

Alternative medicine on trial

Clinical trials home in on complementary therapies and complex natural products

Philip Hunter

Natural products have been a major source of drug discovery dating back well before the discovery of penicillin, but this has usually involved the isolation and purification of single compounds that can readily be tested for efficacy and safety through clinical trials. Yet, developments in biotechnology and changes in drug-testing regulations have encouraged the search for complex therapeutic formulations from living organisms, especially plants. In 2006, the US Food and Drug Administration (FDA) introduced a new regulatory class called 'botanical drugs', defined as multicomponent extracts of plants intended to cure or prevent disease. This move, in turn, has triggered a spate of clinical trials [1]. Such 'natural' products have two potential advantages over synthetic drugs: the multiple components might act synergistically to exert a greater effect than any one component alone, and many natural compounds have a long history of use in traditional medicine, potentially providing valuable initial evidence of efficacy and tolerance.

There has also been an increase in the number of clinical trials focused on evaluating non-drug therapies including exercise, meditation and treatments often referred to as 'alternative' or 'complementary', such as acupuncture. At the same time, scientists have also begun to study the previously much disputed placebo effect, which is now being explored from the perspective of how it can be harnessed to enhance the effect of drugs or surgical treatments.

The success of these new treatments has been mixed. Advocates of acupuncture, for example, should be pleased by the findings of numerous clinical trials showing that it performs better than placebo—where the practitioner

only pretended to insert needles—to treat conditions including relief of chronic pain. But they will be disappointed that it appears not to matter where the needles are inserted [2]. In general, clinical trials for therapies such as acupuncture, as well as exercise or meditation, have largely focused on efficacy for a broad spectrum of conditions.

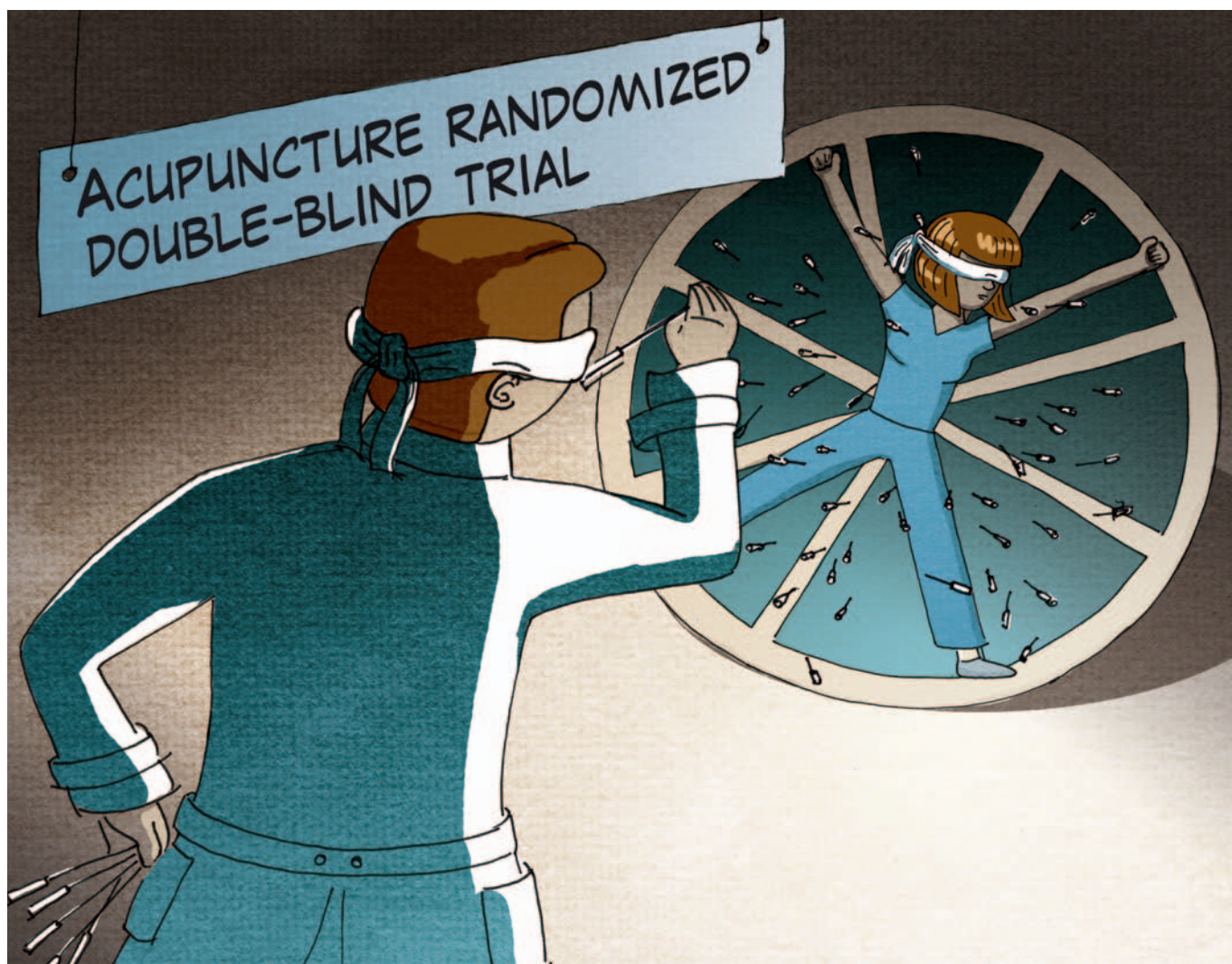
In the case of botanical drugs, the objective has been slightly different: first to establish safety and tolerance and then to investigate efficacy against specific conditions. Few botanical drugs have actually gained approval, but several have progressed far along the clinical trial route to phase III trials. One such drug is the anti-rheumatic PMI-001. It is derived from the perennial vine-like plant *Tripterygium wilfordii*, popularly known as 'thunder god vine', which has been used in China for centuries to treat fevers, and more recently for inflammatory and autoimmune diseases such as rheumatoid arthritis, systemic lupus and psoriatic arthritis.

PMI-001 is produced by extracting the active ingredients from the outer bark of the roots with ethanol, followed by ethyl acetate partitioning. This process yields a cocktail of about 400 compounds, including several now associated with anti-inflammatory effects. The bioactive compounds together have been shown to suppress transcription of pro-inflammatory genes including interleukin 2 (*IL-2*), tumour necrosis factor, inducible nitric oxide synthase and cyclooxygenase 2 [1]. The extract also has a steroid-sparing effect, which means that it reduces the need to also administer the corticosteroid prednisone when used in clinical trials [1]. The extract also has a better side-effect profile than conventional steroids and is being tested in phase III.

One issue with products comprising multiple active compounds, such as PMI-001, is that it is difficult to unravel the precise molecular mechanisms of each component, and even less how they act in synergy. Much the same is the case for Grazax, an extract of grass pollen that has been approved for reducing the incidence and severity of hay-fever. Grazax was approved in 27 European countries under the European mutual recognition procedure, which essentially shortens the regulatory process for new drugs once they have been approved in one country. Grazax showed apparent success in tackling the underlying allergic pathway that produces immunoglobulin E (IgE) in response to grass pollen. IgE binds to mast cells and basophils containing histamine and, thereby, triggers inflammation of the nasal pathways and sometimes the eyes.

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In 2009, Grazax, manufactured by ALK-Abello based in Denmark, obtained a disease-modifying indication. "This label was obtained based on findings from our long-term GT-08 trial in which subjects were followed for five years in a double-blind placebo-controlled manner, including three years with treatment and two years follow-up," explained ALK-Abello's International Medical Director Simon Lawton. "Disease-modifying effect was demonstrable by statistically and clinically significant sustained reduction



in rhinoconjunctivitis symptoms in the post-treatment years of trial.”

Lawton commented that, although the trial demonstrated a lasting reduction of hay-fever symptoms even after the patients had stopped taking the medication, and that although Grazax is known to target the IgE mechanism leading to downstream histamine production, the precise mechanisms are still unclear. The mystery of the efficacy of Grazax has been deepened by the finding that patients actually remain sensitized to grass pollen after taking Grazax, as they still have elevated levels of IgE antibodies, despite displaying reduced symptoms. “The process must therefore target the immune response downstream from this,” Lawton explained. “It is now widely accepted though that, at least in part, allergen-specific immunotherapy results in the production of blocking antibodies and/or

regulatory signals that inhibit the binding of allergen to IgE, and/or the activation of effector cells” [3].

Grazax is an example of a complex natural product that is refined in a way that removes unwanted impurities that might cause side-effects. This is not the case with all biological drugs. Curcumin, the active ingredient of the spice turmeric, for example, requires processing to increase bioavailability and stability [4]. There is accumulating evidence from animal studies—and anecdotally from observations of humans—that curcumin acts as a free radical scavenger and hydrogen donor, as well as having anti-inflammatory and antioxidant properties. However, the case has yet to be established beyond all doubt in a large double-blind clinical trial [5].

This interest in curcumin reflects a broader growing interest in applying rigorous testing to complex preparations of multiple active compounds taken directly from organisms, such as plant leaves. Many of these have been subjected to clinical trials by the National Center for Complementary and Alternative Medicine (NCCAM) at the US National Institutes of Health (NIH; Bethesda, USA). One such product is an ointment derived from green tea that contains antioxidants called catechins and that has been approved in the USA for topical treatment (direct application) to genital warts caused by human papillomavirus [6].

A complex product with broad-spectrum antibiotic activities is Manuka honey, which has received approval for medical use. Its anti-bacterial properties have been firmly established in a clinical setting by a study

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at Cardiff Metropolitan University in the UK, which found that small concentrations of the honey killed 85% of the population of established biofilms comprising the bacterium *Streptococcus pyogenes* within two hours [7]. The bacterium is a big problem for wound healing, especially among immunocompromised patients. Given this, preparations derived from Manuka honey are now used in wound healing and integrated into dressings in some countries, including in the USA.

However, the problem with many natural products is that they can have unusually high placebo effects, which might sometimes be the reason why they were selected as candidates for trials in the first place. "We have learned that the placebo response is high in some of these studies," noted Craig Hopp, Program Officer for NCCAM's Division of Extramural Research. He referenced a study of 89 menopausal women that compared the effectiveness of two popular plant remedies with placebo and conventional hormone replacement therapy for the treatment of hot flushes [8]. The most significant improvements were seen in the women who took menopausal hormone therapy, for whom the average number of symptoms experienced per week fell by 94%. But placebo came second, showing a decline of 63%, compared with 57% for red clover and 34% for black cohosh, indicating that the latter might even have had a negative effect. The phenomenal level of success of the placebo in the study exceeds that of many approved drugs, whereas the poor performance of black cohosh seems disastrous given that it has been approved for use as Remifemin in Germany, where it is the most popular alternative to oestrogen therapy. However, NCCAM pointed out that this is just one of several studies, some of which have reported that black cohosh does better than placebo in reducing hot flushes in women (<http://nccam.nih.gov/health/blackcohosh/ataglance.htm>). Trials are ongoing and have yet to reach any firm conclusion.

These kind of results, in which placebo seems to be so effective, have inspired more rigorous studies of the placebo effect itself. "The placebo effect is now considered to be something 'real'," commented Karin Meissner, who specializes in Placebo Research at Ludwig-Maximilians-University (LMU) in Munich, Germany. "This has been demonstrated by many brain-imaging and neurophysiological studies in the last decade. It has also been shown that verbal suggestions combined with conditioning can affect the efficacy of real drugs. Thus, the placebo effect is no longer considered a sham effect."

Meissner argues that this has implications across the whole of medicine, not least for the conduct of clinical trials themselves, in which the results can be highly dependent on the reputation of the drug or of the centres involved. "There is a lot of evidence now that patients' expectations of outcomes and side-effects in clinical trials predict their individual response," she explained. "There are a few studies in which expectations for side-effects have been manipulated by different informed consent procedures, and results also suggest a close relationship between the expectation of specific side-effects and their actual occurrence."

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The Meissner lab has been investigating many aspects of the placebo effect in an attempt to identify some of the pathways involved and determine how it can be exploited in clinical settings, including general practice surgery. "Training doctors to better empathize with patients is a promising approach," Meissner said. "However, doctors should not simply sympathize with patients, for example by warning them before noxious stimuli, 'you will feel a little sting, now', or by asking 'did I hurt you?' afterwards, since this has been shown to enhance pain. Instead, the patient should be instructed to focus on sensations of cool, tingling, or spreading during painful procedures, and doctors should avoid asking about pain afterwards" (see for example [9]).

There is also scope for exploiting one of the main placebo mechanisms whereby patients become conditioned to a drug and increasingly produce the physiological response as if in expectation

of receiving their regular dose. "The pharmacological conditioning of drug effects may allow us in the future to reduce the dosage of drugs by replacing them from time to time with placebos, without diminishing the clinical benefit for the patient," Meissner explained. "In this way, the toxicity of pharmacological drugs could be reduced."

It is with relation to conditioning, specifically for pain relief, where most progress has been made in identifying the underlying molecular mechanisms of the placebo effect: it operates through expectation or conditioning. If an active drug is used in diminishing doses, the relevant pathways continue to operate as if they 'remember' what they are supposed to do. This has been demonstrated not just for opioid pain relievers, but also for non-opioid drugs that operate on different receptors. "Interestingly, when opioid drugs are used to condition placebo analgesia, the effect can be antagonized by naloxone, an opioid-antagonist, whereas when non-opioid drugs are used to condition placebo analgesia, this response can only be antagonized by rimonabant, a blocker of cannabinoid receptors," Meissner explained. "These results extend earlier findings that different endogenous neuronal networks are activated during placebo analgesia, depending on the way placebo analgesia is induced" [10].

The therapeutic benefits of exercise and meditation have also lately received more attention. Both have been tested in clinical trials to see whether they protect against colds or influenza, measured in terms of reduced absenteeism and less severe symptoms, corresponding to underlying clinical effects. Both have shown highly significant benefits, greater than expected. One US study, published in August 2012, compared the impact of exercise, meditation and doing neither on the incidence and severity of colds or flu in a group of 149 people over an eight-month period [11]. The first group practiced so-called 'mindfulness meditation' during a 45-minute daily individual practice and weekly 2.5-hour group sessions. The second group did moderate-to-intense exercise for the same amount of time, and the third group acted as a control. The meditating group reported a combined total of 257 days of suffering from symptoms of the common cold or flu, the exercise group reported a total of 241 days of illness, whereas the control group reported 453 days. This equated to almost a 50% reduction for the exercise group.

The study's lead author, Bruce Barrett at the University of Wisconsin Madison (USA), commented that a bigger study is needed to confirm these findings, but that he is confident that the benefits of both exercise and meditation will be proven and that this should have serious implications for upper respiratory infections. "If it turns out to be confirmed by another group, providing mindfulness training might be a cheaper way to go than trying to develop anti-viral medications that don't work very well, or that only work for influenza," Barrett commented. The study he led indicates that exercise and mindfulness work by reducing the inflammatory response to the viruses. "Our hypothesis now is that it is not so much about better resistance, but improving the response to the virus," Barrett explained, noting that about half of the people with rhinovirus, the main agent of the common cold, experience no symptoms at all.

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Although breaking new ground for meditation, the Wisconsin study does raise questions about how much exercise is best and whether too much can be counter-productive. However, the Human Performance Lab at North Carolina Research Campus, Appalachian State University (USA), has looked deeper into the relationship between exercise and immunity in general, with one study finding that moderate exercise reduces absenteeism caused by cold or flu by 43% [12]. "We now have results from randomized studies, taking people who were sedentary and starting some of them off on a walking programme lasting 45 minutes a day, and we saw a 40% to 50% reduction in

sick days for that group compared with the others who remained sedentary," said David Nieman, Director of the North Carolina Human Performance Lab.

But an earlier study of 350 athletes, running the 160 km point-to-point trail run in the Sierra Nevada Mountains of Northern California, indicated that extreme exercise increases the risk and severity of infection, at least in the short term [13]. The study reported wide-spread disruption in both innate and adaptive immunity after the event. This period of decreased host protection often occurred one to two weeks after the competition, with elevated rates of upper respiratory tract infections in the athletes. Yet Nieman noted that marathon runners actually experienced low rates of systemic inflammation in their normal resting state, suggesting that even extreme exercise might confer long-term protection against chronic inflammatory conditions.

The combined outcome of Nieman's studies has led him to the belief that around 30–60 min of moderate cardiovascular exercise a day—such as jogging, brisk walking or cycling—is the optimum amount for achieving the greatest protection against all manner of diseases. This is certainly more than most people do and is probably more time than many are willing or able to commit, especially if they are also expected to meditate for 45 minutes a day. But the combined impact of these studies, coupled with the emerging work on natural products and the placebo effect, should give health policy-makers plenty to think about when considering where to direct resources. The outcome might well be a more rounded approach to health care that is more interested in helping the body heal itself where it can, and less focused on finding wonder drugs for every ailment.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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