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Chinese Proprietary Medicine in Singapore

Regulatory Control of Toxic Heavy Metals and Undeclared Drugs

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Abstract

Traditional Chinese medicine (TCM) is gaining popularity as a form of complementary and alternative medicine. Reports of efficacy of TCM are increasing in numbers. TCM includes both crude Chinese medicinal materials (plants, animal parts and minerals) and Chinese proprietary medicine (CPM) [final dosage forms]. Despite the belief that CPM and herbal remedies are of natural origin, unlike Western medicine, and are hence safe and without many adverse effects, there have been numerous reports of adverse effects associated with herbal remedies. Factors affecting the safety of herbal medicines include intrinsic toxicity, adulteration, substitution, contamination, misidentification, lack of standardisation, incorrect preparation and/or dosage and inappropriate labelling and/or advertising. Hence, new regulations on the control of CPM were enforced in Singapore with effect from 1 September 1999. These include licensing and labelling requirements, as well as control of microbial contamination. This article also reviews reports of excessive toxic heavy metals and undeclared drugs in CPM in Singapore between 1990 and 1997. The names, uses, toxic heavy metal or drug detected and the year of detection are tabulated. Information on the brand or manufacturer's name are provided whenever available. The public and healthcare professionals should be better informed of the basic concept of TCM and its usefulness, as well as the potential adverse effects associated with its use. Greater control over the safety and quality of CPM could be achieved through good manufacturing practice, regulatory control, research, education, reporting usage of Chinese medicine (as in drug history) as well as reporting of adverse events.

Herbal medicine is one form of complementary and alternative medicine widely used by people all over the world. The World Health Organization estimates that 65 to 80% of the world's population use traditional medicine as their primary form of healthcare.[1] A US telephone survey of 1539 adults showed that 34% of the respondents had used 1 form of unconventional therapy in the previous year and a third of these had seen a practitioner.[2] A South Australian survey of 3004 people aged 15 years or older reported that 48.5% used at least 1 non-medically prescribed 'alternative' medicine in the previous year and 20.3% had visited at least 1 practitioner during the year.[3] Growing worldwide interest in the

use of traditional Chinese medicine (TCM) as a form of complementary and alternative medicine results in ready availability of Chinese medicine from Chinese medicine shops, pharmacies, health food outlets, supermarkets and even through mail order (including via the Internet).[4] TCM includes both crude Chinese medicinal materials (CMM) [e.g. herbs, animals and minerals subject to simple processes like cutting and drying] and Chinese proprietary medicine (CPM). CPM are CMM which have been formulated into finished products in the form of capsules, tablets, pills, powders, mixtures, etc. In Singapore, CPM are not allowed to have western chemicals or drugs added. In some countries, such as China, synthetic drugs in CPM are allowed if the information is made known to the health authorities at the time of registration and is indicated in the package insert, subject to approval.

In Hong Kong, a survey of 1004 pregnant Chinese women[5] suggested that the prevalence of use of Chinese herbal medicine was 54%. Another study involving 166 Chinese mothers in Hong Kong and their babies[6] reported that 89% of these babies were given Chinese herbs or medicinal foods during the first 30 months after birth. Singapore is a densely populated, multiracial country with a population of 3.9 million (mid 1999 estimate). In 1994, a survey carried out by the Ministry of Health (Singapore)[7] showed that 45% of Singaporeans had consulted a TCM practitioner (Chinese Sinseh) in the past and 19% of the population had consulted one in the previous year. Not unexpectedly, the proportion who had ever consulted a TCM practitioner was the highest among the Chinese (54%); a much smaller proportion of Indians (16% of the Indians surveyed) and Malays (8% of the Malays surveyed) had also done so. In the same survey, it was found that the 3 most common forms of treatment used are CPM, acupuncture and crude drugs, in that order. With the easy accessibility and prevalence of use of both CPM and CMM, the issue of safety of such remedies needs to be addressed.

1. Safety of Herbal Medicine

Despite the belief that CPM are of natural origin, unlike Western medicine, and are hence safe and without many adverse effects, there have been numerous reports of adverse effects associated with herbal remedies.[5,6,8-15] Extensive and comprehensive reviews are available.[16-22] De Smet[16] gave an overview of herbal quality control and outlined the importance of quality control of herbal remedies by providing an overview of the types of toxic and pathogenic contaminants which may occur. These included toxic botanicals (*Spartium juncium, Aristolochia fangchi, Aristolochia manshuriensis, Teucrium* species, species containing tetrahydropalmatine, belladonna alkaloids and yohimbine, etc.), microorganisms, microbial toxins, pesticides, fumigation agents, radioactivity, toxic metals, synthetic pharmaceuticals and animal substances.

1.1 Factors Affecting Safety

Factors predisposing to intoxication by herbal products have been reviewed.[18,21,22] Alternatively, this subject can also be viewed from a slightly different angle – from a classification of the adverse effects. A comprehensive classification of adverse effects has been reported.[17] The adverse effects can be broadly divided into 2 main groups: intrinsic and extrinsic. The intrinsic adverse effects can be further divided into type A, B C and D reactions, as in orthodox medicine. Type A reactions are predictable toxicity, overdosage and interactions with pharmaceuticals, while type B reactions are idiosyncratic reactions, such as allergy and anaphylaxis. Type C reactions develop during long term therapy, and type D reactions are delayed effects, such as carcinogenicity and teratogenicity. The extrinsic adverse effects are largely due to failure of good manufacturing practice arising from adulteration, substitution, contamination, misidentification, lack of standardisation, incorrect preparation and/or dosage and inappropriate labelling and/or advertising. The relative importance of intrinsic and extrinsic factors leading to adverse reactions varies with the nature of the CMM. Except for some CMM which are intrinsically toxic (e.g. *Aconitum* species), most of them are not toxic. For the toxic CMM, intrinsic factors leading to adverse reactions are more im-

portant while for the rest, more often than not, the adverse effects are due to extrinsic factors.

1.2 Chinese Medicinal Materials

It has been estimated that there are over 5000 species of medicinal plants in China.[4] In TCM, the materia medica are largely derived from plants. This represents about 400 materia medica from plant sources (88%) that are in daily use, followed by animal sources (8%) and finally mineral sources (4%). These may be in their natural states or after being processed, often with water or heat or both. Many potent western drugs have originated from plants. Some important examples include the sympathomimetic amine ephedrine from *Ephedrae* species, anticholinergic substances from *Datura* species and the anticancer agent taxol from *Taxus brevifolia*. A survey of the literature found various reports[5,6,8-13] of toxicity of various TCM from plant sources. These are due mainly to the following common herbs: *Aristolochia fangchi, Coptis species, Salvia miltiorrhiza, Glycyrrhiza glabra, Panax ginseng, Dysosma pleianthum, Podophyllum emodi* and, in particular, *Aconitum* and *Datura* species.

TCM has been practised since time immemorial. With the vast amount of knowledge accumulated over thousands of years, what then is known in the Chinese literature to be toxic? Often, what is published in the Chinese literature is not indexed by major databases and vital information is not accessible to the billions who have a direct interest in this information. With this aim in mind, the currently available edition of the Chinese Pharmacopoeia[23] was scrutinised for information on toxicity of CMM. The toxicity documented is divided into 3 categories: very toxic, toxic and slightly toxic. Out of a total of 522 individual entries and 398 formulae, 9 entries are documented to be very toxic, 38 toxic and 22 slightly toxic. As the interpretation of toxicity of medicinal materials by a medical doctor may be very different from that by a TCM practitioner, these numbers must be viewed with caution. One should also be aware that although the CMM is largely herbal, some are from animal and mineral sources. The toxicity may be reduced or removed by the appropriate processing method. An example is the tuber of *Aconitum* species. Heating raw tubers of *Aconitum japonicum* and *A. carmichael* at 100°C in water (conditions employed for decoction) had been found to transform toxic aconitines into the less poisonous benzoylaconines, with a reduction in the acute toxicity of the tubers in mice.[24] In general, relatively few CMM used are toxic. An overview of published reports[25,26] of poisonings from China due to CMM is presented here. Du et al.[25] reviewed the adverse effects due to CMM for the period 1915 to 1990 in China. A total of 460 types of CMM gave rise to 2788 clinical cases of adverse effects. This represented 39.48% (460 out of 1165) of the total adverse effects due to drugs. About 45.62% (1272 out of 2788) of the cases were mainly due to 36 types of CMM (each accounting for at least 5 reported cases), with aconitum species accounting for the most number of cases (576) alone. There were 104 deaths associated with the use of CMM during that period. Adverse effects due to CMM for the year 1990, as reported in major medical and pharmacological journals in China, have also been reviewed by Yuan and Tan.[26] 192 reports of adverse effects, due to single medicinal materials, combinations of materials in standard formulae, medicated soup, known active ingredients and preparations of the above have been reviewed.[26]

2. Chinese Proprietary Medicine (CPM)

2.1 Definition of CPM

CPM is defined as any medicinal product used in the system of therapeutics according to the traditional Chinese method in its final dosage form.[27] It has been manufactured into a finished product and contains 1 or more active substances, all of which are derived wholly from plants, animals or minerals or a combination of any 1 or more of them. The medicinal product or all of its active substances are described in the current edition of *A Dictionary of Chinese Pharmacy*,[28] *The Chinese Herbal Medicine Materia Medica*[29] or other approved publication. CPM does not include any medicinal product

to be injected into the human body, any item specified in the Poisons Act,[30] or any medicinal product which contains as an active substance any chemically defined, isolated constituents of plants, animals or minerals or a combination of any one or more of them.

2.2 Regulatory Control of CPM in Singapore

In Singapore, legislation governing the control of CPM are: (i) Medicines Act[27] and its regulations; (ii) Poisons Act[30] and its rules; (iii) Medicines (Advertisement and Sales) Act[31] and its regulations; and (iv) the Sale of Drugs Act[32] and its regulations. Prior to 1 September 1999, the control included the following:

- CPM must not contain any substances controlled under the Poisons Act, e.g. aconite alkaloids (if more than 0.02%), ephedrine (if more than 1%), podophyllum resin (if more than 1.5%), atropine, berberine, cinnabaris, colchicine alkaloids, digitalis glycosides, hyoscine, quinidine, quinine and tetrahydropalmatine.
- The products must also not contain any substance listed under the Sale of Drugs (Prohibited Drugs) Regulations, namely amygdalin, pangamic acid, including its salts, danthron, suprofen, including its salts, and rhodamine B.
- The products do not contain any other substances except those stated in the labels.
- The heavy metal contents of the products do not exceed the limits shown in table I, as stipulated under the Medicines (Prohibition of Sale and Supply) [Amendment] Order 1995.
- The composition and quantities of all the ingredients of the products are printed in the English language on the product labels and cartons.
- The labels and packaging materials do not stipulate any of the diseases/conditions specified in the schedule to the Medicines (Advertisement and Sale) Act, namely blindness, cancer, cataract, drug addiction, deafness, diabetes, epilepsy or fits, hypertension, insanity, kidney diseases, leprosy, menstrual disorders, paralysis, tuberculosis, sexual function, infertility, impotency, frigidity, conception and pregnancy.
- The advertising and sales promotion of the products require a permit from the Ministry of Health.

With effect from 1 September 1999, greater control of CPM was enforced. This was to ensure that the CPM sold in Singapore are safe and of good quality and that they are labelled according to requirement, and to allow efficient withdrawal from sale when such an action is deemed necessary.

In addition to previous regulations, the new regulations are enforced in 3 phases according to dosage forms:

- from 1st September 1999 (tablets and capsules for oral consumption)
- from 1st September 2000 (in tablet or capsule form for oral consumption, or in liquid form for oral consumption or external application), and
- from 1st September 2001 for any dosage forms.

2.2.1 Licensing

All local manufacturers, assemblers, wholesalers and importers of CPM must be licensed by the Ministry of Health before they can conduct their business.

2.2.2 Labelling Requirements

Labelling requirements are clearly stipulated. Full labelling in English is required for all CPM. Chinese or other languages, if any, may be used in addition to English. The details required are as follows:

- The inner label must state the trade/brand name, product name, batch number, expiry date and names and quantities of ingredients (except for formula certified secret or protected by the relevant health authority of the exporting country).
- The outer label must state the trade/brand name, product name, batch number, expiry date, importer's or wholesaler's name and address, manufac-

Table I. Legal limits of 4 toxic heavy metals as stipulated under the Singapore Medicines (Prohibition of Sale and Supply)[Amendment] Order 1995

Metal	Legal limits (ppm)
Arsenic	5
Copper	150
Lead	20
Mercury	0.5

Table II. Microbial limits in Chinese proprietary medicine (CPM) as stipulated under the Singapore Medicines (Prohibition of Sale and Supply) [Ammendment] Order 1998

Type	Oral preparation	Topical preparation
Total aerobic microbial count[a]	Not > 10^5 per g or ml	Not > 10^4 per g or ml
Yeast and mould count[a]	Not > 5×10^2 per g or ml	Not > 5×10^2 per g or ml
Escherichia coli, *Salmonellae*, *Staphylococcus aureus*	Absent in 1g or ml	Not applicable
Pseudomonas aeruginosa, *S. aureus*	Not applicable	Absent in 1g or ml

a Do not apply to CPM derived from fermentation processes.

turer's name and address, and assembler's name and address (if any).

- The package insert must state the trade/brand name, product name, manufacturer's name and address, names and quantities of ingredients (except for secret and protected formulae), dosage, indication, contraindications (if any), adverse effects, and frequency and method of administration.

2.2.3 Reporting of Adverse Drug Reactions

License holders shall report any adverse drug reactions arising from the CPM which they are dealing within 7 days upon receipt of such information.

2.2.4 Testing for Microbial Contamination

Microbial limits are shown in table II.

3. Toxic Heavy Metals and Undeclared Drugs in CPM

The Ministry of Health has been conducting regular checks for undeclared drugs for more than 20 years. The detection and quantification of 4 toxic heavy metals, namely mercury, arsenic, copper and lead are routinely carried out using atomic absorption spectroscopy and inductively coupled plasma mass spectrometry. For undeclared drugs, high performance liquid chromatography, thin layer chromatography, Fourier transform infrared spectroscopy, ultraviolet spectroscopy, gas chromatography-mass spectrometry, electrospray mass spectrometry-mass spectrometry are employed.

We conducted a review of reports of excessive toxic heavy metals and undeclared drugs in CPM in Singapore between 1990 and 1997. Data on the toxic heavy metals and drugs detected were obtained from published reports (press releases and newspapers) and the National Pharmaceutical Administration of the Ministry of Health. A total of 2080 CPM were screened. These samples were obtained via both routine sampling and tip-offs by the public. Many of the CPM products cited in sections 3.1 and 3.2 are imported from China and are not limited to the Singapore market. Batches of CPM that are found to contain excessive amounts of the 4 toxic heavy metals above the legal limit and undeclared drugs are banned. Future consignments without these substances are allowed to be sold. It is beyond the scope of this study to review the toxic effects of toxic heavy metals and adverse effects of drugs. Interested readers are referred to other references.[33-36]

3.1 Excessive Toxic Heavy Metals Detected Between 1990 and 1997

The legal limits for mercury, arsenic, lead and copper are shown in table I. Between 1990 and 1997, 2080 CPM were screened for these metals and 42 different CPM were found to contain these metals in amounts exceeding the legal limits. Table III shows the names of the CPM (with brand or manufacturer's names in parenthesis where available), their uses, the excessive toxic heavy metal detected and the year of detection. If the information is available only in Chinese, the Chinese phonetic alphabet (i.e. the Han Yu Pin Yin form) is given. Table IV lists the number of CPM found to have these 4 metals in excess of the legal limits.The numbers do not add up to 42, as some CPM (table III, numbers 7 and 42) contain several excessive toxic heavy metals.

The most common excessive toxic heavy metal detected is mercury. It was detected in a total of 28 CPM, representing 66.7% of the 42 CPM with excessive toxic heavy metals, followed by lead (19.0%), arsenic (16.7%) and copper (2.4%).

Table III. Names of Chinese proprietary medicines (CPM) with brand or manufacturer's names where available, their uses, the type of excessive toxic heavy metals detected and the year of detection

Number	CPM (brand and/or manufacturer's names)	Uses	Toxic heavy metals detected	Year
1	Babaodan (Li Zhi[a])	Rheumatism, appendicitis, hepatitis and internal wounds	Lead	1995
2	China Ling Zhi Capsules	Tonic	Mercury	1995
3	Ching Fei Yi Huo Wan (Golden Lily)	Cough, sore throat, etc	Mercury	1996
4	Chunbaodai Tablet (Cang Song[a], Huanren Chinese Traditional Medicine Factory, China)	Tonic	Arsenic	1997
5	Danggui Yang Xue Pian (Da Ming Gong[a])	Anaemia	Mercury	1996
6	Dendrobium Moniliforme Night Sight Pills [superior]	Eye problems	Mercury	1990
7	Ding Xin Wan Concentrated	Heart problems	Mercury, lead	1995
8	Fargelin for Piles [high strength] (Yang Cheng)	Piles	Arsenic	1990
9	Gan Mao Ling (Snow Lotus)	Influenza	Mercury	1996
10	Haiodin	Not available	Mercury	1995
11	Hindu Magic Pills	Insomnia and loss of appetite	Copper	1995
12	Jin Kui Shen Qi Wan (Bao Lu[a])	Sperm production problems and kidney ailments	Mercury	1995
13	Jin Suo Gu Jing Wan (Bao Lu[a])	Kidney ailments and diabetes mellitus	Mercury	1995
14	Kar Liu Sum Yung pills (Yeung Ng Tong Medical)	Tonic	Mercury	1997
15	Kwei Be Wan (Min Shan[a])	Boost appetite and relieve insomnia	Mercury	1995
16	Liuwei Dihuang Wan (Nature's Green)	Tonic	Mercury	1997
17	Oukang San Powder Spray (Guangzhou Qixing Pharmaceutical Factory)	Throat ailment	Mercury	1997
18	Pai Foong Pill (Qin Mei[a], Hong Kong Tin Lok Medicines Co.)	Tonic	Mercury	1997
19	Pear Water Melon Frost (Jian Shen[a], Tian Jin Da Zhong[a])	Sore throat	Lead	1997
20	Pienzihuang Xiao Zhi Wan (Hai Ta[a], Tientsin Da Chong Medicine Works)	Piles	Mercury	1997
21	Po Ying Tan Babies Protector (Po Che Tong Poon Mo Um, Hong Kong)	Cholera, cold, cough, belly-ache, etc	Lead	1997
22	Shanhaidan Capsules (Qindan)	Coronary disease	Lead	1996
23	Shen Zhou Wild Ling Zhi Capsules (Fei Yien)	Tonic	Arsenic	1995
24	Shi Hu Pian (China's Guiyang Chinese Medicine Factory)	Poor eyesight	Mercury	1990
25	Shu Wei Hua Qi Jiao Nang (Zhong Ti)	Stomach upset, loss of appetite, etc	Mercury	1996
26	Specific Juk Tsyn Wan (Kwangchow United Manufactory of Chinese Medicine in China)	Diabetes mellitus	Mercury	1990
27	Su Shi Bai Feng Wan (Hua Ling[a])	General weakness	Mercury	1995
28	Te Zhi Du Zhong Ta Huo Lo Tan (Hai Ta[a])	Muscular pain	Lead	1997
29	Three Fives Shenwei Pill (Chun Liu[a])	Tonic	Lead	1997
30	Tien Wang Pu Hsin Tan (Min Shan[a])	Heart ailment, cancer, etc	Mercury	1995
31	Tien Wang Pu Sin Tan (Golden Lily)	Dizziness, palpitation, shortness of breath, etc	Mercury	1996
32	Tien Wang Pu Xin Wan	Heart problems	Mercury	1995
33	Tienqi Dieda Wan (Xing Qun[a])	Tonic	Lead	1997
34	Tze Pao Sampien Pill (Yantai Pharmaceutical Works in Chefoo, China)	Tonic	Mercury	1990
35	Wild Ling Chih Capsules (Mei Hua)	Tonic	Arsenic	1995

Table III. Contd

Number	CPM (brand and/or manufacturer's names)	Uses	Toxic heavy metals detected	Year
36	Xi Ling Jie Du Pian (Zhan Qiao[a])	Cold, fever, headache	Mercury	1995
37	Xiang Sha Yang Wei Wan	Stomach problems	Mercury	1995
38	Xiang Sha Yang Wei Wan (Golden Lily)	Stomach complaints, vomiting, diarrhoea	Mercury	1996
39	Xie Tu Ling	Vomiting	Mercury	1995
40	Xuan Fei Zhi Sou Dan	Cough	Arsenic	1995
41	Zhong Guo Xiong Dan Zhi Chuang Wan	Piles	Arsenic	1995
42	Zhu Bei Dinchuanpian (Golden Sun)	Cough	Mercury, arsenic	1997

a The brand or manufacturer's name in the Chinese phonetic alphabet (i.e. in Han Yu Pin Yin) when the information is only available in Chinese.

Mercury is the most toxic of the 4 metals. It is actually a component of some Chinese medicine.[4,23,37] It may be included as cinnabaris (zhu sha), which contains mercuric sulphide, or as calomel (mercurous chloride). In TCM, cinnabaris has various uses, for example as a tranquiliser, an antiepileptic, for ulcers and insomnia, and as an antidote. The CPM found to contain excessive mercury generally had multiple indications, including acting as a tonic, and for cough, sore throat, stomach upset, piles, etc. (table III).

Lead can exist as Mi Tuo Seng (Lithargyrum).[4] As seen in table III, lead appears to be associated with CPM indicated for various kinds of pain, e.g. muscular and stomach pain, sore throat, bruises, etc. It was also found in CPM indicated for coronary diseases and rheumatism.

Arsenic compounds used in TCM include Xiong Huang (Realgar),[4,23] which is actually arsenic sulphide. It is used for snake and insect bites, malaria and as an antidote, etc. Arsenic has been found in CPM for cough and piles and in tonic CPM.

Copper can exist as Dan Fan (Chalcanthitum)[4] in TCM. It was found in a CPM for insomnia.

Poisoning due to toxic heavy metals in Chinese herbal medicine and other non-Western traditional medicine had been previously reviewed.[18] Prior to 1990, the most notable report[38] of excessive toxic heavy metal in Singapore was that of arsenic found in a preparation called Sin Lak asthmatic pill. It was found to contain 12 000ppm of inorganic arsenic sulphide, giving rise to a daily arsenic intake of about 10.3mg. Yeung[39] has previously compiled a list of 12 Chinese herbal formulae containing arsenic and mercury salts. One of those listed was 'Tien Wang Pu Hsin Tan' (The King's Mind-Easing Tonic Pills). In the present study, there are 3 CPM (table III, numbers 30 to 32) with identical or similar names, namely 'Tien Wang Pu Hsin Tan' (Min Shan brand, according to the Chinese phonetic alphabet), 'Tien Wang Pu Sin Tan' (Golden Lily brand) and 'Tien Wang Pu Xin Wan'. No details of the brand or manufacturer's name of the last CPM (number 32) was available. However, an available photograph shows that it is different from the other 2 CPM. All 3 CPM were found to contain excessive mercury.

The exact reasons for the presence of excessive toxic heavy metals in CPM is not known. Possible reasons include deliberate inclusion as intentional ingredient, deliberate adulteration or contamination during manufacture from grinding weights,[40] lead releasing brewing pots[41] and other metal utensils. The herbs might have been grown in soil rich in certain metals.[42] Due to the nature of the source of the information, we are not able to confirm whether the metal detected was an intended ingredient of the CPM.

Table IV. Number of Chinese proprietary medicines (CPM) with excessive toxic heavy metals from 1990 to 1997

Type of toxic heavy metal	Number of CPM
Mercury	28
Lead	8
Arsenic	7
Copper	1

Table V. Names of Chinese proprietary medicines (CPM), with brand or manufacturer's names where available, their uses, the type of drugs detected and the year of detection

Number	CPM (brand and/or manufacturer's names)	Uses	Drugs detected	Year
1	Ba Bao Feng Shi Huo Luo Dan (Mei Hua)	Rheumatism	Diclofenac	1996
2	Black pills	Weight gain	Cyproheptadine	1993
3	Black pills marked	Weight gain	Cyproheptadine	1993
4	Dahuo Luodan (Golden Sun)	Pain, rheumatism	Berberine	1996, 1997
5	Dr Yap Condensed Honey Chon Poei Pei Pa Lo	Bronchitis and cough	Chlorpheniramine	1997
6	Fuchingsong Shaiodu Chie Yang Capsule (Yue Ling[a])	Anti-inflammatory, anti-itch	Chlorpheniramine, paracetamol (acetaminophen)	1995
7	Ginseng Zaizaowan (Golden Sun)	Pain	Berberine	1997
8	Gu Ben Wan (Chengdu Chinese Medicine Factory)	Treat many medical conditions	Caffeine, dexamethasone, diazepam, hydrochlorothiazide, indomethacin, prednisolone	1997
9	Huang Lian Shang Qing Pian	Sore throat, fullness of head, tinnitus, etc	Berberine	1996
10	Jin Bu Huan Anodyne Tablets (Zhong Guo Guang Xi Bai Se[a])	Gastric or duodenal ulcer pain, nervous insomnia, spasmodic cough	Tetrahydropalmatine	1995
11	Kuek Hum Siau Asthma Cure Powder (Swee Hoe Merchant)	Asthma, cough, whooping cough	Ephedrine	1992
12	Life Blood Medicine	Boost body's immune system, enhance red blood cell production, etc	Dexamethasone	1993
13	Nasalin	Rhinitis, nose blockage, headache, influenza, runny nose	Chlorpheniramine	1994
14	Nasalin High Strength	Rhinitis, nose blockage, headache, influenza, runny nose	Chlorpheniramine	1994
15	Pearl and Antelope Throat Powder Spray (Guang Rong[a])	Sore throat, mouth ulcer	Berberine	1996
16	Shang Feng Gan Mao Qing (Fei Yien)	Cold	Chlorpheniramine, paracetamol	1995
17	Shenchin herb (Sheng Chih Wei)	Pain in muscles or bones	Diazepam, ibuprofen, paracetamol	1994
18	She Tu Chieh Tu Wan	Contains venoms, effective for many medical conditions	Chlorpheniramine	1991
19	She Xiang Zhui Feng Tou Gu Wan (Mei Hua)	Rheumatism	Diclofenac	1996
20	Skimtan (Liow Phui Yee, Tai Sang Thong)	Throat disease, sore throat, goitre, inflammation of mouth	Berberine	1997
21	S-Magon Morning	Chronic bronchial asthma, bronchitis, hay fever, hepatitis, skin scaling	Promethazine, theophylline	1993
22	S-Magon Night	Chronic bronchial asthma, bronchitis, hay fever, hepatitis, skin scaling	Promethazine, theophylline	1993
23	Suxiao Gan Mao Pian (Yulin)	Cold	Chlorpheniramine, paracetamol	1995
24	Te Xiao Zhi Chuang Wan (Zhu Cheng)	Piles	Berberine	1997
25	Tou Tong Wan	Migraine, headache	Tetrahydropalmatine, diclofenac	1996
26	Tung Shueh Wan	Rheumatism	Caffeine, diazepam, indomethacin, prednisolone	1992
27	Unguentum Fluocinonidi	Skin (itching, dermatitis, eczema)	Fluocinonide	1996
28	101 Wei Yao Ling (Mei Hua)	Stomach problems	Diclofenac	1996
29	Wonder pills	Diabetes mellitus	Phenformin	1990

Table V. Contd

Number	CPM (brand and/or manufacturer's names)	Uses	Drugs detected	Year
30	Yan Sheng Hu Bao Jiao Nang (Shen Yang Fei Long[a])	Tonic	Berberine	1997
31	Zhen Zhu Tou Tong Ling (Fei Yien)	Headache	Diclofenac	1996
32	Zhong Gan Ling	Cold	Dipyrone	1995

a The brand or manufacturer's name in the Chinese phonetic alphabet (i.e. in Han Yu Pin Yin) when the information is only available in Chinese.

3.2 Undeclared Drugs Detected Between 1990 and 1997

Out of 2080 CPM screened during the period 1990 to 1997, a total of 32 CPM were found to contain 19 different drugs. The names of these CPM, their uses, the drugs detected and the year of detection are listed in table V. The names of the drugs detected and the number of CPM found to contain these drugs are listed in table VI.

Berberine is the drug most frequently encountered, followed by chlorpheniramine, diclofenac and paracetamol [acetaminophen]. In terms of therapeutic classes, there are antihistamines (e.g. chlorpheniramine, promethazine, cyproheptadine), nonsteroidal anti-inflammatory drugs (e.g. diclofenac, indomethacin, ibuprofen), analgesic antipyretics (paracetamol, dipyrone), corticosteroids (e.g. prednisolone, dexamethasone, fluocinonide), sympathomimetic agent (ephedrine), bronchodilator (theophylline), diuretic (hydrochlorothiazide) and antidiabetic (phenformin).

There were previous reports of some of these CPM products from different countries, indicating the wide distribution of such products. Of particular interest are 'Jin Bu Huan Anodyne' (table V, number 10)[43,44] and 'Tung Shueh Wan' (table V, number 26).[45,46] 'Jin Bu Huan Anodyne' (from Kwangsi Pai Se Pharmaceutical/Bose Drug Manufactory, Kwangsi, China) was found to contain levo-tetrahydropalmatine, an alkaloid present in *Stephania* and *Corydalis* species, but not in the genus *Polygala* (the plant indicated in the package insert).[43] Ingestion of Jin Bu Huan caused acute hepatitis.[43] The manufacturer's name of the Jin Bu Huan Anodyne tablets in the present study was only available in Chinese but appeared to be from the same source as previously reported.[43] Tetrahydropalmatine was detected in these tablets locally in 1995.[44] It may also cause blood pressure, heart rate and respiratory function to fall, causing lethargy and weakness. These adverse effects may begin after less than 12 hours of taking the tablets. 'Tung Shueh pills' (from Ta Ang Pharmaceutical Co, Taipeh, Taiwan) were reported to contain unlabelled mefenamic acid and diazepam.[46] They were also found to be the cause of acute renal failure in a woman taking 8 herbal pills daily for 4 weeks.[46] In the Chinese language, 'Wan' means 'pill'. The product 'Tung Shueh Wan' in the present study was found to contain 4 undeclared drugs, namely caffeine, indomethacin, diazepam and prednisolone.[45] The brand name or manufacturer's name was not available. The product is packed in red gelatin capsules with a label claiming that it contains herbal ingredients. It is sought after by people with rheumatism. 'Tung Shueh Wan' can cause mental depression, bone loss and spontaneous fractures, intestinal bleeding and even coma.[45] In the present study, 'Gu Ben Wan' was found to contain 6 drugs, namely indomethacin, hydrochlorothiazide, diazepam, dexamethasone, prednisolone and caffeine.[47] It is used as a tonic. The product is packed in yellow/black gelatin capsules and labelled as manufactured by Chengdu Chinese Medicine Factory. No other previous reports on 'Gu Ben Wan' were found.

Berberine, ephedrine, tetrahydropalmatine and caffeine may be of herbal origin: berberine from *Coptis* (Huanglian) and other plants, ephedrine from *Ephedrae* (Mahuang) and tetrahydropalmatine from *Corydalis* (Yanhusuo).[23,48] The adverse effects of some drugs and herbs have been reviewed.[18-20,35] Of particular interest are berberine, dipyrone, phenformin and tetrahydropalmatine. The risk of neonatal jaundice from the use of ber-

Table VI. Number of Chinese proprietary medicines (CPM) found to contain undeclared drugs from 1990 to 1997

Drug	Number of CPM
Berberine	8
Chlorpheniramine	7
Diclofenac	5
Paracetamol (acetaminophen)	4
Diazepam	3
Cyproheptadine	2
Dexamethasone	2
Indomethacin	2
Prednisolone	2
Promethazine	2
Tetrahydropalmatine	2
Theophylline	2
Caffeine	2
Dipyrone	1
Ephedrine	1
Fluocinonide	1
Hydrochlorothiazide	1
Ibuprofen	1
Phenformin	1

berine in neonates has been reported.[49] In Singapore, the use of berberine is banned.

Dipyrone has been associated with agranulocytosis.[50] Phenformin, an antidiabetic drug, was found in a CPM indicated for diabetes mellitus. It is very dangerous for patients with diabetes mellitus to unknowingly consume phenformin found in herbal medicine. Fatal lactic acidosis caused by phenformin has resulted in the withdrawal of the drug in many countries, including the US, China and Singapore. In fact, in this study, the 'Wonder Pills' (table V, number 29) which contained phenformin resulted in the deaths of 2 men, aged 60 and 80.[51] The 60-year-old man obtained the drug during a holiday in China and had been taking it for more than 1 year. The 80-year-old man had obtained the drug from his relative in China and had taken it for 3 months before his death. Phenformin has been banned in Singapore since 1977.

Unsupervised consumption of drugs could lead to adverse or toxic effects or even fatal consequences. Some patients may be under the care of Western medical doctors and receiving medications. Undeclared drugs may also lead to overdose. Besides, some detected drugs present in the CPM have no desirable effects as indicated at all, or could even worsen the condition. For example, dexamethasone was found in a CPM claimed to boost the immune system. However, being a corticosteroid, it is anti-inflammatory and is actually an immunosuppressant. Diazepam is a benzodiazepine type of anxiolytic. It alleviates anxiety states. It is indicated for short term relief of severe anxiety. Long term use should be avoided. It is also used in acute alcohol withdrawal, status epilepticus and febrile convulsion. TCM are often used on a long term basis as the effects are believed to take a longer time to manifest. Hence, although the CPM found with diazepam are indicated for pain in muscles/bone and rheumatism, long term consumption of undeclared diazepam is dangerous.

A Taiwanese study[52] reported 66 synthetic therapeutic substances present as adulterants in TCM. The 5 most frequently detected adulterants are caffeine, paracetamol, indomethacin, hydrochlorothiazide and prednisolone, in decreasing order of frequency.[52] All 5 of these drugs have also been found in the CPM locally. On the other hand, some drugs reported in the present study had not been detected in Taiwanese CPM. They are promethazine, phenformin, fluocinonide and dipyrone. Berberine, tetrahydropalmatine and ephedrine detected in Singapore are natural ingredients of some herbs and are hence not included in the Taiwanese study.

Drugs which are natural ingredients of herbs have long been used in TCM. In fact, some currently available drugs, such as the anticancer drug taxol and antimalarial artemisinine, are isolated from plants which have been used for centuries in China. Berberine and tetrahydropalmatine have potent effects. Being part of TCM, instead of banning products containing these drugs, a better way to safeguard the safety and interest of patients may be to regulate the use and prescription of such products. The beneficial effects can thus be optimised. Unsupervised use leading to toxic effects can thus be prevented.

The Taiwanese study[52] reported a prevalence of adulteration of 23.7% (n = 618). Here, based on

the data available, the prevalence is about 4.5% (counting each detection as 1, there are 93 detections out of a total of 2080 CPM products screened) for the period between 1990 and 1997. The high prevalence in the Taiwanese study is largely due to the nature of the samples – those associated with reports of adverse effects and poisoning and which may also include low grade folk remedies, possibly locally produced. In Singapore, the samples are obtained via both routine sampling and tip-offs by the public. One should be aware that many CPM preparations have similar or identical names. The actual ingredients and undeclared metals or drugs, even in products with identical names, may vary, for example with the country of origin or manufacturers from different provinces.

4. Conclusions

Between 1990 and 1997, 42 different CPM available in Singapore were found to contain excessive toxic heavy metals while 32 different CPM were found to contain a total of 19 drugs. In total, 93 cases of excessive toxic heavy metals and undeclared drugs were detected.

It is clear that the presence of undeclared drugs and toxic heavy metals can be hazardous to the health of patients. The public and healthcare professionals should be better informed of the basic concept of TCM and its usefulness, as well as the potential adverse effects associated with its use. The regulatory control in Singapore prior to 1 September 1999 was in place for many years and was very useful in controlling the presence of toxic heavy metals and undeclared drugs. New additional legislation effective from 1 September 1999 further helps to ensure that the CPM sold in Singapore are safe and of good quality. Greater control over the safety and quality of CPM could be achieved through good manufacturing practice, research, education, reporting of usage of Chinese medicine (as in drug history) as well as reporting of adverse events.

Addendum

Following are articles of interest, related to this subject, which have been published recently. The authors recently reported the detection and quantification of undeclared codeine in a CPM for asthma.[53] The product AsthmaWan (Yangcheng brand from China) has since been banned in Singapore. Ko[54] reviewed the causes, epidemiology and clinical evaluation of suspected herbal poisoning, mainly with respect to herbs used in traditional Chinese medicine. Tomlinson et al.[55] looked at the toxicity of complementary therapies from an eastern perspective. Boullata and Nace[56], as well as Marrone[57], reviewed safety issues of herbal medicine, while Miller et al.[58] discussed various issues (e.g. regulation, safety, research and the role of pharmacists) associated with herbal products.

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