

## ‘Complementary ENT’: a systematic review of commonly used supplements

P D KARKOS, S C LEONG\*, A K ARYA, S M PAPOULIAKOS†, M T APOSTOLIDOU‡, W J ISSING§

### Abstract

**Objective:** To assess the evidence surrounding the use of certain complementary supplements in otolaryngology. We specifically focussed on four commonly used supplements: spirulina, *Ginkgo biloba*, Vertigoheel® and nutritional supplements (cod liver oil, multivitamins and pineapple enzyme).

**Materials and methods:** A systematic review of the English and foreign language literature. Inclusion criteria: *in vivo* human studies. Exclusion criteria: animal trials, *in vitro* studies and case reports. We also excluded other forms of ‘alternative medicine’ such as reflexology, acupuncture and other homeopathic remedies.

**Results:** Lack of common outcome measures prevented a formal meta-analysis. Three studies on the effects of spirulina in allergy, rhinitis and immunomodulation were found. One was a double-blind, placebo, randomised, controlled trial (RCT) of patients with allergic rhinitis, demonstrating positive effects in patients fed spirulina for 12 weeks. The other two studies, although non-randomised, also reported a positive role for spirulina in mucosal immunity. Regarding the use of *Ginkgo biloba* in tinnitus, a Cochrane review published in 2004 showed no evidence for this. The one double-blind, placebo-controlled trial that followed confirmed this finding. Regarding the use of Vertigoheel in vertigo, two double-blind RCTs and a meta-analysis were identified. The first RCT suggested that Vertigoheel was equally effective in reducing the severity, duration and frequency of vertigo compared with betahistine. The second RCT suggested that Vertigoheel was a suitable alternative to *G biloba* in the treatment of atherosclerosis-related vertigo. A meta-analysis of only four clinical trials confirms that Vertigoheel was equally effective compared with betahistine, *G biloba* and dimenhydrinate. Regarding multivitamins and sinusitis, two small paediatric pilot studies reported a positive response for chronic sinusitis and otitis media following a course of multivitamins and cod liver oil. Regarding bromelain (pineapple enzyme) and sinusitis, one randomised, multicentre trial including 116 children compared bromelain monotherapy to bromelain with standard therapy and standard therapy alone, for the treatment of acute sinusitis. The bromelain monotherapy group showed a faster recovery compared with the other groups.

**Conclusion:** The positive effects of spirulina in allergic rhinitis and of Vertigoheel in vertigo are based on good levels of evidence, but larger trials are required. There is overwhelming evidence that *G biloba* may play no role in tinnitus. There is limited evidence for the use of multivitamins in sinus symptoms, and larger randomised trials are required.

**Key words:** Complementary Therapies; Spirulina; Ginkgo Biloba; Vitamins; Vertigoheel; Otolaryngology

### Introduction

There are many otolaryngological symptoms with an unknown or unclear mechanism. Often, when conventional therapy fails, patients turn to alternative or complementary medicine, despite the scepticism, controversy and lack of evidence that may or may not exist.

### Aims

We attempted to undertake a systematic review of the literature, in an effort to assess the levels of

evidence surrounding the treatment of otolaryngological symptoms with ‘non-traditional’ remedies. We specifically focussed on four widely used supplements: spirulina, *Ginkgo biloba*, Vertigoheel® and nutritional supplements (cod liver oil, multivitamins and pineapple enzyme). As the subject of our review was supplements in ENT practice, we chose to ignore other forms of ‘alternative medicine’ such as reflexology, acupuncture and other homeopathic remedies, which, we believe, should be the subject of a different, separate review.

From the Department of Otolaryngology, University Hospital Aintree, Liverpool, UK, the \*Department of Otolaryngology, Royal National Throat, Nose and Ear Hospital, London, UK, the †Department of Otolaryngology, University of Athens, Greece, the ‡Department of Otolaryngology, University of Thessalia, Larissa, Greece, and the §Department of Otolaryngology, Freeman Hospital, Newcastle upon Tyne, UK.

Accepted for publication: 4 September 2006.

## Materials and methods

We undertook a systematic review of the English and foreign language literature. We included *in vivo* (human studies) only. Animal trials, *in vitro* studies and case reports were excluded.

## Results

### *Spirulina in allergy, rhinitis and immunomodulation*

*Spirulina* or *arthrospira* is a blue-green alga that has gained its claim to fame after it was successfully used by the US National Aeronautical Space Agency as a dietary supplement for astronauts on space missions. *Spirulina* is a microscopic and filamentous cyanobacterium that derives its name from the spiral or helical nature of its filaments. It has a long history of use as a food, with reports of its use during the Aztec civilisation.<sup>1</sup> *Spirulina* refers to the dried biomass of *Arthrospira platensis*, an oxygenic, photosynthetic bacterium found worldwide in fresh and salt water. This alga represents an important dietary staple for humans and has been used as a source of protein and vitamin supplementation, without any significant side effects. Apart from a high (up to 70 per cent) protein content, it also contains vitamins, especially B<sub>12</sub> and provitamin A ( $\beta$ -carotenes), and minerals, especially iron. It is also rich in phenolic acids, tocopherols and  $\gamma$ -linolenic acid.<sup>1</sup> *Spirulina* lacks cellulose cell walls and therefore can be easily digested.<sup>1</sup> There are many toxicological studies that have proven its safety. *Spirulina* belongs to the substances classed as 'generally recognized as safe' by the US Food and Drug Administration.<sup>2</sup>

*Spirulina* is relatively easy to cultivate but flourishes only in alkaline lakes with an extremely high pH and in large outdoor ponds under controlled conditions. There are only a few areas worldwide that have the ideal sunny climate for production of this alga, including Greece (Nigrita, Serres), Japan, India, the United States and Spain. Currently, *spirulina* can be found in health food stores and is sold mainly as a dietary supplement in the form of health drinks or tablets. Microalgae have been used for more than 10 years as dietary supplements, without significant side effects.<sup>3</sup>

It has been well documented that *spirulina* exhibits anti-inflammatory properties by inhibiting the release of histamine from mast cells.<sup>4</sup>

In a recent randomised, double-blinded, placebo-controlled trial,<sup>5</sup> individuals with allergic rhinitis were fed daily for 12 weeks with either *spirulina* or placebo. Peripheral blood mononuclear cells were isolated before and after this period and the level of cytokines (interleukin-4, interferon- $\gamma$  and interleukin-2), important in regulating immunoglobulin (Ig) E mediated allergy, were measured. A high dose of *spirulina* was shown to significantly reduce interleukin-4 levels, by 32 per cent, demonstrating the protective effects of this microalga against allergic rhinitis.

Ishii *et al.* studied the influence of *spirulina* on Ig A levels in human saliva<sup>6</sup> and demonstrated enhanced IgA production, suggesting a pivotal role of the microalga in mucosal immunity.

A Japanese team identified the molecular mechanism of *spirulina's* effects on the human immune system by analysing the blood cells of volunteers before and after oral administration of a hot water extract of *Spirulina platensis*. Interferon- $\gamma$  production and natural killer cell damage were increased after administration of the microalga extracts to male volunteers.<sup>7</sup>

It is well understood that nutrient deficiency can alter immunity, prompting changes in T-cell production, secretory IgA antibody response, cytokines and natural killer cell activity. The above studies suggest that *spirulina* may modulate the immune system via its role in addressing nutritional deficiencies. More randomised, controlled trials are required before *spirulina* can be used for allergic rhinitis patients. A multicentre, placebo-controlled trial is under way in Greece, where *spirulina* is widely produced.

### *Ginkgo biloba in tinnitus*

*Ginkgo biloba*, or maiden hair tree, has been well known for its medicinal value for thousands of years. Chinese manuscripts dating from the Han dynasty (circa 206BC to 220AD) mention the use of ginkgo leaf extracts for skin problems, lung ailments and to improve blood circulation. Traditionally, the leaves have either been eaten raw or drunk as a tea. Whilst scientific evidence remains lacking, this has not prevented the growing popularity of complementary and alternative medicine; sales of herbal medicines have boomed into a 4 billion dollar industry in the United States. *Ginkgo biloba*, now marketed as an extract, is one of the top 10 best-selling herbs in health food stores.

The two main active ingredients in ginkgo, flavonoids and terpenoids, are responsible for a vast array of pharmacologic functions, including neuroprotection, antioxidation, free-radical scavenging and membrane stabilisation.<sup>8</sup> In addition, ginkgo improves microcirculation by increasing the fluidity of blood through inhibition of platelet-activating factor. These characteristics have resulted in *G biloba* being commonly used to improve cognitive function, memory, peripheral vascular disease and even tinnitus. Whilst studies<sup>8</sup> have supported the use of *G biloba* in early-stage Alzheimer's disease, vascular dementia and intermittent claudication, its role in tinnitus remains equivocal.

Various studies over the last two decades have attempted to show the benefits of *G biloba* in tinnitus. Unfortunately, early trials were hampered by small sample size, unrandomised sampling or sub-optimal dosing. Ernst and Stevinson suggested that extracts of *G biloba* were effective in treating tinnitus but concluded that further trials, both methodologically rigorous and consistent in outcome measures, were first needed.<sup>9</sup> Of the five studies analysed by these authors, only one was included in the Cochrane review.<sup>10</sup> The other trials were deemed too methodologically weak to be accepted as evidence of a beneficial effect. It was concluded that the limited evidence available did not demonstrate the

effectiveness of *G biloba* for tinnitus, especially in cases in which tinnitus was the primary complaint. Furthermore, *G biloba* had no significant benefit over placebo.<sup>11,12</sup> There was also no reliable evidence to assess the use of *G biloba* in cases in which tinnitus was associated with cerebral insufficiency.

Although the majority of trials have been proved wanting, many do report an improvement in tinnitus. This positive benefit cannot be explained by a placebo effect alone. This has led to a theory that some patients who derive benefit from *G biloba* may have a degree of cerebral insufficiency. Were this to be true and *G biloba* proved to be an effective treatment, the question arises of its mechanism of action. The pharmacological profile of *G biloba* is complex and its action in tinnitus unknown. Moreover, the aetiology of tinnitus remains unanswered and is presumably multi-faceted. Objective methods for assessing the severity of tinnitus are also unavailable. It is thus unsurprising that no 'gold standard' treatment for tinnitus exists.

Tinnitus in cognitive insufficiency is fundamentally different from primary tinnitus. For example, the former condition may be caused by central vascular insufficiency or a neural metabolic disorder, whereas the initiating pathology of the latter condition is a cochlear disorder. Changes in vascular perfusion and neuronal metabolism are well documented effects of *G biloba*.<sup>11,12</sup> Improved cognitive functioning due to *G biloba* allows habituation to the tinnitus. If *G biloba* causes a significant improvement in overall cognitive functioning, then a positive effect on tinnitus may be real but non-specific. Thus, *G biloba* may be effective in this subgroup of patients. More work is needed to verify this before the case is closed on the use of *Ginkgo biloba* in tinnitus.

#### *Nutritional supplements in sinusitis*

Vitamins and nutritional supplements are extremely popular, especially in a modern society which actively pursues healthy living and a wholesome lifestyle. What is commonly overlooked is the fact that a balanced diet would in itself meet all nutritional requirements. Whilst vitamins are important to prevent or treat deficiency, the fad for mega-vitamin therapy is unscientific and can be harmful. This section focuses on three supplements used in the context of sinusitis: cod liver oil, multivitamins and pineapple enzyme.

Cod liver oil is derived from the livers of white fish such as cod and halibut. It is an important source of both vitamin D and long chain fatty acids. These constituents have an anti-inflammatory role. Linday *et al.* studied four children diagnosed with chronic or recurrent sinusitis who were given a course of cod liver oil and a multivitamin.<sup>13</sup> Three had a 'positive response', reported as improved sinus symptoms, reduced frequency of acute sinusitis and fewer visits to the doctor. Based on the results of this small study, these authors concluded that this adjunctive therapy was an inexpensive, non-invasive intervention for children with chronic or recurrent sinusitis.

An earlier trial by the same group, this time studying the effects of multivitamins and cod liver oil on otitis media, showed that responders required a shorter duration of antibiotics than before supplementation.<sup>14</sup>

Bromelain is a complex mixture of proteinases derived from pineapple stem. Anecdotal use of bromelain includes the treatment of sinusitis, arthritis, dental pain, and post-operative pain and inflammation, presumably through an anti-inflammatory mechanism, inhibition of platelet aggregation or fibrinolytic activity. Only one relevant study was found, involving 116 children recruited from 19 centres located throughout Germany.<sup>15</sup> These children were randomised into three treatment groups: bromelain monotherapy, bromelain with standard therapy and standard therapy alone. The primary measure of effectiveness in the different treatment groups was the duration of symptoms. Patients in the bromelain monotherapy group showed a statistically significantly faster recovery from symptoms compared with the other treatment groups.

Although the benefits of dietary supplementation in cases of nutritional deficiency are undeniable, there is a lack of evidence-based trials to support its use in the prevention or adjunctive treatment of otolaryngological infections.

#### *Vertigoheel in vertigo*

Vertigoheel<sup>®</sup> (US, Albuquerque, NM, Heel Inc) is a composite remedy containing four active ingredients: ambra grisea, cocculus indicus, conium maculatum and petroleum. It has botanical, zoological and mineral origins. It is believed to have a positive effect on microcirculation.<sup>16</sup> In an unrandomised, open study of 12 patients, both flow rates and haematocrit improved after 12 weeks of Vertigoheel therapy. Early results published by the manufacturers showed that Vertigoheel was equally effective in reducing the severity, duration and frequency of vertigo compared with betahistine.<sup>16</sup> The authors concluded that Vertigoheel had a similar efficacy to betahistine. These collaborators then performed a meta-analysis of four studies evaluating Vertigoheel compared with betahistine, *G biloba* and dimenhydrinate.<sup>17</sup> This review suggested that Vertigoheel resulted in an equivalent reduction of symptoms compared with each of the other control groups. A recent randomised, controlled trial also showed that Vertigoheel was a suitable alternative to *G biloba* in the treatment of atherosclerosis-related vertigo.<sup>18</sup> The frequency, duration and intensity of vertigo episodes after a six week course of Vertigoheel were comparable to those after *G biloba* therapy.

#### **Conclusions**

The positive effects of spirulina in allergic rhinitis and Vertigoheel in vertigo are based on good levels of evidence, but larger trials are required. There is overwhelming evidence that *Ginkgo biloba* plays no role in tinnitus. There is only limited evidence for the use of multivitamins in patients with sinus symptoms, but large randomised trials are required.

- **This paper assesses the evidence surrounding the use of certain complementary supplements in otolaryngology**
- **The positive effects of spirulina in allergic rhinitis and Vertigoheel in vertigo are based on good levels of evidence, but larger trials are required**
- **There is overwhelming evidence that *Ginkgo biloba* is ineffective in tinnitus management**
- **There is limited evidence for the use of multivitamins in sinus symptoms, and larger randomised trials are required**

Whilst it is undeniable that there is increasing popularity and social acceptance of homeopathy and complementary medicine, much scepticism remains within the medical profession. Meta-analyses of homeopathy treatment compared with conventional therapy for similar ailments have supported the conclusion that the clinical effects of homeopathy may simply be placebo effects.<sup>19</sup> What remains unanswered is the complex question of whether homeopathy and complementary medicine have any role in the management of symptoms which are difficult to address by other means.

#### References

- 1 Dillon JC, Phuc AC, Dubacq JP. Nutritional value of the alga *Spirulina*. *World Rev Nutr Diet* 1995;**77**:32–46
- 2 Tarantino LM. Agency Response Letter GRAS Notice No. GRN 000127. FDA Home page [October 2003]
- 3 Kay RA. Microalgae as food and supplement. *Crit Rev Food Sci Nutr* 1991;**30**:555–73
- 4 Yang HN, Lee EH, Kim HM. *Spirulina platensis* inhibits anaphylactic reaction. *Life Sci* 1997;**61**:1237–44
- 5 Mao TK, Van de Water J, Gershwin ME. Effects of a *Spirulina*-based dietary supplement on cytokine production from allergic rhinitis patients. *J Med Food* 2005;**8**:27–30
- 6 Ishii K, Katoch T, Okuwaki Y, Hayashi O. Influence of dietary *Spirulina platensis* on IgA level in human saliva. *J Kagawa Nutr Univ* 1999;**30**:27–33
- 7 Hirahashi T, Matsumoto M, Hazeki K, Saeki Y, Ui M, Seya T. Activation of the human innate immune system by spirulina: augmentation of interferon production and NK cytotoxicity by oral administration of hot water extract of *Spirulina platensis*. *Int Immunopharmacol* 2002;**2**:423–34
- 8 Sierpina VS, Wollschlaeger B, Blumenthal M. Ginkgo biloba. *Am Fam Physician* 2003;**68**:923–6
- 9 Ernst E, Stevinson C. Ginkgo biloba for tinnitus: a review. *Clin Otolaryngol Allied Sci* 1999;**24**:164–7
- 10 Hilton M, Stuart E. Ginkgo biloba for tinnitus. *Cochrane Database Syst Rev* 2004;**2**:CD003852
- 11 Drew S, Davies E. Effectiveness of Ginkgo biloba in treating tinnitus: double blind, placebo controlled trial. *BMJ* 2001;**322**:1–6
- 12 Rejali D, Sivakumar A, Balaji N. Ginkgo biloba does not benefit patients with tinnitus: a randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. *Clin Otolaryngol Allied Sci* 2004;**29**:226–31
- 13 Linday LA, Dolitsky JN, Shindledecker RD. Nutritional supplements as adjunctive therapy for children with chronic/recurrent sinusitis: pilot research. *Int J Pediatr Otorhinolaryngol* 2004;**68**:785–93
- 14 Linday LA, Shindledecker RD, Dolitsky JN, Pippenger CE. Lemon-flavoured cod liver oil and a multivitamin-mineral supplement for the secondary prevention of otitis media in young children: pilot research. *Ann Otol Rhinol Laryngol* 2002;**111**:642–52
- 15 Braun JM, Schneider B, Beuth HJ. Therapeutic use, efficiency and safety of the proteolytic pineapple enzyme Bromelain-POS in children with acute sinusitis in Germany. *In Vivo* 2005;**19**:417–21
- 16 Weiser M, Strösser W, Klein P. Homeopathic vs conventional treatment of vertigo: a randomized double-blind controlled clinical study. *Arch Otolaryngol Head Neck Surg* 1998;**124**:879–85
- 17 Schneider B, Klein P, Weiser M. Treatment of vertigo with a homeopathic complex remedy compared with usual treatments: a meta-analysis of clinical trials. *Arzneimittelforschung* 2005;**55**:23–9
- 18 Issing W, Klein P, Weiser M. The homeopathic preparation Vertigoheel versus Ginkgo biloba in the treatment of vertigo in an elderly population: a double-blinded, randomized, controlled clinical trial. *J Altern Complement Med* 2005;**11**:155–60
- 19 Ernst E. Herbal medicines: where is the evidence? *BMJ* 2000;**321**:395–6

Address for correspondence:  
Mr Peter D Karkos,  
Specialist Registrar in Otolaryngology,  
36 Hopkinsons Court,  
Walls Ave,  
Chester CH1 4LN, UK.

E-mail: pkarkos@aol.com

---

Mr P D Karkos takes responsibility for the integrity of the content of the paper.  
Competing interests: None declared

---