

# A case study of illicit preparation of antirheumatic analgesic with phenylbutazone as active ingredient

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## Summary

The abuse of phenylbutazone among rheumatoid arthritis patients has recently become a subject of interest. Unscrupulous manufacturers take advantage of the miraculous analgesic property of phenylbutazone and deliberately add this toxic drug in their preparations without declaring its presence on the label. In a recent survey, many such illicit preparations were seized from Chinese medical halls in Johor and sent to the Department of Chemistry, Johor Bahru for analysis. Here a Gas Chromatograph Mass Selective Detector (GC-MSD) method was developed for the determination of phenylbutazone in illicit traditional preparations.

*Key words:* Phenylbutazone, illicit preparation, GC-MSD

## Introduction

Phenylbutazone is used in many illicit traditional preparations which are freely available from many Chinese medical halls. This is not declared on the label. Most of these preparations are in pill or capsule forms (Fig. 1). Many of them are made up of a mixture of eight to ten herbs. (Fig. 2 shows some product inserts of this illicit preparation which only stipulate Chinese herbs as their active ingredients.) Each usually contains about five natural products. Hence, it is definitely not an easy task to carry out a qualitative and quantitative determination on phenylbutazone by the usual colour tests, TLC and GC methods.<sup>1</sup> Same R<sub>f</sub> value in TLC and retention time in GC will not give a definite conclusion of the presence of phenylbutazone due to the variety of natural chemicals in it. In view of the above, a GC-MSD method has been developed to solve this problem. A total of 30 illicit preparations, of which 14 were declared to contain various common analgesic substances and the remaining 16 herbal mixtures, were analysed for scheduled drugs.

## Materials and method

### 1) Chemicals

- a) Phenylbutazone (purity 99.0%) was supplied by courtesy of Warszawskie Zakłady Farmaceutyczne Poland.
- b) All other chemicals were of analytical reagent grade.

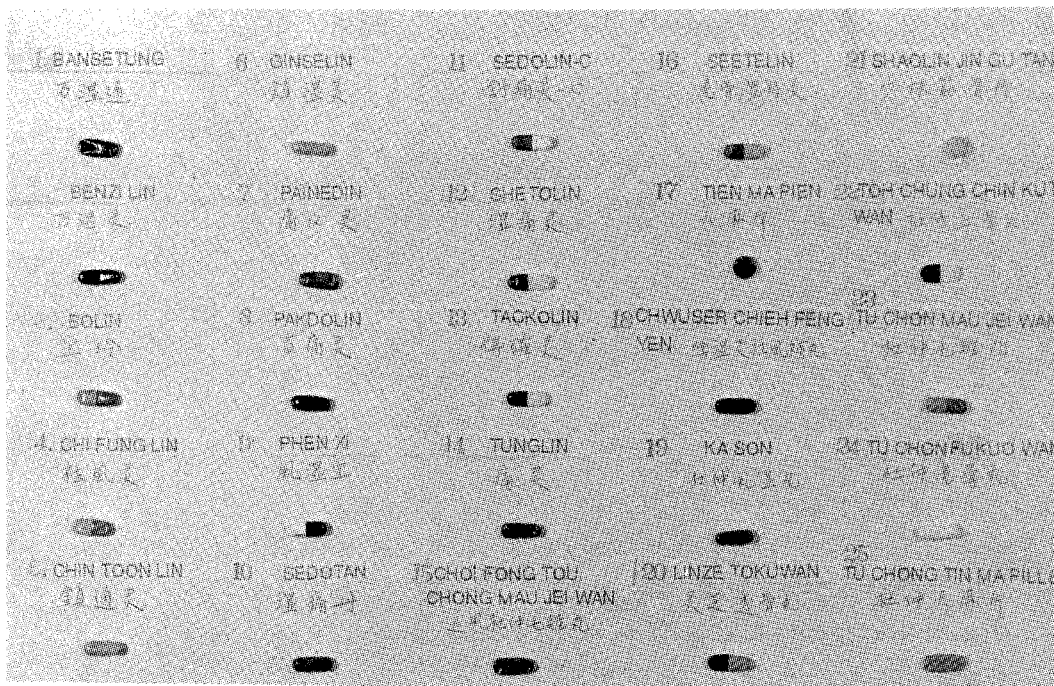


Fig. 1: The types of illicit preparations of antirheumatic containing phenylbutazone

## 2) Apparatus

A Hewlett-Packard 5890 Gas Chromatograph/5970 Mass Selective Detector (GC-MSD) interfaced with H/P 9000 series 300 Computer incorporated H/P 59970 Chem-Station Analytical Workstation and H/P 7673A Autosampler.

## 3) Procedure

Standard phenylbutazone and sample solutions were prepared by dissolving appropriate amount of each in chloroform.<sup>2</sup>

## Results

Phenylbutazone eluted from the column at about 6.5 mins. The identity of the peak was confirmed by its mass spectrum comparing with NBS Mass-Spectra Library incorporated in the HP59970 ChemStation system. A typical GC chromatogram and mass-spectrum of pure phenylbutazone is shown in Fig. 3.

The response of phenylbutazone was linear throughout the range of concentration studied. A calibration curve was prepared (Fig. 4).

The programmed least-square calculation produced the linear equation

$$C = 14.602 \times \frac{\text{Peak Area}}{10^{10}} - 0.002$$

where C is the concentration of phenylbutazone in mg/ml.

# 風濕杜仲虎骨丸

# Rheumatic Tu Chon Fu Kuo Wan

中國古代醫學中，定必選用虎骨和杜仲治療筋骨疼痛和痛風等症，虎骨與杜仲能追風，定痛，健骨，由此可見虎骨對治療筋骨疼痛的醫療效果，很早就被我國醫學界所肯定。

風濕杜仲虎骨丸係根據虎骨的醫療效聖，配以杜仲，虎骨，當歸等八種名貴藥材，經科學提煉而成，功效神速，絕無副作用。

## 適應症：

消炎止痛，活血舒筋，肩背酸疼，腰腿疼痛，行走困難或手足麻木，風濕性關節痛等。

## 服法：

成人每日三次，每次一至二粒，用開水送服。

The use of Tiger-bone & Tu Chon for curing diseases has been recorded in ancient Chinese medical classics, which also certify that Tiger-bone & Tu Chon has good therapeutic effect in treating muscular, osseous and flatulent and relevant ailments.

The Rheumatic Tu Chon Fu Kuo Wan is prepared on the basis of the therapeutical efficacy of the Tu Chon & Tiger-bone, medicated with *Cornus cervi parvum*, *Angelica polymorpha* and some 8 kinds of rare drugs by means of scientific refining process.

## Indications:

For Rheumatic, Lumbago Backache, Pain in the Joints, Stiff Joints and Constipation Etc

## Dosage:

Adults 3 times a day. Each time 1-2 pills with lukewarm water.

## 成份 Formula

杜仲	Encommia	25%	雙寄生	Loranthus	10%
虎骨	Tiger Bone	20%	白術	Atractylis Alba	10%
當歸	Ligusticum	15%	威靈仙	Veronica	7%
牛七	Achyranthes	10%	木瓜	Cydonia Lagernea Lois	3%

## CHWUSER CHIEH FENG YEN

This preparation originates from an effective formula handed down from a famous Chinese Herbal Specialist in the province of KWANG TUNG. The main active ingredients are made into capsules by a scientific process of extraction and concoction.

## COMPOSITION:

Phellodendron amurense	15%
Radix angelicae sinensis	15%
Anemarrhena asphodeloides	10%
Rehmannia glutinosa	15%
Cynomorium songaricum	10%
Citrus sinensis	5%
Paeonia latiflora	10%
Achyranthes bidentata	5%
Panthera tigris	10%
Caretta caretta	5%

## INDICATIONS:

Weakness of liver and kidneys, disturbance of the nerves and blood circulation, numbness of the limbs, pain in the loins and legs.

## DOSAGE:

Twice daily, 2 capsules each time, to be taken after food with warm soured water.

Fig. 2: The product inserts of TU CHON FU KU WAN and CHWUSER CHIEH FENG YEN

The amount of phenylbutazone in the pills or capsules can thus be calculated using the above equation as follows:

$$\text{Amount (mg) of phenylbutazone per pill or capsule} \\ = C \times 100 \times \frac{\text{weight of a pill or powder in a capsule}}{\text{total weight of powder used}}$$

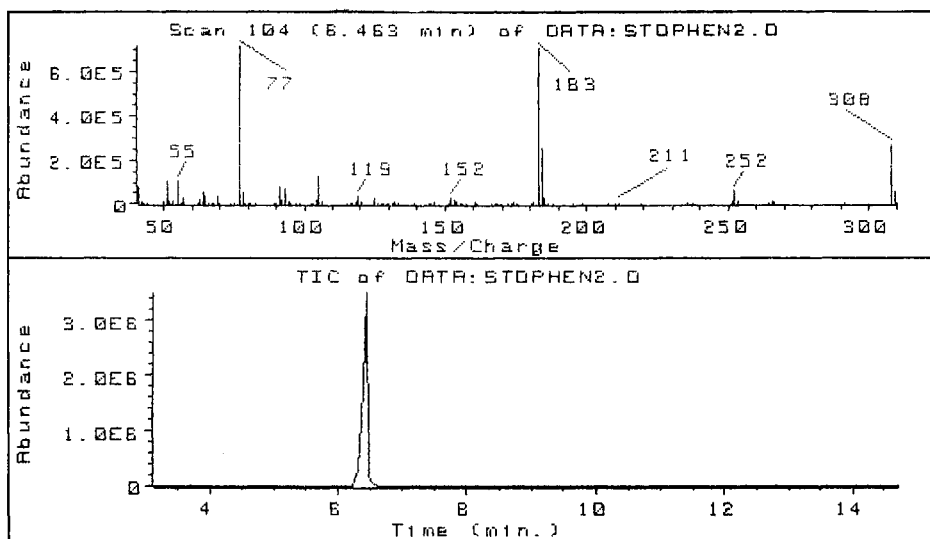


Fig. 3: Mass-spectrum (top) and elution chromatogram (below) of phenylbutazone.

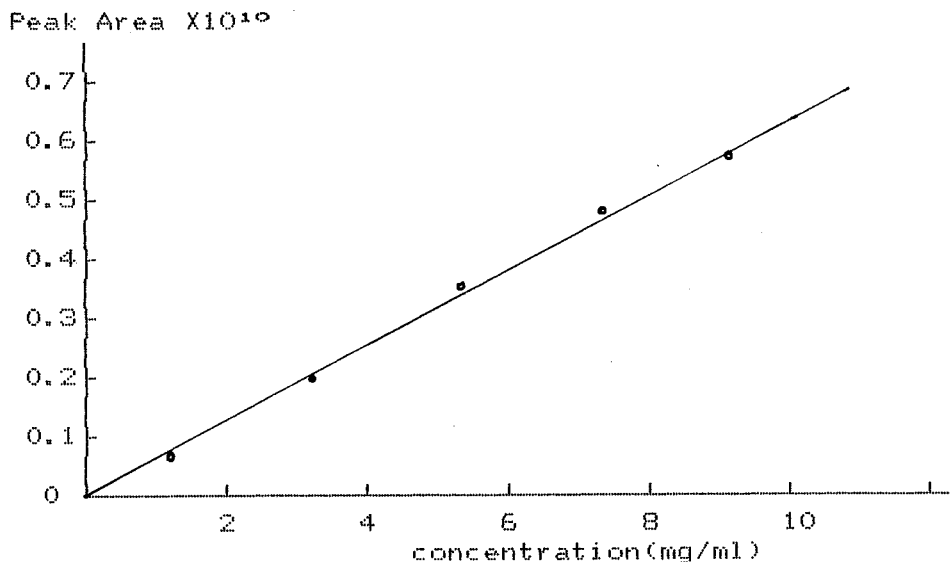


Fig. 4: Calibration curve of peak area against concentration of phenylbutazone

Figure 5, the elution profile of sample 17, is used to illustrate the efficiency of the GC-MSD method. It shows a rather complicated chromatogram because of the number of natural products. However phenylbutazone, even though in such low concentration, is still easily identified by the peak at 6.44 minutes.

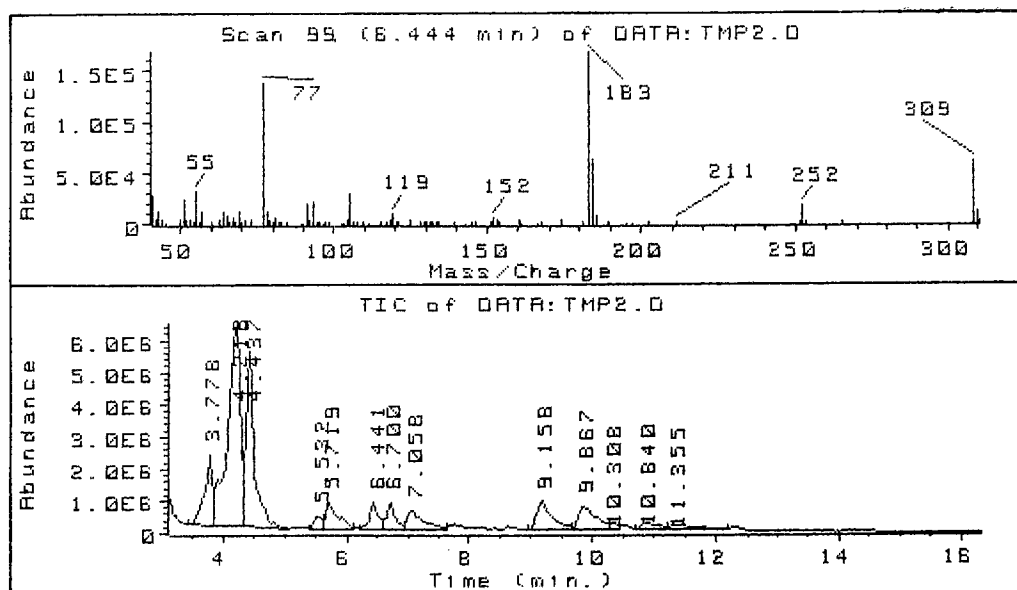


Fig. 5: Elution profile of the extract from "TIEN MA PIEN" pill and the mass-spectrum of the peak at 6.44 min.

## Discussion

Of the 30 antirheumatic drugs analysed, 25 were found to contain varying amounts of phenylbutazone ranging from 0.6 mg per capsule to 198 mg per capsule (or pill) as shown in Table I. The remaining five herbal mixture preparations were found not to be adulterated with phenylbutazone.

Among the 25 positive cases, sample one to 14 had been declared by their manufacturers to contain only common analgesics such as salicylamide, paracetamol, guaiacum resin BPC, caffeine and vitamin B. There was no mention of phenylbutanone present in the preparations. However, the analytical result showed that the active ingredient in all cases is actually phenylbutazone. The remaining 11 samples, sample 15 to 25, were claimed by their manufacturers to be traditional herbal mixtures but on analysis, they were found to contain phenylbutazone admixed with many natural products derived from the added herbs.

It is hoped that this survey will expose the unscrupulousness of those involved in the manufacture and sale of such preparations. Could it be that their greed for profits has proved greater than their conscience or could it be that they are ignorant of the harm they are causing to the innocent consumers?

The existing legislation has some control on the usage of pyrazolones, but its effectiveness could be improved. It is hoped that the following suggestions will help to reduce the abuse of phenylbutazone:—

- i) Stricter enforcement on the manufacture and sale of all the antirheumatic preparations especially those from local manufacturers. Products must be analysed for pyrazolones, cortisteroids and other scheduled drugs which are popularly used as antirheumatic and anti-inflammatory analgesics, before they are registered and sold/supplied to the consumers.

**Table I**  
**The types of antirheumatic preparations containing phenylbutazone**

Generic Name	Generic name in Chinese character	Appearance of the Capsule/Pill	Amount of Phenylbutazone (mg/capsule or pill)	Declared active ingredients
1) Bansetung	万湿通	Black/ruby red	96.2	a, b, c, d.
2) Benzi Lin	万湿灵	Black/Rose red	198.3	a, b, c, d.
3) Bolin	宝玲	Light green/pink	37.6	a, f.
4) Chi Fung Lin	祛风灵	Light green/pink	90.4	a, b, c, d, e
5) Chin Toon Lin	镇通灵	Light green/Light green	72.6	a, b, d.
6) Ginselin	镇湿灵	Light green/Light green	103.6	a, b, d.
7) Painedin	痛必灵	Reddish orange/Reddish orange	105.4	a, b, c, d.
8) Pakdolin	百痛灵	Black/Dark red	96.0	a, b, c, d.
9) Phen Xi	风湿宝	White/Brownish red	12.4	a, b, c, d.
10) Sedotan	湿痛丹	Reddish orange / Reddish orange	104.4	a, b, c, d.
11) Sedolin_C	舒痛灵-C	Princess blue/Transparent	106.8	a, b, c, d.
12) Shetolin	湿痛灵	Deep green/White	76.6	a, b, c, d, e.
13) Tackolin	得确灵	Deep green/White	119.7	a, b, d, e.
14) Tunclin	痛灵	Reddish orange/Reddish orange	4.1	a, b, d.

- ii) Introduce a stiffer penalty, like the recent amendment made on "Psychotropic substances".<sup>10</sup> Any offender shall, on conviction, be liable to a fine not exceeding ten thousand ringgit or to imprisonment for a term not exceeding four years or to both such fine and imprisonment.
- iii) Better control of imported chemicals at source; if in doubt, samples to be sent for analysis.
- iv) Publicity and dissemination of such information through the mass media so as to achieve greater awareness of the danger of such preparations.

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cont.

15)Choi Fong Tou Chong Mau Jei Wan	追風杜仲毛雞丸	Reddish orange/ Reddish orange	104.4	herbal mixtures
16)Seetelin	虎骨濕特靈	Grey/Greyish brown	68.0	herbal mixtures
17)Tien Ma Pien	天麻片	Red pill	0.6	herbal mixtures
18)Chwuser Chieh Feng Yen	除濕靈祛風補丸	Ruby red/Ruby red	130.0	herbal mixtures
19)Ka Son	杜仲風濕丸	Reddish orange/ Reddish orange	100.8	herbal mixtures
20)Linze Tokuwan	靈芝透骨丸	Grey/Ruby red	72.2	herbal mixtures
21)Shaolin Jin Gu Tan	少林筋骨丹	Greyish blue pill	traces	herbal mixtures
22)Toh chung Chin Kut Wan	杜仲正骨丸	Brownish red/white	traces	herbal mixtures
23)Tu Chon Mau Jei Wan	杜仲毛雞丸	Light green/pink	1.8	herbal mixtures
24)Tu Chon FU Kuo Wan	杜仲虎骨丸	White/White	63.8	herbal mixtures ;tiger bone
25)Tu Chung Tin Ma Pill	杜仲天麻片	vivid yellow/vivid yellow	3.8	herbal mixtures

NOTE: a-paracetamol; b-Vitamin B; c-caffeine; d-salicylamide. e-guaicum resin BPC; f-sodium phenyldimethylpyrazole.

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