

# SAFETY OF CHINESE HERBAL MEDICINE

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## INTRODUCTION

The issue of safety of Chinese herbal remedies must be paramount in the mind of practitioners for two reasons. First and foremost, because, as practitioners, we must strive to give patients the best possible care and minimize possible side-effects and adverse reactions; secondly, we need to be seen to practise in a professional and responsible manner that ensures the maximum safety if we are to satisfy potential regulatory authorities. There are more and more negative reports regarding the alleged toxicity of herbal remedies (many of them misguided or plainly wrong) and we need, as practitioners, not only to practise in the safest way possible, but also to *be seen* to do so.

In the hands of experienced practitioners, Chinese herbs are very safe. This booklet aims, on the one hand, to give guidelines for a safe use of herbs and, on the other hand, to show the flaws in many of the reports on the alleged toxicity of Chinese herbs. Not by chance, the title of this booklet is “Safety of Chinese Herbal Medicine” rather than “Safety of Chinese Herbs”. The issue of safety of Chinese herbs cannot be considered in isolation from the principles, philosophy, diagnosis, guidelines, rules and methods of Chinese herbal medicine: it is my belief that, when used according to such rules, Chinese herbs are remarkably safe. Many of the reports of alleged toxicity of Chinese herbs concern situations when they were self-administered, prescribed without regard to the principles of Chinese herbal medicine, wrongly identified, or used as single herbs for dubious aims. The tragic case of the Belgian women who were subjected to a slimming regime with a dubious cocktail of conventional drugs and two Chinese herbs is simply the result of a reckless use of drugs and herbs without any adherence not only to the principles of Chinese medicine but not even to basic principles of good practice of Western medicine: it is simply an example of “bad medicine” and tells us nothing about the safety or otherwise of Chinese herbs.

The booklet starts with an introduction to the pharmacokinetics of drugs: although, as stressed later, herbs do work differently from drugs, it is still useful to understand how drugs, and therefore herbal compounds, are absorbed, metabolized and excreted. The booklet then analyzes the differences between herbal medicine and drugs, the issue of safety of Chinese herbs, and interactions between Chinese herbs and Western drugs. Practitioners in the UK are urged to read the paper written by Trina

Ward BSc “*Formulating RCHM policy on blood testing*” for members of the Register of Chinese Herbal Medicine (RCHM). Those with access to the Internet should also read the article “*Recognition and Prevention of Herb-Drug Interaction*” by Dr John Chen, Ph.D., Pharm.D. posted on the site “[www.acupuncture.com](http://www.acupuncture.com)”.

# SAFETY OF CHINESE HERBAL MEDICINE

## INFORMATION FOR PRACTITIONERS

The booklet will be set out in the following sections:

1. How drugs are metabolized and excreted
2. Factors affecting dosage of drugs
3. Description of side-effects, adverse reactions, idiosyncratic reactions and allergic reactions to drugs
4. Differences in the pharmacodynamics of drugs and herbs
5. Side-effects, adverse reactions, idiosyncratic reactions and allergic reactions to herbal medicines: a review of the literature with identification of some mistakes
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### 1. **HOW DRUGS ARE METABOLIZED AND EXCRETED**

This discussion will describe the factors affecting the metabolism and excretion of drugs (whether synthetic or herbal). Pharmacokinetics is the study of how a drug is absorbed, distributed in the organism and excreted. There are basically five processes involved:

- *Absorption*: the process by which drugs are absorbed by the wall of the small intestine (or the large intestine in the case of enteric-coated medicines)

- *Distribution*: the process of distribution of the drug in the body and protein-binding
- *Serum concentration*: the level of concentration of the drug in serum and how it falls in time
- *Metabolism*: the metabolism of the drug by the liver
- *Excretion*: the process that takes place in the kidneys

Figure 1 illustrates how drugs pass through the body.

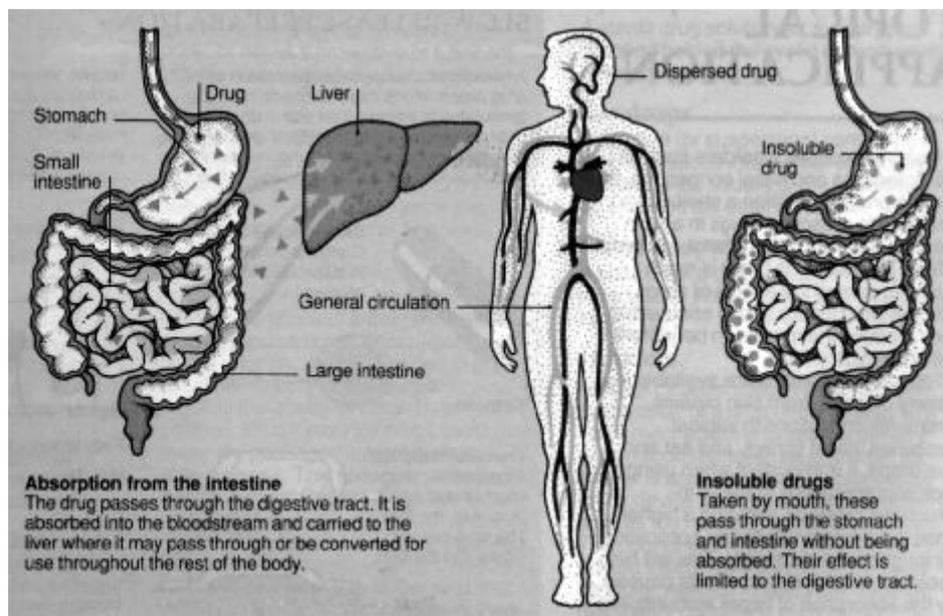


Fig. 1. How drugs pass through the body. Reproduced with permission from British Medical Association, "Guide to Medicines and Drugs", Dorling Kindersley, London, 1991.

Soluble drugs are absorbed by the lipid membranes of the cells lining the wall of the small intestine and stomach. Absorption can take place in four ways:

- *Diffusion*, whereby the drug goes through the membrane in solution
- *Filtration*
- *Transport*, whereby the drug is transported across the membrane by an active mechanism requiring energy

- *Pinocytosis*, whereby small particles of the drug are engulfed by the cells of the wall

The most common process is that of diffusion. This depends on the difference of concentration of the solution across the membrane. Absorption is directly proportional to the water and lipid solubility of the drug. Molecular size also affects absorption: the smaller it is, the faster the absorption. Formulation also affects this.

Drugs exist in a solution in two forms: undissociated (or un-ionized) or as ions (ionized). How much or how little they are undissociated depends on the pH of the medium in relation to that of the drug. If the pH of the medium is the same as that of the drug, the drug is 50% undissociated and 50% ionized. At a low pH (i.e. acid) weakly acid drugs will be more undissociated than ionized; at a high pH (i.e. alkaline), weakly acid drugs will be more ionized than undissociated. Herbal remedies usually contain weak acids and will therefore be better absorbed in the stomach (which is acid) because only undissociated molecules are lipid-soluble.

Many drugs have a physiochemical affinity for plasma protein and this leads to *plasma protein-binding* of the drug. Drugs are therefore carried in the blood in two forms: free (pharmacologically active, diffusible and available for metabolism and excretion), and *protein-bound* (pharmacologically inert, not diffusible and not available for metabolism and excretion). The protein-binding is generally weak so that, as the concentration of free drug in the plasma falls, a supply of drug is quickly released from the protein. Thus, protein-binding can be regarded as a drug storage mechanism.

The concentration of a drug in the serum is a function of liver metabolism and kidney excretion and falls in an exponential fashion; the time taken by the concentration to fall to half its initial level is called the *half-life* of the drug. A drug's half-life is used to determine frequency of dosage and amount of drug administered. Enzymes such as monoamine oxidase (MAO) can greatly reduce the concentration of a drug (unless the person takes a monoamine oxidase inhibitor, MAOI; these are often used for depression).

Lipid-soluble drugs are easily absorbed from the alimentary tract; they later appear in the glomerular filtrate of the kidneys and are then re-absorbed into the bloodstream via passive diffusion in the proximal tubules.

While circulating in the body, a drug undergoes chemical changes as it is broken down: this process is called metabolism. Most of the chemical changes take place in the liver where various enzymes oxidize (add oxygen to), reduce (remove oxygen from) or hydrolyze (add water to) a drug. These changes produce chemicals (metabolites). They are carried in the portal circulation to the liver, where they undergo metabolism and ionization into more polar, lipid-insoluble metabolites, so that they can be absorbed by passive diffusion into the renal tubules for elimination through urine. The polarity of these metabolites determines how they become excreted. Following ionization, the relative acidity or basicity of a metabolite will determine excretion via the urine. Urine is acidic and will therefore favour the excretion of weakly acid metabolites (such as those in herbal remedies).

To be useful, a drug must not only enter the body reliably and reach the site of action but it must also be eliminated in a reasonable time. Drugs can be classified into two types: ionised, lipid-insoluble and non-diffusible; or un-ionised, lipid-soluble and diffusible. Diffusion is the most important means by which drugs enter the body and are distributed within it. It is dependent on the drug being *lipid-soluble*. As far as metabolism of drugs is concerned, drugs that are highly lipid-soluble and un-ionised will be re-absorbed by diffusion from the glomerular filtrate (in the kidneys) and would remain in the body indefinitely unless altered by enzymes. To be eliminated, these highly lipid-soluble drugs must be converted into lipid-insoluble and ionised metabolites. Most herbs contain lipid-soluble compounds and must therefore be metabolized by metabolizing enzymes. These enzymes were developed by evolution to permit the organism to dispose of lipid-soluble substances found in foods (and therefore also herbs). These enzymes are extremely non-specific, attacking types of molecule rather than specific compounds.

Drug *metabolism* occurs chiefly in the liver. Therefore in a patient with liver disease drugs may have a greater or lesser effect than expected. The amount and kind of drug-metabolizing enzymes are genetically determined and the rate of drug metabolism varies greatly between individuals, e.g. by a factor of 10 for *dicoumarol* and more for some antidepressants. Drugs are metabolized mainly by enzymes in hepatic microsomes (a fraction of the cell endoplasmic reticulum).

Some chemicals, when administered over a few days or more, induce an increase in drug-metabolizing enzymes (practitioners of Chinese medicine will see the 5-Element Controlling and Generating cycles at work here): thus, a drug can stimulate its own metabolism and since these enzymes are non-specific, the rate of metabolism of other substances may be affected.

Certain drugs may affect liver function in various ways:

- By interference with bilirubin metabolism
- By direct liver cell injury (carbon tetrachloride, tetracyclines, tannic acid, arsenic, iron, cytotoxic drugs, chloroform).
- By triggering allergy or hypersensitivity:
  - Hepatitis-like reaction (MAO inhibitors)
  - Cholestatic injury, manifesting with jaundice. This may be dose-related as with steroids; it may be due to a genetic predisposition; it may be allergic.
  - Generalized drug allergies may also involve the liver.

Needless to say, we should always ask about any pre-existing liver disease and, if the patient is affected, we should be extremely careful in prescribing Chinese herbs. They are not contraindicated in liver disease: indeed, Chinese medical literature abounds in references to the treatment of chronic hepatitis (A, B or C) with Chinese herbs. However, for obvious reasons, unless the practitioner is experienced in this field, it is better not to prescribe Chinese herbs in such cases. If Chinese herbal remedies *are* prescribed, the effect should be monitored with regular liver function tests.

*Excretion* of drugs occurs chiefly in the kidneys. Because they play a major role in it, impaired or reduced kidney function will therefore lead to drug toxification, due to accumulation of unexcreted drug. The tubular pH will affect elimination of drugs by influencing the ratio of ionized vs. un-ionized forms. Urine is acidic and therefore favours the excretion of basic or weakly acid drugs. The acidity of the urine can be altered to determine the life-span of the drug as required. Oral administration of ammonium chloride increases the acidity of urine and therefore enhances the secretion of weakly basic drugs, thus shortening the drug's half-life. The opposite effect can be achieved by oral administration of ammonium bicarbonate, as this will decrease the acidity of urine and prolong the half-life of the drug. The active constituents of most herbal remedies are basic (i.e. weakly acid). Their plasma half-life is therefore increased by factors which lower the pH of the urine (i.e. make it more acid). A vegetarian diet rich in alkaline foods raises the pH and so reduces plasma concentration. Hence, when compared with meat-eaters, vegetarians might need slightly higher doses of herbal remedies. However, the difference is quite small and is not usually of practical significance.

Chemicals damage the kidneys by:

- Direct biochemical effect
- Indirect biochemical effect
- Immunological effect

The kidney is particularly vulnerable to direct chemical injury because it receives the peak plasma concentration of all substances entering the blood and because the process of concentrating the glomerular filtrate into urine inevitably means that renal tubule cells are exposed to much higher concentrations of chemicals than are other cells in the body.

Substances that can cause renal damage include:

- Heavy metals (cadmium, mercury, arsenic, gold, lead: these may be present in Chinese herbal remedies not subject to strict quality controls)
- Antimicrobials
- Analgesics
- Anticonvulsants

Heart disease may cause reduced flow of blood to the liver, resulting in renal insufficiency or slower clearance of products by the liver.

Some drugs also cause renal damage by indirect biochemical mechanisms, e.g. uricosurics (drugs for gout) may cause precipitation of uric acid in the tubule and damage can result from the hypercalcaemia of calciferol (a vitamin D compound) overdose as well as from severe electrolyte depletion (Na, K) due to excessive use of diuretics and purgatives. Because of this, particular caution should be exercised if a patient is taking diuretics or purgatives (e.g. *Senokot*): in such cases, we should not give herbal diuretics or purgatives. It is important to bear in mind that tea and coffee are also diuretics and we should therefore ask the patient to discontinue their use (or limit it to a minimum) during Chinese herbal therapy. The concomitant administration of diuretic drugs and Chinese herbs was a factor (not the only one) in the renal damage suffered by Belgian women treated in a slimming clinic (this is described on page 21). Needless to say, extreme caution should be exercised in patients suffering from chronic glomerulonephritis.

## 2. FACTORS AFFECTING DOSAGE OF DRUGS

There is an enormous variation in the response to drugs by individuals. For any one drug, there will be individuals who are naturally intolerant, those who will show the expected pharmacological effect at a very low dose, and a few who will show it only at a very high dose. Thus, before abandoning a drug (or a herbal remedy) as useless, it is important to consider whether an adequate dose has, in fact, been given. The only rational way to make a decision would be to measure the plasma concentration of the drug, but this is very seldom done. Therefore, the physician making a decision on dosage is often under a considerable handicap because, although he or she may be using the dosage in the recommended range, plasma concentrations commonly vary by a factor of 5 or more. Some even say that individual variations vary from 4-fold to 40-fold.<sup>1</sup>

Factors affecting the response of an individual to a dose of a drug (or herb) are many and they include *race, sex, diet, size, metabolic rate, environmental temperature, body*

*temperature, mental state, route of administration, pharmaceutical formulation, state of the gut, circulation, whether or not the drug is protein-bound, the rate and path of bio-transformation and excretion (largely genetically determined), the health of liver and kidneys, the presence of other drugs, alcohol consumption, whether the individual has taken the drug before, etc.*

**Age** is an important consideration when adjusting the dosage of a drug. The very old and very young are liable to be intolerant to many drugs. The *newborn* child has lower glomerular filtration and renal plasma flow than adults and for at least the first month its liver is seriously deficient in drug-metabolizing enzymes. These deficiencies are enhanced in premature babies. It is therefore important not to treat newly born babies for at least two months; six months is preferable since during the first half year, the kidney's glomerular filtration rate is much slower than that of an adult. In the elderly, renal glomerular filtration rate declines and this leads to increased half-life of drugs (i.e. the time it takes to reduce the plasma concentration of a drug to half). This extension of half-life is a factor contributing to the increased liability of the elderly to adverse reactions. All central nervous system depressants are likely to have a greater effect in the elderly.

The dosage is also affected by any pre-existing liver or kidney disease. Severe liver disease such as cirrhosis or hepatitis affects the way the body breaks down drugs and herbs. This can lead to dangerous accumulation of drugs in the body and lower doses should therefore be used. Kidney disease affects drug absorption and excretion in two ways. Firstly, drugs (and herbs) may build up in the body because the glomerular filtration rate of the diseased kidney is slow. Secondly, in kidney disease, protein escapes from the tubules and causes *proteinuria* (protein in the urine). Since a proportion of the drug is bound to protein molecules (as discussed above), loss of protein frees more drug molecules which become pharmacologically active (see figure 2).

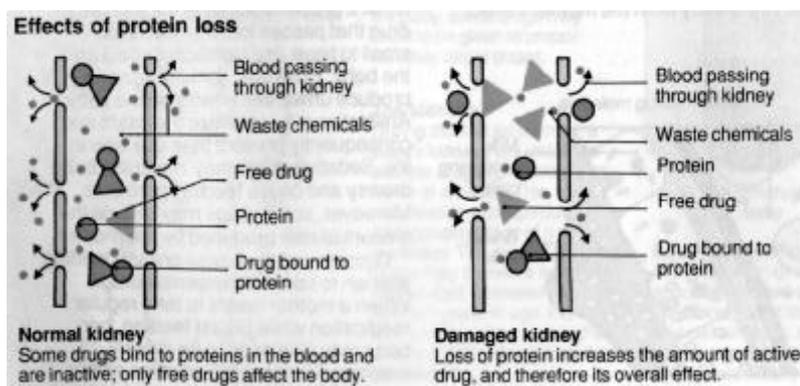


Fig. 2. Protein loss in diseased kidney and increase of free drug (or herb) molecules. Reproduced with permission from British Medical Association, “Guide to Medicines and Drugs”, Dorling Kindersley, London, 1991.

We are often told that one of the drawbacks of using whole plants is that we cannot measure exactly the quantity of active ingredients delivered and therefore we cannot adjust the dosage accurately. Quite apart from the different mode of actions of whole plants (see below), the dosage of drugs is far from accurate, precisely-calculated or “scientific”. Practically all adverse drug reactions (ADR) occur at the standard, manufacturer-recommended dose which is the dose usually used irrespective of age, body build, condition of liver and kidneys, etc. Cohen gives the example of loratadine (*Claritin*), the most popular antihistamine in the USA. The standard dose is 10mg regardless of whether a patient weighs 100 or 300 pounds (50 or 150 Kg), is aged 25 or 95 or 6 year old. Yet, the *Physicians’ Desk Reference* states that in healthy subjects 66-78-year-old, the plasma level and AUC of loratadine are 50% greater and the half-life is significantly longer than in younger patients.<sup>2</sup> At any one time 70% of doctors treating Medicare elderly patients in the USA failed in an examination concerning their knowledge of geriatric prescribing; also, 22% of geriatric patients who were given three or more prescriptions upon discharge had prescriptions errors that were serious of life-threatening.<sup>3</sup> A study conducted in the UK, Sweden, Germany, the Netherlands and Italy in paediatric wards found that over 67% of all drug prescriptions were for either unlicensed drugs or “off-label” drugs (i.e. medicines prescribed at a different dose or frequency, in a different formulation, or for an age group for which they have not been licensed).<sup>4</sup>

### 3. DESCRIPTION OF SIDE-EFFECTS, IDIOSYNCRATIC REACTIONS AND ALLERGIC REACTIONS TO DRUGS

Unwanted effects of drugs may be classified as follows:

- Intolerance
- Side-effects
- Secondary effects
- Idiosyncratic reactions
- Allergic reactions

**Intolerance** means a low threshold to the normal pharmacological action of a drug. Individuals vary greatly in their susceptibility to drugs, those at one extreme of the normal distribution being intolerant, those at the other, tolerant. This can be occasionally observed also with herbal medicine; although the reaction is very rare, some patients seem not to tolerate it.

**Side-effects** are therapeutically *unwanted but unavoidable* because they are normal pharmacological actions of the drug. They may extend a therapeutic effect to an undesirable extent (e.g. drowsiness with phenobarbitone) or may produce an effect which is not wanted (e.g. vomiting with digoxin). The list of side-effects from drugs is, of course, endless as there is absolutely no drug that has no side-effects. In this respect, there is a noticeable difference between drugs and herbs: herbs act more in a *physiological* way on the body (like foods) while drugs are usually isolated chemicals that have a specific chemical effect on the body. The compounds in drugs are usually present in larger doses than the compounds in herbs, since synergy or the hepatoprotective effect of other compounds in a given herb may modify its action: this results in far fewer adverse reactions from herbs compared with drugs.

It is precisely this selective chemical effect that leads to side-effects. There is a crucial difference between using whole plants and using isolated active constituents: it is when we use the latter that side-effects are much more pronounced. For example, *ephedrine*, an isolated herbal constituent, has the well-known side-effect of speeding up the heart rate, but the whole plant *Ephedra sinica* does not have this effect as, apart from ephedrine, it contains other alkaloids that *slow down* the heart rate. This is a major reason why herbs generally produce

fewer side-effects than chemical drugs. Several examples of this principle can be found in the vegetable world. Aflatoxins increase the rate of tumours in animals exposed to it. However, when we eat aflatoxins in peanuts, for example, we are eating them together with iron, zinc, selenium, manganese, fibre and vitamin A. The net effect of being exposed to aflatoxins in this form is negligible.<sup>5</sup> The same applies to heterocyclic amines which in human cell cultures are potent carcinogens. However, when we eat heterocyclic amines in whole foods containing anticarcinogens and antioxidants, the net effect of our exposure is negligible.<sup>6</sup> Dr Andrew Weil makes the same point: *‘It is simply not true that the actions of medicinal plants are reproduced by their isolated dominant constituents. Whenever I have had a chance to compare the therapeutic effect of a whole plant to that of its isolated active principle, I have found important differences’*.<sup>7</sup>

However, Chinese herbs also inevitably have “side-effects” deriving from their intrinsic nature: for example, Yin tonics are “sticky” in nature and their long-term administration may weaken the Spleen. It can be definitely said, however, that the side-effects of Chinese herbs are much milder than those of drugs and may occur only after a prolonged time. This question will be discussed in more detail below.

We have to be familiar with the side-effects of drugs taken by our patients, lest they be attributed to our herbal treatment. I have indicated in the bibliography good sources for the side-effects of drugs.

**Secondary effects** are the indirect consequences of a primary drug action. Examples are vitamin deficiency or superinfection which may occur in patients whose normal bowel flora has been altered by antibiotics. Herbal remedies are usually free of such secondary effects.

**Adverse reactions** will be described in Section 5.

**Idiosyncratic reactions** imply an inherent, qualitatively abnormal reaction to a drug usually due to a genetic abnormality. The haemolytic anaemia caused by anti-malaria tablets (such as

primaquine, pentaquin and parmaquine), due to a deficiency of glucose-6-phosphate-dehydrogenase in red cells, is an example. Idiosyncratic reactions may occur with herbal remedies too.

**Allergic reactions** are mediated either by classic antigen-antibody reaction or by a cell-mediated immune reaction involving sensitised lymphocytes. The reaction requires previous exposure either to the drug itself or to a closely related drug or other chemical. Lack of previous exposure is not the same as lack of *history* of previous exposure, i.e. a person may not know or not remember having been exposed to a given allergen. People with an atopic constitution have a greater tendency to develop allergic reactions to drugs. Allergic reactions are not dose-related and may occur with very small doses; they may occur to herbal remedies too. Allergic reactions include:

- Anaphylactic shock
- Asthma
- Urticaria
- Serum-sickness syndrome
- Thrombocytopenic purpura
- Granulocytopenia leading to agranulocytosis
- Aplastic anaemia
- Haemolysis
- Fever
- Non-urticarial rashes
- Syndromes resembling collagen disease
- Hepatitis and cholestatic jaundice

Anaphylactic shock may occur when a drug is given to a patient sensitized to that drug. The combination of antigen with antibody in the cells is followed by release of histamine and other substances from tissue stores, with a severe fall in blood pressure, bronchoconstriction, laryngeal oedema and sometimes death. These may occur within one hour of taking the drug orally or within minutes if it has been given intravenously.

Asthma as an allergic reaction is due to a Type-I antigen-antibody reaction in the mast cells lining the bronchi. The antigen-antibody reaction causes local liberation of histamine and other inflammatory substances which cause contraction of the smooth muscles and therefore wheezing and breathlessness.

Urticarial rashes are the commonest type of drug allergy. They are accompanied by itching and oedema of the eyes, face and lips.

Injury to the liver may be of an allergic nature. A hepatitis-like reaction may occur up to 3 weeks after stopping the drug (with up to 20% mortality). Cholestatic injury may occur, causing obstructive jaundice though the block may be biochemical rather than mechanical.

#### **4. DIFFERENCES IN THE PHARMACODYNAMICS OF DRUGS AND HERBS**

Plants contain compounds such as alkaloids, saponins, oils, volatile oils, glycosides, tannin, saccharides, polysaccharides, etc. whose absorption, distribution, metabolism and excretion may be studied in the same way as those of drugs; however, there are important differences between the use of drugs and that of *whole* plants. When we use the whole plant, this contains a balanced mixture of many different compounds which have an effect on the body that is very different from that of a synthetic drug, or indeed that of an isolated active constituent of a plant. A synthetic drug (or a single, isolated active ingredient of a plant such as glycyrrhizic acid) has a specific chemical action on a certain site of the body. For example, monoamine oxidase inhibitors (MAOI) given for depression prevent the re-uptake of noradrenaline by monoamine oxidase across the neuron synapses in the brain: the end result is an increase in noradrenaline in the brain. Another example could be the use of anticholinergic drugs (that block the parasympathetic response) to reduce spasticity of the colon. The trouble with this approach is that, after absorption, a drug is distributed throughout the body, thus affecting other parts in addition to the intended one. Thus, an anticholinergic drug prescribed for the bowel will also reduce gastric secretion, raise intra-ocular pressure (dangerous if the person has glaucoma), increase the heart rate, stimulate the CNS, etc. This is, of course, when side-effects occur:

there is no synthetic drug that is free of side-effects. The same applies to isolated active ingredients of a plant. As mentioned above, *ephedrine* has pronounced sympathomimetic effects (increasing the heart rate, for example), but the source of it, the plant *Ephedra sinica*, has no pronounced sympathomimetic effects when given as a whole because the balance of alkaloids contained in it is such that through checks and balances it results in fewer or no side-effects. There are many examples of such homeostatic effects of the compounds present in the whole plant: Ren Shen *Radix Ginseng*, for example can stimulate but also depress the CNS, Dang Gui *Radix Angelicae sinensis* can contract but also relax the uterus, etc. Some scientific sources acknowledge this too. For example, a pharmacognosy textbook says: *“Procedures involving continuous monitoring of fractions for biological activity are not free from anomalies. It is quite well known that isolated constituents of a plant drug may not give the same clinical response as a crude preparation of that plant drug. Very often, the total therapeutic activity is greater than, or different from, the therapeutic activity of the individuals. Synergism or antagonism resulting from the complex nature of the extract are probably the causes of such observations. It is thus possible that a fraction from a plant extract, although showing significant biological activity, possesses no single constituent with this activity. Conversely, a fraction showing no activity may still contain an active constituent.”*<sup>8</sup>

To sum up, it can be said that whole plants act on the body in a complex, balanced, homeostatic, physiological way rather than acting in a chemical way as drugs do: from this point of view, whole plants are closer to foods than to drugs. The synergy among herbs in a prescription is such that compounds are formed that are not in the individual herbs. For example, a study conducted in Japan on the formula Xiao Chai Hu Tang has shown that its ethanol-precipitated fraction contains a polysaccharide that enhances phagocytosis by macrophages.<sup>9</sup> The methoxylated flavonoids of Qing Hao *Herba Artemisiae annuae* have a marked and selective potentiating effect on the antiplasmodial activity of artemisin although they do not have antimalarial properties themselves.<sup>10</sup>

Also, when herbs are used in a prescription, it can be said that their action is greater than or different from the sum total of the prescription's ingredients; this is due to the synergistic action of the various herbs. Ancient Chinese prescriptions are balanced in a way that reduces side-effects of their individual constituents. Borchers *et al.* say: "A mixture of several crude herbs could have greater beneficial effects compared with a single plant extract. First, crude drugs given in combination could act synergistically. Second, they could have unknown interactions but could interact to diminish possible adverse side effects of one or more of the components."<sup>11</sup> Indeed, that is the art of making a balanced herbal prescription. Chinese herbalists have handed down a fourfold structure to formulate balanced prescriptions. This is based on the use of four classes of ingredients: the emperor herb (or herbs) that performs the main function of the prescription; the minister herb (or herbs) that assists the main herb; the assistant herb (or herbs) that usually moderates the influence of the previous two herbs or counteracts their side-effects; and the messenger herb that directs the prescription to a defined organ or part of the body. A researcher reports finding 12 different classes of chemical compounds in a formula of 10 herbs for eczema. To his surprise, he found that none of these worked when given alone and that all 10 were needed for a clinical effect. He noted that the traditional structuring of a formula with an "emperor", a "minister", and assistant and a messenger herb modifies the activity and toxicity of the whole.<sup>12</sup>

Of course, some plants are more potent than others and one could classify them according to their pharmacological potency. For example, most plants containing alkaloids (although not all) have a potent, predictable pharmacological effect similar to drugs. Examples of such plants are *Ephedra sinica*, *Hyosciamus niger*, *Atropa belladonna*, *Digitalis lanata*, etc. Of course, all the herbs mentioned are potentially toxic (depending on the dosage) and none of them is present in the *Three Treasures* or *Women's Treasure* ranges.

A classification of herbal medicines according to their potency is, in fact, very old. The *Shen Nong Ben Cao* (AD 100) itself distinguishes three classes of herbs: those in the upper class that are totally non-toxic and can be taken for a long time to nourish the body; those in the middle class that have a specific medicinal action to cure specific diseases; and those in the lower class

that are toxic and should be used only when imperative.

## **5. SIDE-EFFECTS, ADVERSE REACTIONS, IDIOSYNCRATIC REACTIONS AND ALLERGIC REACTIONS TO HERBAL MEDICINES: A REVIEW OF THE LITERATURE WITH IDENTIFICATION OF SOME MISTAKES**

In this section I shall concentrate on Chinese herbs. The safety of herbal medicines is being questioned more and more by various authors and by potential regulatory authorities (Medicines Control Agency, Medical Toxicology Unit, the FDA in the USA, etc.). Their views are usually based on various reports of alleged side-effects, adverse reactions, allergic reactions and idiosyncratic reactions to Chinese herbs. Of course, Chinese herbs can cause such side-effects and reactions but they do so very rarely indeed. Most of the reports fail to:

- a) put the incidence of adverse reactions into context (i.e. what is the proportion of adverse reactions in the total of all therapeutic interventions with herbs)
- b) explain the individual circumstances under which the adverse reactions occurred.

Regarding the first point, there have been few attempts to quantify the incidence of adverse reactions to Chinese herbs. Chan *et al.* undertook a prospective study of hospital admissions over an 8-month period in Hong Kong. Adverse reactions from Chinese herbs accounted for only 0.2% of admissions.<sup>13</sup> If we consider that most of these admissions were due to poisoning by untreated aconite (which we do not use), we can see that the incidence of adverse reactions to Chinese herbs is very small indeed.

As for the second point, many of the adverse reactions reported can be explained. They were caused by poor practice, self-medication, wrong identification of herbs, etc. Regarding adverse reactions related to the practitioner's clinical judgement, it is as if a doctor prescribed a hypotensive for the treatment of diabetes and the reaction to the hypotensive were then reported as an "adverse reaction". The report on the practice of Chinese medicine in Australia, "Towards a Safer Choice", reports that there is an inverse proportional relation between the length of training of practitioners and the incidence of adverse reactions.<sup>14</sup> Similarly, when

adverse reactions are due to wrong identification of a plant, this cannot be presented as an example of toxicity of herbs. The point is that when good quality controls are applied and Chinese herbs are prescribed by experienced practitioners according to a proper diagnosis and identification of patterns, adverse reactions are extremely rare. I can say that in the course of 16 years of practice, I have not noticed any adverse reactions in any patient. The most “serious” side-effects I have ever seen are simply transient vomiting or diarrhoea.

It should also be said that adverse reactions to herbs attract a disproportionate amount of attention in certain quarters, compared with the scale of adverse reactions to drugs. Dr Malcom Rustin says: *“The safety aspect of the herbal treatment has raised concerns but if you look at this within the context of orthodox drugs and their side-effects, it is a different ball game. There is total astigmatism which minimises the side-effects of drugs, but causes immediate hysteria if a few relatively minor side-effects are associated with herbal treatment. You get one problem with a herb and the whole herbal therapy is tarred with the same brush.”*<sup>15</sup>

The possible explanation of adverse reactions to Chinese herbs could be classified as follows:

- Wrong identification of herb
- Contamination with heavy metals
- Contamination with Western drugs
- Wrong use of a herb, i.e. wrong diagnosis
- Bad practice
- Wrong use through self-medication
- Administration of Chinese herbs with Western drugs

The first three causes are due to quality issues. When each case of adverse reaction is examined closely, it most probably falls under one of the above categories and cannot be therefore attributed to an intrinsic toxicity of Chinese herbs. A few examples will be given below.

Ernst reports two cases of liver toxicity from germander used as a slimming aid for several months.<sup>16</sup> This is an example of bad practice: we should never use herbs as “slimming aids”. Paul But reports that by far the most common cause of adverse reactions from Chinese herbs in Hong Kong is aconite poisoning (from Chuan Wu or Cao Wu).<sup>17</sup> Again, this problem does not apply to our practice as we do not use Chuan Wu or Cao Wu which are *untreated* aconite. Treated aconite (*Fu Zi Radix lateralis Aconiti carmichaeli praeparata*) is much less toxic, but its use is illegal in Britain, and I have omitted it from the *Three Treasures* or *Women’s Treasure* formulae; for example, I omit Fu Zi from the root formula for *Strengthen the Root* (You Gui Wan).

The tragic case of Belgian women suffering kidney damage and death after attending a slimming clinic is always quoted in reports questioning the safety of Chinese herbs.<sup>18</sup> However, this unfortunate case only serves to illustrate a case of appallingly bad practice (by Belgian medical doctors), poor quality control (wrong identification of a herb), and an irresponsible mixing of Chinese herbs with a “cocktail” of Western drugs. First of all, the doctors were using Fang Ji believing it to be *Han Fang Ji*, i.e. *Stephania tetrandia*, which is not toxic, when it was *Guang Fang Ji*, i.e. *Aristolochia fangchi*, which is toxic. Secondly, and most importantly, the use of Chinese herbs as part of a slimming regime is very bad practice indeed and something we should never do. To make matters worse, these women, who were made more vulnerable by the imposition of a calorie-controlled diet, were also given amphetamines, theophylline, belladonna, diuretics and herbs of dubious provenance; I understand that they may also have been given injections of serotonin. That this appalling practice is presented as a case of toxicity of Chinese herbs is extraordinary. It is also interesting to note that 185 Kg of the implicated herb, i.e. *Guang Fang Ji Aristolochia* (instead of the intended one, *Han Fang Ji Stephania*) were distributed to practitioners throughout Belgium but problems of toxicity occurred only in this slimming clinic: bad medicine produces bad results.

Some cases of adverse reactions are due to the use of Chinese herbs (often as self-medication) in ways that are markedly different from their traditional use. For example, Ma Huang *Ephedra sinica* is frequently used in the USA as a “stimulant” for its sympathomimetic effect, a use which is of course at total variance from its traditional use to expel Wind-Cold within the context of a prescription with this aim.

Some cases of adverse reactions reported concern substances that we never use in our practice, such as toad venom, blister beetles, untreated aconite and realgar.<sup>19</sup>

Interestingly, many of the adverse reactions concerning raised liver enzymes occur in patients with skin disease (especially eczema and psoriasis). It may be that the damaged skin cannot get rid of toxins effectively. The Medical Toxicology Unit in the UK reports that of 18 cases of alleged hepatotoxicity (idiosyncratic) from Chinese herbs, 17 were patients taking herbs for a skin disease.<sup>20</sup> Because of this, it has been suggested that all patients suffering from eczema and psoriasis should undergo regular liver-function tests. Opinions regarding this in the Chinese herbal profession are divided. I personally think that, unfortunately, due to the relentless reporting of adverse reactions in the press, we will be forced to ask our skin-disease patients to undergo such tests. On the other hand, two controlled clinical trials on the efficacy of Chinese herbs in the treatment of eczema all participants were given liver function tests and there were no reports of toxicity at all (although admittedly, the numbers were small).<sup>21</sup>

The WHO Monitoring Centre in Uppsala in Sweden issued a summary of reports of adverse reactions to herbs over a 20-year period worldwide. Two interesting observations emerge from an analysis of this summary. First of all, the total number of adverse reactions reported is 8984, a relatively low figure (at least when compared with adverse reactions to drugs) considering that it covers the whole world and extends over a period of 20 years. Secondly, combinations of herbs seem to cause fewer adverse reactions than single herbs. In fact, the summary breaks down the reports into four categories: single herbs; combinations of herbs; herbal and non-herbal combinations as sole suspect drug; and more than one suspect drug, at least one of which is non-herbal. The reported adverse reactions in the second category, i.e.

all-herbal combinations, are only 368 (those in the other categories being 2487, 3832 and 2297 respectively): this is a very small percentage (4%) of the total reports of adverse reactions.

Many studies confirm the low incidence of adverse reactions to herbal remedies. An article in *Phytotherapy* analyses 34 trials conducted on ginkgo (involving 2326 patients), 28 trials on *Hypericum* (involving 2120 patients), 6 trials on kava and 4 trials on *Valeriana*: in all the trials, the botanicals were used for their psychopharmacological effect. One of the most impressive features of these trials was the remarkable safety of botanicals when compared with conventional synthetic drugs used for similar purposes: side-effects were reported by only 3% of patients.<sup>22</sup>

Of the true adverse reactions to Chinese herbs, the vast majority is due to unpredictable idiosyncratic reactions.<sup>23</sup> Idiosyncratic reactions are dose-independent and produce zonal necrosis and fatty changes. There are two types of idiosyncratic reactions - those due to an immunoallergic basis, and those due to metabolic idiosyncrasy.<sup>24</sup> When the idiosyncratic reaction is immunological, it usually develops after a sensitization period of 1 to 5 weeks: fever, rash and eosinophilia will accompany it.<sup>25</sup> Although idiosyncratic reactions are by definition unpredictable there are certain risk factors. These include:

- A history of atopy
- Old age
- Female gender
- Diabetes mellitus or thyroid disease
- Obesity
- Drug therapy
- Chronic alcohol consumption, smoking (both tobacco and marijuana), “recreational” drugs, pesticides, herbicides.

Ward summarizes these risks with the following patient profile: Mrs A. Risky, 60-year-old, overweight, diabetic, taking several prescription drugs, allergic to penicillin, eczema since childhood, working in a solvent factory, her son is a Hep B carrier and she likes to smoke dope or snort cocaine to unwind!<sup>26</sup>

De Smet classifies four types of adverse reactions to herbs:

- *Type A* reaction. Example: the induction of anticholinergic symptoms (palpitations, dryness of mouth, dilatation of pupils) by herbal medicines containing belladonna alkaloids. Such reactions are pharmacologically predictable and dose-dependent.
- *Type B* reaction. There are reactions that are not related to the pharmacological property of a herb and are not dose-dependent: they are often immunologically mediated or they may have a genetic basis.
- *Type C* reaction. These are reactions that develop slowly and chronically over months in a pharmacologically predictable way. Example: the occurrence of muscular weakness due to hypokalaemia in long-term users of herbal anthranoid laxatives.
- *Type D* reaction. This category consists of certain delayed effects such as teratogenicity or carcinogenicity.<sup>27</sup>

To summarize, I would list the conditions for a safe practice of Chinese herbal medicine as follows:

- Good quality control of herbs used
- Good command of Chinese diagnosis and identification of patterns
- Good command of treatment principles and differentiation between Root (*Ben*) and Manifestation (*Biao*) and between the need to tonify (*Bu Zheng*) and the need to expel pathogenic factors (*Gong Xie*)
- In-depth knowledge of Chinese herbs and formulae
- Careful analysis of the patient's condition and adjustment of the dosage
- Careful inquiry about any previous liver or kidney disease
- Careful instruction of the patient in reporting any adverse symptoms and signs

- Determination of any possible interaction of herbal remedies with drugs being used concurrently, including over-the-counter medicines or “health foods”

I believe that when all these factors are applied, adverse reactions to Chinese herbs are extremely rare. Those that do occur can be due only to idiosyncratic or allergic reactions, which, by definition, no-one can predict; some people are allergic to Chinese herbs just as some people are allergic to peanuts. The point I am making is not that Chinese herbs are “always safe because they are natural” (a statement often derided in the literature reporting cases of adverse reactions), but that a good quality control and professional practice are the best safeguards of safe practice. We should not become unduly concerned in general terms, although we should of course be vigilant.

Dr M. Al-Khafaji performed liver function tests checking levels of alanine aminotransferase (ALT) on 1265 patients before beginning of treatment with Chinese herbs and at regular intervals afterwards. 8.46% of patients experienced raised levels of ALT after commencement of treatment but, interestingly, 7.43% returned to normal levels after a few weeks and only 0.32% of cases remained raised (0.71% ceased treatment). For the patients whose ALT remained raised, treatment was ceased and all returned to normal without any adverse reaction. Furthermore, of the 10 patients who had to discontinue treatment, in 8 cases it is highly probable that other factors besides Chinese herbs played a role. An interesting observation of Dr Al-Khafaji’s study is that raised levels of ALT occurred *only* in patients treated for skin diseases (psoriasis, eczema, atopic eczema, acne and rosacea).<sup>28</sup>

For those who use only patent remedies, Blackwell suggests the following cautionary measures:

- Never prescribe a patent remedy unless you know all its ingredients
- Avoid all patent remedies containing Western drugs (which is in any case illegal). Chinese patent remedies containing Western drugs can often be identified by the words *Fu Fang*, *Qiang Li* or *Su Xiao* before their name
- Avoid all patent remedies containing heavy metals which are toxic (and illegal)
- Use reputable suppliers.<sup>29</sup>

In the UK, some herbs are banned and these are listed in Appendix 1.

Finally, although even a single adverse reaction to herbs is regrettable and to be taken seriously, adverse reactions to herbs should be put in context and compared to the adverse reactions from drugs. A statistic from the *Journal of the American Medical Association* of 1998 reports that approximately 106,000 deaths occur annually (in the USA only) from medications and over 2 million serious adverse drug reactions (defined as requiring hospitalization or causing permanent disability) occur each year.<sup>30</sup> This figure would make ADR the fourth cause of all deaths in the USA.

Moreover, while many voices call for more double-blind, randomized clinical trials on herbs in the name of “evidence-based medicine”, drugs are far from safe and are often marketed after inadequate trials. Indeed, the pharmaceutical industry has actively campaigned to lower drug approval standards, resulting in the Prescription Drug User Fee Act of 1992 in the USA and the 1997 Food and Drug Administration Modernization Act. These acts allow the FDA to collect fees from manufacturers to review new drug applications, transforming the pharmaceutical industry from a regulated industry into an FDA client.<sup>31</sup> For example, the 10th fluoroquinolone antibiotic -trovafloxacin- was approved by the FDA in 1997 despite a pre-marketing clinical trial for prostatitis in which 10% of patients had liver function tests results greater than three times the upper limit of normal. Since February 1998, 140 documented cases of serious hepatic events have been reported, including 9 patients who died or required liver transplants.<sup>32</sup> Similarly, troglitazone, the 11th drug for diabetes in the USA, was approved even though 1.9% of patients in the pre-marketing trials had liver function test results greater than three times the upper limit of normal, and 0.4% and 0.2% had 10-fold and 20-fold elevations respectively. Troglitazone has now been associated with a minimum of 43 cases of liver failure, including 28 deaths.

## 6. INTERACTIONS BETWEEN DRUGS AND CHINESE HERBS

### Warfarin

Interactions between herbs and drugs are more likely to occur if the drug has a narrow safety index and is highly protein-bound: warfarin is an example of such a drug and particular caution should be exercised if a patient is taking this drug. Warfarin interacts with many drugs and foods such as aspirin, ibuprofen, vitamin K, some types of tea, green leaf vegetables, etc. These items interact with warfarin by either enhancing its effect and thus leading to prolonged bleeding or by decreasing its effect thus increasing the risk of blood clots.<sup>33</sup>

A coagulation abnormality may result from the interaction between Dan Shen *Radix Salviae miltiorrhizae* and/or Dang Gui *Radix Angelicae sinensis* with warfarin.<sup>34</sup> Interestingly, different authors present different views of this interaction. Chan, Lo, Yeung and Woo have noticed that Dan Shen potentiates warfarin by increasing its plasma concentration and prothrombin time.<sup>35</sup> Another author reports a case of overcoagulation caused by the interaction of Dan Shen with warfarin.<sup>36</sup> Lo *et al* report that the concurrent administration of warfarin and Dang Gui *Radix Angelicae sinensis* lowered the prothrombin time (i.e. increased coagulation) as compared with warfarin only.<sup>37</sup> Ginger is an inhibitor of thromboxane synthetase: this action could cause bleeding if used concomitantly with warfarin over a long period of time.<sup>38</sup> Concomitant use of warfarin and Ginkgo is not recommended: spontaneous bilateral subdural haematomas have occurred. These haematomas have been attributed to ginkgolide B, a potent inhibitor of platelet activating factor that is needed to induce platelet aggregation.<sup>39</sup> A patient previously well controlled on warfarin therapy experienced a loss of anticoagulant control after the initiation of ginseng.<sup>40</sup> The patient's INR (international normalized ratios) decreased to 1.5 from 3.1 after two weeks of taking ginseng. Following the discontinuation of ginseng therapy the INR returned to 3.3 within two weeks. The mechanism underlying this drug-herb interaction is unknown but may be related to the anti-platelet components in ginseng.<sup>41</sup>

### **Cholestyramine and colestipol**

These are drugs used to reduce cholesterol levels and they may bind to some herbs forming an insoluble complex thus decreasing the absorption of both substances because the size of the insoluble complex is too large to pass through the intestinal wall.<sup>42</sup>

### **Antacids**

Antacid preparations change the pH of the stomach and may therefore interfere with the absorption of herbs. Drugs such as cimetidine (*Tagamet*), ranitidine (*Zantac*) and omeprazole (*Losec*) inhibit the secretion of stomach acids and therefore herbs may not be broken down properly, leading to poor absorption in the intestines.<sup>43</sup> This interaction can be avoided simply by taking the herbs separately from these drugs by at least two hours.

### **Drugs that inhibit liver metabolism**

Some drugs slow down or inhibit liver metabolism: examples are cimetidine (*Tagamet*), erythromycin, ethanol, fluconazole (*Diflucan*), itraconazole (*Sporanox*) and ketoconazole (*Nizoral*). These drugs slow down liver metabolism and therefore herbs active ingredients will be inactivated more slowly and their overall effectiveness may be prolonged: for this reason, if the patient is taking any of the above drugs, we may need to lower the dosage of the herbs.<sup>44</sup>

### **Drugs that inhibit kidney excretion**

Any slowing down of kidney excretion will lead to an accumulation of herbs (and drugs) in the body. Drugs that tend to damage the kidneys include methotrexate, tobramycin and gentamicin: as a safety precaution, if the patient is taking these drugs, it may be necessary to lower the dose of the herbs.<sup>45</sup>

### **Diuretic drugs**

If the patient is taking diuretic drugs, diuretic herbs (e.g. Fu Ling, Zhu Ling, Ze Xie, etc.) should be used with caution and their dosage adjusted as their action may potentiate that of the drugs.

### **Yu Xing Cao and Bai Guo**

The bioflavonoid quercetin present in many plants (e.g. *Yu Xing Cao Herba cum Radice Houittunya cordatae* and *Bai Guo Semen Ginkgo bilobae*) could interact with haloperidol, clozapine, olanzapine, tricyclic antidepressants, caffeine and theophylline to reduce metabolism of the liver enzyme 1A2 of the cytochrome P450 (CYP) liver enzyme system.<sup>46</sup>

### **Ginseng**

Two reports on the interaction of ginseng with drugs exist. A patient previously well controlled on warfarin therapy experienced a loss of anticoagulant control after the initiation of ginseng.<sup>47</sup> This has been described above under “warfarin”. Another patient taking both ginseng and digoxin experienced an elevated digoxin level.<sup>48</sup> Some case reports have documented headache, trembling and manic episodes in patients treated with phenelzine (a MAOI) when they started therapy with ginseng.<sup>49</sup> As ginseng is a central nervous system stimulant, it would be wise to avoid its use in patients with manic-depressive disorders and psychosis.

Insulin dosage may need adjusting due to ginseng’s hypoglycaemic effect in diabetic patients: this is not an undesirable interaction.

### **Gan Cao**

Glycyrrhiza (Gan Cao) may cause sodium retention and excessive potassium excretion but this happens only at quite high doses over a prolonged period of time. It is worth remembering, however, that caution should be exercised in patients taking digoxin as high doses of Gan Cao could potentiate the drug’s toxic effects.

Gan Cao should not be used together with diuretics such as thiazides, spironolactone or amiloride as it may induce excessive potassium excretion.<sup>50</sup> Glycyrrhetic acid may potentiate the effects of hydrocortisone due to inhibition of the catalytic enzyme 11 $\beta$ -hydroxysteroid dehydrogenase.<sup>51</sup> However, this would happen only at very high doses and not in the normal dose we would use in a decoction (although it might happen after long-term use). There is a desirable interaction with aspirin in so far as Gan Cao reduces ulcer formation and gives protection from aspirin-induced gastric mucosal damage when used with cimetidine (another positive interaction).<sup>52</sup> Glycyrrhizin may interact with insulin in causing hypokalaemia and sodium retention (speculative interaction).<sup>53</sup>

Gan Cao may also interact with oral contraceptives leading to hypertension, hypokalaemia and oedema. However, these interactions are also theoretical ones and they would also be very unlikely to occur at the small dosage of Gan Cao in prescription.<sup>54</sup>

### **Ma Huang**

Ma Huang *Ephedra Sinica* may potentiate MAOI antidepressants and it should therefore not be used together with them. Although the whole plant Ma Huang does not have the same sympathomimetic effect as the isolated alkaloid ephedrine, it would be prudent not to use Ma Huang in conjunction with sympathomimetic drugs. It should also be used with caution in patients suffering from hypertension, seizures, diabetes and thyroid conditions.<sup>55</sup> Ma Huang should not be used together with theophylline as it would potentiate the latter's sympathomimetic effect.<sup>56</sup> Ephedrine increases the clearance and thereby reduces the effect of dexamethasone.<sup>57</sup> Ephedrine and pseudoephedrine are excreted more slowly when combined with urinary alkalinizers such as sodium bicarbonate: this means that if a patient take sodium bicarbonate the concentration of ephedrine is higher than normal and therefore its dosage should be reduced.<sup>58</sup>

### **Suan Zao Ren**

Suan Zao Ren *Semen Ziziphi spinosae* has a synergistic effect with many other sedatives and hypnotic agents: thus, the dosage of any sedatives and hypnotic drugs the patient might be taking should probably be reduced.

### **Ginger (Sheng Jiang or Gan Jiang)**

Ginger has been found to be a potent inhibitor of thromboxane synthetase which prolongs bleeding time.<sup>59</sup> This has adverse implications for pregnant women and it would also be preferable to avoid concomitant use with warfarin.

### **Bai Guo (Ginkgo)**

Bai Guo *Semen Ginkgo bilobae* contains ginkgolide B which is a potent inhibitor of the platelet-activating-factor that is needed to induce platelet aggregation and therefore blood coagulation. It would therefore be prudent to avoid prolonged use of Ginkgo together with aspirin, warfarin, heparin and non-steroidal anti-inflammatory drugs.<sup>60</sup> Ginkgo contains a

neurotoxin but in concentrations that are too low to have a detrimental effect.<sup>61</sup> However, it would be prudent to avoid using Ginkgo for prolonged times in epileptic patients who are on medication because it may diminish the effectiveness of anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital). For the same reason, it would also be prudent to avoid use together with medications which decrease the seizure threshold, such as tricyclic antidepressants. Highly-concentrated extracts of Bai Guo may potentiate monoamine oxidase inhibitors (MAOI, used for depression) by inhibiting the re-uptake of serotonin.<sup>62</sup> However, this interaction is speculative and would occur only with highly-concentrated extracts and not with the normal dosages we would use in a decoction.

Ginkgo may interact with paracetamol and ergotamine possibly causing bilateral subdural haematoma.<sup>63</sup> Ginkgo may also interact with thiazine diuretics causing hypertension.<sup>64</sup>

### **Dang Gui**

Dang Gui *Radix Angelicae sinensis* may potentiate the effect of benzodiazepines and calcium channel blockers (used to lower blood pressure).<sup>65</sup>

### **Da Fu Pi** (*Semen Arecae catechu*)

The anti-parkinsonian effects of phenothiazines and anticholinergic effects of procyclidine may be reduced due to the cholinergic alkaloid arecoline present in betel nut.<sup>66</sup>

Da Fu Pi *Pericarpium Arecae catechu* may interact with Flupenthixol and procyclidine causing rigidity, bradykinesia and jaw tremor. It may also interact with Fluphenazine causing tremor and stiffness and with prednisone and salbutamol causing inadequate control of asthma.

<sup>67</sup>

Certain drugs such as anti-emetics (e.g. metoclopramide) may speed the rate at which the stomach empties and therefore may increase the rate at which another drug (or herb) is absorbed and takes effect. Some drugs also combine with another drug or food in the intestines to form a compound that is not so readily absorbed. This occurs when tetracycline

and iron tablets or antacids are taken together. Milk also reduces the absorption of certain drugs in this way. This applies to herbs too and patients taking Chinese herbs should preferably not take iron tablets or drink milk.

Often the interaction of Chinese herbs with drugs is not necessarily an undesirable one. For example, Shimiza *et al* report that Xiao Chai Hu Tang *Small Bupleurum Decoction* administered with prednisolone noticeably potentiates its anti-inflammatory action.<sup>68</sup>

We should not think that there is always an interaction between Chinese herbs and drugs; as mentioned above, they work in different ways and some studies show that there is no interaction between certain Chinese herbs and drugs. For example, Qi *et al* report that the concurrent administration of Ge Gen Tang (*Pueraria Decoction*) with acetaminophen produced no difference compared with acetaminophen alone.<sup>69</sup> In another example, a study by Lin *et al* showed that there was no interaction between aminophylline and Ding Chuan Tang *Stopping Asthma Decoction* or Xiao Qing Long Tang *Small Green Dragon Decoction*.<sup>70</sup> Homma *et al* studied the effects of three herbal prescriptions (Xiao Chai Hu Tang *Small Bupleurum Decoction*, Chai Po Tang *Bupleurum-Magnolia Decoction* and Chai Ling Tang *Bupleurum-Poria Decoction*) all containing Gan Cao *Radix Glycyrrhizae uralensis* (which has a mineralo-corticoid effect) in equal doses, on prednisolone. The results showed that one formula *potentiated* prednisolone, one *decreased* its plasma concentration, and one made no difference to it.<sup>71</sup> This study is interesting as it shows clearly that the effect of the sum-total of herbs in a prescription is different from that of the single constituents; it is quite surprising that researchers even thought of obtaining similar results with three different prescriptions simply because they all contained equal amounts of Gan Cao. This also highlights the reductionist (and ultimately not “scientific”) thinking of Western pharmacology in its attempts to interpret the action of herbs on the organism simply in chemical terms of “active constituents”. Incidentally, Ernst reported this study simply saying that “*Chinese herbs containing glycyrrhizin were shown to affect prednisolone pharmacokinetics*”.<sup>72</sup> This is potentially misleading: first, because they were not “herbs” but prescriptions; and second, because the study actually showed that one prescription did *not* affect prednisolone pharmacokinetics.

**Herb-drug interactions**Da Fu Pi *Pericarpium Arecae catechu*

Da Fu Pi *Pericarpium Arecae catechu* may interact with Flupenthixol and procyclidine causing rigidity, bradykinesia and jaw tremor. Also with Fluphenazine causing tremor and stiffness. Also with prednisone and salbutamol causing inadequate control of asthma.

Bai Guo *Semen Ginkgo bilobae*

Aspirin	Spontaneous hyphema (blood-shot eyes) as ginkgolides are potent inhibitors of PAF
Paracetamol	Bilateral subdural haematoma and ergotamine
Warfarin	Intracerebral haemorrhage
Thiazide diuretic	Hypertension

Ren Shen *Radix Ginseng*

Warfarin	Decreased INR (International Normalized Ratio)
Phenelzine	Headache and tremor, mania
Alcohol	Increased alcohol clearance

Gan Cao *Radix Glycyrrhizae uralensis*

Prednisolone	Glycyrrhizin decreases plasma clearance, increases AUC, increases concentrations of prednisolone
Hydrocortisone	Glycyrrhetic acid potentiates cutaneous vasoconstrictor response
Oral contraceptives	Hypertension, hypokalaemia, oedema

Xiao Chai Hu Tang

Prednisolone	Decreased AUC for prednisolone
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-Any laxative (e.g. Da Huang *Radix et Rhizoma Rhei*) will speed intestinal transit and thus may interfere with the absorption of almost any intestinally-absorbed drug.

In conclusion, Chinese herbs may in general be used in conjunction with Western drugs without unduly worrying about negative interactions (apart from the exceptions mentioned above). However, I tend not to use Chinese herbal remedies if the patient is taking many different drugs (say, over four) or very potent drugs such as Roaccutane, cyclosporin or cytotoxic drugs (although herbs can be used to minimise the side-effects of cytotoxic drugs).

## **7. SIDE-EFFECTS OF CHINESE HERBAL FORMULAE AND HOW TO DEAL WITH THEM**

Side-effects occur with Chinese herbs too, but the manner of their occurrence is completely different from that of synthetic drugs. The latter cause side-effects because they are single chemicals designed to affect certain sites in the body but, in most cases, unable to avoid affecting other sites too. Chinese herbs cause “side-effects” only due to their intrinsic nature and only over a fairly long period of time. Indeed, one aspect of the art of Chinese herbal medicine is concerned with preventing the development of these side-effects. Furthermore, over the centuries, Chinese pharmacy practice has developed very sophisticated ways of “treating herbs” to minimize their side-effects (e.g. frying Ban Xia with ginger juice, etc.).

“Side-effects” with Chinese herbs derive from their intrinsic quality, but usually only after some time. For example, Yin tonics are “sticky” and cold by nature and long-term administration may weaken the Spleen, causing Dampness, and lead to digestive upsets and diarrhoea. Herbs that clear Heat are also cold by nature and long-term administration may also weaken the Spleen making it cold and causing loose stools. Herbs that move Qi and invigorate Blood are pungent in nature and their long-term administration may injure Qi. Yang tonics may be drying after long-term administration, injuring Yin. These are well-known qualities of Chinese herbs and, indeed, the art of prescribing consists precisely in balancing the nature of different herbs in a harmonious way that minimizes their side-effects. Many of the traditional formulae already take this into account. For example, the formula Xiao Qing Long Tang contains quite hot and drying ingredients to dry up Cold Phlegm: it therefore also contains Wu Wei Zi to nourish fluids and

moderate the influence of the hot and drying ingredients. This is the function of the “assistant” herb (*zuo*) within a prescription.

As for the *Three Treasures* and *Women’s Treasure* formulae, I have tried, as much as possible, to minimize side-effects by adding one or two herbs that moderate the overall effect of the formula: the last ingredient of a formula often aims at doing this. For example, *Strengthen the Root* (a Kidney-Yang tonic) contains Zhi Mu *Rhizoma Anemarrhenae asphodeloidis* to moderate the heating influence of all the other ingredients and prevent injury of Yin from long-term administration.

Users of the *Three Treasures* and *Women’s Treasure* formulae who also practise acupuncture can use this modality to counteract the possible side-effects of the formulae. For example, if a patient takes *Nourish the Root* for a long time to nourish Yin, this may eventually weaken the Spleen causing Dampness: acupuncturists may therefore pay attention to supporting the Spleen in their treatments, thus preventing this particular side-effect. Vice versa, if a patient is prescribed *Clear Lustre* (a remedy that may cause Cold if taken for a long time), the acupuncturist may occasionally tonify Yang with moxa to prevent the formation of internal Cold.

In any case, when a remedy is used for a prolonged period (of several months) it is advisable to have occasional breaks of about 2-3 weeks in between.

## 8. SYMPTOMS AND SIGNS OF LIVER FAILURE AND RENAL FAILURE

Contaminants that may cause acute parenchymal liver disease and that may be found in herbs that are not subject to quality controls, include:

- Aflatoxins from *Aspergillus flavus*
- Antimony
- Arsenic
- Ferrous salts
- Gold
- Poisonous fungi

Drugs that may cause parenchymal liver disease include:

- Alcohol
- Carbon tetrachloride
- Chloroform
- Cinchophen
- Corticosteroids
- Dinitrophenol
- Ethylene glycol
- Halothane
- Isoniazid
- Mepacrine
- Methyl chloride
- Monoamine oxidase inhibitors (MAOI)
- Nialamide
- Para-aminosalicylic acid
- Paracetamol
- Phenezine
- Phenipraxine
- Phenylbutazone
- Phosphorus
- Sulphonamides
- Tetrachlorethane
- Thiouracil

It is important to check that the patient is not taking any of these substances if any adverse reaction occurs, lest Chinese herbs be blamed unjustly for such reactions (halothane and chloroform are anaesthetics).

The possible symptoms of liver failure are:

- Loss of appetite

- Nausea or vomiting
- Fever
- Non-colicky upper abdominal pain or right-sided hypochondrial pain
- Itching
- Malaise
- Headache
- Jaundice
- A distaste for cigarettes (in smokers)
- Dark urine
- Pale stools

Of course, it is the combination of three or four of these symptoms that may alert the practitioner to the possibility of a liver disease. If such symptoms and signs occur, the herbal remedy should be discontinued IMMEDIATELY.

The possible signs of kidney failure are:

- Proteinuria
- Oedema
- Scanty urine
- Urine containing red and/or white blood cells
- Loss of appetite
- Nausea, vomiting
- High blood pressure
- Lassitude

Again, if these symptoms appear after administration of herbs, they should be discontinued immediately.

## 9. HERBAL REMEDIES IN PREGNANCY

Great care must be exercised in the choice of remedies administered in the first trimester of pregnancy because this is the period of organogenesis and hence adverse effects may cause congenital abnormalities of the foetus. The critical periods when various organ systems are formed are as follows:

- Nervous system: between 15th and 25th day
- Eyes: between 24th and 40th day
- Heart: between 20th and 40th day
- Legs: between 24th and 36th day

It is wise, during the first three months of pregnancy, to discontinue treatment if possible. This means that if we are treating a woman for infertility we should advise her to discontinue the remedy as soon as she knows she is pregnant. Since at least two weeks would elapse before a pregnancy can be confirmed, when I treat infertility with decoctions, I usually add one or two herbs to “calm the foetus” just in case the patient falls pregnant.

Dr Chen Zi Ming of the Song dynasty listed the herbs forbidden in pregnancy as being *Shui Zhi Hirudo seu Whitmania*, *Wu Tou Radix Aconiti carmichaeli*, *Fu Zi Radix lateralis Aconiti carmichaeli praeparata*, *Niu Huang Calculus Bovis*, *She Tui Exuviae Serpentis*, *Ba Dou Semen Croton tiglii*, *Wu Gong Scolopendra subspinipes*, *Niu Xi Radix Achyranthis bidentatae seu Cyathulae*, *Li Lu Radix et Rhizoma Veratri*, *Yi Yi Ren Semen Coicis lachryma jobi*, *Xiong Huang Realgar*, *Mang Xiao Mirabilitum*, *Di Bie Chong Eupolyphaga seu Opisthopteria*, *She Xiang Secretio Moschus moschiferi*, *Yan Hu Suo Rhizoma Corydalis Yanhusuo*, *San Leng Rhizoma Sparganii stoloniferii*, *Qian Niu Zi Semen Pharbitidis*, *Zao Jiao Fructus Gleditsiae sinensis*, *Tao Ren Semen Persicae*, *Bai Mao Gen Rhizoma Imperatae cylindrica*, *Ting Li Zi Semen Descurainiae seu Lepidii*, *Qu Mai Herba Dianthi*, *Ban Xia Rhizoma Pinelliae ternatae*, *Tian Nan Xing Rhizoma Arisaemati*, *Tong Cao Medulla Tetrapanacis papyriferi*, *Gan Jiang Rhizoma Zingiberis officinalis*, *Da Suan Bulbus Alli sativi*, eggs, mule meat and rabbit meat.

Dr Han Bai Ling also adds *Ban Mao Mylabris phalerata*, *Meng Chong Tabanus bivittatus*, *Ming Fan Alumen*, *Yuan Hua Flos Daphni genkwa*, *Dai Zhe Shi Haematitum*, *Chan Tui*

*Periostracum Cicadae*, *Mu Dan Pi Cortex Moutan radicis*, *Rou Gui Cortex Cinnamomi cassiae*, *Huai Hua Flos Sophorae japonicae immaturus*, *Mu Tong Caulis Mutong*, *Huai Zi Semen Sophorae japonicae*.<sup>73</sup>

In any case, one should avoid remedies that invigorate Blood or move downward. *Women's Treasure* formulae contraindicated in pregnancy are:

*Clear Empty Heat and Cool the Menses*

*Clear the Moon*

*Clear the Palace*

*Drain the Jade Valley*

*Drain Redness*

*Free Flow*

*Free-Flowing Sea*

*Freeing Constraint*

*Invigorate Blood and Stem the Flow*

*Penetrating Vessel*

*Stir Field of Elixir*

*Warm the Mansion*

*Warm the Menses*

*Warm the Palace*

The following *Three Treasures* remedies are contraindicated in pregnancy:

*Break into a Smile*

*Clear the Root*

*Drain Fire*

*Ease the Muscles*

*Red Stirring*

*Release Constraint*

*Separate Clear and Turbid*

*Stir Field of Elixir*



Incidentally, Western herbs forbidden in pregnancy are *Berberis vulgaris*, , *Caulophyllum thalictroides*, *Chelidonium majus*, *Colchicum autumnale*, *Hydrastis canadensis*, *Phytolacca americana*, *Podophyllum peltatum* and *Thuja occidentalis*.

As for *breast-feeding*, the milk-producing glands in the breast are surrounded by a network of fine blood vessels. Small molecules may pass from the blood into the milk. This happens more easily in the case of lipid-soluble compounds (which herbs usually are). This means that a breast-fed baby may receive small doses of whatever drugs or herbs the mother is taking. In most cases this is not a problem because the amount of drug or herbs that passes into the milk is too small to have any significant effect on the baby. However, some herbs should not be given to breast-feeding mothers: these include moving-downwards herbs such as Da Huang *Radix et Rhizoma Rhei* (none of the *Three Treasures* or *Women's Treasure* remedies contains this herb).

#### **10. HOW TO ADVISE PATIENTS REPORTING ALLEGED SIDE-EFFECTS, ADVERSE REACTIONS OR UNSPECIFIED REACTIONS**

The use of herbal remedies is inevitably linked to possible side-effects or adverse reactions. This is not because they are toxic, but because human metabolism differs widely from person to person and although side-effects are undesirable effects that can be foreseen, individual patients' reactions cannot.

*Side-effects* are predictable. We know, for example, that Yin-nourishing herbs are “sticky” in nature and have a cloying effect and if they are used continuously for a long time, they may injure the Spleen: this is a possible side-effect and a skilled practitioner should always keep it in mind. Similarly, if we prescribe a Yang tonic we should be aware that its long-term use may injure Yin and cause dryness and we should therefore either discontinue its use at intervals or support the Yin with acupuncture. Likewise, cold herbs that clear Heat and cool the Blood may also damage the Spleen; drying herbs that dry Dampness and resolve Phlegm may injure Yin.

*Adverse reactions* are undesirable effects that cannot be foreseen and that occur regularly in several patients. They are practically unknown with herbal remedies due to the intrinsic safety of this form of medication (unless, of course, toxic substances are used, or herbs are contaminated by other substances) as explained above.

*Unspecified “reactions”*, on the other hand, depend on individual metabolism and cannot be replicated in other patients. For example, if a patient develops a nosebleed following the administration of *Ease the Journey - Yin* (an actual example from practice), this would be an unexplainable, unspecified reaction. It cannot be explained because, even if the diagnosis had been wrong (i.e. the patient was given a Yin instead of a Yang tonic), Yin-nourishing herbs should not cause bleeding.

If an unexpected “reaction” occurs, the first thing to establish is that it is *truly* a reaction to the herbal remedy. Patients tend to attribute any new or unexpected symptom to any herbal remedy they may be taking; this happens especially with patients who are new to herbal medicine. In my clinical experience, the overwhelming majority of “reactions” are not related to the herbal remedy but are acute infections: a bad cold, for instance, influenza or an especially acute, gastro-intestinal infection. Thus, unless the reaction is an allergic one (see below), the first approach to take when a patient telephones about a certain reaction is to advise him or her to stop taking the remedy for a few days and then to start it again: if exactly the same reaction occurs again, then it is most probably due to the remedy. In such a case, the remedy should not necessarily be discontinued but one should try to reduce the dosage: if the reaction still occurs then its use should be discontinued. However, as mentioned above, in the overwhelming majority of cases, the reaction does not occur again when the use of the remedy is resumed.

Allergic reactions are an important exception to the practice of discontinuing a remedy for a few days and then starting it again. If the original reaction was an allergic one, a re-challenge with the same substance could have serious repercussions with the possibility of anaphylaxis (see the

discussion of allergic reactions above). How do we know that an initial reaction was an allergic one? This may be difficult, and sometimes impossible, to establish. However, two particular cases of allergic reactions are easy to diagnose and these are a Type-I asthmatic reaction and an urticarial reaction: if the patient develops severe wheezing and breathlessness or a severe urticarial rash a few hours after taking herbs, these are obviously allergic reactions and the herbs should be stopped immediately and not be given again. As discussed above, some allergic reactions involve the liver causing a hepatitis-like reaction or cholestatic injury. The possible symptoms of liver failure are loss of appetite, nausea or vomiting, fever, non-colicky upper abdominal pain or right-sided hypochondrial pain, itching, malaise, headache, jaundice, dark urine, pale stools. In the presence of such symptoms we should suspect liver injury (which may be allergic) and it would be very unwise to continue the treatment or to re-start it after a period of suspension (in case the original reaction was an allergic one). In conclusion, a simple reaction such as vomiting and/or diarrhoea is unlikely to be an allergic one and it is safe to stop the herbs for a few days and then start them again.

A remedy should also be discontinued if the patient suffers an acute illness such as a cold, influenza, a stomach virus, etc.

Whilst some patients are overanxious about taking herbal remedies and may wrongly attribute every little symptom to them, others err in the opposite direction and put up with side-effects in the mistaken belief that these are a “process of elimination” or a “healing crisis” (this tends to occur more frequently in patients who have previously received homoeopathic treatment). For example, if we prescribe a Yin tonic and the patient develops daily diarrhoea, this should not be interpreted as a “process of elimination” or a “healing crisis”, but as a side-effect of the Yin tonic which should therefore be discontinued.

Finally, all practitioners should be vigilant and always be alert to the development of symptoms and signs of liver failure, as indicated above.



## 11. DOSAGE OF HERBAL REMEDIES

The question of dosage is a very complex one for which there are no hard and fast rules. In many cases, it is a matter of trial and error; patients often find their own "correct" level of dosage. Even for drugs, the question of dosage is far from being as "scientific" and accurate as we are led to believe. As we have seen above, reaction to a drug varies enormously and unpredictably between individuals as plasma concentrations commonly vary by a factor of 5 or more.

One of the criticisms often levelled at herbal remedies is that, because they are not standardised, there is no way of saying how much of the remedy's active constituents a patient is taking, and therefore no way of adjusting the dose accurately. There are two basic faults in this argument: first of all, with drugs, too, finding the correct dosage is often a matter of trial and error due to individual variations in reaction; secondly, and most importantly, herbal remedies containing *whole* plants act in a physiological rather than chemical way, more like a food than a drug. Thus, adjusting the dosage of individual active constituents is not necessary: it is precisely when active constituents are isolated that herbal remedies cause side-effects and adverse reactions in the same way as drugs. For example, *ephedrine* causes many more side-effects than Ma Huang *Herba Ephedrae*, glycyrrhizinic acid causes many more side-effects (water and sodium retention) than Gan Cao *Radix Glycyrrhizae uralensis*, etc.

Furthermore, since herbal remedies are safer than drugs, the therapeutic range is far broader than for drugs. Indeed, the harmful dosage of herbs is so high that it would be impossible to ingest in one day. There are, in fact, reports of adverse reactions to herbal remedies in people who used them (unsuccessfully) in suicide attempts. The difference between the therapeutic range of drugs and herbal remedies can be illustrated in a diagram; figure 3 shows herbal remedies on the left, drugs on the right.

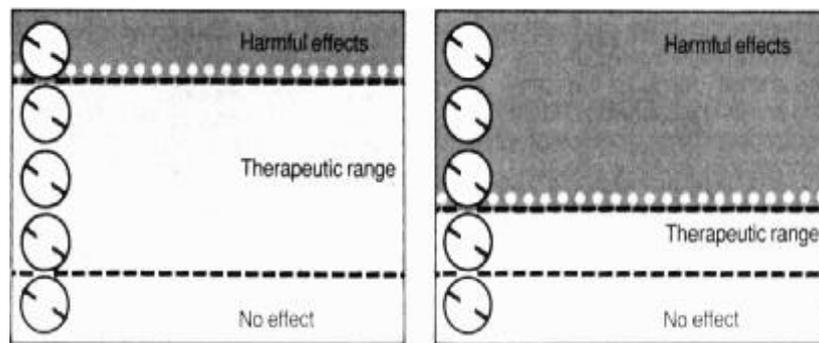


Fig. 3. Therapeutic range of herbal remedies (left-hand side) and drugs (right-hand side). Reproduced with permission from the British Medical Association “Guide to Medicine and Drugs”, Dorling Kindersley, London, 1991.

Of course, there are toxic plants for which the dosage is crucial and the therapeutic range quite narrow (e.g. Lei Gong Teng *Radix Tripterigii wilfordii*, Huang Yao Zi *Semen Dioscoreae bulbiferae*, Ma Qian Zi *Semen Strychni nux-vomica*, etc.) but the *Three Treasures* and *Women's Treasure* ranges do not contain any of these toxic herbs.

Many factors influence dosage, and I am going to discuss them one by one: it should be stressed that *all* the following factors need to be taken into account in every case. As a very general guideline, the dosage for the *Three Treasures* and *Women's Treasure* remedies is 1-3 tablets, 2-3 times a day, i.e. from 2 to 9 tablets a day. However, this dosage can be exceeded and, in a few cases, an even lower dose may be applicable.

### **The Full or Empty character of the condition**

In Empty patterns the dosage can be lower than in Full patterns. Thus, for all the formulae in the Clearing category and the Nourishing and Clearing category, the dosage should be higher than for those in the Nourishing category. For example, if we are prescribing *Stir Field of Elixir* for abdominal pain from stasis of Blood with some abdominal masses (such as small fibroids), one might use 6 tablets a day or more. Vice versa, if one were treating a deficiency condition with *Brighten the Eyes*, then 3-4 tablets a day might be enough.



**Chronic vs Acute conditions**

The distinction between chronic and acute conditions is an important one. In acute cases, the dosage should be higher. For example, if we are using *Expel Wind-Heat* for a severe invasion of Wind-Heat with fever, swollen tonsils, pronounced aches, etc., then the patient can take 12 or even more tablets in 24 hours. In contrast, there is no point in treating a chronic condition with a high dose, because it can change only slowly. Please note that some formulae used for chronic cases can be adapted to treat acute cases. For example, *Bend Bamboo* (for chronic headaches from Liver-Yang rising) can be used to treat acute migraine attacks by increasing the dosage substantially, i.e. 6-9 or even more a day.

**Age of the patient**

Old people and children need lower doses. As stated above, a newborn baby should not be treated at all and it is preferable not to treat any baby under 6 months of age unless absolutely imperative. Infants and children up to 6 years old should have a third of a dose; children between 6 and 14 half a dose; after that, a full dose. With drugs, the dosage for children is now adjusted according to body surface rather than body weight. The average body-surface area of a 70-Kg human is about  $1.8\text{m}^2$ . Thus, to calculate the dose for a child, the child's surface area is multiplied by the adult dose and divided by 1.8, giving the following table:

Age	Kg	Height cm	Body surface m <sup>2</sup>	Percentage of adult dose
Newborn	3.4	50	0.23	12.5%
1 month	4.2	55	0.26	14.5%
3 months	5.6	59	0.32	18%
6 months	7.7	67	0.40	22%
1 year	10	76	0.47	25%
3 years	14	94	0.62	33%
5 years	18	108	0.73	40%
7 years	23	120	0.88	50%
12 years	37	148	1.25	75%
Adult	70	173	1.80	100

As indicated above, babies under 6 months of age should not be treated at all and the above values are given only for reference.

The values of this table can be followed when prescribing herbal remedies too, although precision is less important here than for drugs. A simpler formula to calculate the dosage for children is as follows:

$$\frac{\text{Age}}{\text{Age} + 12} \times \text{dose.}$$



For example, if an adult dose is 6 grams per day, the dosage for a 6-year-old would be:

$$\frac{16}{6+12} \times 6 \text{ grams} = 1.99 \text{ grams}$$

The dosage should also be reduced in the elderly: approximately half a dose after 70 and a third of a dose after 80.

### **Condition and body-build of the patient**

The weaker the patient, the lower the dose. Thus, a frail old lady should have a lower dose than a large, corpulent man.

### **The condition itself**

The dosage should be adjusted also according to the severity of symptoms. For example, the dosage of *Chemo-* and *Radio-Support* should be varied according to the severity of the adverse reactions to chemo- or radio-therapy. For example, an average dose for these remedies might be about 4-6 tablets a day, but if the adverse reactions to the therapy are severe this dosage can be increased.

### **The digestive system**

The weaker the patient's digestive system, the lower the dose. This is a very important consideration: Western patients have weaker digestive systems than Chinese people and are easily upset by herbal tablets (more than by decoctions). If a patient experiences a digestive upset, make sure that he or she is taking the tablets after food and with hot water.

### **Pregnancy**

It is prudent not to prescribe any formulae during the first three months of pregnancy. From the fourth month onwards, formulae can be prescribed, unless, of course, they are specifically forbidden in pregnancy. This is indicated under "Caution and contraindications" within the explanation for each formula. When prescribing formulae to women of child-bearing age, it is advisable to ask them whether they are actively trying to conceive: if they are, be sure not to

prescribe one of the formulae that are contraindicated in pregnancy, lest the woman take the formulae during the first few weeks of pregnancy before she knows she is pregnant.

In conclusion, my advice is always to *start* with a relatively low dose (except, of course, in very clear-cut, acute, Full conditions), as the dose can always be increased, whereas the patient who has a poor reaction may give up the treatment altogether.

Finally, a word of warning about liver disease. If a patient is known to be infected with the hepatitis virus (A, B or C), particular care should be exercised by using a lower dosage than normal. In such cases, it is strongly advisable to ask the patient to undergo a liver-function test prior to starting herbal therapy so that herbs are not wrongly blamed for affecting the liver function negatively.

The tablets should generally be taken approximately at least 1 hour after a meal preferably with hot water and definitely not with tea, coffee or fruit juices. They should not be taken at or within an hour of a meal because absorption of a compound may be reduced if it combines with a food molecule. If possible, the tablets should not be taken after 8-9 pm. It is preferable if the tablets are chewed before being swallowed: however, if the patient finds them distasteful, it is acceptable to swallow them. It is particularly desirable to chew the tablets that treat problems in the head such as *Welcome Fragrance*, *Jade Screen*, *Brighten the Eyes*, *Bend Bamboo*, *Expel Wind-Heat* and *Expel Wind-Cold*.

Some of the formulae produce best results if taken at specific times:

- *Strengthen the Root* and *Ease the Journey-Yang*: take a higher dose in the morning;
- *Nourish the Root* and *Ease the Journey-Yin*: take a higher dose in the evening, and to maximize the effect take it with very slightly salted water;
- *Soothe the Centre*: take half an hour before a meal;
- *Brocade Sinews*: take a higher dose half an hour before breakfast;
- *Clear the Soul* and *Root the Spirit*: take a higher dose in the evening;

- *Expel Wind-Heat* and *Expel Wind-Cold*: take after meals, preferably with hot ginger water;
- *Separate Clear and Turbid*: take before meals.

If two or three different formulae are combined, it is advisable to reduce their individual dosage accordingly and take them at different times. For example, if one combines *Ease the Journey - Yin* with *Ease the Journey - Yang*, the former is best taken in the evening and the latter in the morning. In such cases, the dosage should be adjusted according to the therapeutic aim: for example, if deficiency of Yin predominates, the dosage of *Ease the Journey - Yin* should be double that of *Ease the Journey - Yang*. Another example could be the combination of *Brighten the Eyes* to nourish Liver-Blood and *Freeing the Moon* to move Qi and pacify the Liver in pre-menstrual tension. If deficiency of Liver-Blood predominates, the dosage of *Brighten the Eyes* should be double that of *Freeing the Moon*, and vice versa if stagnation of Liver-Qi predominates. As for the time of administration, *Brighten the Eyes* could be taken in the morning and *Freeing the Moon* in the afternoon.

The *Three Treasures* formulae are intended for use only after consultation with a qualified practitioner of traditional Chinese medicine. Any questions regarding the use and dosage of the formulae should be referred to the practitioner.

## 12. WHEN NOT TO USE HERBAL REMEDIES

To summarize what has been said, the following are situations when herbal remedies should not be used:

- During the first three months of pregnancy
- In babies under six months
- When the patient takes many different drugs
- When the patient is taking Roaccutane, cyclosporin or cytotoxic drugs (unless to treat their side-effects)
- When, after administration of herbs, previously normal liver-function tests become

abnormal

- When there are symptoms of liver or renal failure
- When the patient has suffered a previous allergic reaction to herbs

### 13. QUALITY CONTROLS OF CHINESE HERBAL REMEDIES

Stringent quality controls for herbal products are absolutely necessary to ensure the maximum safety for treatment. Quite apart from the safety issue, strict quality controls are also extremely important to ensure acceptance of herbal medicine by the regulatory authorities. If it can be demonstrated that the herbal industry applies strict quality controls which ensure safety, this will constitute an important step towards acceptance of herbal medicine and may help to put an end to constant ôsnipingö regarding the alleged toxicity of herbs.

Quality controls for Chinese herbs should ensure the following:

- Correct identification of each herb
- Checking that herbs are free of contamination from heavy metals, pesticides, aflatoxins and any foreign matter
- Manufacturing according to GMP standards which ensure hygienic conditions and allow identification of each batch of production

The quality controls governing *The Three Treasures* and *WomenÆs Treasure* remedies may be taken as an example of exemplary quality controls. These remedies are made in Taiwan by Kaiser Pharmaceutical Co. Ltd (KP). KaiserÆs modern scientific processing methods and standards of rigorous quality control set them apart from all other sources of Chinese herbs.

Each herbal remedy is made from good quality, fresh herbs. The raw herbs are first inspected for conformity and species verification by experienced botanists in Taiwan and Europe. Then volatile oils are removed, to be reintroduced later on. All the herbs for a single remedy are subsequently decocted *together*, rather than separately, greatly

strengthening the synergy of the herbs. All of these processes take place in a closed and controlled environment.

The herbs then undergo several further processes to create the finished product: *evaporation*, the introduction of the collected volatile oils and the further concentration of the liquid extract, and then *granulation*, during which the concentrate is sprayed onto starch particles of the same herbs and is vacuum-dried at a low temperature. This takes place in a completely enclosed chamber to protect against cross-contamination. During the final process of *formulation*, the modified formulae, now in their dry granular form, are bottled and sealed. Labelling takes place in the UK under GMP (Good Manufacturing Practice) standards.

After processing, the remedies are subject to a number of strict quality controls. Each batch of every product is subject to a detailed and careful analysis to ensure a consistent and stable amount of active ingredients. The solubility and stability of each product is tested. Each product is tested for bacteria (for example, salmonella, col-bacteria and a total bacteria count), moulds and yeasts. High Performance Liquid Chromatography (HPLC) measures potency by substantiating the presence of active ingredients. Thin Layer Chromatography (TLC) (re) confirms identity by using a chemical fingerprint unique to each species. Each remedy also undergoes an analysis of heavy metal values known as Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). This state-of-the-art geophysical technology ensures absolute safety of each product, with reference to the limit values of the Japanese and European pharmacopeias. This system is sensitive to sub-parts per billion, compared to other systems which detect elements only in sub-parts per million. Gas Chromatography (GC) further ensures safety by testing for over 200 potentially harmful substances such as pesticides, herbicides and fungicides. Herbs susceptible to contamination by aflatoxins are tested separately.

Quality control is reflected in a final certificate which lists the botanical name of the herb and itsÆ organoleptic properties, all test results and relevant information.

**14. REPORT FORM****1. PATIENT'S DETAILS**

- a. Age
- b. Sex
- c. Weight
- d. Western diagnosis (if any)
- e. Chinese disease (e.g. *Abdominal Pain, Heavy Periods*, etc.)
- f. Pattern diagnosis (e.g. *Liver-Qi stagnation, Phlegm-Heat*, etc.)
- g. Symptoms and signs (brief description)
- h. Pulse
- i. Tongue
- j. Previous medical history (brief)
- k. Orthodox medication taken (including OTC medicines and food supplements)
- l. Any history of liver disease

**2. FORMULA'S DETAILS**

- a. Formula prescribed
- b. Dosage
- c. Date started

**3. RESULTS**

(A brief description of results obtained)

**4. INTOLERANCE, SIDE-EFFECTS, ADVERSE REACTIONS, IDIOSYNCRATIC REACTIONS**

- a.. Description of suspected side-effect/adverse reaction
- b. Action taken
- c. Outcome

***Intolerance** is a low threshold to the normal pharmacological action of the herbs.*

***Side-effects** are undesired but unavoidable effects that we can expect. For example, we know that long-term administration of Yin tonics may weaken the Spleen and cause diarrhoea.*

***Adverse reactions** are unexpected undesired effects that are replicable in several patients. All the herbs in the Three Treasures, East West Treasures and Women's Treasure are normally free of any adverse reaction.*

***Idiosyncratic reactions** are unexpected, undesired effects that are usually due to a genetic abnormality of the patient (an allergic reaction is a type of idiosyncratic reaction). Such a reaction is individual to the patient and is not replicable in other patients.*

## **5. ANY OTHER COMMENT/CASE HISTORY**

## APPENDIX 1

### REGISTER OF CHINESE HERBAL MEDICINE (UK) RESTRICTED SUBSTANCES LIST (AUGUST 1999)

#### 1. CITES restrictions (endangered species)

- Hu Gu *Os Tigris*
- She Xiang *Secretio Moschus*
- Xi Jiao *Cornu Rhinoceri*
- Xiong Dan *Vesica Fellea Ursi*
- Bao Gu *Os Leopardis*
- Dai Mao *Carapax Ertmochelydis*
- Mu Xiang *Saussurea lappa*

#### 2. CITES List of trade allowed with appropriate trade permits

- Chuan Shan Jia *Squama Manitis pentadactylae*
- Hou Zao *Calculus Macacae mulattae*
- Ling Yang Jiao *Cornu Antelopis*
- Shi Hu *Dendrobium*)
- Bai Ji *Rhizoma Bletillae striatae*
- Tian Ma *Rhizoma Gastrodiae elatae*
- Gou Ji *Cibotium barometz*
- Xi Yang Shen *Radix Panax quinquefolium* (whole root form only)
- Lu Hui *Aloe ferox*
- Gui Ban *Chinemys reevesii*
- Xiao Ye Lian *Podophyllum emodii*

#### 3. Banned by law - single herbs

- Guang Fang Ji *Aristolochia fangji*
- Guang Mu Tong *Aristolochia manshuriensis*
- Qing Mu Xiang *Aristolochia debilis*

- Ma Dou Ling *Aristolochia contorta*
- Ma Huang *Ephedra chinensis* (Schedule 3, max dose 0.6g three times daily)
- Zhu Sha *Cinnabar*
- Ma Qian Zi *Strychnos Nux vomica*
- Hei Xi *Lead*
- Ying Su Ke *Papaver somnifera*
- Cao Wu/Fu Zi *Aconitum*

#### **4. Banned by law - patent remedies**

- Niu Huang Jie Du Pian
- Tian Wang Bu Xin Dan (if it contains Zhu Sha)
- Jin Bu Huan
- Pi Yan Ping/999 Skin Cream
- Madame Pearl's Cough syrup
- Products containing surgical spirit
- All products containing Western medicines

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