Phytotherapy for osteoarthritis

Evidence derived from two Cochrane reviews

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Summary

Background. In order to present recent findings on the effectiveness and safety of phytotherapy for treatment of osteoarthritis (OA) we summarized the two latest Cochrane reviews (Cameron & Chrubasik, 2013; Cameron & Chrubasik, 2014). One of them included oral and the other topical herbal treatment options as a treatment for OA.

Methods. We conducted a thorough evaluation of the Cochrane reviews. We assessed methodological quality of the reviews and extracted evidence.

Results. Meta-analyses found evidence for effects of the oral herbal products *Boswellia serrata* and only partially for avocado-soybean unsaponifiable (ASU). However, they included only a small number of primary studies. The systematic review on topical herbal treatments included fewer trials and did not include a meta-analysis.

Discussion. Based on the qualitative synthesis *Boswellia serrata* can be applied in the treatment of OA. It is not clear if ASU can be recommended. No valid recommendation can be given for or against other herbal therapies due to a lack of randomized clinical trials in the field.

Osteoarthritis (OA) is a very common illness. 12.4 million people in Germany suffer from this degenerative illness of the joints, which represents the major cause of disability among adults [1]. Approximately half of the general population will experience osteoarthritis in their lifetime [1]. Typical symptoms of OA include pain, stiffness and limitation of movement, which leads to impairment in quality of life [2]. OA commonly affects knee, hip and hand joints. The main problem related to OA derives from its chronic and progressive course [1]. Despite a relative broad spectrum of available treatment options the illness is still considered as incurable [3]. Established standard therapies such as pharmacological options (usually with non-steroidal anti-inflammatory drugs, NSAIDs) and physiotherapy or in advanced stages a surgical intervention, which aims to replace the affected joint-arthroplasty, usually include a substantial risk of relevant side effects and their effectiveness has been controversially discussed [4–5]. Phytotherapy has been used for centuries as treatment of OA [6–7]. Nowadays, there are many herbal products on the market, which promise to aid patients suffering from OA. However, a valid recommendation for a specific herbal product can be only based on serious research.

Many herbal products are sold as treatments for OA. What do we know about their level of evidence? © istockphoto

Two recently published Cochrane reviews conducted by the same research group cover a large number of different herbal treatments for OA. In addition, the results of the reviews will be presented. Finally, the practical implementation of those findings will be discussed.

Methods used in the Cochrane reviews

One of the reviews focused on oral [6] and the other on topical herbal therapies [7]. Considering that oral herbs have a mechanism of action which substantially differs from the mechanisms of topical herbs the proposed differentiation seems to be appropriate.

Subjects of interest were patients diagnosed with OA of the knee, hip or hand according to established diagnostic criteria proposed by American Colleague of Rheumatology (ACR) or European League Against Rheumatism (EULAR). To be included in the systematic reviews, studies had to be conceptualized as randomized controlled trials. Studies which compared an active group to placebo or any other active control were eligible. Both reviews included studies which reported findings for pain intensity, physical function, ad-

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verse events, withdrawals due to adverse events and quality of life. Radiographic joint changes were only eligible in the review, which summarized the findings of effectiveness and safety of oral herbs, expecting only oral herbs to aid renewing the joint structure.

Besides a computerized search of databases (Cochrane Central Register of Controlled Trials, DARE, MEDLINE (via Ovid), MEDLINE (Ovid MEDLINE In-Process & Other Non-Indexed Citations) EMBASE (via Ovid), CINAHL (via Ovid); CINAHL via EBSCOhost, AMED (via Ovid) and ISI Web of Knowledge), the systematic search strategy also included steps which aimed to find so-called "grey literature", i.e. non-published trials which explored the effects of oral herbal products. Study selection and data extraction procedures were conducted independently by two authors.

Results of the Cochrane reviews

Oral herbs

A total of 49 RCTs, which tested the effectiveness and safety of 33 different interventions, were finally included in the systematic review, which covered the oral herbal products. According to the flow chart and the description in the chapter "Results of the search" only 7 [9–16] of those 49 RCTs were pooled to conduct meta-analyses. Those studies covered two herbal preparations: *Boswellia serrata* and Avocado-soybean unsaponifiables (ASU). Heterogeneity across the trials made a quantitative analysis of a larger number of individual findings not feasible. Heterogeneity was caused by different characteristics of the included studies regarding the choice of population, intervention and outcome measurement. However, it seems that the major reason for heterogeneity were the diversities in the type of intervention. ▸ **Table 1** shows characteristics of the studies covering *Boswellia serrata* and ASU.

Boswellia serrata

Four RCT's examined effects of oral *Boswellia serrata* [8–11]. However, the authors could not pool the results of all of the extracted studies due to variable brand names of the herbal products administrated across the studies: Cap-Wokvel®, 5-Loxin® and Aflapin®. The results for each of the products were reported separately. There is only one high quality study with Cap-Wokvel® [8] which reported positive effects in comparison to placebo on pain relief and improvement of function. In addition, two RCTs which tested effects of 5-Loxin® met the eligibility criteria [9–10] and were included in a meta-analysis. The studies were comparable regarding the type of intervention in terms of the kind and dose of the active substance (100 mg/day of enriched *Boswellia serrata*) and the duration of the intervention (90 days).

According to the text, there have been three meta-analyses conducted in terms of *Boswellia serrata*: the first one included pain as a dependent variable, the second one function (both of them operationalized by means of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), measured by visual analogue scale (VAS) from 0–100; higher scores stand for more intensive symptomatic), and the third one included adverse events operationalized as relative risk. Mean differences between active and placebo group have been reported as well as equivalent 95% confidence intervals for the first (pain) and the second (function) meta-analysis in the text. Neither results of heterogeneity tests nor results of significance tests of effect size were referred to in the text. Further analysis with a corresponding forest plot can only be seen in the appendix. The meta-analysis of pain delivered following findings: MD=–16.94, 95% CI [–22.39; –11.50]. The risk of adverse events was slightly lower in the 5-Loxin® group than in the placebo group (5-Loxin® 18/48 events, placebo 30/48 events; RR=0.60, 95% CI [39 to 0.92]).

The analyses reveal that *Boswellia serrata* was superior in comparison to placebo in all of the three points: pain, function and risk of adverse events. In case of discreet outcomes (pain and function) the standard measure of effect size has not been reported.

Aflapin® was significantly superior in outcomes: pain, function over placebo in short-term (30 days) and long-term (90 days) but also over 5-Loxin® [10].

The comparison between *Boswellia serrata* and cyclo-oxygenase-2 (COX-2) inhibitor anti-inflammatory drug valdecoxib only showed superiority of the group treated with *Boswellia serrata* in terms of pain [12]. Function was significantly better in the comparison group. Adverse events appeared more often in the group with *Boswellia serrata*. The study, on which the findings were relied on, was not of convincing quality with a high risk of bias in the categories allocation concealment and blinding.

Avocado-soybean unsaponifiable (ASU)

Avocado-soybean unsaponifiable (ASU) is a herbal product from two plants, *Persea gratissma* and *Glycine max*. Its proprietary name is Piascledine®. Six studies examined the effectiveness of it, five studies compared it with placebo [13–17], and one with chondroitin sulfate [18].

Two studies were included in a meta-analysis with a 300 mg daily dose of ASU [13–14]. The effects of Piascledine® were not significantly superior in comparison to placebo SMD=–11.90 95% CI [–23.95; 0.15], Z=1.93, P=0.05, with substantial heterogeneity I^2=77%, three months after the beginning of the intervention. Only effects after a period of six month were significant MD=–10.40, 95% CI [–17.20; –3.60] according to a single study [16]. After 12 months the results were back to insignificance: MD=1.00, 95% CI [–6.58; 8.58] according to another study [16]. With a 600 mg/day dose the effects of the herbal product were significant over placebo in the short-term [15]. Long-term effects (12 months after baseline) were, in contrast, insignificant MD=–0.66, 95% CI [–7.39; 6.07] [17]. The reviewers referred to one study which compared different subgroups of patients who suffer from OA [16]. This study did not shed any new light on the question if patients who suffer from OA of the knee, hip or hand benefit from this intervention. The quality of the study was characterized as low and its results are not reliable.

Taking a daily dose of 300 or 600 mg of ASU was favourable to the patients' func-

▸ **Table 1** Characteristics of the studies covering oral *Boswellia serrata* and Piascledine®.

Herbal product derived from	First author, year	Proprietary name (dose)	N (experimental/ control group)	Comparison	Outcome	Items with unclear or high risk of bias (risk of bias tool)	Conclusions
Boswellia serrata	Kimmatkar 2003	Cap-Wokvel® (1000 mg / day)	30 (15 / 15)	placebo	pain, function	other bias, diagnose not according to ACR or EULAR (unclear risk)	significant stronger effects of *Boswellia* on pain and function over placebo
Boswellia serrata	Sengupta 2008	5-Loxin® (100 and 250 mg / day)	70 (24 / 23 / 23)	placebo	pain, function, adverse events	allocation concealment, incomplete outcome data, selective reporting and other sources of bias (unclear risk of bias)	*Boswellia* showed stronger effects on pain and function and equivalent relative risk of adverse events. Stronger doses were not more favourable
Boswellia serrata	Sengupta 2010	5-Loxin®, Aflapin® (100 mg/day)	60 (19 / 19 / 19)	placebo	pain, function, adverse events	incomplete outcome data – attrition bias (unclear risk)	both products of *Boswellia* showed stronger effects on pain, function over placebo and equivalent relative risk of adverse events like in the placebo group
Boswellia serrata	Vishal 2012	Aflapin® (100 mg / day)	60 (30 / 30)	placebo	pain, function, adverse events	incomplete outcome data – attrition bias (unclear risk)	*Boswellia* showed stronger effects on pain, function and equivalent relative risk of adverse events in comparison to the placebo group
Persea gratissma and *Glycine max* (avocado-soybean unsaponifiables (ASU)	Appelboom 2001	Piascledine® (300 mg / 600 mg)	260 (86 / 86 / 88)	placebo	NSAID use (diclofenac equivalents), days without NSAIDs, pain, function, adverse events	random sequence generation, allocation concealment and blinding (unclear risk of bias)	ASU was superior over placebo for pain relief, function improvement and NSAID use. Adverse events were equivalent to the placebo group
Persea gratissma and *Glycine max* (ASU)	Blotman 1997	Piascledine® (300 / 600 mg / day)	163 (80 / 83)	placebo	NSAID use, pain, function	allocation concealment, selective reporting (unclear risk)	ASU showed significant effects on pain reduction and improvement of function over the placebo group
Persea gratissma and *Glycine max* (ASU)	Lequesne 2002	Piascledine® 300 (300 mg / day)	55 (30 / 25)	placebo	NSAID use, pain, function, joint space width		neither pain reduction nor improvement of function were significant stronger over placebo 12 months after the beginning of the intervention. Adverse events were equivalent to the placebo group
Persea gratissma and *Glycine max* (ASU)	Maheu 1998	Piascledine® 300 (300 mg / day)	162 (84 / 78)	placebo	pain, function, adverse events		significant effects of pain relief and function improvement in comparison to placebo. Adverse events equivalent to the placebo group
Persea gratissma and *Glycine max* (ASU)	Maheu 2013	Piascledine® 300 (300 mg / day)	345 (166 / 179)	placebo	pain, function, adverse events	selective reporting (unclear risk)	no significant effects on pain relief, improvement of function over placebo 36 months from the baseline. Adverse events equivalent to the placebo group
Persea gratissma and *Glycine max* (ASU)	Pavelka 2010	Piascledine® 300 (300 mg / day)	361 (183 / 178)	chondroitin sulphate, 1200 mg	pain, function and use of rescue medication		when compared to chondroitin sulphate, ASU was not inferior on any outcome

The preparation of the *Boswellia serrata* resin is the only recommended herbal medicine in treating osteoarthritis. © Dinesh Valke

tioning during the first three months. The effects of ASU were significantly stronger than the effects of placebo on improvement of physical functions. Meta-analysis of two studies was conducted as seen before and showed following results: SMD = –1.80 95% CI [–2.68; –0.92], Z = 4.03 (P = 0.000057), I^2 = 32%. One study revealed that the effects of ASU remained significant after a period of six months MD = –13.20, 95% CI [–20.00; –6.40] [16]. Based on one trial the effects of ASU were insignificant after 12 months: MD = 0.10; 95% CI [–0.78; 0.98], Z = 0.22, P = 0.82. Additionally the effects of ASU stayed insignificant after 36 months: MD = –1.00; 95% CI [–7.14 to 5.14] [17]. The overall effect was: SMD= –0.42, 95% CI [–0.73; –0.11]; Z = 2.63, (P = 0.0085), with a high heterogeneity I^2 = 74%.

There is no convincing evidence that Piascledine® can improve the joint structure. There are two studies which tried to answer the question if ASU can improve joint space width. One of those studies failed to deliver sufficient data for extraction; therefore, its results could not be discussed in the review [17]. In the other study the group which had space joint width above the median at baseline showed no superiority in comparison to the placebo group. Participants with space joint width under the median at baseline showed a significantly smaller reduction of joint space width after the treatment with ASU than placebo. Compared to baseline changes the effects stayed insignificant. The study delivering these findings was of a high quality [15].

All of the five studies reported adverse events, showing principally that patients treated with ASU reported no more adverse events than in the placebo groups. All of them were meta-analyzed: ASU 267/521, placebo 270/529, Risk Ratio (RR) = 1.04, 95% [0.97; 1.12], Z = 1.09, P = 0.28, I^2 = 0%.

Other herbs derived from one plant

The review included 12 other monoherbal products besides *Boswellia serrata*. Based on the evidence presented in the review a valid conclusion about the effectiveness of *Curcuma domestica*, *Derris scandens*, *Garcinia kola*, *Harpagophytum procumbens* (devil's claw), *Petiveria alliacea* (tipi tea), *Pinus pinaster*, *Ricinus communis*, *Rosa canina lito*, *Salix daphnoides*, *Uncaria guianensis* (cat's claw), *Vitellaria paradoxa* and *Zingiber officinale* (ginger) could not be made. In most of the studies, the monoherbal products were compared to one of the NSAIDs. The results were generally favourable to herbal interventions. Nonetheless, the evidence level does not allow to explicitly recommend any of the mentioned monoherbal products.

Herbal preparations derived from two or more plants

There are four herbal preparations included in the review, which consist of two herbals each: *Boswellia carteri* and *Curcuma longa*, *Phellodendron amurense* and *Citrus sinensis* (NP 06-1), *Uncaria guianensis* and *Lepidium meyenii* (Reparagen®) and *Zingiber officinale* and *Alpinia galangal*. Except of Reparagen® all active herbal preparations were significantly better compared to a control group, mostly placebo. Polyherbal products were also included in the review: Korean herbal mixture: SKI306X®, Phytodolor®N, Reumalex®, Chinese herbal mixture: Duhuo JishengWan, Chinese herbal mixture: blood-nourishing, hard-softening, Ayurvedic formulae: A, B, C, D and E, Ayurvedic formula: Antarth, Ayurvedic formula: RA-11, SGC and SGCG, and Japanese herbal mixture: Boiogito. Generally, we cannot state a valid conclusion about the effectiveness of those products. More high quality trials are necessary for future statements.

Topical herbs

Seven different herbs were included in the review.

A topical tincture of *Arnica montana* (Arnica) showed similar effects as a topical gel which contained the NSAID Ibuprofen. There was also no significant difference in adverse events between the Arnica and Ibuprofen group. The study that examined those effects is of high quality [19]. However, based only on this one study it is difficult to bring an overall conclusion and recommendation for practical implementation of topical Arnica. The reviewers graded the evidence level as moderate.

In contrast, topical *Capsicum* showed no significant stronger performance than placebo regarding pain reduction and improvement of function [20]. The risk of adverse events was significant higher in *Capsicum* group (*Capsicum* 278/338, placebo 66/338, RR = 4.12 95% CI [3.30, 5.15]). The evidence was graded as moderate. The study, which examined the mentioned effects, had an unclear risk of bias concerning random sequence, alloca-

tion concealment and incomplete outcome data.

An ointment containing comfrey root (Symphyti radix) showed positive effects on pain relief over the placebo group without any higher risk of adverse events. This study reported an unclear risk of bias regarding selective reporting and other bias [21]. For all other criteria the risk of bias was low.

Topical herbal mixture Marhame-Mafasel [22] as well as stinging nettle (*Urtica dioica*) [23–24] and Chinese herbal mixtures Fufang Nanxing Zhitong Gao (FNZG) or Shangshi Jietong Gao (SJG) [25] showed positive effects on pain relief and improvement of function over the placebo group. But the quality of evidence was varying. The duration of the Chinese studies was limited to seven days. Quality of all the other studies was graded as very low.

In sum, there is some evidence that Arnica and comfrey root may be beneficial for patients who suffer from OA. But these assumptions are based on only one study. Therefore, no serious conclusions can be made regarding the usability of topical herbal products for patients who suffer from OA.

Discussion

Boswellia serrata can be offered to patients as a complementary therapy adjunctive to standard treatment options. Based on the findings the optimal daily dose of the herbal product is 100 mg / day. *Boswellia serrata* can be considered as safe. The evidence level for *Boswellia serrata* was rated as high in the review. Products containing *Boswellia serrata* as an active substance are not approved in Germany. Nevertheless, the compounding pharmacies are allowed to manufacture products with *Boswellia serrata* on physicians' and patients' request.

It is not clear if Piascledine® can be recommended for patients who suffer from OA of the knee due to the inconsistent findings across the studies. This herbal product might help improving the function in short term but it seems that it cannot contribute to pain relief in both short and long term among patients who suffer from OA.

In absence of enough high quality studies, general conclusions cannot be drawn about the effectiveness of the other oral mono- and polyherbal products.

Three RCTs, which investigated the effectiveness and safety of the ginger products acetone extract [25], carbon dioxide extract [26], and a mixture of two ginger species *Zingiber officinale* and *Alpinia galangal* [27], were included. The authors did not pool the results due to the different preparations of ginger.

The evidence for the topical herbal products is limited mostly to one study per product.

The study investigating the effectiveness of Arnica represents a high quality trial. The topical herb seems to be a promising therapy option for patients, who suffer from OA. Further studies should reveal if Arnica can be actually recommended.

The review covering topical herbs revealed that there are solid indications that Capsicum cannot be included in the treatment of OA.

Cameron and Chrubasik [7] could not make valid conclusions on the effectiveness of topical herbal product from *Symphytum officinale* (comfrey) based on one study. Frost et al. 2013 included two other RCTs on comfrey in their systematic review [28]. They argued that comfrey might be beneficial for patients who suffer from OA. Nevertheless, the studies were of low quality. Therefore, a recommendation for comfrey cannot be given.

Safety

The included herbal products can be generally considered as safe. Most of the studies reported the rates of advert effects. Generally, there was no significant difference between the rate of adverse events in the active herbal groups and placebo. In addition, the groups which were treated with herbal products usually reported less adverse events than the groups treated with NSAIDs.

Expectations

At present the efficacy of many herbal products as treatment for OA remained unclear. However, the number of trials covering phytotherapy for OA has been rapidly increasing. It is very likely, that further research can reveal if the certain herbal product can be considered as effective and safe for patients who suffer from OA. Therefore, it would be very helpful to medical practitioners as well as to patients to follow new developments in the research field. We expect that the further findings will help them make informed decisions about the inclusion of the herbal product in the treatment of OA.

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Zusammenfassung

Phytotherapie bei Arthrose: Evidenz zweier Cochrane-Reviews

Hintergrund. Um aktuelle Erkenntnisse über Wirksamkeit und Sicherheit von phytotherapeutischen Präparaten bei der Behandlung von Osteoarthritis (OA) zu erlangen, wurden die beiden neuesten Cochrane-Reviews (Cameron & Chrubasik, 2013; Cameron & Chrubasik, 2014) zusammengefasst. Ein Review befasste sich mit oralen und der andere mit topisch-pflanzlichen Behandlungsmöglichkeiten bei OA.

Methodik. Es wurde eine gründliche Bewertung der beiden Cochrane-Reviews durchgeführt. Wir beurteilten die methodische Qualität der Bewertungen und leiteten daraus Aussagen zur Evidenz ab.

Ergebnisse. Die Metaanalysen offenbarten Nachweise für die Wirkung der oralen *Boswellia-serrata*-Produkte sowie der teilweisen Wirksamkeit der Avocado-Soja (ASU)-Präparate. Die Primärstudien enthielten jedoch nur eine kleine Anzahl von Stichproben. Die systematische Überprüfung der topisch-pyhtotherapeutischen Produkte enthielt nur wenige klinische Studien und beinhaltete keine Metaanalyse.

Schlussfolgerung: Basierend auf der qualitativen Synthese kann eine Behandlung von OA mit *Boswellia-serrata*-Präparaten empfohlen werden. Zur Anwendung von ASU liegt nur unzureichende Evidenz hinsichtlich der Wirksamkeit vor. Aufgrund mangelnder randomisierter klinischer Studien kann keine gültige Empfehlung für oder gegen andere pflanzliche Präparate gegeben werden.