Herbal remedies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Lipton et al, 2004[506] **Study design:** RCT **Comparison:** Butterbur vs placebo **Setting:** 9 primary care or specialist centres in USA and Germany **Duration of follow-up:** 4 week baseline, randomised to treatment for 16 weeks	**Patient group:** Adults with migraine with or without aura. **Inclusion criteria:** Aged 18-65. Range of 2-6 attacks per month for 3 months prior to study. Age at onset of migraine was younger than 50. Patients required to have a minimum of 2 attacks during baseline phase. Other prophylactic medication had to be discontinued at least 3 months prior to study participation. Participants excluded if they had more than 6 non-migraine headaches per month during the previous3 months prior to the study. **Exclusion criteria:** Non- migraine attacks for >6 days per month during the previous 3 months prior to start of the study. women who were pregnant, breast feeding, or of child bearing potential not using medically accepted birth control measures were excluded. **All patients** **N:** 245 **Drop outs:** 31 **Group 1 – 50 mg bid [mean, range]** **N:** 79 **Age (mean, range):** 41 (22-60) **Female (%):** 87 **Drop outs:** 8 **Type of migraine: with aura:** 16	**Group 1 – 50 mg bid butterbur root extract** Single capsule, twice a day **Group 2 – 75 mg bid butterbur root extract** Single capsule, twice a day **Group 3 - placebo** Single capsule, twice a day 4 week baseline then, 16 week treatment	**Change in patient-reported headache/migraine frequency** Mean % change in headache frequency	**Month 3** **Group1:** 42 **Group 2:** 58 **Group 3:** 26 **Month 4** **Group1:** 40 **Group 2:** 51 **Group 3:** 32	**Funding:** NR **Limitations:** >10% study population dropped out. Reported as mean % change therefore data cannot be pooled. **Notes:** Patients taking <80% of medication considered non compliant. Randomisation schedule performed by computer program. Each centre allocated a block of patient numbers and associated treatments. Double blind study medication assembled for each patient number according to the randomisation code prepared by an independent statistician. Analyses carried out on ITT population. *n calculated by NCGC.
			Responder rate* 50% reduction in migraine attack frequency per month relative to baseline	**Month 3** **Group1:** 47/79 (59%) **Group 2:** 53/75 (71%) **Group 3:** 39/75 (52%) **Month 4** **Group1:** 44/79 (56%) **Group 2:**51/75 **(**68%) **Group 3:** 37/75 (49%)	
			Incidence of serious adverse events (number of patients) None judged to be treatment related	**Group1:** 0/79 **Group 2:** 3/75 (4%) **Group 3**: 3/75 (4%)	

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	without aura: 55 **both:** 0 **Attack frequency:** 3 (2-6) **Attack days/month:** 3 (2-7) **Attack duration (h):** 13 (4-61) **Attack intensity score:** 2 (1.5-3) **<u>Group 2</u> - <u>75 mg bid</u> [mean, range]** **N:** 77 **Female (%):** 79 **Age (mean, range):** 42 (22-60) **Drop outs:** 9 **Type of migraine:with aura:** 19 **without aura:** 49 **both:** 0 **Attack frequency:** 3 (2-7) **Attack days/month:** 3 (2-7) **Attack duration (h):** 12 (4-45) **Attack intensity score:** 2 (1.5-3) **<u>Group 3</u> – <u>placebo</u> [mean, range]** **N:** 77 **Female (%):** 79 **Age (mean, range)**: 42 (22-58) **Dropout:** 14 **Type of migraine: with aura:** 12 **without aura:** 48 **both:** 3 **Attack frequency:** 3 (2-7) **Attack days/month:** 3 (2-8) **Attack duration (h):** 11 (2-46) **Attack intensity score:** 2 (1.7-2.7)				

Abbreviations: NR=not reported, M/F=male/female, N= number of patients, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, CI=confidence interval,

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Author & Year: Grossman & Schmidramsl, 2000[344] **Study design:** Double blind RCT **Comparison:** Butterbur (Petasites) vs placebo **Setting:** Outpatients, Department of neurology of municipal hospital, Munich-Harlaching **Duration of follow-up:** 4 week run in , 12 week therapy	**Patient group:** Adults with migraine with or without aura. **Inclusion criteria:** Aged 18- 60 years. Minimum of 3 attacks per month within the last 3 months prior to the start of the study and a minimum of 2 attacks in the run-in phase after 4 weeks without trial medication necessary for recruitment. Other inclusion criteria defined by IHS. **Exclusion criteria:** Treatment with other agents known to have an effect on migraine within 4 weeks prior to the start of the run-in phase and regular consumption of analgesics for more than 12 days per month. Other exclusion criteria defined by IHS. **<u>All patients</u>** **N:** 60 **Drop outs:** 2 **<u>Group 1 –</u> 150 mg Petasites hybridus (Butterbur) [mean, SD]** **N:** 33 **Age (mean):** 29 (9.26) **Drop outs:** 2 **Gender % (m/f):** 51/49 **Age at first attack:** 17.6 (4.82) **Attacks per month:** 3.4 (1.06) **Previous therapy (months):** 13.8 (17.23) **Attacks per month:** 3.4 (1.48) **Days with attacks per month:** 3.6	**Group 1- 150 mg Petasites hybridus (butterbur root extract) Diener states 2 x 50 mg per day** 2 capsules twice daily **Group 2- Placebo** 2 capsules twice daily Both groups Patients seen at 4 week intervals	**Patient-reported migraine frequency** Number of days with attacks per 4 weeks (Mean, SD)	**<u>Baseline:</u>** **Group1:** 3.6 (1.93) **Group 2:** 3.0 (1.27) **<u>12 weeks:</u>** **Group1:** 1.8 (0.95) **Group 2:** 2.6 (1.15) **p value:** 0.7172	**Funding:** NR **Limitations:** Grossman 2000 randomisation and AC NR, Diener 2004C both reported. Discrepancy between what Grossman and Diener report in intervention group. **Additional outcomes:** Change in migraine duration. Mean number of accompanying symptoms. **Notes:** Diener 2004C was a reanalysis of Grossman 2000. Re-analysed using Mann Whitney U as data skewed. Reported mean (SD) as first publication did. Figures from Diener 2004C. *n calculated by NCGC.
			Patient-reported migraine intensity Mean per month, SD (VAS)	**<u>Baseline:</u>** **Group1:** 3.9 (0.91) **Group 2:** 3.6 (0.73) **<u>12 weeks:</u>** **Group1:** 3.1 (1.73) **Group 2:** 3.4 (1.08) **p value:** 0.6257	
			Responder rate* 50% reduction in migraine attacks per month from baseline	**Group1:** 16/33 (48%) **Group 2:** 4/27 (15%) **p value:** NR	
			% of patients using acute pharmacological treatment*	**<u>Baseline:</u>** **Group1:** 15/33 (44%) **Group 2:** 7/27 (27%) **<u>12 weeks:</u>** **Group1:** 6/33 (18%) **Group 2:** 7/27 (26%) **p value:** NR	

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	(1.93) **Duration of attacks per month:** 9.4 (3.32) **Intensity of attacks per month:** 3.9 (0.91) **Attacks with acute medication (%) during 4 week run in period:** 20.6 (31.51) **<u>Group 2 - Placebo</u>** **N:** 27 **Age (mean):** 29.1 (9.46) **Drop outs:** 0 **Gender (m/f):** 55/45 **Age at first attack:** 19.7 (5.15) **Attacks per month:** 3.1 (0.85) **Previous therapy (months):** 13.1 (18.51) **Attacks per month:** 2.9 (1.15) **Days with attacks per month:** 3.0 (1.27) **Duration of attacks per month:** 9.3 (3.94) **Intensity of attacks per month:** 3.6 (0.73) **Attacks with acute medication (%):** 12.8 (25.41)				

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Author & Year: Pfaffenrath et al, 2002[625] **Study design:** RCT **Comparison:** Feverfew vs placebo **Setting:** Outpatients, 10 centres in Germany. **Duration of follow-up:** 84 days	**Patient group:** Adults with migraine with or without aura **Inclusion criteria:** Male or female outpatients between 18 and 65 years. Diagnosis of migraine with or without aura according to IHS, migraine attacks for at least 1 year and age of onset <50 years, average of 2 to 6 migraines per month, within the last 3 months prior to study entry, 2-6 migraine attacks within the 4 week baseline period, a total of at least 36 hrs with migraine during the baseline period, stable drug treatment regimen of migraine attacks, patients ability to distinguish between migraine and other headaches, no prophylactic migraine treatment within 4 weeks prior to screening. **Exclusion criteria:** Hypersensitivity to study medication, pregnancy, intake of analgesics, ergot preparations or other established drugs for acute migraine attack on >10 days per month, the use of antidepressants, neuroleptics, tranquilisers, medications for headache prophylaxis, medications with headache as side effect, magnesium containing drugs as well as additional non drug therapies for migraine, >10 days with headaches other than migraine per month, experience with more that 3 different migraine prophylactic drugs in the past, drug misuse or dependency, expected lack of compliance, psychiatric disorders according to DSM-IV, confirmed diagnosis of GI or CV complaints, other severe disease, participation in clinical trials within the last 3 months or simultaneous participation in another clinical investigation.	**Group 1 – 2.08 mg Feverfew** **Group 2 - 6.25 mg Feverfew** **Group 3 – 18.75 mg Feverfew** **Group 4- placebo**	**Patient-reported migraine frequency** Mean (SD) **Group 1 n=28** **Group 2 n=28** **Group 3 n=29** **Group 4 n=25**	**<u>Baseline</u>** **Group1:** 2.8(1.2) **Group 2:** 4.0(1.4) **Group 3:** 3.0(0.9) **Group 4:** 3.3(1.2) **<u>Individual last visit</u>** **Group1:** 2.6(1.8) **Group 2:** 3.2(1.4) **Group 3:** 2.7(1.7) **Group 4:** 2.6(2.1) **<u>Mean change</u>** **Group1:** -0.2(1.3) **Group 2:** -0.9(1.8) **Group 3:** -0.3(1.7) **Group 4:**-0.7(1.9) **95% CI:** NR **p value:** NR	**Funding:** NR **Limitations:** Allocation concealment unclear. 35 dropouts (>10%). Per protocol analysis (n=110) exclude all patients with major protocol violations. **Additional outcomes:** Maximum intensity of migraine attacks (VAS). Attacks with confinement to bed. Missed working days due to migraine. Type and amount of additionally taken medications for the treatment of migraine attacks, but NR. **Notes:** Randomisation after 4 week baseline period. Traditional effective dose 1.05g, equivalent to 6.25 mg extract. Medications prepared as soft gelatine capsules identical in appearance weight size taste and smell. Randomisation in centre
			Responder rate * (More than 50% improvement of migraine attack frequency) N=147	**Group1:** 6/37 (16.2) **Group 2:** 10/36 (27.8) **Group 3:** 9/39 (23.1) **Group 4:** 11/35 (31.4) **95% CI:** NR **p value:** NR	

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	<u>All patients</u> **N:** 147 **<u>Group 1 –</u> Feverfew 2.08 mg [mean (SD)]** **N:** 37 **Age (mean):** 42 (15) **Drop outs:** 11 **m/f:**2/7 **attacks of migraine: total #:**2.9+/-1.1 **total duration (h/month**): 86+/-53.1 **attack duration (h):** 33 (21.3) **max intensity (cm/ vas):** 7.3 (1.4) **max severity (score):** 3.3 (0.6) **Days with accompanying migraine symptoms:** 1.7 (1.3) **Missed working days due to migraine:** 0.6 (1.2) **<u>Group 2</u> - Feverfew 6.25 mg [mean (SD)]** **N:** 36 **Age (mean):** 44 (10) **Drop outs:** 8 **m/f:** 5/14 **attacks of migraine: total #:** 3.7 (1.4) **total duration (h/month):** 89.5 (54.6) **attack duration (h):** 26.7 (19.3) **max intensity (cm/ vas):** 7.6 (1.7) **max severity (score):** 3.3 (0.7) **Days with accompanying migraine symptoms:**1.5 (2.0) **Missed working days due to migraine:** 1.3 (1.7) **<u>Group 3</u> - Feverfew 18.75 mg [mean (SD)]** **N:** 39 **Age (mean):** 49 (9)				specific blocks on basis of randomisation code generated by alphamed. Assignment of random numbers to patients was carried out in consecutive order according to time of enrolment into study. -1 serious AE in placebo group- hospitalisation due to ovarian cyst- not related to drug treatment *n calculated by NCGC

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	Drop outs: 7 **m/f:** 1/7 **attacks of migraine: total #:** 3 (1.1) **total duration (h/month):** 96 (69.6) **attack duration (h):** 31.4 (15.7) **max intensity (cm/ vas):** 7.3 (1.5) **max severity (score):** 3.2 (0.6) **Days with accompanying migraine symptoms:** 2.0 (3.1) **Missed working days due to migraine:** 1.2 (2.0) **Group 4 - Placebo [mean (SD)]** **N:** 35 **Age (mean):** 45 (13) **Drop outs:** 9 **m/f**:5/8 **attacks of migraine:** **total #:** 3.2 (1.3) **total duration (h/month):** 92 (63) **attack duration (h):** 30.5 (20.1) **max intensity (cm/ vas):** 7.4 (1.7) **max severity (score):**3.3 (0.7) **Days with accompanying migraine symptoms:** 1.7 (2.2) **Missed working days due to migraine**: 0.9 (1.6)				

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Author & Year: Diener et al, 2005A[224] **Study design:** RCT **Comparison:** Feverfew vs Placebo **Setting:** Outpatients, 10 centres in Germany, 4 in France **Duration of follow-up:** 112 days	**Patient group:** Adults with migraine with or without aura. **Inclusion criteria:** 18 and 65 years. Diagnosis of migraine with or without aura according to IHS, migraine attacks for at least 1 year and age of onset <50 years, average of 2 to 6 migraines per month, within the last 3 months prior to study entry, 2-6 migraine attacks within the 4 week baseline period, a duration of migraine attacks within the baseline period of 4-72 hr, patients ability to distinguish between migraine and other headaches, discontinuation of prophylactic migraine treatment at least 4 weeks (8 weeks for flunarizine) prior to beginning of baseline period. **Exclusion criteria:** Hypersensitivity to study medication, pregnancy, intake of analgesics, ergot preparations or triptans for acute migraine attack on >10 days per 4 weeks, >10 days with headaches other than migraine per month, drug misuse or dependency, expected lack of compliance, psychiatric disorders according to DSM-IV, confirmed diagnosis of GI or CV complaints, other severe disease, participation in clinical trials within the last 3 months or simultaneous participation in another clinical investigation. **All patients**	**Group 1 6.25 mg feverfew (MIG-99)** three times a day for 16 weeks **Group 2 placebo** three times a day for 16 weeks 4 week baseline without migraine prophylaxis followed by 16 week active treatment phase	**Patient-reported migraine days** (baseline and final values) **Mean (SE) [SD*]** Group 1 n=89 Group 2 n=81	**Baseline** **Group1:** 7.04 **Group 2:** 7.04 **3 months** **Group1:** 4.74(0.3) [2.83*] **Group 2:** 5.33(0.31) [2.79*] **4 months** **Group1:** 4.53(0.3) [2.83*] **Group 2:** 5.60(0.31) [2.79*]	**Funding:** Grant from Schaper & Brummer (manufacturer of MIG 99). **Limitations:** Group 1, 22 dropouts (1 early study termination, 18 major violation of inclusion criteria, 3 major violation during treatment phase). Group 2, 35 dropout (2 early termination, 27 major violation of inclusion criteria, 6 major violation during treatment phase). Data unavailable for 45 patients that were randomised without fulfilling IHS criteria (218 patients randomised, ITT n=170 and per protocol n=161). Change in patient-reported headache days- not very clear what population this was calculated from. **Notes:** Randomisation after 4 week baseline period. Randomisation of 4 in centre-specific blocks on the basis of randomisation code generated by Alphamed.
			Responder rate Patients with a >50% decrease of migraine attacks Based on ITT population Average of periods p2 and p3 (2nd and 3rd 28 days)	**Group1:** 27/89 (30.3%) **Group 2:** 14/81 (17.3%) **95% CI:** NR **p value:** 0.047	
			Number of patients with serious adverse events (%) Paper states they had no relationship to study medication	**Group1:** 3/108 (2.7%) **Group 2:** 2/110 (1.8%) **p value:** NR	

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	N: 218 **Age (mean):** 43.1 (12) **<u>Group 1 – Feverfew</u>** **N:** 108 **Age (mean):** 43.5 (12) **Drop outs:** 19 **m/f:** 18/ 89 **Migraine without aura (%):** 90 (84.1) **Age of first onset of migraine:** 21.7 (9.3) **Average duration of migraine attack:** 27.1 (21.4) **Average number of migraine attacks per 4 weeks:** 4.7 (1.0) **<u>Group 2</u>** - <u>Placebo</u> **N:** 110 **Age (mean, SD):** 42.7 (12) **Drop outs:** 29 **m/f:** 19/89 **Migraine without aura (%):** 87 (80.6) **Age of first onset of migraine:** 22.1 (11.2) **Average duration of migraine attack (h):** 25.3 (19) **Average number of migraine attacks per 4 weeks:** 5.0 (1.7)				Assignment of random numbers to patients was carried out in consecutive order according to time of enrolment into study. ITT analysis on 170 patients and per protocol analysis on 161 patients. SD* values calculated by NCGC.

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