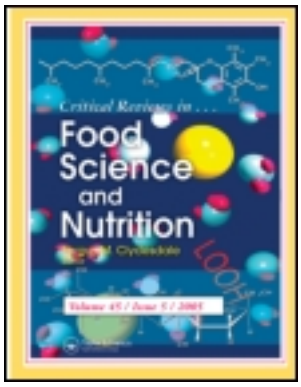

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Plant Food Supplements with Anti-Inflammatory Properties: A Systematic Review (II)

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Plant Food Supplements with Anti-Inflammatory Properties: A Systematic Review (II)

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The aim of this systematic review is to summarize the evidence for or against the efficacy of plant food supplements (PFS) for coping inflammatory conditions by considering epidemiological and human intervention studies. The review considers six botanical species commonly used as food supplements/medicinals: Urtica dioica L., Symphytum officinalis L., Calendula officinalis L., Curcuma longa L., Boswellia serrata Roxb., and Harpagophytum procumbens L. The search retrieved 579 publications. By removing the duplicates and applying the inclusion/exclusion criteria, the final number of papers was 47. No epidemiological data were found. The bibliographic search found no paper regarding the anti-inflammatory effects of Calendula officinalis L. and Symphytum officinalis L. by oral use. In spite of the long-term traditional use for inflammatory disorders, Curcuma longa L. and Harpagophytum procumbens L. warrant further investigation, whereas the efficacy of Urtica dioica L, even if the available data on hard endpoints are promising, requires other trials. Boswellia serrata Roxb. was found to be the most promising, since it shows the best efficacy for the treatment of pain/inflammatory conditions. In conclusion, it is advisable to conduct further studies with more homogeneous population and larger number of subjects by avoiding the heterogeneity of the herbal preparations considered.

Keywords Curcuma longa, boswellia serrata, symphytum officinalis, urtica dioica, harpagophytum procumbens, calendula officinalis

INTRODUCTION

Inflammation is a complex series of physiological events designed to repair bodily damage as a result of injury or infection. The short-term inflammatory response, defined as acute inflammation, eliminates infections and promotes tissue repair by activating the innate immune cells (mast cells, leukocytes, dendrite cells). In humans, cytokine and chemokine levels are consistently low and typically increase only in response to physiologic stress for attracting the immune cells to the site of injury and infection. Elevated levels of these cytokines (TNF, IL 1 β etc.) and C reactive protein (CRP) have been studied extensively as predictors of disease and disability in humans. Chronic inflammation is a critical factor in the pathogenesis of many disease states including cardiovascular, neurodegenerative and degenerative joint diseases, cancer, and diabetes. It can be considered the result of a delayed or deregulated inflammation, which in turn leads to macrophage recruitment along with T-cells. The byproducts of macrophage activation are toxic reagents, including reactive oxygen species (ROS), elastase and other proteases, including cathepsin G, which are responsible for tissue damage. The body must balance homeostatic state and response to injury, and mediators of inflammation play a key role in maintaining this balance.

Over recent times the link between inflammation and nutrition has become increasingly apparent (Pischon et al., 2003; Zhao et al., 2004; Karin et al., 2006); it has been demonstrated that an excessive macronutrient intake can contribute to inflammatory response as well as some dietary polyphenols are able to reduce the incidence of cardiovascular mortality and certain types of cancer due to their anti-inflammatory properties (Lucas et al., 2011).

PlantLIBRA (PLANT food supplements: Levels of Intake, Benefit and Risk Assessment) is an EC funded project aiming to foster the safe use of food supplements containing botanicals or

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their preparations, by evaluating the quality and health benefits of plant food supplements (PFS), and by increasing science-based decision-making by regulators and food chain operators.

PlantLIBRA is structured to develop, validate and disseminate data and methodologies for risk and benefit assessment and implement sustainable international cooperation. Part of the project is dedicated to the methodology of benefit assessment for PFS, application and validation. The first step was to review the evidence for PFS benefits from epidemiological, clinical, and intervention studies. A number of pathological conditions where PFS are commonly used were identified and inflammation was one of those.

The aim of the systematic review is to summarize and critically evaluate the evidence for or against the efficacy of PFS or substances (compounds or foods) relevant to PFS for coping inflammatory conditions. Ten plants were considered: *Olea europea* L. (olive), *Camellia sinensis* L. (as green or black tea), *Vitis vinifera* L. (Vine), *Boswellia serrata* Roxb. (Indian Frankincense), *Matricaria recutita* L. (Chamomile), *Symphytum officinalis* L. (Comfrey), *Calendula officinalis* L. (Marigold), *Curcuma longa* L. (Turmeric), *Urtica dioica* L. (Nettle), and *Harpagophytum procumbens* L. (Devil's claw). The choice of these botanicals in the reviewing process was based on PlantLIBRA partners' suggestions and the list of plants present in Annex 1 of the project.

Epidemiological, human intervention studies using PFS were then systematically examined and reviewed. The reviewing work on *Olea europea* L., *Camellia sinensis* L., *Vitis vinifera* L., and *Matricaria recutita* L., frequently used as food, is part of a first publication (submitted to Critical Reviews in Food Science and Nutrition). This work deals with *Urtica dioica* L., *Symphytum officinalis* L., *Calendula officinalis* L., *Curcuma longa* L., *Boswellia serrata* Roxb. ex Colebr., and *Harpagophytum procumbens* L. botanical species more commonly used as food supplements/medicinals.

METHODS

Source and Search strategy

Electronic literature searches were conducted using the following databases: Cochrane library, Scifinder Scholar, Embase, and Pubmed from 1970 to 2010. They were searched for title and abstract using the following search terms: Latin name of the plant **or** common name matched with inflamm* **or** phlogosis **or** anti-inflammatory. Search limits were human trial and the English language. Keywords relevant to inflammation (i.e., cyclooxygenase, cytokines, adhesion molecules, etc.) were also used as search terms. Bibliographies of the articles thus located were scanned for further relevant publications.

For collecting epidemiological studies, the same terms were used for searching title, abstract, and index terms for the six PFS (1) and for health area inflammation (2). Terms used for searching epidemiological studies (3) were: epidemiology/exp **or** epidemiolog* **or** case control **or** cohort. We selected epidemiological studies for applicable PFS and inflammation in two different ways and then merged the results: (1) **and** (2) filtered by study type or (1) **and** (2) **and** (3).

Inclusion and Exclusion Criteria

Controlled human studies performed on healthy/unhealthy populations were included. Randomization, even if preferable, was not considered essential. Inclusion criteria were the use of PFS as food, pill/powder/extract, etc. Among the evaluation criteria, it was considered of relevance the presence of these data, such as botanical name of the plants, the used preparation as extract, tincture, decoction, infusion, etc., and the daily intake. Publications reporting incomplete qualitative and quantitative analysis of PFS were flagged but not excluded. Studies reporting co-treatments with other PFS or other bioactive compounds were included. Studies where general foodstuffs were fortified with PFS or studies reporting on individual compounds were not considered.

Other criteria of exclusion were: the use of botanicals for cosmetic, homeopathy, aromatherapy, topical use, aerosol/inhalation, and hygiene products (toothpaste, mouth rinse, etc). Publications regarding reviews, commentary, letters to the Editor, and patents were not considered. Similar inclusion/exclusion criteria were used for epidemiological studies. From the bulk of papers selected by the search strategy described above, those not fulfilling the inclusion criteria were excluded by reading the abstract. For remaining studies, a customized version of the extraction database was used.

Data Extraction

A database (written in MS Access) was designed and implemented to aid the data extraction process. Publications were checked for duplicates, read in full by two authors, and subjected to the in/out process following the inclusion/exclusion criteria described above. Ten percent of the publications found were checked by a second reviewer and compared, whereas 5% of the publications not excluded by the in/out procedure were checked by a second reviewer and compared. Papers were stored in a reference manager (Endnote X1.0.3). A pdf file of each publication was retrieved.

Quality Assessment

The methodological quality of the studies was independently evaluated by two reviewers (MDA and CDL) using the Jadad score (Jadad et al., 1996). Particular attention was given to the presence of adequate statistical analysis and a well-characterized experimental design; other quality assessment criteria were based on the recommendations from The Cochrane

Handbook of Systematic Reviews of Interventions (Cochrane Collaboration, 2008) and from CONSORT statement for herbal medicine (Gagnier et al., 2006). The same criteria were used for the quality assessment of epidemiological studies.

RESULTS AND DISCUSSION

Human/Intervention Studies

The search by title and abstract retrieved 579 publications. By removing the duplicates and applying the inclusion/exclusion criteria above described, the final number of papers was 47. These publications were uploaded in the database and the in/out process lead to 27 publications accepted and used for this systematic review.

The papers rejected in the in/out sheet process were excluded for the following reasons: (1) the clinical trial was not controlled; (2) the study was not related to inflammation; (3) the study was not dealing with the six plants chosen for the systematic review; (4) the study was performed in vitro or ex vivo; (5) the plant material was not used as supplement or food; and (6) scientific quality was considered insufficient.

According to ESCOP the indication of use of Marigold is for the treatment of minor inflammations of the skin and mucosa. Several national authorities recommend Comfrey only for external use due to the presence of pyrrolizidine alkaloids. Accordingly, the bibliographic search found no paper regarding the anti-inflammatory effects of Marigold and Comfrey by oral use. Table 1 reports the preparations used for clinical trials, the active principles identified, and the daily intake of the publications considered in the present review. Fifty percent of the studies give the precise composition/concentration of the active principle in the pharmaceutical form used for the clinical study. The majority of the studies with *Boswellia serrata* Roxb. ex Colebr reported the analytical composition of the active principle, whereas for *Urtica dioica* L., any information was given. Tables 2–5 report the human trials related to *Urtica dioica* L., *Harpagophytum procumbens* L., *Curcuma longa* L., and *Boswellia serrata* Roxb. ex Colebr. For each PFS, the publications are listed in two columns: benefit/no benefit, depending on whether the study reported beneficial/nonbeneficial results. The change of biomarkers or hard endpoints (a symptom or the change of a physiological state) was used as a criterion by which a publication is listed under the "benefit" or "no benefit" column.

Urtica Dioica L.

Urtica dioica L. is listed in Deutsches Arzneibuch or Pharmacopoea Helvetica and ESCOP monographs as leaf, herb (dried flowering part), or dried rhizomes and roots. Four publications on Nettle met the inclusion/exclusion criteria and three out of four were accepted for the present systematic review: the leaves were used in one study, the freeze-dried herb in gelatin capsules in the second, and the third was performed to test Phytalgic®, an association of *Urtica dioica* L. (the part of the plant used was not specified), fish oil rich in omega-3 and omega-6 fatty acids, zinc, and vitamin E. The results are reported in Table 2. Chrubasik et al. (1997) measured C reactive protein and evaluated the response to pain by WOMAC test in 36 subjects with acute arthritis finding no effect. In studies reporting hard endpoints, the number of subjects reporting benefits was 150 vs. 36 subjects with no benefits. A positive response was seen on rhinitis (Mittman, 1990), pain (Jacquet et al., 2009), and the physical impairment caused by arthritis (Chrubasik et al., 1997). The decrease of the intake of analgesic drugs (Jacquet et al., 2009) was another parameter to assess beneficial effects. Thus, the search has clearly evidenced a highly limited documentation and the paucity of the number of subjects. Even if the available data on hard endpoints are promising, the assessing of the efficacy requires other trials.

Harpagophytum Procumbens L.

Devil's claw root consists of the cut and dried tuberous, secondary roots of *Harpagophytum procumbens* L. Six studies were included. One study (Moussard et al., 1992) recruited 25 participants and reported no effect of Devil's claw on inflammatory biomarkers (PGE_2, TXB_2, LTB_4, and 6-keto-$PGF_{1\alpha}$) (Table 3). The lack of inhibitory effect of devil's claw on the biosynthesis of prostanoids was interpreted as positive, since adverse effects commonly associated with NSAIDs are not to be expected with the use of *Harpagophytum procumbens*. In the studies ($n = 5$) evaluating hard endpoints, a positive response was observed: 502 subjects showed benefits for chronic low back pain and disability due to osteoarthritis of knee. Several studies, which failed to meet the inclusion criteria for this systematic review, tend to point for the effectiveness of *Harpagophytum procumbens* to treat conditions maintained by inflammatory processes. However, two systematic reviews (Gagnier et al., 2006; Gagnier et al., 2007) of randomized controlled clinical studies of herbal medicines for low back pain reported contradictory results: either strong evidence, moderate evidence, or no significant difference with respect to placebo for the treatment of acute episodes of chronic low back pain with devil's claw extract. Thus, this topic urges welldesigned studies, also for the lack of epidemiological studies. In spite of the long-term traditional use of this plant in Southern Africa for inflammatory disorders, the existing data warrant further investigation.

Curcuma Longa L.

Turmeric consists of the scalded and dried rhizomes of *Curcuma longa* L. The majority of the studies were performed using extracts rich in curcuminoids or curcumin that are considered the active principles of turmeric; the use of the rhizome as a

Table 1 Preparations used, active principles, and daily intake of PFS

Publications	Preparation	Active principles	Daily intake
(Chainani-Wu et al., 2007)	Capsules containing standardized extract of turmeric	Curcuminoids (95%) containing curcumin (70–80%), demethoxycurcumin, and bisdemethoxicurcumin	2 g/day
(Durgaprasad et al., 2005)	Capsules (containing each 500 mg of extract of *Curcuma longa*)	Curcumin (95%)	1500 mg/day
(Hanai et al., 2006)	Tablets containing curcumin	Curcumin	2 g/day
(Usharani et al., 2008)	Capsules of NCB-02 (standardized formulation of curcuminoids)	Standardized preparation of C3 curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin)	600 mg/day
(Kositchaiwat et al., 1993)	Capsules (250 mg each) containing *Curcuma longa* powder	NR	250 mg/day
(Hamblin et al., 2008)	Tincture 1:5 from *Curcuma longa*	NR	930 mg/day
(Satoskar and Shenoy, 1986)	Capsules containing curcumin	Curcumin	400 mg/day
(Van Dau et al., 1998)	Tablets containing *Curcuma longa* powder	NR	2 g/day
(Houssen et al., 2010)	Capsules with *Boswellia carterii* and *Curcuma longa* extracts	Boswellic acid, curcumin	450 mg boswellic acid/day; 45 mg curcumin/day
(Kulkarni et al., 1991)	Capsules	NR	*Boswellia serrata*: 100 mg/day; *Curcuma longa*: 50 mg/day
(Sengupta et al., 2008)	5-Loxin®: capsules containing *Boswellia serrata* extract	30% 3-O-acetyl-11-keto-beta boswellic acid	100 or 250 mg/day
(Sengupta et al., 2010)	Capsules containing standardized extract of *Boswellia serrata*	5-Loxin®: 30% of 3-O-acetyl-11-keto-beta boswellic acid (AKBA). Aflapin®: *Boswellia serrata* extract enriched with AKBA and non-volatile oil	5-Loxin®: 100 mg/day; Aflapin®: 100 mg/day
(Sontakke et al., 2007)	Capsules containing standardized extract of *Boswellia serrata*	40% total boswellic acids (BA). 11-keto-beta BA (6.44%), 3-O-Acetyl-beta BA (8.58%), alpha BA (6.93%), and 3-O-acetyl alpha BA (1.853%)	999 mg/day
(Usha and Naidu, 2006a)	Capsules containing herb mixture, including standardized extract of *Boswellia serrata* (Eazmov plus)	Standardized extract from *Boswellia serrata* (composition is not reported).	50 mg/day
(Usha and Naidu, 2006b)	Capsules containing a herb mixture including standardized extract of *Boswellia serrata* (Eazmov plus)	Standardized extract from *Boswellia serrata* (composition is not reported)	50 mg/day

(Gupta et al., 1997)	Capsules of powdered gum resin of *Boswellia serrata*	11-keto-beta boswellic acid (1.8%), acetyl 11-keto-beta boswellic acid (1.4%), acety-beta-, and beta boswellic acid (2%)	1050 mg/day
(Gupta et al., 1998)	Capsules of powdered gum resin of *Boswellia serrata* (300 mg each)	11 keto beta boswellic acid (0.63%), acetyl 11 keto beta boswellic acid (0.70%), acetyl beta boswellic acid, and beta boswellic acid (1.5%)	900 mg/day
(Gupta et al., 2001)	Capsules of powdered gum resin of *Boswellia serrata* (300 mg each)	11 keto beta boswellic acid (0.63%), acetyl 11 keto beta boswellic acid (0.70%), acetyl beta boswellic acid, and beta boswellic acid (1.5%)	900 mg/day
(Kimmatkar et al., 2003)	Capsules of powdered gum resin of *Boswellia serrata*	Standardized extract of *Boswellia serrata* containing 40% total boswellic acids. Main components: 11 keto beta BA (6.44%), 3-O-Acetyl 11-ketobeta BA (2%), beta-BA (18.51%,) 3-O-Acetyl-beta, BA (8.58%), alpha BA (6.93%), and 3-O-Acetyl-alpha BA (1.853%)	999 mg/day
(Chrubasik et al., 1999)	Tablets (each containing 200 mg of *Harpagophytum procumbens* extract)	Harpagoside (17 mg/tablet)	600 and 1200 mg/day
(Chrubasik et al., 1996)	Tablets containing *Harpagophytum procumbens* extract	Harpagoside	6 g/day (corresponding to 50 mg harpagoside)
(Chrubasik et al., 2003)	Capsules (400 mg each) containing *Harpagophytum procumbens* extract	Harpagoside	60 mg harpagoside/day
(Chrubasik et al., 2005)	Capsules (400 mg each) containing *Harpagophytum procumbens* extract	Harpagoside	60 mg harpagoside/day
(Chantre et al., 2000)	Capsules containing *Harpagophytum procumbens* powder (Harpadol®)	Total iridoid glycosides	2610 mg/day
(Moussard et al., 1992)	Capsules (500 mg each) containing *Harpagophytum procumbens* powder	3% of total glucoiridoids	2 g/day
(Chrubasik et al., 1997)	Capsules containing powdered extract of *Urtica dioica*	Caffeoylmalic acid	1340 mg/day
(Jacquet et al., 2009)	Capsules of Phytalgic® containing *Urtica dioica*	NR	NR
(Mittman, 1990)	Capsules containing *Urtica dioica* freeze dried	NR	600 mg/day

NR: not reported.

Table 2 *Urtica dioica* L.

	No benefit		Benefit		Comments
	N° studies	N° participants	N° studies	N° participants	Efficacy
		Biomarkers			
C reactive protein (CRP)	1 (Chrubasik et al., 1997)	36			OSN*
TOTAL	1[a]	36[b]	0[c]	0[d]	
		Hard endpoints			
Physical impairment score in arthritis	1 (Chrubasik et al., 1997)	36			
Decrease in intake of analgesic drugs			1 (Jacquet et al., 2009)	81	OSN
Pain (WOMAC test)	1 (Chrubasik et al., 1997)	36	1 (Jacquet et al., 2009)	81	OSN
Overall rating of treatment (rhinitis)			1 (Mittman, 1990)	69	OSN
TOTAL	1[a]	36[b]	2[c]	150[d]	

*Other studies needed.
[a]Number of studies where the effect was not observed.
[b]The total number of subjects recruited in the studies which reported no benefit.
[c]Number of studies where the effect was observed.
[d]The total number of subjects recruited in the studies which reported benefit.

tincture is documented in only one study (Hamblin et al., 2008). The two studies included were performed using *Curcuma longa* L. in combination with *Boswellia serrata* Roxb. (Houssen et al., 2010).

The in/out process selected eight studies. Those ($n = 4$) investigating the effect on inflammatory biomarkers concluded that the treatment reduced TNF, IL-6, nitric oxide, LTC_4, and MDA (Table 4). Conversely, ESR (erythrocyte sedimentation rate) did not change following turmeric treatment (Kulkarni et al., 1991); the efficacy of the treatment was considered convincing only for MDA, since all studies ($n = 3$) gave positive results (altogether 155 participants). The total number of subjects recruited in the studies ($n = 5$) showing positive results on hard endpoints was 256 versus 213 in the studies with no benefits ($n = 4$). At this stage, the number of studies is insufficient for supporting the claim of the anti-inflammatory activity of turmeric. Validation for the use of turmeric deserves further studies.

Boswellia Serrata Roxb. Ex Colebr

Indian Frankincense (*salai guggal*) is the oleo-gum resin of *Boswellia serrata* Roxb. ex Colebr used in Ayurvedic system of medicine for degenerative joint diseases.

The search retrieved seven publications reporting the positive effect of *Boswellia serrata* on several biomarkers such as nitric oxide, MDA, LTC_4, metalloprotease-3, eosinophils count, leukocyte infiltration, etc. (Table 5); conversely, controversial

Table 3 *Harpagophytum procumbens* L

	No benefit		Benefit		Comments
	N° studies	N° participants	N° studies	N° participants	Efficacy
		Biomarkers			
PGE2	1 (Moussard et al., 1992)	34			OSN*
Thromboxane	1 (Moussard et al., 1992)	34			OSN
6-keto-PGF1α	1 (Moussard et al., 1992)	34			OSN
LTB4	1 (Moussard et al., 1992)	34			OSN
TOTAL	1[a]	34[b]	0[c]	0[d]	
		Hard endpoints			
Pain in osteoarthritis of the knee			1 (Chantre et al., 2000)[#]	122	OSN
Disability in osteoarthritis of the knee			1 (Chantre et al., 2000)[#]	122	OSN
Chronic low back pain			4 (Chrubasik et al., 1996);(Chrubasik et al., 1999);(Chrubasik et al., 2003);(Chrubasik et al., 2005)	380	YES
Reduction of NSAIDs intake			1 (Chantre et al., 2000)[#]	122	OSN
TOTAL	0[a]	0[b]	5[c]	502[d]	

*Other studies needed.
[#]Also published as (Leblan et al., 2000).
[a]Number of studies where the effect was not observed.
[b]The total number of subjects recruited in the studies which reported no benefit.
[c]Number of studies where the effect was observed.
[d]The total number of subjects recruited in the studies which reported benefit.

Table 4 *Curcuma longa* L.

	No benefit		Benefit		Comments
	N° studies	N° participants	N° studies	N° participants	Efficacy
Biomarkers					
MDA			3 (Durgaprasad et al., 2005);(Houssen et al., 2010); (Usharani et al., 2008)	155	YES
Leukotriene C4			1 (Houssen et al., 2010)	63	OSN*
Nitric oxide			1 (Houssen et al., 2010)	63	OSN
ESR (erythrocyte sedimentation rate)	1 (Kulkarni et al., 1991)	42			OSN
TNF			1 (Usharani et al., 2008)	72	OSN
IL-6			1 (Usharani et al., 2008)	72	OSN
TOTAL	1[a]	42[b]	3[c]	155[d]	
Hard end-points					
Pain	1 (Durgaprasad et al., 2005)	20	3 (Satoskar and Shenoy, 1986);(Hamblin et al., 2008);(Kulkarni et al., 1991)	107	YES
CAI (Clinical Index Activity)			1 (Hanai et al., 2006)	89	OSN
Oral lichen planus	1 (Chainani-Wu et al., 2007)	33			OSN
EI (Endoscopic Index)			1 (Hanai et al., 2006)	89	OSN
Tenderness			1 (Satoskar and Shenoy, 1986)	45	OSN
Cord oedema			1 (Satoskar and Shenoy, 1986)	45	OSN
Disability score			1 (Kulkarni et al., 1991)	42	OSN
Joint score	1 (Kulkarni et al., 1991)	42			OSN
Duodenal ulcer	1 (Van Dau et al., 1998)	118			OSN
Gastric ulcer			1 (Kositchaiwat et al., 1993)	60	OSN
TOTAL	4[a]	213[b]	5[c]	256[d]	

*Other studies needed.
[a]Number of studies where the effect was not observed.
[b]The total number of subjects recruited in the studies which reported no benefit.
[c]Number of studies where the effect was observed.
[d]The total number of subjects recruited in the studies which reported benefit.

results were observed for ESR and the leukocyte count. However, at an overall view, six studies reported benefits, with a total number of subjects much higher with respect to the number of subjects showing no benefits (308 vs. 72). The number of subjects participating to the nine studies showing positive results on hard endpoints was 443 versus 82 subjects in the two studies with no benefits. Pain is the symptom, which seems to better respond to the treatment: 353 subjects in seven studies witnessed a reduction of pain after treatment.

Ernst (2008) carried out a systematic review from all randomized clinical trials with *Boswellia serrata* extracts and concluded that the evidence for the effectiveness is encouraging, but not compelling.

Epidemiology Studies

The bibliographic search retrieved 38 papers for *Boswellia serrata* Roxb.; 23 for *Harpagophytum procumbens* L. and *Urtica dioica* L.; 16 for *Symphytum officinalis* L.; 12 for *Curcuma longa* L.; and 8 for *Calendula officinalis* L. By application of the exclusion criteria, no epidemiological studies were accepted through the in/out process.

Conclusive Remarks and Future Work

The aim of this systematic review was to evaluate efficacy of PFS against inflammation and to direct researchers, Health Authorities, and decision makers/opinion leaders about future research for the purpose of making claims on product labels or in promotional material. This work represents the second part (see previous submission) of a reviewing process of studies (clinical, intervention, and epidemiological) performed with PFS derived from plants known for their use in inflammatory conditions.

With the exclusion of *Boswellia serrata* for all the botanicals considered in this review, an ESCOP monograph exists with the indication for use (ESCOP, 2009). Marigold is indicated for the treatment of minor inflammation of the skin and mucosa and for healing of minor wounds, and the oral use is not considered. Then the use of Marigold as PFS has to be fully investigated. Comfrey should not be consumed as food supplement for the presence of toxic pyrrolizidine alkaloids. In Germany, Comfrey is restricted to external use (Stickel and Seitz, 2000) and daily dose is limited to a maximum of 100 μg per day. A considerable fraction of externally applied pyrrolizidine alkaloids is absorbed through the skin (0.1–0.4%) and has been detected in urine (Lin et al., 1998). Turmeric is indicated for mild digestive complaints and minor biliary dysfunction. Only devil's claw and nettle

Table 5 Boswellia serrata Roxb

	No benefit		Benefit		Comments
	N° studies	N° participants	N° studies	N° participants	Efficacy
Biomarkers					
Leukocyte infiltration			1 (Gupta et al., 1997)	50	OSN*
Number of leukocytes	1 (Gupta et al., 2001)	30	1 (Gupta et al., 1997)	50	OSN
Eosinophils			2 (Gupta et al., 1998); (Gupta et al., 2001)	70	OSN
ESR (Erythrocyte Sedimentation Rate)	1 (Kulkarni et al., 1991)	42	2 (Gupta et al., 1998); (Usha and Naidu, 2006a)	100	OSN
Leukotriene C4			1 (Houssen et al., 2010)	63	OSN
MDA			1 (Houssen et al., 2010)	63	OSN
Nitric oxide			1 (Houssen et al., 2010)	63	OSN
MMP-3			1 (Sengupta et al., 2008)	65	OSN
TOTAL	2[a]	72[b]	6[c]	308[d]	
Hard endpoints					
Pain			7 (Usha and Naidu, 2006b); (Kulkarni et al., 1991); (Gupta et al., 1997); (Sengupta et al., 2008); (Sengupta et al., 2010); (Sontakke et al., 2007); (Kimmatkar et al., 2003)	353	YES
Ulcerations			1 (Gupta et al., 1997)	50	OSN
Properties of stools			1 (Gupta et al., 2001)	30	OSN
Disability score			1 (Kulkarni et al., 1991)	42	OSN
Joint score	1 (Kulkarni et al., 1991)	42	1 (Usha and Naidu, 2006a)	60	OSN
Knee circumference	1 (Usha and Naidu, 2006b)	40			OSN
TOTAL	2[a]	82[b]	9[c]	443[d]	

*Other studies needed.
[a]Number of studies where the effect was not observed.
[b]The total number of subjects recruited in the studies which reported no benefit.
[c]Number of studies where the effect was observed.
[d]The total number of subjects recruited in the studies which reported benefit.

leaf/herb have indications for the treatment of degenerative joint disorders.

The conditions, against which the PFS discussed in the present review were employed included osteoarthritis, chronic low back pain, and ulcer.

The outcome of the evaluation process indicates the need of well designed randomized controlled trials for *Urtica dioica*, *Harpagophytum procumbens*, and *Boswellia serrata.* For these botanicals, although the studies are insufficient, all outcomes support for a positive effect. Conversely, *Curcuma longa* does not seem to affect significantly inflammatory conditions. Even though some inflammatory biomarkers were reduced by the treatment, the effect on hard endpoints does not show a significant difference between subjects reporting benefits and subjects with no benefits.

Major drawbacks hampering the assessment of the beneficial health effect are insufficient characterization of PFS and heterogeneity in dosing and time of exposure between studies, small sample size and incomplete reporting of data (see Table 1). Little independent replication was found. If any information is given about the phytochemical composition of a preparation and the content of the active ingredient, it is difficult to evaluate the efficacy of the plant or to distinguish between a placebo effect and the actual effect due to the active ingredient when properly dosed.

Where it is possible to identify likely active components within PFS, these levels should be reported to allow for future stratified meta-analysis. Interventions should be carried out over a timescale sufficient to observe a change in the endpoint measured. Studies must be controlled for the full length of the intervention, and the placebo effect must be included. The use of solely positive controls where a high placebo effect might be reasonably expected could be considered misleading. The metabolism of suspected active ingredients must be considered during study design, randomization, and analysis. The use of an adequate statistical analysis must be considered as a priority to evaluate the good quality of the work.

In conclusion, in the future, it is advisable to conduct studies with more homogeneous population and larger number of subjects by avoiding the heterogeneity of the herbal preparations considered.

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