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Parthenolide Content and Bioactivity of Feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.). Estimation of Commercial and Authenticated Feverfew Products

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Abstract—Three physicochemical methods (HPLC, NMR spectroscopy, and HPLC of a derivative) have been used to measure parthenolide in authenticated *Tanacetum parthenium* (feverfew) and in several commercial purported feverfew products. A bioassay based on inhibition of the secretory activity of blood platelets by extracts of feverfew in comparison with parthenolide was also used. Similar results were obtained for all three physicochemical assays and also for the bioassay. Thus different methodologies yield consistent values for parthenolide content of feverfew preparations. Parthenolide appears to be mainly responsible for the antisecretory effects of extracts of feverfew. Authenticated *Tanacetum parthenium* grown in the UK contained a high level of parthenolide in leaves, flowering tops and seeds but a low level in stalks and roots. The level of parthenolide in powdered leaf material fell during storage. The purported feverfew products varied widely in their parthenolide content and in some products parthenolide was not detected. Possible reasons for the variation in parthenolide content are discussed. Since therapeutic efficacy has only been demonstrated for preparations of feverfew that contain parthenolide, it is suggested that manufacturers of feverfew products should use measurements of parthenolide as a means of standardization and quality control.

Feverfew (*Tanacetum parthenium*) has been shown to be of value in migraine prophylaxis (Johnson et al 1985; Murphy et al 1988). The active constituents and mechanism of action are uncertain, but a major component of the feverfew that has been shown to be efficacious in migraine is parthenolide and this sesquiterpene lactone appears to be mainly responsible for the bioactivity that has been demonstrated for feverfew in-vitro (Heptinstall 1988).

Several commercial preparations of feverfew are available through pharmacies and health food outlets. In a preliminary investigation, Groenewegen & Heptinstall (1986) assessed some feverfew products and found that extracts prepared from those products varied widely in their capacity to inhibit secretion of 5-hydroxytryptamine (5-HT) from blood platelets. The components of feverfew that seem to be mainly responsible for inhibition of 5-HT secretion are sesquiterpene lactones such as parthenolide (Groenewegen et al 1986) and there is a close correlation between the anti-secretory effects of extracts of feverfew and of parthenolide (Groenewegen & Heptinstall 1990). Consequently it is possible that the variation in anti-secretory activity observed in feverfew preparations was a result of different types and amounts of sesquiterpene lactones present in the preparations.

Until recently there has been no satisfactory quantitative assay for parthenolide in feverfew, although an HPLC procedure, using gradient elution, has been used for separation of sesquiterpene lactones, including parthenolide, and has been applied to the determination of costunolide (Strack et al 1980). There is now, however, a direct HPLC assay that has been confirmed by ^{1}H-NMR spectroscopic analysis (Awang et al 1991), and also an assay based on derivatization with an alkylthiol followed by HPLC of the Michael addition product (Dolman et al 1992).

In this investigation we have measured parthenolide in authenticated *Tanacetum parthenium* grown in the UK and in a variety of preparations of commercial purported feverfew products from the UK and Canada using these three physicochemical assays. We have compared the results with each other and with those obtained using a bioassay based on inhibition of secretory activity. This was a collaborative study in which two of the assays, the bioassay and the assay by derivatization/HPLC (HPLC method 1) were performed in Nottingham, UK, and two of the assays, the direct HPLC assay (HPLC method 2) and the ^{1}H-NMR analysis were performed independently in Ottawa, Canada. The feverfew products came from a variety of sources. Some were purchased from pharmacies or health food outlets. Some were submitted to Health and Welfare Canada for consideration for allocation of a Drug Identification Number (DIN). Others were prepared locally. Analysis of leaves and other parts of authenticated *Tanacetum parthenium* was carried out to provide a reference for comparison with the commercial preparations currently available and those which will become available in the future.

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Materials and Methods

Anti-secretory activity

Extracts of the feverfew preparations were obtained as follows. Air-dried leaves or feverfew tablets were powdered

using a mortar and pestle; seeds and the powdered contents of feverfew capsules were used directly. An amount equivalent to 240 mg feverfew was stirred in acetone (5 mL) for 3 h. The suspension was then filtered through Whatman No. 1 filter paper, and the residue washed with more acetone. The filtrate and washings were evaporated to dryness and redissolved in an accurately measured volume of acetone (2 mL).

An aliquot of this acetone extract (1 mL) was dried and the residue dissolved in ethanol (30 μL); the volume was made up to 1 mL by adding Dulbecco A phosphate buffered saline (PBS, Oxoid Ltd). The insoluble material was removed by filtration using a Sartorius Minisart NML filter (0·45 μm) and the clear filtrate was subjected to analysis for anti-secretory activity.

The anti-secretory activity of the extract was assessed by comparison with that of a solution of parthenolide. Parthenolide (40 mM in ethanol) was diluted with solutions of PBS/ethanol and 100 μL aliquots (each containing 3% ethanol) with 0–120 nmol were placed in polystyrene test tubes. Samples (24 μL) of a solution (0·25 mM in 0·9% NaCl (saline)) of flurbiprofen were then transferred to each tube, followed by 452 μL of human platelet-rich plasma (PRP) which had been pre-labelled with [^{14}C]5-HT. The contents were then stirred at 1000 rev min^{-1} for 2 min in a water bath maintained at 37°C; 24 μL of a solution of the thromboxane

Table 1. The parthenolide content of different preparations of feverfew.

Preparation			% parthenolide			
Feverfew brand or source	Unit	Lot or quality assurance no.	Bioassay	HPLC method 1	HPLC method 2	NMR
Tablets and capsules						
Nottingham*	Capsule	BN 72	1·03	1·00	0·97	0·83
Nottingham*	Capsule	BN 80	0·56	0·68	0·77	0·80
Herbal Labs (Tanacet Feverfew 125)	Tablet	263002	0·52	0·35	0·45	0·62
Bio-Health (Purefil)	Capsule	BN 85001	0·18	0·29	0·25	0·25
Power Health	Capsule	BN 9207	0·20	0·19	0·18	0·56
Potters (Barefoot)	Tablet	BN 0269	0·19	0·14	0·17	0·08
Matrem-Plus	Tablet	A 0392	0·12	0·13		
Eclectic Institute	Capsule		0·09	0·07	0·08	†
Seven Seas	Tablet	1001002	0·07	0·04	0·07	0·07
Christmas Natural Foods	Capsule		0·05	0·02	0·08	†
Yerba Prima	Tablet		0·05	0·03	0·06	0·06
Floris	Capsule		0·05	0·05		
Nature's Way	Capsule	1171627	0·05	0·04	0·05	0·05
FSC Feverfew	Tablet	BN 83288	0·04	0·04	0·03	0·02
Golden Health	Tablet	BN 8F01A	0·02	0·01	0·01	†
Matremin	Tablet	044	0·01	0·01		
Dr Dunner	Tablet	802			†	†
Dr Dunner	Tablet	805	0·03	n.d.	n.d.	n.d.
Dr Dunner	Tablet	807			n.d.	n.d.
Heath and Heather	Tablet	BN B8P 5776	n.d.	n.d.	0·04	†**
Holland and Barrett	Tablet	BNB 8W 5775	n.d.	n.d.	0·01	n.d.
Cantassium (Best Feverfew)	Tablet	BN 17905A	n.d.	n.d.	<0·01	n.d.
Lifeplan (Country Collection)	Capsule	BN 9B10	n.d.	n.d.	<0·01	n.d.
Reevecrest (Feverfew Forte)	Tablet	BN 00812076	n.d.	n.d.	n.d.	n.d.
Arkopharma (Phyto-Feverfew)	Capsule	117 4	n.d.	n.d.	n.d.	n.d.
Nature's Sunshine	Capsule	285-2	n.d.	n.d.	n.d.	n.d.
Tinctures						
Gerard tincture			(1·2 μg mL^{-1})			
GAIA tincture		3N1874588		(320 μg mL^{-1})†		
Leaf, powdered leaf, bulk or herb						
Green Products	Leaf		1·16	0·80		
Herbal Labs*	Powder	550601	0·73	0·49	0·78	1·09
Herbal Labs*	Powder				0·92	0·67
Nottingham*	Leaf	C10-1			0·83	0·85
Nottingham*	Leaf	C10-2	0·81	0·64	0·81	1·02
Nottingham*	Leaf	C10-3	0·56	0·50	0·62	0·83
Midland Herb	Herb		0·45	0·31	0·35	0·45
Dooley	Herb		0·31	0·24	0·30	0·32
Sigma Feverfew	Powder	87F-3802	0·08	0·05		
Abco Laboratories	Powder	56821	n.d.	n.d.	0·01	†***
Global Botanical	Herb	2209	n.d.	n.d.	n.d.	n.d.
Global Botanical	Powder	1844	n.d.	n.d.	n.d.	n.d.
Aliments Naturels Sol	Bulk				n.d.	n.d.
Ottawa Chemists	Bulk	2544			n.d.	n.d.
Other preparations						
Nottingham*	Seeds		1·36	1·16	1·52	1·82
Nottingham*	Seeds	C10-3S	0·86	0·70	0·89	1·12

* Authenticated *Tanacetum parthenium*. † Parthenolide detected but not quantitated. n.d. = parthenolide not detected. no entry = the assay was not performed. ** Not quantitated due to interference with the TCB signal by extract resonance. *** Detected in a fraction of the extract which was isolated by preparative TLC. % parthenolide is w/w (dry weight).

mimetic U46619 (0·25 mM in 0·3% ethanol in saline) was then added and stirring was continued for a further 6 min. At this point 50 μL of a solution of acetylsalicylic acid (2·5 mg mL^{-1} saline) was added and the tubes placed in ice. After 5 min, they were centrifuged at 3000 *g* for 8 min and duplicate 50 μL aliquots of the clear supernatants were analysed for released [^{14}C]5-HT. The amount released was expressed as a percentage of that present in the platelets before stimulation with U46619. To obtain a standard curve of inhibition of secretion by parthenolide, the experiment was performed six times using PRP from six different volunteers and mean data were obtained.

To quantitate anti-secretory activity in the feverfew extracts 100 μL aliquots of the extract (or of dilutions of the extract in 3% ethanol in PBS) were subjected to the procedure described above and the activity (expressed in terms of parthenolide) was determined with reference to the parthenolide standard curve.

HPLC, method 1

An acetone extract was obtained in exactly the same way as for the anti-secretory assay and dissolved in a measured volume (2 mL) of acetone as before.

An aliquot of this acetone extract (1 mL) was dried and weighed. The residue was dissolved in chloroform (0·75 mL) and an excess by weight of 9-thiomethylanthracene (as derivatizing agent) was added followed by 3 drops of triethylamine. The mixture was vortexed and left in a graduated, stoppered glass tube at room temperature (21°C) for 3 h. The volume of the sample was adjusted to 1·0 mL by addition of chloroform and samples were subjected to HPLC using a 25 cm, 5 μm Partisil column and n-hexane/ethyl acetate (1 : 1) as mobile phase with the flow set at 2 mL min^{-1}. Products were detected using a spectrophotometer operating at 369 nm. Under these conditions the retention time for parthenolide was 3·0 min and it was well-separated from excess derivatising agent. The quantity of parthenolide present was obtained with reference to an anthracene standard as described by Dolman et al (1992).

HPLC, method 2

Dried leaves, seeds, and tablets were powdered in a Tecator Cyclotec 1093 Sample Mill, while the contents of gelatin capsules were used directly. The powdered feverfew samples were extracted in a Soxhlet apparatus for 24 h using 450 mL petroleum ether (30–60°C). Samples were removed for HPLC and ^{1}H-NMR analysis and brought to dryness under reduced pressure at temperatures not exceeding 40°C. The residues were treated with acetonitrile, passed through a Millex-HV filter (0·45 μm), and injected directly onto an HPLC system utilizing a Brownlee Spheri-10-RP-18 column (250 × 4·6 mm, 10 μm) with a water-acetonitrile (55:45) mobile phase at a flow rate of 2 mL min^{-1}. Quantitation was at 210 nm with reference to a parthenolide standard curve as described by Awang et al (1991).

^{1}H-NMR

Spectra for parthenolide quantitation were obtained from deuterochloroform solutions of the extracted materials used in HPLC method 2 analyses. Estimation of parthenolide levels was based on comparison of peak heights of an internal standard, 1,2,4,5-tetrachlorobenzene (δ 7·56), with the sum of the peak heights of the doublet at δ 5·63 (due to the 13-H_a proton of parthenolide) using a correction factor, as described by Awang et al (1991).

Authentication of feverfew

When possible, samples of feverfew were authenticated as *Tanacetum parthenium* by a qualified botanist. The Nottingham samples were examined by Dr J. B. Power. The source of material used by Herbal Laboratories had been examined by Dr M. I. Berry.

Results and Discussion

Results are given in Table 1. They are divided into four sections: tablets and capsules; tinctures; leaf, powdered leaf, bulk or herb; other preparations (seeds). The samples that were authenticated *Tanacetum parthenium* are indicated. The values obtained for each of the four assays are given separately.

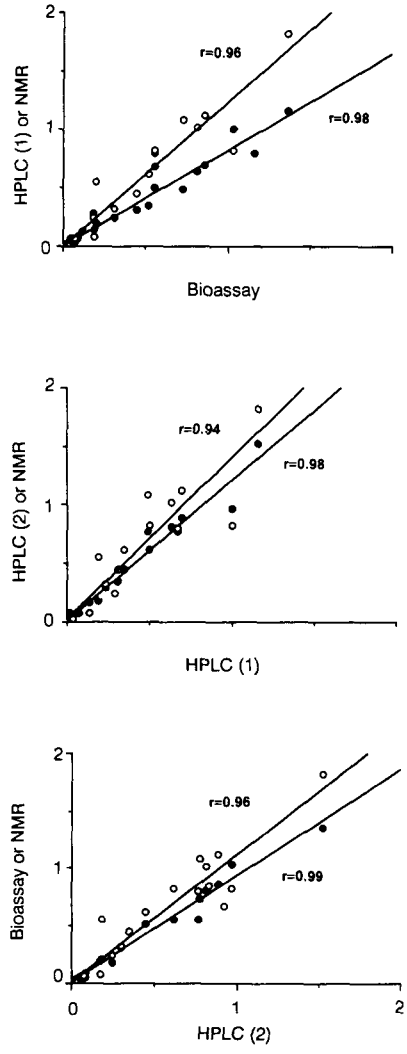

FIG. 1. Correlations between % parthenolide determined by the four different procedures. The data is taken from Table 1. Upper panel, ● HPLC method 1, ○ NMR; middle panel, ● HPLC method 2, ○ NMR; bottom panel, ● bioassay, ○ NMR.

There was wide variation in the amounts of parthenolide in the different materials. Despite this, there was a close correlation between the values for parthenolide obtained using the three physicochemical assays and also between the values for the physicochemical assays and the bioassay. Fig. 1 shows the correlation coefficients for the various pairs of data. Overall the ^{1}H-NMR assay yielded the highest values for parthenolide followed by HPLC method 2, the bioassay and HPLC method 1. The most sensitive assay was HPLC method 2; there were four occasions when small amounts of parthenolide were detected using this particular assay while parthenolide remained undetected using the other methodologies.

The closeness of the results obtained for the bioassay compared with the physicochemical assays suggests that the parthenolide content of feverfew preparations is mainly responsible for the bioactivity that is measured. This was surprising since some sesquiterpene lactones other than parthenolide might be expected to inhibit secretion of 5-HT from platelets (Groenewegen et al 1986). Presumably either other sesquiterpene lactones are present in only small amounts in the materials that were investigated, or their specific bioactivity is much less than that of parthenolide.

Leaf, powdered leaf, and capsules from sources of feverfew that were authenticated *Tanacetum parthenium* always contained high levels of parthenolide (Table 1). However, it must be noted that these were samples of feverfew grown in the UK and which are well known to have high parthenolide content. Feverfew grown in Germany was also shown to have a high parthenolide content (Bohlmann & Zdero 1982) but, in contrast, no parthenolide was found in feverfew grown in Mexico (Romo et al 1970) or Yugoslavia (Stefanovic et al 1985). These latter feverfew samples contained other sesquiterpene lactone types (mainly eudesmanolides and guaianolides) but not parthenolide or related germacranolides. Furthermore, parthenolide has so far been found in 34 plant species, 25 of the Asteraceae, including *Tanacetum vulgare* (common tansy), and 9 of the Magnoliaceae (Farnsworth 1990). It is clear from these findings that the presence and absence of parthenolide are not reliable indicators of feverfew identity.

We examined the different parts of a locally grown UK plant using the bioassay and found the highest activity to reside in the flowering tops (equivalent to 1·38% parthenolide) followed by the leaves (0·95%) with only 0·08% in the stalks and 0·01% in the roots. We also examined the seeds from British plants and found these to contain high levels of parthenolide (Table 1). Thus, varying amounts of different parts of a particular plant in a preparation of feverfew could lead to varying amounts of parthenolide. This may be of particular relevance to large scale manufacture when it may be impractical to achieve efficient separation of leaf from stalk material, perhaps the basis for France allowing the sale of feverfew herbage (leaf plus stalk). We have already reported that leaves obtained at different stages of cultivation (i.e. pre-flowering vs post-flowering) can vary in their parthenolide content (Awang et al 1991), another factor that could influence the parthenolide content of commercial preparations. Also, we have an indication that the parthenolide content of leaves can fall during storage. Part of a powdered sample of C10-3 leaf from Nottingham was kept unprotected from light at room temperature for 9 months and then re-analysed. The parthenolide content had fallen to 61, 50 and 65% of the starting value (as judged by bioassay,

Table 2. The dose of parthenolide in different tablets, capsules and tinctures.

Preparation		Dosage			
Feverfew brand or source	Unit	Lot or quality assurance no.	Feverfew (mg unit^{-1})	Parthenolide (μg unit^{-1})	Parthenolide* (μg day^{-1})
Nottingham	Capsule	BN 72	83	795	795
Nottingham	Capsule	BN 80	88	618	618
Herbal Labs (Tanacet Feverfew 125)	Tablet	263002	125	606	606
Bio-Health (Purefil)	Capsule	BN 85001	100	242	242
Power Health	Capsule	BN 9207	200	565	565 or 1130
Potters (Barefoot)	Tablet	BN 0269	200	290	290
Matrem-Plus	Tablet	A 0392	125	156	156
Eclectic Institute	Capsule		140	112	?
Seven Seas	Tablet	1001002	100	63	63
Christmas Natural Foods	Capsule		125	63	63
Yerba Prima	Tablet		50	25	?
Floris	Capsule		200	100	100
Nature's Way	Capsule	1171627	380	190	570 to 1140
FSC Feverfew	Tablet	BN 83288	150	49	49
Golden Health	Tablet	BN 8F01A	100	17	34
Matremin	Tablet	044	125	13	13
Dr Dunner	Tablet	805	125	< 10	< 10 or < 20
Heath and Heather	Tablet	BN B8P 5776	25	< 10	< 10 or < 20
Holland and Barratt	Tablet	BNB 8W 5775	25	< 10	< 10 or < 20
Cantassium (Best Feverfew)	Tablet	BN 17905A	125	< 10	< 20
Lifeplan (Country Collection)	Capsule	BN 9B10	250	< 10	< 10
Reevecrest (Feverfew Forte)	Tablet	BN 00812076	150	< 10	< 10
Arkopharma (Phyto-Feverfew)	Capsule	117 4	200	< 10	< 60
Nature's Sunshine	Capsule	285-2	390	< 10	< 40 to < 60
Gerard tincture				1·2 (μg mL^{-1})	0·6
GAIA tincture		3N1874588		320 (μg mL^{-1})	?

* These values are calculated from the manufacturer's recommended dosage in units per day. ? Recommended dose not supplied

HPLC method 1 and HPLC method 2, respectively). There is also evidence that growth conditions influence parthenolide content (Groenewegen 1988).

The various purported feverfew products that we analysed varied widely in their parthenolide content, and in some products parthenolide was not detected. Clearly such variation could be explained by some of the factors already referred to above. However, another possibility is that authentic *Tanacetum parthenium* may not always have been used. We obtained information from Arkopharma that the preparation that we analysed, in fact, was *Matricaria maritima* which had been supplied to the manufacturers as feverfew. Also there are recorded incidences of British importers of feverfew being provided with *Tanacetum vulgare* and *Matricaria recutita* (German chamomile) by Eastern European growers (Berry 1984).

For the tablets, capsules and tinctures that were analysed, it is of interest to convert the results of the analyses into the amounts of parthenolide unit^{-1} and the amounts recommended for daily consumption. This data (Table 2) indicate that the actual amounts of parthenolide that would be consumed by those using different preparations would vary from < 10 to 1140 μg day^{-1}.

The demonstration of efficacy of feverfew in migraine in the study by Murphy et al (1988) was achieved using feverfew capsules of known parthenolide content. The mean dose per day was one capsule containing 82 mg of feverfew containing a mean of 0·66% parthenolide. Thus the actual mean amount of parthenolide administered per day was 543 μg. Feverfew was administered for a period of four months. If the study by Murphy et al (1988) is used as a guide for amounts of parthenolide that are required for therapeutic efficacy, then the recommended doses of several of the commercial preparations that are currently available are providing far smaller amounts of parthenolide than may be required for the purposes for which the preparation is intended (Table 2).

In an attempt to ensure some degree of uniformity and quality the Health Protection Branch of Health and Welfare Canada has proposed that feverfew products for which an application for a DIN is made should be accompanied by certification of botanical identity, and be only dried leaf material containing a minimum level of 0·20% parthenolide. Also, a proposal of a minimum level of 0·10%, perhaps reflecting the acceptance of herbage there, has been made in a document (Special Issue No. 86/20b: Notice to manufacturers concerning requests for authorization to market plant-based pharmaceutical specialities) under consideration by the French Ministry of Health and the Family.

Such requirements help define the quality of the product but are not sufficient to control the amount of feverfew or parthenolide that is actually administered. Manufacturers are still free to incorporate as little or as much feverfew into a unit (tablet, capsule etc.) as they wish and to recommend a dose regimen of any number of units and any duration of treatment. On the one hand, the amounts of parthenolide administered may be too low for any therapeutic benefit to be obtained. On the other hand, the amounts of parthenolide administered may be higher than the amounts administered as feverfew in clinical trials. Although there has been no indication of any serious adverse effects of taking feverfew in the trials that have been performed so far, this does not preclude the possibility of higher doses producing such effects.

Now that techniques for quantitating parthenolide are readily available, it is to be hoped that this will encourage manufacturers to move towards standardization of their products and the application of appropriate quality controls. Also, it should be remembered that feverfew and its components, in common with all herbal medicines, have not been exhaustively evaluated for their safety, and those who promote the use of feverfew should exercise a high degree of responsibility in suggesting dose regimens.

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