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STANDARDISED HERBAL FORMULAS,

A BEST PRACTICE GUIDE

Su Wen Herbs

De NatuurApotheek®
farmacie op maat

Sponsored by Su Wen Herbs

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In 1994 he founded Su Wen Herbs, a company which oversees the production of his line of herbal formulas under three lines: The Three Treasures®, Women's Treasure®, and The Little Treasures®. The formulas are based on classical Chinese formulae, adapted by Giovanni to address patterns more commonly seen in clinical practice in the West. Well known for his rigorous and meticulous style, he combined a thorough knowledge of Chinese medicine with 39-years clinical experience. While firmly rooted in traditional Chinese medicine, Giovanni's ideas were nonetheless innovative. He adapted the theories of Chinese medicine to better address Western conditions not prevalent in ancient China.

Giovanni is also the author of several seminal textbooks on Chinese Medicine:

- The Practice of Chinese Medicine (1994), (2007), (2021)
- Tongue Diagnosis in Chinese Medicine (1987), (1995), (2021)
- Diagnosis in Chinese Medicine (2003), (2018)
- The Foundations of Chinese Medicine (1989), (2005), (2015)
- Obstetrics & Gynaecology in Chinese Medicine (1998), (2011)
- The Psyche in Chinese Medicine (2009)
- The Channels of Acupuncture (2006)
- Clinical Pearls (2014)
- The Energetics and Treatment of Body Areas – The Face (2012)
- The Energetics and Treatment of Body Areas – The Occiput & Neck (2012)
- The Energetics and Treatment of Body Areas – The Throat (2012)
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INTRODUCTION

This booklet is an educational guide for both students and practitioners on herbs and standardised herbal formulas, which are placed on the UK market in compliance with the definition of 'food supplements', or as 'dietary supplements' in the USA and EU; i.e. manufactured to a pre-set composition and quality controls. Nonetheless, the term 'patent' is commonplace amongst practitioners, despite the fact such products can not be 'patented'.

This booklet, which has been sponsored by Su Wen Herbs but not specifically about its products, aims to educate students and practitioners on how standardised herbal formulas work in the body compared to medicines and the differences; it will show how standardised herbal formulas work like foods in the body. It will strive to demystify terms such as 'concentration ratio' and others. The hope is to lay a foundation of what constitutes best practice in terms of quality controls in producing modern standardised herbal formulas. It also offers practitioners a check-list to assist them in conducting due diligence, for example when evaluating one product provider's formulas over another. Price alone is a poor factor when choosing between formulas as it can mask insufficient quality controls which are not in patients' best interest.

The genesis of this book began with Giovanni Maciocia who wrote a booklet on the safety of Chinese herbs. With the help of industry experts and pharmacists, it has been updated and expanded to cover other areas such as manufacturing processes, quality controls and best practice in a clinical setting. It also touches on the fluid state of regulation of such formulas.

The question of good practice in using standardised herbal formulas 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 minimise possible side-effects and adverse reactions; secondly, we need to practice in a professional and responsible manner that ensures the maximum safety. Although there are many highly informative papers on the toxicity of herbs, the majority of these focus on *in vitro* studies. In terms of actual reported adverse reactions, these are extremely rare for standardised herbal formulas of high quality and that are professionally recommended by qualified practitioners.

In the hands of practitioners, standardised herbal formulas that have been produced to high standards are very safe. This booklet aims, on the one hand, to give guidelines for a safe use of standardised herbal formulas and, on the other hand, to help put some historical toxicology studies already published into context. Additionally, we will look at how other contributing factors, including good manufacturing practices, quality assurance and regulation all play a part in the delivery of safe and effective standardised herbal formulas. The question of safety of Chinese herbs cannot be considered in isolation from the principles, philosophy, diagnosis, guidelines, rules and methods of traditional doctrine: when used according to such rules, herbs are

remarkably safe. Many of the reports of toxicity of herbs concern situations when they were self-administered, recommended without regard to the principles of Chinese herbal therapy, wrongly identified, contaminated or adulterated, or used as single herbs inappropriately.

This booklet starts with an introduction to the pharmacokinetics of drugs: although, as stressed later, herbs work differently from most drugs (especially aqueous extracts), it is still useful to understand how drugs, and therefore some herbal compounds, are absorbed, metabolised and excreted. The booklet then analyses the differences between herbal formulas and drugs, the question of safety of Chinese herbs, as well as interactions between herbs and drugs. Finally, we will look at different processing methods and how standardised herbal formulas are regulated.

Words highlighted in blue can be found in the glossary.

NOTE: The pharmacological names used are in line with Bensky D., & Stöger E. (2004) Materia Medica (3rd edition), Eastland Press, Seattle.

1. HOW DRUGS ARE DIGESTED (PHARMACOKINETICS)

Learning Objectives

- Key stages of drug processing within the body
- How drugs may affect the liver
- Dangers of toxicity

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, metabolised and excreted (ADME). There are normally four 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). Some absorption takes place in the stomach.
- **Distribution:** the process of distribution of the drug in the body and protein-binding.
- **Metabolism:** the metabolism (breaking down) of the drug by the liver.
- **Excretion:** the process that takes place mainly through the kidneys.

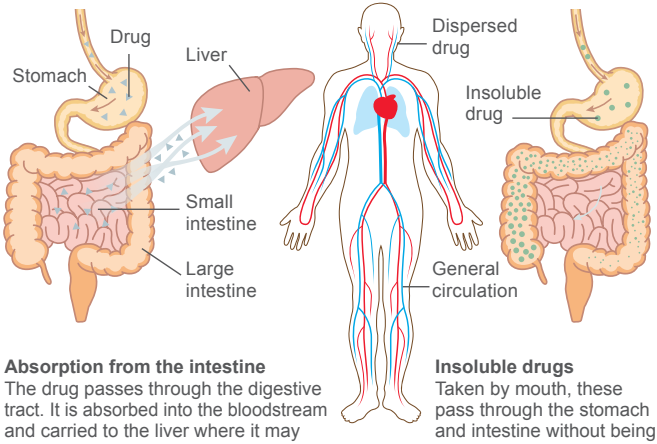

Fig. 1. How drugs pass through the body.

Reproduced with permission from British Medical Association, 'Guide to Medicines and Drugs', Dorling Kindersley, London, 1991.

ABSORPTION

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.

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.

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.

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*. 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.

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 metabolised by metabolising 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.

Drugs exist in a solution in two forms: *undissociated* (or un-ionised) or as *ions* (ionised). 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% ionised. At a low pH (i.e. acid) weakly acidic drugs will be more undissociated than ionised; at a high pH (i.e. alkaline), weakly acidic drugs will be more ionised than undissociated. Herbal formulae usually contain weak acids and weak bases and will therefore be better absorbed in the stomach (which is acidic) because only undissociated molecules are lipid-soluble.

DISTRIBUTION

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* (i.e. pharmacologically active, diffusible and available for metabolism and excretion), and *protein- bound* (i.e. 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).

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 oxidise (add oxygen to), reduce (remove oxygen from) or hydrolyse (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 ionisation 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 ionisation, 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 found in herbal formulae).

METABOLISM

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-metabolising 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 metabolised 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-metabolising enzymes (acupuncturists 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 and chemicals 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.
- Generalised drug allergies may also involve the liver.

One should always ask about any pre-existing liver disease and, if the patient is affected, we should be extremely careful in recommending herbs. They are not contraindicated in liver disease: indeed, Chinese literature abounds in references to the use of herbs with patients with the hepatitis viruses. However, for obvious reasons, unless the practitioner is experienced in this field, it is prudent **not** to recommend herbs in such cases. If herbal formulae are recommended, the effect should be monitored with regular liver function tests.

EXCRETION

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 ionised vs. un-ionised 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 formulae are basic (i.e. weakly alkaline). Their plasma half-life is therefore increased by factors which enhances the pH of the urine (i.e. make it more alkaline). A vegetarian diet rich in alkaline foods raises the pH and so reduces plasma concentrate.

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 formulae not subject to strict quality controls)
- Antimicrobials

- Analgesics
- Anticonvulsants
- Aristolochic acids

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. Senna based products): 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 herbal therapy.** Needless to say, extreme caution should be exercised in patients suffering from chronic glomerulonephritis.

2. FACTORS AFFECTING DOSAGE OF DRUGS

Learning Objectives

- Individual responses to drugs
- Dosage planning
- Demographical considerations

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, it is important to consider whether an adequate dose has 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.[1]

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 also an important consideration when adjusting the dosage of a drug. The very old and also 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-metabolising 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).

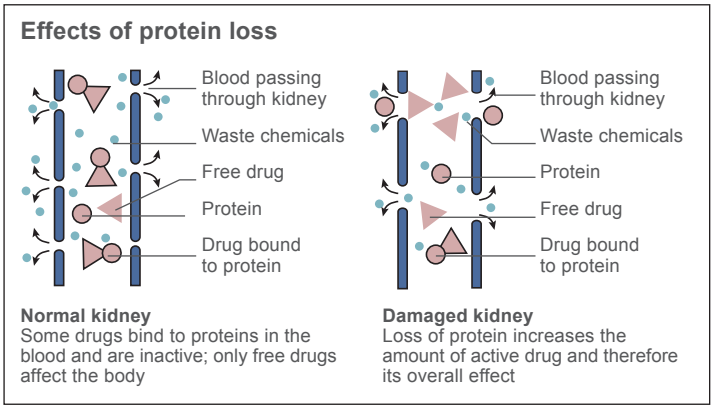

Fig. 2. Protein loss in diseased kidney and increase of free drug (or herb) molecules.

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 of 150 Kg), is aged 25 or 95 or 6 years 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.[2]

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).[3]

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

Learning Objectives

- Different types of unwanted effects
- Causes of side-effects
- Symptoms of adverse events

Unwanted effects of drugs may be classified as follows:

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

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: most 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. 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.[4] 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*".[5]

However, 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, causing associated side-effects, e.g. tiredness, digestive upsets, loose stools. It can be said, however, that the side-effects of herbs are typically 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 therapy. Good sources for the side-effects of drugs have been indicated in the bibliography.

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 formulae 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 formulae 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 formulae too. Allergic reactions include:

- Anaphylactic shock
- Asthma
- Urticaria
- Serum-sickness syndrome
- Thrombocytopoenic purpura
- Granulocytopoenia 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 sensitised 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.

Additive effects a herb may increase the effects of a particular medication e.g. *shan yao* has a hypoglycemic action and may add to the action of prescribed hypoglycemic drugs resulting in undesirable blood sugar levels.

4. DIFFERENCES IN THE ACTIONS OF DRUGS AND HERBS

Learning Objectives

- Chemical comparisons of drugs and plants
- The regulating effects of whole plants
- Synergism in herbs and standardised herbal formulas

Plants contain compounds such as alkaloids, flavonoids, saponins, oils, volatile oils, glycosides, tannins, 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 glycyrrhizinic acid) has a specific chemical action on a certain site of the body. For example, monoamine oxidase inhibitors (MAOIs) 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, and at a correct dose, 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 homoeostatic 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*."[6]

It can be said that whole plants act on the body in a complex, balanced, homoeostatic 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 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.[7] 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.[8]

Therefore, when herbs are used in a fornula, it can be said that their action is greater than or different from the sum total of the formulas ingredients; this is due to the synergistic action of the various herbs. Ancient Chinese formulas 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."[9] Indeed, that is the art of making a balanced herbal formula.

Ancient Chinese herbalists have handed down a fourfold structure to formulate balanced formulas. This is based on the use of four classes of ingredients: the 'emperor herb' (or herbs) that performs the main function of the formula; 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 formula to a defined organ or part of the body.

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 effects similar to drugs. Examples of such plants are *Ephedra sinica*, *Hyoscyamus niger*,

Atropa belladonna, *Digitalis lanata*, etc. Of course, all the herbs mentioned are potentially toxic (depending on the dosage).

A classification of herbs according to their potency is, in fact, very old. The *Shen Nong Ben Cao* (AD 200) 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 action to address specific patterns; 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

Learning Objectives

- Unwanted effects of herbs
- Causes of adverse reactions
- Strategies for minimising adverse reactions

The safety of herbs has been raised by various authors and regulatory authorities. Evidence is generally based on *in vitro* studies or *in vivo* reports of side-effects, adverse reactions, allergic reactions and idiosyncratic reactions to herbs. Of course, herbs can cause such side-effects and reactions but they do so very rarely.

Most of the reports do not lead to further action by the regulatory authorities once they have been investigated and

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 herbs. Chan et al undertook a prospective study of hospital admissions over an 8-month period in Hong Kong. Adverse reactions from herbs accounted for only 0.2% of admissions.[11] 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 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.[12]

Similarly, when adverse reactions are due to the incorrect identification of a plant, this should not be presented as an example of toxicity of herbs. The point is that when good quality controls are applied and herbs are recommended by qualified practitioners according to a proper identification of patterns, adverse reactions are extremely rare.

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*."[13]

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

- Incorrect identification of herb
- Contamination e.g. heavy metals, pesticide residues, aflatoxins
- Adulteration with Western drugs
- Incorrect use of a herb, i.e. incorrect clinical application
- Poor practices
- Incorrect use through self-medication
- Administration of 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 herbs. A few examples include:

Ernst (1998) reports two cases of liver toxicity from germander used as a slimming aid for several months.[14] 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 herbs in Hong Kong is aconite poisoning (from Chuan Wu or Cao Wu).[15] 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 internal use is illegal in Britain.

Some cases of adverse reactions are due to the use of 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 recommendation with this aim.

*Please refer to Chapter 15 The Regulatory Landscape for a list of banned and restricted herbal ingredients in the UK.

Some cases of adverse reactions reported concern substances that are not used in modern practice, such as toad venom, blister beetles, untreated aconite and realgar.[16]

Interestingly, many of the adverse reactions concerning raised liver enzymes occur in patients with skin disease (especially eczema and psoriasis). The Medical Toxicology Unit in the UK reports that of 18 cases of hepatoxicity (idiosyncratic) from herbs, 17 were patients taking herbs for a skin disease.[17]

On the other hand, two controlled clinical trials on the efficacy of 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).[18]

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 8,984, 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 2,487, 3,832 and 2,297 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 standardised herbal formulas. Zhang et al (2015) asserts the need to recognise that herbal products are widely considered to be of lower risk compared with synthetic drugs.[19] An article in *Phytomedicine* analyses 34 trials conducted on ginkgo (involving 2,326 patients), 28 trials on *Hypericum* (involving 2,120 patients), 6 trials on kava* and 4 trials on *Valerian*: 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.[20]

Of the true adverse reactions to herbs, the vast majority is due to unpredictable idiosyncratic reactions.[21] 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.[22] When the idiosyncratic reaction is immunological, it usually develops after a sensitisation period of 1 to 5 weeks: fever, rash and eosinophilia will accompany it.[23] Although idiosyncractic reactions are by definition unpredictable there are certain risk factors. These include:

- A history of atopy

*Please refer to Chapter 15 The Regulatory Landscape for a list of banned and restricted herbal ingredients in the UK.

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

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 herbs 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.[24]

To summarise, below is a list of conditions for a safe practice of herbs:

- Good quality control of herbs used
- Good command of Chinese diagnosis and identification of patterns
- Good command of 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*)
- Knowledge of 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 formulae with drugs being used concurrently, including over-the-counter medicines or 'health foods'.

When all these factors are applied, adverse reactions to 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 herbs just as some people are allergic to peanuts.

NB: it is not the case that 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 1,265 patients before beginning of treatment with herbs and at regular intervals afterwards. 8.46% of patients experienced raised levels of ALT after commencement but, interestingly, 7.43% returned to normal levels after a few weeks and only 0.32% of cases remained raised (0.71% ceased testing). For the patients where whole ALT remained raised, tests were ceased and all returned to normal without any adverse reaction. Furthermore, of the 10 patients who had to discontinue testing, in 8 cases it is highly probable that other factors besides 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).[25]

Liu et al 2016 concluded that reports of liver toxicity, due to herbs were over-exaggerated and that the content of toxic substances within complex herbal mixtures was minimal.[26]

For those who use only standardised herbal formula, Blackwell suggests the following cautionary measures:

- **Never recommend a standardised herbal formula unless you know all of its ingredients**
- **Avoid all standardised herbal formulas containing Western drugs (which is in any case illegal). Products containing Western drugs can often be identified by the words *Fu Fang, Qiang Li* or *Su Xiao* before their name**
- **Avoid all standardised herbal formulas containing heavy metals which are toxic (and illegal)**
- **Use reputable suppliers**[27]

In the UK, some herbs are banned. For an up-to-date list, please refer to the following UK government web page:

https://www.gov.uk/government/publications/list-of-banned-or-restricted-herbal-ingredients-for-medicinal-use/banned-and-restricted-herbal-ingredients

From an international perspective, CITES (the Convention on International Trade in Endangered Species of Wild Fauna and Flora) is an international agreement between governments. Its aim is to ensure that international trade in specimens of wild animals and plants does not threaten their survival. An up-to-date list of restricted herbs can be found on their website: *https://cites.org/eng/disc/what.php*

6. INTERACTIONS BETWEEN DRUGS AND HERBS

Learning Objectives

- Example of drug-herb interactions
- How additive effects can be useful in clinical practice

Herbs may in general be used in conjunction with Western drugs without unduly worrying about negative interactions (apart from the exceptions mentioned below). However, we tend not to use herbal formulae 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).

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.[28]

A coagulation abnormality may result from the interaction between Dan Shen *Radix Salviae miltiorrhizae* and/or Dang Gui *Radix Angelicae sinensis* with warfarin.[29] 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.[30] Another author reports a case of overcoagulation caused by the interaction of Dan Shen with warfarin.[31]

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.[32] Ginger is an inhibitor of thromboxane synthetase: this action could cause bleeding if used concomitantly with warfarin over a long period of time.[33]

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.[34] A patient previously well controlled on warfarin therapy experienced a loss of anticoagulant control after the initiation of ginseng.[35] The patient's INR (international normalised 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.[36]

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.[37]

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.[38] 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.[39]

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, tobramicin and gentamicin: as a safety precaution, if the patient is taking these drugs, it may be necessary to lower the dose of the herbs.[40]

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 (*Houttuniae Herba*) and Bai Guo (*Ginkgo Semen*)

The bioflavonoid quercitin present in many plants (e.g. Yu Xing Cao *Herba cum Radice Houttunya 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.[41]

Ren Shen (*Ginseng Radix*)

Two reports on the interaction of Ren Shen with drugs exist. A patient previously well controlled on warfarin therapy experienced a loss of anticoagulant control after the initiation of Ren Shen.[42]

This has been described above under 'warfarin'. Another patient taking both Ren Shen and digoxin experienced an elevated digoxin level.[43] Some case reports have

documented headache, trembling and manic episodes in patients treated with phenelzine (a MAOI) when they started therapy with ginseng.[44] As Ren Shen 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 providing that it is expected and closely monitored.

Gan Cao (*Glycyrrhizae Radix*)

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.[45] Glycyrrhetinic acid may potentiate the effects of hydrocortisone due to inhibition of the catalytic enzyme 11ß-hydroxysteroid dehydrogenase.[46] 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).[47] Glycyrrhizin may interact with insulin in causing hypokalaemia and sodium retention (speculative interaction).[48]

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 formulas.[49]

Ma Huang* (*Ephedrae Herba*)

Ma Huang* 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.[50]

Ma Huang* should not be used together with theophylline as it would potentiate the latter's sympathomimetic effect.[51] Ephedrine increases the clearance and thereby reduces the effect of dexamethasone.[52] 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.[53]

*Please refer to Chapter 15 The Regulatory Landscape for a list of banned and restricted herbal ingredients in the UK.

Suan Zao Ren (*Ziziphi spinosae Semen*)

Suan Zao Ren 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.

Sheng Jiang and Gan Jiang (*Zingiberis Rhizoma recens* and *Zingiberis Rhizoma*)

Ginger has been found to be a potent inhibitor of thromboxane synthetase which prolongs bleeding time.[54] This has adverse implications for pregnant women and it would also be preferable to avoid concomitant use with warfarin.

Bai Guo (*Ginkgo Semen*)

Bai Guo 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 Bai Guo together with aspirin, warfarin, heparin and non-steroidal anti-inflammatory drugs.[55] Bai Guo contains a neurotoxin but in concentrations that are too low to have a detrimental effect.[56] However, it would be prudent to avoid using Bai Guo 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.[57] 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.

Bai Guo may interact with paracetamol and ergotamine possibly causing bilateral subdural haematoma.[58] Bai Guo may also interact with thiazine diuretics causing hypertension.[59]

Dang Gui (*Angelicae sinensis Radix*)

Dang Gui may potentiate the effect of benzodiazepines and calcium channel blockers (used to lower blood pressure).[60]

Da Fu Pi* (*Arecae Pericarpium*)

Da Fu Pi* (and Bing Lang* from the same plant) are restricted herbs and can only be sold in a pharmacy under the supervision of a registered pharmacist.

The anti-parkinsonian effects of phenothiazines and anticholinergic effects of procyclidine may be reduced due to the cholinergic alkaloid arecoline present in betel nut.[61] Da Fu Pi* 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.[62]

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

*Please refer to Chapter 15 The Regulatory Landscape for a list of banned and restricted herbal ingredients in the UK.

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 herbs should preferably not take iron tablets or drink milk.

Often the interaction of 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.[63]

We should not think that there is always an interaction between herbs and drugs; as mentioned above, they work in different ways and some studies show that there is no interaction between certain 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.[64] 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*).[65]

Homma et al studied the effects of three herbal formulas 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.[66] This study is interesting **as it shows clearly that the effect of the sum-total of herbs in a formula is different from that of the single constituents;** it is quite surprising that researchers even thought of obtaining similar results with three different formulas 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*".[67] This is potentially misleading: first, because they were not 'herbs' but formulas; and second, because the study actually showed that one formula did not affect prednisolone pharmacokinetics.

Herb-drug interactions

Bai Guo (*Ginkgo Semen*)

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

*Please refer to Chapter 15 The Regulatory Landscape for a list of banned and restricted herbal ingredients in the UK.

Da Fu Pi* (*Arecae Pericarpium*)

Da Fu Pi* 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.

Gan Cao (*Glycyrrhizae Radix*)

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

Ren Shen (*Radix Ginseng*)

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

Xiao Chai Hu Tang (*Minor Bupleurum Decoction*)

Prednisolone	Decreased AUC for prednisolone

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

7. SIDE-EFFECTS OF HERBS AND HOW TO DEAL WITH THEM

Learning Objectives

- Recognising and managing side-effects
- The role of acupuncture in moderating side-effects

Side-effects occur with 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. 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 standardised herbal formulas 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 minimise their side-effects (e.g. frying Ban Xia with ginger juice, etc.).

'Side-effects' with herbs derive from their intrinsic quality, but usually only after some time. For example:

*Please refer to Chapter 15 The Regulatory Landscape for a list of banned and restricted herbal ingredients in the UK.

- 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 herbs and, indeed, the art of formulating consists precisely in balancing the nature of different herbs in a harmonious way that minimises 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 formula.

Side-effects of standardised herbal formulas can be minimised 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, Zhi mu *Rhizoma Anemarrhenae asphodeloidis* can be added to a Kidney-Yang tonic to moderate the heating influence of all the other ingredients and prevent injury of Yin from long-term administration.

Users of standardised herbal formulas who also practice acupuncture can use this modality to counteract the possible side-effects of the formulae. For example, if a patient takes a Yin tonic for a long time to nourish Yin, this may eventually weaken the Spleen causing Dampness: acupuncturists may therefore pay attention to supporting the Spleen, thus preventing this particular side-effect. Vice versa, if a patient is recommended a formula 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 standardised herbal formula 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

Learning Objectives

- Causes of serious side-effects
- Recognising symptoms of serious adverse events

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

- Aflatoxins
- Antimony
- Arsenic
- Ferrous salts
- Gold
- Poisonous fungi

Drugs and chemicals 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-aminosalicylis acid
- Paracetamol
- Phenelzine
- Phenipraxine
- Phenylbutazone
- Phosphorus
- Sulphonamides
- Tetrachlorethane
- Thiouracil

It is important to check that the patient is not taking or exposed to 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 formula 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. STANDARDISED HERBAL FORMULAS IN PREGNANCY

Learning Objectives

- Herbal use in different stages of pregnancy
- Herbs contra-indicated in pregnancy
- Herbs and breast feeding

Great care must be exercised in the choice of standardised herbal formula 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 use. This means that if we are treating a woman for infertility we should advise her to discontinue the formula as soon as she knows she is pregnant. Since at least two weeks would elapse before a pregnancy can be confirmed, when treating infertility with decoctions, one or two herbs can be added to 'calm the foetus' just in case the patient falls pregnant.

Dr Chen Zi Ming of the Song dynasty listed some other (often toxic) herbs forbidden in pregnancy including:

- **Ba Dou** *Semen Croton tiglii*
- **Bai Mao Gen** *Rhizoma Imperatae cylindricae*
- **Ban Xia** *Rhizoma Pinelliae ternatae*
- **Da Suan** *Bulbus Alli sativi*
- **Fu Zi*** *Radix lateralis Aconiti carmichaeli praeparata*
- **Li Lu** *Radix et Rhizoma Veratri*
- **Niu Xi** *Radix Achyranthis bidentatae seu Cyathulae*
- **Qian Niu Zi** *Semen Pharbitidis*
- **Qu Mai** *Herba Dianthi*
- **San Leng** *Rhizoma Sparganii stoloniferii*
- **Tao Ren** *Semen Persicae*
- **Tian Nan Xing** *Rhizoma Arisaemati*
- **Ting Li Zi** *Semen Descurainiae seu Lepidii*
- **Tong Cao** *Medulla Tetrapanacis papyriferi*
- **Wi Tou*** *Radix Aconiti carmichaeli*
- **Yan Hu Suo** *Rhizoma Corydalis Yanhusuo*
- **Yi Yi Ren** *Semen Coicis lachryma jobi*
- **Zao Jiao** *Fructus Gleditsiae sinensis*

*Please refer to Chapter 15 The Regulatory Landscape for a list of banned and restricted herbal ingredients in the UK.

Dr Han Bai Ling also adds:[68]

- **Huai Hua** *Flos Sophorae japonicae immaturus*
- **Huai Zi** *Semen Sophorae japonicae*
- **Mu Dan Pi** *Cortex Moutan radicis*
- **Mu Tong*** *Caulis Mutong*
- **Rou Gui** *Cortex Cinnamomi cassiae*
- **Yuan Hua** *Flos Daphni genkwa*

In any case, one should avoid formulae that invigorate Blood or move downward.

Incidentally, Western herbs forbidden in pregnancy are *Berberis vulgaris*, *Caulophyllum thalictroides*, *Chelidonium majus*, *Colchichum 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*.

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

Learning Objectives

- Management of adverse reactions
- Recognising different types of reaction
- Reassuring patients

The use of standardised herbal formulas 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

*Please refer to Chapter 15 The Regulatory Landscape for a list of banned and restricted herbal ingredients in the UK.

should always keep it in mind. Similarly, if we recommend 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. They are practically unknown with standardised herbal formulas 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.

Adverse drug (herb) reactions (ADRs) should be reported by the practitioner directly to their professional association (PA), who will advise on whether a formal report needs to be presented. As a matter of professional protocol the practitioner or PA should advise the manufacturer/supplier that there has been a potential issue. The manufacture/supplier should open up a case so that similar ADRs are noted and correlated if they are observed. The manufacturer/supplier should inform the PA (where relevant) if there is a cluster of events, so suitable action can be taken.

Unspecified 'reactions', on the other hand, depend on individual metabolism and cannot be replicated in other patients. For example, if a patient develops a nose bleed following the administration of a nourishing Yin standardised herbal formula, 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 standardised herbal formula. Patients tend to attribute any new or unexpected symptom to any standardised herbal formula they may be taking; this happens especially with patients who are new to herbal therapy. In our clinical experience, the overwhelming majority of 'reactions' are not related to the standardised herbal formula 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 formula 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 formula. In such a case, the formula 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 formula is resumed.

Allergic reactions are an important exception to the practice of discontinuing a formula 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).

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 formula 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 formulae 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 recommend 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. EXTRACTION, DOSAGE AND DOSAGE FORMS OF HERBAL FORMULAE

Learning Objectives

- History of formula manufacturing
- Understanding extraction ratios
- Different types of products available
- Dosage considerations

When considering dosage when recommending herbal formulae and single powders and granules it should be remembered that these products were originally developed in Japan, adopted by Taiwan over fifty years ago, widely available in the UK from the 1990s and very recently introduced into mainland China. The historical development is relevant because it explains how the original strategies regarding dosage were based primarily on the clinical safety and effectiveness of the products rather than any attempt to translate the formula from what would be recommended for dosage in raw herb decoctions. In clinical use they can be regarded as two connected but different herbal therapeutic systems.

One particular misconception is in the realm of concentrated powders and granule ratios, for example, one company may declare a 3:1 extract ratio and another company may declare 7:1 and the practitioner may formulate the impression that the 7:1 powders or granules are stronger. This conclusion however is not true for two reasons. The first being that individual plants have different extraction ratios and the figures given out are averages and so depending on the extraction ratios of all the herbs extracted by a particular company, this figure will change accordingly. Secondly a lower extraction ratio just means that either the raw materials have a greater initial concentration of extractable compounds or that the extraction technology is more efficient. This means that by using fresh ingredients and having state of the art equipment a company can extract more from a plant than another company. Consequently a 3:1 extract may well contain a wider spectrum of available compounds than a 7:1 extract of the same plant.

Generally lower doses of extract can be used than when using raw herbs because efficient extraction processes result in stronger extracts than what can be achieved with home decocting. High temperatures and sealed vessels allow for controlled extraction with minimum loss of active ingredients. With the home decoction of raw herbs many of the more volatile components are lost during the decoction process through evaporation. However, in industrial manufacture, these volatile components are trapped and re-introduced once the mixture has cooled, once again increasing the spectrum of available compounds. It is important to note that many of these more volatile compounds, e.g. terpenoids found in essential oils, have a greater ability to penetrate the cell wall *in vivo* and so are likely to be more pharmacologically active than many of the compounds extracted in water.

This leaves the question as to what dosage should be used? The answer being, it depends on the individual product and manufacturer and it is inextricably linked to the manufacturing and formulation process. Typically, in Taiwan, dosages between 6g to 18 g daily are common for different formulations, however in the West we may use slightly lower dosages depending on the age and constitution of the patient.

In terms of overall effectiveness of extracts versus raw herbs there is no definitive answer, although there is much debate from advocates on both sides. From a purely scientific perspective there is no reason why powdered or granulated extracts should be considered any less effective than raw herbs and their preservation of volatile compounds gives them some advantages.

Solid dosage forms

Powder and granule extracts are produced using similar extraction processes, a granulation step towards the end of production results in the end product. Although therapeutically similar, granules may dissolve better in water than powders and so improve patient compliance. Both can be encapsulated but powders are generally better for producing tablets. Although not always evident from the label, all powder and granule extracts contain excipients, examples of these are corn starch, lactose and maltodextrin, some extracts also contain the raw powder of the particular herb. Without these excipients it would not be possible for these products to be manufactured in bulk as the crude extract itself tends to clump together and cannot be processed along a filling line, also they can improve stability and shelf-life.

Liquid dosage forms

As an alternative to the solid dosage forms of powders, tablets and capsules, herbs may also be prepared as liquid extracts. There are several ways that these extracts can be prepared and presented.

Tinctures

These are typically alcoholic extracts. The concentration of alcohol can vary depending on the nature of the herbal constituents but is usually in the range of 20-80%, with 45% being common. The herb-alcohol extraction ratio (often termed drug extraction ratio DER) is typically between 1:3 up to 1:10, again depending on the nature of the herbal material. (Concentration ratios for solid forms are given as the amount of herbal material needed as starting material compared to the amount of solid extract obtained e.g. 5:1)

The preferred technique for extraction is through maceration, where fresh or dried herbs are steeped in the hydro-alcoholic solvent at room temperature over a course of days or weeks. An advantage of this method is that no heating is needed and so any temperature sensitive compounds can be preserved. A secondary advantage is that the alcohol acts as a preservative so these products can be stored for extended periods of time.

Liquid extracts

These are similar to tinctures in that they usually are alcohol based using the same percentage of alcohol that would be used for the corresponding tincture. However they are more concentrated. using a 1:1 extraction ratio or occasionally 1:2. An advantage of a liquid extract is that lower dosages can be used to achieve the same results.

Fluid extracts

These are often associated with traditional East Asian medicines, where water is commonly used as the extraction solvent. The herbs are extracted following the method for making decoctions by boiling in water for up to one hour. The herb-water mixture is filtered to remove the solid material and the resulting solution is left to cool. Alcohol is then added as a preservative. If preferred, it is possible to remove the alcohol prior to ingestion by heating. An advantage of these fluid extracts is that they are prepared based on traditional use and are generally very safe to use.

Its important to note that a herb that is extracted in alcohol is a very different product and has some additional safety concerns. Before using alcohol extracts, practitioners should satisfy themselves that there is some evidence of traditional use, e.g. Dang Gui is often stir-fried in alcohol prior to decoction in order to increase its analgesic effects and there is a tradition of Chinese herbal wines e.g. dan shen is commonly used in wines to support cardiac health. However, the practice of extracting herbs in high concentrations of alcohol, when there is not a long history of this type of dosage form, is potentially dangerous. It may be that a herb will have a stronger effect but equally it may have a stronger or dangerous side-effect and whereas these may be interesting questions in research, they should not be part of regular clinical practice.

Many factors influence dosage, and we are 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.

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 recommending a formula for stasis of Blood with some abdominal masses (such as small fibroids), one might use 3g a day or more. Vice versa, if a deficiency condition prevails, 1.5g – 2g 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 a formula to Expel Wind-Heat for a severe invasion of Wind-Heat, then the patient can take 6g plus in 24 hours.

Age of the patient

Old people and children need lower doses. As stated above, a newborn baby up to 6 months should not be given herbs or herbal formulae at all. 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 1.8m^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^2	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 given herbs or herbal formulae at all and the above values are given only for reference.

The values of this table can be followed when recommending herbal formulae too, although precision is less important here than for drugs.

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 patterns.

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 recommend any formulae during pregnancy. **When recommending 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 recommend any herbs or formulae that are contraindicated in pregnancy.**

In conclusion, the advice given 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 any of the hepatitis viruses, 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.

Formulae 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 possible, herbs should not be taken after 8-9pm.

When recommending tablets, it is preferable if the tablets are chewed before being swallowed: however, if the patient finds them distasteful, it is acceptable to swallow them.

If two or three different formulae are combined, it is advisable to reduce their individual dosage accordingly and take them at different times.

12. WHEN NOT TO USE HERBAL FORMULAE

Learning Objectives

- Contra-indications and cautions with herbal formulae

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

- During 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. CONSERVATION, SUSTAINABILITY AND LIVELIHOODS

Learning Objectives

- Supply chain management
- Environmental concerns

In China, the cultivation and collection of medicinal herbs is an important source of income for many farmers and collectors. Marginalised minorities particularly rely on wild collection of plants as their main source of income. Inevitably this causes some tension between the protection of species in the wild and peoples' livelihoods, but it also is an important issue in relation to the quality and safety of Chinese herbs.

Standards of cultivation and collection of medicinal plants are extremely variable and the herbs that can be found in the large herbal markets in China often are lacking in any traceability. Although there are international initiatives such as the Convention on International Trade in Endangered species of wild fauna and flora (CITES), implementing this at a local level is often difficult. It is really up to the major manufacturers and suppliers of Chinese herbal medicines to take the lead and to develop and implement policies that are both sympathetic and supportive to workers in the beginning stages of the supply chain but also recognise the growing threat to plants in the wild.

Some companies have recognised the need for better integration within the supply chain and have developed strategies whereby they make direct contracts with farmers and collectors rather than going through middlemen. This approach is beneficial for the workers at the beginning of the supply chain as a price and a quantity of herbal material can be agreed from the start and for the buyers it allows them to have greater input into cultivation and collection practices and gives greater traceability and transparency along the whole length of the chain.[69]

Without effective protection, in a world where demand is on the increase, these herbs may be lost forever. For practitioners, these issues may seem very distant to daily practice and out of an individual's control but by asking the right questions to suppliers and by only buying supplies through professionally approved sources, everyone can play a part in supporting sustainable, safe and ethical production of Chinese herbal formulae.

14. QUALITY CONTROLS OF STANDARDISED HERBAL FORMULAS

Learning Objectives

- The importance of quality
- Essential elements of good quality

Stringent quality controls for herbal products are absolutely necessary to ensure maximum safety. Quite apart from the safety issue, strict quality controls are also extremely important to ensure acceptance 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 products.

Quality controls for 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

Questions that should be asked to suppliers:

- Are you able to trace herbal supplies to their source?
- Are you able to provide certificates of analyses?
- Do you have standard operating procedures in place?
- Do you have a system for recalling a product if a problem is identified?
- What excipients do your products contain?
- Are any of the ingredients used on the Restricted substances list or CITES list?
- Do you have a policy regarding conservation and sustainability?
- Are your supplies approved by a relevant professional body?

The British Herbal Medicines Association (BHMA) has released The Good Herbal Manufacturing and Supply Standard, to accredit manufacturers and distributors who are working to best practice, delivering a quality and safe product, with the BHMA HerbMark logo.

The standard was developed by a combination of 40 years GMP and Food Safety Standards experience supplemented by site visits to herbal product manufacturing companies, to gain an understanding of their processes. The standard is an easy to follow and useful assessment tool to establish best practice. Organisations are audited against this standard on a regular basis, typically every two years.

The key elements are as follows:

1. **Quality Management System**: A defined and workable system, commensurate with the complexity of the business. This is supported by a quality policy endorsed by the senior management. This will include risk assessment and HACCP.
2. **Personnel**: Adequately resourced. All staff to be suitably qualified, trained with clearly defined roles and responsibilities.
3. **Premises and Equipment**: Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.
4. **Documentation**: All documents need to be controlled and reviewed. Designed to be easily understood, providing clear and unambiguous information.
5. **Production**: All processes to be clearly defined with supporting procedure sand work instructions.
6. **Quality**: Ensuring all materials, intermediates, and finished products meet their specification with regards to safety and quality
7. **Out-Sourced Activities**: Managing suppliers and contractors, with documented agreements defining responsibilities and deliverables.
8. **Complaints and Recalls**: Formalised process for dealing with customer complaints and nonconformances.
9. **Self- Inspection**: Self-evaluation and monitoring through internal audits.

The BHMA scheme is complementary to the well-established Register of Chinese Herbal Medicine (RCHM) approved suppliers scheme and together they form a robust strategy for helping to assure product quality for all practitioners of Chinese herbal medicine.

The RCHM, (www.rchm.co.uk) recommends only using herbs sourced from suppliers on the ‘Approved Suppliers Scheme’, which sets minimum safety, quality and ethical standards for suppliers of Chinese herbal medicines in the UK. For thorough training on herb safety and legal issues with regards to herbal medicine, the RCHM recommends training on an EHTPA accredited course.

15. THE REGULATORY LANDSCAPE

Learning Objectives

- Different approaches across the world
- Classification of plant-based products
- Sources of information

The regulations applied to medicinal plants are complex and diverse, with different countries having a range of attitudes towards regulation. In the USA, for instance almost all medicinal plants are regulated as dietary supplements, whereas in Germany the same plants would be regarded as medicines and regulated as such. In the UK, we fall somewhere in the middle, with some plants being regulated as food supplements and some plants being regulated as medicines or traditional herbal medicines.

Herbalists in the UK, however, are in a somewhat unique position within Europe, in that they are allowed to recommend herbal medicines to their patients following a face-to-face consultation and providing the plants in question are not on any restricted list or are not manufactured finished products, they have enormous flexibility in the range of medicinal plants supplied, the conditions treated and the dosages given.

However, manufactured finished products in the UK are regulated differently and will fall under three main regulatory categories, medicines, traditional herbal medicines and food supplements.

Products that are regulated as medicines have generally been available for some time and were originally granted a product license (PL) as medicines, examples of these can be found in pharmacies and other health store outlets and have included products containing plants such as senna, ipecacuanha and ispaghula husk. It is unlikely that future products will be regulated in this way since the introduction of a special category for the regulation of traditional herbal medicines (THR). This category, which came fully into fruition in 2011, allows for certain medicinal claims to be made for medicinal plants based on over thirty years of traditional use. This means that although they must satisfy the same quality and safety standards as all medicines, they do not have to go through clinical trials to prove efficacy. For manufacturers of these products, this represents a substantial financial saving although there is still considerable investment needed before these products can be licensed.

The majority of commonly known plants can also be placed on the UK market as food supplements providing that the plants have been available for public consumption since 1997, no medical claims are made, the labelling complies to UK food standards regulations and that the product does not contain compounds that are regarded as having a medicinal activity at the dosage given. In practice, this means that most known plants can legally be placed on the UK market as

food supplements, with a notable exception being *Hypericum perforatum* (St Johns Wort) which has significant medicinal effects and known drug interactions, and those restricted herbs listed in Schedule 20 Part 1 and Part 2, outlined below:

Restrictions Under Statutory Instruments: SI 2130 1997 – NB this has now become schedule 20, under regulation 241 of the Human Medicines Regulations 2012 No.1916 (14th August 2012) These herbs were listed as an addition to the 1968 Medicines Act as being potent and hence in need of dosage regulation. In some cases they are forbidden at any internal dosage. MD= Maximum single dose MDD=Maximum Daily Dose:

FU ZI/CAO WU (Aconitum species). NOTE: Permitted to use externally at a dose of 1.3% or below. Internal use prohibited.

SHI LIU PI (*Punica granitum*). Internal use prohibited.

BING LANG (*Areca catechu*) Pharmacy use only.

DA FU PI (*Areca catechu*) Pharmacy use only.

MA HUANG (*Ephedra sinica*). MDD: 1800mg. MD: 600mg.

YANG JIN HUA (*Datura stramonium*). MDD: 150mg. MD: 50mg.

DIAN QIE CAO (*Atropa belladona*). MDD: 150mg. MD: 50mg.

TIAN XIAN ZI (*Hyocyamus niger*). MDD: 300mg. MD: 100mg. NOTE: SI 2130 also applies to other herbs not employed in Chinese medicine.

SI 1841 2002 This ban relates to all Aristolochia species but also includes herbs which have been confused with Aristolochic species due to poor quality assurance. The sale, supply and importation of the following is banned: MU TONG (*Aristolochia manshuriensis*). NOTE: this ban also applies to *Akebia quinata*, *Akebia trifoliata*, *Clematis montana* and *Clematis armandii*. FANG JI (*Aristolochia fangji*). NOTE: this ban also applies to *Stephania tetrandra*, *Cocculus laurifolius*, *Cocculus orbiculatus* and *Cocculus Trilobus* MA DOU LING (*Aristolochia contorta*, *Aristolochia debilis*) TIAN XIAN TENG (*Aristolochia contorta*, *Aristolochia debilis*) QING MU XIANG (*Aristolochia debilis*).

SI 548 2008 All species of Senecio are prohibited for internal use due to the presence of toxic pyrrolizidine alkaloids (PA). This mainly applies to the use of *Senecio scandens* QIAN LI GUANG.

Banned and Restricted Herbal Ingredients – UK

Botanical source	Common name	Legal category	Maximum dose where permitted for internal use only. Max dose (MD)1, max daily dose (MDD)2	Maximum dose where permitted for external use only. Percentage (%)
All Aconitum species including: *Aconitum napellus, Aconitum stoerkianum, Aconitum uncinatum var japonicum, Aconitum deinorrhizum, Aconitum balfourii, Aconitum chasmanthum, Aconitum spicatum, Aconitum lycoctonum*	Aconite, Fu Zi, Chuan Wu, Cao Wu, Wu Tao	POM and SI 2130 – Parts II & III	No permitted dose unless made available by a prescription from a registered doctor or dentist	1.3% or below
Akebia quinata, Akebia trifoliata	Mutong, Bai Mutong	SI 1841	Prohibited in all unlicensed medicines	
Areca catechu	Areca, Bing Lang, Da Fu Pi	SI 2130 – Part I	Can only be sold in premises which are registered pharmacies and by or under the supervision of a pharmacist	
Aristolochia, Aristolochia clematis, Aristolochia contorta, Aristolochia debelis, Aristolochia fang-chi, Aristolochia manshuriensis, Aristolochia serpentaria	Mu tong; Guan Mu Tong, Fangji; Birthwort; Long Birthwort; Indian Birthwort	POM	No permitted dose unless made available by a prescription from a registered doctor or dentist	
Aristolochia, Aristolochia clematis, Aristolochia contorta, Aristolochia debelis, Aristolochia fang-chi, Aristolochia manshuriensis, Aristolochia serpentaria	Mu tong; Fangji; Birthwort; Long Birthwort; Indian Birthwort	SI 1841	Prohibited in all unlicensed medicines	
Clematis armandii, Clematis montana	Mu tong; Chuan Mu Tong	SI 1841	Not permitted in any unlicensed medicines	
Ephedra sinica, Ephedra equisetina, Ephedra distachya, Ephedra intermedia, Ephedra gerardiana	Ephedra; Ma Huang	SI 2130 – Parts II & III	600mg (MD), 1800mg (MDD)	Can only be sold in premises which are registered pharmacies and by or under the supervision of a pharmacist
Papaver somniferum	Ying Su Ke, Poppy Capsule, Opium Shell, Opium Husk	POM	Can only be made available via a prescription from a registered doctor or dentist	
Piper methysticum	Kava-kava,	SI 3170	Not permitted in unlicensed medicines, except those exclusively for external use	
Punica granatum	Pomegranate Bark	SI 2130 – Part I	Can only be sold in premises which are registered pharmacies and by or under the supervision of a pharmacist	
Stephania tetrandra	Fangji, Han Fang Ji	SI 1841	Not permitted in any unlicensed medicines	
Strychnos nux vomica seed, Nux vomica seed;	Ma Qian Zi, Poison Nut	POM	Can only be made available via a prescription from a registered doctor or dentist	

1. 'Maximum dose' or 'MD' means the maximum quantity of the substance contained in the amount of the medicinal product for internal use, which it is recommended should be taken or administered at any one time.

2. 'Maximum daily dose' or 'MDD' means the maximum quantity of the substance contained in the amount of the medicinal product for internal use, which it is recommended should be taken or administered in any period of 24 hours.

So although the regulatory situation in the UK is certainly complex, this complexity allows for a wider range of treatment options and greater plant accessibility than most European countries and a sustained strategy of product development, quality assurance and professional expertise are the key factors that must be maintained in order to give the public continued access to high quality, safe and ultimately effective plant based products.

The standards applied to regulation of herbal medicines and food supplements are under regular review and are therefore subject to change. The following regulatory authorities and professional bodies can provide up to date information on current standards, guidelines and requirements.

The Medicines and Healthcare Products Regulatory Agency (MHRA)

The Food Standards Agency (FSA)

The British Herbal Medicine Association (BHMA)

The Health Food Manufacturers Association (HFMA)

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GLOSSARY

Aflatoxins	poisons produced by fungi
Alanine aminotransferase (ALT)	an enzyme used in liver function testing
Anaphylaxis	a potentially life-threatening allergic reaction that happens very quickly. It is often caused by exposure to certain foods, medicines or insect stings.
Anthranoid	containing anthroquinone, a chemical laxative
Anticholinergic	blocks the neurotransmitter acetyl choline
Anticonvulsants	antiseizure medications
Antiplasmodial	having an effect against parasites
Antigen	a molecule that can trigger an immune response
Aqueous extracts	plant extracts that use water as the extraction solvent
Aristolochic acids	a group of toxins commonly present in the plants of genus Aristolochia and Asarum
Arsenic	a toxic heavy metal element
Bilirubin metabolism	a yellow bile pigment produced through the breakdown of red blood cells. Bilirubin is metabolised prior to excretion through the faeces and urine
Bradykinesia	slowness of movement
Carbon tetrachloride	an organic solvent with the formula CCL4
Chloroform	an organic solvent with the formula CHCL3
Cholestatic injury	relating to the gall bladder
Chronic glomerulonephritis	damage to the tiny filters inside your kidneys (the glomeruli)
Cytotoxic drugs	drugs that kill cells, including cancer cells
Diuretics	help rid your body of salt (sodium) and water
Drug half-life	the time it takes for the amount of a drug's active substance in your body to reduce by half
Electrolyte depletion	occurs when you have not enough of certain minerals in your body

Enzymes	Compounds that help speed up biological processes
Glomerular filtrate	the process that your kidneys use to filter excess fluid and waste products out of the blood into the urine collecting tubules of the kidney, so they may be eliminated from your body
Granulocytopoenia	low granulocytes in the blood
Haemolysis	rupture of red blood cells
Haemolytic anaemia	where red blood cells are destroyed faster than they are made
Hepatitis	inflammation of the liver
Hepatoprotective	the ability of a chemical substance to prevent damage to the liver
Heterocyclic amine	organic compound linked to cancer
Homoeostatic	the regulated environment that organisms require to live
Hypercalcaemia	increased levels of calcium
Hypoglycemic	when the level of sugar (glucose) in your blood drops too low
Hypotensive	lowering of the blood pressure
Idiosyncratic	unique, unusual, unpredictable
Immunological effect	the effect on the immune system
In vitro	medical procedures, tests, and experiments that researchers perform outside of a living organism in a controlled environment, such as a test tube or petri dish
In vivo	tests, experiments, and procedures that researchers perform in or on a whole living organism, such as a person, laboratory animal, or plant
Iron	an essential component of hemoglobin, an erythrocyte (red blood cell) protein that transfers oxygen from the lungs to the tissues
Lipid soluble	fat soluble
Macrophage	specialised cell that destroys bacteria
MAO inhibitors	a class of drugs that inhibit the activity of one or both monoamine oxidase enzymes

Metabolism	the process by which the body changes food and drink into energy
Methoxylated flavonoids	natural antioxidants
Phagocytosis	where cells are engulfed digested by other cells
Pharmacodynamics	a medicines effect on the body
Pharmacognosy	knowledge relating to drugs obtained from natural sources
Pharmacokinetics	how the body processes medicines
Pharmacology	the study of the uses, sources and mechanisms of the action of drugs
Phenothiazines	an antipsychotic medication
Polysaccharide	a large carbohydrate molecule
Purgatives	to get rid of unwanted waste from your body
Renal plasma flow	the amount of blood that reaches the glomerulus of the kidneys over a period of time
Renal tubule cells	are responsible for the reabsorption of solutes from the excretion of metabolic waste products
Sensitised lymphocytes	a method used when studying immunity
Sympathomimetic	promotes stimulation of sympathetic nerves
Tannic acid	a naturally occurring plant polyphenol
Tetracyclines	a drug used to treat bacterial infections
Thrombocytopoenic purpura	blood condition resulting in low platelets
Tubular pH	acidity or alkalinity within the kidneys
Type-I asthmatic reaction	Also known as a type 1 hypersensitivity reaction, this is an immediate allergic reaction leading to an asthma attack.
Urticarial rashes	a raised, itchy rash that appears on the skin
Zonal necrosis	necrosis involving a particular zone of the acinus