

Over the counter (OTC) oral remedies for arthritis and rheumatism: how effective are they?

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Abstract---Background: Increasingly patients resort to alternative remedies for arthritis and rheumatism, perhaps partly impelled by reports of toxicities from prescribed non-steroid anti-inflammatory drugs (NSAID). There is uncertainty about whether the most common alternative treatments provide relief or may cause adverse reactions.

Aim: To ascertain the validity of manufacturers' claims permitted by the Therapeutic Goods Administration (TGA) in Australia for a range of self-medication products to treat the pain and inflammation of arthritis, available in local pharmacies, supermarkets or by mail order and in other countries.

Methods: OTC products were administered orally to rats in standard assays for suppressing experimental arthritis and fever and for determining potential gastrotoxicity.

Results: The three NSAIDs available OTC were efficacious but gastrotoxic. Of the 37 herbal formulations examined, seven were as effective as ibuprofen in the anti-arthritic assay without causing gastric bleeding. Five of the 10 animal-sourced products tested were also effective without evident toxicity. Within a certain class of product, e.g. celery seed extracts or dried mussel preparations, efficacies ranged from almost zero to highly effective.

Conclusions: Consumers currently have no guide to the likely efficacy of TGA-approved remedies. Quality control is urgently needed to justify the veracity of TGA-permitted and other claims on product labels.

Key words: Anti-inflammatory; antipyretic; gastrotoxicity; herbal medicines; celery; N.Z. mussel; holothurians; ginger; efficacy; safety.

1. INTRODUCTION

Arthritis and rheumatism are major problems affecting up to 80% of Australians at some period in their lives. Musculoskeletal complaints are the second most common reason for consulting a doctor in Australia (A.B.S., 1990), and cause significant disability in Canada and Britain (Badley, 1994). In the USA, musculoskeletal diseases cost nearly \$150 billion in 1992, caused significant disability and affected the psychological status of the both the patients and their families (Yelin and Callaghan, 1995). The majority of musculoskeletal complaints are osteoarthritis or soft tissue rheumatic disorders and patients frequently self-medicate.

The first line of drug treatment is with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Products containing NSAIDs are well defined chemically and strictly controlled for purity and labelling. Only a few of these NSAIDs are readily available in OTC formulations from pharmacies without prescription as potential treatments for (the pain of) arthritis and rheumatism, and for other pain-syndromes. They include: (i) aspirin and some of its water-soluble salts (Na, glycine), ibuprofen (Nurofen®, Actiprofen., ACT-3®, etc.) and the sodium salt of naproxen (NaprogesicR) for oral ingestion and (ii) certain salicylate products for dermal application (methyl

ester or salts formed with copper, diethylamine, triethanolamine, etc.). Standard references to the therapy of rheumatic disease attest to both the efficacy and adverse effects of these particular NSAIDs (Group A, Table 1) as analgesic/antipyretic/anti-inflammatory agents and to paracetamol as having only analgesic/antipyretic activity (Brooks, 1998; Brooks and Day, 1991; Brune and McCormack, 1994; Clements and Paulus, 1997; Insel, 1996; Mowat, 1992; Nishihara and Furst, 1997; Rainsford and Powanda, 1998).

In addition, alternative medicines of both plant and animal origin, such as celery, willow bark, mussel, and ginger extracts, are being increasingly used in the self-management of arthritis and rheumatism. These particular 'anti-rheumatic' products are likely to account for a considerable proportion of (a) the \$A0.6 billion/year spent by Australians on alternate therapies (McLennan *et al.*, 1996) or (b) the \$US5 billion/year spent by North Americans on herbal remedies (Eisenberg *et al.* 1998). In Australia, these products are available from both pharmacies and non-pharmaceutical outlets and are subject to regulation by the Therapeutic Goods Administration (TGA) of the Commonwealth government; being given either an AUST R or an AUST L number. AUST R medicines are assessed for safety, quality and effectiveness. Those carrying an AUST L number are considered much lower risk products being reviewed only for safety and quality. All these OTC products for arthritis and rheumatism may be classified according to their proven efficacy or the type of labelling they carry (Table 1).

Table 1.

An arbitrary classification of (UC remedies for arthritis and rheumatism*

Group A Non-steroidal anti-inflammatory drugs and paracetamol with proven clinical efficacy as analgesics.

Group B Those stating that they 'may temporarily relieve the pain of arthritis' (with TGA approval for this claim in Australia).

Group C Those claiming to afford pain relief or benefit in inflammatory condition, but without specific reference to arthritis.

Group D Dietary supplement: in Australia, not permitted (by the TGA) to refer to inflammation or arthritis but sustaining their position in the market place through traditional belief in their efficacy for arthritis or rheumatism.

None of these alternative products (Groups B, C or D) is discussed in the references cited above. A few are listed without supportive clinical data in respected pharmaceutical compendia (e.g. Mattindale, British Herbal Pharmacopoeia) and a review of non-prescription treatments for the rheumatic diseases (Champion, 1998). Little research appears to have been published regarding their efficacy. Published work undertaken in rheumatology clinics to evaluate the stated (Group B) or implicit (Group C/D) claims is *certainly* limited. There appear to be few criteria by which their potential efficacy has been objectively assessed and there is much uncertainty about the reliability of the claims (approved or implied) on their labels.

We have, therefore, evaluated a number of representative products from all four classes of these remedies, as formulated for oral consumption, for their ability to beneficially limit the onset or

progression of the adjuvant-induced polyarthritis in laboratory rats (Whitehouse, 1988; Billingham, 1995). This is a standard experimental model of chronic inflammation which has been widely used by the pharmaceutical industry to find and develop many of the currently available NSAIDs (Rainsford, 1982; Billingham, 1983; Bliven and Otterness 1985; Hunneyball *et al.* 1989). Our findings suggest (i) that not all products on the market are likely to be efficacious and that even within one class of product, there may be great variability in potency and (ii) that the present TGA classification and approved labelling is little guide to any pharmacological activity.

2. MATERIALS AND METHODS

Products were purchased from local pharmacies and supermarkets in south Brisbane and overseas or by mail order within Australia. Tablets were ground in a mortar. Gelatin capsules were emptied (the shells being discarded) and their contents further pulverised. The resulting powders (or oils) were dispersed in distilled water with no more than 0.04% Tween-20 and briefly sonicated. Alcoholic extracts were freshly mixed with water immediately before dosing to reduce ethanol levels to 30% (v/v) or less.

All test agents were administered orally to rats given an experimental arthritigen (see below) on a once daily basis (10 ml/kg) with oral doses not exceeding 2.5 g/kg, on at least one of the following regimens:

I. Prophylactic mode = 1 day before arthritigen and for subsequent 15 days (total doses = 16).

II. Therapeutic mode = from time of first appearance of arthritic signs (usually 10 days post-arthritigen) for 4 days only.

111. Toxicity evaluation = single dose given to untreated polyarthritic rats (day 16 post-arthritigen) fasted overnight, to assess potential gastrotoxicity. Control groups received only Tween-20 or other vehicle(s) as appropriate.

The polyarthritis was initiated by injecting an arthritigenic adjuvant (800 µg heat *Mycobacterium tuberculosis* suspended in 100 µl squalane per rat) into the tailbase of female Wistar rats (University of Queensland Animal Farm) on day 0. Activity of disease was assessed by weight change (over days 0-15 or 10-14), swelling of all four paws and tail and the incidence of splenitis on day 18 (Whitehouse, 1988). Rear paw and tail swellings were quantified with a screw gauge micrometer. Clinical impressions were collected from at least two independent observers regarding the health and vigour of the treated animals.

Animals treated therapeutically (days 10 - 13) were scored for signs of arthritis on days 10, 14 and 17; the day-17 reading affirms (any) rebound of symptoms after ceasing therapy. Animals with minimal arthritis on day 14 but failing to show any rebound (by day 20) were considered non-responders to the original arthritigen and therefore discarded from data assessment. (Non-responders and hypo-reactors numbered no more than 14% in a respective survey of 480 rats challenged with the arthritigen.)

Gastrotoxicity was quantified by obtaining a lesion index for incidence and severity of gastric haemorrhage (Rainsford and Whitehouse, 1992) 2.5 hours after giving test formulations to disease-stressed (arthritic) rats fasted overnight. Selected products were also given orally to normal rats with yeast-induced fever to assess antipyretic activity (Whitehouse, 1986). These experiments had the approval of the University of Queensland Animal Ethics Committee.

3. RESULTS

Table 2 indicates that (i) some products were just as effective as OTC NSAIDs in controlling the development of arthritic inflammation when evaluated in the *therapeutic* assay i.e. administering test formulations to animals with pre-established polyarthritis; but (ii) other products, reputedly derived from the same natural source(s) were much less potent in exhibiting this type of NSAID-like activity.

Products were further evaluated in the *prophylactic* assay, with extended dosing for 16 days (Table 3). This was to detect a possible slower onset of action, particularly for those products showing little or no activity in the (acute) therapeutic assay and perhaps manifesting anti-arthritic activity (if any) through an immunoreaction. Since these studies were conducted over a period of four years with some inevitable variation in the severity of arthritis in the untreated controls, the experimental data for each product tested is given as the percentage of the mean data for the corresponding control group.

Table 3 also records the gastrotoxicity, after a single acute dose, of only those products significantly inhibiting arthritis development (i.e. inhibition of arthritic paw swelling > 40%, $p < 0.05$). The principal findings were:

1. Products obtained from celery 'seed' were either effective anti-inflammatories or almost inactive (the latter seemingly predominating).
2. Two particular types of marine-derived products, from a NZ mussel or edible Australian holothurians (sea cucumbers) respectively, likewise ranged in potency from highly effective to lacking measurable anti-inflammatory activity.
3. Aspirin was relatively ineffective in suppressing this experimental arthritis and was also particularly gastrotoxic in fasted rats at an effective dose.
4. The OTC formulations of ibuprofen and naproxen, though active, were also quite gastrotoxic, a problem not seen with some other OTC products confirmed to be active in this anti-arthritic assay (e.g. at least four celery and two mussel preparations).
5. Several products, widely advertised as being effective for treating arthritis (e.g. fish oils, ginger extracts, glucosamine sulphate) had no effect on the development of this rat polyarthritis even after extending dosing (for 16 days). A commercial sample of cetyl myristoleate, claimed to be anti-arthritic in rats (Diehl and May, 1994) also showed no activity.

Methyl sulfonyl methane (MSM), also known as dimethylsulfone is described as an (oral) analgesic offering pain relief in rheumatoid arthritis and osteoarthritis (Jacob *et al.*, 1999). It demonstrated no anti-inflammatory effect after extended prophylactic dosing. By contrast, its desoxy analogue, dimethylsulfoxide (DMSO) did show some oral activity (though not sold as an OTC for oral use). Several reviews discuss the topical anti-inflammatory activity of DMSO (Jacob, 1975; McGrady, 1979; Jacob and Kappel, 1988).

4. DISCUSSION

Alternative, non-prescription, therapies for arthritis have attracted much criticism, mostly negative, e.g. junk science/charlatanism/quackery (Arthritis Foundation, 1997; Barrett, 1980; Fernandez-Madrid, 1989; Panush, 1994, 1997; Romos-Remus and Russell, 1997; Schaller and Carroll, 1976, Weissmann, 1996) with all too little objective evaluation in controlled animal or clinical studies.

Considerable concern has been expressed about the general *safety* of herbal remedies (Angel and Kassirer, 1998; Atherton, 1994; Brooks and Lowenthal, 1977; Bury *et al.*, 1987; Chan, 1997; Ernst 1998; Huxtable, 1992; Macia *et al.*, 1996; Moulds and McNeil, 1988; Shaw *et al.*, 1997; Talalaj and Czechowicz, 1988, 1989). So it seems pertinent to also enquire if herbal (and animal-sourced) remedies are *effective* and might be utilised more rationally to support, or perhaps even replace, some prescription drugs? (Talalaj and Czechowicz, 1989; Tyler, 1994)

The animal tests used here would not have detected euphoric or other activities altering pain threshold. They do however provide evidence for (i) anti-inflammatory or immunoregulant activity in controlling a polyarthritis that damages articular joints, and (ii) concomitant antipyretic activity or potential gastrotoxicity of the products which were arthro-suppressant. This experimental arthritis does not respond to certain slow-acting drugs such as the antimalarials or D-penicillamine, used as second line therapy for severe rheumatoid disease. Other reservations may be justified in extrapolating from animal data to potential efficacy in patients with inflammatory disorders. Nevertheless a wide range of activities was discernible amongst these non-prescription OTC products (Tables 2 and 3). Some of the natural products showed arthritis-suppressant activity in rats that was certainly equivalent to the OTC NSAIDs and **with less adverse** reaction.

The doses administered were fairly high being based on the following formula: either a single dose of 2.5 g listed active principle(s)/kg/day or a lesser amount = x (mg)/kg/day, where x = half the cumulative recommended human daily dose. This latter dose in rats (x/kg) was therefore 37 times the human daily dose, assuming average human weight = 75 kg. In other rat studies, repeated doses that are 3 to 10 times the human dose have generally been found to give similar pharmacological activities and/or stable blood levels to those observed in the clinic. The repeated once-daily dosing schedules employed here would have limited the detection of those agents that either (a) have short half-lives (like aspirin) or (b) induce their own metabolic inactivation. Nevertheless it seems reasonable to infer that products with specific claims (Groups B or C) but found to be virtually inactive in this anti-arthritic assay, are not demonstrating anti-inflammatory activity of the same order as the reference OTC formulations (ibuprofen, naproxen). Likewise, products not showing activity in this antipyretic assay are unlikely to be potential analgesics mimicking paracetamol (itself not anti-inflammatory).

This preliminary survey certainly indicates the great variability in activity of products derived from celery 'seed'. Three commercial samples of authentic celery seed oils (Kancour, India; Bronson & Jacob, Australia), used as a flavourant, and obtained either by steam distillation or by hexane extraction, were found to be inactive in these assays (data not shown). The principle sources of the celery (*Apium graveolens*) used in these products are India, China and Belgium; the fruit being harvested as a fresh product (green) or an aged one (usually brown), the latter predominating. Clearly, some form of quality control is required to alert consumers to the now evident fact that not all celery-derived products are equal. It is repeatedly demonstrated in the pharmacognosy literature that the content of individual pharmacologicals from herbal sources may vary widely with the method of agriculture, harvesting and preparation for product distribution.

Similar wide variations in potency are evident with preparations of the New Zealand (green lipped) mussel *Perna canaliculus*. This problem of variable/uncertain potency is compounded by the fact that products carrying the *same* trade name (Seatone) but sold in different countries (by different manufacturers), may exhibit greater/ lesser potency. Part of this variation is certainly due to use (or lack) of effective stabilising processes and avoidance of heat (often employed for opening mussels); factors that will conserve, rather than degrade, the pharmacologically active polyunsaturated mussel lipids that are enriched in the Lyprinol product (Whitehouse *et al.* 1997).

This same problem of variable/uncertain potency is further compounded when *different* species are being used as sources of 'active' material. The beche-de-mer products shown in Table 2 are actually derived from tropical, subtropical and temperate holothurian species from the Pacific and

Southern Oceans, being sold with/without added non-holothurian materials e.g. certain seaweeds (Whitehouse and Farlie, 1994).

The consistent inactivity of the Zinax(in) and other ginger preparations, despite giving quite massive doses (i.e. full, not half, suggested human daily dose/kg rat), affirms that these products are not NSAID-like. There are reports that ginger (Srivastava and Mustafa 1992) or its constituent phenolic gingerols (Kiuchi *et al.*, 1992) might inhibit prostaglandin and leukotriene biosynthesis. However, to date we have found no evidence that ginger inhibits cyclooxygenase in whole animal assays (using Wistar rats), as evidenced by failure to inhibit carrageenan-induced paw oedema, reduce yeast-induced fever or to induce gastric haemorrhage in fasted animals (data not shown). These studies were conducted with OTC ginger products, freshly prepared ginger powders (Buderim Ginger Limited, Queensland) and ethanolic or supercritical fluid extracts rich in gingerols. 6-Gingerol itself has a very short half-life in rats <10 Mins (Dingh *et al.* 1991). Claimed benefits for treating osteoarthritis (Bliddell, 1997) must therefore depend on other mechanisms of action (?analgesic or anabolic) not demonstrable in the animal models used here.

The amino sugar, D-glucosamine, advocated as a nutritional supplement for osteoarthritis (McCarty, 1994) certainly had no effect on disease development in this rat model of immuno-inflammatory arthritis.

It is of concern that although some of the products appear to be inactive in this anti-arthritic assay, their manufacturers may claim temporary relief of pain in musculoskeletal disorders under the current TGA guidelines. In contrast, other natural products (e.g. in Group D), found active in this anti-inflammatory assay, can only be marketed under current TGA regulations as food supplements, without any reference to their potential activity. The Therapeutic Goods Act (1989) is concerned with good manufacturing practice, quality and safety of the listed goods without certifying efficacy or validity of the permitted claims (sic).

Inspection of Tables 2 and 3 show there are (a) Re-listed products for which the only permitted claim is 'special dietary supplement'; and (b) L-listed products which out-perform several R-listed products. This shows that the present practice of assigning an L-listing is no guide to whether a given product is inferior in potency/efficacy to one given the R-listing, nominally attached to drugs or other products whose efficacy is accepted by the Australian government. Of perhaps more concern is the matter of permitted labelling with so many products making specific claims to afford pain relief in the context of arthritic inflammation, despite showing no aspirin-like (i.e. anti-inflammatory) or paracetamol-like (i.e. antipyretic) activities in these relatively unambiguous rat models

The TGA noted problems with labelling of herbal products citing the fact that among 20 '*Echinacea*' products analysed, four contained no *Echinacea* at all and two others were mislabelled (anon 1993). Similarly, analyses of over 50 brands of the herbal product, 'ginseng', revealed that almost 20% contained no ginseng glycosides (Cud *et al.*, 1994; Kedar, 1996).

The TGA now requires one form of quality control with specific description of the contents of any TGA-listed herbal remedies, but still permits unproven claims for efficacy: a position which allows continual proliferation of TGA-listed nostrums with no quality control regarding merit. In contrast, herbal products in Germany must list the content of known active principles (Tyler, 1994; De Smet, 1995).

This limited survey also revealed another problem associated with product labelling as noted above, two products bearing the same brand name (e.g. Seatone), but in fact presented by different manufacturers/marketing organisations, may exhibit quite different potencies (see also 'max EPA'). In at least two cases known to us, this was associated with changes in the supply of source material (Sea Care; Herbs of Gold's Triad *versus* Eco Herbs celery products). This is

particularly pernicious if a 'good' product, justly earning a reputation for efficacy, is then manipulated by substitution of inferior *materia medica* or cheaper manufacturing process.

Such debasement of a herbal remedy has inevitable "wash-over" effects, particularly on the general perception of alternative/complementary therapies by the public at large and medical practitioners in particular.

Unless standards and quality controls, such as those provided by the German Commission E (Blumenthal *et al.*, 1998), the European Scientific Cooperative on Phytotherapy or indicated in the PDR for Herbal Medicine (1998) can be extended to include the types of natural anti-inflammatories/analgesics surveyed here, the product labelling may be almost worthless.

It is clear from this study that not all herbal/animal products from a given species may be equally efficacious. This was found to be the case also with emu oils, an animal-sourced traditional arthritis remedy (Whitehouse *et al.*, 1998). Clinical trials should be carried out on some of the more potent herbal/animal products to validate their true worth for human medicine. As Tyler (1994) has stated, translating the words of B. Lehmann,, a German physician:

"Phytomedicines, exactly like other medicines, must stand up to the challenge of modern scientific evaluation. They need no special consideration when it comes to the planning and conduct of clinical trials intended to prove their safety and efficacy. The distinctive feature of phytotherapy is its origin, namely, the many years of empirical use of plant drugs. Experience gained during this period should be taken into account, along with clinical testing, in evaluating the effectiveness of phytomedicines."

These views have been supported by others (Moulds and McNeil, 1988; De Smet, 1995). The frequency of musculoskeletal disease and the cost of OTC medications should require that consumers worldwide are provided with a proper evaluation of these products. This study highlights not only the variable potencies of some herbal and animal-sourced preparations but also their lack of gastrotoxicity. There is no reason to treat the evaluation of herbal/animal products differently from that of other medications. They should be evaluated clinically and then labelled appropriately by the TGA and other regulatory authorities.

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REFERENCES

1. ABS (1990). Australasian Bureau of Statistics National Health Survey, Summary of results. Canberra ABS 1989-1990 (catalogue no. 4364.0).
2. Angell, M. and Kassirer, J. P. (1998). Alternative medicine ---- the risks of untested and unregulated remedies, *New Engl. J. Med* **339**, 839-841.
3. Anon (1993). Survey of Echinacea products, p. 9. TGA News No. 15.
4. Arthritis Foundation (199?). Unproven remedies: resource manual. Atlanta.
5. Atherton, D. J. (1994). Towards the safer use of traditional remedies. Greater awareness of toxicity is needed, *Brit Med. J.* 308, 673-674.

6. Badley, E. M. (1994). Provision of rheumatologic services, in: *Rheumatology*, Klippel, J.H. and Dieppe, P.A. (Eds), Vol. 1, pp. 9.1-9.10. London Mosby-Yearbook, Europe.
7. Barrett, S. (Ed.) (1980). *The health robbers*, pp. 196-207. Philadelphia, G. F. Stickley Company, 2nd Edn.
8. Billingham, M. B. J. (1983). Models for arthritis and the search for anti-arthritis drugs. *Pharmacol Ther.* 21, 389-417.
9. Billingham, M. E. J. (1995). Adjuvant arthritis: the first model, in: *Mechanism and Models in Rheumatoid Arthritis*, Henderson, B., Edwards, J.C.W. and Pettipher, E. (Eds), pp. 389-410. Academic Press, New York.
10. Bliddal, H. (1997). Abstr. 19th ILAR Congress, Singapore.
11. Bliven, M. and Otterness, I. (1985). Laboratory models for testing non-steroidal anti-inflammatory drugs, in: *Non-steroidal anti-inflammatory drugs*, Lombardino, J. G. (Ed.), pp. 111-252. Wiley-Interscience, New York.
12. Blumenthal, M., Busse, W. R., Goldberg, A., Gruenwald, J., Hall, T., Riggins, S. W. and Riste, R. (Eds) (1998). *The Complete German Commission E Monographs Therapeutic Guide to Herbal Medicines*, American Botanical Council, Austin, Texas.
13. Brooks, P. M. (1998). Drug modification of inflammation ---- non-steroidal anti-inflammatory drugs, in: *Oxford Textbook of Rheumatology*, Maddison, P. J., Isenberg, D. A., Woo, P. and Glass, D. N. (Eds), pp. 575-581. Oxford, O.U.P., 2nd edition.
14. Brooks, P. M. and Day, R. O. (1991). Nonsteroidal anti-inflammatory drugs ---- differences and similarities, *New Engl. J. Med.* 324, 1716- 1725.
15. Brooks, P. M. and Lowenthal, R. M. (1977). Chinese herbal arthritis cure and agranulocytosis, *Med. J. Austr.* 2, 860- 861.
16. Brune, K. and McCormack, K. (1994). Over-the-counter use of NSAID's and other antipyretic analgesics, in: *Non Steroidal Anti-inflammatory Drugs: Mechanisms and Clinical Uses*, Lewis, A. J. and Furst, D. E., Marcel Dekker (Eds), pp. 97- 126. 2nd edn, New York.
17. Bury, R. W., Fullinaw, R. O., Barraclough, D., Muirden, K. D., Moulds, R. F. W. and Anghie, T. (1987). Problems with herbal medicines, *Med J. Austr.* 146, 324-325.
18. Champion, G. D. (1998). Unproven remedies: Alternative and complementary medicine, in: *Rheumatology*, Klippel, J. H. and Dieppe, P. A. (Eds), pp. 13.1-13.12. 2nd edn, London, Mosby-Yearbook, Vol. 2.
19. Chan T. Y. K. (1997). Monitoring the safety of herbal medicines, *Drug. Safety* 17, 209-215.
20. Clements, P. J. and Paulus, H. E. (1997). Non-steroidal anti-inflammatory drugs, in: *Textbook of Rheumatology*, Kelley, W. N., Harris, E. D., Ruddy, S. and Sledge, C. B. (Eds), pp. 707-740. 5th edn., Philadelphia, W. B. Saunders Co.
21. Cui, J., Garle, P., Eneroth, P. and Bjorkhem,1. (1994). What do commercial ginseng preparations contain?, *Lancet* 344, 134.
22. De Smet, P. A. G. M. (1995). Should herbal medicine-like products be licensed as medicines?, *Brit. Med J.* 310, 1023- 1024.
23. Diehl, H. W. and May, E. L. (1994). Cetyl myristoleate isolated from Swiss Albino mice: an apparent protective agent against adjuvant arthritis in rats, *J. Pharm. Sci.* 83, 296-299.
24. Dingh, G. H., Naora, K., Hayashibara, M., Katagiri, Y., Kano, Y. and Iwamoto, K. (1991). Pharmacokinetics of gingerol after intravenous administration in rats, *Chem. Pharm. Bull*, Tokyo 39, 1612-1614.
25. Eisenberg, D. M., Davis, R. B., Ettner, S. L., Appel, S., Wolkey, S., Van Rompay, M. and Kessler, R. C. (1998). Trends in alternate medicine: use in the United States 1990-1997, *J. Amer. Med. Assoc.* 280, 1569- 1575.
26. Ernest, E. (1998). Harmless herbs? A review of the recent literature, *Amer. J. Med.* 104, 170- 178.
27. Fernandez-Madrid, F. (1989). *Treating arthritis ----- medicine, myth and magic*. New York, Plenum.

28. Hunneyball, I. M., Billingham, M. E. J. and Rainsford, K. D. (1989). Animal models of arthritic disease: influence of novel compared with classical anti-rheumatic agents, in: *New Developments in Anti-rheumatic Therapy*, K. D. Rainsford (Ed.), pp. 93-132. Dordrecht, Kluwer Academic.
29. Huxtable, R. J. (1992). The myth of beneficent nature: the risks of herbal preparations, *Ann. Int. Med.* 117, 165-166.
30. Insel, P. A. (1996). Analgesic-antipyretics and anti-inflammatory agents, in: *The Pharmacological Basis of Therapeutics*, Hardman, I. G., Limbird, L. E., Molinoff, P. B., Rudden, R. W. and Goodman, A. G. Goodman & Gillman's ((Eds.)), pp. 617-644. 9th edn.. Pergamon, New York, Pergamon.
31. Jacob, S. W. (ed.) (1975). Biological action of dimethylsulfoxide. *Ann. N. Y. Acad. Sci.* Vol. 243.
32. Jacob, S. W. and Kappel, J. G. (1988). *DMSO*. Munich, Springer Verlag.
33. Jacob, S. W., Lawrence, R. M. and Zucker, M. (1999). *The Miracle of MSM: the natural solution for pain*, p. 250. New York, Penguing Putnam.
34. Kedar, I. (1996). Complementing mainstream medicine, *Nature Medicine* 2, 619-620.
35. Kiuchi, F., Iwakami, S., Shibuya, M., Hanaoka, F. and Sankawa, U. (1992). *Chem. Pharm. Bull.*, Tokyo 40, 387-391.
36. Macia, M., Navarro, J., Garcia-Nieto, V. and Garcia, J. (1996). Chinese herbs can themselves be harmful, *Arthritis Rheum.* 39, 354-355.
37. McCarty, M. F. (1994). The neglect of glucosamine as a treatment of osteoarthritis ----- a personal perspective, *Medical Hypotheses* 42, 323-327.
38. McClennan, A., Wilson, D. H. and Taylor, A. W. (1996). Prevalence and cost of alternative medicine in Australia, *Lancet* 347, 569-573.
39. McGrady (Sr) P. (1979). *The persecuted drug: the story of DMSO* (revised edn). New York, Charter Books, 312 pp.
40. Moulds, R. F. W. and McNeil, J. J. (1988). Herbal preparations ----- to regulate or not to regulate, *Med. J. Austr.* 149, 572- 574.
41. Mowat, A. G. (1992). The drug therapy of disorders of bones and joints, in: *Oxford Textbook of Clinical Pharmacology and Drug Therapy*, Grahame-Smith, D. G. and Aronson, J. K. (Eds.), pp. 414-426, 2nd edn. Oxford, O.U.P..
42. Nishihara, K. K. and Furst, D. E. (1997). Aspirin and other nonsteroidal anti-inflammatory drugs, in: *Arthritis and Allied Conditions*, Koopman, W. J. (Eds), pp. 611-654. 13th edn. Baltimore, Williams & Wilkins.
43. Panush, R. S. (1994). Alternative medicine: Science or superstition?, *J. Rheumatol.* 21, 8-9.
44. Panush, R. S. (1997). Questionable remedies, in: *Primer on the Rheumatic Diseases*, Klippel, J. H. (Ed.), pp. 450-452. Arthritis Foundation, Atlanta.
45. PDR (1998). *Physicians' desk reference for herbal medicine*. First edition, Montvale, N. J., Medical Economics Co.
46. Rainsford, K. D. (1982). Adjuvant polyarthritis in rats: is this a satisfactory model for screening anti-arthritic drugs?, *Agents & Actions* 12, 452-455.
47. Rainsford, K. D. and Powanda, M. C. (Eds) (1998). Safety and efficacy of non-prescription (OTC) analgesics and NSAIDs. Dordrecht, Kluwer Academic Publ.
48. Rainsford, K. D. and Whitehouse, M. W. (1992). Anti-ulcer activity of a slow-release zinc complex, zinc monoglycerolate, *J. Pharm. Pharmac.* 44, 476-482.
49. Ramos-Remus, C. and Russell, A. S. (1997). Alternative Therapies ----- medicine, magic or quackery. Who is winning the battle? *J. Rheumatol.* 24, 2276-2279.
50. Schaller, W. E. and Carroll, C. R. (1976). *Health, Quackery and the Consumer.*, pp. 273-285. W. B. Saunders, Philadelphia.

51. Shaw, D., Leon, C., Koley, S. and Murray, A. V. (1977). Traditional remedies and food supplements A 5-year toxicological study(1991-5) drug safety, 17, 342-356.
52. Srivastava, K. C. and Mustafa, T. (1992). Ginger (*Zingiber officinale*) in rheumatism and musculoskeletal disorders, *Med. Hypotheses* 39, 342-348.
53. Talalaj, S. and Czechowicz, A. (1988). Are herbal remedies safe?, *Med J. Aust.* 148, 102- 103.
54. Talalaj, S. and Czechowicz, A. S. (1989). Herbal remedies: harmful and beneficial effects. Melbourne, Hill of Content, 379 pp.
55. Tyler, V. E. (1994) Herbs of Choice: the therapeutic use of phytomedicinals. Binghamton, N. Y., Pharmaceutical Products Press.
56. Weissmann, G. (1996). Sucking with vampires. The medicine of unreason, *Ann. N. Y. Acad. Sci.* 775, 179-187.
57. Whitehouse, M. W. (1986). Oxicams: Relative safety and anti-injury effects in rats, *Brit. J. Clin. Pharmac.* 22, 11 IS- I 16S.
58. Whitehouse, M. W. (1988). Adjuvant-induced polyarthritis in rats, in: *CRC Handbook of Animal Models for the Rheumatic Diseases*, Greenwald, R. A. and Diamond, H. S. (Eds), pp. 3-16. CRC Press, Boca Raton, Vol. 1.
59. Whitehouse, M. W. and Fairlie, D. P. (1994). Anti-inflammatory activity of a holothurian (sea cucumber) food supplement in rats, *Inflammopharmacol.* 2, 411-417.
60. Whitehouse, M. W., Macrides, T. A., Kalafatis, K., Betts, W. H., Haynes, D. R. and Broadbent, J. (1997). Anti-inflammatory activity of a lipid fraction (Lyprinol) from the NZ green-lipped mussel, *Inflammopharmacology* 5, 237-246.
61. Whitehouse, M. W., Turner, A. G., Davis, C. K. C. and Roberts, M. S. (1998). Emu oil(s), a source of non-toxic transdermal anti-inflammatory agents in Aboriginal medicine, *Inflamnopharrrracology* G. I -8.
62. Yelin, E. and Callaghan, L. F. (1995). The economic cost and social and psychological impact of musculoskeletal conditions, *Arthritis Rheum.* 38, 1351- 1362

Table 3.

For column headings, see Table 2 or below. Test formulations given orally for 16 days.

1. Relative to untreated controls: +indicates increase; -indicates decrease. .

2. Duration of action in yeast-fevered rats = 2 h (++) or greater than 3 h (+++) at stated dose. Gastric lesion indices in fasted rats (n)5/gp) at stated

dose.

Not tolerated at higher doses.

a) contains *Perna canaliculis* (N.Z.) green lipped mussel.

b) contains beche-de-mer (mixed holothurians i.e. sea cucumbers).

c) each capsule contains CS oil (eqt. to 5 g dry CS), 350 mg evening primrose oil, 350 mg salmon oil, 100 mg cod liver oil, 250 mg willowbark, 150 mg

devil's claw tubers.

d) each capsule contains extract equivalent to 3000 mg C.S. and 160 mg Willow Bark.

e) each 5 ml contains 2.1 ml ethanol and extracts equivalent to dry weight: 800 mg celery seed, 800 mg bogbean leaf, 500 mg black cohosh root, 600 mg

devil's claw root, 1.5 gm willow bark, 800 mg *Guaiacum officinale* wood. (#) Higher doses were toxic.

f) each capsule contains 750 mg devil's claw and 150 mg German chamomile.

g) each tablet contains N.Z. mussel (150 mg), devil's claw (250 mg), yucca (250 mg), Willow bark (200 mg), Alfalfa (10 mg).

h) each tablet contains 250 mg green lipped NZ mussel, 250 mg willowbark, 200 mg devil's claw tubers, 200 mg *Yucca Elata* leaves.

i) each tablet contains rhus (5x), colchicum (5x), arnica (5x), ruta (4x), phytolacca (5x), bryona (5x).

j) 1 ml contains bambusa root (5 mcg), ginseng root (10 mcg), *Lycopodium clavatum* (0.1 mg), *Salvia mitorrhiza* (0.1 mg).

k) data for steam distilled oil (Swift) alone as added to PluravitR Profiles 50 Plus; dose of oil equivalent to 3000 mg/kg celery seed.

l) each capsule contains 50 mg CS oil, 350 mg evening primrose oil, 350 mg fish oil, 250 mg cod liver oil, 250 mg

willowbark and 150 mg devil's claw.

m) each capsule contains extract equivalent to 3000 mg CS, 250 mg willowbark, 150 mg feverfew, 100 mg devil's claw and 100 mg *Yucca elata*.