THE HOMEOPATHIC ANTIARTHRITIC PREPARATION ZEEL COMP. N: A REVIEW OF MOLECULAR AND CLINICAL DATA

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Zeel comp. N (Zeel) is a homeopathic medication that has been widely used for many years for the treatment of arthritic disorders in a large number of countries worldwide. In recent years, a growing body of clinical and molecular evidence has been accumulating that shed light on the possible antiarthritic effects of this preparation. A number of studies report anti-inflammatory effects from Zeel. In vitro studies have indicated Zeel-mediated inhibition of the pathways involving the enzymes cyclooxygenase-1 and -2, and also the 5-lipoxygenase pathways, affecting levels of both eicosanoids and leukotrienes. Thus, Zeel may reduce the main two classes of molecules responsible for arthritic pain and inflammation. This review describes recent research on Zeel and discusses the need for further studies to clarify the role of the compound in the antiarthritic armamentarium of complementary medicine.

Key words: Arthritis, leukotrienes, homeopathy, cyclooxygenases, prostaglandins

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INTRODUCTION

Zeel comp. N (Zeel, Heel GmbH, Baden-Baden, Germany) is a homeopathic medication that has been widely used for many years for the treatment of arthritic disorders in a large number of countries worldwide. The formulation is prepared according to the guidelines in the German homeopathic pharmacopoeia Homöopathisches Arzneibuch 2000,[1] based on a combination of highly diluted extracts from the plants *Arnica montana* (arnica root), *Sanguinaria canadensis* (bloodroot), *Rhus toxicodendron* (poison oak), and *Solanum dulcamara* (climbing nightshade), and sulfur. Zeel is available as tablets or as injection solution, with slightly different compositions (listed in Table 1). The surge in interest in controlled research on complementary and alternative medicine (CAM) in recent years has led to a number of clinical and laboratory studies on the efficacy and mode of action of Zeel. The findings are beginning to provide a more rounded picture of the mode of action and possible clinical benefits from Zeel, which may be an alternative to commonly used conventional therapies for arthritis, such as nonselective nonsteroidal anti-inflammatory drugs (NSAIDs).

This review surveys the current status of scientific research on Zeel.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs, and until the withdrawal of rofecoxib threw doubt on the entire class, COX-2 inhibitors, are a mainstay of antiarthritis medications. These drugs derive their antiarthritic efficacy from their actions on eicosanoid synthesis. Eicosanoids like prostaglandin, thromboxane, and leukotrienes have important roles in pain and inflammation and are also important in the regulation of vascular homeostasis, gastroprotection, renal homeostasis and bone formation, and pathophysiological processes.[2,3] Two isoforms of cyclooxygenases exist, involved in the generation of eicosanoids. COX-1 converts arachidonic acid to a number of prostaglandins and also to thromboxanes such as TXA_2 (Figure 1). The prostaglandins PGI_2 and PGE_2 are involved in the mediation of inflammatory pain. They also have potent effects on vasodilation and vascular permeability and are involved in modulating normal glomerular filtration rate and blood flow.[4] PGI_2 is a potent vasodilator and inhibitor of platelet aggregation. Additionally, PGE_2 may stimulate bone resorption by increasing the number of osteoclasts, which could contribute to the joint damage seen in osteoarthritis.[5] The common painkiller acetaminophen (paracetamol) has little effect on COX-1 or COX-2 and thus lacks anti-inflammatory activity.

COX-1 is constitutively expressed in a variety of tissues, prominently in the gastrointestinal tract. COX-2 catalyzes the formation of PGE_2 and PGI_2 but is not involved in the production of thromboxanes. Besides the constitutively expressed COX-2 in the kidney, small intestine, central nervous system, and endothelium, the enzyme is rapidly induced (10 to 20-fold) by proinflammatory mediators when the body is under systemic or local stress, such as during shock, injury, infection, or inflammation (Figure 1). The enzyme TXA_2, which is inhibited by NSAIDs but not by coxibs, causes platelet aggregation and vasoconstriction, and the inhibition of this enzyme is the reason for the gastrointestinal bleeding seen with NSAIDs.

Moreover, inhibition of prostaglandin synthesis, both by NSAIDs and by COX-2 inhibitors, is associated with an increased production of leukotrienes. These eicosanoids are also generated from arachidonic acid, mainly by the enzyme 5-lipoxygenase (5-LOX), which thus shares the same substrate as the COX isoenzymes. Inhibiting one or both isoforms of the COX

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Table 1. Constituents of Zeel Comp N

Extract	Amount in mother tincture mg		Dilution of mother tincture	
	Tablets	Injection solution	Tablets	Injection solution
Toxicodendron quercifolium	1.0	10.0	10^{-2}	10^{-4}
Solanum dulcamara	0.3	1.0	10^{-2}	10^{-4}
Sulphur	0.75	3.0	10^{-6}	10^{-10}
Arnica montana	0.5	2.0	10^{-2}	10^{-4}
Sanguinaria canadensis	0.45	1.0	10^{-4}	10^{-4}

enzymes will increase the amount of arachidonic acid substrate available to 5-LOX, with a corresponding increase in leukotriene synthesis. Leukotrienes have similar effects to prostaglandins, that is, they contribute to inflammatory processes and are also implicated in the development of gastrointestinal ulcers.[6] In addition, leukotrienes are potent bronchoconstrictors and are thought to be a major factor responsible for the "aspirin asthma" observed in susceptible patients receiving NSAIDs.[7] There are attempts to develop dual inhibitors capable of inhibiting both the COX and the 5-LOX pathways.[8,9] To date, no such compound is available to the medical community, although several are in late-stage clinical trials, the most advanced being licofelone (Merckle GmbH, Ulm, Germany).[10]

The disadvantages with NSAIDs and COX inhibitors are well known. On average, 1 in 1200 patients taking NSAIDs for at least two months will die from gastroduodenal complications attributable to the NSAID use.[11] Data from the United States show NSAIDs to cause more deaths than multiple myeloma, asthma, cervical cancer, and Hodgkin's disease.[12] Safety concerns with NSAIDs prompted the US Federal Drug Administration to post a white paper on these drugs on the administration Web site.[13] Thus, today there is a lack of attractive alternatives to NSAIDs and emerging conventional drugs and CAM preparations such as Zeel deserve to be surveyed critically for evidence of benefits.

RESEARCH ON THE INDIVIDUAL CONSTITUENTS OF ZEEL

As shown in Table 1, Zeel is comprised of extract from four medicinal plants and of sulfur at low concentrations. Laboratory

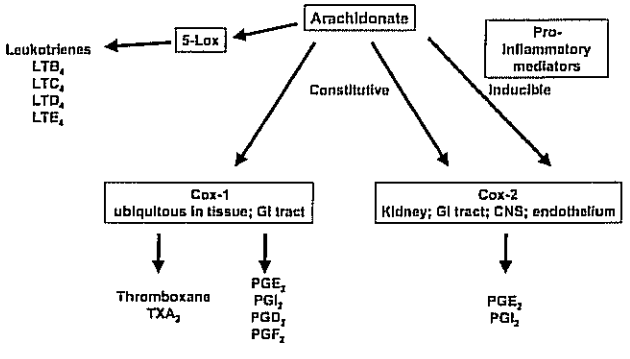

Figure 1. Pathways for the generation of prostaglandins and leukotrienes from arachidonate.

findings from a variety of settings have reported biological activities from compounds extracted from all these biological constituents of Zeel in vitro. Although these findings are not from work on homeopathically prepared solutions, they give information about the phytochemical ingredients of Zeel.

Arnica spps. contain a number of sesquiterpene lactones, mainly helenalin, 11α,13-dihydrohelenalin, chamissonolid, and their ester derivatives. Lyss et al[14] reported that preparations of helenalin specifically inhibit the transcription factor NF-κB. Preparations of 11α, 13-dihydrohelenalin or chamissonolid all had far lower activity against this transcription factor. NF-κB is associated with the expression of proinflammatory genes during the onset of inflammation and with the expression of anti-inflammatory genes during the resolution of inflammation.[14] The inhibition was selective, as the activities of four other transcription factors, Oct-1, TBP, Sp1, and STAT 5 were not affected by treatment with helenalin preparations. This anti-inflammatory activity is different from that of NSAIDs such as indomethacin and acetyl salicylic acid. Inhibitory activity with arnica extract has also been reported against the transcription factor NF-AT in experiments in vitro and in vivo.[14,15]

The *Sanguinaria*-derived benzophenanthridine alkaloid sanguinarium has long been known to have broad antimicrobial activity with minimal inhibitory concentrations in ranges from 1 to 32 μg/mL. Sanguinarium also has anti-inflammatory properties and has also been shown to inhibit bacterial adherence surfaces in vitro. The substance is commonly used as an antibacterial agent in toothpaste and oral rinse products.[16] *Rhus* species is a source of several molecules with antiviral activity; two major antiherpex simplex virus (HSV) compounds, moronic acid, and betulonic acid have been isolated from herbal extracts. In plaque-reduction assays, concentrations for 50% plaque reduction (IC_{50}) could be determined for both moronic acid (3.9 μg/mL) and betulonic acid (2.6 μg/mL) for wild-type HSV virus.[17] In this assay, moronic acid also inhibited acyclovir-phosphonoacetic acid–resistant HSV-1 and thymidine kinase–deficient HSV-1. In vivo studies administering moronic acid orally to mice infected subcutaneously with HSV-1 indicated that moronic acid significantly retards the development of skin lesions and might prolong mean survival times of infected mice.[17]

Besides moronic acid and betulonic acid, *Rhus* species also are a source of a wide range of bioflavonoids, some of which have antiviral activity in assays. Lin et al[18] conducted an extensive characterization of the anti-HIV activities of eleven bioflavonoids isolated from *Rhus succedanea*, as well as their methyl ethers. The compounds amentoflavone, agathisflavone, morel-

loflavone, GB-1a, and GB-2a, were all moderately active against HIV-1 RT, with IC_{50} values of 119 μM, 100 μM, 116 μM, 236 μM, and 170 μM, respectively. Morelloflavone also demonstrated significant antiviral activity against HIV-1 in phytohemagglutinin-stimulated primary human peripheral blood mononuclear cells. Not only viruses are inhibited by bioflavonoids from *Rhus*; Saxena et al[19] reported antimicrobial activity of methanol extracts from *Rhus glabra* with effects both on gram-positive and gram-negative bacteria. Furthermore, *S dulcamara* extract has been demonstrated to contain anti-inflammatory agents in an assay based on inhibitory activity on prostaglandin biosynthesis and platelet activating factor–induced exocytosis in vitro.[20] Of 52 different plants in 28 families, the most potent extracts were from *Geum rivale*, *Geum urbanum* and *S dulcamara*. The same study also reported inhibition of platelet factor–induced exocytosis of the matrix metalloproteinase (MMP), elastase.[21] The expression of several MMPs is increased after injury,[22] and modulation of MMPs can suppress cartilage destruction in experimental osteoarthritis.[23] Disruption of the equilibrium of MMPs and tissue inhibitors of metalloproteinase are observed in pathological situations such as rheumatoid arthritis and osteoarthritis, atherosclerosis, tumor growth, metastasis, and fibrosis.[24-27]

In Vitro Studies With Reconstituted Zeel

The preliminary findings described above indicate anti-inflammatory and antiviral effects from the constituents of Zeel. However, the only certain conclusions that can be drawn from these experiments are that Zeel consists of generally bioactive and anti-inflammatory substances. None of the studies aimed specifically at the eicosanoid system involved in arthritis. It is also unclear how close in vitro assays with isolated compounds relate to the medication itself. A recent series of assays by Jäggi et al[28] with reconstituted Zeel specifically investigated the effects of the preparation and its constituents on components in the eicosanoid pathways: the activities of COX-1 and COX-2 isoenzymes, 5-LOX activity, and the generation of PGE_2 production.

Because homeopathic medications use high dilutions of their components, a concentrating procedure is necessary to conduct dilution assays and to determine IC_{50} values. In the case of commercially available Zeel, such concentration is not easily possible due to the presence of salts in the final product. Thus, to generate dilution series, Zeel was reconstituted from the mother tinctures under controlled conditions without the addition of NaCl. The basis for the reconstitution was the mother tinctures of *A montana*, *S canadensis*, *R toxicodendron*, and *S dulcamara* which were combined with sulfur at a ratio of $2:1:10:1:(3 \times 10^{-6})$, respectively, which accord with the ratios in the commercially available drug. This was done under controlled laboratory conditions, although strict homeopathic procedures were not followed.

The effects of Zeel on the COX-1 and COX-2 isoenzymes were investigated in assays with purified enzymes: COX-1 was from ram seminal vesicles and used at 2 U/mL in the assay; COX-2 was from sheep placenta, used at 1 U/mL. The substrate was arachidonic acid (10 μM), and the amount of PGE_2 produced in the reaction was determined by enzyme-linked immunosorbent assay.[29] In this assay, reconstituted Zeel inhibited both COX-1 and COX-2 activities. Both inhibitory effects were dose-dependent, and IC_{50} values for the inhibition were similar for both enzymes, 50 μg/mL for COX-1 and 60 μg/mL for COX-2. A notable observation was that activities were not restricted to one of the component mother tinctures; separate assays with *A montana*, *S canadensis*, *R toxicodendron*, and *S dulcamara* all showed effects on both isoenzymes. The effects were strongest on the COX-1 enzyme; IC_{50} values ranged from 80 μg/mL, (*A montana*) to 40 μg/mL (*S canadensis* and *S dulcamara*) and 20 μg/mL (*R toxicodendron*). For the COX-2 enzyme, IC_{50} values were 110 μg/mL for *A montana*, 50 μg/mL for *S canadensis*, 150 μg/mL for *S dulcamara*, and 20 μg/mL for *R toxicodendron*. As a comparison, the positive control indomethacin, a common NSAID, showed IC_{50} values of 0.4 μM for COX-1 and 4.0 μM for COX-2, corresponding to 0.2 μg/mL and 2 μg/mL, respectively, for the pure compound. Sulfur did not inhibit the prostaglandin synthesis by isolated COX enzymes.

In an attempt to take another step closer to living systems, the effects of Zeel on PGE_2 synthesis were investigated in a cellular model with phorbol ester myristate–differentiated human macrophages (line THP-1). Cells were activated with lipopolysaccharide (LPS) for 24 hours (stimulating the eicosanoid-synthesis system) before coincubation with arachidonic acid (10 μM) and Zeel at different concentrations for 15 minutes. In this model, a dose-related reduction of the synthesis of PGE_2 was observed (Figure 2). The calculated IC_{50} value for Zeel was 10 μg/mL. This is a low concentration compared with the values obtained with the mother tinctures in the previously mentioned enzyme assays. Comparing different assays is fraught with difficulties, and although the authors speculate on synergistic effects from the compounds when mixed in Zeel, such conclusions seem premature given the differences between cultured macrophages and purified enzymes. The authors reported IC_{50} values for indomethacin of 2 nM in the macrophage model, which would correspond to 1 ng/mL, a substantially lower concentration than in the assay with purified enzymes. This argues for differences between the assays used. Nevertheless, there is a consistency of

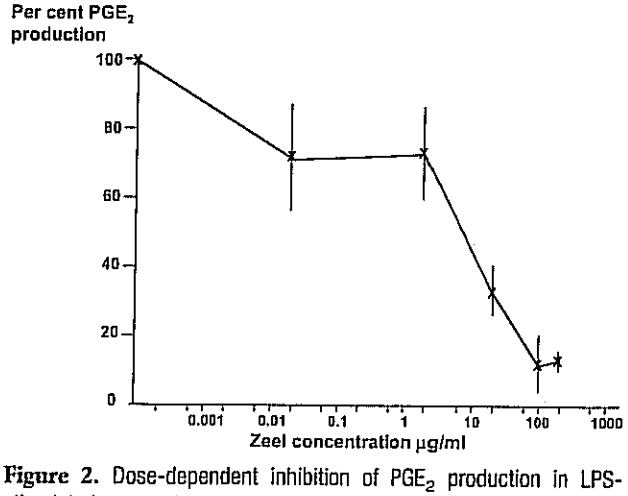

Figure 2. Dose-dependent inhibition of PGE_2 production in LPS-stimulated monocytes treated with reconstituted Zeel comp. N (Zeel). Adapted from Jäggi et al.[28]

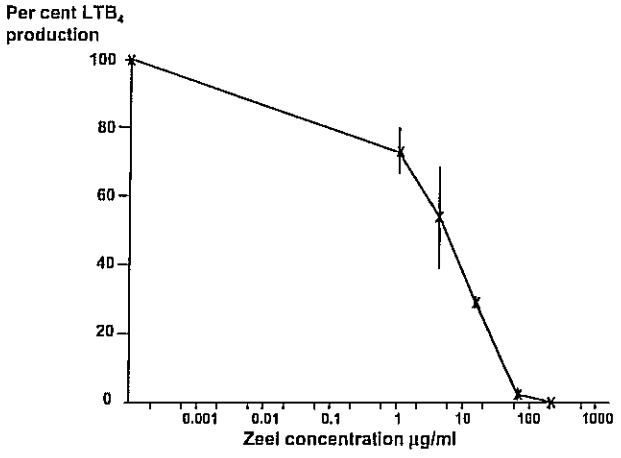

Figure 3. Dose-dependent inhibition of LTB_4 production in dimethyl-sulfoxide differentiated cells and calcium-ionophore stimulated HL-60 cells treated with reconstituted Zeel. Adapted from Jäggi et al.[27]

observations claiming inhibition of leukotriene synthesis with Zeel and its constituent solutions.

The same authors also investigated possible inhibitory effects from reconstituted Zeel and its mother tinctures on the 5-LOX pathways. This was studied an in vitro system of dimethyl-sulfoxide differentiated cells and calcium-ionophore stimulated HL-60 (myeloid leukemia) cells. Such cells express 5-LOX at a high level and react to stimulation with calcium ionophore with an increased production of leukotrienes.[30,31] Cells were differentiated for 6 to 8 days with dimethyl sulfoxide, and differentiated cells were incubated with sample or vehicle for 15 minutes at room temperature before stimulation with calcium ionophore A 23187 (5 µM) and addition of the substrate arachidonic acid (final concentration 10 µM). The concentration of leukotriene B4 (LTB_4) produced by the cells under these conditions was determined by enzyme-linked immunosorbent assay. As shown in Figure 3, reconstituted Zeel combination inhibited LTB_4 production in a dose-dependent manner, with an IC_{50} value of 10 µg/mL. Inhibition of 5-LOX was further observed with the mother tinctures from the constituents *A montana*, *S canadensis*, and *R toxicodendron*, with IC_{50} values of 20 µg/mL, 2 µg/mL, and 5 µg/mL, respectively. The extract of *S dulcamara* did not inhibit LTB_4 synthesis. As a control, nordihydroguaiaretic acid was tested in the same assay and showed an IC_{50} value of 0.5 µM, which corresponds to 0.15 µg/mL. Because of its limited solubility, sulfur was only tested up to a concentration of 10 µg/mL in this assay. At this concentration, the production of LTB_4 was inhibited by approximately 45%.

One drawback of these studies is the uncertainty of generalization to the actual Zeel preparation. As investigations focused on dilution assays, the clinically used homeopathic preparation was not tried in the different models.

ZEEL CLINICAL STUDIES

Reports of clinical benefits of Zeel have come from a variety of settings. One of the earliest clinical reports was a multicenter, randomized, single-blind actively controlled study published in 1996.[32] Patients in this trial (N = 114) had osteoarthritis of the knee (one or both), manifested as pain and verified by radiography showing narrowing of the joint cavity, peripheral osteophyte development, and/or compact ossification of the subchondral bone. Patients with secondary arthritis or acute inflammations were excluded.

Zeel was used in the injectable solution, which was compared with injectable sodium hyaluronate. Because the two medications have visibly different viscosities, the trial was designed as a single-blind study. Patients in the Zeel group received two injections weekly, and patients in the hyaluronate group received one injection weekly. Efficacy was evaluated as a decrease in pain with active movement of the arthritic joint, measured on a visual analog scale from 0 (no pain) to 100 mm. During the five-week treatment period, symptoms improved in both treatment groups. The decrease in pain was 36 mm (range, 67-31 mm) in the Zeel group and 37 mm (range, 63-26 mm) in the control group (P = NS for the comparison). Comparable degrees of improvement were also seen in nocturnal joint pain (reduced from 33 mm to 9 mm with Zeel, and from 35 mm to 7 mm with hyaluronate) and in the duration of morning stiffness. The differences in therapeutic efficacy between the treatments were not significant. After five weeks of treatment, the percentages of patients who were able to walk more than 1 km had increased from 55% to 67% in the Zeel group and from 68% to 79% in the control group. Tolerability, assessed by the physicians as well as by the patients, was considered equally good in both groups.

The definition of therapeutic equivalence used in this study had not been otherwise validated, and the study can be criticized for a certain arbitrariness in setting the boundaries for equivalence, as well as for its single-blinded design. Also, orally available agents would be preferable to injections where possible. Later studies of varying design seem to support the results from this first attempt to investigate clinical benefits from Zeel.

Zeel in the form of tablets was compared with diclofenac in a randomized, double-blind, double-dummy study by Maronna et al.[33] This trial included 121 patients with osteoarthritis of the knee, diagnosed by standard criteria[34] including radiological assessments[35] and a pain index[36] between 5 and 16. Patients were given oral Zeel (1 tablet three times daily) or diclofenac (25 mg three times daily) for 10 weeks. The primary variable was change from baseline to week six in global Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index.[37] Secondary endpoints included change from baseline in global WOMAC score at weeks two, four, and 10, and change in the WOMAC components pain, stiffness, and physical function. The patient groups were balanced at baseline, with similar clinical severity of osteoarthritis; mean WOMAC global score was 5.1 cm in the Zeel group versus 4.9 cm in the group receiving diclofenac. Both treatments reduced global WOMAC scores by similar amounts over 6 weeks: by 26% on Zeel and by 35% on diclofenac ($P < .01$ vs baseline for both therapies). Component scores were also reduced similarly on both therapies, albeit with slightly lesser effect in patients receiving the homeopathic preparation. The benefits increased over time in both treatment groups (with a somewhat more rapid initial improvement on diclofenac) throughout the study.

A prespecified noninferiority analysis was carried out. The criterion for noninferiority was that differences in mean changes between the groups divided by the total standard deviation should be <.01 (one-sided *t* test). Using this criterion, Zeel was shown to be noninferior to the NSAID therapy, with a *P* value <.05.

Tolerability was good in both groups over the 10 weeks, with slightly fewer treatment-related adverse events in the homeopathic group (n = 9) compared with the diclofenac group (n = 12). All adverse events were mild and mainly of gastrointestinal character. There was no bleeding observed on diclofenac during the study.

The main criticism of the Maronna trial[33] is the somewhat arbitrary definition of noninferiority. Also, both studies discussed were on relatively small scales, which may push results towards noninferiority. However, they are consistent in showing benefits with Zeel therapy.

Further data from a pragmatically designed study in a large set of patients were provided in 2003 by Birnesser et al,[38] who investigated 592 patients with stage I or stage II osteoarthritis of the knee as defined by Richter.[39] In contrast to the earlier studies, this was an open, prospective, multicenter, reference-controlled cohort study. Patients received Zeel (three to five tablets per day) or COX-2 inhibitors (109 patients received celecoxib, 100- or 200-mg hard capsules and 160 received rofecoxib, 12.5- or 25-mg tablets). Nonpharmaceutical therapies and short-term use of over the counter pain medications were permitted. Efficacy was evaluated by both physician and patient by using the same validated German version of the WOMAC index as that used by Maronna et al.[33] Individual test parameters were documented for each patient at an entry examination, an interim examination after approximately four weeks, and a final examination after at least six but no more than 10 weeks.

At enrollment, the four cardinal symptoms (initial pain with movement, pain continuing during movement or weight-bearing exercise, pain when fatigued, and joint stiffness or sensation of tension) were of moderately severe intensity in both treatment groups. Efficacy in the Zeel group (n = 323) was generally comparable to that in the coxib group (n = 269). The main differences were in the onset of symptomatic improvements, which tended to be more rapid in the coxib group than in the homeopathic group. Forty-eight percent of patients on coxibs (compared with 20% on Zeel) reported symptomatic improvement within two weeks. However, after six weeks of treatment, there were no significant differences between the groups. Zeel was found to be noninferior to treatment with the two coxibs at an equivalence limit of 10% (one-sided probability of error = 0.025).

More patients (90%) in the Zeel group reported tolerability as "very good" than patients receiving coxibs (74%; $P < .0001$ for between-treatment comparison). No adverse events were reported with Zeel in this study, and the coxibs were also well tolerated, with only one incidence of unspecified gastric complaints that was considered treatment related. These findings are in accordance with the generally excellent tolerability profile of homeopathic medications.[40,41]

Although this was not a randomized study, because of its size and design it may give an insight into the effects of Zeel as perceived by patients and practitioners who opt for a homeopathic treatment rather than conventional therapy.

DISCUSSION

The laboratory and clinical investigations reviewed above provide an unusually large evidence base for a CAM medication, although the number of studies is still low in comparison with research on conventional therapies. Although the definitive clinical trial is still lacking, the consistency of the findings available to date indicate that the benefits reported from Zeel in everyday use may reflect real biological actions of this remedy.

All studies can be criticized on some points. This is true for all scientific endeavors, and no one trial will be able to answer all questions posed by investigators. The published research on effects of extracts from the plants upon which Zeel is based did not specifically target the eicosanoid system. The relevance of the different in vitro assays to what happens in the human body under pathological conditions is unclear. Still, the concordance between findings in such varied settings seems good.

One problem arising in the clinical trials is how to best define noninferiority in a consistent way to compare the effects of treatments. All studies employed a wide use of relatively arbitrary methods for the quantification of results, which relied frequently on patients' subjective experiences of treatment effects and tolerability. A general difficulty is the fact that pain research is an area of medicine where placebo effects are marked, and it is extremely difficult to control and adjust for subjective impressions of effects.[42] Further, the clinical studies with Zeel had modest sample sizes at best. Also, as pilot studies, intentionally none of the studies above was powered to analyze possible superiority of Zeel to the comparator substances. However, the trials represent an interesting initial attempt at studying the effects of a homeopathic preparation under controlled conditions. There is a risk that randomized controlled trials, the gold standard of medical research, may fail to capture the wide range of patients who are attracted by CAM.[43,44] A complicating point is that most randomized trials explicitly do not individualize treatment, which is the hallmark of homeopathic practice.[45] Thus, it would be desirable to complement the evidence base for Zeel with more clinical trials of various designs and in various populations.

In the trade-off between efficacy and tolerability, tolerability scores seem more favorable with Zeel compared with NSAIDs and coxibs, whereas efficacy, at least during the relatively short-treatment periods of the available studies, is similar or slightly lower. This tolerability advantage over conventional medications is common to many CAM remedies and may be particularly relevant for the treatment of arthritic symptoms with their long durations of therapies. It should be pointed out that the long-term tolerability profile of Zeel has not been addressed in the available clinical trials, and discussions on this topic remain speculative.

Long-term studies are expensive, but some potential benefits from Zeel would only emerge over years of treatment. One such effect, unproven today, regards the potential benefits from the *S dulcamara* component of Zeel to inhibit platelet factor–induced exocytosis of elastase.[21] Among other activities, elastase is in-

volved in matrix breakdown by macrophages, a critical process in adaptive remodeling of vessels and in the pathogenesis of arterial diseases.[46] Reduced elastase levels have been suggested as an etiological factor in atherosclerosis,[47] and increased levels have been shown to reduce cholesterol accumulation in the rabbit aorta.[48] Such potential atherosclerotic benefits from a CAM remedy would be highly promising, but today there is no evidence to support this.

In summary, although the evidence base is still relatively weak, research on Zeel indicates benefits beyond placebo and has produced some mechanistic data to support speculation about possible modes of action. Patients with arthritis are known to take recourse widely to CAM remedies; studies have indicated that 60% to 90% of persons with arthritis, particularly those with rheumatoid arthritis, have used CAM.[49-53] With such great interest, the need for objective assessments of available CAM remedies is urgent.

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