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A systematic review and meta-analysis on the use of *Hypericum perforatum* (St. John's Wort) for pain conditions in dental practice

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Background: ***Hypericum perforatum*** **(St. John's Wort) has been used for a variety of medicinal indications. Most recent research has focussed on its use in herbal form for depression, but its claimed analgesic and anti-inflammatory properties in homeopathic form have also led to a number of studies in patients with acute pain conditions. This systematic review overviews the literature on the use of St. John's Wort for pain conditions in homeopathic dental practice.**
Material and methods: **PubMed, EMBASE, AMED, CAMbase and the electronic archives of Thieme Publishers were searched with the search terms "*(Hypericum OR St. Johns Wort) AND pain*". We reviewed and meta-analysed the evidence on *Hypericum* in pain after tooth extraction was carried out.**
Results: **Twenty one relevant articles were found: four described general recommendations, three basic research, six reported studies in dental care and eight were expert opinions or case reports. Four studies were eligible for the meta-analysis. There was marked high heterogeneity in the effects pain (Chi-Squared = 26.46; $I^2 = 0.89$). The overall effect of 0.24 (95% CI: [0.06; 1.03]) favours *Hypericum* but is not statistically significant.**
Conclusion: **Although case reports suggest therapeutic potential of *Hypericum* for pain conditions in dental care, this effect is not currently supported by clinical studies. All studies included in this meta-analysis used *Arnica montana* as well as *Hypericum* the results are more influenced by *Arnica* than *Hypericum*. Further clinical controlled trials of *Hypericum* alone in dental practice should be performed.** *Homeopathy* (2012) **101**, 204–210.

Keywords: *Hypericum perforatum*; Meta-analysis; Systematic review; Dental care; Pain

Background

From the rich diversity of medicinal plants in herbal and homeopathic remedies *Hypericum perforatum* (St. John's Wort) is one of the oldest with a history of more than 2000 years.[1] It is a member of the Guttiferae family, there are about 400 known species of *Hypericum* in Europe, North America, Australia, New Zealand, Eastern Asia and South America. *H. perforatum* grows in sunny locations with well-drained, limey soil mostly at roadsides, slopes, wood borders and stone quarries and reaches a height of 50–100 cm. The bright yellow, star-shaped flowers, often clustered in a trio, have five petals and the leafs contain tiny transparent oil glands resembling perforations containing hypericin. Hippocrates and other classical physicians recommended St. John's Wort for a variety of medicinal indications. For instance, *Pedanius Dioscorides* recommended *H. perforatum* in his "*De materia medica*" for the healing of burns or sciatic pain syndrome.[2]

In the homeopathic tradition, in 1887 W. J. Guernsey described the use of *Hypericum* in a single case in his "*Keynotes of the Materia Medica*" as follows[3]: "*A boy, nine, was bitten by a pet rat on the first finger of the left hand. Nothing particular was observed at the time, but some time after, he*

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became ill, and when Dr. Guernsey was called his state was alarming. The boy could talk with great difficulty; teeth firmly locked; conscious; neck so stiff the head could scarcely be moved. There was more tenderness about the wound than the appearance would indicate. Hence Hyp(ericum) was preferred to Led(um). It was given (8 p.m.) in the 500th, dissolved in water, at first every fifteen minutes; later every two hours. At 3 a.m. there was improvement, he fell asleep, and the next morning was practically convalescent.".

Since then several clinical studies have examined the use of *Hypericum* in dental conditions (see Table 1).[4–7]

A recent comprehensive literature review of case reports of homeopathic medicines in dental care found several remarks on the use of *Hypericum* in dental practice particularly for dental pain.[8] However, less is known about its use in primary care[9] and Levenson[10] suggested that physicians need to increase their knowledge of Complementary and Alternative Medicine (CAM) treatments. CAM remedies are often only discussed with respect to their potential risks, adverse effects and drug interactions[11] but not with respect to potential benefit in clinical practice.

No systematic review has so far investigated *H. perforatum* for pain reduction in dental care. The objective of this overview is to systematically summarize and meta-analyse the relevant literature on the use of *H. perforatum* as a sole intervention as well as part of a complex homeopathic intervention for pain conditions in homeopathic dental practice.

Material and methods

Search strategy

The following electronic databases were used to find articles on *H. perforatum* in dentistry: PubMed, EMBASE, AMED, CAMbase[12] and the electronic archives of the journals "*Zeitschrift für klassische Homöopathie*" and "*Allgemeine Homöopathische Zeitung (Erfahrungsschatz Homöopathie)*". Each database was searched from its inception until February 2010.

We applied two search strategies

(1) We collected relevant articles on basic research on *H. perforatum* and pain related outcome. The search terms for pain related articles on *H. perforatum* were "*(Hypericum OR St. Johns Wort) AND pain*" and their translations to German and French.
(2) Articles in which the application of *H. perforatum* in dental care was described in clinical studies, case reports or expert opinions were identified. To retrieve evidence on the use of *H. perforatum* in dental care the search terms were "*(Hypericum OR St. Johns Wort) AND (dental OR dentistry)*" and their translations to German and French. Finally, we searched our CAM library and our literature review of case reports of homeopathic remedies in dental care[8] for literature not listed in the above mentioned databases. Duplicated were identified and only the original study was included if it fulfilled the inclusion criteria. All articles were read fully and their reference lists were checked for further relevant publications. The search was performed between October 2009 and February 2010.

The articles found were heterogeneous; including a variety of perspectives. We classified them into (a) studies and (b) single case reports and expert opinions both with respect to indication, drug concentration/potency, main results and if applicable the number of patients involved. Only RCTs were included in the meta-analysis. Expert opinions were collected but were not used for the meta-analysis. The reporting of the results adhered, if possible and appropriate, to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).[13]

Statistical analysis

In addition we carried out a meta-analysis on the effects of *Hypericum* in pain after tooth extraction. When a trial was found to be eligible, data were extracted and entered into a data form and converted into log-Odds-Ratios (Log-OR) and their standard errors using the standard formulas given in Borenstein et al.[14] by using Review-Manager Version 5. A Log-OR < 1 indicated superiority of *Hypericum* while a Log-OR > 1 indicated superiority of the control condition. Heterogeneity between trials was assessed by standard Chi-Square−tests and the I^2-coefficient measuring the percentage of total variation across studies due to true heterogeneity rather than chance. Overall estimates of the treatment effect were obtained from random effects meta-analysis. Results were displayed using a forest plot. Due to the small number of eligible studies further analysis by means of meta-regression was omitted.

Quality assessment

Each study was rated according to an adapted version of the Quality Assessment Tool for Quantitative Studies, developed by the Effective Public Health Practice Project as a tool for knowledge synthesis.[15] This instrument provides a standardized means to assess study quality and develop recommendations for study findings.

Rating included (A) selection bias, (B) study design, (C) confounders, (D) blinding, (E) data collection methods, (F) withdrawals and dropouts, (G) intervention integrity, and (H) appropriateness of analysis. A global rating of the study as 'strong' was obtained if there are no WEAK ratings. In the case of one WEAK rating, the study quality is considered to be 'moderate and in cases of two or more WEAK ratings the study is classified as 'weak''. Both data extraction and quality assessment was cross-checked by an independent rater. In case of disagreement consensus between the raters was obtained.

Results

We found a total of 49 articles (38 in PubMed, EMBASE, AMED and CAMbase). After removing the duplicates (n = 12) and excluding descriptive literature and popular articles (n = 16), we identified a total of 21 relevant articles. Of those, four articles described general recommendations on the use of homeopathically diluted

Table 1 Overview on indications, setting, study type and outcome parameters of the studies on the application of *Hypericum* in dental care.

Authors	*Year*	*Indication*	*Number of individuals*	*Type of study/article*	*Drug concentration / potency*	*Main results*
Bendre et al.	1980	Post extraction pain and swelling	*N* = 200 (150 verum and 50 placebo)	Randomized Controlled Trial (verum/placebo)	4 globuli of *Arnica*/*Hypericum* directly after tooth extraction and 15 min after	93% of patients showed significant improvements in pain relief and swelling after 48 h
Albertini et al.	1984	dental neuropathic pain	*N* = 60 (2x30) patients	Randomized clinical trial(verum/placebo)	4+4 granula of *Arnica*/*Hypericum* directly after the visit and for 2 days	Significant improvements in pain reduction after Day 2
Lökken et al.	1995	Postoperative pain and other inflammatory events after bilateral oral surgery	*N* = 24 (2x12) patients	Randomized Controlled Trial (verum/placebo)	3 globuli of Arnica/*Hypericum* D30 3 h after tooth extraction and 2 doses before bedtime and the morning after	No significant results for pain relief, swelling and postoperative bleeding but treatment tended to improve the ability to open mouth.
Rafai et al	2004	Trismus and postoperative pain after third molar surgery	*N* = 41 (21 verum and 20 placebo) patients	Randomized Controlled Trial (verum/placebo)	3+3 globuli of *Arnica*/*Hypericum* D30 before surgery and continued for 5 postoperative days	No significant results for reduction of trismus and pain relief.
Studies not included in meta-analysis						
Mathie et al.	2007	Systematic recording of practice data in dental homeopathy	*N* = 726 patients	Multi-practitioner pilot study	*Hypericum* was the fifth often prescribed homeopathic drug (*N* = 30) mainly in combination with Arnica for postsurgery pain (*N* = 23). In 80% of the cases, *Hypericum* was rated to be effective	
Sardella et al.	2008	Intensity of burning pain in patients with Burning mouth syndrome	*N* = 39 patients	Randomized Controlled Trial (verum/placebo)	300-mg capsules containing *H. perforatum* extract (hypericin 0.31% and hyperforin 3.0%) three times a day for 12 weeks	No significant pain relief, while number of sites with reported burning sensation was reduced significantly.

Hypericum in pain and three articles reported basic research on *Hypericum* in pain.

Six articles reported studies of homeopathic *Hypericum* in dental care and eight articles gave expert opinions, recommendations and case reports on the use of homeopathic *Hypericum* in dental care. Four studies were eligible for inclusion into the meta-analysis (See Figure 1 for the complete inclusion process).

Expert opinions, recommendations and case reports on homeopathic *Hypericum* in dental care

Before examining the results of the clinical studies of *Hypericum* in dental care we will review expert opinions, recommendations and case reports extracted from eight articles in our literature search. In 1953 Wicht[16] proposed the use of *Hypericum* D3 for wound healing and tooth hypersensibility. In 1976, Steinlechner[17] recommended *Hypericum* C5−C9 for hemorrhagic diathesis, wound healing and dry socket. He also proposed the use of wound tamponades with *Hypericum* oil. A subsequent article by the same author focused on the use of homeopathic *Hypericum* for acute pain conditions, stabbing pain and neuralgic pain after tooth extraction without specifying the dilution.[18] In 1978 Raspe described the prophylactic use of *Hypericum* D12 before and after tooth extraction.[19] Two years later, Vogel described the use of homeopathic *Hypericum* in traumatic nerve injury after operation, paresthesia and anesthesia in the trigeminal nerve distribution, without specifying the dilution.[20] Similar medical conditions were described by Stay in 1996: she recommended *Hypericum* in injuries to nerves as in deep cavities and for pain control after major dental treatment.[21] Two other articles make similar recommendations: Bhat[22] recommends *Hypericum* for neuralgic pain after tooth extraction and Freihöfer[23] for acute pain after root canal treatment or tooth extraction.

Studies on the use of *Hypericum* in dental practice

A recent study by Sardella et al. investigated the intensity of burning pain in 39 patients with burning mouth syndrome in a randomized clinical controlled trial of herbal capsules containing *H. perforatum* extract 300 mg (hypericin 0.31% and hyperforin 3.0%) three times a day for 12 weeks.[24] There were no significant between group differences in pain relief, although the number of sites with reported burning sensation was reduced significantly.

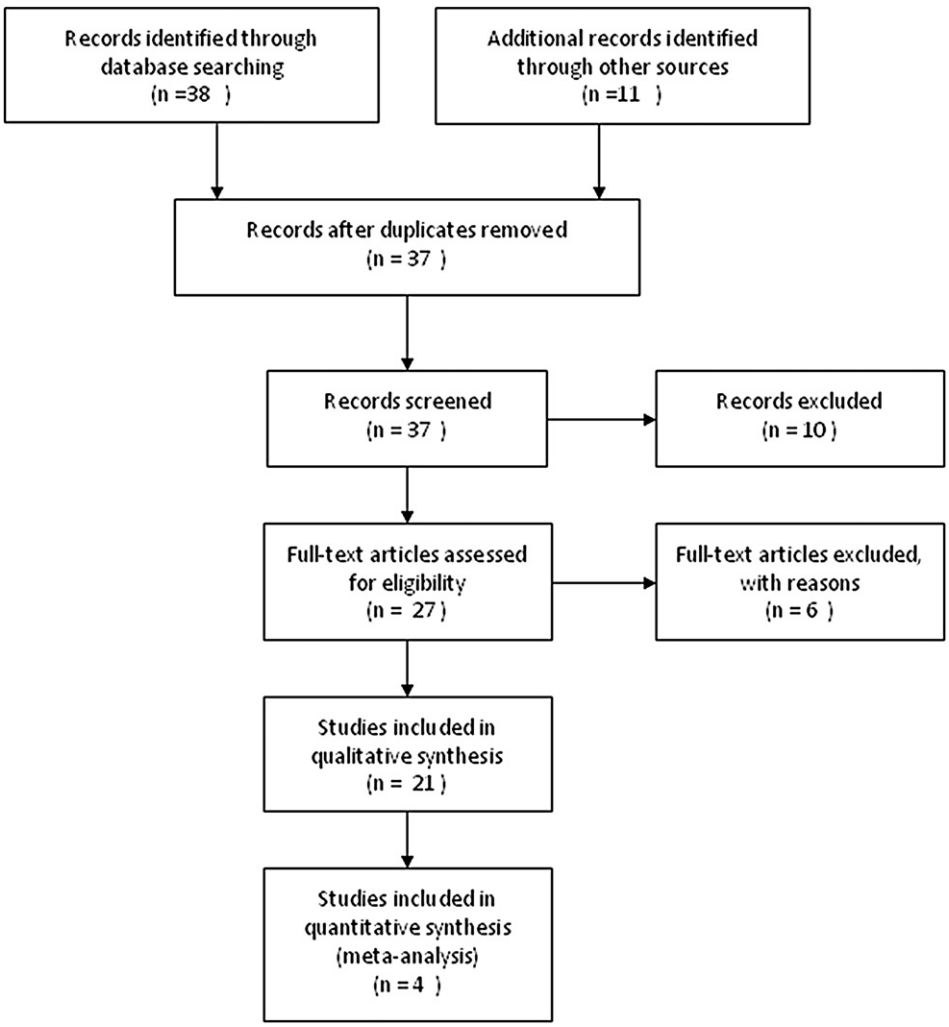

Figure 1 Results of the literature search.

Mathie et al. systematically collected and analysed homeopathic prescription and application data obtained by 14 dentists in clinical practice. They retrieved data on the use of *Hypericum* from practice data in dental homeopathy in a multicenter study and found that homeopathic *Arnica montana* and *Hypericum* was often for postsurgery pain and that the practitioners reported good results.[25]

Neither of these studies was eligible to be included in our meta-analysis. The study of Mathie et al. was uncontrolled, Sardella et al. used a phytotherapeutic extract of *H. perforatum.*

Meta-analysis

The main indications of the four clinical studies included for meta-analysis that used homeopathic *Hypericum* were pain conditions mostly after surgery (3 of 4). In three trials *Hypericum* was applied in combination with *Arnica*. In two early studies (Albertini et al.[26], Bendre et al.[27]), both conducted in the early 1980's, significant improvements in pain reduction/relief and swelling after 48 h were reported, but two subsequent studies by Rafai et al. and Lökken et al.[28,29] did not reproduce these results (Table 1). Lökken et al. study is of individualized homeopathy, the majority of patients received *Arnica*, *Phosphorus* was the 2nd most commonly prescribed medicine. *Hypericum* was only given to five patients and their results were not reported separately.

Another difference in these two groups of studies is quality of reporting. Lökken et al. and Rafai et al. used standardized measures for pain intensity and adequately reported patient characteristics and homeopathic treatment regimen, while in the earlier studies reporting quality is poor both in terms of outcome measures and patient data. In particular Albertini et al.[26] and Bendre et al.[27], did not report on the blinding of outcome assessor and on the method of data collection. Moreover there is no information on patient withdrawals and dropouts. This is reflected in the summary of the Quality Assessment Tool for Quantitative studies (Table 2). Only Rafai et al. is good quality, all the other studies suffer more than one weakness.

Hence it is not surprising, that a meta-analysis of these four studies indicates a high heterogeneity in the effects of *Hypericum* on dental pain (Chi-Square = 26.46; $I^2 = 0.89$). However, the overall effect of 0.24 favours *Hypericum*, but just misses statistical significance (95% CI: [0.06; 1.03]). The results become much less significant if Bendre et al. is excluded (OR of 0.66 [0.36, 1.19]; $Chi^2 = 6.49$; $I^2 = 0.69$). If Albertini et al. is excluded the OR is 0.24 [0.04, 1.49]; $Chi^2 = 60.87$; $I^2 = 0.97$ (Figure 2).

If the study of Lökken et al. is excluded from meta-analysis due to the low proportion of patients receiving *Hypericum*, the OR is 0.14 with a confidence interval of [0.01, 1.45]. If the overall results of Lökken et al. are assumed to hold for the subgroup of five patients treated with *Hypericum*, this leads to a higher standard error of 0.66 in the meta-analysis and a similar overall OR of 0.23 with a broader 95% CI of [0.04, 1.40]. Thus neither exclusion nor parameter adjustment of the study of Lökken et al. yields significant results.

Discussion

Because of the dominance of biomechanical procedures like grinding, drilling and refilling and highly technical applications like tooth desensitization applying laser,[30] homeopathy and integrative approaches like bionator therapy[31] or acupuncture[32] may not come to the mind as the first choice of therapeutic options for dentists today. However, since the medical and dental profession is becoming increasingly aware of the indivisibility of dental health from overall health particularly in the case of chronic oral diseases such as periodontal diseases[33] the role of homeopathy in dentistry might be greater than is sometimes appreciated.

Table 2 Quality assessment of the studies on the application of *Hypericum* in dental care according to the quality assessment tool for quantitative studies.

	Bendre et al. (1980)	*Loekken et al. (1995)*	*Albertini et al. (1985)*	*Rafai et al. (2005)*
Representativeness	Very likely	Very likely	Very likely	Somewhat likely
% Agreed to participate	Can't tell	80–100%	80–100%	80–100%
Selection bias	**Moderate**	**Strong**	**Strong**	**Moderate**
Study design	RCT	RCT	RCT	RCT
Randomized?	Yes	Yes	Yes	Yes
Randomization method described?	No	Yes	No	Yes
Method appropriate?	No	Yes	No	Yes
Study design	**Strong**	**Strong**	**Strong**	**Strong**
Group differences?	Can't tell	Can't tell	Can't tell	No
% Of controlled confounders	Can't tell	Can't tell	Can't tell	80–100%
Confounders	**Weak**	**Weak**	**Weak**	**Strong**
Blinding of outcome assessor	Can't tell	Yes	Can't tell	No
Blinding of participants	Can't tell	Yes	Yes	No
Blinding	**Moderate**	**Strong**	**Moderate**	**Strong**
Valid data collection tools	Can't tell	No	Yes	Yes
Reliable data collection tools	Can't tell	Yes	Yes	Yes
Data collection method	**Weak**	**Weak**	**Strong**	**Strong**
Reported	Can't tell	Yes	Can't tell	Yes
% Completed study	Not appropriate	Yes	Not appropriate	Yes
Withdrawels and dropouts	**Weak**	**Strong**	**Weak**	**Strong**
Global rating	**Weak**	**Weak**	**Weak**	**Strong**

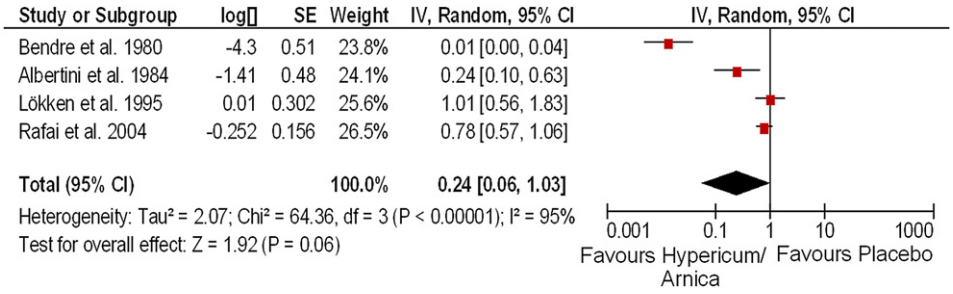

Figure 2 Forest plot for meta-analysis of *H. perforatum* for pain in dental care.

Hypericum is one of the most frequently mentioned homeopathic remedies for pain conditions in dental practice. While there are several reviews on *H. perforatum* and its chemistry, pharmacology and clinical outcomes[34], this is the first systematic review of the use of *Hypericum* in homeopathic form for dental problems. Although the current review is not a best-evidence synthesis (such as a Cochrane review), we can nevertheless draw some conclusions from it. There is a clear gradient in outcome with respect to the types of evidence. Single case studies and expert opinions described successful application of *Hypericum*, while study results were very heterogenous: earlier studies were positive more recent studies were not.

This might be due to methodological problems. The two older studies by Albertini et al.[26] and Bendre et al.[27] lack a clear description of materials and methods. Bendre et al. only reports on success rates in pain relief without giving a clear definition of what is meant. Moreover important data on clinical setting and patients are missing. A crucial point concerns the selection process: 200 patients were randomly allocated into 150 receiving *Hypericum* and *Arnica* and 50 receiving placebo. Neither the proportion of 3:1 in the two groups nor the randomization process is explained or justified. It thus can not be ruled out that the results are skewed, and the numbers are suspiciously round. In addition, all studies included in this meta-analysis also involved homeopathic *Arnica*: 3 used *Hypericum* in a fixed combination with *Arnica,* one used individualized homeopathy with more patients receiving *Arnica* than *Hypericum*. Thus the results are more influenced by *Arnica* than *Hypericum*, especially the high quality trials.

The regime for indications like tooth extraction is a matter of discussion. According to Raspe[19] decimal potencies should be applied hourly. Thus regime used by Lökken et al: *Hypericum* 3 h after tooth extraction and two doses before bedtime and the morning after might be insufficient and an explanation for a missing effect in the study. The recommendation of Lavatin[35] that severe acute conditions should be treated by 30C or 200C should be taken into account for future studies.

In addition to properly conducted homeopathic clinical trials it should be interesting to further evaluate the beneficial effect of *H. perforatum* in basic research with respect to post periodontal surgery pain control and especially with respect to its anti-inflammatory properties. Recently Mohammadi et al reported positive effects on nerve regeneration from homeopathic *Hypericum* 30C, in a rodent model.[36] Hammer et al. reported the influence of *H. perforatum* in herbal form on the genes that were involved in the Janus kinase and on the signal transducer and activator of transcription (JAK-STAT) expression and eicosnoid pathways to be responsible for the reduced Prostaglandin E2 (PGE2) expression in Lipopolysaccharide (LPS) challenged RAW 264.7 mouse macrophages.[37] So far four components within flavonoid extract (amentoflavone, chlorogenic acid, pseudohypericin and quercetin) have been identified to be responsible for PGE2 reduction.[38] A study by Paterniti et al. reported on the effects of *H. perforatum*, again in herbal form in a rodent model of periodontitis.[39]

Conclusion

Although case reports suggest a therapeutic potential of *H. perforatum* for pain conditions in dental care,[12] this effect is currently not adequately supported by properly conducted clinical trials with *H. perforatum* alone. Thus, as there is there is no such data in dental practice, and the results presented here are confounded, mostly by *Arnica,* no final conclusions can be drawn from this meta-analysis for the use of *H. perforatum* in dental practice. Some studies in basic research however do report on anti-inflammatory and analgesic effects of *H. perforatum*. We therefore encourage further studies with homeopathic *Hypericum* in both basic research and randomized controlled clinical trials in dental practice.

Authors contributions

TO wrote the initial manuscript and calculated the meta-analysis. CR did the literature search, extracted the data into the tables and was responsible for the homeopathic parts of the manuscript. AB contributed to the phytotherapeutic and experimental parts of the manuscript. KB was responsible for quality assessment of the studies. GG contributed to the discussion, was responsible for the dental parts of the manuscript and rechecked the complete final version.

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