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PROCESSING TECHNOLOGIES AND GOOD MANUFACTURING PRACTICES
FOR THE PRODUCTION OF MEDICINAL PLANT-BASED PRODUCTS
AND QUALITY ASSESSMENT OF PRODUCTS

Discussion paper

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INTRODUCTION

Medicinal plants contribute a great deal to the health care of people all over the world. They have been, and are being, used by a large portion of the population of developing countries, and in least developed countries, more than 90 per cent of the population has no other means of medication than locally grown medicinal plants. Over 30 per cent of the pharmaceuticals produced in developed countries are estimated to be plant-based. These products have an estimated retail value of 20 billion to 40 billion United States dollars, amounting to between 13 and 26 per cent of the world market for drugs. In the United States of America, the United Kingdom of Great Britain and Northern Ireland and especially in European countries and Japan, plant-based medicines are available everywhere, and are exported to developing countries. Yet, most of the plant-based medicines originated in the developing countries of Africa, Asia and Latin America. The tremendous wealth of medicinal plant resources in the developing countries is still not fully utilized. Many traditional medicines are still prepared by conventional methods. Developing countries now have no option but to establish and strengthen their capabilities for the industrial utilization of medicinal plants.

The promotion of industries based on medicinal plants in developing countries is essential for health care and the development of economic and human resources. The use of modern processing technologies will enhance the efficiency of extraction leading to the upgrading of quality and increased stability of the preparations. The standardized extracts could also be converted into modern dosage forms in order to achieve uniformity, stability and easy transport. The industrial processing of medicinal plants can provide a larger quantity and higher quality of cheaper plant-based medicines than traditional processing. Most of the products may be used to meet the health-care needs of the population in developing countries. Some of the products, including extracts, pure compounds, intermediates and finished products, can be exported to earn the hard currency needed for the economic and educational development of developing countries. Promoting the industrial utilization of medicinal plants also stimulates human resource development, since many people – from the farmer to the highly skilled professional scientist – are required to work in established phytopharmaceutical factories and related institutions.

The industrial utilization of medicinal plants involves many fields of science and technology, such as botany, taxonomy, plant-resource science, pharmacognosy, phytochemistry, analytical chemistry, pharmacology, toxicology, machine building, marketing etc. The present paper deals with only a few of the fields closely related to the industrial utilization of medicinal plants, including the following:

- Prerequisites for industrial production
- Selection of plants and preprocessing
- Processing methods
- Technologies that could be appropriate for developing countries
- Dosage forms and tests required
- Quality assurance
- Research and development requirements
- Good manufacturing practice
- Waste disposal
- Scheme for small-scale processing of medicinal plants.

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I. PREREQUISITES FOR INDUSTRIAL PRODUCTION

Industrial production is the only way to supply the population with safe and effective drugs in large quantities. Some prerequisites are necessary for industrial production.

A. Rich raw-material resources

The first and most important prerequisite for the industrial utilization of medicinal plants is abundant plant resources consisting of wild and cultivated plants. Medicinal plant resources are extremely abundant in developing countries in Africa, Asia and Latin America, but a considerable part of the resources is exported to developed countries as pharmaceutical materials. Among the raw materials of plant-based drugs made in developed countries, at least 25 per cent of the materials come from the tropical rain forests of Africa, Asia and Latin America. West Africa abounds in *Physostigma venenosum*, used as the material for producing physostigmine, *Cinchona spp.*, used as the material for producing quinine, *Catharanthus rosea*, used as the material for producing vincristine and vinblastine, and *Strophanthus kombe*, used as the material for producing strophanthin.

West Africa has a land area of 6,500,000 square kilometres with a climate that supports the growth of abundant and diverse plant and animal life. Its wealth of medicinal plants provides a very good basis for industrial production.

B. Broad markets

Industrial products must have a broad market, including domestic and overseas markets. About 90 per cent of the population of West Africa lives in rural areas and depends mainly on traditional medicine. As a result, traditional herbal medicines, especially those for the treatment of common diseases, usually have broad markets, and the industrial production of such medicines is very important for meeting health-care needs.

Some products, such as physostigmine, vincristine, vinblastine and strophanthin have strong international markets. The industrial production of such compounds will be of great benefit to developing countries seeking to increase their foreign currency earnings.

C. Technology

Processing technologies are essential for industrial production of plant-based pharmaceuticals. Processing technologies can be obtained in the following ways:

(a) Technologies of extraction and preparation can be obtained by research and development in developing countries;

(b) The technologies can also be obtained through international cooperation, especially UNIDO technical assistance. UNIDO has been making a valuable contribution to Africa, Asia and Latin America in the industrial utilization of medicinal and aromatic plants, including personnel training, technology transfer, selection and installation of equipment, determination of processing technologies and quality assurance;

(c) Processing technologies can be introduced from abroad (technology transfer).

Sometimes it is necessary to introduce advanced processing technologies from other countries to develop the national phytopharmaceutical industry. In this respect, UNIDO can also help with evaluating the advantages and feasibilities of the imported technologies.

D. Qualified personnel

Qualified personnel is required for the industrial production of plant-based medicines, including engineers, technologists, pharmacists, analysts, pharmacologists, toxicologists and market development experts. Such personnel could be trained by developing countries themselves, or through various forms of international cooperation, such as domestic training by international experts sent by UNIDO. Personnel could also be sent abroad for training by arrangement with UNIDO. The National Institute for Pharmaceutical Research and Development in Nigeria, the Anadolu University Medicinal Plants Research Center in Turkey and the Natural Pharmaceutical Engineering and Technology Research Center of the State Pharmaceutical Administration of China could make a contribution to the training of qualified personnel.

E. Processing equipment and analytical apparatus

The processing equipment and analytical apparatus required for the industrial production of plant medicine and preparations include extracting, filtering, concentrating and drying equipment, as well as tablet, capsule and packing machines. Analytical instruments for high-pressure liquid chromatography (HPLC) and thin-layer chromatography (TLC), including TLC scanners, are needed to control the quality of medicines.

II. SELECTION OF PLANTS AND PREPROCESSING

A. Selection of plants

Medicinal plants that meet the following requirements can be considered for industrial production:

- (a) The selected plant should be abundantly available or capable of large-scale cultivation locally to supply sufficient materials for industrial production;
- (b) The medicinal plants selected should have definite therapeutic effects, or have been locally and widely used as traditional medicines and well received by local doctors, practitioners and patients, or have special uses, or be suitable for export. For example, *Strophanthus* is used to produce strophanthin, which, together with its preparations, can be exported;
- (c) The product made with the selected plants should have solid and wide domestic and foreign markets;
- (d) The technologies used should be simple, and the investment in equipment and energy consumption, as well as the production cost, should be low;
- (e) As far as possible, plants that can be comprehensively utilized should be selected. Multi-purpose use of the plant can increase its social and economic benefits. For example, in the case of the orange peel, its volatile oil extracted by steam distillation can be used in food, beverages, candy, flavouring and cosmetics; the residue can be used for extracting edible pigments; hesperidin can be extracted as pharmaceutical material; and pectine can be extracted for use in the food industry. The processing procedure is shown in figure 1 below;^{1, 2}
- (f) Sufficient amounts of the solvents used in the processing of the plants should be locally supplied;
- (g) Industrial production based on the medicinal plant should not pollute the environment.

Medicinal plants that meet the above-mentioned requirements can be selected for industrial production. The methods of selection are outlined below.

Survey of medicinal plant resources. Botanists, taxonomists and pharmacognosists should be organized to survey the local medicinal plant resources, including plant species, so as to assess the possibility of their industrial utilization.

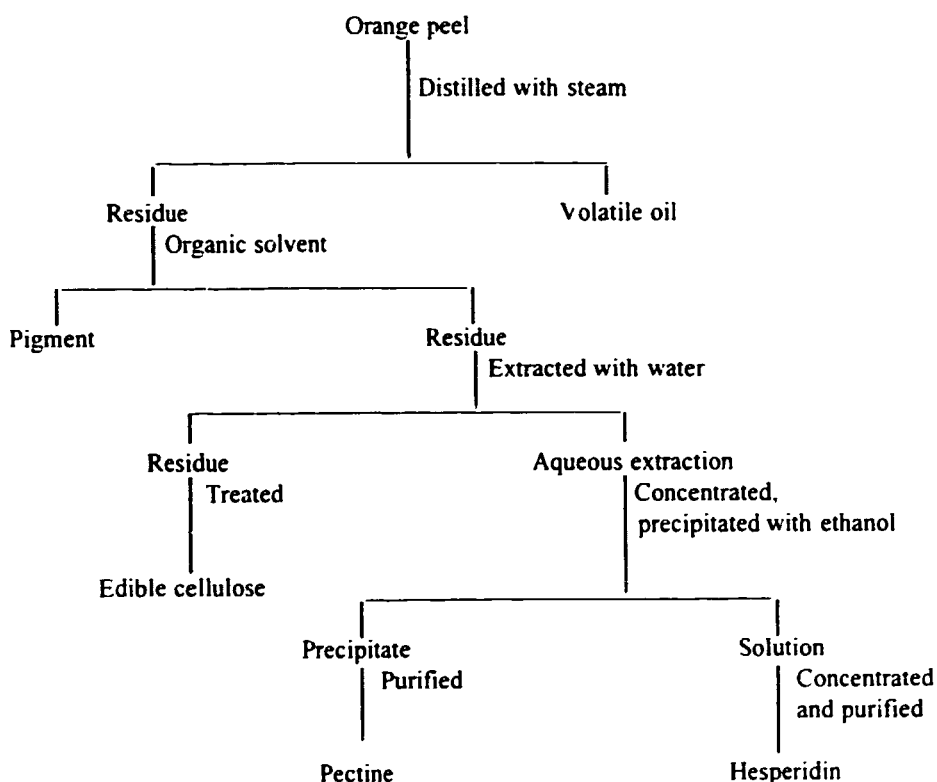
Survey of traditional practice. Interview folk practitioners, go to the countryside and mountain areas to investigate traditional medicines and prescriptions used in the treatment of commonly encountered diseases with demonstrated therapeutic effects, and find out whether the plant resources are abundant, and whether the plant can be cultivated and is suitable for industrial production.

Survey of medicinal plant exports. Through the relevant government departments, find out about the species and amount of the medicinal plants available for export, the countries to which they are exported, their uses, the technologies used in processing the plants abroad and the possibility of local processing of medicinal plants for export.

Literature search. A search of the relevant literature, including magazines, books, patents and monographs, will shed light on the state of industrial production of medicinal plants in some countries. The same species or genus of plants in one country may be industrially processed in other countries. Search the

literature for effective constituents of the medicinal plants, pharmacodynamics data, toxicity findings, extraction technologies, preparation methods etc. It may also be possible to acquire information through a database or data bank, for example, that of the Anadolu University Medicinal Plants Research Center, which receives UNIDO technical cooperation, is able to retrieve information instantly through its on-line access to major international data banks, and has been developing two data banks in English on plants in Turkey. The data bank developed at the Chinese University of Hong Kong can also provide a great deal of information on plant-based medicines.

Figure I. Comprehensive utilization of the orange peel



B. Preprocessing of medicinal plants

Procedures used in preprocessing medicinal plants include collecting, washing, cutting, drying and grinding.

Rational collection of medicinal plants. Plans for the collection of medicinal plants should be worked out on the basis of the plant resources available, their distribution, the period of growth and regeneration and the scale of industrial production. Collecting can be carried out by stages and by tracts, for example, a certain amount of the plant can be collected in area A one year, but in area B the next year. During collecting, a certain amount of the plant must be preserved for regeneration. Planned collecting will be beneficial for the protection and regeneration of the plant resources and for the protection of the ecosystem.

Attention should be paid to the time for collecting and harvesting. Based on the determination of seasonal changes of the active constituents of the plant, the optimum collecting and harvesting period can

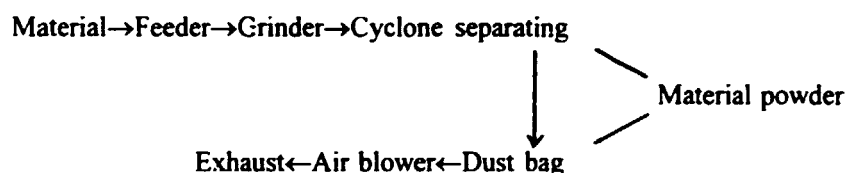
be decided, and collecting should be carried out at the time when the yield and the active constituents are at their peak.

Sifting of materials. The main purpose of sifting is to pick out foreign plants and non-medicinal parts of the plant.

Washing, cutting and drying. The steps in the process are as follows: medicinal materials are washed, cut, dried and then transferred to the storehouse for use in the next procedure. Plant raw materials are washed by using different types of washers, including roller, vibrating and ultrasonic washing machines. The models of cutting mills usually used include rotary disk, reciprocating, chip cutter and cylinder cutter mills. The drying equipment usually used includes infrared, microwave and vibration dryers and drying chambers (for example, electric- or solar-energy-operated).

Grinding. Roller mills and hammer mills are in common use. The roller mill is mostly used for seeds and extracts. The hammer mill is used for further reduction of products preground in a cutting mill. However, materials containing volatile oil may not be ground by a hammer mill.

In order to meet good-manufacturing-practice requirements, a grinder should be used in combination with material-feeding, powder-sieving, dust-eliminating equipment to avoid producing dust. The flow process is as follows:



III. PROCESSING METHODS

A. Unit operations in processing

1. *Solid-liquid extraction*

Solid-liquid extraction is the operation by which the solid powder or slices of plant materials are extracted with water, alcohol or other organic solvents to obtain extracts containing effective fractions of constituents. Extraction efficiency will be affected by the following factors: granule sizes of material powder; extraction temperature; extraction time; operation techniques for extracting; and selection of solvents for extracting.

The selection of solvents should meet the following criteria:

- (a) Good selectivity;
- (b) High solvent capability *vis-à-vis* extracted constituents;
- (c) Stability, whereby the solvent will not be destructive of the desired constituents;
- (d) Low prices and ready availability;
- (e) No toxicity to humans, safety and reliability.

Water and ethanol are commonly used for extraction.

The equipment and methods used for solid-liquid extraction are described below.

Percolator. Plant material powder is packed into a percolator, then soaked and percolated with solvents. Various percolators, such as rotor pulse, gravity, automatic and belt percolators, can be selected for the extraction operation.

Multifunction extractor. It would be worthwhile to promote the more widespread use of multifunction extractors for extracting medicinal plants. Both water and ethanol can be used as extracting solvents. Multifunction extractors have various capacities, such as 0.18, 0.5, 1, 3 and 5 cubic metres. Equipment used in combination with an extractor includes condensers, coolers, filters, oil-water separators, buffers and circulating pumps. Combining an extractor with the above-mentioned equipment would be suitable for various extraction technologies. Options for a polyvalent pilot plant unit for the distillation and extraction of medicinal and aromatic plants, designed by UNIDO, provide valuable reference models.³

Supercritical fluid extraction. Supercritical fluid extraction methods developed in recent years are very promising. Among them, supercritical CO₂ fluid extraction is most commonly used. The critical temperature of CO₂ is 31.1 °C, its critical pressure is 7.38 x 10³ kilopascals (kPa). Under its critical temperature and pressure, the density of CO₂ is similar to that of a liquid, its viscosity is two or three times that of a gas, its diffusion coefficient is a hundred times higher than that of a liquid, and its dielectric constant will rise with the increase in pressure. The above-mentioned properties facilitate extraction operations. The method shows the following advantages:

- (a) It is especially suitable for extracting lipophilic substances, such as perilla-seed oil, vitamin E, limonene, orange-peel oil, clove oil and caffeine from coffee or tea. Cold-press and steam distillation methods were usually used in the preparation of orange-peel oil. Now, by means of supercritical CO₂ fluid

extraction, the oil can be obtained with a higher yield and quality than in the past.⁴ Supercritical CO₂ fluid extraction used for extracting caffeine from coffee can reduce the content of caffeine in coffee from between 0.7 and 3 per cent to below 0.02 per cent. The technology has been used by industries in Germany;⁵

(b) It is suitable for extracting heat-unstable substances, since heating is not required in the extraction process. CO₂ can be removed easily from any solute upon reduced pressure.

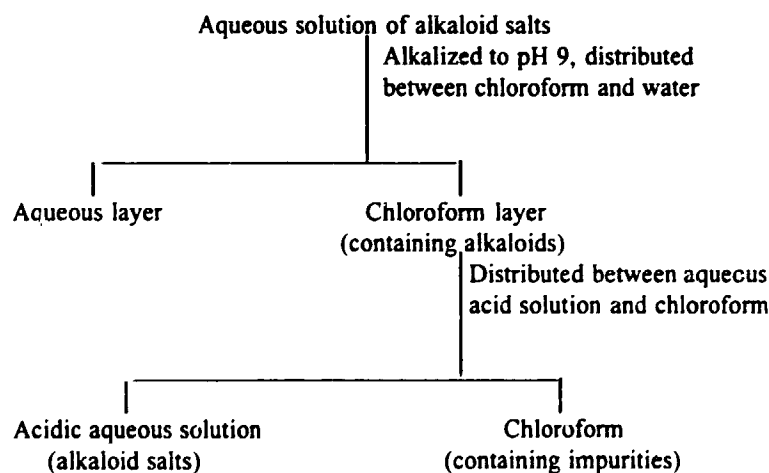
The operating pressure required for this method is usually from 3.00×10^3 to 3.00×10^4 kPa. High-pressure equipment is therefore essential for supercritical fluid extraction.

Ultrasonic extractor. Extraction efficiency can be greatly increased by fixing an ultrasonic wave generator in an extractor. Extraction time will be shortened, and the average rate of recovery can reach 91.3 per cent by means of ultrasonic extraction.

2. Liquid-liquid extraction

Liquid-liquid extraction, which is based on the differences between the partition coefficients of substances in water and in water-immiscible organic solvents, is an effective means of extracting effective constituents. For example, most alkaloids are soluble in organic solvents, such as chloroform, and insoluble in water. The solubility of alkaloid salts, however, is different from that of alkaloids. Liquid-liquid extraction can thus be used in the isolation and purification of alkaloids. The procedure is shown in figure II.

Figure II. Isolation and purification of alkaloids with liquid-liquid extraction



Liquid-liquid extraction generally involves the use of an extraction tower and a centrifugal extractor.

The heavy phase solvent flows from the top of the tower to the bottom, the light phase solvent flows from the bottom to the top. The two phase solvents are mixed in the tower to carry out the extraction operation. Then the light phase solvent flows out of the top and the heavy phase solvent flows out of the bottom of the tower.

3. Distillation

Steam distillation is generally used for the preparation of volatile oil. Medicinal materials are put into an extractor, then distilled with steam to give volatile oil after the oil and water are separated.

4. Solid-liquid separation

Solid-liquid separation is the operation of separating solids from liquid in the course of extraction. The methods of precipitating, centrifugalizing, filtrating and pressing are often applied. The centrifuge, the pipe ultracentrifuge, filtrators, vacuum filtrators and plate press filters are commonly used equipment.

5. Evaporation

Since many constituents in medicinal plants are easily hydrolysed or decomposed, equipment used in evaporation must be suitable for evaporating or concentrating at a low temperature and in the shortest possible time.

Equipment for vacuum evaporation is generally used, including a vacuum spherical evaporator and a vacuum thin-layer evaporator.

The spherical evaporator consists of a lower hemispherical heating surface.

6. Drying

The following types of dryers are most commonly used:

- (a) Tray drying cabinet operating at atmospheric pressure or by a vacuum process;
- (b) Spray dryer operating at atmospheric pressure;
- (c) Drum (roller) dryer operating at atmospheric pressure or under reduced pressure.

The choice of the dryer is determined by the properties of the products, mainly viscosity, hygroscopicity and heat sensitivity. In the case of aqueous extraction, a tray dryer or drum dryer could be selected. A spray dryer is generally used for processing a single product in large quantities.

B. Technological methods

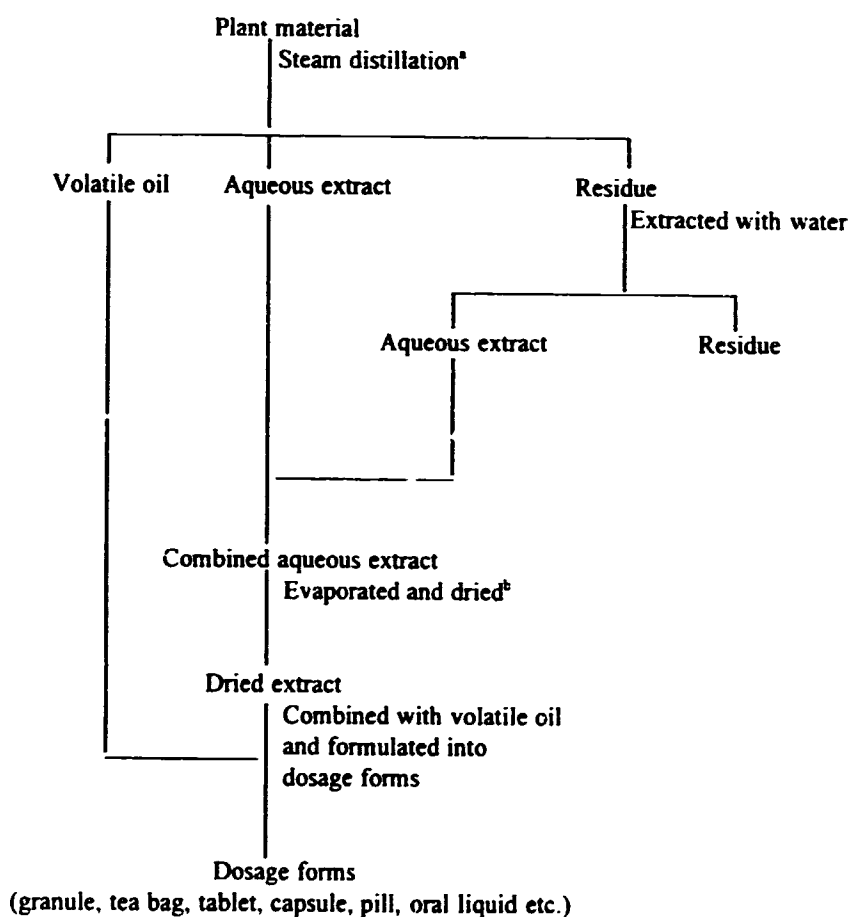
Six technological methods are commonly used for the extraction of medicinal plants.

1. Aqueous extraction

Aqueous extraction is commonly used for industrial processing of medicinal plants, because most active plant constituents, such as glycosides and alkaloid salts, are water-soluble. Lipophilic constituents can also be forced into an aqueous extract when plant materials are extracted with hot water. Solubility promoting interaction among complex constituents may be an important factor in making water-insoluble constituents enter an aqueous extract. For example, saponin often helps lipophilic constituents to dissolve in water. The technological scheme of aqueous extraction is shown in figure III.

Most compound traditional medicines could be produced by this method. For example, over 200 "Kanpohozai" produced in Japan and more than 50 per cent of compound traditional Chinese medicines manufactured in China are processed by using the aqueous extraction.

Figure III. Industrial processing of aqueous extraction of medicinal plants

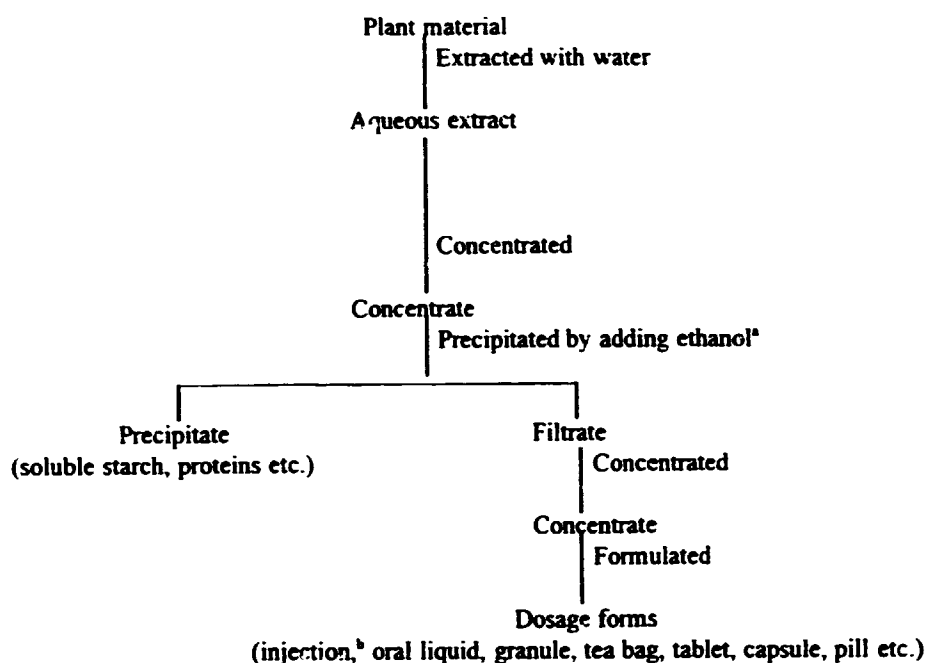


*Steam distillation may be omitted if there is no volatile oil in the materials.

*Production of oral liquid does not require drying the extract.

The so-called water-alcohol method is a modified form of aqueous extraction. The key point of this method is to precipitate a large quantity of impurities by adding an adequate amount of ethanol into the concentrate of aqueous extract as shown in figure IV.

Figure IV. Extraction of medicinal plants by the water-alcohol method



^aThe amount of ethanol added depends on the quantity of impurities to be removed from the concentrate. The larger the amount of ethanol added, the greater the quantity of impurities removed. Generally, the alcohol is added until the content of ethanol in the concentrate reaches 60 per cent.

^bIn the case of injections, precipitation with alcohol is performed two or three times for further removal of impurities.

The main advantages of the water-alcohol method are as follows:

(a) The dosage is greatly reduced as compared with the simple aqueous method, because a large quantity of impurities is removed from the extract;

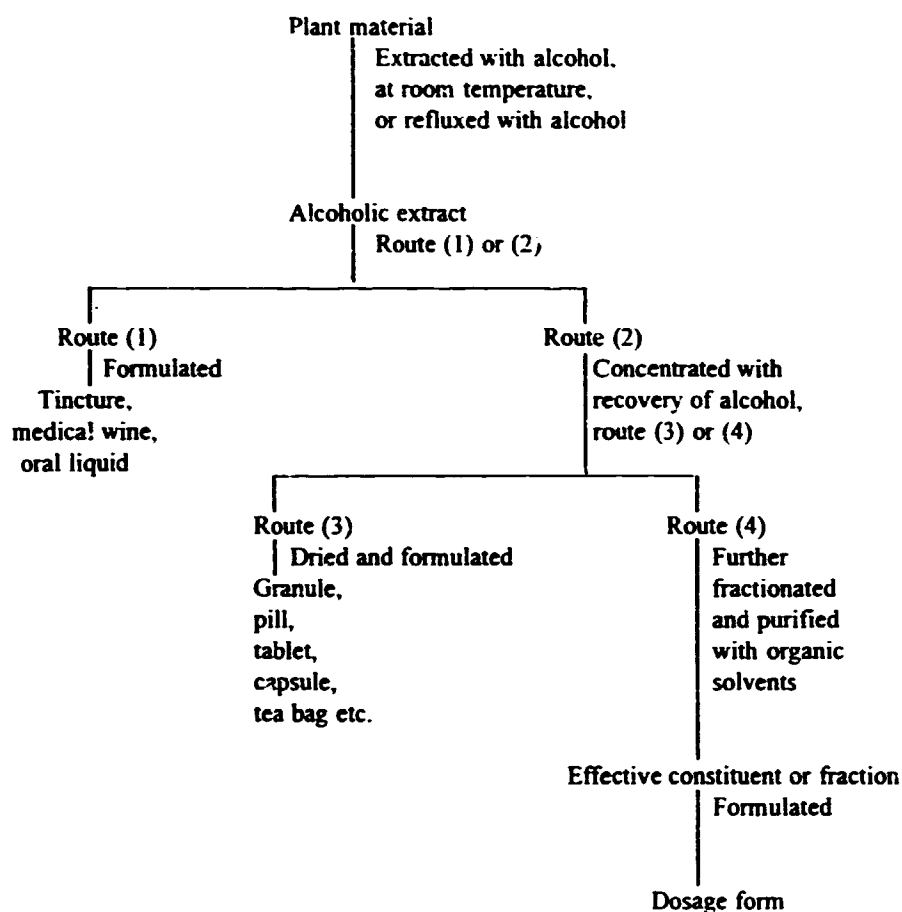
(b) Injections can be produced by this method. Many injections produced in the Democratic People's Republic of Korea and in China were processed by this method.

The disadvantage of the method is the partial loss of some effective constituents that are also precipitated by alcohol. The method cannot be applied if the effective constituents are polysaccharides, peptides, enzymes and proteins.

2. Alcoholic extraction

Since both lipophilic and lipophobic components can dissolve in alcohols such as ethanol, the method of alcoholic extraction is also commonly used in the industrial processing of medicinal plants (see figure V).

Figure V. Industrial processing by alcoholic extraction of medicinal plants



3. Extraction with organic solvents

In addition to methanol and ethanol, other organic solvents, such as petroleum ether, benzene, toluene, chloroform, methylene chloride, ethyl acetate, butanol and acetone are used for industrial extraction when effective pure constituents or effective fractions are required for formulating pharmaceuticals.

For some constituents, the extraction of plant materials can be carried out directly by using organic solvents. For example, arteannuin (artemisinin, qinghaosu), an antimalarial constituent, is prepared by extraction of *Artemisia annua* leaves with petroleum ether.⁶ Vinblastine and vincristine, the anti-cancer components, can be prepared industrially by extraction of *Catharanthus roseus* with benzene, followed by further separation and Al_2O_3 chromatography.

An alternative method is to separate effective constituents or fractions from aqueous extracts of plant material by using water-immiscible organic solvents.

Digoxin, a cardiac glycoside, was produced industrially by the following method. The leaves of *Digitalis lanata Ehrh.* were fermented at 45 °C for 20 hours, then extracted with 80 per cent ethanol. The alcoholic extract was concentrated to recover most of the ethanol. After filtration, the concentrate was extracted with chloroform, the $CHCl_3$ layer was concentrated to recover $CHCl_3$. The residue was first recrystallized with acetone, then with 70 per cent ethanol, to give digoxin.

4. Acid and alkali method

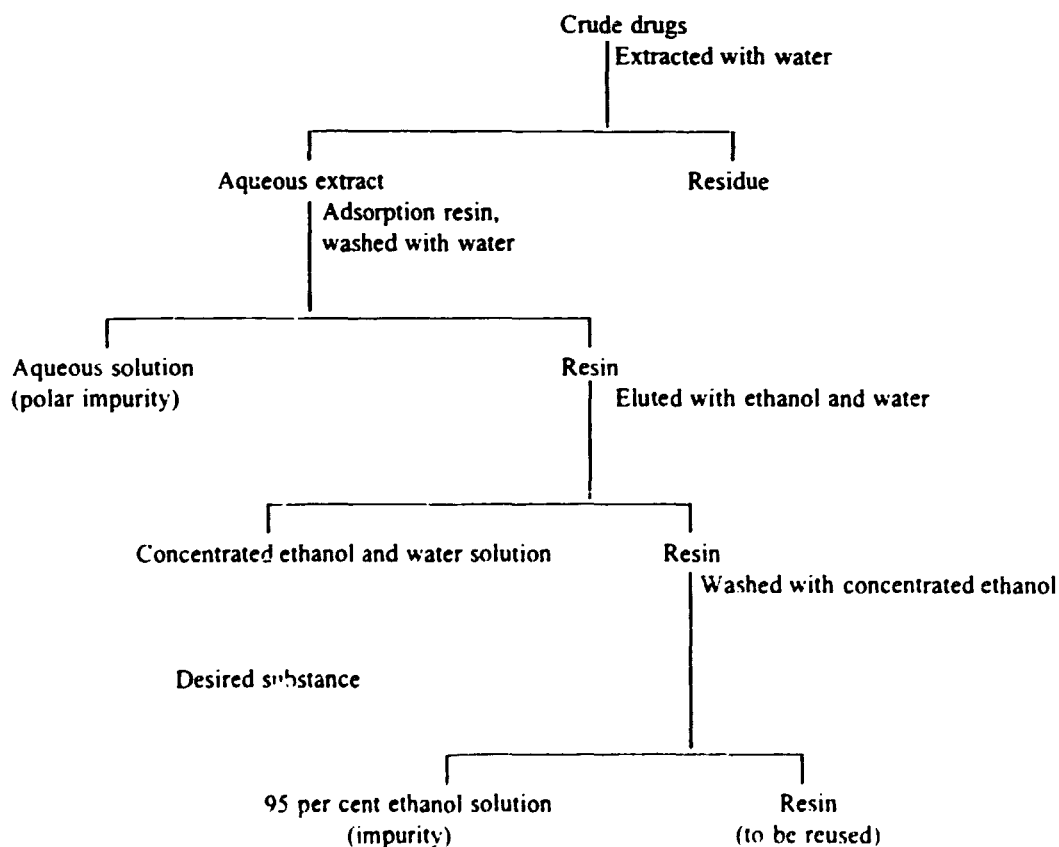
The acid and alkali method is generally used for production of organic acids or alkaloids from plant materials. Since most organic acids are soluble in alkaline water and insoluble in acidic water, the organic acids and related compounds can be produced by extraction of plant materials with alkaline water. The alkaline aqueous extract is then acidified to precipitate the organic acids. For example, glycyrrhizic acid is produced industrially from *Glycyrrhiza uralensis* Fisch. The powder of the roots and rhizomes is percolated with 0.5 per cent ammonium water. The alkaline aqueous percolate is then adjusted to pH 3.0. The precipitate formed is washed with water and dried. The dried extract is refluxed with alcohol to produce an alcoholic liquid that is neutralized to pH 7.5 with NH_3 gas in order to obtain a precipitate (triammonium of glycyrrhizic acid). Some flavonoids can also be prepared by using the acid and alkali method. For example, rutin can be prepared from *Sophora japonicus* as follows. The flower bud is extracted with $\text{Ca}(\text{OH})_2 \cdot \text{H}_2\text{O}$. The alkaline aqueous liquid is adjusted to pH 4 and allowed to stand for 24 hours to produce a precipitate that is recrystallized with alcohol to give rutin.

5. Resin method

Resins, including ion-exchange resins and adsorption resins, are widely used for the industrial processing of medicinal plants, with the following obvious advantages: no organic solvents are required other than ethanol; lower energy consumption; lower production costs; higher purity, easier formulation and quality control; and higher stability.

Figure VI shows the steps in the processing of medicinal plants with adsorption resins.

Figure VI. Processing of medicinal plants by the resin method



Some pure compounds, such as ginsenoside-Re, many effective fractions, such as standardized extracts of *Ginkgo biloba*, and especially compound traditional medicines can be processed by this method.

6. Chromatography

In some cases, chromatography is used to isolate pure compounds for manufacturing preparations. Alumina and silica gel are most commonly used in chromatographic separation.

In practice, the methods described above are usually combined with others and may be applied together with the chromatographic method in the manufacture of certain products. For example, Podophyllin, an anti-cancer principle, is produced from *Diephyllia sinensis L.* as follows. The rhizome powder of the plant is refluxed with 95 per cent ethanol to give an alcoholic extract which is then concentrated and dried. The residue is dissolved into chloroform and chromatographed on an alumina column with benzene-ethanol (1:1) as an eluent, providing podophyllin which is made into tincture for the effective treatment of fig wart (*verruca acuminata*).⁷

IV. APPROPRIATE TECHNOLOGIES FOR DEVELOPING COUNTRIES

Appropriate technologies for developing countries should offer the following advantages:

- (a) Simpler operating procedures;
- (b) Lower investment requirements for industrial production;
- (c) No special solvents needed, other than water and alcohols;
- (d) Lower energy consumption and production costs;
- (e) Stable dosage forms;
- (f) Quality control.

To meet the above-mentioned requirements, the technologies applied in aqueous extraction, the water-alcohol method, alcoholic extraction and the resin method are recommended to developing countries for the industrial utilization of medicinal plants. Most dosage forms, such as pills, extract powder, tea bags, tablets and capsules, can be formulated by using the extracts prepared by those methods.

In recent years, standardized extracts have been emphasized in the production of medicinal preparations. For example, standardized *Ginkgo biloba* extract (GB24) contains 24 per cent of flavonoids and approximately 6 per cent of ginkgolides. Standardized ginseng extract (G115) contains 4 per cent of ginsenosides. It would be better to manufacture the final product with the standardized extract. For example, Tebonin made in Germany and Tanakan made in France were manufactured with GB24, and Ginsana made in Switzerland was manufactured with G115.

The resin method is once more strongly recommended for use in developing countries. In most cases, this method would be the first and best choice for the industrial processing of plant-based pharmaceuticals. Many organic solvents can be replaced by the resin method when pure compounds or effective fractions are produced. Lower cost and no pollution are additional advantages of the resin method.

V. DOSAGE FORM AND TESTS REQUIRED

The extracts obtained from medicinal plants are usually formulated into powder, granules, tablets, capsules, pills, mixtures, tinctures etc. for clinical use.

A. Powder and granules

Powder is the simplest dosage form. Methods of production of powders and granules are outlined below.

The crude drug is pulverized into fine powder, then sterilized and packed into bags.

The crude drug is extracted with boiling water, and the aqueous liquid obtained is vacuum-concentrated and dried to produce an extract powder that is granulated and finally packed into aluminium-plastic bags. The crude drug, if it contains volatile oil should be steam-distilled to extract the volatile oil which is sprayed on the granules before packing.

Dried extracts obtained by the alcohol, the acid-alkali or the resin methods can also be granulated and divided into bags.

Tests of homogeneity, moisture (<9.0 per cent), weight difference and sanitary condition are especially required for powder.

Tests of size, moisture, dissolvability, hardness and weight difference are especially required for granules.

B. Tablets

Methods of production of tablets are outlined below.

Granules prepared by the methods described above can be directly formulated into tablets.

Powder of crude drugs can be mixed with a binding agent, granulated and formulated into tablets.

In the case of compound traditional medicines, a part of the crude drug content, which is rich in starch, can be pulverized into a fine powder. The remaining part is steam-distilled to obtain volatile oil. The aqueous extract is processed to obtain concentrated extract. The fine powder and the concentrated extract are then mixed and granulated. Finally, the volatile oil is sprayed on the granules which are formulated into tablets.

Tests of weight difference, disintegration time limit (30 minutes for tablets of crude drug powder; 60 minutes for tablets of extract) and sanitary condition are required for tablets.

C. Capsules

Capsules are produced by the methods outlined below.

The powder of crude drugs can be directly packed into capsules such as American ginseng capsules.

The granules prepared by the methods described above in the sections on granules and tablets can be made directly into capsules.

In addition to hard capsules, soft capsules are recommended because of their better stability. In the case of lipophilic extracts, such as extracts obtained by alcoholic extraction, the soft capsule is a good choice.

Tests of moisture content (<9.0 per cent), weight difference, disintegration time limit and sanitary condition are required for capsules.

D. Pills

Pills can be formulated as outlined below.

Honey pills. Sterilized fine powder of crude drugs is mixed with boiled honey and formulated into pills by pill-forming machine.

Common pills. Sterilized powder of crude drugs is mixed with a binder and formulated into pills which are finally dried and packed.

Extract pills. Crude drugs are extracted by using appropriate methods, such as the aqueous, alcoholic or resin methods, and the extract is then formulated into pills.

In some cases, a part of the crude drugs is ground into powder, and the remaining part is extracted. The powder and the extract are then mixed and formulated into pills.

Tests of moisture content (<15.0 per cent for honey pills; <9.0 per cent for other pills), weight difference (9 grams \pm 5 per cent; 0.1 gram \pm 10 per cent) and dissolution time limit are required for pills.

E. Mixtures

Mixtures can be produced by extracting crude drugs with boiling water and simultaneously collecting the volatile oil. The aqueous liquid is then concentrated and mixed with the volatile oil. Finally, the mixture should be sterilized and bottled.

Tests of relative density, pH value and weight difference are required for mixtures.

F. Syrup

Syrup can be made as described below.

An aqueous extract of crude drugs is concentrated and filtered to produce a concentrate which is mixed with a simple syrup.

Tests of relative density, weight difference and sanitary condition are required for syrups.

G. Tinctures

Tinctures can be made as described below.

Percolation. Crude drugs are pulverized and then percolated with aqueous ethanol at room temperature to produce tinctures.

Extraction. Crude drugs are pulverized and repeatedly extracted with aqueous ethanol. The combined extract is adjusted to the appropriate volume according to standard specifications.

Tests of ethanol content and precipitate are required for tinctures.

The common tests for all dosage forms are as follows:

- (a) Identification, for which colour reactions and TLC are normally used;
- (b) Quantitative determination of major or effective constituents.

VI. QUALITY ASSURANCE

Quality assurance and control are essential for ensuring the safety and efficacy of plant medicines.

A. Organizing and carrying out quality assurance

Quality assurance should be organized and carried out in accordance with the requirements of good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP).

B. Standardization

Plant formulations and their raw materials, intermediates should be standardized. A standard specification usually includes the following items:

- (a) *Name*. The names of crude drugs, extracts, preparations etc.;
- (b) *Botanic origin*. Latin name of the plant and the part of the plant used, for example, the root or the flower;
- (c) *Appearance*. Colour, odour, taste etc.;
- (d) *Identification*. Macroscopic and microscopic assays and physical, chemical and chromatographic identification.
- (e) *Assays*. Impurity content, moisture, ash, weight, relative density, optical rotation, pH values, chloride tests, heavy metals, arsenic tests, agrochemical residues, loss on drying, residue on ignition, alcohol content, microbiological assay etc.;
- (f) *Quantitative determination*. The quantity of major or effective constituents should be determined by using chromatographic, spectrophotometric or classic methods.

C. Quality control in the processing of plant medicines

Quality should be carefully controlled in the processing of plant medicines from raw materials to finished products.

Raw materials used for production should be identified and assayed. Only raw materials whose analytical results are consistent with the standard specification can be used for processing.

Intermediates obtained in processing should also be assayed. The amount of extract should be determined and effective or major constituents of the extract should be adjusted to provide a standardized extract which is then formulated into dosage form.

The finished products, that is, different plant-based medicines formulated into different dosage forms, should be thoroughly assayed, and the quality and quantity of their constituents determined. All tests required for corresponding dosage forms should be performed.

D. Quality control methods

The four main quality control methods are described below.

1. Classic methods

Classic methods have hitherto played an important role in quality control of plant medicines. For example, the dragendorff reaction can be used for detection of alkaloids in crude drugs and preparations, and titration can be used for determining the quantity of total alkaloids. Most of the methods of determining ash, moisture etc. are classic methods.

2. Chromatographic methods

Thin layer chromatography. TLC is the most commonly used method for quality control of natural medicines. It can be used for identification of pure effective constituents, crude drugs, intermediates, standardized extracts and finished products by comparison of TLC behaviour of samples tested with that of authentic samples. TLC can also be used for determining the quantity of major or effective constituents in raw materials, intermediates and final products. The components of the sample are first separated on the TLC plate, and the zone containing effective or major constituents is stripped off and eluted with solvents. The eluate is determined by a suitable method, such as the spectrophotometric method.

TLC scanning is a powerful means of determining the quantity of natural medicines, including raw materials, intermediates, finished products and traditional medicines. The obvious advantage of TLC scanning is that, compared with the HPLC method, it provides a great deal of data in a shorter time. The major disadvantage of TLC scanning is the bigger analysis error as compared to HPLC.

Gas liquid chromatography. Gas liquid chromatography (GC) is the most efficient chromatographic technique for separating volatile oils and mixtures that can be vaporized by heating.

High-pressure liquid chromatography. HPLC is a very important tool for analysing most natural compounds. In addition to normal phase columns, reverse phase columns are widely used in HPLC. A series of chiral columns can be used for separation of chiral substances.

3. Spectroscopic methods

Ultraviolet and infrared spectroscopy, mass spectrometry and nuclear magnetic resonance (NMR) techniques, including ^1H , ^{13}C and advanced two-dimensional NMR methods, are widely used for analysing natural substances as described below.

Known substances, including pure compounds, crude drugs, intermediates and finished products, can be identified by comparison of spectroscopic characters of tested samples with those of authentic samples.

Structures of new compounds isolated from medicinal plants can be elucidated by using ultraviolet, infrared, mass spectrometry and NMR spectroscopic methods. Most new compounds with molecular weight less than 2,000 can be structurally elucidated by using these spectral methods.

Ultraviolet and visual spectrophotometrics are widely used for determining the quantity of major or effective constituents and effective fractions, including total flavonoids, total saponins etc. Mass, NMR and infrared spectroscopic techniques can also be occasionally used for quantitative determination.

4. Coupling techniques

Coupling techniques require instrumental on-line couplings of chromatographic separation devices to spectrometers. The advantage of such techniques is that complex mixtures can be analysed rapidly by spectral interpretation of chromatographically separated components. The main coupling instruments are as follows:

- (a) Gas chromatograph and mass spectrometer coupling instrument for analysing volatile substances;
- (b) Gas chromatograph and ultraviolet spectrophotometer coupling instrument for analysing volatile substances;
- (c) Gas chromatograph and Fourier transform infrared spectrometer coupling instrument for analysing volatile oil;
- (d) Gas chromatograph and atomic emission spectrometer coupling instrument, based on the coupling of a capillary GC with an atomic emission spectrometer. By means of this coupling, any element in a compound that can be separated by GC can be selectively detected, providing valuable information on the elemental composition of the individual components of a mixture;
- (e) High-pressure liquid chromatograph and ultraviolet spectrometer coupling instrument, which is increasingly used to analyse natural medicines, including compound traditional medicines;
- (f) High-pressure liquid chromatograph and infrared spectrometer coupling instrument, high-pressure liquid chromatograph and mass spectrometer coupling instrument etc.

VII. RESEARCH AND DEVELOPMENT REQUIREMENTS

Research and development (R&D) play a very important role in the industrial utilization of medicinal plants. The main areas of R&D are described below.

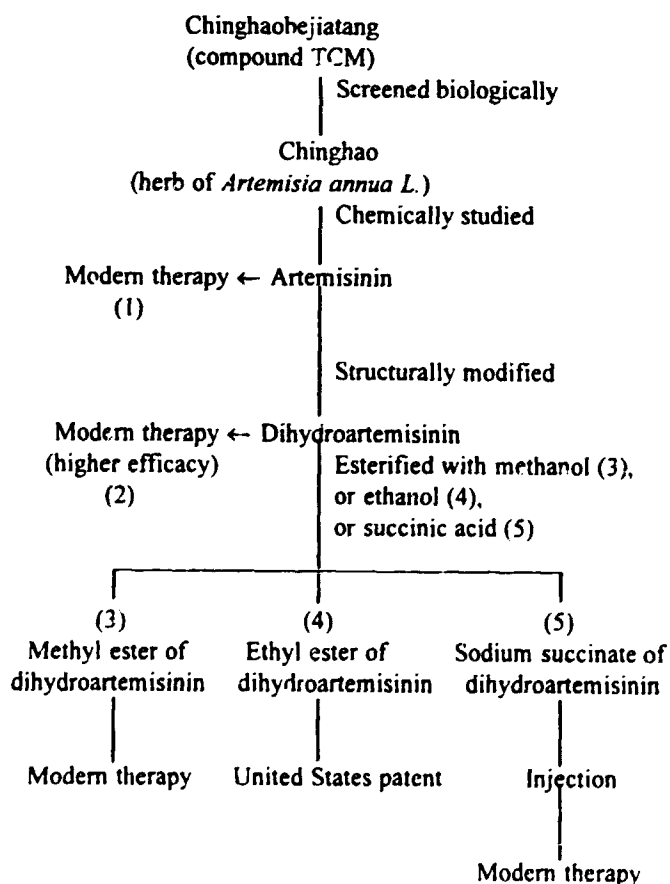
A. Selection of medicinal plants

Plant species of reputed therapeutic value may be selected for industrial processing on the basis of various types of information.

1. Information from traditional medicine

The information for selecting plants could be obtained from traditional medicine, carried through the following sequence of steps, and applied to industrial production: traditional medicine; ethnomedical leads; biological screening and chemical studies; methods for processing and quality control; and industrial production. A typical example is the research on, and development of, artemisinin, an anti-malaria medicine (see figure VII).

Figure VII. Research on, and development of, artemisinin through the application of traditional medicine



2. Information from folk medicines

Folk medicines can sometimes yield very important information. For example, the root-bud of *Agrimonia pilosa* was used for treatment of tapeworm by folk practitioners. Biological screening and chemical studies on it led to the development of a new drug, agrimophol.

3. Information from abroad

Through the international exchange of information and from foreign journals, much information can be obtained about taxol, an anti-cancer drug, and artemisinin. Such information is very important for R&D work on natural resources in developing countries. Plants of the same genus usually contain the same types of compound. Look for plants of a particular genus, such as *taxus* trees containing taxol, in your own country or region. If such plants are found, a phytochemical factory can be established to produce taxol which can be used domestically as well as exported.

B. Ensuring quality and consistency in plant materials

Ensuring the quality and consistency of plant materials requires the following: rational collection and protection of natural resources; research on cultivation; domestication of plants from abroad; and research on optimum harvest periods.

C. Chemical studies

Selected plants are extracted and isolated by solid-liquid and liquid-liquid extraction, followed by the use of chromatography to determine fractions and individual constituents. The separation should be guided by biological activities, thus enabling effective fractions and constituents to be found. The compounds obtained are identified and elucidated on the basis of chemical and spectral analyses. The results of chemical studies will be useful for determining optimum harvest periods, processing technologies, quality assessment measures etc.

D. Biological Studies

Three types of biological studies are usually conducted for R&D work on a new medicine.

1. Pharmacodynamic study

Special study. The conduct of the study depends on the type of medicine involved. The basic principles are as follows:

(a) More than two methods must be used to verify the pharmacological action of the new medicine, and one method must be applied *in vivo*;

(b) The medicine must be administered by different routes and in different doses and the dosage determined according to the verification method used.

General study. To study the nervous system, animal activities and behavioural changes after administration of the medicine must be observed. For the cardiovascular system, the heart rate, electrocardiogram, blood pressure etc. must be observed and recorded. Respiratory frequency and deepness are measured in studying the respiratory system.

Compound preparations. The dominant component of the compound preparation must be compared to the whole compound preparation to determine their synergetic or antagonistic action.

2. Pharmacokinetic study

Absorption. Bioavailability and absorptive rates are analysed.

Distribution. Drug concentration in each organ, including the heart, liver, spleen, lung, kidney, gastrointestinal tract, reproductive organs, adipose tissue, adrenal glands and skeletal muscle, are analysed.

Metabolism. Liver clearance rates are analysed.

Elimination. Kidney clearance rates are analysed.

On the basis of the above-mentioned analyses, a primary mathematical model (including clearance, volume of distribution, elimination rate constant and half-life time) can be constructed to explain the pharmacokinetic behaviour of the medicine.

3. Toxicological study

Acute toxicity. The Bliss method (LD_{50}) is used to study mice over a seven-day period.

Chronic toxicity. To study chronic toxicity, rats and dogs undergo general observation, biochemical examination of blood and bone marrow and pathological examination for three to six months.

Special toxicity. Studies of mutagenicity, carcinogenicity and teratogenicity are required on new compounds that are to be developed into drugs.

E. Developing modern process technology

Process technologies should be designed, screened and optimized at the experimental level according to the physico-chemical properties of effective constituents or fractions.

Optimized process technology should then be expanded through research at a pilot plant to obtain necessary parameters which then can be tested for use in industrial processing.

F. Developing standards of quality assessment and assurance

Methods of quality control of raw materials and intermediate and finished products should be developed according to the physico-chemical properties of effective constituents.

Standard specifications for raw materials, intermediates and finished products should be established.

G. Investigation of new drugs

Investigations leading to the development of new drugs, particularly where remedies are currently unavailable or unsatisfactory, should be undertaken.

H. Clinical trials

Comprehensive clinical trials should be conducted before the marketing of a new drug.

VIII. GOOD MANUFACTURING PRACTICE

The World Health Organization, the European Economic Community, the United States of America and many other countries have published documents on GMP. The standards of GMP are set forth by a recognized body (usually governmental) in regulations, guidelines or advice outlining the minimum requirements for manufacturing quality control and quality assurance in the preparation of drugs, including herbal drugs. The principles of GMP are concerned with the organizational processes and conditions under which medicinal plant production, manufacturing and marketing are planned, performed, recorded and reported.

A. Major aspects of good manufacturing practice

The major aspects of GMP are outlined below.⁸

Personnel. Managers, directors and other staff must have the requisite qualifications and training, and be available in adequate numbers to meet the production requirements. In particular, all production supervisors and quality assurance managers should have a university diploma and wide experience in their field.

Building and equipment. Buildings should be located in clean and healthy surroundings, and equipment should be designed, constructed, adapted and maintained to suit the operations for which they are used.

Processes. Facilities, systems and methods should meet high standards of safety, orderliness and hygiene.

Procedures. The procedures used must be clearly described in master documents and carefully filed.

Products. The procedures followed and the results obtained for each manufacturing batch must be immediately recorded in the notebooks provided for this purpose. Quality control must be carefully conducted throughout the production process, from starting materials to finished products.

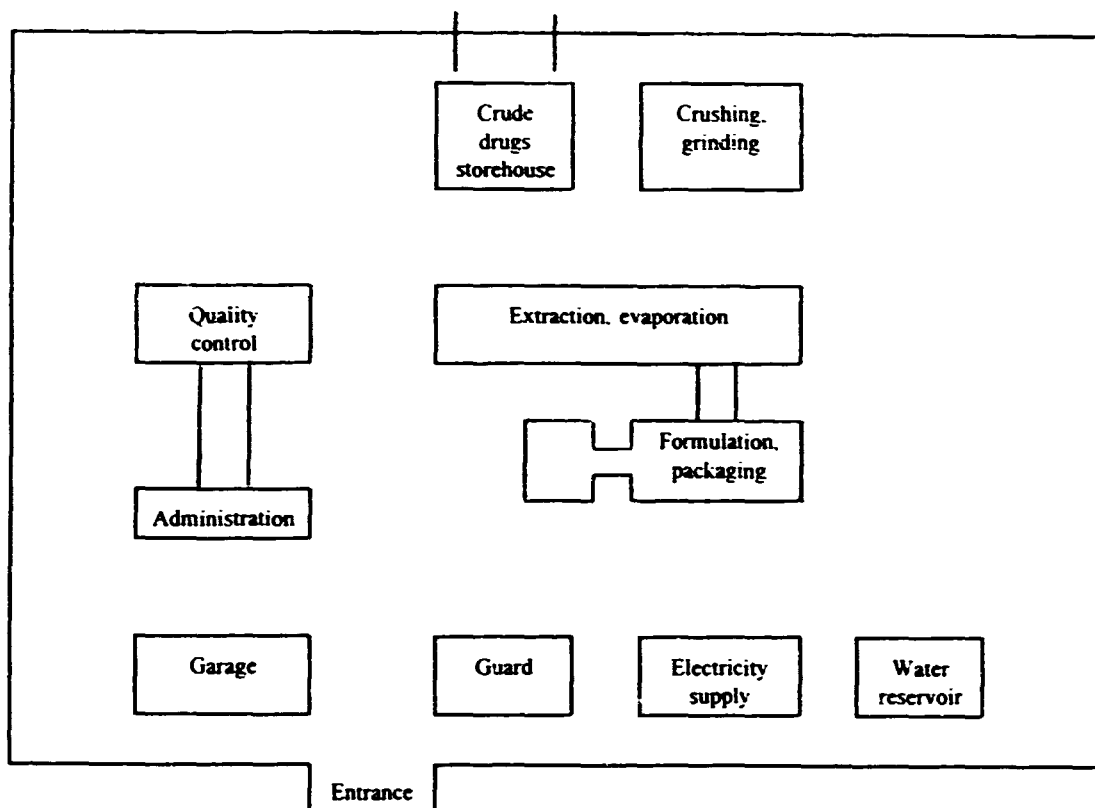
B. Designing and establishing a phytopharmaceutical plant according to the requirements of good manufacturing practice

In designing and establishing a phytopharmaceutical plant, GMP requirements should be observed. Generally, GMP requirements can be divided into two parts, one for software and one for hardware. Software means advanced and reliable processing technology, management and administration systems. Hardware means physical environment, buildings, equipment etc. The hardware requirements that should be considered in designing and establishing a plant for the manufacture of plant-based medicines are outlined below.

1. Entire-body designing

The surroundings should be clean and pollution-free, with a lower content of dust in the air and lawn- and tree-covered plant grounds. The layout of the buildings should be rationally designed according to the technological procedure used. Personnel and substance routes or flows should be separated. The substance flow should be divided into routes for raw materials and for finished products. As an example, the building layout of the Otarō Kampou Company in Japan is shown in figure VIII.

Figure VIII. Building layout of the Otaro Kampou Company



2. Workshop department designing

Workshop departments should be divided into different zones according to cleanliness requirements. There are four levels of cleanliness: A, B, C and D. The workshop for manufacturing preparations that contain no bacteria should reach a corresponding level of cleanliness. For example, preparations that can be finally sterilized should be prepared in a zone with a C level of cleanliness, while preparations that cannot be finally sterilized should be prepared in a zone with A or B levels of cleanliness.

In the pretreatment workshop, crude drugs are cleaned, cut and ground. As the dust and noise in this workshop is heavier, it should be located in a separate building away from extraction and formulation units. It requires air-conditioning, and measures should be taken to prevent noise.

The extraction workshop also requires air-conditioning. Safety measures should be taken in this workshop when organic solvents, such as methanol, ethanol, acetone, benzene and petroleum ether, are used. The workshop may be equipped with a polyfunctional extractor.

The formulation workshop may be divided into two parts. One for liquid formulations, another for solid formulations.

The factory and all workshops should be constructed with the appropriate materials. All quality control measures and production processes should meet GMP requirements.

IX. WASTE DISPOSAL

Waste residues and liquids formed during industrial processing of medicinal plants should be reprocessed into harmless substances or recycled for further use.

A. Waste residues

Industrial processing of medicinal plants will produce a large quantity of plant waste residues that can be used to make by-products such as medicines, animal feeds, fertilizers or fuels.

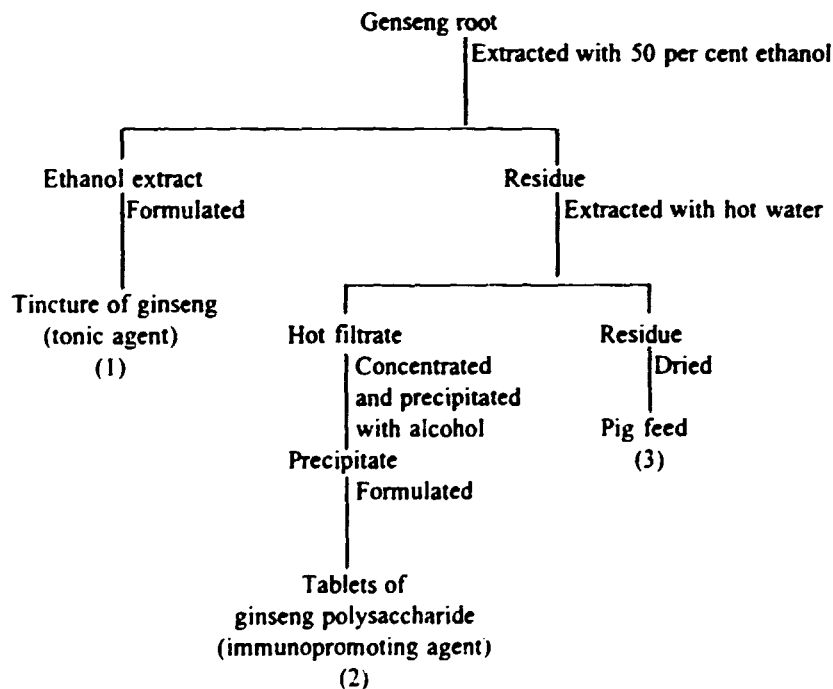
A medicinal plant usually contains many kinds of effective constituents or fractions. Those constituents or fractions could be comprehensively utilized. For example, essential oil and hesperidin can be obtained from orange peel. And from the roots of *Berberis amuresis*, the compounds berberine and berbamine can be isolated and formulated into different drugs.

Some plant residues are rich in proteins and starch, and can be used as animal feed. For example, the ginseng residue formed during extraction of ginsenosides from the roots is used in China as pig feed. Pigs fed with this residue produced 3 per cent more meat than pigs in a control group.

Some waste residues are fibrous, and may be used as raw materials for the paper industry. Many waste residues can be used as fuels, and the fuel ash can be used as fertilizer. An experiment indicated that cultivation of a medicinal plant with the ash of the waste residue of the same plant as fertilizer could increase harvest yield by approximately 5 per cent.

An example of the comprehensive utilization of medicinal plants is shown in figure IX.

Figure IX. Comprehensive utilization of ginseng roots



B. Waste liquid

In the case of pure compounds or purified fractions to be separated, organic solvents other than ethanol are sometimes used. Steps should be taken to prevent air and water pollution caused by these organic solvents, such as benzene and chloroform.

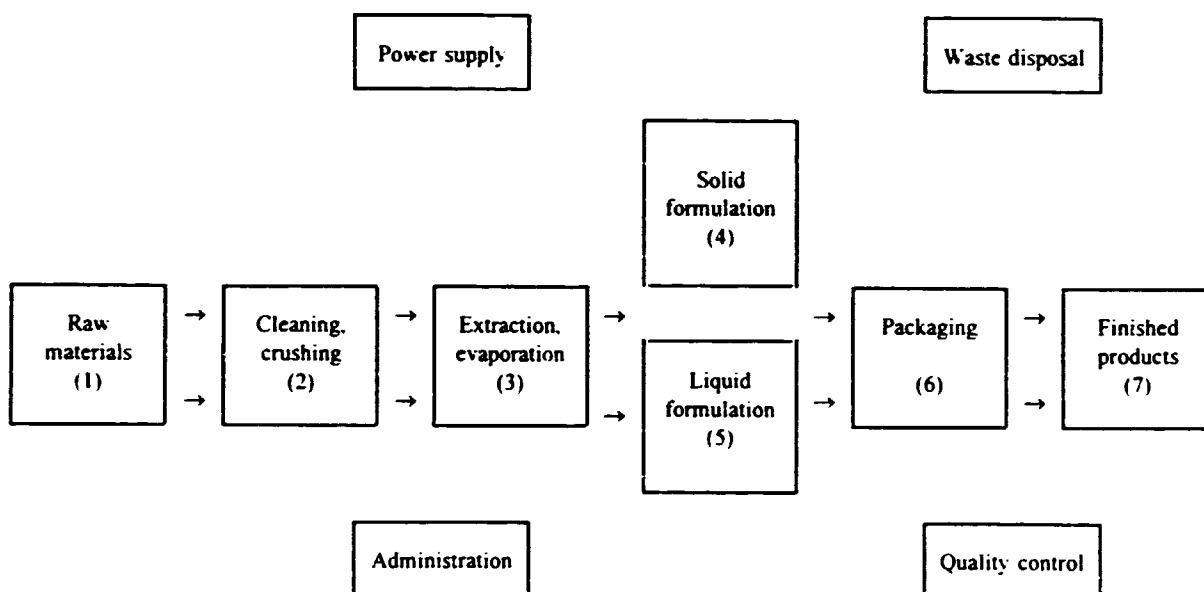
Waste water containing organic solvents can be treated with adsorption resins or paraffin. For example, in the production of ephedrin, the aqueous extract of *Ephedra sinica* is alkalized and extracted with benzene or toluene. The alkaloids are transferred into the layer of organic solvent. The layer of aqueous waste that contains a trace of benzene or toluene is allowed to flow through a paraffin layer that can dissolve benzene or toluene. The paraffin solution is then treated by steam distillation to recover the solvents.

X. SCHEME FOR SMALL-SCALE PROCESSING OF MEDICINAL PLANTS

Since plant-based medicines have played, are playing and will continue to play a very important role in health care in the world, especially in developing countries, industrial processing of medicinal plants with modern technologies and equipment is essential. UNIDO has provided considerable assistance to developing countries in the industrial utilization of medicinal and aromatic plants. With UNIDO technical assistance, many pilot plants have been designed and established for processing plant-based products in developing countries. A UNIDO study of design options for a polyvalent pilot plant unit provides valuable guidance on the small-scale processing of medicinal plants (cf. annexes 1 and 2).³

It is recommended that a small factory be built outside cities in clean surroundings. Departments of the factory can be arranged according to the process diagram shown in figure X.

Figure X. Arrangement of departments in a small-scale factory



The cleaning and crushing department (2) can be divided into the following rooms:

- (a) Selecting room for selecting raw materials and removing impurities;
- (b) Washing room for washing raw materials with water;
- (c) Cutting room for cutting raw materials into the proper size;
- (d) Sterilizing room for drying and sterilizing raw materials or cut raw materials;
- (e) Grinding room for making raw materials and cut raw materials into powder for extraction or formulation.

The procedure occurs in the following sequence: selecting; washing; cutting; drying; sterilizing and grinding.

The extraction and evaporation department is the key unit of a phytopharmaceutical factory. The above-mentioned UNIDO study may be useful for establishing the layout and equipment needed for this department.

The solid formulation department may consist of rooms for each of the following procedures: mixing powders, including extract powders, and making them into a soft mass; granulating; drying; tableting; coating; and capsulating.

The liquid formulation department includes rooms for washing, filling, sterilizing and packaging. All bottles should be washed with distilled water and dried. A series of filling machines can be used for filling liquid into bottles.

Each developing country should establish a modern small-scale factory for industrial processing of medicinal and aromatic plants according to GMP requirements. This modern pilot plant will serve as a model for developing a phytopharmaceutical industry.

XI. CONCLUSIONS AND RECOMMENDATIONS

Promotion and development of industrial utilization of medicinal and aromatic plants are of far-reaching importance for the health care of developing countries. Each country should build its own plant production industry, beginning with the establishment of a modern small-scale factory for the processing of medicinal and aromatic plants.

Selection of medicinal plants for industrial processing is a crucial step. This can be decided by using information from ethnomedical practice, literature from abroad and results of the investigation of plant resources. The medicinal plants selected should have greater therapeutic effects in the treatment of common diseases and less toxicity. The product should have strong domestic or international markets.

R&D is very important in the promotion and development of industrial utilization of medicinal and aromatic plants. An institute should be established for R&D according to the standards of GLP and GCP. In such an institute, a pilot plant is necessary for scaling up bench research into industrial production. R&D work should cover pharmacodynamic, pharmacokinetic, toxicological, chemical, technological, analytical and clinical studies.

Among processing technologies, aqueous extraction, alcoholic extraction and the resin method are recommended for industrial production of plant-based pharmaceuticals in developing countries. In many cases, the resin method would be the best choice because of its obvious advantages, such as lower cost of production, lower energy consumption, higher purity of the extract, lack of air and water pollution and no special safety requirements. The resin method is therefore strongly recommended.

Quality assurance is of vital importance in manufacturing plant-based medicines. A good quality control laboratory should be established, and all activities, including R&D and manufacturing, should follow GLP, GCP and GMP requirements.

Steps should be taken to prevent pollution in the industrial utilization of medicinal plants. Waste liquids and plant residues should be reprocessed into harmless substances. Comprehensive utilization of medicinal plants is the best choice for waste disposal.

Personnel training is essential. R&D and GMP cannot be conducted without an adequate number of qualified personnel. The required personnel can be trained both domestically and abroad. International training with UNIDO assistance is one of the best means of achieving this objective.

International cooperation is a valuable means of promoting and developing the industrial utilization of medicinal and aromatic plants. UNIDO assistance has a key role to play in R&D and the establishment of pilot plants. UNIDO has considerable experience in assisting developing countries in implementing essential oil projects and plant-based medicine projects through the sourcing of experts, technical evaluation of project progress, formulation of training programmes, selection, procurement and installation of equipment, and provision of technical support of all kinds.

Notes

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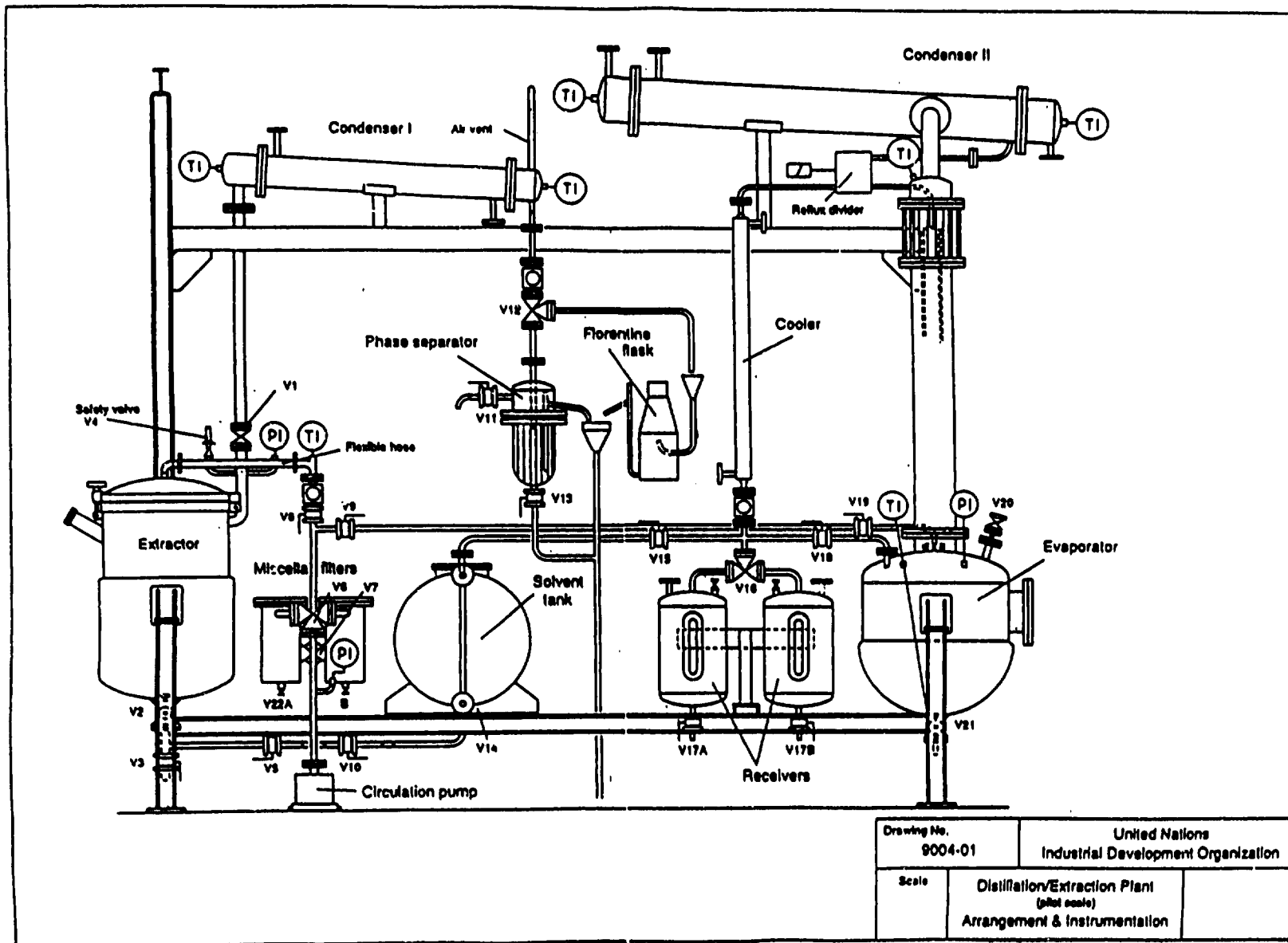
⁶Y. Y. Li and J. Chin. *Materia Medica*, voi. 13, No. 7 (1988), p. 10.

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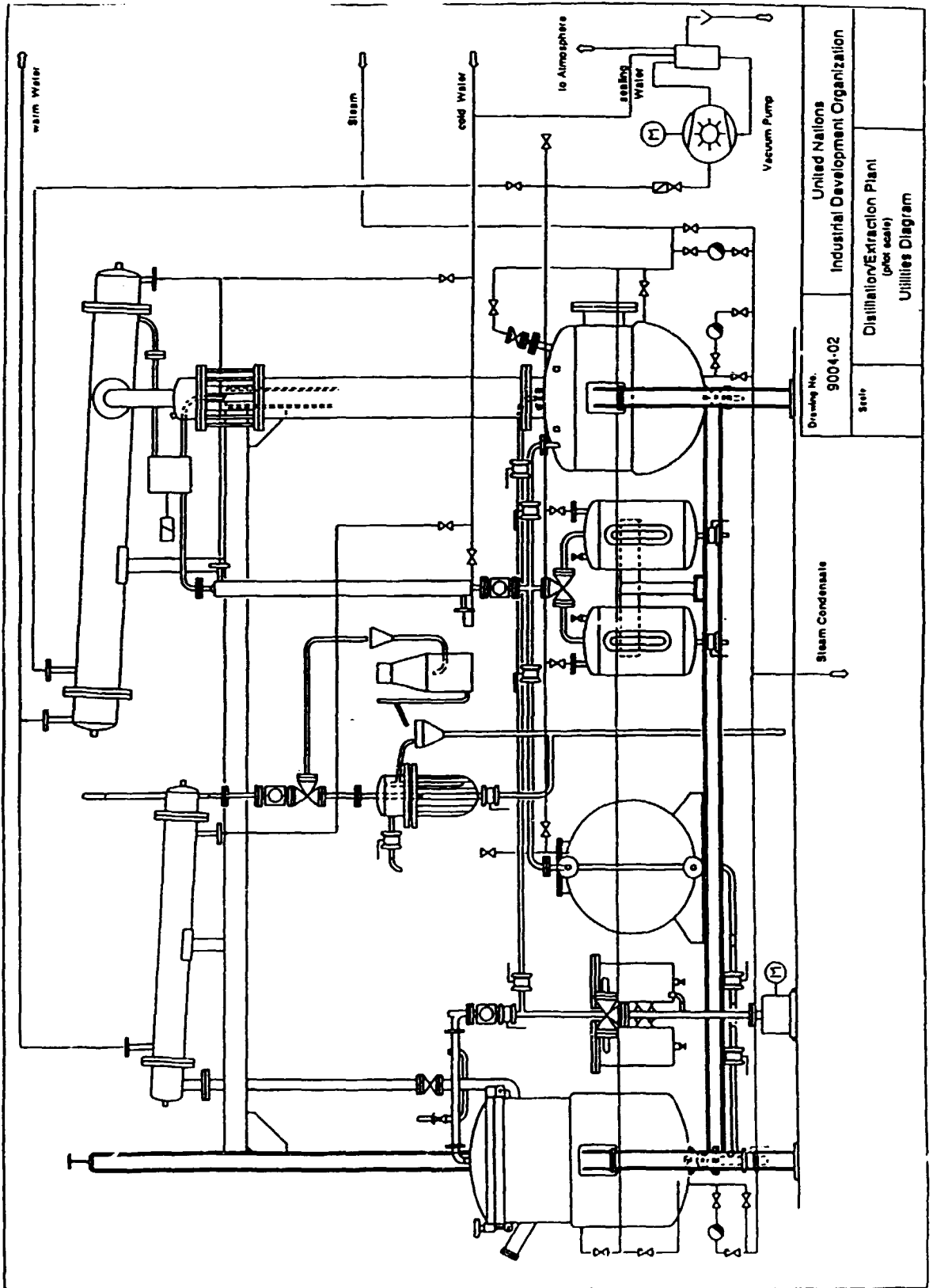
Annex I

ARRANGEMENT AND INSTRUMENTATION OF POLYVALENT PILOT PLANT UNIT



Annex II

UTILITIES DIAGRAM OF PILOT PLANT UNIT



United Nations Industrial Development Organization
Disillation/Extraction Plant (pilot scale)
Utilities Diagram
Drawing No. 9004-02
Scale