

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

M. W. WHITEHOUSE^{1,*}, M. S. ROBERTS¹ and P. M. BROOKS²

¹ *Department of Medicine, University of Queensland, Princess Alexandra Hospital, Woolloongabba, Queensland 4102, Australia*

² *Executive Dean (Health Sciences), University of Queensland, Royal Brisbane Hospital, Herston, Queensland 4029, Australia*

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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

*E-mail: dbutters-michaelw@powerup.com.au

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-inducing 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 (Naprogesic^R) 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 A\$0.6 billion/year spent by Australians on alternate therapies (MCLennan *et al.*, 1996) or (b) the US\$5 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

Table 1.

An arbitrary classification of OTC 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 conditions, 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.

* Available in Australia, 1994–1998.

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).

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. Martindale, 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.

III. Toxicity evaluation = single dose given to untreated polyarthritic rats (day 16 post-arthritis) 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 arthritogenic adjuvant (800 μg heat-killed *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 \rightarrow 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 retrospective 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 immunoregulant action. 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 $\geq 40\%$, $p < 0.05$). The principal findings were:

Table 2. Anti-inflammatory activity of some OTC products in a therapeutic assay using polyarthritic female Wistar rats

Treatment/Product/Source ¹	ARTG no ²	Format ³	Dose ⁴ mg/kg	Claims ⁵	Mean changes in arthritis signs (± SE)		Rats/gp
					Increase in Rear paw thickness (mm) ⁶	Fore paw inflmn ⁷ Δwt. (gm)	
							Δ Arthr. score ⁸
Vehicles:							
Tween 20 (10 ml/kg)				—	1.05 (0.07)	2.3 (0.3)+	2.2(0.2)
Olive Oil (2 ml/kg)				—	1.24 (0.19)	2.4 (0.4)+	2.3 (0.2)
Celery Seed (CS) Products:							
CS extract (Moons, Eumundi Qld)		T	'1250'	D	0.28 (0.01)	0 (0.2)	0.9 (0.4)
Celtech Forte (Beagle Int. Nerang Qld)	L55831	T	'1500'	B	0.15 (0.07)	0.6 (0.2)+	1.1 (0.3)+
CS-2500 (Chemline P/L, SA)	L49060	C	'2500'	B	0.68 (0.12)	1.7 (0.7)+	1.8 (0.3)+
Celery-2500 (Soul Pattinson, NSW)	L50957	T	'2500'		0.68 (0.19)	1.9 (0.3)+	1.7
Celery-5000 (Natures Way/Roche, NSW)	L44037	C	'5000'	B	1.21 (0.2)	2.1 (0.4)+	2.0 (0)
CS Tablets (Heath & Heather, UK)	—	T	'1800'	C	0.95 (0.23)	2.7 (0.5)+	2.3 (0.4)+
Celersoothe (Cape Town, S. Africa)	—	T	'3000'	D	0.51 (0.17)	1.5 (0.4)+	1.2 (0.2)
Celery-Liq (Qld Biochemics)	L45013	L	'2500'	C	0.90 (0.12)	2.3 (0.4)+	2.1 (0.3)+
NZ green-lipped mussel (GLM):							
Seatone (MacLab/Biomex, Melbourne Vic)	R14575	C	240	D	0.02 (0.15)	0.5 (0.3)+	0.1 (0.2)+
Seatone (McFarlane, Auckland NZ)	—	C	300		0.56 (1.1)	1.5 (0.4)+	1.6 (0.3)+
Seatone (Ferosan, Surrey UK)	—	C	300	C	0.79 (0.13)	2.4 (0.6)+	2.4 (0.3)+
GLM (Holland & Barrett, UK)	—	T	'300'		0.44 (0.05)	1.3 (0.5)+	0.7 (0.3)+
Pernamer (Health Dynamics, Bolton, UK)	—	C	300	D	0.97 (0.10)	2.3 (0.6)+	1.9 (0.4)+
Musselstone (Meadowcroft, Auckland NZ)	R10893	T	300	D	0.54 (0.12)	0.9 (0.2)	1.2 (0.3)
Musselstone (Healththeries, Auckland NZ)	—	T	300	D	0.72 (0.14)	2.9 (0.5)+	2.4 (0.1)+
Aotea Pacific Moana extr. (Japan)	—	C	300		0.59 (0.13)	2.1 (0.2)+	1.7 (0.2)
Lyprinol = GLM lipids (Pharma Link, Dk)	—	C	20		0.01 (0.13)	0.6 (0.8)+	0.4 (0.2)+

Table 2.
(Continued)

Treatment/Product/Source ¹	ARTG no ²	Format ³ mg/kg	Claims ⁵	Mean changes in arthritis signs (\pm SE)			Δ Arthr. score ⁸	Rats/ gp	
				Increase in		Δ wt. (gm)			
				Rear paw thickness (mm) ⁶	Fore paw inflamm ⁷				
Beche-de-Mer:									
Sea Care (La Mer, Qld)	R18678	C	300	D	0.29 (0.08)	0.4 (0.2)+	+05	0.7 (0.2)+	8
Sea Care (Pacific Grant Corp, Qld)	R18678	C	300	B	0.60 (0.09)	0.9 (0.2)+	-08	0.8 (0.2)+	8
Sea Cucumber Extr (21st Century, Arizona, USA)	---	C	750	D	1.15	2.1 (0.3)+	+01	2.9 (0.3)+	7
SA Sea Cucumber (Adelaide, SA)	---	C	300	D	0.16 (0.05)	0.9 (0.2)	-03	0.4 (0.1)+	7
Cartilage Support ⁹ (General Nutrition, Pittsburgh, PA)	---	T	300		0.50 (0.07)	1/3 (0.3)+	+10	1.2 (0.2)+	4
Ginger extracts:									
Zinax (Eurovita, Dk)		C	10000*	B	0.94 (0.14)	2.3	+12	1.8 (0.2)+	8
Zinaxin (Bionax Australia, NSW)	L56411	C	13200*	B					
in Tween 20					1.01 (0.05)	2.9 (0.3)+	+08	1.9 (0.4)+	9
in Olive Oil					0.88 (0.09)	2.7 (0.5)+	+12	1.8 (0.2)+	5
Zingiber complex (Qld Biochemics)	L61633	C	6000*	B	0.99 (0.18)	2.1 (0.5)+	+10	2.2 (0.4)+	4
Arthritis Calm ¹⁰ (Darwin Health Products, NSW)	L64890	T	150	B	1.08 (0.08)	2.1 (0.4)+	+03	2.7 (0.3)+	4

Table 2.
(Continued)

Treatment/Product/Source ¹	ARTG no ²	Format ³	Dose ⁴ mg/kg	Claims ⁵	Mean changes in arthritis signs (\pm SE)			Δ Arthr. score ⁸	Rats/ gp
					Increase in Rear paw thickness (mm) ⁶	Fore paw inflamm ⁷	Δ wt. (gm)		
Ibuprofen (Boots, NSW)	R13818	T	40 [*]	A	0.65 (0.17)	1.4 (0.5)+	+05	1.4 (0.4)+	10
Naproxen (Roche, NSW)	R10175	T	15	A	0.47 (1.3)	1.5 (0.3)+	+07	0.8 (0.3)+	7
Indomethacin (Sigma Chem, St Louis, USA)	—	—	03	(A)	0.21 (0.6)	0.5 (0.1)+	-01	0.7 (0.2)+	4

Reference NSAIDs:

Ibuprofen (Boots, NSW)
 Naproxen (Roche, NSW)
 Indomethacin (Sigma Chem, St Louis, USA)

Protocol: Rats with pre-established inflammatory arthritis treated orally on days 10 through 13 (post-adjuvant). Changes in signs of arthritis were determined over days 10 through 14.

1. New South Wales (NSW), Queensland (Qld), South Australia (SA), and Victoria (Vic) are States in Australia. NZ = New Zealand, Dk = Denmark.
2. Australian Register of Therapeutic Goods (Canberra Australia) Registration (R) or Licence (L) number for OTC usage.
3. Format of OTC product = Tablets (T); Capsules (C); Liquid (L) or (non-OTC) powder (—).
4. Dose of source material, with figures in inverted commas referring to extracts based on the mass given.
5. Claims for activity appearing on the label (see Table 1) i.e. B = explicit, C = implicit, D = no claims for treating inflammation/pain of arthritis.
6. In mm, determined with micrometer.
7. Each fore paw assessed for inflammation, wrist and digit swelling on score of 0-4+.
8. Arthritis score assigned on scale of 0-4+, on basis of clinical impressions (piloerection, grooming, mobility, sensitivity to handling) and overall inflammatory signs in ears, tail as well as paws.
9. Beche de Mer (300 mg/kg), glucosamine sulphate (300 mg/kg), hydrolysed gelatin (300 mg/kg).
10. Ginger with feverfew (600 mg/kg), Ca pantothenate (210 mg/kg) and vitamins.

Table 3.
Prophylactic activity of some OTC products in suppressing the development of an experimental polyarthrititis in rats

PRODUCT Labelled as	ARTG No	Format	Label claims	Dose mg/kg	% INHIB. SWELLING OF		Weight change	Anti- pyretic activity ²	Gastro toxicity ³
					Rear paw	Front paw			
<i>Analgesics:</i>									
Aspirin (Sigma, Vic.)	R19793	T	D	300	34	22	0	+++	>100
Ibuprofen (Boots, NSW)	R13818	T	C	50	44	30	0	++	87
Naproxen (Roche, NSW)	R10175	T	C	25	77	67	++	++	38
Paracetamol (Sigma, Vic.)	R24142	T	D	500	19	25	0	+++	0
<i>Celery (C) Seed (S) Products:</i>									
C-3000 (Blackmores Ltd., NSW)	L47890	T	B	'2500'	24	27	0		0
C-2500 (Bullivant's, Qld)	L41461	C	B	'2500'	40	35	0		
C-2500 (Cenovis Health, NSW)	L43747	C	B	'10500'	0	0	0		
C-2500 (Vitelle Health, NSW)	L43616	C	B	'2500'	0	0	—		
C-Power Triad (Herbs of Gold, NSW)	L44888	T	B	'2500'	27	0	0		
C-Power Triad (Herbs of Gold, NSW)	L39878	L	B	'4200'	0	0	0		
C-2000+ (Eco Herbs/Herbs of Gold, NSW)	L17298	L	C	'2500'	67	50	0	0	0
CS-3000 (Herron Pharm., Qld)	L46232	T	B	'2500'	10	0	0		
C-4000 (Twin Labs, Vic)	L48453	C	B	'2500'	37	46	+		0
CS-extr (Moons Products, Qld)	L39931	L	B	'2700'	67	59	++		
CS-extr (Moons Products, Qld)	L46524	C	B	'2500'	79	54	+	0	0
Celtech ^R (CT) (Moons Products, Qld)	L46525	C	B	'2500'	84	48	0	0	0
CT-Forte (Beagle Int., Qld)	L55831	T	B	'2500'	94	64	+	0	0
CS-2500 (Vitaplex Product, NSW)	L46711	T	B	'2500'	29	20	0	0	0
CS-Oil (Nature's Way, NSW)	L44037	C	B	'5000'	0	07	0		
C-7000 (oil) (Vitaglow, NSW)	L47185	C	B	'7000'	16	20	0		

Table 3.
(Continued)

PRODUCT Labelled as	ARTG No	Format	Label claims	Dose mg/kg	% INHIB. SWELLING OF		Weight change	Anti- pyretic activity ²	Gastro toxicity ³
					Rear paw	Front paw			
<i>Marine Products:</i>									
Musselstone ^a (Meadowcroft Auckland NZ) ^a	R10893	T	D	300	36	35	+		
Seatone (MacLab, Melbourne Vic)	R14575	C	D	300	82	63	0	0	0
Sea Care ^b (La Mer Qld)	R18678	C	D	300	52	51	+	0	0
Sea Care ^b (Pacific Grant Qld)	R18678	C	B	300	43	58	+	0	0
<i>Other Single Products:</i>									
Bromelain (Bullivant's Qld)	R27086	T	C	900	0	12	0		0
Willowbark (Bullivant's Qld)	L28193	T	B	1500	0	0	0	0	
Ca Pantothenate (Qld Biochemics)	L26599	T	B	250	0	0	-		
Glucosamine sulphate (Holland & Barrett UK)	-	C	C	500	0	0	-		
Glucosamine hydrochloride (Sigma Chem USA)	-	-	-	473	0	0	-		
Methylsulfonylmethane (Natrol, Ca, USA)	-	C	-	1500	05	-10	-		
Dimethylsulfoxide (Sigma Chem. USA)	-	-	-	1200	75	63	0		
Cetyl myristoleate (Gen, Nutrition, Pittsburgh, PA)	-	C	-	300	07	10	0		
<i>Mixed Products:</i>									
Celery & Juniper	L20282	T	C	'2500'	14	08	0		
C-5000 Complex ^c	L51979	C	B	'2500'	39	48	+		
C-3000 ^d (Kordel's, NSW)	L45771	C	B	'3000'	18	08	-		
C Complex ^e (Greenridge Botan. Qld)	L41813	L	B	'1500'#	32	40	-		
Arthritis relief ^f (Kordel's, NSW)	L50882	C	B	'1500'	0	0	0		
Arthritis & Rheumatism Therapeutic Formula ^g (Bullivant's Nat. Health, Qld)	R30629	T	B	'2500'	0	0	0		
Arthritis Formula ^h (Qld Biochemics)	R26412	T	B	300	06	24	+		

Table 3.
(Continued)

PRODUCT Labelled as	ARTG No	Format	Label claims	Dose mg/kg	% INHIB. SWELLING OF		Weight change	Anti- pyretic activity ²	Gastro toxicity ³
					Rear paw	Front paw			
Arthritis — homeopathic formula ¹ (Bullivant's Nat. Health, (Qld))	None	T	B	300	02	08	0		
CS Oil & Vitamins ^k (Sterling Health, NSW)	L 49478	C	B	90	04	19	—	0	
Arthri-eze (Bullivant Qld) ^l	L 51979	C	B	'5000'	39	48	25		
CS-3000 (Kordel, Bradford UK) ^m	—	T	D	'2500'	30	17	18		

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 ($n \geq 5$ /gp) at stated dose. # Not tolerated at higher doses.

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

b) contains beche-de-mer (mixed hothothurians 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 *Guaiaacum 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 ribus (5x), coichicum (5x), ruta (4x), phytolacca (5x), bryona (5x).

k) data for steam distilled oil (Swift) alone as added to Pluravit^R 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*.

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 gastrototoxic in fasted rats at an effective dose.
4. The OTC formulations of ibuprofen and naproxen, though active, were also quite gastrototoxic, 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 (Schaller and Carroll, 1976; Barret, 1980; Fernandez-Madrid, 1989; Panush, 1994, 1997; Arthritis Foundation, 1995; Weissmann, 1996; Ramos-Remus and Russell, 1997) with all too little objective evaluation in controlled animal or clinical studies.

Considerable concern has been expressed about the general *safety* of herbal remedies (Brooks and Lowenthal, 1977; Bury *et al.*, 1987; Moulds and McNeil, 1988; Talalaj and Czechowicz, 1988, 1989; Huxtable, 1992; Atherton, 1994; Macia *et al.*, 1996; Chan, 1997; Shaw *et al.*, 1997; Angel and Kassirer, 1998; Ernst, 1998). 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 gastrototoxicity 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 pharmaca 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 Fairlie, 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) R-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, normally 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 (Cui *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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