

CHRISTMAS 2008: SEASONAL FAYRE

Frankincense: systematic review

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Cite this as: *BMJ* 2008;337:a2813
doi:10.1136/bmj.a2813

ABSTRACT

Objective To assess evidence from randomised clinical trials about the effectiveness of extracts of *Boswellia serrata* (frankincense).

Design Systematic review.

Data sources Electronic searches on Medline, Embase, Cinahl, Amed, and Cochrane Library. Hand searches of conference proceedings, bibliographies, and departmental files.

Review methods All randomised clinical trials of *B serrata* extract as a treatment for any human medical condition were included and studies of *B serrata* preparations combined with other ingredients were excluded. Titles and abstracts of all retrieved articles were read and hard copies of all relevant articles were obtained. Selection of studies, data extraction and validation were done by the author. The Jadad score was used to evaluate the methodological quality of all included trials.

Results Of 47 potentially relevant studies, seven met all inclusion criteria (five placebo controlled, two with active controls). The included trials related to asthma, rheumatoid arthritis, Crohn's disease, osteoarthritis, and collagenous colitis. Results of all trials indicated that *B serrata* extracts were clinically effective. Three studies were of good methodological quality. No serious safety issues were noted.

Conclusions The evidence for the effectiveness of *B serrata* extracts is encouraging but not compelling.

INTRODUCTION

When they saw the star, they rejoiced exceedingly with great joy. And going into the house they saw the child with Mary his mother, and they fell down and worshiped him. Then, opening their treasures, they offered him gifts, gold and frankincense and myrrh. (Matthew 2, 10-11, English Standard Version)

Frankincense, also known as olibanum, is the resin from the trees of the genus *Boswellia*, native to Arabia and India. It has a long history of use—for example, in religious ceremonies and for perfume production—and its medicinal properties have been appreciated for millennia.¹ Recently, the pharmacological properties and clinical effectiveness of *Boswellia serrata* have been studied systematically.

The aim of this systematic review was to summarise and critically evaluate the evidence from all randomised clinical trials of *B serrata* extracts.

METHODS

Searches were done of Amed, Cinahl, Embase, and Medline databases (on 18 August 2008, each from its inception, using the Ovid Sp Interface), the Cochrane Library, and our departmental files, including conference proceedings. Four search terms (*Boswellia*.mp, *Boswelli*/mesch, “*Boswellia serrata*”.mp, *Frankincense*.mp) were constructed using a combination of MeSH and free-word terms on the individual databases. Results were initially screened by title to exclude any obviously irrelevant articles, and potential hits were downloaded into Endnotes files. No language restrictions were applied.

Clinical trials had to be randomised, include human patients with any medical condition, and use *B serrata* extracts as a monopreparation. Studies of preparations containing *B serrata* in combination with other ingredients,^{2,3} non-randomised trials,^{4,5} and abstracts reporting incomplete data for evaluation were excluded.

Data were extracted and validated in accord with predefined criteria (table). Two independent reviews assessed methodological quality with the Jadad score.⁶ A meta-analysis was not possible because of heterogeneity, so results are presented in narrative form.

RESULTS

Seven randomised clinical trials were included (fig 1).⁷⁻¹³ The table summarises key data. The studies were published between 1998 and 2008 and most came from India. Methodological quality was variable but three trials reached the maximum on the Jadad scale.^{10 11 13} Five trials were placebo controlled and two were comparisons against active treatments. All studies used oral administration of *B serrata* extracts.

Boswellia extracts showed some promise in treating asthma,⁷ rheumatoid arthritis,⁸ Crohn's disease,⁹ knee osteoarthritis,^{10 12 13} and collagenous colitis.¹¹ However, all the included trials had flaws: the most common limitations were small sample size and incomplete reporting of data. The largest study included 102 patients, which is not large considering that this was a

non-superiority trial.⁹ Crucially, little independent replication was found; for only one of the five different indications (osteoarthritis) had more than one randomised clinical trial been published.^{10 12 13}

Adverse effects of *B serrata* were minor and were judged as not causally related to the treatment and not markedly different from those noted in the placebo

groups (table). Diarrhoea, abdominal pain, and nausea were reported in more than one study.

DISCUSSION

Collectively, these data seem to indicate that *B serrata* extracts are effective in treating a range of conditions caused or maintained by inflammatory processes. The

Key data from randomised clinical trials included in systematic review

First author (year), country	Condition (sample size)	Design (Jadad score)*	Interventions	Nature of extract†	Primary outcome measure	Main results/ effect size‡	Adverse effects of BSE (A) and control intervention (B)	Comment
Gupta (1998), India/Germany ⁷	Asthma (80)	DB, PC, 2 PG (3)	(A) BSE (350 mg 3×day) for 6 weeks; (B) placebo	"Boswellic acid containing drug 300 mg"	Percentage of patients showing clinical improvement	(A) 70% remission; (B) 27% remission§	(A) 2 patients experienced stomach pain, hyperacidity, nausea; (B) no information	Group (A) had more severe asthma than group (B); other endpoints also suggested efficacy of BSE
Sander (1998), Germany ⁸	Rheumatoid arthritis (37)	DB PC, 2 PG (2)	A) BSE (3600 mg 9×day) for 12 weeks; (B) placebo; both groups also received conventional drugs	H15§	Ritchie Index	Non-significant trend in favour of BSE§	(A) Stomatitis (1 patient); (B) eczema (1 patient), nausea (1 patient), increase of joint pain (1 patient)	Report only relates to subset of patients from larger unpublished study
Gerhardt (2001), Germany/Austria ⁹	Crohn's disease (102)	DB, 2PG, non-inferiority (3)	(A) BSE (3.6 g per day) for 8 weeks; (B) mesalazine (4.5 per day)	H15‡	Crohn's Activity Index (CAI)	Non-inferiority of BSE confirmed: (A) CAI from 301 (63) to 192 (114); (B) from 282 (72) to 163 (96)	(A) No causally related adverse effects; (B) 13 causally related adverse effects	Data refer to intention to treat analysis
Kimmatkar (2003), India ¹⁰	Osteoarthritis of the knee (30)	DB, PC, crossover (5)	(A) BSE (333 mg per day) for 8 weeks; (B) placebo	"Standardized extract of <i>Boswellia serrata</i> gum: minimum 65% organic acids or min 40% total BA. Main components of BA: 11-keto-β BA—6.44%, 3-O-Acetyl-11-ketoβ BA—2%, β-BA—18.51%, 3-O-Acetylβ BA—8.58%, α-BA—6.93%, 3-O-Acetyl-α-BA—1.853%."	Pain, function (VAS)	Significant intergroups differences in favour of BSE; intergroup difference for pain 2.3 (0.61)	(A) Diarrhoea (1 patient), epigastric pain, nausea (1 patient); (B) no information	Authors state that the differences are clinically relevant
Madisch (2007), Germany ¹¹	Collagenous colitis (31)	RCT, DB, PC, 2 PG (5)	(A) BSE (400 mg 3×day) for 6 weeks; (B) placebo	"High performance liquid chromatography analysis... 21.2 mg 11-keto-β-boswellia acid, 27.3 mg α-boswellia acid, 50.9 mg β-boswellia acid, 11.3 mg acetyl-11-keto-β-boswellia acid, 9.8 mg acetyl-α-boswellia acid, 28.7 mg acetyl-β-boswellia acid."	Percentage of patients with remission	(A) 64% remission (95% CI 30.8 to 89.1, ITT 44%); (B) 27% (7.7 to 55.1, 27%)	(A) Dizziness, hypoglycaemia, lack of appetite, diarrhoea (1 patient), bacterial enteritis (1 patient); (B) no information	Other outcome measures (such as stool frequency) also suggest efficacy of BSE
Sontakke (2007), India ¹²	Osteoarthritis of the knee (66)	RCT, open, active control, 2PG (2)	(A) BSE (333 mg 3×day) for 6 months; (B) valdecoxib (10 mg, 1×day)¶	"Standardized extract of BSE having minimum 40% total BA. Main components of BA: 11-keto-β BA—6.44%, 3-O-Acetyl-β BA—8.58%, alpha BA—6.93% and 3-O-acetyl α BA—1.853%."	WOMAC scale	Pain: (A) from 245.3 (77.6) to 82.9 (62.3) at 6 months; (B) from 246.0 (71.4) to 85.4 (68.9)	(A) Diarrhoea (1 patient); (B) no adverse effects	1 month after discontinuation of therapy, patients in group (A) maintained benefit while those in (B) deteriorated
Sengupta (2008), India ¹³	Osteoarthritis of the knee (75)	RCT, DB, PC, 3 PG (5)	(A) BSE (100 mg per day) for 90 days, (B) BSE (250 mg per day), (C) placebo	"5-Loxin(R), novel <i>B. serrata</i> enriched to 30%, 3-O-acetyl-11-keto-β-boswellic acid (AKBA) (US-Patent publication no.: 2004/007306041)."	Pain (VAS), Lequesne Index, WOMAC Index	Significant inter-group differences in favour of (A) and (B) versus (C); pain: (A) from 57.1 (8.7) to 21.4 (7.1); (B) from 55.6 (9.3) to 14.2 (6.8); (C) from 55.9 (12.0) to 41.8 (16.0)	Diarrhoea, nausea, abdominal pain, fever, weakness; evenly distributed between groups	Other outcome measures also suggest efficacy of BSE

BA=boswellic acid; BSE=*Boswellia serrata* extract; CRP=C-reactive protein; DB=double blind; ESR=erythrocyte sedimentation rate; MC=multicentre; PC=placebo controlled; PG=parallel groups; VAS=visual analogue scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

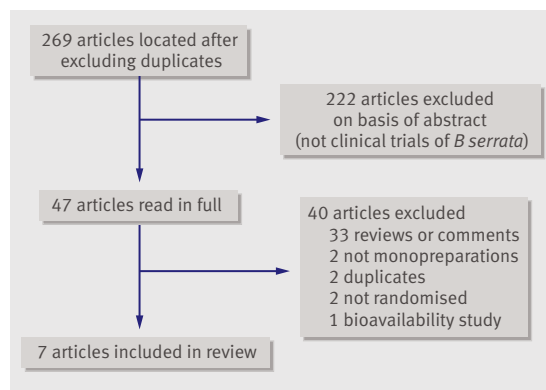
*Studies were superiority trials unless otherwise stated.

†Inverted commas indicate quote from publication.

‡Values are mean (SD) unless otherwise indicated; values in parentheses not identified in Sontakke study.

§No further information provided.

¶Trial done before withdrawal of valdecoxib from market.



Flow chart showing study selection

results of non-randomised studies and trials of herbal mixtures containing *B serrata*, which failed to meet the inclusion criteria for this systematic review, tend to point in the same direction.^{4,5,14} *B serrata* has been used traditionally against inflammatory diseases.¹⁵ Its main pharmacologically active ingredients are α and β boswellic acid, as well as other pentacyclic triterpenic acids.¹⁶ These compounds have been shown to inhibit pro-inflammatory processes by their effects on 5-lipoxygenase and cyclo-oxygenase and on the complement system.^{15,17}

The evidence evaluated here may be encouraging, but it is not convincing. Not enough large randomised clinical trials have been published for any condition. The medications used in these trials cannot be directly compared in terms of contents and strength. The pharmacokinetics and optimal dose of *B serrata* extracts are largely unknown; usually 600-3000 mg gum resin per day or equivalents are recommended for oral intake.¹⁸ Source of funding or sponsorship was undisclosed in all but one trial.¹³

Dozens of *B serrata* preparations for oral intake are commercially available. The majority are not regulated as medicines but sold as food supplements. Fortunately, the safety profile of *B serrata* seems good.¹⁸ In the included trials, no serious, long term, or irreversible adverse effects were noted. Other data indicate that mild adverse effects such as nausea, acid reflux, and gastrointestinal upset may occasionally occur.¹⁸ No evidence of serious interactions with drugs has been noted.¹⁸ However, absence of evidence is not the same

as evidence of absence, which is particularly relevant in herbal medicine, where pharmacovigilance is often less than optimal.¹⁹

Many of the medical, quasimedical, or cosmetic claims made implicitly or explicitly for *B serrata* products are not supported by the available evidence. Their trade names speak for themselves: regeneration body balm, intensive eye serum, supernatural instant youth serum, lifting and firming body lotion, joie de vivre face lotion, radiance anti-ageing, joint and muscle balm, ultra inflammactin, to name a few. Currently more than one million websites on “Frankincense” and half a million on “Boswellia” exist (Google searches, November 2008); the majority fail to offer reliable information on its medicinal uses.

This systematic review has several limitations. Although the search strategy was thorough, some randomised clinical trials might not have been located. A positive publication bias cannot be excluded—complementary medicine journals rarely publish negative results.²⁰ The overall picture generated by a systematic review could thus be false positive. Methods for assessing the extent of publication bias are not very effective if, as in the present case, few trials are available. Mandatory worldwide registration of clinical trials in herbal medicine seems unlikely to happen at present. Incomplete reporting is another problem. One trial related to a subset of patients from a larger multicentre study that has never been published in full.⁸ Crucially, the paucity of rigorous studies prevents any definitive judgement about the effectiveness of *B serrata* extracts.

In conclusion, it might be tempting to buy “instant youth” in the form of a *B serrata* product for Christmas, but sadly the evidence for this claim is nonexistent. For other indications, evidence is encouraging but not convincing. The existing data do, however, warrant further investigation of this herbal medicine.

I thank Shao Kang Hung for doing the duplicate Jadad scores and Kate Boddy for the literature searches.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: None declared.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Frankincense has a long history of use
Some of its ingredients have anti-inflammatory activity
Several clinical trials have been done

WHAT THIS STUDY ADDS

This is a systematic review of data from randomised clinical trials
It shows encouraging results for conditions caused or maintained by inflammation
Several caveats exist and independent replications are needed

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Accepted: 23 November 2008