



INNOVATIVE INTEGRATED TRAINING IN  
**HEALING PLANTS  
BUSINESS**

## **IO3 - The Total Business Plants**

### **Training Material**

#### **Module No. 5**

### **“Medical use of therapeutic plants”**

#### **Unit 5**

## **Biognosis**

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## Unit 5

### **Limitations in medicinal use, Efficacy & Safety**

#### **Summary**

Here are presented: important to be known Contraindications, side effect, toxicity and other limitations in use, as interactions of known phytomedicines with other drugs; the meaning of these terms, and gives some examples of the cautions, contraindications, side effects and interactions for different herbs.

- **Learning outcome descriptors**

By the end of the course, the trainee should be able to demonstrate:

#### **Knowledge, understanding and professional skills:**

1. Understands the terms Contraindications, Side effect, Toxicity and Interactions with other drugs.
2. Recognize limitations in medicinal use of herbs and the adverse effects of the use of herbal medicines
3. Discuss Clinical efficacy of phytomedicines and peculiarities of treatment in certain population groups

#### **General and transferable skills:**

1. Show good written and oral communication skills.
2. Demonstrate general computer literacy
3. Perform computer search to retrieve information from other sources
4. Show ability to use information retrieved for improving professional status
5. Plan tasks and work independently
6. Work in team with minimal guidance where appropriate

## Unit 5

### Limitations in medicinal use, Efficacy & Safety

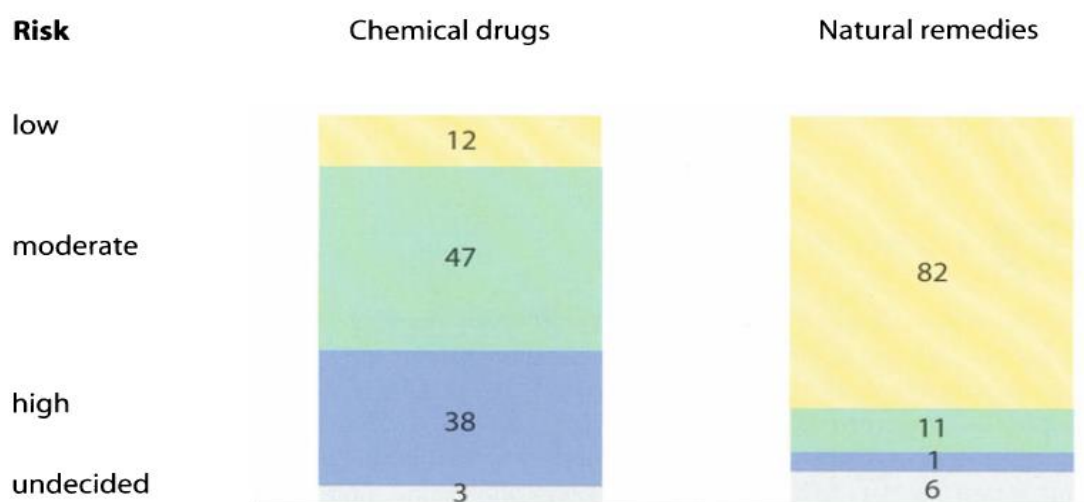
Contraindications, Side effect, toxicity and interactions with other drugs.

### Clinical efficacy of phytomedicines

Through ages many traditional herbs have been used by humans to treat or prevent diseases. Recently, there is an increasing interest in alternative or herbal medicine use, and this leads to an also increasing concern about the safety of medicinal plants application. Many people mistakenly believe that herbal products are safe. Although most herbal medicines are relatively safe in comparison with modern drugs, results from toxicological studies show that this is not always true. (Claude, J.R. and Claude, N. 2004)

### Patient Expectations

A well-known German institute of demographic research conducts regular opinion surveys to explore the attitudes of the German public toward natural remedies (IFD Survey 7016, 2002). In 2002 the institute surveyed a representative cross section of 2172 people ranging from 16 to 90 years of age. Thirty-five percent of the responders considered the prescription of natural remedies to be “very important,” 41% rated it as “important,” and 13% rated it as “not very important”. This survey demonstrates the generally high regard in which phytomedicines are held by the German public. When asked whether these products were effective, 4% said no, 38% had no opinion, and 54% were convinced that herbal remedies are effective. Most of the responders believed, however, that natural remedies worked differently from synthetic drugs.



**Figure 1. Results of a representative survey of 2172 German citizens on the risks of synthetic drugs versus natural remedies. The latter are believed to have a very large therapeutic range and a high safety margin (IFD Survey 7016, 2002).**

Opinions on product safety were even more revealing: 82% of those surveyed rated the risk of treatment with natural remedies as “low,” while 84% rated the risks of synthetic drugs as “moderate to high” (Fig. 1). Devotees and opponents of natural remedies held about this opinion equally. Thus, the demand of many patients, especially the elderly, for herbal remedies is rooted partly in the emotional perception, that natural products are gentler and safer than chemical products. Beyond some very concrete evidence for certain active plant constituents, even a consultation with their doctor would be unlikely to shake patients from this preconceived notion. A more reasonable approach is to base the prescription and recommendation of herbal remedies, on the way in which patients actually use these products, which presupposes that the products generally have a broad, safe therapeutic range. (Ernst E, Pittler MH, Stevinson C, White A 2001).

Potent plant-based medicines, such as preparations made from cardiac glycoside-containing plant parts like the foxglove (*Digitalis spp.*), tropane alkaloids from belladonna (*Atropa Belladonna*), or colchicine from the autumn crocus (*Colchicum Autumnale*) do not meet these safety criteria, and so it is best not to use the term “herbal” or “botanical” when referring to these products. For these indications it is better to prescribe pure “chemical” compounds such as digitalis glycoside, atropine, colchicine, etc. (Anderson, H. and Spliid, H. (2000)

At the same time, confidence on a remedy is the best foundation for its successful use in selected therapeutic applications. Once the treatment decision has been made, it is better to encourage patients’ confidence and their self-healing powers by educating them about the selected medication (and any associated risks!) in positive terms. The basic background information about a synthetic drug mainly involves its chemical structure, which is of little interest to most patients. But with an herbal medication, the patient can be shown a picture of the medicinal plant and told its history, providing an excellent context for the treatment interview.

Doctors, who recommend plant-derived medicines, should become familiar with the plants from which they are derived. They should know about their botanical characteristics, the plant parts that are used medicinally, and their traditional therapeutic uses.

## **SAFETY PHARMACOLOGY**

The criteria of safety for herbal medicine should be the same as for chemical drugs. Therefore, it is necessary to give a brief introduction about the guidance and regulation of the safety of drugs. Unfortunately, many countries have no official regulations for quality control on the manufacturing or labeling claims of herbal remedies and dietary supplements.

When performing safety pharmacological studies on herbal materials, two issues must be considered:

a) The concentration of active or toxic compounds and other chemicals varies in different parts of the plant, for different harvest seasons, and when extracted with different methods.

b) The geography, soil composition and its contaminants, and year-to-year variations in soil acidity, water, weather conditions, and other growth factors all have significant effects on the therapeutic properties and safety of the medicinal plants.

The guideline ICH S7A has been adopted by the regulatory authorities of Europe, the United States, and Japan, and referenced by the relevant departments of many other countries. A number of important issues relating to safety pharmacology as it is currently defined by regulatory agencies are described in this section. According to this guideline, pharmacological studies can be divided into three categories: primary pharmacodynamic studies, secondary pharmacodynamic studies, and safety pharmacology studies. The specific objectives of safety pharmacology studies include:

- To identify undesirable pharmacodynamic properties of a substance that may have relevance to human safety.
- To evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies.
- To investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected.

A successful clinical trial depends on accurate scientific design. The trial of an herbal product is more complicated due to the complex composition and difficult quality control of the components in comparison to the trial for a single chemical drug.

Similar to conventional drugs, clinical evidence on herbal medicine comes primarily from case reports, uncontrolled clinical trials and randomized controlled trials (RCTs). Randomized controlled trials, especially if double blind, are considered as the most rigorous system for evaluating the efficacy of drugs. Unfortunately, many of the reported results of clinical studies on herbal medicine so far are not reliable due to more or less unscientific design. Quite often, the results of clinical trial for one herbal medicine obtained by different research groups vary significantly. However, it may happen that diverse, even rigorous, clinical trials do not always yield the same conclusion. Hence, only the totality of the available data, which can be collected in a systematic review, offers the most reliable evidence of efficacy. Systematic reviews and meta-analyses are at the top of the pyramid of the clinical evidence. (Valentin, J.P. and Hammond, T.J. 2008)

#### **Terminology of: Contraindications, Side effect, Toxicity and Interactions with other drugs.**

<b>TERM</b>	<b>MEANING</b>
<b>Contraindications</b>	A remedy's contraindications inform you when it is unsuitable to be used. Contraindication makes a particular treatment or procedure inadvisable. A contraindication is a condition or factor that serves as a reason to withhold a certain medical treatment due to the harm that it would cause the patient.

<b>Cautions</b>	A caution means that it is possible the remedy may not be recommended in some circumstances, but it is not as strong as a contraindication. Cautions include the fact that some herbs may irritate the stomach. It is up to the individual to decide if they mind the possibility of this side effect.
<b>Side Effects</b>	Side effects of a medicine are effects, which may occur to the body due to taking the medicine, in addition to the desired effect. Side effects may include effects that are seen in most people taking that medicine, or side effects that may have occurred only once!
<b>Interactions</b>	An interaction occurs when the administration of one medication (whether herbal or not) affects the action of another medication. These interactions can occur either by one medication directly acting on the other, or through their effects on the human body.

Up to now, only the most popularly used herbs, very few have been well known with respect to pharmacological effects on animals. In the past 3 years, a discrete number of systematic reviews/meta-analyses concerning the clinical efficacy of herbal extracts used mainly in western countries have been published. Furthermore, other recently published systematic reviews provided evidence of efficacy for black cohosh (*Cimicifuga Racemosa*) in menopausal women, Dang Shen (*Codonopsis Pilosula*) for chronic obstructive pulmonary disease and some botanical preparations for dermatological conditions but failed to show clear beneficial effects for pomegranate (*Punica Granatum*) in the prevention and treatment of cardiovascular diseases, for Hibiscus sabdariffa in lowering serum lipids and for saw palmetto (*Serenoa Repens*) in patients with benign prostatic hyperplasia. (Saad, B., et al. 2006)

### Adverse effects of the use of herbal medicines

There are general and herb-specific concerns regarding herbs and their potential to produce adverse effects. The assumption that 'natural' equals to 'safe' is obviously deceptive. Natural products contain pharmacologically active molecules potentially able to cause danger to human health. Classical examples of toxicity associated with herbal use include the hepatotoxicity due to pyrrolizidine alkaloids-containing plants, Aconitum poisoning due to Aconitum alkaloids, which are highly toxic cardiotoxins and neurotoxins and the severe – in some cases lethal – cardiovascular side effects associated with Ephedra sinica, whose sales have been prohibited by the Food and Drug Administration since 2004. (Dunnick, J.K., et al. 2007)

Not many people realize that when herbs are extracted and purified, the toxicity might be increased along with the increase in therapeutic efficacy. Here, take the rhizome of Angelica Pubescens f. biserrata, a Chinese herb used for arthritis with anti-inflammatory activity. When this herb was extracted and then fractionated with petroleum benzene, chloroform,

ethyl acetate and, n-butenol, respectively, into several fractions and given to a mouse with ear swelling, induced by mixed inflammatory solution for pharmacological study in our lab, the petroleum benzene fraction showed not only the highest potential inhibition on ear swelling, but also the highest toxicity. Three out of 10 mice died after administration.

Accidental herbal adverse effects may occur as a result of collecting wrong raw materials and inappropriate preparation due to a lack of knowledge on active and toxic components in the materials and pharmaceutical quality control, or overdosed or over-lasting administration due to the mistaken belief that herbal remedies are harmless. Unfortunately, many countries have no official regulations for quality control on the manufacturing or labeling claims of herbal remedies and dietary supplements. (Colson, C.R. and De Broe, M.E. 2005)

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### **Herb drugs interactions**

In the last 20 years, multiple case reports, case series and pharmacokinetic trials have clearly highlighted that herbal medicines can interact with prescribed medicines.

The drug interactions that have reported are from:

- I. human studies – published research done on healthy individuals human clinical studies – published research from therapeutic trials on patients being treated for a condition
- II. empirical – traditional knowledge or consensus based on experience from extensive use human case reports – published individual responses to using herbal products human case series – published responses from several patients using a preparation of the same herb
- III. in animals (types listed) – laboratory tests using live animals (*in vivo*) and various modes of administering the herb or herbal component(s)
  - a. *ex vivo* –laboratory interaction finding on cells, tissue, or organs from animals or humans who were administered the herbal agent (as contrasted to *in vivo* when studies are done on the living organisms themselves)
  - b. *in vitro* –laboratory interaction finding with cell or tissue samples from animals or humans speculative – using pharmacological evidence from *in*

*vitro* research, animal studies, or human studies to infer probable or potential interactions or effects in humans

- IV. [dubious interactions], as shown in brackets with the drugs underlined rather than in bold type, are based on preliminary findings, speculation, inaccurate information, and/or false assumptions that have been contradicted by established evidence.

From a mechanistic viewpoint, interactions can have either a pharmacokinetic and pharmacodynamic basis or both, and herbal medicines may interact with prescribed drugs at the intestine, liver, kidneys and targets of action. Most of herbal remedies involved in drug interactions have been shown to up-regulate or down-regulate cytochrome P450s and/or P-glycoprotein, but the roles of drug transporters including the organic anion and cation transporters and the nuclear pregnane-X receptor are now becoming increasingly apparent. (Claude J. and Claude, N. (2004). For example the herb St John's Wort (*Hypericum Perforatum*) causes one of the processes in the liver (the P450 enzyme system) to be more efficient. While this is not normally considered as an issue in a healthy person not taking any medication, it does cause some drugs that are metabolized by the liver to be removed from the body more quickly - meaning that they would no longer be as effective. This includes the contraceptive pill!

The use also of *Hypericum Perforatum* with immunosuppressive (e.g. cyclosporine), antiretroviral (e.g. indinavir and nevirapine), cardiac (e.g. digoxin) or antineoplastic (e.g. irinotecan and imatinib) drugs may result in reduced plasma concentration of the prescribed drug and, hence, reduced efficacy, and patients with cardiovascular conditions are therefore greatly at risk, as are those taking immunosuppressant drugs. The anticoagulant warfarin is the most common drug involved in all kinds of drug interactions, including herbal, and St John's wort the most common herb involved in all herb–drug interactions, so caution should be used whenever these are used in combination with other drugs. (Shayne, C. 2003)

### **Use of herbal remedies during pregnancy and by breastfeeding women**

Complementary and alternative therapies, including herbal medicines, are widely used during the third trimester of pregnancy, and pregnant women tend to believe that such treatments are safer than prescribed drugs. According to a British survey, 57.8% of pregnant women used one or more herbal remedies, the most common being ginger (*Zingiber Officinale*), cranberry (*Vaccinium Macrocarpon*), raspberry (*Rubus Ideaus*) leaf, chamomile (*Matricaria Recutita*), peppermint (*Mentha Piperita*) and echinacea (*Echinacea spp.*). Herbal medicines are also used by breastfeeding women. According to recent systematic reviews, herbal medicines have been evaluated in survey studies, safety studies and efficacy studies. However, because of the poor methodological quality of the clinical data, there is little evidence supporting their efficacy and safety among the lactating women.

### **Use of herbal remedies in the pediatric and adolescent population**

Herbal remedies are popular in pediatric and adolescent populations. For example, in 2014, an estimated 5.8% of German children and adolescents between the ages of 0 and 17 years





and 3.9% among children 0–17 years old in the USA used herbal remedies (CDC National Health Statistics Report, 2007). It is therefore crucial to define their efficacy and possible risks in children. Main adverse events reported include neurological (35% seizures, central nervous system depression and lethargy), cardiovascular (10% hypertension and blood concerns) and gastrointestinal (14% nausea, vomiting and diarrhea) systems as well as liver toxicity and jaundice (11%). Also many of the case reports were poorly documented. Among the best-documented case reports, fleece flower (*Polygonum Multiflorum*) root and kava (*Piper Methysticum*) were associated with acute hepatitis, blue cohosh (*Caulophyllum Thalictroides*) with neonatal congestive heart failure and Siberian ginseng (*Eleutherococcus Senticosus*) with neonatal hirsutism. The accidental ingestion of tea tree (*Melaleuca Alternifolia*) oil was associated with ataxia and unresponsiveness. (Colson, C.R. and De Broe, M.E. 2005)

### **Use of herbal remedies in the geriatric population**

Many elderly subjects use herbal products for the relief of symptoms or medical diseases that are believed to be not easily treated by conventional prescribed remedies. The majority of the studies were performed in the USA. The most commonly used herbs were ginkgo (*Ginkgo biloba*) and garlic (*Allium Sativum*), and both of them have the potential to interact with prescribed drugs, especially in patients under anticoagulants. Other herbal remedies frequently used by elderly subjects include ginseng (*Panax Ginseng*), Aloe Vera, chamomile (*Matricaria Recutita*), ginger (*Zingiber Officinale*) and spearmint (*Mentha Spicata*).

Assessing the safety and efficacy of herbal medicines remains problematic, with inadequate or inconsistent methods being used, and the issues have been discussed here using examples of recent systematic reviews and meta-analyses. It is apparent that generalizations about the efficacy and safety of herbal remedies are not advisable, even though many have been effectively used for diseases and as functional foods, especially in Asian countries. Certain herbal medicines have been shown to be efficacious (e.g. ginger for preventing and treating nausea and vomiting), whereas others have been shown to be effective for a specific indication but not others (e.g. ginseng for improving glucose metabolism, but not for Alzheimer's disease). Several herbs have been associated with serious adverse events, including herb–drug interactions (St John's wort in particular). However, many clinical studies have been performed without sufficient rigor and recorded detail; therefore, the findings must be interpreted cautiously. (Porsolt, R.D., et al. 2002)

Clearly, more high quality research in this field is needed to firmly establish the efficacy and/or safety of many herbal products. Most importantly, herbal research should be conducted with the same meticulous care as any other medical research, and as part of this, all herbal products administered to patients should ideally be chemically characterized, standardized if possible, and of known quality. For many herbs, monographs of pharmacopoeia standards are available and contain validated general methods for testing for microbiological and other forms of contamination. Furthermore, all clinical studies should conform to the standards reported in the Consolidated Standards of Reporting Trials and Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. (Sullivan, A.T. and Kinter, L.B. 1995)

Information about drug components: interactions, usage in pregnancy or while breastfeeding for pediatric patients, and dosing limits, are outlined and made available in standard references for doctors treating patients. Furthermore, the formulations of the drugs must satisfy strict quality control standards to ensure conformity. In contrast to conventional medications, unconventional treatments (such as herbs) have little or no actual scientific basis, so doctors to be able to guide their patients regarding proper usage or potential toxicity. There are no standardized references and most of the herbal formulations have not been analyzed, are not uniform, and have not been quality controlled. One batch can be very different from the next one. Moreover, even if a given herb has a known toxicity, the manufacturer may or may not warn consumers. Manufacturers are not required to alert consumers to known dangers. Doctors, who recommend plant-derived medicines, should become familiar with the plants from which they are derived. They should know about their botanical characteristics, the plant parts that are used medicinally, and their traditional therapeutic uses.

### General Considerations

In general, the key thing to consider is that if you are deciding to use herbal medication by yourself, then you are responsible for your own healthcare. The following list indicates when you should be especially careful when using herbal remedies.

- Where the patient is young (i.e. from infant to approximately 11 years old).
- If you are taking any prescription medicines.
- If you are treating a significant health complaint.
- If you are normally sensitive or allergic to substances.
- If you do not have a diagnosis from a medical professional.
- Pregnancy: During pregnancy and breastfeeding professional advice is essential.

### Examples of Cautions and Contraindications of Some Herbs

(Specific information on each plant is given in TBP project's online encyclopedia)

#### St John's Wort (*Hypericum Perforatum*)

**Contraindications:** Pregnancy due to its ability to stimulate the uterus, and if breastfeeding. If you are taking conventional anti-depressants or you are suffering from severe depression.

**Cautions:** It is recommended that foods containing tyramine, such as cheese, wine, yeast and beer, are avoided whilst taking St. John's Wort. If you are HIV positive and receiving treatment it is recommended that you consult a qualified medical practitioner before taking St. John's Wort.

**Side-effects:** Some individuals with fair skin have experienced an increased sensitivity to the sun whilst taking St. John's Wort. It is therefore recommended that you avoid excessive amounts of sun exposure and wear a good quality sunscreen (as you should do anyway!) if you anticipate being exposed to the sun for long periods of time.

**Interactions:** St John's Wort affects the function of a group of liver enzymes termed the Cytochrome P450 enzymes, and can therefore affect the metabolism of a variety of drugs by either clearing them more quickly or slowly from the body. This is of particular importance if you are taking the contraceptive pill, anti-coagulants (such as warfarin), digoxin, cyclosporine, theophylline tablets for asthma or chronic bronchitis, statin drugs, protease inhibitors, e.g. Indinavir, or medication for epilepsy or migraines as the herb may stop them from acting properly.

### **Raspberry Leaf (*Rubus Idaeus*)**

**Contraindications:** Raspberry leaf is contraindicated in pregnancy, if the pregnant lady has a history of early labor.

**Cautions:** Raspberry leaf tea should be taken as a tea only during the last trimester of pregnancy (Week 28-36 and onwards).

### **Ginkgo Biloba**

**Contraindications:** Ginkgo Biloba is contraindicated if you are undergoing surgery. You should stop taking the herb at least 7 days prior to any surgery.

### **Chamomile drug interactions**

Allergic reactions can occur, particularly in persons allergic to ragweed. Reported reactions include abdominal cramps, tongue thickness, tightness in the throat, and swelling of the lips, throat and eyes, itching all over the body, inflammation, and blockage of the breathing passages. Close monitoring is recommended for patients who are taking medications to prevent blood clotting (anticoagulants).

### **Echinacea drug interactions**

The most common side effect is an unpleasant taste. Echinacea can cause liver toxicity. It should be avoided in combination with other medications that can affect the liver.

### **Garlic Drug interactions**

Allergic reactions, skin inflammation, and stomach upset have been reported. Bad breath is a notorious accompaniment. Studies in rats have shown decreases in male rats' ability to make sperm cells. Garlic may decrease normal blood clotting and should be used with caution in patients taking medications to prevent blood clotting (anticoagulants).

Reference:

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