SHREE H. N. SHUKLA INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH

B.PHARM

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SUBJECT NAME:HERBAL DRUG TECHNOLOGY

SUBJECT CODE: BP603TP

UNIT 4:EVALUATION OF DRUGS

Content

Evaluation of Drugs WHO & ICH guidelines for the assessment of herbal drugs

Stability testing of herbal drugs.

Patenting and Regulatory requirements of natural products:

a) Definition of the terms: Patent, IPR, Farmers right, Breeder's right, Bioprospecting and Biopiracy

b) Patenting aspects of Traditional Knowledge and Natural Products. Case study of Curcuma & Neem.

Regulatory Issues - Regulations in India (ASU DTAB, ASU DCC), Regulation of manufacture of ASU drugs - Schedule Z of Drugs & Cosmetics Act for ASU drugs

EVALUATION OF DRUGS

WHO & ICH GUDELINES FOR THE ASSESSMENT OF HERBAL DRUGS

Assessment/Evaluation/Standardization of drug means confirmation of its identity and determination of its quality and purity and detection of nature of adulterant by various parameters like Morphological, Microscopic, Physical, Chemical and Biological observations. The Evaluation of herbal drugs is necessary because of three main reason.

1. Biochemical variation in drug.
2. Deterioration due to improper processing and storage.
3. Adulteration and Substitution.

Crude Drugs

Crude drugs are plant, animal or their parts which after collection are subjected to only drying or making them into transverse/ longitudinal slice piece or peeling them in some cases.

Crude Drug Occurrence

Crude drug are generally obtained by plant, animal and mineral origin.

1. Plant Origin: Whole plant or part of plant like leaves flowers, seed and barks or vegetable saps, extracts and secretions.
2. Animal Origin: Whole animals, glands or organs, extracts and secretions
3. Mineral Origin: Ferrous sulfate, Magnesium, Zinc, Gold etc.,

Herbal Drug/Formulation

According to WHO, a herbal drug or formulation is regarded as finished labelled products that contain active ingredients such as aerial or underground parts of plant or other plant material or combinations thereof, whether in the crude state or as plant preparations.

Guidelines for Quality Control of Herbal formulations

WHO (World Health Organization) has given certain guidelines for assessment of herbal drugs and most of the countries have adopted these guidelines. The following are the aims and objectives of WHO guidelines in standardizing the herbal drugs.

- Quality Control of crude drugs material, plant preparations and finished products.
- Stability assessment and shelf life.
- Safety assessment; documentation of safety based on experience or toxicological studies
- Assessment of efficacy and evaluating their biological activity.

Definition of Drug Evaluation

Drug Evaluation may be defined as the determination of identity, purity and quality of a drug.

Identity: Identification of biological Source of the drug.

Quality: The Quantity of the active constituent present.

Purity: The extent of foreign organic material present in a crude drug.

Importance of Evaluation of Crude Drugs

Determination of biochemical variation in the drugs. Identification of deterioration due treatment and Storage.

Reporting substitution and adulteration, as result of carelessness, ignorance and fraud.

METHODS OF STANDARDIZATION AND HERBAL DRUG EVALUATION

The evaluation of a drug is done by following methods

1. Organoleptic evaluation
2. Morphological evaluation
3. Microscopic evaluation
4. Physical evaluation
5. Chemical evaluation
6. Biological evaluation

AUTHENTICATION OF HERBAL DRUGS

The existence of numerous plant species and subspecies make it difficult to properly identify them, hence it is essential that before starting any processes on herbs, they need to beproperly identified and authenticated from a reputed institution or organization. The following institutes are involved in the authentication of herbs.

NAME OF INSTITUTES

- Central Council for Research in Ayurveda and Siddha (CCRAS)
- Central Council for Research in Unani Medicine (CCRUM)
- Central Council for Research in Homeopathy (CCRH)
- Central Council for Research in Yoga and Naturopathy (CCRYN)
- Central Council for Indian Medicine (CCIM)
- Central Council for Homeopathy (CCH)

LABORATORIES

- Pharmacopoeial Laboratory for Indian Medicine (PLIM)
- Homeopathy Pharmacopoeia laboratory (HPL)

NATIONAL INSTITUTES

- National Institute of Homeopathy (NIH)
- National Institute of Ayurveda (NIA)
- National Institute of Unani Medicine (NIUM)
- National Institute of Naturopathy (NIN)
- National Institute of Siddha (NIS)
- Institute of Post-Graduate Training and Research in Ayurveda (IPGTRA)
- Rashtriy aayurved Vidyapeeth (RAV)
- Morarji Desai National Institute Of Yoga (MDNIY)

1. ORGANOLEPTIC EVALUATION

- This refers to drug evaluation by means of organs of sense and includes other sensory
- organs like color, odor, taste, size, shape and texture.
- It includes the study of morphology and other sensory characters

A. Odour

- Distinct
- Indistinct
- Aromatic

B. Taste

- Acidic (sour)
- Saccharine(sweet) indicates sugar or sugar like substance **e.g**liquorice
- Saline (salty)
- Alkaline
- Bitter: indicates presence of substance such as bitter principle **e.g**alkaloids, glycosides
- Tasteless
- Distinctive sensation to the tongue

➢Mucilaginous and Oily (soft feeling) **e.g**linseed

➢Astringent indicates presence of tannin

➢Pungent (warm biting sensation) **e.g**Ginger

➢Acrid (irritant sensation) **e.g**Aconite, coca

➢Nauseous (tending to excite vomiting) **e.g**Ipecac

C. Colour

•White **e.g** Starch

• Pale yellow **e.g**Ginger, quill, White Pepper

• Deep yellow **e.g**Peeled Liquorice

• Light pale brown **e.g**Nux vomica, Fennel

• Dark brown **e.g**Cloves bud

• Dark reddish brown **e.g**Cinchona

• Red (brick red): **e.g**Cinnamon bark inner portion

•Pale green :**e.g**Lobelia

• Greenish brown: most of the leaves herb

2.MORPHOLOGICAL EVALUATION

Study of morphology includes visual examination of drug like study of shape & size of various parts of crude drug.

A. Flower

• Floral parts, corollas, anther, Ovary and receptable

B. Leaves and leaflet

• Length, width, apex, margin, venation, the texture of the leaf and the hairs in upper and lower surface

• The feel of the surface described as soft, hairy smooth etc.,

C. Bark

The barks occur in three shapes

• Flat or curved pieces

• Single quill

• Double quills

Barks have two surfaces, an outer and an inner. The inner surface is usually lighter incolor, than the outer surface.

D. Roots and Rhizome

A general scheme of examination of subterranean parts includes the size, shape, colour, surface, direction of growth, fracture, transverse surface, fractured surface, odour and taste, food reserves, chemical tests and special features etc.,

E. Fruit

A general method of macroscopical examination of fruit drug includes

- Exocarp
- Mesocarp
- Endocarp
- Seed

3.MICROSCOPICAL EVALUATION

Helps in the study of the presence of adulterants & correct identification of the medicinal plants. Drug is soaked in water if it is not fresh, then fine T.S is taken and stainedfor study of the arrangement of the cells important staining liquids used are

phloroglucinoland **HCl**for lignified tissues, **Chlor-zinc iodide** for cellulose tissues, **Ruthenium Red** for gums & mucilage containing cells.

The slides of this test drug are compared with the slides of the authentic crude drugs.

This helps in the study of substances like starch, fixed oils, aleurone grains, calcium oxalate, mucilage etc., **e.g.**P-amarous shows wavy walled epidermal parenchyma whereas P madraspatensis shows straight walled epidermal parenchyma.

A. Palisade Ratio

It represents the average number of palisade cells beneath one epidermal cell, using four continuous epidermal cells for the count.It is determined from powdered drug with the help of camera lucida.

Examples

• Adhatoda vasica:5.5-6.5

• Cassia angustifolia:5.5-10.0

• Digitalis lanata:2.5-6.5

B. Stomata

A minute epidermal opening present on arial parts of plants, stomata consists of central pore, two kidney shaped similar cells(guard cells) and varying number of subsidiary cells. Epidermal of leaf shows different characteristics

e.g. Cuticle, stomata, trichome

Types of Stomata

- 4 types

• Moss type

•Gymnospermous type

• Gramineous type

• Dicotyledonous → It is having diagnostic significance and classified based on form of arrangement of subsidiary cells.

Dicotyledons types

→5 types

1. Paracytic or rubiaceous or parallel stomata: In these stomata two guard cells covered by two subsidiary cells **e.g.**Senna

2. Diacytic or caryophyllaceous or cross celled stomata: In these stomata the guard cells are covered by two subsidiary cells on right angle to that of stomata. **e.g.**Peppermint

3. Anisocytic or cruciferous or unequal celled stomata: In these stomata number of guard cells is two but covered by three subsidiary cells and in that one is small in size with other two **e.g.** Datura

4. Anomocytic or ranunculaceous or irregular celled stomata: In these type stoma is surrounded by varying number of subsidiary cells **e.g.**Digitalis

5. Actinocytic or radiate celled stomata: Two guard cells are surrounded by radiating subsidiary cells.

C. Stomatal number

The average number of stomata present per square per square millimeter of the

epidermis is known as stomatal number.

D. Stomatal index

• It is the percentage proportion of the number of stomata to the total number of epidermal cells.

• Stomatal number varies considerably with the age of the leaf but stomatal index is relatively constant for a given species.

Stomatal index calculated by:

S.I=S/E+S

Where, S.I →Stomatal index

S→ Number of Stomata per unit area

E→ Number of epidermal cells in the same unit area

E. Vein-islet Number

Vein-islet number is defined as the number of vein-islets per sq.mm of leaf surface.

F. Vein-termination Number

It is defined as the number of veinlet termination per sq.mm of the leaf surface between midrib and margin.

G. Trichomes or plant hairs

• These may be referred to as plant hairs. These are warty outgrowth of epidermal cells. A trichome consists of two parts, root which is based in the epidermal lining and body which is outside the epidermal lining.

• Trichomes are of three types

➢Covering Trichomes

➢Glandular trichomes

➢Hydatodes

They may be unicellular or multicellular.

I. Quantitative Microscopy:

Lycopodium spore method: It is used especially chemical and other methods of evaluation of drugs fail to determine quality. Lycopodium spores are much

characterized in shape and appearance and uniform in size (25pm) on average, 94000 spores present/mg of Lycopodium powder.

It consist of

➢➢Well defined particles which may be counted.

➢ Single layered cells or tissues the area of which may be traced under suitable magnification and actual area calculated.

➢The objects of uniform thickness, the length of which can be measuredand actual area calculated.Well defined particles which may be counted.

➢ Single layered cells or tissues the area of which may be traced under suitable magnification and actual area calculated.

➢The objects of uniform thickness, the length of which can be measured and actual area calculated.

4.PHYSICAL EVALUATION

A.Determination of foreign Organic matter

Drugs should be free from moulds, insects, animal, faecal matter and other contamination such as earth stones and extraneous matters. Foreign organic matter should be not more than 2% W/W.

B. Determination of Ash value

• Total Ash

Total Ash is designed to measure the amount of inorganic impurities present in the crude drug. The drug material is subjected to incineration at a temperature of about 500-6000C to remove all the carbons. Total ash usually consist of carbonates, phosphates, silicates and silica.

• Acid Soluble Ash

Acid insoluble Ash is the residue obtained after extracting the total ash with HCl. It gives an idea about the earthy matter present in the drug.

• Water Soluble Ash

The total ash content which is soluble in water is known as water soluble ash. It gives an idea about the presence of water-soluble salts present in the drug.

C. Determination of Extractive value

It gives an idea about the amount of chemical constituents present in the drug. Extractive value are again sub classified based on the nature of constituents present in the drug as water soluble extractive, alcohol soluble extractive and non-volatile ether soluble extractive value.

D. Determination of Moisture content

10gm of drug is taken in an evaporating dish. Then it is dried at 1050C for 3 hours and weighed again. Drying and weighing is continued for an hour interval until difference between two successive weighing corresponds to not more than 0.25 percent. The reading is taken after a constant weight is reached and the moisture content is determined.

E. Refractive Index

When a ray passes from one medium to another of different density, it is bent from original path. Thus,the ratio of velocity of light in vacuum to its velocity in a substance is termed as refractive index of the second medium. Depending upon purity, it is constant for a liquid and can be consider as one of its standardization.

5.CHEMICAL EVALUATION

It consists of Qualitative and Quantitative methods.

A. QUALITATIVE CHEMICAL EVALUATION

Qualitative tests comprise of various chemical tests to identify the nature of compounds present in the crude drugs.

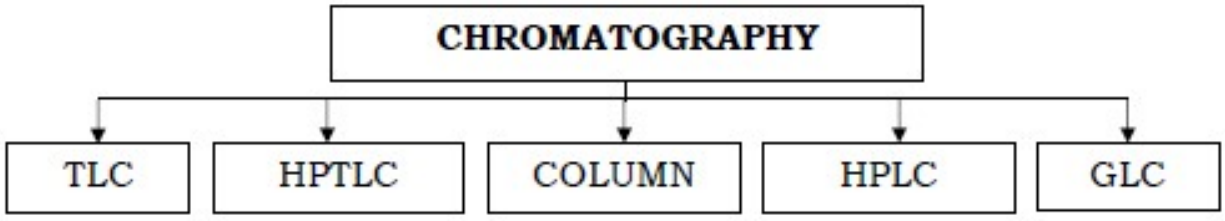
- Test for Alkaloids: Mayer's test, Dragendroff's test, Hager's test, Wagner's test
- Test for Glycosides and sugars: Borntrager's test, Molisch's test, killer killiani test, legal test etc.,
- Test for Phytosterols: Liebermann's and Burchard tests.

- Test for Tannins and Phenols: Ferric chloride test.
- Test for Proteins and Amino acids: Millen's test, Ninhydrin test, Biurett's test etc.,
- Test for Gums and Mucilage: Swelling Index.

B. QUANTITATIVE CHEMICAL EVALUATION

- **It** includes chemical assays and chromatographic methods which are used to quantify the chemical compounds present in the crude drug.
- **Chromatographic Techniques**

  The Chromatographic techniques are the new and most common methods used to separate, identify and quantify the plant constituents. It consists of various methods which are as follows



Thin Layer Chromatography (TLC)

TLC technique has become a most important analytical tool for separation and determination of natural products. It is simple, economical and rapid method to analyse plant extracts and carryout the fingerprinting of samples by using the standard or marker compounds.

High Performance Thin Layer Chromatography (HPTLC)

It is one of the very useful methods for the qualitative and quantitative analysis of plant extracts. It is advanced form of TLC with shorter time and precise results.

Column Chromatography

Basically, it is a liquid chromatography in which mobile phase in the form of liquid phases over the stationary phase packed in a column. The column is made of either glass or metal. It is the oldest method and most commonly practiced method for the isolation of pure compounds.

High Performance Liquid Chromatography (HPLC)

It is one of the most versatile, safest, dependable, fastest and sensitive chromatographic techniques for the quality control of drugs. The term liquid chromatography refers to those

methods where separation takes place in a packed column which act as stationary phase. A mobile phase is used as eluent. In HPLC, the mobile phase is forced through the column under high pressure.

Gas Liquid Chromatography (GLC): It is the most selective and versatile form of gas chromatography. Commonly it is used in the assay and analysis of starting materials and drug substances, quantification of drug substances in formulations and assay of impurities and solvents in the drug substances.

6. BIOLOGICAL EVALUATION

It consist of following evaluation methods

- Bitterness value
- Haemolytic activity
- Swelling Index
- Foaming Index
- Pesticide Residues
- Heavy Metals
- Micro-organism
- Aflatoxins
- Radioactive Substances

STABILITY TESTING OF HERBAL DRUGS

Stability testing is required to determine the shelf life and assign expiry dates to medicines.

Herbal drugs may be single active constituent or entire herb r combination of herbs consisting of mixture of constituents. Most of herbal drug products used are group of constituents.

Stability testing of herbal products is a complicated issue because the entire herbal product is regarded as the active substance, regardless of whether constituents with defined therapeutic activity are known.

Trace metals contamination leaching from the container, etc., and also provides statistics for determination of shelf life.

The stability testing of herbal products includes checking the quality which varies with the time under the influence of environmental factors, such as temperature, humidity, light, oxygen, moisture, other ingredient or excipients in the dosage form, particle size of drug, microbial contamination.

Therefore evaluation of the parameters based upon chemical, physical, microbiological, therapeutic and toxicological studies can serve as an important tool in stability studies.

PROBLEMS RELATED TO THE HERBAL PRODUCT STABILITY

PHYSICAL INSTABILITY

Natural medicines are usually prone to physical instability due to presence of impurities and reaction with the container. Conditions like growth of the micro-organisms and insect feeding affect the secondary metabolites and chemical composition of plants.

Volatile active components of natural medicine have the problem of volatility and decreasing activity during storage for a long time.

ENVIRONMENTAL CONDITIONS

Environmental conditions such as rainfall, altitude, temperature, soil, storageconditions as well as different harvesting procedures, time and method of collection,manufacturing processes such as selecting, drying, purifying, extracting and geneticvariability can create substantial variability in the product quality, stability and in theconcentration of plant constituents.

Light is also an important factor affecting phytomedicines by generating free radicals.

CHEMICAL INSTABILITY

Herbal drugs are subjected to degradation during storage by oxidation, hydrolysis,crystallization, emulsion breakdown, enzymatic deterioration and chemical reactions withthe additives & excipients. Temperature & Moisture are the two major factors that affectquality & stability of a herbal product.

A chemical reaction increases by 2 to 3 fold for every 100C rise in temperature.

Moisture absorbed on to the surface of solid drug often increases the rate of decomposition if it is susceptible to hydrolysis. Presence of enzymes in the product also increases the rate of chemical degradation.

COMPLEX MIXTURE VARIABILITY AND INCONSISTENCY

Herbal formulation are complex mixtures of different components obtained duringextraction process. Each component has variable shelf life, activity, concentration andconsistency.

It creates a problem during storage condition determination as it is not easy todetermine the stability of final herbal preparation based on the activity and stability profile ofa single component.

DRUG INTERACTION DETERIORATION DECOMPOSITION AND STORAGE

Moisture content above the critical value and mould growth in natural products cancause the interactions of the active components with the packaging materials.

Also interactions of active components with the other ingredients of formulations usedsuch as additives cause alterations in the novel drug activity.

Stability studies should be performed on at least three production batches of the herbalproducts for the proposed shelf life, which is normally denoted as long term stability and isperformed under natural atmospheric conditions.With the help of modern analytical techniques like spectrophotometry, HPLC, HPTLCand by employing proper guidelines it is possible to generate a sound stability data of herbalproducts and predict their shelf life, which will help in improving global acceptability ofherbal products.

ROLE OF MARKERS IN DETERMINING THE STABILITY OF HERBAL DRUGS

Markers are chemically known compounds, which may or may not have the therapeutic effect, they are used to calculate the quantity of herbal medicinal ingredients inherbal medicinal products.

It is important to isolate and structurally elucidate chemically defined substances inplants, drug and / or drug preparations so that they can be used as markers that not only helpto better understand the active principles of herbal drugs but also can enhance analyticalquality control.

ANALYTICAL METHODS TO DETERMINE STABILITY OF HERBAL DRUGS

The analysis of herbal preparations is mostly done by modern chromatographic or spectroscopic methods like HPLC, gas Chromatography (GC), TLC, Quantitativedeterminations by UV visible spectroscopy or combinations of these.HPLC and GC methods can be used for identification and purity testing, as well as thedetection of single compounds for assay is possible during one analysis. LC and GC masscoupling are also the tools for determinations.

METHODS TO DEAL WITH HERBAL DRUG INSTABILITY

Determination of the Physical Parameter

Depending on type of preparation, sensory properties, physical constants, moisture, ash content, solvent residues & adulteration have to be checked to prove identity and puritymicrobiological contamination and foreign materials such as heavy metals, pesticidesresidues, alfatoxins& radioactivity also need to be tested.To prove the constant composition of herbal preparations, appropriate analyticalmethods have to be applied and different concepts have to be used in order to establishrelevant criteria for uniformity.

Determination of the impurity profile

This technique helps in the identification of impurities that result from degradation of active constituents. The active constituents are subjected to a known degradation process andthe

degradation products are identified.Degradation may be due to oxidation, reduction or hydrolysis hence we can have anidea of what could be the degradation products.

These can be listed and kept as a reference library of degradation products. For routinely doing an impurity profile, this library can be referred and the nature and structureof the impurity can be traced.Since impurities decreases the stability of the natural medicines, it is important to note the type of impurities.

It can be done by the analytical methods as HPLC, TLC, capillary electrophoresis, spectrophotometry, GC, MS etc.,

Identification and quantification of all metabolites

Nonbiased identification and quantification of all metabolites in herbal or other natural products is vital to determine the status and stability of the complex mixtures.IR spectroscopy in combination with chemometric data processing could provide totalmetabolic fingerprint profile of phyto formulations

Controlled storage conditions:

Control measure to protect against deterioration includes the use of airtight container made of materials that will not interact physically or chemically with the material beingstored.

Storage in ventilated cool, dry area and periodic spraying of the stored area with insecticide will help to prevent the spread of infestation.

Influence of environmental factors such temperature, light, oxygen, moisture, other ingredient or excipients in the dosage form particle size of drug, microbial contamination, trace metal contamination, leaching from the container etc., should be established torecommend proper storage conditions.

PATENTING AND REGULATORY REQUIREMENTS OF NATURAL PRODUCTS

PATENT

An exclusive and absolute right granted to the owner or inventor of an invention to create, utilize produce and market the invention is termed a **Patent**.

Such rights are awarded by the country of a limited time period, presuming that the invention fulfil all the conditions specified in the law.

These rights are said to be ‘exclusive’ because no other person can create, utilize,produce or market the invention in the absence of proper approval of the patent holder. Theright of granting a patent is territorial in nature.

For all the types of products, the validity of patent is 20 years from the date on which the patent application is filed.

IPR

Intellectual property rights refers to the general term for the assignment ofproperty rights through patents, copyrights and trademarks. These property rights allow theholder to exercise a monopoly on the use of the item for a specified period.

Intellectual property protection isn't as simple as declaring ownership of aparticular product or asset. In most countries, there are four primary types of intellectualproperty (IP) that can be legally protected: **patents**, **trademarks**, **copyrights**, and **trade secrets.**

The Patent **Act**, 1970 (Patents | **Intellectual Property India**) For protection of Inventions. The Trademark **Act**, 1999 (Trade Marks | **Intellectual Property India**) forprotection of a word, phrase, symbol, and/or design that identifies and distinguishes thesource of the goods of one party from those of others.

The regulatory authority for patents is the Patent Registrar under the office of the Controller General of Patents, Designs and Trade Marks, which is part of **India's** Ministry ofCommerce and Industry. Patents are valid for 20 years from the date of filing an application,subject to an annual renewal fee.

FARMERS RIGHT

Farmers' Rights are critical to ensuring the conservation and sustainable use of plant genetic resources for food and agriculture and consequently for food security – today and in the future.

It gives governments the responsibility for implementing Farmers' Rights, and lists measures that could be taken to protect, promote and realize these rights:

• The protection of traditional knowledge relevant to plant genetic resources for food and agriculture;

• The right to equitably participate in sharing benefits arising from the utilization of plant genetic resources for food and agriculture;

• The right to participate in making decisions, at the national level, on matters related to the conservation and sustainable use of plant genetic resources for food andagriculture; and

• The right that farmers have to save, use, exchange and sell farm-savedseed/propagating material, subject to national law and as appropriate.

BREEDER'S RIGHT

Plant breeders' rights (**PBR**), also known as **plant variety rights** (**PVR**) .These are rights granted to the breeder of a new variety of plant that give thebreeder exclusive control over the propagating material (including seed, cuttings, divisions,tissue culture) and harvested material (cut flowers, fruit, foliage) of a new variety for a number of years.With these rights, the breeder can choose to become the exclusive marketer of thevariety, or to license the variety to others. In order to qualify for these exclusive rights, avariety must be new, distinct, uniform and stable.

A variety is:

• new if it has not been commercialized for more than one year in the country of protection;

• distinct if it differs from all other known varieties by one or more important botanical characteristics, such as height, maturity, colour, etc.;

• uniform if the plant characteristics are consistent from plant to plant within the variety;

• stable if the plant characteristics are genetically fixed and therefore remain the same from generation to generation, or after a cycle of reproduction in the case of hybrid varieties.

The breeder must also give the variety an acceptable "denomination", which becomes its generic name and must be used by anyone who markets the variety.

BIOPROSPECTING

Bioprospecting is the process of discovery and commercialization of new productsbased on biological resources. These resources or compounds can be important for anduseful in many fields, including pharmaceuticals, agriculture, bioremediation, andnanotechnology, among others.

Bioprospecting can be also defined as the systematic search for and development of new sources of chemical compounds, genes, micro-organisms, macro-organisms, and othervaluable products from nature. It entails the search for economically valuable genetic andbiochemical resources from nature.Bioprospecting has only recently begun to incorporate such knowledge in focusing screening efforts for bioactive compounds.

BIOPIRACY

Biopiracy means the patenting of life.Biopiracy is defined as ‘the illegal appropriation of life micro-organism, plants and animals including humans and the traditional knowledge that accompanies it”.

Biopiracy is the situation where the indigenous knowledge of nature, originating with indigenous people, is used by others for profit, without permission from and with littleor no compensation or recognition to the indigenous people themselves.

PATENTING ASPECTS OF NATURAL PRODUCTS

Patentable Natural Products

The following are the list of natural products which can be patentable

1. Novel isolation process of natural products from its surroundings. Example an Indian patent for process of isolation of azadirachtin from the seeds of neem plant.
2. Characterization of new product either by its structure or by other physical parameters.
3. A new application of isolated product provided unless such knowledge or invention donot exist anywhere. Example a Japanese patent for the use of turmeric as a stabilizerfor an anti-fungal agent.
4. Invention and Novelties. For Example products like biopesticides.
5. Patenting in relation to biotechnology.
6. Patenting for Biological matter. For Example micro organism like *E.coli* in which human genes are introduced for the production of human insulin, HGH, HumanTissue, plasminogen activators are patented. Patentable microbial inventions includethe following.

• Processed products
• Methods for producing new organism
• Reducing pathogenicity
• Increasing biological activity.
• Invention of new organism and their composition.

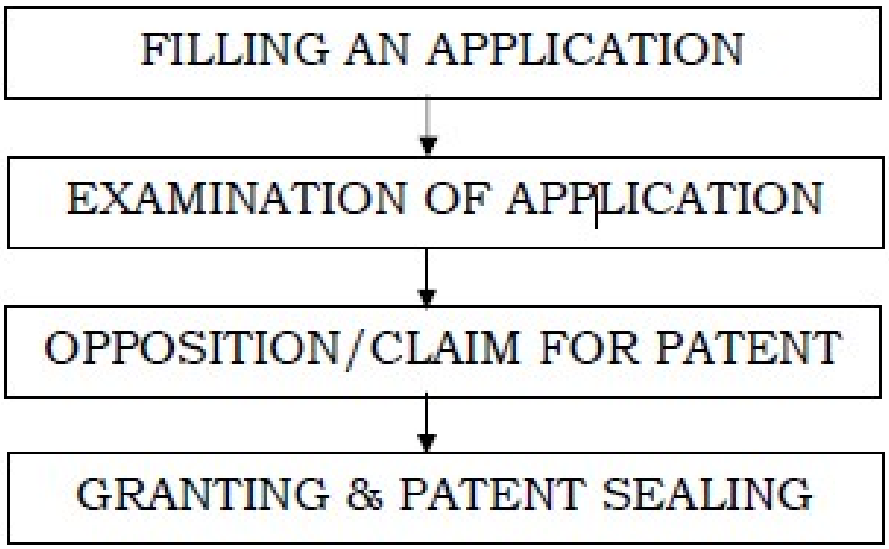
7. Transgenic plants: plants can be altered genetically to obtain transgenic plants of desired characters. Example herbicide resistant cotton plant, insecticidal resistanttobacco plant. Such techniques are patentable.
8. Patenting of secondary metabolites by cell culture which include sophisticated and specific methods can be patented. Example production of taxol by cell culturing oftaxus species.

Non-Patentable Natural Products

1. Plants grown in wild
2. Plants adopted for cultivation.
3. Hybrids or other cultural varieties which have been tried for particular use.

PROCEDURE FOR OBTAINING PATENT

It involves the following steps



a) Filling an application for patent

A patent application can be made on prescribed application form. This can be obtained from patent office, the applicant have to furnish the following information.

- Title, name, address and nationality of inventor.
- Specification: Giving the details of invention.
- Claims: Definition and Scope of invention.

b) Examination of application

Patent office examines patent applications with respect to usefulness, nature of claim and weather the patent has been filed earlier.

c) Opposition/claim for patent

A three month time is given for any application before granting and sealing of the patent.

d) Granting & patent sealing

Incase of no opposition or clearly satisfaction of all the objections by the applicant, the pantent is granted by the patent office and published in the official gazette. A patent can be kept alive by paying an annual fee within date which increases the age of the patent. It can be renewed after its expiry.

Advantage of Patenting

- A patent gives the right to stop others from copying, manufacturing, selling or importing the invention without the permission of inventor.

A protection is provided for a predetermined period keeping the competitors at bay

The inventor has the authority to license his invention to others to use or sell it.

CASE STUDY OF NEEM

the neem tree *Azadirachtaindica*is a tropical evergreen tree native to India and is also found in other south east countries.

The seeds, bark and leaves contain compounds with proven antiseptic, antiviral, antipyretic, anti-inflammatory, anti-ulcer and anti-fungal properties.

In 1971, US timber importer "Robert Harson" observed that the trees usefulness in India and began importing neem seeds to his company head-quarters.

He conducted safety and performance test of neem.

• Three years later he sold his invention to the US Department of agricultural and Multinational chemical corporation WR Grace and co.

• In 1992 the WR Grace and co secured its right to the formula that used the emulsion from the neem trees, seeds to make a powerful fungicide.

• In applying for the patient, the company had argued that it had used an extract of thetrees, seed to make a new fungicide but the Indians claim that its patent was notsufficiently novel as Indian farmers have used this fungicide for decade.

• The Indians and members of the green party in the European union opposed the patent because they believed that the rights of the poor farmers in developing countries will be harmed. The neem patent became the first to challenge European and US patents on grounds of biopiracy.

• The Indian scientists argued that the Indians have known the medicinal properties of neem long back.

• The European Patent Office EPO accepted the arguments offered by Indian scientists and rejected the order of the US patent office to award the patent to WR Grace and co.

• The victory is a result of four year long effort by the research foundations for science technology and environment.

CASE STUDY OF CURCUMA

• Turmeric is a tropical herb grown in east India. Turmeric powder has a deep distinct color and bitter taste.

• It is used as dye, cooking, ingredient, litmus in chemical tests and for medicinal purposes.

• A United States patent on turmeric was awarded to the university of Mississippimedical centre in may 1995, specifically for the use of turmeric in wound healing.

• Two years later, a complaint was filed by India's Council of Scientific and Industrial Research (CSIR).

CSIR argued that turmeric has been used in India for thousands of years for healing wounds and rashes and therefore the patent on its medical use was not a novel. invention.

• The CSIR claim was supported by documentary evidence of traditional knowledge including ancient Sanskrit text and paper published in 1953 in the journals of Indian Medical Association.

• United states patent and trade mark office (USPTO) investigated the validity of thepatent.

• In 1997 despite an appeal made by the patent holders, the USPTO upheld the CSIR objection and cancelled the patent due to lack of novelty.

REGULATORY ISSUES

HERBAL DRUG REGULATIONS IN INDIA

Provisions relating to the manufacture and control of Ayurvedic, Siddha and Unani (ASU) drugs have been prescribed in the Drugs and Cosmetics act.

This acts describes the formation of Drugs Technical Advisory Board (DTAB), Whichconsists of various nominated members and the Drugs Consultative Committees (DCC).

The Ayurvedic, Siddha and Unani Drugs Technical Advisory Board (ASU-DTAB)

The central government shall constitute a board by notifying in the official gazette. The board shall advice the central as well as state governments on technical matters arisingout of the section 33-C of the Drugs and Cosmetics act and carry other functions assigned.

A) Constitution of the board

The board shall consist of the following members.

1. The Director general of Health services, Ex officio
2. The Drugs controller, Ex officio
3. The Director of Central Drugs laboratory, Calcutta, Ex officio
4. One Government analyst nominated by the central board.
5. One Pharmacognocist nominated by the Central Government.
6. One Phytochemist nominated by the Central Government.
7. Four persons nominated by the central Government, among which two from the members of Ayurvedic pharmacopeia committee and one each from Unani andSiddha pharmacopeia committee.
8. One teacher in Dravyaguna and BhaishajyaKalpana to be nominated by the Central Government.

9. One teacher from Ilmul-Advia and taklis-wa-Dawasai to be nominated by the Central Government.

10. One teacher in Gunapadam to be nominated by the Central Government.

11. Three persons, one each represent the Ayurvedic, Siddha and Unani drug industry to be nominated by the Central Government.

12. Three persons, one each from amogst the practitioner of Ayurvedic, Siddha andUnani, Tibb systems of medicine to be nominated by the Central Government.

B) Functioning of the board

• The Central Government shall appoint a chairman from amongst its members

• The nominated members of the board shall hold office for three years but shall be eligible for renomination.

• The board may make bye laws to regulate its functioning and conduct of all activities.

• The central government shall appoint a secretary of the board and shall provide the board with such clerical and other staff.

The Ayurvedic, Siddha and Unani Drugs Consultative Committee (ASU-DCC)

The Central Government may constitute an advisory committee as mentioned in the section 33-D of the Drugs and Cosmetics Act. This committee may advise the central andstate governments and the Ayurvedic, Siddha and Unani drugs technical advisory board(ASU-DTAB) on any matter for the purpose of securing uniformity in the administration ofthis act (section 33-D) throughout India.

Constitution and Functioning of ASU-DCC

• The ASU-DCC shall consist of two persons nominated by central government and one person from the state government eho act as representative of the respectivegovernments.

• The ASU-DCC shall meet when required to do so by the central government and shall regulate its own activities as per their requirements.

REGULATIONS FOR THE MANUFACTURE OF AYURVEDIC, SIDDHA AND UNANI (ASU) DRUGS

The section 33-EEB of the Drugs and Cosmetics act describes the regulation for the manufacture and sale of ASU drugs. The Act has set some standards related to the hygienicconditions, factory premises, prohibition of manufacture and sale of certain drugs andpenalties for contravention of this act. The following requirements are taken into account.

A. Requirements of factory premises and hygiene Conditions

As per the act, it is mandatory to maintain proper hygienic conditions in the factory premises along with the following requirements.

• Factory or industry involved in the manufacture of ASU drugs should not besituated adjacent to open sewage, drain, public lavatory or any other factorywhich produces obnoxious odour, large quantities of waste, dust or smoke

• The premises of manufacturing unit shall be clean, hygienic and free from insects, rodents and other contamination.

Note: All the sections fall under the Schedule Z of the Drugs & Cosmetics Act

• The walls and floor of manufacturing rooms should be smooth, easily cleanable with water and should not accumulate dust or waste products.

• The water used in the manufacture shall be pure and drining quality. It should be free from pathogenic organisms. Adequate facility should be provided toprocesses the containers and closures for washing, cleaning, drying, etc., and itshould be separated from the manufacturing unit.

• Suitable arrangements shall be provided for disposing waste water and other materials in a manner that it does not affect the health of people in thesurrounding area.

• Personnel working in the factory should be free from contagious diseases.

• Appropriate dress should be provided to the workers based on the nature of their work.

• Adequate facilities for personal cleanliness such as soap, towel, and antiseptics should be provided.

• Facilities for drinking water and separate wash rooms should be provided formen and women.

B. Prohibition of manufacture and sale of certain ASU drugs

The act prescribes some criteria to prohibit the manufacture and sale of certain ASU drugs which are not manufactured or sold in accordance of the rules.

The following categories of ASU drugs can be prohibited from manufacture and sale.

• Any misbranded, adulterated or spurious ASU drugs.

• Any proprietary or patented medicine which does not display the list of all ingredients on the label of the container.

• The selling, stocking and distribution of any ASU drug which has been manufactured in contravention of the provision of this act.

• The manufacture, sale and distribution of any ASU drugs for which license has not been issued by the prescribed authority.

The above rules do not apply to Vaidyas and Hakims who prepared ASU drugs for the use of their own patients.

The above rules do not apply to ASU drugs which are manufactured in small quantities for the purpose of examination, test or analysis.

C. Power of central Government to prohibit the Manufacture, sale & distribution of ASU drugs in public interest

• The Section 33-EED of the Drugs and Cosmetics act prescribes certain powers of the central Government based on which the government can prohibit themanufacture, sale and distribution of ASU drugs which involve any risk tohumans or animals or such drug does not have therapeutic value as claimed bythe manufacturer or any misbranded and spurious drugs.

• Hence in such circumstance, the government may prohibit the manufacture, sale & distribution of drugs in public interest.

D. Penalty for the manufacture, sale and distribution of prohibited ASU drugs

As prescribed under the section 33-1 of the Drugs and Cosmetics act, any person himself on his behalf is engaged in the manufacture, sale and distribution ofprohibited ASU drugs, penalty has been fixed as per the following guidelines

1. Any ASU drug which is deemed to be adulterated or manufactured without a valid license shall be punishable up to one-year imprisonment and with fine upto 2000 rupees.

2. Any ASU drug which is deemed to be spurious shall be punishable with imprisonment up to 1-3 years and with fine up to 5000 rupees.

3. Any ASU drug which contravenes any other provision of the act shall bepunishable with imprisonment up to 3 months and with fine up to 500 rupees.

E. Manufacture on more than one set of premises

It ASU drugs are manufactured on more than one set of premises, a separate application shall be made and a separate license shall be obtained for each premises.