the active components have not been unequivocally identified. Nevertheless, there is a consensus that the core of the effect is the decrease of prolactin secretion by dopamine receptor agonism, [6–9] which is linked to the reduction of mastalgia. [10] Furthermore, the activity on opioid receptors may also be related to the relief of PMS symptoms. [11,12] The clinical efficacy of different VAC products has been studied, as a result of which several medicines have been approved in different European countries. In 2011, the European Medicines Agency published a monograph acknowledging the well-established use of a special extract of VAC for the treatment of PMS.

Although several trials have been undertaken to study the clinical efficacy of VAC for PMS, the overall positive effects regarding the efficacy were not always reflected in therapeutic guidelines. The (since retracted) clinical guidelines of The American Congress of Obstetricians and Gynecologists (2000) and the Association of Women's Health, Obstetric and Neonatal Nurses (2003) did not mention VAC among the proposed therapeutic modalities for PMS. [13] According to the Guide of the Association of Reproductive Health Professionals (2008), VAC (30–40 mg) is a suggested therapeutic option for mild to moderate PMS. [14] The second consensus meeting of the International Society for Premenstrual Disorders in 2011 concluded that "encouraging results exist for chasteberry for decreasing premenstrual emotional and physical symptoms of PMDs compared to placebo" without any further recommendation. [15] The therapeutic guidelines of the Royal College of Obstetricians and Gynaecologists [16] classifies VAC as a complementary therapy. The conclusion of the guideline was based on one meta-analysis [17] and 7 randomised clinical trials. [18–24] The overall conclusion was that" studies have shown a dose dependent treatment response; however, due to the variability in quality and content of preparations a dosage range to treat PMS cannot be recommended". [16] VAC was not mentioned in the decision-making algorithm of this guideline. The National Association for Premenstrual Syndrome guidelines offer a similar conclusions. [25] The regularly updated UpToDate® guideline qualified VAC as ineffective because it was claimed that there was inconsistent evidence regarding superior efficacy when compared with a placebo, without referring to any primary clinical literature or meta-analysis. [26] The only guideline in which VAC was mentioned as a first-line treatment was issued in Switzerland. [27]

Previous meta-analyses on the efficacy of chasteberry did not focus on the proper characterization of the applied products in the included studies. The goal of our work was to perform a meta-analysis of randomised, placebo-controlled trials using products with sufficiently

characterised composition to provide reliable conclusions on the clinical efficacy of VAC for PMS. We used the PICOS (problem, intervention, comparison, outcome, study design) format for our study.

2. Methods

We included trials designed to analyse the efficacy of VAC preparations in reducing PMS symptoms. Only trials with sufficiently characterised VAC preparations (i.e., minimum criteria: unequivocal plant name, extracting solvent and drug-extract ratio) were included. Trials that studied homeopathic preparations of VAC or VAC in combination with other treatments were excluded. Only placebo-controlled, double-blind, randomised trials were included. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) a priori (registration number CRD42017065047).

The following electronic databases were searched by two researchers (MM and DC, both pharmacists) without language limitation: PubMed, Embase, the Cochrane Central Register of Controlled Trials and Web of Science (last search: 25. 02. 2018). The search strategy was developed combining terms related to any study among females with PMS and VAC restricted to studies on humans (**Appendix S1**). The PICOS approach was used to answer our clinical questions and applied as follows: P: premenstrual syndrome, I: chasteberry, C: placebo, O: responder rate, S: randomised, placebo-controlled trials. The study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. [40] For the purpose of transparency, this meta-analysis was only based on publicly available data, authors of included articles and manufacturers were not contacted to obtain additional information.

Potentially relevant studies were independently screened by two reviewers. Studies were excluded if titles and abstracts clearly did not meet eligibility criteria. Discrepancies were resolved by dialogue and if necessary, by appeal to a third reviewer. Using a data extraction form, two reviewers extracted data independently. Differences in extracted data were discussed with the professional statistician. The following data items were extracted from the papers that were included: characteristics of the study design, characteristics of the patient population (e.g. age groups), method of diagnosis, sample size, intervention details, duration of the study, outcome measures, and overall results.

The random effects model [41] was used to calculate pooled relative risk (RR) and 95% confidence interval (CI) for the VAC vs. placebo analysis. Summarised RRs were estimated using the average of the natural logarithm of the RRs of each study weighted by the inverse of its variance and then unweighted by a variance component that corresponded to the amount of heterogeneity in the analysis. A two-tailed $p < 0.05$ was considered statistically significant.

For the test of heterogeneity across studies, we used Higgins' I,[2,42] which measured the percentage of total variation across studies. I^2 was calculated as follows:

$$I^2 = 100\% \times (Q - df) / Q$$

where Q was Cochran's heterogeneity statistic, [43] and df was the degree of freedom. Negative values of I^2 were set to zero so that I^2 was between 0% (no observed heterogeneity) and 100% (maximal heterogeneity). Although thresholds for the interpretation of I^2 can be misleading, a rough guide to interpreting its value was as follows [44]: low (0–40%), moderate (30–60%), substantial (50–90%) and considerable (75–100%).

Two reviewers independently rated the studies according to the Jadad score. [45] Only published data (including supplementary data) were evaluated. To ascertain the validity of eligible randomised trials, two reviewers independently determined selection bias, performance bias, detection bias, attrition bias, and reporting bias, according to the Cochrane risk of bias criteria. [46] We intended to assess the publication

Table 1

Characteristics of placebo-controlled randomised clinical trials included in the final analysis.

First author (year) language	Drug type, dose	Country, patient number	Jaded scale	Patients age (inclusion criterion)	Method of diagnosis	Outcome measures	Efficacy
He (2009) English	BNO1095 4mg	China, 208	4	women aged ≥ 18 years and < 45	DSM-IV	PMTS, PMSD	minimum 60% decrease in PMSD score
Schellenberg (2001) English	ZE 440 20mg	Germany, 170	4	women aged ≥ 18 years	DSM-III-R	VAS, CGI	minimum 50% decrease in TSS
Schellenberg (2012) English*	ZE 440 8, 20 and 30 mg	Germany, 142	4	women aged ≥ 18 years and < 45	DSM-III-R	VAS, TSS	minimum 50% decrease in TSS

CGI: Clinical Global Impression, DSM: Diagnostic and Statistical Manual of Mental Disorders, PMSD: Premenstrual Symptom Diary, PMTS: Premenstrual Tension Syndrom Self-rating Scale, TSS: Total Symptom Score.

bias with funnel plot techniques, Begg's rank test [47] and Egger's regression test, [48] as appropriate given the known limitations of these methods. All the statistical analyses were conducted using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

3. Results

3.1. Selection of studies

In total 205 records were collected, and according to the PRISMA flow diagram presented in **Appendix S2**, 21 full-text articles were assessed further for eligibility for analysis. Of these 184 studies were excluded as not being clinical studies. The most frequent reason for excluding studies from the remaining articles was the use of an undefined VAC product (**Table S1**). Finally, three placebo-controlled, double-blind randomised trials were included in the qualitative analysis involving 520 females (Table 1). [21,23,36] All the articles were written in English.

Using the binarised data on efficacy (based on the measure of scale score reduction), risk ratio (RR) was used as an effect size. The efficacy of the treatment is summarised in Table 2. Two studies assessed the efficacy of the special extract Ze 440. [21,36] This was prepared from VAC fruit using 60% ethanol (m/m) as the extracting solvent, and standardised for casticin. Calculating with the drug-extract ratio of 6–12:1, the daily 20 mg dose of the extract corresponded to 120–240 mg of plant material. In one further study, [23] BNO 1095 special extract was used. This was extracted from VAC fruits using 70% ethanol, with a daily dose of 4 mg corresponding to 40 mg of plant material.

In the studies using Ze 440, the efficacy was determined by the participants' assessment using the decrease of Total Symptom Score (TSS; the individual had to assess the intensity of each of the 6 items: irritability, mood alteration, anger, headache, bloating, and breast fullness on a visual analogue scale (VAS). Treatment responders were defined by the authors of the studies as those showing a decrease in TSS

Table 2

Distribution of efficacy of VAC compared to a placebo in the treatment of PMS.

Author, year	VAC			Placebo		
	N	Efficacy	Inefficacy	N	Efficacy	Inefficacy
He (2009)	104	83 (80%)	21	104	52 (50%)	52
Schellenberg (2001)	86	45 (52%)	41	84	20 (24%)	64
Schellenberg (2012) (8 mg)	36	5 (14%)	31	35	4 (11%)	31
Schellenberg (2012) (20 mg)	35	28 (81%)	7	35	4 (11%)	31
Schellenberg (2012) (30 mg)	36	22 (61%)	14	35	4 (11%)	31

of ≥ 50%. [21,36] In the study on BNO 1095, the Premenstrual Syndrome Diary (PMSD) was used as the measure of efficacy. Participants completed a questionnaire using a 4-point rating scale from absent (0) to severe (3) consisting of 17 items with factor scales measuring negative affect (mood swings, depression–sadness, tension–irritability, anxiety–nervousness, anger–aggression–short temper and crying spells), water retention (swelling of extremities, tenderness–fullness of breasts, abdominal bloating, headache and fatigue), food (increased or decreased appetite, cravings for sweets or salts) and pain (lower abdominal cramping, generalised aches and pains and low backache) and insomnia. [49] In this trial, clinical efficacy was defined by the authors of the studies as ≥ 60% improvement of total scores for PMSD. [23]

### 3.2. Efficacy: quantitative analyses of results

Analyses were carried out with the binarised results on efficacy, because the data on TSS or PMSD scores were incomplete (missing correlation coefficients) and therefore could not be used as a basis for statistical analyses. The efficacy of treatment was assessed based on the ratios of responders, as determined by the authors of the articles included (no less than 60% improvement in PMSD in the case of BNO 1095 extract [23] and no less than 50% improvement in TSS for Ze 440 extract [21,36]).

The pooled logRR for the whole dataset was 0.94 (*p*-value: 0.0004), and because of considerable heterogeneity ($Q = 15.32$; *df*: 4; $p = 0.004$; $I^2 = 74\%$), the random-effect model (using the DerSimonian and Laird method) was applied (Fig. 1–4).

The results of the primary analysis suggested that VAC was effective in the reduction of PMS symptoms: women taking VAC were more than two times (RR: 2.57, 95% CI 1.52–4.35) (Fig. 1) as likely to experience a remission in their symptoms compared to those taking the placebo. The subgroup analysis of the two different products support the superiority over placebo (for BNO 1095 RR 1.60, 95% CI 1.29–1.98; for Ze 440 RR 3.19, 95% CI 1.58–6.44) (Fig. 2). When comparing the lower with higher the doses (below or above 15 mg/day), higher doses seemed to be more effective (RR 3.96 (95% CI 1.79–8.78) than lower (RR 1.58 (95% CI 1.28–1.96) (Fig. 3). When analysing only the accepted therapeutic doses of the extracts (4 mg for BNO 1095 and 20 mg for Ze 440), similar superiority was observed over placebo (RR 2.45, 95% CI 1.36–4.43) as in the whole dataset (Fig. 4). Since the number of included studies and involved patients were relatively low, it was not possible to obtain statistical results with narrower CI.

3.3. Methodological quality and risk of bias

On the Jadad scale, all the 3 trials included were rated with a score of 4 by both reviewers. Risk of bias was low or unclear (Fig. 1). Overall, a low risk of bias was identified for attrition and reporting (except in one study). Selection, performance and detection bias were unclear in all cases due to inadequate reporting, except in two trials where random sequence generation was described appropriately to refer to a low risk of bias. [21,36] Publication bias was not assessed because the
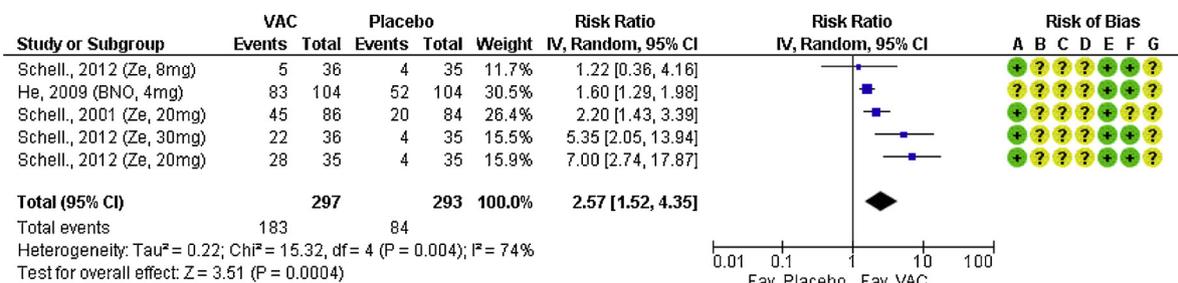
Fig. 1. Forest plot of the whole dataset included in the final analysis. Efficacy of VAC versus a placebo for PMS was compared in a random effects meta-analysis, and the risk of bia ⊕ low risk of bias ?: unclear risk of bias) is also presented. Risk of bias legend: (A) Random sequence generation (selection bias). (B) Allocation concealment (selection bias). (C) Blinding of participants and personnel (performance bias). (D) Blinding of outcome assessment (detection bias). (E) Incomplete outcome data (attrition bias). (F) Selective reporting (reporting bias) (G) Other bias.

number of trials included was too low to properly assess a funnel plot or more advanced regression-based assessments.

The descriptors of item 4A-B of the supplemented CONSORT statement [29] ensure the unequivocal identification of clinically studied herbal products. This item consists of a checklist with 7 questions. Although none of the studies included in our meta-analysis contained information concerning all of these questions, the identity and posology of the study medicines could be determined univocally.

4. Discussion

The meta-analysis of the three clinical trials demonstrated the superiority of VAC over placebo in the treatment of PMS [RR 2.57, 95% CI (1.25–4.35)]. All the subgroup analyses resulted in similar conclusions. Higher doses compared to lower doses (RR 2.57 vs RR 1.58) and Ze 440 compared to BNO 1095 (RR 3.19 vs- RR 1.60) were more effective; however, all the subgroups were more effective than placebo. In this meta-analysis, only double-blind, placebo-controlled, randomised trials were included with Jadad scores 4 and fulfilling the criteria of the CONSORT guideline concerning the proper characterization of herbal preparations [29]. The main strength of this analysis over previous ones

[17,28] was that only trials assessing sufficiently characterised VAC-products were analysed. In the cases of synthetic drugs, unequivocal posology is essential for an unambiguous conclusion regarding efficacy. In case of VAC, this was the first meta-analysis that set similarly rigorous rules.

One of the previous papers included several trials that did not characterise the studied medication properly (i.e., equivocal herbal species, extracting solvent and unknown drug-extract ratios), [28] the other article presents a meta-analysis based on two trials, one of which was excluded by us due to improper reporting of the analysed herbal medicinal product. [17] Van Die et al included 8 randomised, controlled trials on the efficacy of VAC for PMS. [17] However, only 2 of these [23,24] were further analysed in a forest plot analysis. In these two trials 2 different products were studied. Verkaik et al included 14 randomised controlled trials, all of which were subjected to forest plot analyses. [28] Although the Consolidated Standards of Reporting Trials (CONSORT) Statement was supplemented with an item containing a checklist for the clear and complete description of herbal intervention in 2006, [29] the majority of the trials are not in line with these recommendations. The trials analysed by Verkaik et al [19,21–24,30–39] represented several different (in many cases unspecified) extracts with different posologies
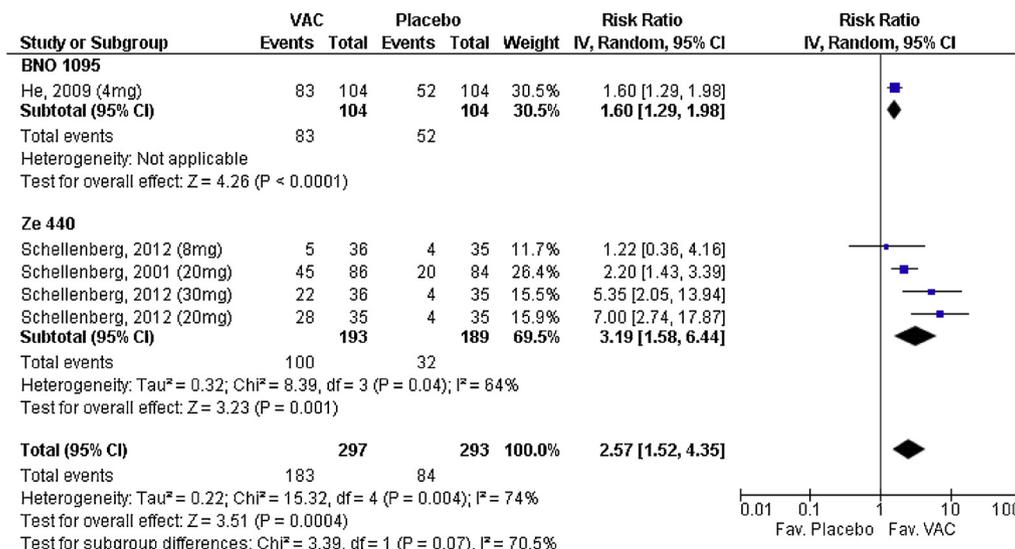

Fig. 2. Forest plot of studies carried out with BNO 1095 and Ze 440.
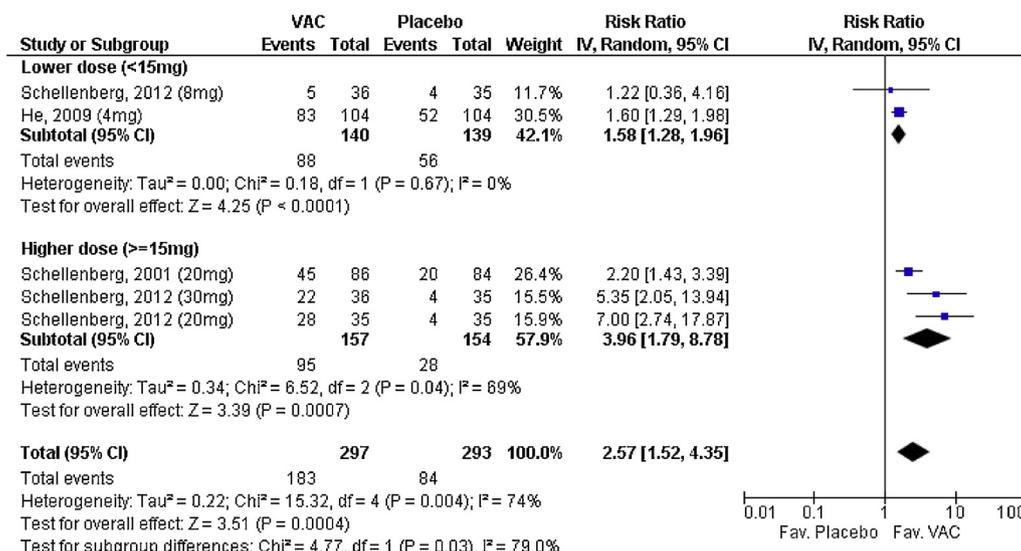
Fig. 3. Forest plot of studies carried out with lower (< 15 mg/day) or higher (≥ 15 mg/day) doses of VAC extracts.

and comparators, which is a main limitation of that meta-analysis. Although this shortcoming could obscure a therapeutic effect, Verkaik et al. found a large pooled effect of VAC in placebo-controlled trials and also in comparison to vitamins, supplements or other herbal comparators.

One of the limitations of our meta-analysis was the low number of available appropriate trials. In addition, data gained with different posologies of two different extracts (4 mg/day for BNO 1095 and 8, 20 and 30 mg for Ze 440) were pooled and analysed together because of the limited number of clinical trials. A further limitation was that both trials involving Ze 440 were conducted in Germany, whereas BNO 1095 was only studied in China. Two studies used the TSS score and one the PMSD score to assess efficacy and the threshold of efficacy was also different (with at least a 50% and 60% decrease, respectively).

VAC is the only medicinal plant that is used as an active component of medicines in treating PMS. Although several clinical trials have assessed the efficacy of VAC and VAC-containing medicines have been approved in a number of countries, this is not always reflected in therapeutic guidelines. Here, we presented a meta-analysis that assessed only properly described products, which made the results more reliable. A meta-analysis of the whole set of trials confirmed the superiority of VAC over a placebo (RR 2.57).

In the case of herbal medicines, the reliability and value of meta-analyses largely depends on the uniformity of the products used in the assessed clinical trials. Synthetic medicines can be sufficiently characterised by the chemical names of the pharmacons and their dosage. However, in the case of herbal products, more data are needed. Beyond the binomial Latin name of the plant and the plant part used, the extracting solvent and the drug-extract ratio are part of the essential dataset. Any of these factors may have a major influence on the composition of the final product, and it is obvious that extracts with different chemical compositions may have remarkably different bioactivities.

Based on the results obtained with products of different compositions it is not acceptable to draw a generalised conclusion regarding the efficacy of a certain plant. In the case of herbal products only results deriving from studies using chemically identical medicines should be analysed together. Unfortunately several clinical trials do not follow the CONSORT recommendations for proper reporting of studies of herbal interventions (item 4 of the checklist). [29] And what is more important, authors of certain meta-analyses also ignore the importance of these recommendations, which results in conclusions that cannot be considered as basis for evidence-based decision-making.

5. Conclusion

This meta-analysis is an assessment of clinical trials carried out with well-defined VAC extract-containing medicines. The uniformity of indication and endpoints analysed renders the results of the trials included comparable. The remission of symptoms was 2.57 times more likely in those taking VAC than in those who received a placebo. These results demonstrated the superiority of the products assessed over a placebo and may be a point of reference for a more established evaluation of the therapeutic value of VAC. However, the number of studies and enrolled patients is limited; therefore, our results should be considered preliminary, and it should be confirmed by further clinical trials on this topic as they become available. More careful design of clinical trials would result in a higher number of studies that can be included in meta-analyses, and bearing in mind the importance of proper characterization of the studied products would result in more reliable meta-analyses.

Authors' contribution

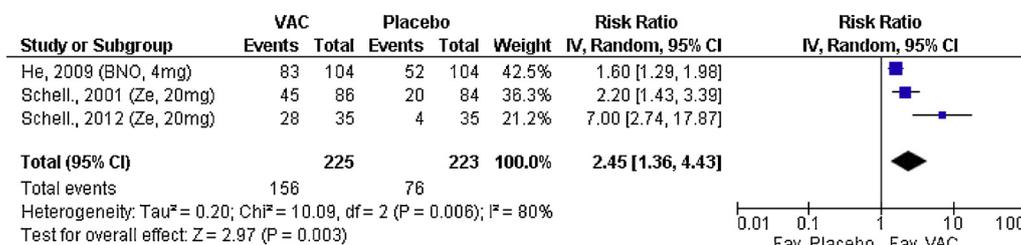All authors had full access to all of the data and can take

Fig. 4. Forest plot of studies carried out with officially accepted therapeutic doses of BNO 1095 and Ze 440.

responsibility for the integrity of the data and accuracy of the data analysis. D.C., M.M., T.L., A.V., P.H. and B.T. contributed to the study concept and design. D.C., M.M. and B.T. wrote the protocol. M.M., R.B., R.V., A.S. and D.C. developed the search strategy. D.C., M.M., Z.G., P.C. and K.M. acquired the data. T.L., Z.G., M.M., I.R. and D.C. contributed to the analysis and interpretation of the data. D.C., M.M. and T.L. developed the first draft of the manuscript, P.H. and Z.G. revised it and M.M., T.L., P.H., R.B., R.V., Z.G., P.C., B.T., A.V., K.M., I.R., A.S. and D.C. approved the final version.

Declaration of Competing Interest

All the authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.08.024.

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