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REVIEW

Effectiveness of *Petasites hybridus* preparations in the prophylaxis of migraine: A systematic review

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Abstract

The objective of this review was to evaluate the strength of evidence of effectiveness for *Petasites hybridus* in the prophylaxis of migraine. Several databases and other sources were searched to identify randomised-controlled trials investigating *P. hybridus* preparations. Two trials totalling 293 patients (60 and 233 patients) were included in this review. Both trials investigated the proprietary *Petasites* root extract Petadolex®. The trials were described in narrative way, taking into consideration methodological quality scores. Pooling of data was not carried out due to the heterogeneity of the results. The extract at higher dose (150 mg) showed a greater decreased frequency of migraine attacks and a greater number of responders (improvement >50%) after treatment over 3–4 months than the extract at lower dose (100 mg) and placebo. Moderate evidence of effectiveness is, thus, available for a higher than the recommended dose of the proprietary *Petasites* root extract Petadolex® in the prophylaxis of migraine. Further rigorous studies are required to confirm effectiveness and safety in long-term use before treatment with *Petasites* root extract can be recommended as an alternative option in the treatment schedule for the prophylaxis of migraine.

Keywords: *Petasites hybridus* root extract; Migraine prophylaxis; Complementary and alternative medicine

Introduction

Information on efficacy and safety of traditional herbal medicines used in Germany is summarised in the Commission E monographs. *Petasites* root was recommended as a supportive treatment for acute spastic pain in the urinary tract (N.N., 1998a) in the 1990 revised version of the Commission E monographs but *Petasites* leaf was not recommended for treating pain, colic and headaches due to risks and lack of documentation (N.N., 1998b). At that time, the anti-spasmodic effect had been demonstrated experimentally for the methanolic extract from fresh roots (Bucher, 1950). Since then, research has shed further light into the mechanism, safety and clinical effects of *Petasites hybridus* root and leaf preparations. Proprietary lipophilic root extracts have been shown to preferentially inhibit cyclooxygenase (COX)-2 independent of their petasin content (Fiebich et al., 2005). Ethanolic root extract and the leaf extract Ze339 have been shown to inhibit the lipoxygenase pathway in various in vitro models (Brune et al., 1993; Thomet et al., 2001) and as effective as the synthetic 5-lipoxygenase inhibitor zileuton (Thomet et al., 2001). The co-active ingredients, the petasins, have been demonstrated to have calcium channel blocking effects (Thomet et al., 2001; Wang et al., 2002; Wu et al., 2002). The combined anti-spasmodic,

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anti-inflammatory and calcium channel blocking effects of *P. hybridus* provide a rationale for its use in the prophylaxis of migraine. The aim of this study was to evaluate the strength of evidence of effectiveness of *P. hybridus* preparations as migraine preventives.

Methods

Computerised literature searches were carried out (MEDLINE, PUBMED, COCHRANE COLLABORATION LIBRARY, EMBASE (Ovid technologies) (back to 1980 until end of july 2005, terms *P. hybridus* ''or'' *Petasites* ''or'' butterbur ''or'' Pestwurz; drug effects; heachache ''or'' migraine) and manually examined to identify randomized controlled trials investigating preparations from *P. hybridus* in the prophylaxis of migraine. Trials were selected and data extracted by two independent reviewers (RKD, JEC). The following data were extracted from each study: authors' names; date of publication; country of origin; type of study, including number of study centres; participants (numbers, disease(s), characteristics of the study population (age, size, weight, gender); duration of acute exacerbation or chronic disease; baseline values with details on pain and previous treatments; additional treatments; types of outcome measures; summary statistics; timing of outcome assessment; withdrawals and drop-outs; and adverse events.

Methodological quality and level of evidence were assessed as described in previous reviews (Gagnier et al., 2004; Chrubasik et al. 2006): Quality items: A, eligibility criteria specified; B, randomisation appropriate; C, treatment allocation concealed; E, similarity at baseline; F, outcome measures and control interventions explicitly described; G, co-interventions comparable; H, outcome measures relevant; I, adverse events; J, drop-outs fully described; K, sample size based on a priori power calculation; L, intention-to-treat analysis; N, point estimates and measures of variability, presented for the primary outcome measure; O, appropriate timing giving a total score (TS) of 13 with a cut off of 10 for high quality. The level of evidence of effectiveness was defined as *strong*-pooling of data or at least two confirmatory studies demonstrating a clinical relevant effect, *moderate*-consistent findings among one confirmatory and one or more exploratory studies of high internal validity with a clinical relevant effect and/or multiple exploratory studies of high internal validity, *insufficient*-multiple exploratory studies of low internal validity or one single study of high internal validity indicate effectiveness, *conflicting*-inconsistent findings among two confirmatory studies and/or multiple exploratory studies, *no evidence* from trials – no randomised-controlled trial.

Results

A total of 101 citations (8 in MEDLINE, 38 in PUBMED, 17 in COCHRANE COLLABORATION LIBRARY, 38 in EMBASE (Ovid technologies) were screened identifying four randomised-controlled studies (RCTs) (Grossmann and Schmidramsl, 2000; Grossmann and Schmidramsl, 2001; Diener et al., 2004; Lipton et al., 2004) of which two being a duplicate preliminary publication (Grossmann and Schmidramsl, 2000, 2001). All trials were carried out with the proprietary extract – Petadolex® – from the underground parts of *Petasites hybridus* (solvent supercritical carbon dioxide) standardised to contain a minimum of 15% petasins and practically free of toxic pyrrolizidine alkaloids (content below 0.088 ppm). Full description of the studies is placed on the webpage http://www.kopfwww.ch, see Services).

Two studies (Diener et al., 2004; Lipton et al., 2004) were of high quality (TS 10, 11; Table 1) but only one was confirmatory with a priori case calculation, power 80% (Lipton et al., 2004). Pooling of data seemed not to be reasonable due to the heterogeneity in the results. Daily consumption of 150 mg root extract over 3 or 4 months was associated with a decreased frequency of migraine attacks and a greater number of responders (improvement $>50\%$) compared to the 100 mg dose or placebo.

Discussion

Preventive treatment of migraine is increasingly used to decrease attack frequency and to prevent disease progression (Silberstein, 2005). However, the risk of adverse events associated with synthetic anti-migraine medications may significantly affect patient compliance (Massiou, 2003). For this reason, complementary and alternative treatments are ''en vogue'' (Edmeads et al., 1993; Von Peter et al., 2002; Rossi et al., 2005), even though their efficacy and safety are insufficiently evaluated. For example, the European Scientific Cooperative on Phytotherapy recommends the use of *Tanacetum parthenium* preparations (English term: feverfew) for the prophylaxis of migraine (N.N., 2003), eventhough a recent systematic review including 5 RCTs (343 patients) did not provide sufficient evidence for its effectiveness (Pittler and Ernst, 2004).

In Germany, the butterbur root extract Petadolex® is advertised as a preventive herbal remedy for the prophylaxis of migraine (e.g. www.worldwidehealthcenter.net/category.php?prod=88). This systematic review shows that there is only moderate evidence for its effectiveness based on one confirmatory and one exploratory clinical trial. Further rigorous studies are still needed to confirm the beneficial effect of the 150 mg dose/day and if possible also for double that dose

Table 1. A, eligibility criteria specified; B, randomization appropriate; C, treatment allocation concealed; E, similarity at baseline; F, outcome measures and control interventions explicitly described; G, co-interventions comparable; H, outcome measures relevant; I, adverse events; J, drop-outs fully described; K, sample size based on a priori power calculation; L, intention-to-treat analysis; N, point estimates and measures of variability presented for the primary outcome measure; O, appropriate timing giving a total score (TS) of 13

Quality items	Eur Neurol 2004;51:89–97 ($N = 60$) (100 mg/day vs. placebo – parallel over 12 weeks)	Neurology 2004;63:2240–2244 ($N = 233$) (100 mg; 150 mg/day vs. placebo – Parallel over 16 weeks)
A	Migraine (IHS)	Migraine (IHS)
B	Yes	Yes
C	Yes	Yes
E	Do not know	Do not know
F	Yes	Yes
G	Do not know	Do not know
H	Yes	Yes
I	Yes	Yes
J	Yes	Yes
K	No	Yes (power 80%)
L	Yes	Yes
N	Yes	Yes
O	Yes	Yes
TS	10	11
See K	Exploratory	Confirmatory

(300 mg) (Schulz, 2005). It is also required that more baseline data are presented, e.g. consumption of nicotine, alcohol, estrogens, which type of anti-migraine treatment was used in the past, its dosage, any migraine triggers, state of depression and many more in order to have greater transparency among the populations to assure their comparability.

So far, the overall effect size of the 150 mg extract dose seems to be small (approximately a 15% lower migraine frequency rate per month or a 15% higher responder rate (in terms of more than 50% improvement) compared to placebo.

Unfortunately, there are no general recommendations on how *changes* in outcome measure (effect size) should be expressed (Chrubasik et al., 2005). We recently used data from a published study to express changes in commonly used modes of presentation (the mean of the change from baseline divided by the individual baseline, the median of the change from baseline divided by the individual baseline, the mean of the change from baseline divided by the SD of baseline and the median of change from baseline divided by the SD of baseline). The results showed that the correlations between different ways of expressing effect sizes were poor and the perceived relative magnitudes of various effects depended on how they were expressed. Organisations aiming at consensus ought therefore to recommend the way in which changes ought to be expressed. Comprehensive description of the baseline data is also necessary to exclude any bias. Authors should therefore present their data as fully as possible on a website.

Gastrointestinal adverse events may occur during treatment with butterbur preparations, but any damaging effect on the gastrointestinal mucosa is not to be expected (Brune et al., 1993). Toxicity studies confirm the safe use of the extract (Danesch and Rittinghausen, 2003). Safety data from clinical trials and post-marketing surveillance studies indicate that the incidence of potential hepatotoxicity associated with long-term administration of the proprietary butterbur extract (which is practically free of toxic pyrrolizidine alkaloids) is very low (Diener et al., 2004). Liver injury may also occur during treatment with NSAIDs (Garcia Rodriguez et al., 1994). Enrichment of the active principle might result in better clinical efficacy but further safety studies are required.

In summary, there is to date moderate evidence of effectiveness for a 3–4 months daily treatment with 150 mg *Petasites* root extract Petadolex® in the prophylaxis of migraine.

Statement

The product manufacturer of Petadolex® Weber and Weber, Germany, has had no involvement (financial, conceptual, or otherwise) in this project.

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