

CPD - Caring for Patients and their Disorders

Last year a medical student brought a 'miracle substance' to be analysed in the toxicology laboratory at MEDUNSA. His grandmother suffered from severe rheumatoid arthritis and was finding it exceptionally helpful. It was supposedly a traditional chinese medicine given to her by a doctor from one of the far eastern countries. It was found to contain methadone.

Many of our patients are ingesting substances which they've obtained from supermarkets, health shops, so-called 'complementary/alternative medicine' (CAM) practitioners, and traditional healers. There's a widespread mythology that 'natural' is better, that herbal remedies are completely safe, and that they're cheap.

Many of the substances are classified as food supplements or nutrients and should not be making any medicinal claims. Unfortunately, reading between the lines, many make 'suggestions' of health benefits but do not give warnings of adverse effects or interactions with other medications. I often don't know what to say when patients ask me about these.

As more and more patients start to use these substances, we are going to have to start asking about them, and ensure we know a little about the problem areas associated with them.

In this edition of SA Family Practice we look at three substances which are being widely used by more affluent South Africans. I make no apology for any apparent bias against these substances. I specifically looked for aspects about their safety. Please note that I am not unequivocally dismissing all herbal medications – there may well be great value in many of them. I do not know. I do however, want to see them being assessed with scientific rigour.

Stephen Barrett (the founder and maintaining force of the excellent 'Quackwatch' website) quotes from a 1998 editorial in the *Journal of the American Medical Association*, as follows:

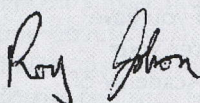
'There is no alternative medicine. There is only scientifically proven, evidence-based medicine supported by solid data – or unproven medicine, for which scientific evidence is lacking.'¹ [The rest of his quote from this editorial is well worth reading. It is one of the most 'holistic' statements about medicine I have encountered.]

My major reference sources include:

1. 'Quackwatch': www.quackwatch.com
2. The National Council against Health Fraud: <http://www.ncahf.org/>
3. Health Care Reality Check: <http://www.hcrc.org/>
4. THE ENTIRELY ON-LINE "ALTERNATIVE MEDICINE PRIMER"
<http://www.seanet.com/~vettf/Primer.htm>

I have deliberately not included further allusions to 'Traditional Medicine' of the South African variety in this article. We have hardly begun to analyse the components of many traditional herbs, let alone do clinical trials.

I've tried to do something a little different for CPD this time round. I do hope you enjoy it!



Roy Jobson

Our Patient

Johannes, our HIV-infected patient (see Feb-March, and April-May 2001 editions of CPD), came to see me again the other day. He is no longer using Virodene, and the palmar erythema noted at his last visit seems to have cleared. He has continued to work on quitting smoking but lapses at least twice a week. He is on triple therapy and his viral load at the visit before this was the lowest it had been for months. His CD-4 count had risen substantially.

Part of our conversation went like this:

- Roy Jobson: You're doing really well.
 Johannes: Ja, and I'm feeling good too. I think I've found something that helps me a lot.
 RJ: Oh yes?
 J: I went to a health shop and told the owner I wanted some natural medicines to boost my energy, to help me when I feel sad, and to make sure I don't get flu this winter.
 RJ: And?
 J: (hauls out three bottles from a packet) She gave me these.
 RJ: (with a hint of sarcasm) Gave them to you? You didn't have to pay?
 J: (laughing) Of course I had to pay, doc. She even said I might be able to claim my money back using the savings account part of my medical aid. Isn't that great?
 RJ: (thinking irritably – 'your medical aid hasn't paid me in months') Did you tell her about your HIV and your triple therapy?
 J: Oh no. I didn't think it was relevant.
 RJ: Mmmmh. Let's see what you've got. (Inspects the bottles.) Spirulina, St John's Wort and Echinacea.
 J: Ja! And they're all harmless herbal medicines. I'm feeling so much better!
 RJ: I'm glad to hear that. But let's look at each of them carefully.

SPIRULINA

This is a particular form of protein-rich blue-green microalgae. Several brands are available in South Africa. It is highlighted in lay publications as diverse as the e-zine 'Quality Life' (The Wellness Update #35, April 2001); the 'Reader's Digest' (as part of a 'healthy living' supplement:

May 2001); as an undated supplement to 'Runner's World' (in association with the Comrades Marathon Association); as an advertorial in 'Odyssey' magazine (August/September, 2000). The claims made in each of these vary according to the target audiences of each of the publications.

One of the claims of spirulina promoters is that it is possibly the 'food of the future'. A major reference book summarising various levels of research is named 'Earth Food Spirulina' and in product information brochures (supplied by one of the manufacturers in South Africa), a 'role [for] spirulina in reducing world hunger' is claimed; and 'so quickly does spirulina grow that an area roughly the size of Natal could feed 6 billion people'.

These claims are made on the basis of the high protein content and presence of all the essential amino acids and a variety of vitamins and minerals in the substance.

One of the major selling points of spirulina is the concept that it contains 'pure sun energy' in the form of 'minute particles of light also known as biophotons'.² This is made possible (in one brand) through storing the processed algae in a particular violaceous form of glass – in one place referred to as 'Viosol' glass and in another as 'Miron' glass. The major effects in humans of spirulina are claimed to be: i) cleansing the body (including the blood), ii) restoring deficiencies in the diet and stimulating the metabolism, and iii) fortifying one's resistance.

One of the products advertises that research (!) has shown that spirulina helps maintain, and reduces fluctuations in, blood glucose levels; cures all symptoms of gastric ulcers and completely cures nearly 80% of duodenal ulcers; and, improves geriatric cataracts if used with medication. Marked improvements were noted in anaemia, liver disease, pancreatitis, heavy metal poisoning and senility.³

Concerns:

- i) *Safety*
 Although spirulina is a non-toxic blue green algae, most blue green algae are toxic to human beings. *Microcystis aeruginosa* is the main toxic contaminant which can inadvertently be harvested along with other blue green algae. *M. aeruginosa* produces compounds called microcystins, which are potent hepatotoxins and probable tumour promoters.⁴ However products made only from spirulina are no longer being considered a microcystin-related health risk in Canada.⁵ I am not aware of any South African mechanism of assessing locally sold products for microcystins.

Despite the high protein content and high levels of phenylalanine, there are no warnings to persons who have phenylketonuria on any of the brands I came across.

In terms of beta-carotene (which converts to Vitamin A), one of the brands proudly claims that 3g of their product 'provides 180% of the beta-carotene needed each day'. [Their recommended maximum daily dose however is six of the 300mg tablets (1.8g).] Barrett quotes an article on 'Vitamin Supplements' in *The Medical Letter on Drugs and Therapeutics* (1998) that 'no one should take beta carotene supplements'.⁶ Also quoted by Barrett is a study published in the *Lancet* in which significantly more deaths from coronary heart disease occurred among men who had had a previous myocardial infarct and who took beta-carotene supplements.⁷ There are however, no warnings about men who have had a previous myocardial infarct. Mega doses of beta carotene are also possibly implicated in increasing lung cancer rates among smokers.⁸ While the manufacturers indicate the high concentrations of beta carotene in their product, they do not warn smokers to avoid using it. Barrett concludes in his excellent article, 'Although some products contain significant amounts of nutrients, these nutrients are readily obtainable at lower cost from foods'.⁸ (One must wonder whether or not spirulina, as one of the blue green algae, is not more suited to being food for 'baby' frogs, flamingoes or fish, than for humans.)

ii) In terms of spirulina as a potential food source, see Table 1.

It should be noted that the maximum recommended daily intake of the particular brand of spirulina analysed above is 2g. The protein intake from this 'dosage' would therefore be 1.24g – a mere 2.25% of the RDA (55g) for protein. At my local supermarket, good quality fillet steak costs less than R50.00/kg. Are huge ethical problems not raised in terms of the costs of a substance claiming to be the 'food of the future', within the context of South African poverty levels?

A common marketing ploy of many food and nutritional supplements (and so-called 'organic foods' – do you know of any that are not?) is that foods today are depleted of vital nutrients, and contain harmful substances as a result of modern farming methods. There is no evidence for this despite its apparent logic. A very useful source of information in this regard is the September 2000 report: *Marketing & The Organic Food Industry: A history of food fears, market manipulation and misleading consumers*.⁹

iii) *False Claims?*

I have not found any evidence of the existence of 'biophotons'. Even if they were to exist, how do we know that they retain their 'properties' with the harvesting and drying processes required in transforming a slimy moisture-filled substance into a dry powder or tablet form. This raises the issue of practitioners who attempt to explain biochemical processes within the human body in terms of quantum physics. I'd recommend reading Victor Stenger's articles, *Quantum-Quackery*¹⁰ and *Quantum Metaphysics*.¹¹

Table 1: Spirulina compared to other processed foodstuffs

| | Spirulina (Brand I) | Bran Flakes | Porridge Oats | Skim Milk Powder |
|-------------------|--------------------------------|--------------------|----------------------|-------------------------|
| Protein/g | 620 mg | 140 mg | 130 mg | 360 mg |
| Fat/g | 121 mg | 30 mg | 65 mg | 10 mg |
| Carbohydrate/g | 81 mg | 560 mg | 650 mg | 480 mg |
| Energy/g | 16.48 kj | 13.01 kj | 16.80 kj | 14.70 kj |
| Rand/g | R1.20 | R0.056 | R0.01 | R0.035 |
| Rand/kg | R1200.00 | R56.00 | R10.00 | R35.00 |
| Rand/serving(40g) | R48.00 | R2.24 | R0.40 | R0.35 |

(Another more prominent brand of spirulina costs nearly R2000.00/kg!)

Johannes and I resumed our conversation:

J: OK, so I've nearly stopped smoking and I haven't had a heart attack before, and I don't have that 'fenny' disease. What's the harm?

RJ: Actually it *is* harming you in quite a different way. It's robbing you of some of your disposable income. Maybe it would be better for your health to take one of your kids to the movies once a month than buy this.

J: But what about all of those vitamins and things?

RJ: The chances are you'd do just as well with 'pap-en-vleis' and a good sauce to go with it; and maybe some fruit every now and then.

J: (pointing to the container) So what about this St John's Wort stuff?

ST JOHN'S WORT (SJW)

SJW is a flowering herb. Its botanical name is *Hypericum perforatum* and it contains several active substances, including hypericin and hyperforin. The concentrations of these vary between the flowers, leaves and stems of the plant. The highest concentration of hypericin is found in the flowers. The plant naturally accumulates the heavy metal cadmium, which is carcinogenic to humans and builds up in the kidneys. There is a relatively small safety margin between cadmium exposure in the normal diet – and exposure that can produce deleterious effects.¹² Some, but not all, of the cadmium is removed in processing the herb. (Is it still 'natural' then?)

SJW is taken for mild to moderate depression and has been shown to be effective in the short term,¹³ although questions have been raised in terms of study design and methodology.¹⁴ Short term psychotherapy could very well be the more 'natural' alternative for mild to moderate depression! SJW has been found to be *ineffective* for treating severe (major) depression.¹⁵ [My emphasis.]

One of the adverts for this drug states: 'No nasty side-effects: The latest worldwide research continues to highlight hypericum ... as the safe natural alternative to chemical anti-depression and anti-anxiety prescription drugs – vast armies of outrageously costly and frequently addictive chemical products.'¹⁶

Concerns:

i) Drug interactions

SJW appears to act on the cytochrome P450 system (particularly the CYP3A4 isoenzyme) and is likely to cause many drug interactions. The most serious of these

interactions for Johannes, is that SJW has been shown to substantially decrease indinavir plasma concentrations.¹⁷ (Indinavir is a protease inhibitor and is one of the antiretroviral agents which can be used in HAART – see SA Family Practice, April-May 2001.)

The indinavir-SJW interaction may result in 'suboptimal antiretroviral drug concentrations, leading to loss of virologic response and development of resistance or class cross-resistance'.¹⁸

SJW may significantly decrease blood concentrations of all of the currently marketed HIV protease inhibitors and possibly other drugs (to varying degrees) that are similarly metabolized, including the non-nucleoside reverse transcriptase inhibitors (NNRTIs).¹⁸

Since the CYP3A4 isozyme is responsible for the metabolism of a large number of prescription medications, when patients also take SJW, there may be reductions in therapeutic efficacy in many types of medications, including oral contraceptives, antiepileptic drugs, antidepressants, calcium channel blockers, digoxin, cyclosporine, fentanyl (and other agents used in general anaesthesia), levo-dopa, and select chemotherapeutics such as certain antibiotics, and some antifungals.^{19,20}

SJW may also reduce the efficacy of warfarin leading to the formation of thrombi and thrombo-emboli in patients on anti-coagulant therapy.²¹

ii) Side-effects

Other side effects of SJW include: skin hypersensitivity to light, hypomania, gastrointestinal irritation, lethargy, restlessness.²¹ A 1999 report links SJW to the development of cataracts if the person on treatment is exposed to bright sunlight. This is said to be because hypericin reacts with visible and ultraviolet light to produce free radicals which cause precipitation of proteins in the lens.²² Cows grazing on St John's wort flowers are known to suffer from extreme photosensitivity that can prove fatal. When exposed to bright sunlight for long periods, these animals develop inflammatory conditions of the upper GIT and trachea that make swallowing and breathing difficult.²²

iii) Quality

One of the major concerns about SJW (and **most** herbal preparations) is the quality of these preparations – which are sold, without prescription, in pharmacies and health shops around South Africa. I've not found published studies for this country, but in overseas studies the

variation in quality is dramatic. One study found that 7 of 10 products contained between 75% and 135% of the labeled hypericin level, while 3 contained no more than about half the labelled potency.²¹ Another analysis showed that a third of the products tested did not pass the quality checks because: a) levels of hypericin ranged from 77% to 85% of that stated on their labels, b) one of the two products claiming to contain hyperforin contained only 21.7% of the claimed amount, and c) nearly a quarter of the products contained cadmium levels that exceeded acceptable levels while some had levels of cadmium more than twice the acceptable amount.¹² One of the forms of SJW available in South Africa is a liquid version which is administered in the form of drops in 'a little water'. The compound is contained in 67% alcohol, and the dosage for 2–6 year olds is 3 drops, three times a day.²³

(Note: The last update to the review on SJW of the Cochrane Collaboration was in 1998. I have therefore not included it here.)

This time when Johannes and I resumed our conversation, he was more subdued:

J: So she gave me something that was actually bad for me.

RJ: Yes.

J: But she was such a sweet young woman! I really trusted her.

RJ: And I'm sure she thought she was doing the right thing for you.

J: I suppose I should have told her about my HIV and all what I'm taking.

RJ: Mmmmh. Maybe she would have asked for help – but maybe not.

J: Do you think I've been permanently damaged?

RJ: No. (a moment of silence) Though I would be happier if you'd first check with me before you start taking other medicines – even food supplements and vitamins.

J: Sure thing, doc. I think I've learnt my lesson.

RJ: Good. Let's look at the last one.

J: Echinacea. I'm convinced this one really works. I've been through nearly the whole winter without getting flu!

RJ: Aren't you forgetting something?

J: I don't get you, doc.

RJ: I gave you a flu injection in March.

J: (amazed) You know, I completely forgot.

ECHINACEA

Echinacea is related to the daisy and sunflower families. Three species — *E. purpurea*, *E. angustifolia*, and *E. pallida* are used in herbal preparations, and different parts of the plant contain different concentrations of a variety of possible active substances.²⁴ It is used primarily for 'the protection from, and treatment of, colds and influenza. Assists in supporting the Immune System.'²⁵

Concerns:

i) Safety

Echinacea should not be used for longer than 8 weeks. Apparently hepatotoxic effects may be associated with persistent use, and it should therefore also not be taken with other known hepatotoxic drugs (eg, anabolic steroids, amiodarone, methotrexate, or ketoconazole).²⁶

People with progressive systemic diseases such as tuberculosis and autoimmune diseases (multiple sclerosis, lupus, rheumatoid arthritis, and inflammatory bowel disease) should avoid the herb. It is not recommended for long-term use, since [it] may actually depress the immune system.²⁷

ii) Efficacy

One very well-designed and clearly reported study using a fairly small sample (ITT analysis of 289 patients) produced the following conclusion:

'In this study a prophylactic effect of the investigated echinacea extracts could not be shown. However, based on the results of this and 2 other studies, one could speculate that there might be an effect of echinacea products in the order of magnitude of 10% to 20% relative risk reduction. Future studies with much larger sample sizes would be needed to prove this effect.'²⁸

Using the Cochrane Collaboration as a source for an evidence-based approach we find:

Main results: Sixteen trials (eight prevention trials, and eight trials on treatment of upper respiratory tract infections) with a total of 3396 participants were included. Variation in preparations investigated and methodological quality of trials precluded quantitative meta-analysis. Overall, the results suggested that some Echinacea preparations may be better than placebo.

Reviewers' conclusions: The majority of the available studies report positive results. However there is not enough evidence to recommend a specific Echinacea product, or Echinacea preparations for the treatment or prevention of common colds.²⁹

iii) Quality

ConsumerLab.com tested a number of available preparations and reported as follows:

Out of the 25 products originally purchased, only 14 products (56%) passed this review. It is possible that the products, which did not contain the expected levels of markers, were made from other types of echinacea or, perhaps, contained other ingredients altogether.²⁴

Johannes leaned back and looked at me.

J: Not as good as they all make out, doc.

RJ: Afraid not. At least you told me about what you've been taking. I know of patients who haven't told their doctors and have had drug interactions. But maybe the most important situation is if someone has to have an operation and they don't tell the anaesthetist what they've been taking.

CONCLUSION:

Family Physicians (and other health care workers) need to be increasingly aware of what our patients are using to treat themselves. Unfortunately, the erroneous epithets of 'natural' and 'harmless' have become so pervasive and so compelling, than an increasing number of people are taking these substances without adequate information. We need to be alert to their side effects, drug interactions and complications.

REFERENCES:

1. Barrett S. Be Wary of 'Alternative' Health Methods. May 17, 2001. <http://www.quackwatch.com/01QuackeryRelatedTopics/altwary.html> [He quotes: Fontanarosa PB, Lundberg GD. Alternative medicine meets science. *JAMA* 280:1618-1619, 1998]
2. Product information/advertising.
3. Advertorial. Holistic Guide to Spirulina. *Odyssey*. 2000. Vol 24(4):40
4. Gilroy DJ, Kauffman KW, Hall RA, Huang X, Chu FS. Assessing Potential Health Risks from Microcystin Toxins in Blue-Green Algae Dietary Supplements. *Environmental Health Perspectives*. 2000. Vol 108 (5): 435-439. <http://ehpnet1.niehs.nih.gov/docs/2000/108p435-439gilroy/abstract.html>
5. <http://www.hc-sc.gc.ca/english/archives/releases/1999/99114ebk.htm>
6. Barrett S. Antioxidants and Other Phytochemicals: Current Scientific Perspective. June 1, 2000. <http://www.quackwatch.com/03HealthPromotion/antioxidants.html> [quoting: Vitamin supplements. *The Medical Letter on Drugs and Therapeutics* 40:75-77, 1998.]
7. Barrett S. Antioxidants and Other Phytochemicals: Current Scientific Perspective. June 1, 2000. <http://www.quackwatch.com/03HealthPromotion/antioxidants.html> [quoting Rapola JM et al. Randomised trial of alpha-tocopherol and beta-carotene supplements on incidence of major coronary events in men with previous myocardial infarction. *Lancet* 349:1715-1720, 1997.]
8. Barrett S. Antioxidants and Other Phytochemicals: Current Scientific Perspective. June 1, 2000. <http://www.quackwatch.com/03HealthPromotion/antioxidants.html>
9. Forrer G, Avery A, Carlisle J. Marketing & The Organic Food Industry: A history of food fears, market manipulation and misleading consumers. September 2000. http://www.nomorescares.com/news/organic_report/iea.pdf
10. Stenger VJ. Quantum Quackery. <http://www.csicop.org/si/9701/quantum-quackery.html> [Skeptical Inquirer magazine. January/February 1997.]
11. Stenger VJ. Quantum Metaphysics. <http://www.phys.hawaii.edu/vjs/www/qmeta.html> [Paper presented at the *Conference on New Spiritualities*, Westminster College, Oxford, England, March 1995. Published in *Modern Spiritualities*, Laurence Brown, Bernard C. Farr; and R, Joseph Hoffmann (eds.) Amherst NY: Prometheus Books, 1997. Also published in *The Scientific Review of Alternative Medicine* 1(1), 26-30, 1997.]
12. Product Review: *St. John's Wort*. ConsumerLab.com, LLC, 2001. <http://www.consumerlab.com/results/sjw.asp>
13. Woelk H, for the Remotiv/Imipramine Study Group. Comparison of St John's wort and imipramine for treating depression: randomized controlled trial. *BMJ* 2000; 321: 536-539.
14. Letters (various authors). *BMJ* 2001;322:493
15. Sheldon RC and others. Effectiveness of St. John's wort in major depression: A randomized controlled trial. *JAMA* 285:1978-1986, 2001. [Reported in <http://www.ncahf.org/digest/01-17.html>]
16. http://www.holotropic.co.za/St_Johns_Wort_Tablets.asp
17. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. *Lancet* 2000, Feb 12;355(9203):547-8.
18. FDA PUBLIC HEALTH ADVISORY: RISK OF DRUG INTERACTIONS WITH ST JOHN'S WORT AND INDINAVIR AND OTHER DRUGS. February 10, 2000. <http://www.fda.gov/cder/drug/advisory/stjwort.htm>
19. Katz S. St. John's Wort Induces Drug-Clearing Enzyme. Reuters Health. 8 June 2000. [quoting: Burstein AH. *Clin Pharmacol Ther* 2000;67:451-457.] <http://primarycare.medscape.com/reuters/prof/2000/06/06.08/20000608clin012.html>
20. Elliott VS. Code green: Seeing the side effects of alternative supplements. *American Medical News*. March 5, 2001. http://www.ama-assn.org/sci-pubs/amnews/pick_01/hlsa0305.htm
21. Barrett S. St John's Wort. April 16, 2000. <http://www.quackwatch.com/01QuackeryRelatedTopics/DSH/stjohn.html> [quoting Jobst KA and others. Safety of St John's wort. *Lancet* 355:576, 2000.]
22. Johnston N. A recipe for disaster: Sun Trap. *New Scientist*. July 24, 1999. <http://www.newscientist.com/ns/19990724/newsstory9.html>
23. http://www.bioforce.co.za/Medicines/hypericum_performatum.htm
24. Product Review: *Echinacea*. ConsumerLab.com, LLC, 2001. <http://www.consumerlab.com/results/echinacea.asp>
25. http://www.bioforce.co.za/Medicines/echinaforce_cold_&_flu_drops.htm
26. Miller LG. Herbal Medicinals — Selected Clinical Considerations Focusing on Known or Potential Drug-Herb Interactions. *Arch Intern Med*. 1998;158:2200-2211
27. Coleman E. Herbs for Health. Georgia Council against Health Fraud. <http://hcrc.org>
28. Melchart D, Walther E, Linde K, Brandmaier R, Lersch C. Echinacea Root Extracts for the Prevention of Upper Respiratory Tract Infections — A Double-blind, Placebo-Controlled Randomized Trial. *Arch Fam Med*. 1998;7:541-545.
29. Melchart D, Linde K, Fischer P, Kaesmayr J. Echinacea for preventing and treating the common cold (Cochrane Review). In: *The Cochrane Library*, 2, 2001. Oxford: Update Software.