ISSUE No. 42

SILVER JUBILEE YEAR 2016

TAMILNADU PHARMACEUTICALS SCIENCES WELFARE TRUST

25 Years

# Pharma Web

## Newsletter of Tamilnadu Pharmaceutical Sciences Welfare Trust

Apr. - May. - Jun. 2019

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Tamilnadu Pharmaceutical Sciences Welfare Trust

# Pharma Web

## Newsletter of Tamilnadu Pharmaceutical Sciences Welfare Trust

ISSUE : 42 Apr. - May. - Jun. 2019



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# EDITORIAL

Dear Readers,

We are happy to publish the 42ndissue of Pharma Web Newsletter for April – June 2019.

This issue cover the the National Seminar on Modern Scientific Approaches for Standardization of Medicinal Plants Used in ASU & H Drugs, which was organized by Captain Srinivasa Murthy Regional Ayurveda Drug Development Institute, Chennai. Dr. R. Ilavarasan, Director In-charge of the Institute has taken lot of pain and time to organise such programme for the benefit of ASU manufacturers to improve the quality of the products. I attended the inauguration of the seminar on the invitation of Dr. R. Ilavarasan. We are thankful to him in providing the soft copies of the technical lectures as well as the highlights of the programme for publication.

This 42nd issue contain the program highlights as well as the ifollowing lectures given by various resource persons .

- Nanoparticles in Ayurveda - **Dr. M. Nappinnai**, Head Formulation R&D, Dhanvantri Nano Aushadhi Pvt Ltd., Chennai.
- Standardization of Botanicals - Regulatory and Analytical Perspectives - **Dr. R. Sundaram**, Head, A-R&D,The Himalaya Drug Company, Bangalore.
- Toxicity/Safety Evaluation of ASU&H Drugs - **Dr. R. Ilavarasan**, Assistant Director (Scientist-4), Institute In-charge, CSMRADDI, Chennai.
- Developing Globally Compliant Proprietary Herbal Products: A Bird's Eye View on General Requirements - **Dr. B.K. Ashok**, Senior Research Scientist, R & D Himalaya Drug Company, Bangalore.
- Shelf Life Studies of ASU&H Drugs - **Dr. R. Ilavarasan**, Assistant Director (Scientist-4), Institute In-charge, CSMRADDI, Chennai.
- Importance of Safety and Efficacy Studies on Traditional Medicines in Context to Reverse Pharmacology - **Dr. Mukesh Kumar Nariya**, Head Pharmacology, Institute of Post Graduate Teaching & Research in Ayurveda, Gujarat

Further We have published the latest Gazette Notification pertaining to the amendment of Drugs & Cosmetics Act & Rules issued by DCGI office

Important news items connected to our Pharmacy profession appeared in various national news papers are published in this issue.

We are very much thankful to M/s. Delvin Formulations, M/s. Medopharm, M/s. Tablets (India) Ltd., for the continuous support by giving advertisement, in order to sustain the cost of publishing of this newsletter.

Our special thanks to M/s. Fourrts (India) Laboratories Pvt. Ltd., for supporting Pharma Web advertisement and also awarding meritorious award for B. Pharm Students of The Tamilnadu Dr. MGR Medical University, Guindy, Chennai.

Hope this Newsletter will benefit our Pharma professionals. Any suggestions to improve our news letter are welcome.

With Best Regards,
**R. NARAYANASWAMY**
Chief Editor

## NATIONAL SEMINAR
## ON
## MODERN SCIENTIFIC APPROACH FOR STANDARDIZATION OF MEDICINAL PLANTS USED IN ASU&H DRUGS

The Two Days National Seminar on Modern Scientific Approach for Standardization of Medicinal Plants used in ASU & H Drugs wasconducted on **25th and 26th March 2019** which was organized by Captain Srinivasa Murthy Regional Ayurveda Drug Development Institute, Ministry of AYUSH, Government of India, duly sponsored by National Medicinal Plants Board, Ministry of AYUSH, Government of India. Experts/Stalwarts from the top most companies from all over India like DABUR India and Himalaya Healthcare were participated and delivered lectures about Standardization of Medicinal plants. More than 100 participants from various AYUSH related disciplines within Chennai and other parts of our country were actively participated as delegates in the seminar.

The Seminar was inaugurated by **Shri. S. Ganesh, I.A.S.,** Director, Indian Medicine and Homeopathy, Government of Tamil Nadu in the august presence of **Prof. Vd. K.S. Dhiman,** Director General, Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India, New Delhi, **Prof. Dr. K. Kanagavalli,** Director General, Central Council for Research in Siddha, Ministry of AYUSH, Government of India and **Dr. R. Ilavarasan,** Assistant Director (S-4), Institute In-charge, Captain Srinivasa Murthy Regional Ayurveda Drug Development Institute, Ministry of AYUSH, Government of India, Chennai and many others.

The valedictory function was conducted on 26th March 2019 in which **Dr. S. Manivannan,** Deputy Drugs Controller, Government of India has participated and chaired as the Chief Guest. At the end of the program, certificates were distributedto all the participants and the program was successfully completed with the National Anthem. As per the feedback received from participants, the lectures delivered by the experts were found to be informative and useful for their respective research activities. The arrangements made by the institute were also in the appreciable manner.

## Day 1: 25th March, 2019 (Monday)

| | |
|---|---|
| 09.00 am to 09.30 am | Registration |
| 09.30 am to 10.30 am | **Inauguration**<br>Chief Guest : Director General, CCRAS, New Delhi<br>Guest of Honor : Director, Indian Medicine and Homeopathy, Tamil Nadu<br>Guest of Honor : Director General, CCRS, Chennai |
| 10.30 am to 11.30 am | **Prof. Vd. K.S. Dhiman,**<br>Director General, CCRAS, Ministry of AYUSH, New Delhi. |
| 11.30 am to 12.00 am | **Tea Break** |
| 12.00 am to 01.00 pm | **Topic:** Nanoparticles in Ayurveda<br>**Speaker: Dr. M. Nappinnai,**<br>Head Formulation R&D, Dhanvantri Nano Aushadhi Pvt Ltd, Chennai. |
| 01.00 pm to 02.00 pm | **Lunch Break** |
| 02.00 pm to 03.00 pm | **Topic:** Standardization of Botanicals- Regulatory and Analytical Perspectives<br>**Speaker: Dr. R. Sundaram,**<br>Head, A-R&D, The Himalaya Drug Company, Bangalore |
| 03.00 pm to 04.00 pm | **Topic :** Toxicity/Safety Evaluation of ASU&H Drugs<br>**Speaker: Dr. R. Ilavarasan,**<br>Assistant Director (Scientist-4), Institute In-charge, CSMRADDI, Chennai. |
| 04.00 pm to 04.15 pm | **Tea Break** |
| 04.15 pm to 05.15 pm | **Topic:** Developing Globally Compliant Proprietary Herbal Products: A Bird's Eye View on General Requirements<br>**Speaker: Dr. B.K. Ashok,**<br>Senior Research Scientist, R & D Himalaya Drug Company, Bangalore. |

Inauguration of Program by lightening the lamp

Inauguration of Program with Prayer Song


Event Banner on the Diaz


Welcome address by Dr. R. Ilavarasan

Presenting Memento to Shri. S. Ganesh I.A.S.


Inauguration Speech by Prof. Vd. K. S. Dhiman


Group Discussion about the Seminar Topics on Day 1

Audience interacting with Speakers on Day 1

Seminar Presentation by Dr. Mukesh Naria

Speakers in the Group Discussion Session on Day 2

Audience and Speakers Interacting in Group Discussion on Day 2


Distributing Certificates to the Participants in the Valedictory function

## Day 2: 26th March, 2019 (Tuesday)

| | |
|---|---|
| 09.00 am to 09.45 am | **Topic :** An IPR Action Plan For AYUSH Systems of Medicine<br>**Speaker: Mrs. SwapnaSundar,**<br>IP Strategist & Patent Agent, Chennai. |
| 09.45 am to 10.30 am | **Topic:** Standardization of Medicinal Plants by Validation of Crude drugs<br>**Speaker: Dr. T. Sekar,**<br>Associate Professor, Pachaiyappa's College, Chennai. |
| 10.30 am to 10.45 am | **Tea Break** |
| 10.45 am to 11.30 am | **Topic :** Challenges in the Formulation Development of Medicinal Plants<br>**Speaker: Dr. D. Natarajan,**<br>Pharmaceutical Consultant for Formulation and Development, Chennai. |
| 11.30 am to 12.15 pm | **Topic** : Herbal Drug Standardization- Fit for Purpose Approach<br>**Speaker: Dr. J. L. N. Sastry,**<br>Head – Healthcare Research,<br>Dabur Research & Development Centre, Sahibabad-210 010. |
| 12.15 pm to 01..00 pm | **Topic:** Shelf Life Studies of ASU&H Drugs<br>**Speaker: Dr. R. Ilavarasan,**<br>Assistant Director (Scientist-4),<br>Institute In-charge, CSMRADDI, Chennai. |
| 01.00 pm to 02.00 pm | **Lunch Break** |
| 02.00 pm to 03..00 pm | **Topic:** Importance of Safety and Efficacy Studies on Traditional Medicines in Context to Reverse Pharmacology<br>**Speaker: Dr. Mukesh Kumar Nariya,**<br>Pharmacologist, IPGT &RA, Gujarat-361 008. |
| 03..00 pm to 04..00 pm | **Visit of the Institute** |
| 04.00 pm to 04.15 pm | **Tea Break** |
| 04.15 pm to 05.15 pm | Valedictory Function & Certificate Distribution<br>· **Chief Guest: Dr.S.Manivannan,**<br>Deputy Drugs Controller, Government of India<br>· A Concluding Speech : Brief about the Seminar<br>**Dr. A.K.Meena,** Assistant Director (Chemistry).<br>· Vote of Thanks: **Dr. S.Chitra,** Assistant Director (Biochemistry) |
| 5.15 pm | **National Anthem** |

# ARTICLES

## NANOPARTICLES IN AYURVEDA

by

**Dr. M. Nappinnai,**
Head Formulation R&D, Dhanvantri Nano Aushadhi Pvt Ltd., Chennai
(Lecture Delivered during the National Seminar on Modern Scientific Approach for Standardization of Medicinal Plants used in ASU & H Drugs on 25th & 26th March 2019)

### Nano- an introduction

- Nanotechnology is a broad term applicable to any branch of science that deals with small things.
- Modern nanotechnology can trace its conceptualisation to Physicist Richard Feyman who in 1959 presented a lecture entitled- THERE IS PLENTY OF ROOM AT THE BOTTOM..
- but the credit for coining the term NANOTECHNOLOGY goes to Professor Norio Taniguchi

### Nano….

- History of origin of the word NANO (Latin – Nanus- meaning Dwarf) can be traced wayback to 1960s where it was officially endorsed by the General Conference on Weights and Measures(CGPM) to be used as a prefix to denote "one billionth"or $10^{-9}$

### In Ayurveda…

- Indian‟s Ayurveda details the preparation of Bhasma which are herbo – mineral preparation containing nanoparticles by specialized processed which are described in the samhitas.

### Bhasma

- The ancient use of nanotechnology in the preparation of Bhasma in Ayurveda is unique due to the nanodimension of the final product.

### Bhasma

- These are the products of classical Indian alchemy, the "Ayurveda Rasa Shastra," used for treating diverse chronic ailments.
- The essence of metal/mineral based drugs is that they function best when converted from their original metal/mineral state .
- The manufacturing process is very systematic and elaborate, called "Bhasmikarana" which converts the metal from its zerovalent state to a form with higher oxidation state, and eliminates the toxic nature of metal .

## Process

- During Bhasmikarana, metals / minerals are subjected to various processes of purification and incineration before internal administration, aimed to reduce the particle size and thus, converting them into
- biocompatible,
- bio-assimilable,
- absorbable,
- and suitable form for the human body.

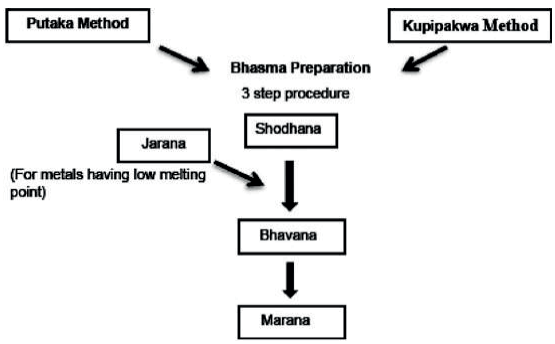
## Bhasma

- Bhasma nanoparticles are organo-metallic/organo-mineral complexes as they are integrated with biological molecules (of organic liquid media), having improved stability,
- functionality,
- absorption,
- assimilation,
- bioavailability,
- biocompatibility,
- targeted delivery of ingredient,
- and effectiveness

## Benefits

- Rasayana (immunomodulation and anti-aging quality),
- Yogavahi(target drug delivery),
- Alpamatra (prescribed in minute doses i.e., 15–250 mg/day),
- Rasibhava (readily absorbable, adaptable, assimilable, and nontoxic),
- Shigravyapi (spreads quickly and fast acting),
- Agnideepana (increases metabolism at cellular level and acts as catalyst)
- Bhasma can be employed for selective / targeted/controlled drug delivery as they are biocompatible, nontoxic, and nonantigenic in nature.

## Traditional method



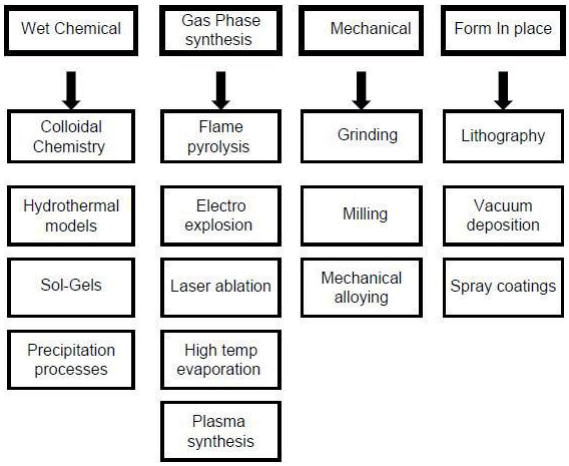
## Tests- characterising

| Sanskrit equivalent | Physical characteristic | Description |
|---|---|---|
| *Visishta Varnotpatti* | Specific colour | There is a specific colour for each *Bhasma*. If there is an alteration in the colour it is suggested that the *Bhasma* is not made properly, since a particular metallic compound is formed during *Bhasma* preparation and every chemical compound possesses a specific colour |
| *Rekhapurantva* | Fineness to enter finger ridges | *Bhasma* particles should be of minimum size so that it can be easily absorbed and assimilated in the body. It should be so fine that it should be able to fill the furrows of finger tips. A little amount of *Bhasma* is rubbed in between index finger and thumb to observe whether the particles can fill furrow of finger tips |
| *Varitaratva* | Lightness to float in water | The test is based on the law of surface tension. Little amount of *Bhasma* is taken in between index finger and thumb, after which it is sprinkled slowly on stagnant water surface from a short distance. If its properly incinerated, the *Bhasma* shall float on the water surface |
| *Gatarastva* | Tastelessness | Properly incinerated *Bhasma* of a metal should be of particular taste. It indicates transformation of particular metallic taste to compounds of specific taste |
| *Nischandratva* | Lustrelessness | The *Bhasma* must not be shiny before therapeutic application. Luster or shine is a character of a metal. After proper incineration the luster of the metal should not remain. Therefore, *Bhasma* is observed under bright sunlight, for assessing whether luster is present or not. If luster is present, it still needs further incineration |
| *Anjanabhatva* | Smoothness | *Anjana* (collyrium) is smooth in character and it doesn't create any irritation when applied. Properly incinerated *Bhasma* should be smooth and should not create any irritation to the mucous membrane of the gastrointestinal tract |
| *Apunarbhavtva* | Permanence | *Apunarbhavtva* means incapability to regain original metallic form. For this test *Bhasma* is mixed with equal quantity of *Mitra Panchaka* (seeds of *Abrus precatorius*, honey, ghee, borax and jiggery) and it is sealed in *Sarava Samputa* (earthen pots), thereafter similar grade of heat used for preparation of particular *Bhasma* is applied and on self-cooling product is observed |
| *Niruthatva* | Irreversibility | It is to test the inability to regain metallic form of metallic *Bhasma*. In this test *Bhasma* is mixed with a fixed weight of silver leaf, kept in earthen pots and similar grade of heat is applied and after self-cooling, weight of silver is taken. Increase in weight of silver indicates improperly prepared *Bhasma* |

## Outsider View

- The major limitation in the traditional method of preparation is the use of heavy metals like mercury and toxic chemicals like sulphur.
- Reproducibility
- Validated method
- Analytical
- Proof – modern scientific system and analytical methods

## General method of preparing nanoparticles



**What is new?**

- Compare
- Limitation
- NOVEL METHOD

**Filling the gap**

- Green nanotechnology
- Unique method
- No synthetic chemicals
- No volatile solvents
- No heating or cooling

**UNIQUE PROPRIETARY INNOVATIVE GREEN NANOTECHNOLOGY**

**Ayurveda- with Nanolife**


**NANOLIFE**

The Natural Circle of Life

where the

The Futuristic Nano Medicines

gets you back to

Good Health, Good Life

For Life **NANOLIFE** works

**Scientific Validation**

- Swarna bhasma & Rajata bhasma are subjected to rigorous analysis
- Subjected to
  PARTICLE SIZE ANALYSIS- malvern particle size analyser
  ZETA POTENTIAL
  ATOMIC ABSORPTION SPECTROSCOPY
- Surface plasmon resonance
  pH
  Density
  TEM( Transmission Electron Microscopy)

**Publications**

- PREPARATION AND CHARACTERISATION OF NANO SWARNA BHASMA
  By Deepak Abhaya et al
- Deepak et.al / IJIPSR / 6 (07), 2018, 68-72 Department of Ayurvedic Science
- ISSN (online) 2347-2154
- DOI: 10.21276 / IJIPSR. 2018. 06.07.720

**Publications**

- PREPARATION OF NANO RAJATA BHASMA AND EVALUATION OF PHYSICOCHEMICAL PARAMETERS
  by Deepak Abhaya et al
- www.wjpps.com Vol 7, Issue 9, 2018. 799

**Characterization of Nanoparticles**

- Physio chemical charcterisation
- Specific analysis – Particle size,Zeta Potential, Surface plasmon resonance ,TEM etc
- Invivo evaluation - absorption, distribution, excretion etc

**Proof of concept**

- Recording observation
- Validating the claim with proof
- Credibility – world wide

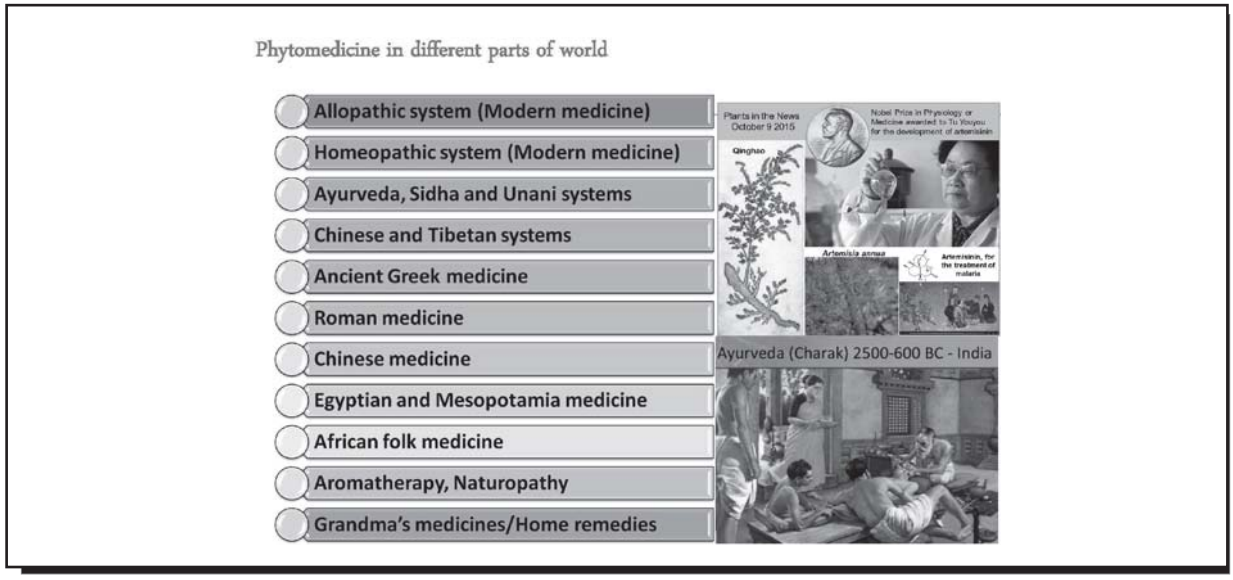
**Further information**

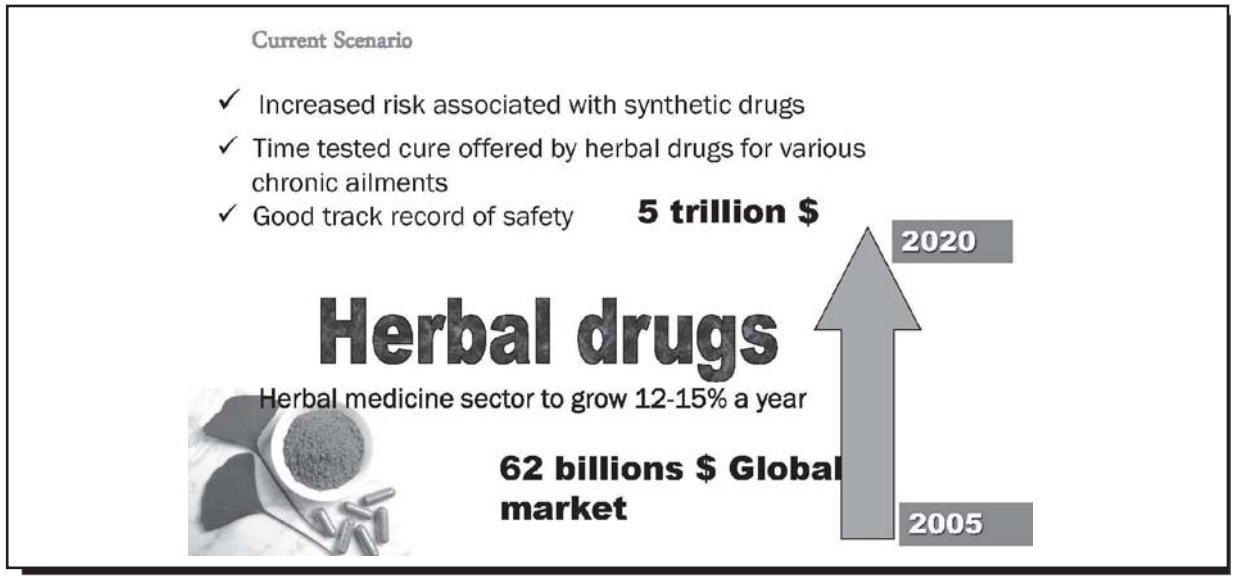
- Please contact
- enquiry@nanolife.in
- 044 40927365

# STANDARDIZATION OF BOTANICALS - REGULATORY AND ANALYTICAL PERSPECTIVES

by

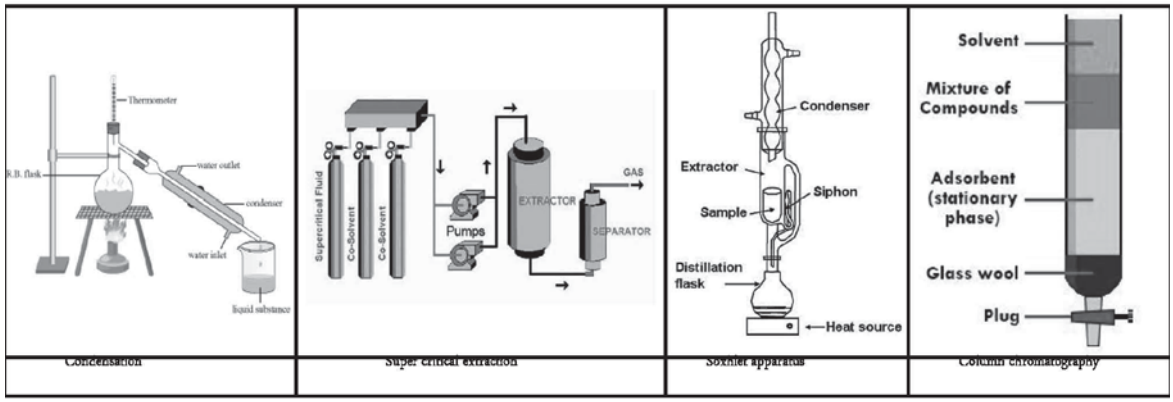
**Dr. R. Sundaram,**
Head, A-R&D, The Himalaya Drug Company, Bangalore
(Lecture Delivered during the National Seminar on Modern Scientific Approach for Standardization of Medicinal Plants used in ASU & H Drugs on 25th & 26th March 2019)



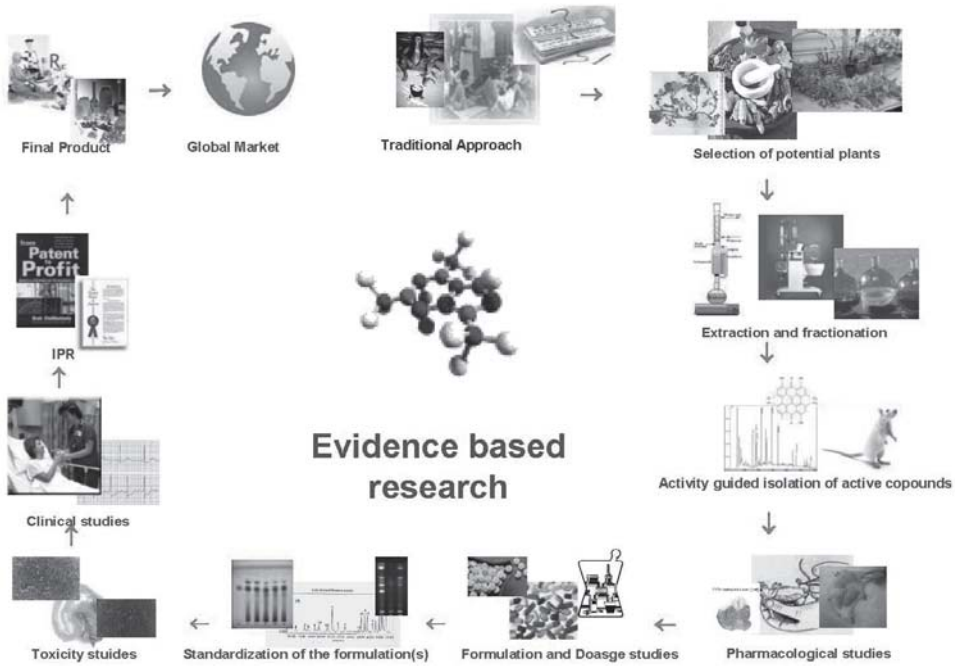



## Herbs may be old- They can be reinvented using novel technologies

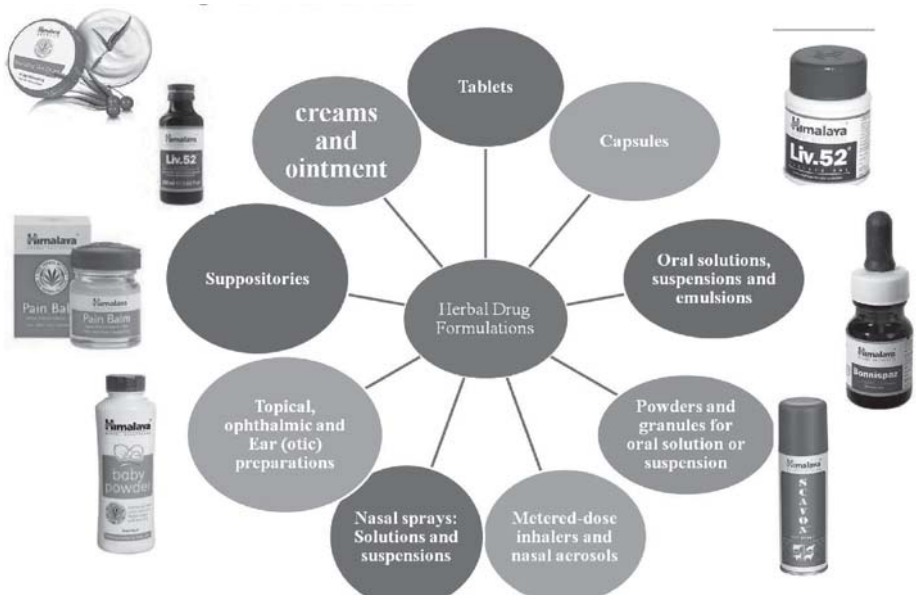
As science is evolving number of novel technologies are being employed for distillation,expression,fractionation,purification,concentration or fermentation. These include powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.




Concentration | Super critical extraction | Soxhlet apparatus | Column chromatography

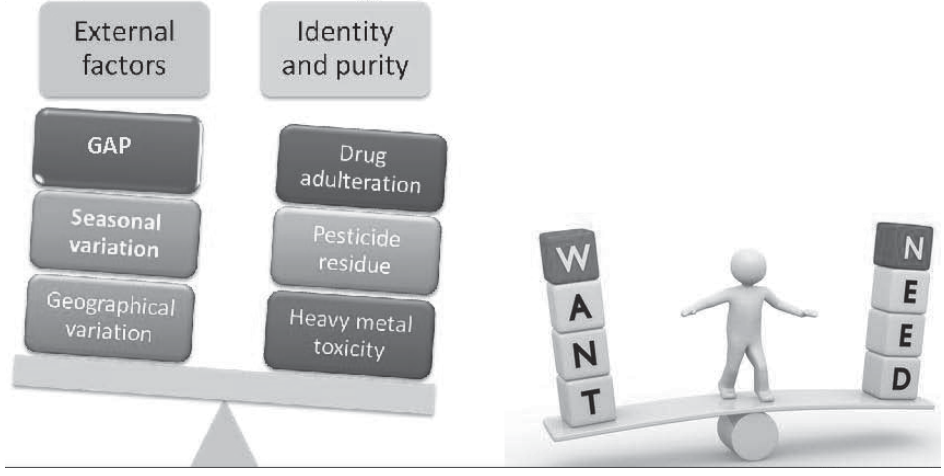


## Herbal Drug Formulations




## Herbal Drug Standardization

Standardization of drugs means confirmation of its identity and determination of its quality and purity and detection of nature of adulterant by various parameters like morphological, microscopical, physical , chemical and biological evaluation.



## Herbal Drug Standardization

*Shivakumar et al., IJPSR, 2016; Vol. 7(1): 244-251.* E-ISSN: 0975-8232; P-ISSN: 2320-5148

IJPSR (2016), Vol. 7, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 July, 2015; received in revised form, 06 October, 2015; accepted, 06 November, 2015; published 01 January, 2016

**PHARMACOGNOSTIC EVALUATION OF *TRIPHALA* HERBS AND ESTABLISHMENT OF CHEMICAL STABILITY OF *TRIPHALA* CAPLETS**

Arun Shivakumar, Sukanya Paramashivaiah, Rakesh Surappa Anjaneya, Jakeer Hussain and Sundaram Ramachandran *

Research and Development, The Himalaya Drug Company, Makali, Tumkur Road, Bangalore-562162 Karnataka, India.

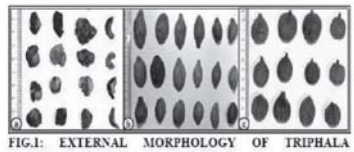
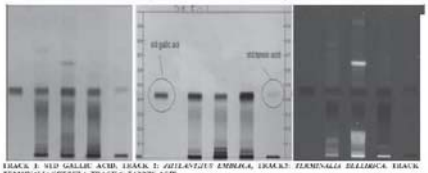


FIG.1: EXTERNAL MORPHOLOGY OF TRIPHALA FRUITS; a. *PHYLLANTHUS EMBLICA;* b. *TERMINALIA CHEBULA;* c. *TERMINALIA BELLIRICA.*

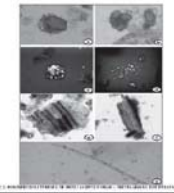
TABLE: 2 STANDARDIZATION OF RAW HERBS USED FOR *TRIPHALA* CAPLETS

| Parameters | *Phyllanthus emblica* Fruit %w/w | *Terminalia bellirica* Fruit %w/w | *Terminalia chebula* Fruit %w/w |
|---|---|---|---|
| Alcohol Extractive value | 41.0 to 44.0 | 41.0 to 44.0 | 41.0 to 54.0 |
| Water Extractive value | 50.0 to 60.66 | 50.0 to 60.66 | 62.0 to 66 |
| Loss on Drying | 5.80 to 7.90 | 5.80 to 7.90 | 5.00 to 9.20 |
| Ash value | 2.65 to 3.45 | 2.65% to 3.45 | 1.50 to 3.00 |
| Acid insoluble ash | 0.20 to 1.55 | 0.20% to 1.55 | 0.050 to 0.30 |



TRACK 1: STD GALLIC ACID, TRACK 2: *PHYLLANTHUS EMBLICA*, TRACK3: *TERMINALIA BELLIRICA*, TRACK *TERMINALIA CHEBULA*, TRACK 4: TANNIC ACID

FIG.7: HPTLC FINGERPRINTS OF RAW HERBS USED IN *TRIPHALA* FORMULATION



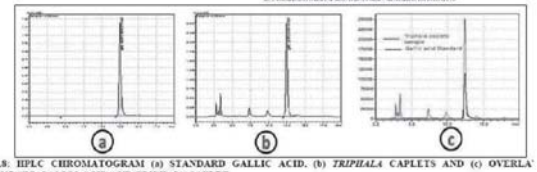
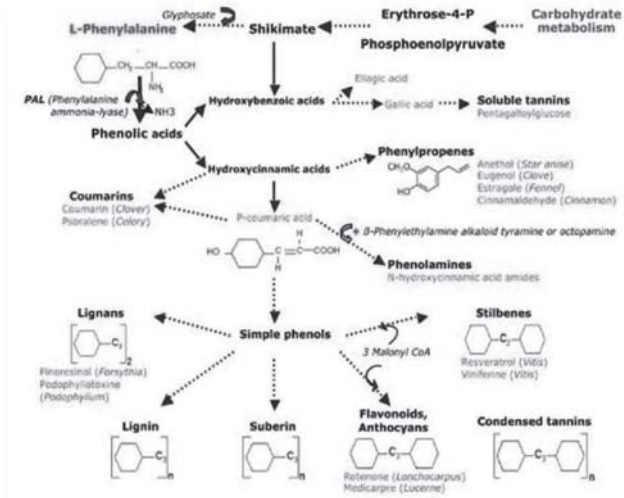


FIG.8: HPLC CHROMATOGRAM (a) STANDARD GALLIC ACID. (b) *TRIPHALA* CAPLETS AND (c) OVERLAY STANDARD GALLIC ACID AND *TRIPHALA* CAPLET

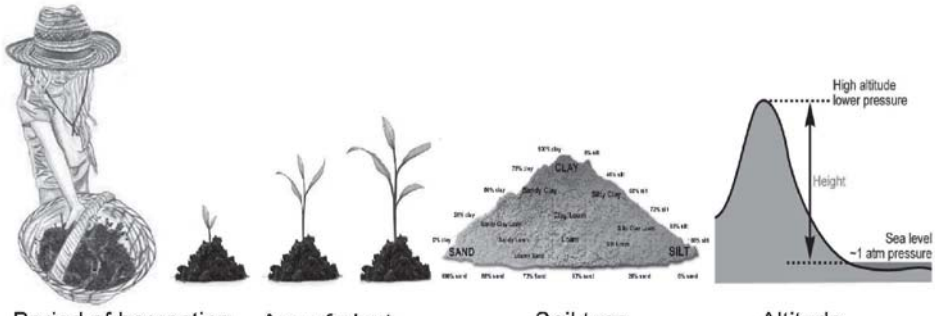
## Seasonal and geographical variations



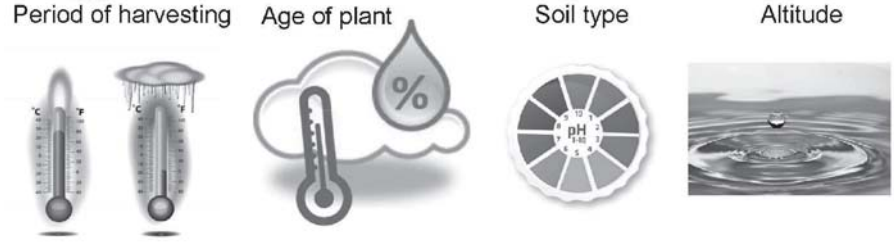

Simplified pathway of phenolic compound synthesis (adapted from Roland Douce, 2005) — *Voie de synthèse simplifée des composés phénoliques (d'après Roland Douce, 2005).*

## Metabolites to phytochemicals

## Seasonal and geographical variations

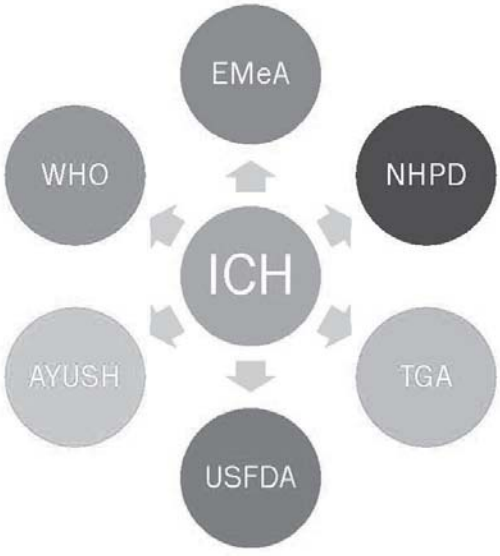



Period of harvesting | Age of plant | Soil type | Altitude




Temperature | Humidity | pH | Water

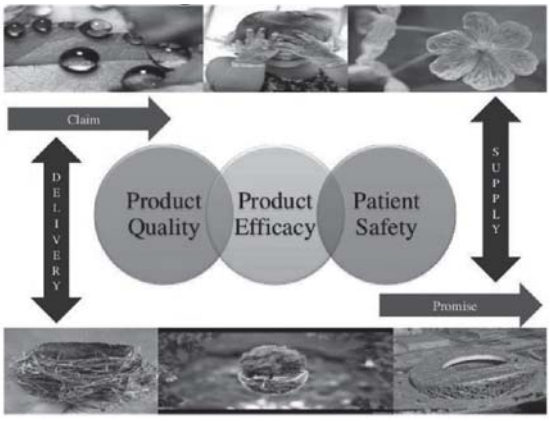
## Global Regulatory Framework



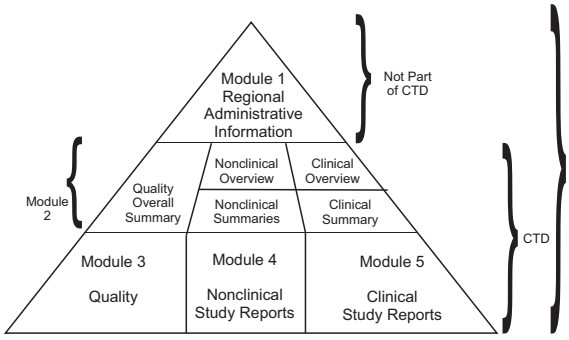

## Classification of natural products by regulators

- Dietary supplements
- Nutraceuticals
- Traditional Herbal Medicines
- Ayurvedic Medicine
- Phyto-pharmaceuticals
- Specialty foods
- Biotechnology derived products

## Key focus of regulators

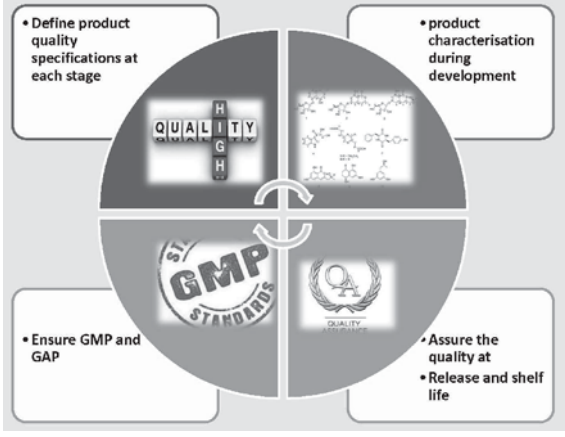



## CTD Triangle

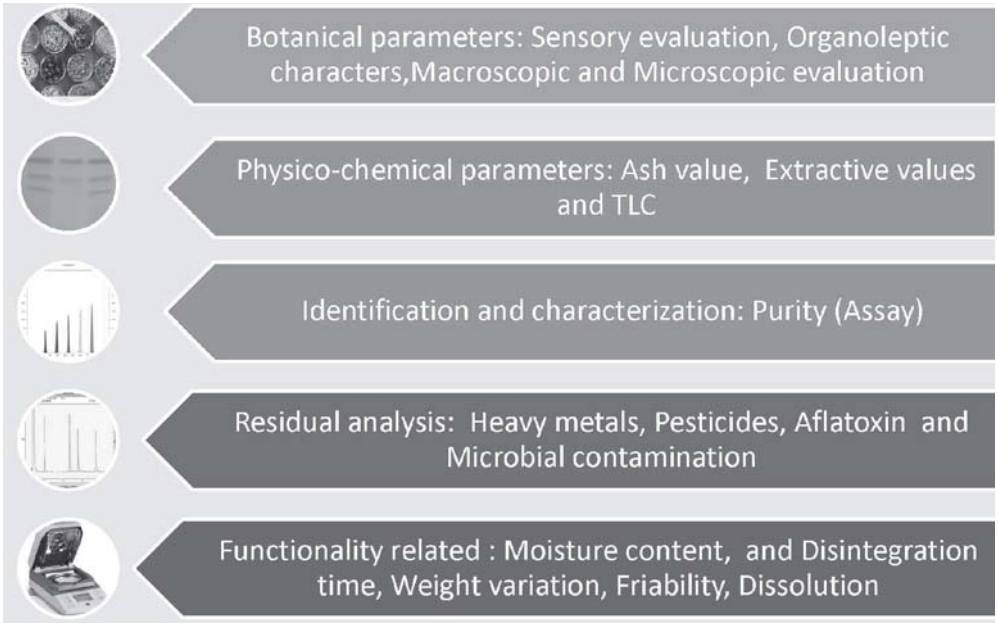



## What's quality?


## How quality can be assured?



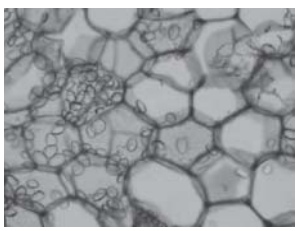
## Specification-Strategy



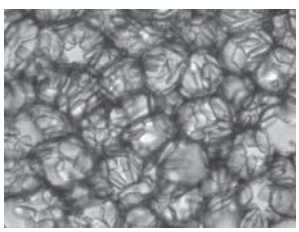

## Hedychium spicatum & Kaempferia galanga-Rhizome

*Hedychium spicatum-Rhizome*

*Kaempferia galanga-Rhizome*

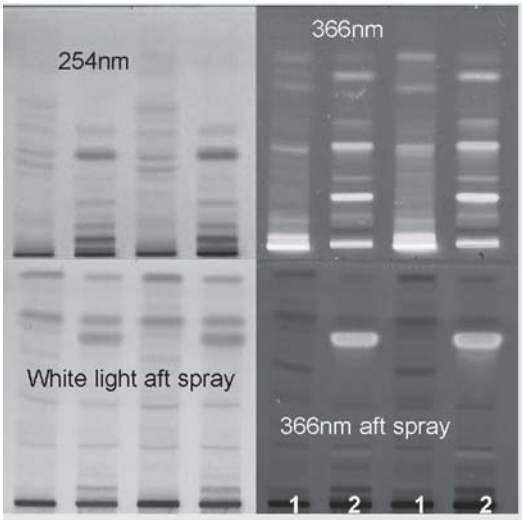


*TS of H.s-rhizome shows oval to oblong simple starch grains (Sg)*



*TS of K. g-rhizome shows the elongated simple starch grains (Sg)*

**E.g:Differentiation b/w hibiscus Rosa sinensis and Rhododendron arboretum flower**

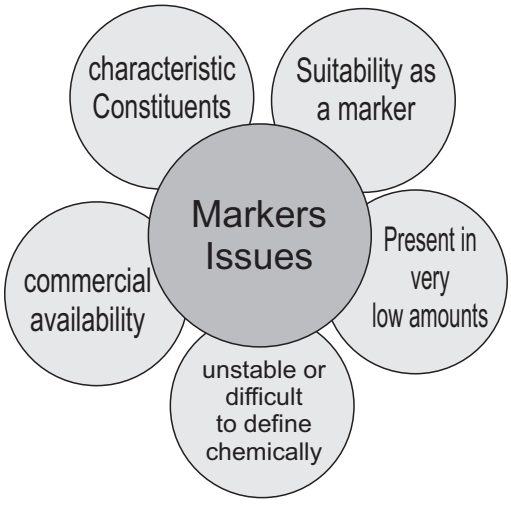



Track-01=Hibiscus rosa sinensis/flower
Track-02=Rhododendron arboreum/flower
(Adulterant for hibiscus rosa sinensis)

Hibiscus rosa sinensis flower

Rhododendron arboretum flower

**Key focus area- Markers**




**Assuring quality through development?**

- Quality control for raw materials
- Process optimization and validation
- Critical process controls
- Accelerated and long term stability studies

**How to ensure purity / strength in botanicals?**

- Authenticity
- Adulteration/substitution
- Seasonal and Geographical variations
- Maturity variations
- Harvesting and processing
- Process in case of biotechnological products

**What Impurities to be controlled?**

- Microbial contamination
- Heavy metals
- Pesticide residues
- Environmental pollutants
- Mycotoxins
- Radioactive substances

**Definition**

**Herbal substances :**

- Mainly whole, fragmented or cut plants, plant parts, in an unprocessed, usually dried form but sometimes fresh.

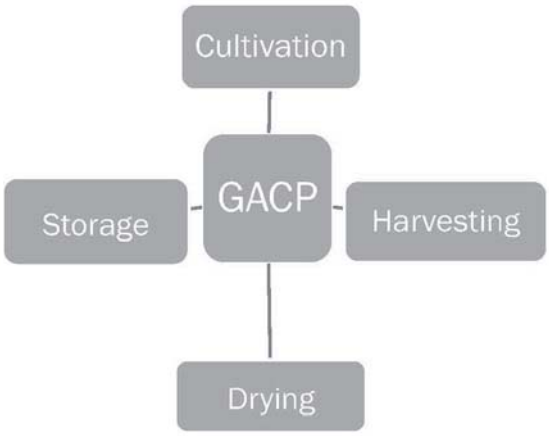
**Herbal preparations:**

- subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation.

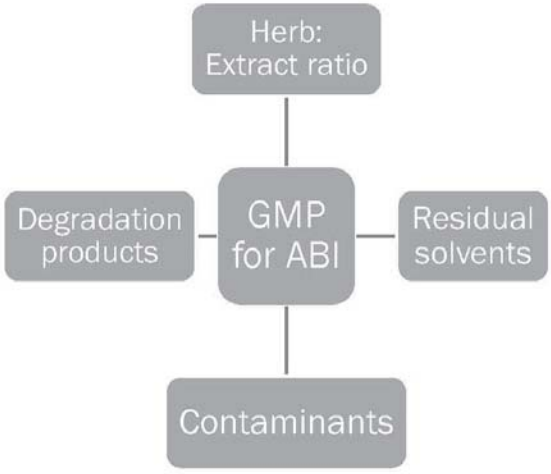
**Herbal medicinal product:**

- exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

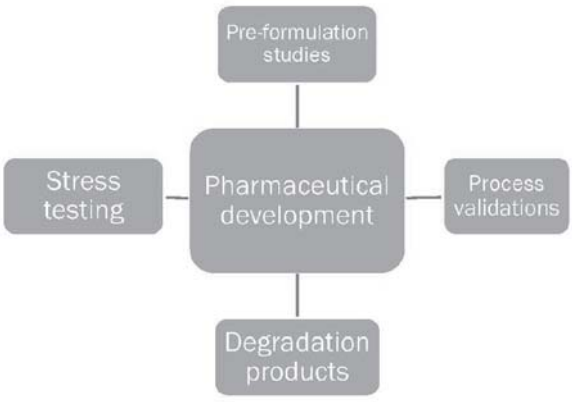
**GACP consideration**



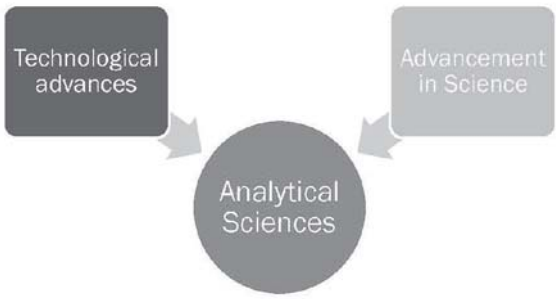

**GMP consideration**




**GMP of formulations**




**Evolving Analytical Sciences**



## HPTLC

- High-performance thin-layer chromatography (HPTLC) is the most advanced version of TLC . In HPTLC, the stationary phase consists of a uniform, typically 200-µm layer of porous (pore size 60 Å), irregular particles of silica gel with a size between 2 and 10µm and an average particle size of 5µm, plus a polymeric binder and a fluorescence indicator (F254) coated onto a support, which is typically a glass plate or aluminum foil.

- Other stationary phases, such as chemically bonded phases (C8, C18, CN, NH2; DIOL) or microcrystalline cellulose, are also available with and without a fluorescence indicator.

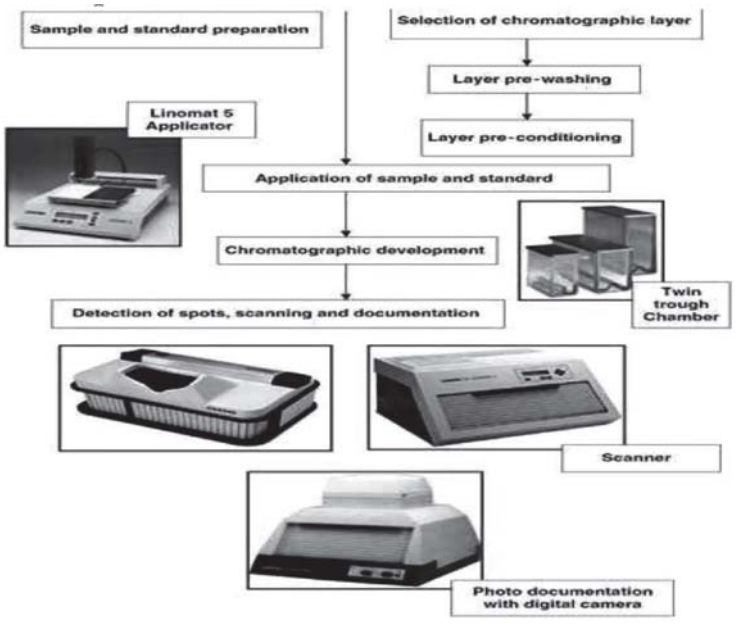
## Difference between TLC and HPTLC

| parameters | TLC | HPTLC |
|---|---|---|
| •Chromatographic plate used | Hand made | Pre-coated |
| •Sorbent layer thickness | 250µm | 100-200µm |
| •Pre-washing of plates | Not followed | must |
| •Application of sample | Manual | automatic |
| •Shape | spot | Spot/band |
| •Sample volume | 1-10µl | 0.2-5µl |
| •Efficiency | Low | High |
| •Analysis time | Slow | Greatly reduced |
| •Development chamber | More amount of solvent | Less amount of solvent |
| •Spots size | 2-4mm | 0.5-1mm |
| •Scanning | Not possible | Use of UV/ Visible/ Fluorescence scanner (densitometer) |

## Instrumentation for HPTLC

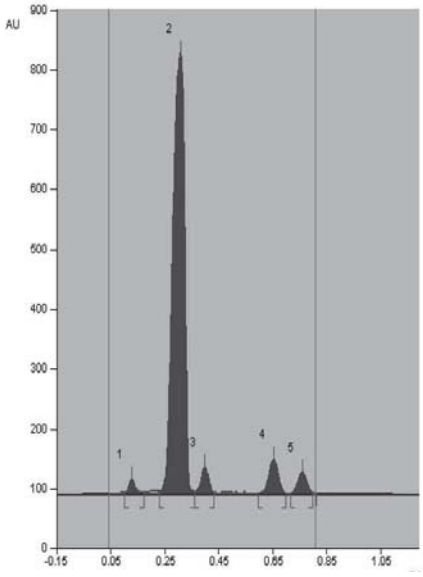
- Linomat IV (Spotting instrument)
- Densitometer (Scanner)
- Reprostar (Photo documentation system)

## Steps in HPTLC

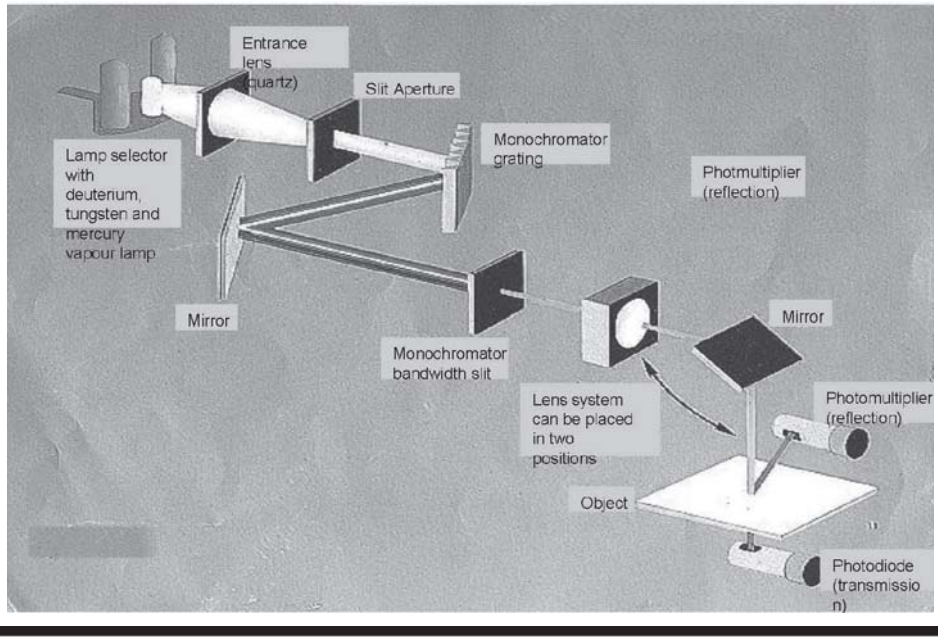


## Densitometer (Scanner)

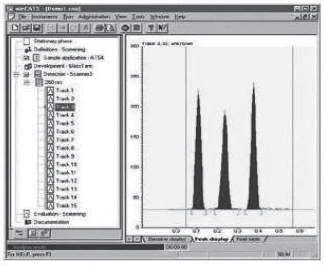
- An instrument which measures optical density by measuring the intensity of transmitted or reflected light D
- Used for chromatogram evaluation
- Gives peak data
- Useful in quantitative estimation
- Densitometry can be performed in absorbance or fluorescence mode
- Spectrum from 190-800nm can be taken
- Absorption spectra for substance identification can be recorded



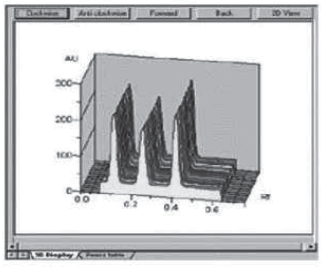

## Scanner instrumentation



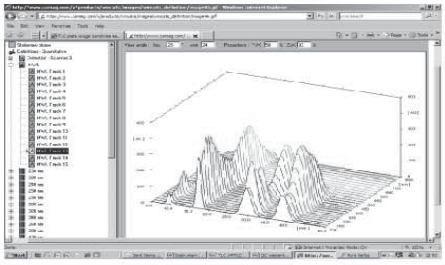
## Chromatographic views



Single integrated chromatogram

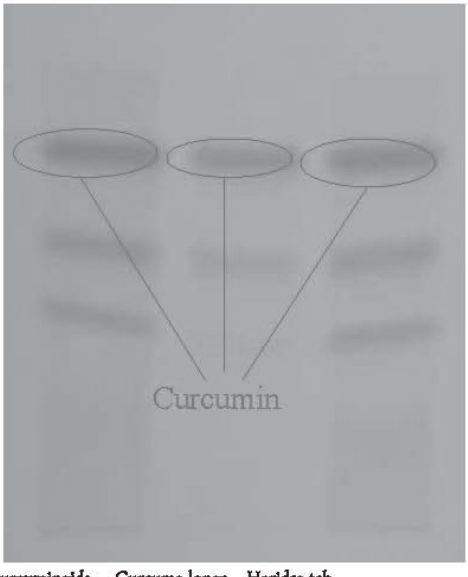


Chromatogram
of multiple tracks

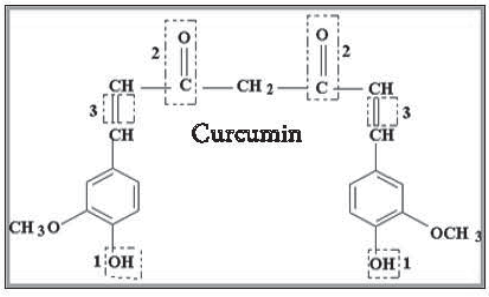


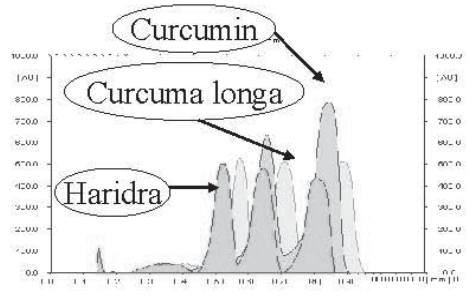
Multi wavelength
chromatogram

## HPTLC of Curcuma longa




Curcuminoids Curcuma longa Haridra tab

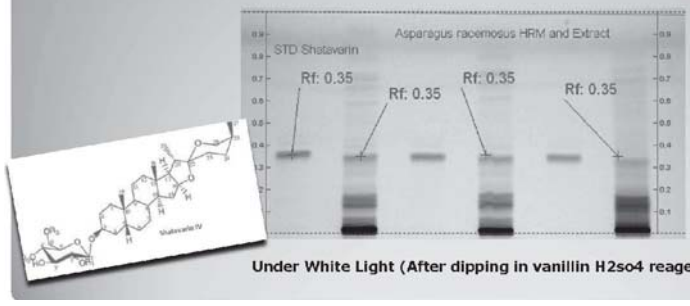


## Identification of Shatavarin in *Asparagus racemosus root*

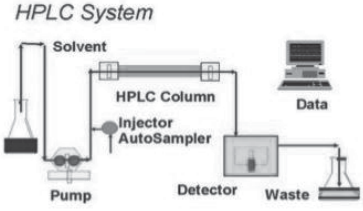
**Chromatographic system :**

| | | |
|---|---|---|
| TLC plate type | : | Pre coated thin layer silica plate 60 $F_{254}$, 10 x 10 cm, E-Merck |
| Mobile phase | : | Chloroform: Methanol :Water(65:35 :10) |
| Spotting volume | : | 10 µl of sample and 10 µl of standard. |
| Saturation time | : | 30 minutes |
| Sample preparation | : | 10 mg/ml with methanol |
| Std preparation | : | 0.1mg/ml with methanol |




Under White Light (After dipping in vanillin H2so4 reagent)

## HPLC




Originally referred to as High-Pressure Liquid Chromatography

Now more commonly called High Performance Liquid Chromatography

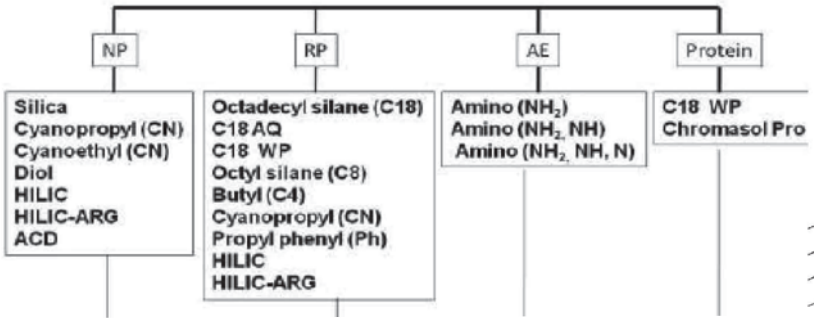
HPLC is really the automation of traditional liquid chromatography under conditions which provide for enhanced separations during shorter periods of time, utilizing very small particles, small column diameters, and very high fluid pressures.

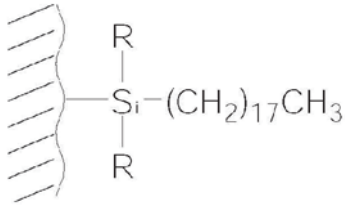
## Four Types of Liquid Chromatography

There are four major separation modes that are used to separate most compounds

- Reverse-phase chromatography
- Normal-phase chromatography
- Ion exchange chromatography
- Size exclusion, or gel chromatography

## Different types of column chemistry

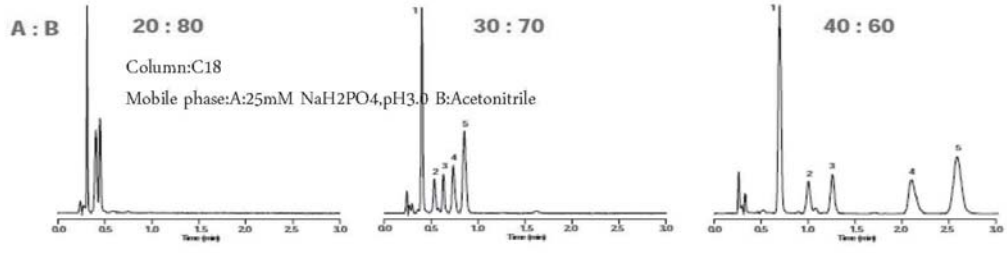


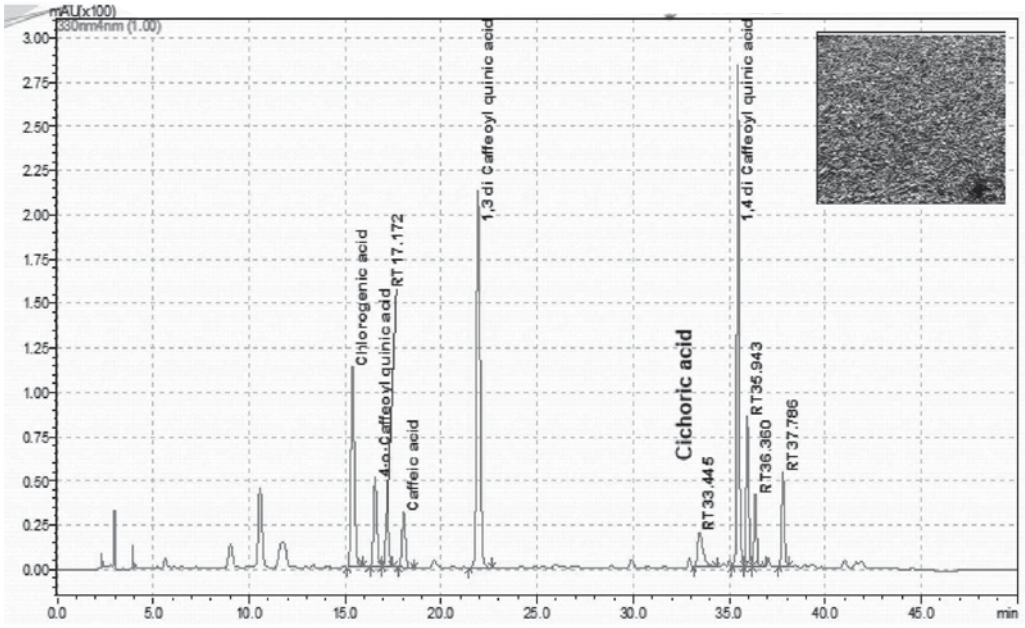

- C-18, C-8 : Rugged, general purpose, highly retentive
- Aqueous : polar molecules.
- Silica,HILIC,C-3, C-4 :Less retentive, used mostly for peptide & proteins.
- Phenyl : Greater selectivity than alkyl-bonded
- Cyano : Moderate retention, normal & rev. phase
- Amino : Weak retention, good for carbohydrates

## Rapid Method Development Scheme – Low pH

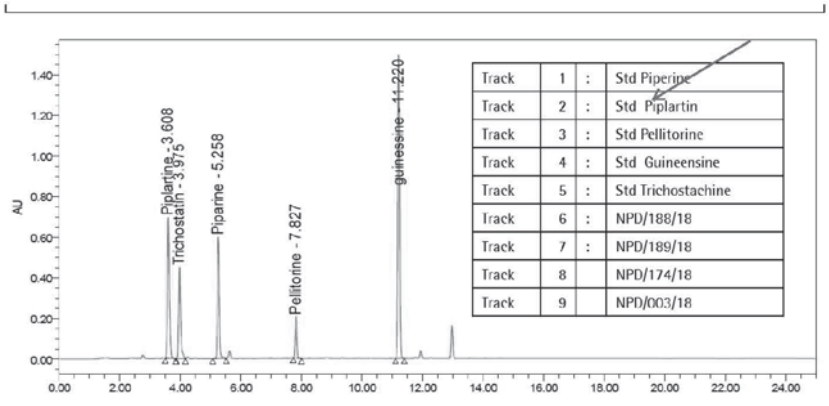
- Start at low pH for best peak shape, retention and long-term reproducibility
- Select starting conditions
- C18 or C8 for maximum lifetime – Rapid Resolution columns
- pH 2 – 3.5 with 20 – 50 mM buffer for best peak shape
- Acetonitrile or methanol – start high to scout
- Adjust organic for maximum resolution and retention
- Change organic if resolution not achieved – MeOH or ACN
- Change bonded phase if resolution not achieved – Different columns
- Using elevated temperature to reduce analysis time further

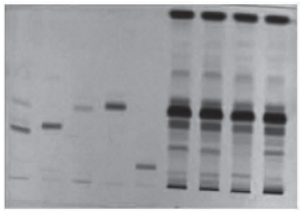


## Cinnamic acid derivatives by HPLC

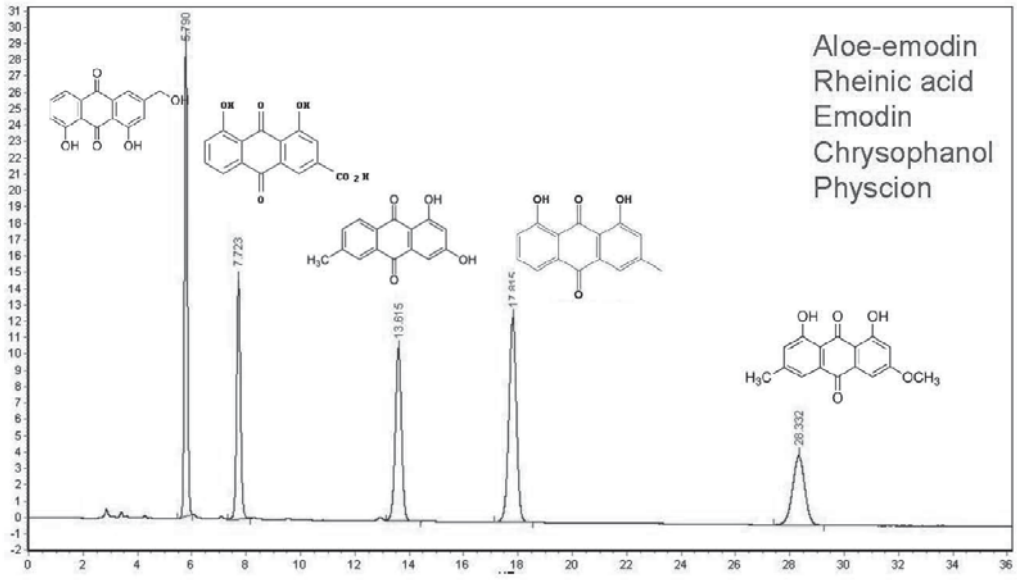



## HPLC & TLC Pattern Piperine Alkaloids in Piper longum fruit: TLC @254 nm

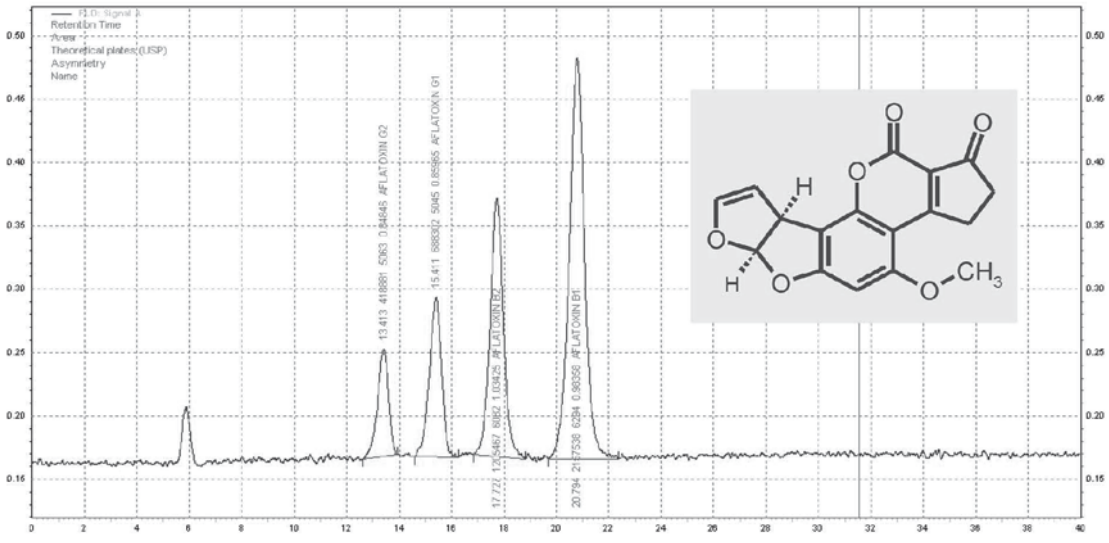


## Separation of anthraquinone mixture by HPLC




## Mycotoxins analysis in THDC




*Standard chromatogram of Aflatoxin G2, G1, B2 & B1*

## Gas Chromatography (GC)

Gas chromatography (GC) is a laboratory technique that separates mixtures into individual components. It is used to identify components and to measure their concentrations.

**COMPOUND REQUIREMENTS FOR GC**

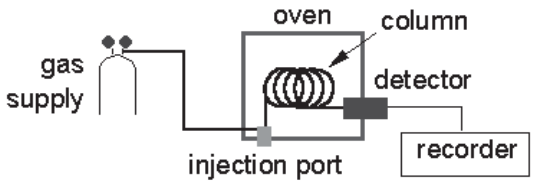
The compounds must have:

- Sufficient volatility
- Thermal stability
- NO Inorganic Acids, Bases and s

## Gas Chromatography (GC)

Gas chromatography is a chromatographic technique that can be used to separate volatile organic compounds. It consists of

- a flowing mobile phase
- an injection port
- a separation column (the stationary phase)
- an oven
- a detector.



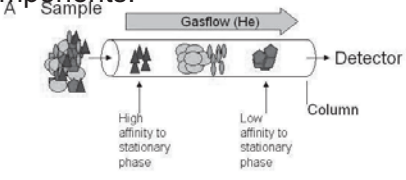

## GC Detectors

After the components of a mixture are separated using gas chromatography, they must be detected as they exit the GC column. Thermal-conduc. (TCD) and flame ionization (FID) detectors are the two most common detectors on commercial Gcs.

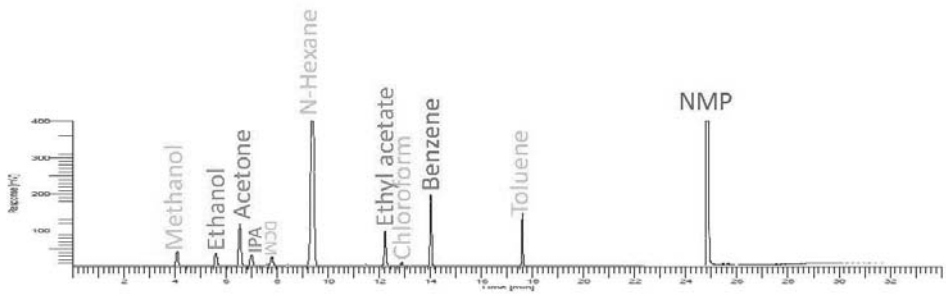
The others are

1.Atomic-emmision detector (AED)
2.Chemiluminescence detector
3.Electron-capture detector (ECD)
4.Flame-photometric detector (FPD)
5.Mass spectrometer (MS)
6.Photoionization detector (PID)
7.Nitrogen phosphorus detector(NPD)

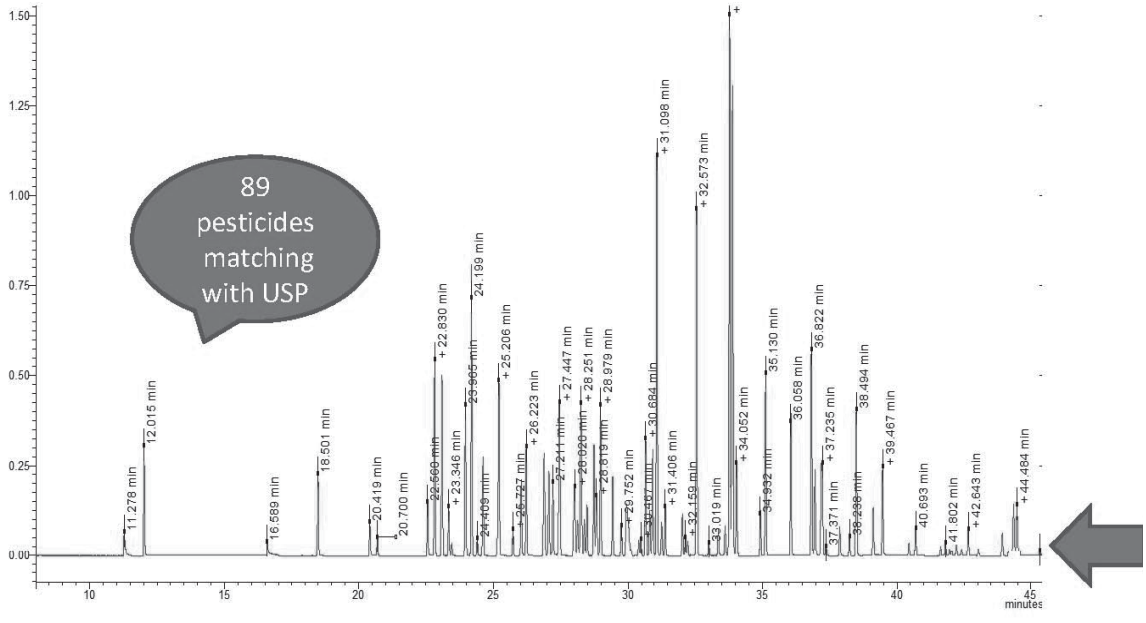
- Mobile phases are generally inert gases such as helium, argon, or nitrogen.
- The injection port consists of a rubber septum through which a syringe needle is inserted to inject the sample.
- The injection port is maintained at a higher temperature than the boiling point of the least volatile component in the sample mixture.
- Separating components with a wide range of boiling points is accomplished by starting at a low oven temperature and increasing the temperature over time to elute the high-boiling point components.



## Residual Solvents Analysed By
## Perkin Elmer Clarus 680 GC with Turbo HS-40

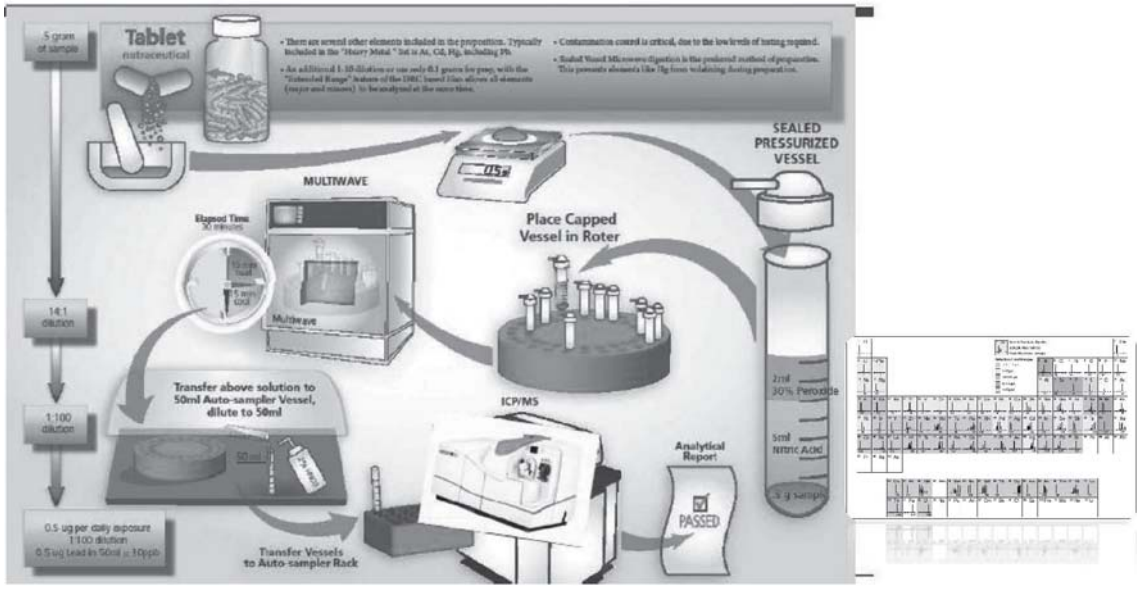


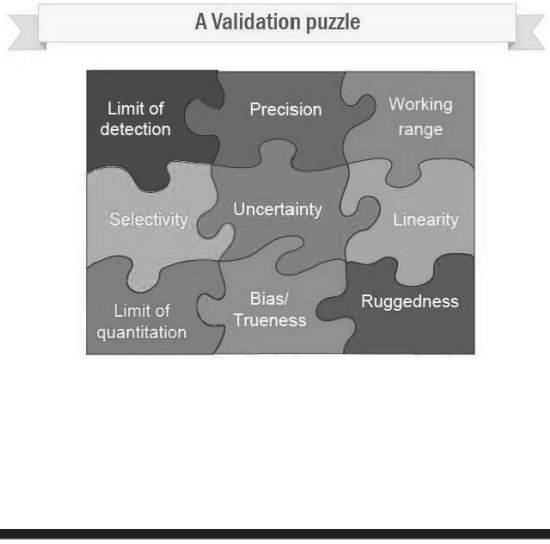

| Peak # | Component Name | Time [min] | Area [uV*sec] | Theoritical plates | Tailing factor | Resolution |
|---|---|---|---|---|---|---|
| 1 | Methanol | 4.093 | 223350 | 17065 | 0.99 | ---------- |
| 2 | Ethanol | 5.601 | 207436 | 19625 | 1.21 | 9.82 |
| 3 | Acetone | 6.539 | 720954 | 24226 | 1.15 | 5.58 |
| 4 | IPA | 6.991 | 203687 | 21524 | 1.16 | 2.50 |
| 5 | DCM | 7.796 | 141486 | 36851 | 1.02 | 4.42 |
| 6 | n-Hexane | 9.377 | 4577998 | 30883 | 1.00 | 7.95 |
| 7 | Ethylacetate | 12.229 | 466320 | 126120 | 1.10 | 15.92 |
| 8 | chloroform | 12.883 | 38122 | 170530 | 1.00 | 4.98 |
| 9 | Benzene | 14.020 | 785004 | 266468 | 1.01 | 9.68 |
| 10 | Toluene | 17.605 | 430889 | 774789 | 1.00 | 37.65 |
| | | | 7795246 | 1488082 | 10.64 | 98.50 |




**GC MS Chromatogram showing the identification of 89 pesticides in a single run**

## Heavy metal analysis by ICP-OES or ICP-MS




# TOXICITY / SAFETY EVALUATION OF ASU&H DRUGS

by

**Dr. R. Ilavarasan,**
Assistant Director (Scientist-4), Institute In-charge, CSMRADDI, Chennai
(Lecture Delivered during the National Seminar on Modern Scientific Approach for Standardization of Medicinal Plants used in ASU & H Drugs on 25th & 26th March 2019)

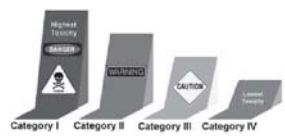
## Introduction

### Toxicology

It is the **study of poisonous effect of drugs** and other chemicals (household, environmental pollutant, industrial, agricultural, homicidal) with emphasis on detection, prevention and treatment of poisonings. It also **includes the study of adverse effects of drugs,** since the same substance can be a drug or a poison, depending on the dose.


## Toxicity- Definition

Toxicity is the degree to which a **chemical substance** or a particular **mixture** of substances can damage an **organism**. Toxicity can refer to the effect on a whole organism such as an **animal**, **bacterium** or **plant** as well as the effect on a substructure of the organism, such as a **cell (cytotoxicity)** or an organ such as the **liver (hepatotoxicity).**




## Toxicity tests

The aim is to determine safety of the compound by oral and parenteral routes mostly in Rodents.

### Acute toxicity

- Single escalating doses are given to small groups of animals
- Observed for overt effects and mortality for 1–3 days
- LD50 is calculated
- Organ toxicity is examined by histopathology

### Subacute toxicity

- Repeated doses are given for 2–12 weeks
- Doses are selected on the basis of ED50 and LD50
- Animals are examined for overt effects, food intake, body weight, haematology etc. and organ toxicity

### Chronic toxicity

- The drug is given for 6–12 months
- Effects are studied as in sub acute toxicity
- Generally undertaken concurrently with early clinical trials

**Special long-term toxicity**

- Generally performed only on drugs which **cross phase I clinical trials**

**Reproduction and teratogenicity**

- Effects on **spermatogenesis, ovulation, fertility and developing fetus** are studied

**Mutagenicity**

- Ability of the drug to induce genetic damage
- Assessed in bacteria (Ames test), mammalian cell cultures and in intact rodents

**Carcinogenicity**

- Drug is given for long-term, even the whole life of the animal and they are watched for development of tumours

Standardized procedures under **'Good Laboratory Practices' (GLP)** have been laid down for the conduct of animal experiments, especially toxicity testing.


**ASU Drugs Definition**

**Ayurvedic, Siddha or Unani drug includes**

- All medicines intended for internal or external use for the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals.

- Manufactured exclusively in accordance with the formulae described in the **authoritative books of Ayurvedic, Siddha and Unani specified in the First Schedule**



**ASU Patent or Proprietary Medicine**

Patent or proprietary medicine‖ means,—

All formulations should contain only ingredients mentioned in the formulae described in the **authoritative books of Ayurveda, Siddha or Unani Tibb systems of medicine - specified in the First Schedule.**

A medicine which is administered by **parenteral route** and also formulation **included in the authoritative books as specified in clause (a).**

**Balya / Poshak / Muqawi / Unavuporutkal /Positive Health Promoter formulations** having ingredients mentioned in books of **first Schedule of D&C Act 1940** and which are recommended for promotional and preventive health.

**Saundarya Prasadak (Husane afza)/ Azhagh-sadhan formulation** having ingredients mentioned in books of **First Schedule of the D&C Act 1940** and recommended for oral, skin, hair and body care.

**Aushadh Ghana (Medicine Plant extracts dry/wet)** obtained from plant mentioned in books of **First Schedule of the Act including Aqueous or Hydro-Alcohols.**

**ASU Preparation**

- Arka/Theeneer
- Asava and Aristha
- Avachurnam Yoga
- Avaleha Leham Ilagam
- Curna, Kvatha Curna
- Lepa, Malhara, Kalimbu, Pasai
- Netra bindu, Anjana and Karna bindu
- Vartti
- Pisti, Chunnam

**ASU Preparation**

- Ghanasatva/ Plant Extract
- Ghrta and Taila
- Guggulu
- Vati and Gutika
- Sharkaar/Sharbat/ Syrup
- Bhasma /Sindhura / Parpam / Chenduram Mandura
- Rasa Yoga
- Lauha
- Single plant material

## Safety Studies & Approval of ASU Drugs

| S. No | Type of ASU & H Preparation | Category | Safety Study | Experience/ Evidence of Effectiveness | |
|---|---|---|---|---|---|
| | | | | Pub. Lit | POE |
| 1 | Sastric Classical Drugs | Any Category | NR | R | R (3A-New indcn.) |
| 2 | Proprietary Drugs | ASU drugs/Preparations with any of the ingredients of Schedule E(1) of DCA, 1940 | R | R | R |
| 3 | Food Products (Balya and Poshak medicines) | | | NR | NR |
| 4 | Food Products (Balya and Poshak medicines) | | | | |
| 5 | Extracts | (B-1) Hydro-Alcohol | R | If Req. | R |
| | | Other than Hydro/ Hydro-Alcohol | R ACMT | If Req. | R |

POE- Proof of Effectiveness, DCA- Drugs and Cosmetics Act, NR- Not Req., R- Req.

### List of Schedule (E1)

**Drugs of vegetable origin:**

Abrus precatorius Linn. (Seed),

Aconitum chasmanthum Stapf.ex Holmes,

Aconitum ferox Wall, ex Ser.,

Baliospermum montanum Mull. Arg.,

Calotropis procera (Ait.) R. Br,

Papaver somniferum Linn. (except seeds),

Croton tiglium Linn.,

Datura metal Linn.,

Gloriosa superba Linn.,

### List of Schedule (E1)

Hyoscyamus niger Linn.,

Nerium indicum Mill,

**Drugs of animal origin:**

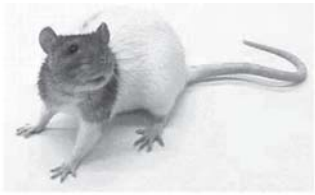
Snake poison

**Drugs of mineral origin:**

Arsenic, Arsenic trisulphide, Arsenic disulphide, Mercury, Red oxide of lead, Copper sulphate and Cinnabar.

### Animals in Research

" Virtually every medical achievement of the last century has depended directly or indirectly on research in animals."



### Pre Clinical Studies

**Objective:**

- To determine whether such studies support the clinical use of a herbal drug.
- To characterize the range of pharmacological action of herbal drug.
- To define the chemical characteristics of pharmacologically active natural products and to elucidate their mechanism of action.
- Pharmacological study: CNS, CVS, RS

### Pre Clinical Studies

- Whole animals, isolated organ and tissues, blood and its components, tissue culture.

**Toxicological study:**

- Assess the safety of herbal drugs
- Define the possible toxicity from short-term and long term use.

### CPCSEA

The committee for the purpose of control and supervision of experiments on animals established under **chapter IV section 15 of prevention of cruelty to animals 1960**

**Functions of CPCSEA & IAEC**

- Procedure for approval of scientific experiments on animals
- Registration of establishments
- Approval of animal house facility
- Animal welfare during experiments
- Rehabilitation of animals
- Euthanasia
- Suspension and revocation of registration of an establishment are governed by relevant rules

**Relevant Acts, Rules, Notifications and Guidelines of CPCSEA**

1. Prevention of cruelty to animals act 1960
2. Breeding of and experiment on animals rules 1998 as amended in 2001, 2006
3. Guidelines for care and management of equines used in the production of biological ( protocol 2, 2001)
4. CPCSEA guidelines on regulation of scientific experiments on animals 2007
5. CPCSEA guidelines for laboratory animal house facility 2008
6. PCSEA standard operating procedures for IAEC 2010
7. UGC notification under section 12 (1 of UGC act ) to stop dissection at undergraduate and postgraduate level of all universities

**Composition of IAEC**

IAEC: Institutional Animal Ethical Committee

**Institute Members**

- 1 - Biological scientis
- 2 - Scientists from different biological discipline
- 1 - Veterinarian
- 1- Scientist in-charge of animal facility

**CPCSEA Nominated members**

- 1 - Scientist from outside the institute
- 1 - Sociologist
- 1 - Main Nominee
- 1 - Link Nominee

**Experimental Animals**

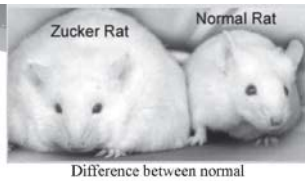
- **Rats -** Sprague dawley (SD), Wistar, Lsiter hooded, Long Evans, Fischer, Brown norway, Lewis, Hybrid and Congenic rats, Mutant rats (Athymic nude, Zuckar)
- **Mice -** Albino, CD1, BALB/C, KK
- **Guinea Pigs -** Short-Haired American, Dunkin Hartley
- **Hamsters -** Syrian Golden Hamster, Chinese Hamster
- **Rabbit -** New Zealand White,

**Experimental Animals**

**Wistar rats**

**Mutant rat**

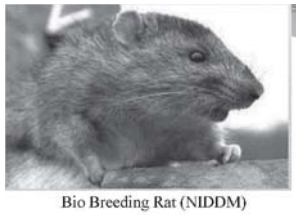
Sprague Dawley




Difference between normal rats and Hyperlipidemic Rats

Fatty Zucker Rats (Hyperlipidemia)

Diabetic Zucker Rat (Diabetes)



Bio Breeding Rat (NIDDM)

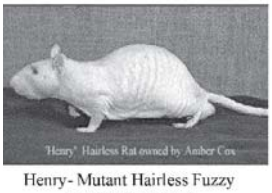
Long Evans Rat (CNS, Card., Hep.)

Satin Ivory Rat (Lymphadenopathy)

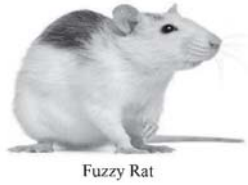
Black Satin Rats (Resp., Fatty liver)

Royal College of Surgeons (RCS) Rat (Retinal Defect)

Cotton Rats (Infectious Diseases)




Henry- Mutant Hairless Fuzzy Rat (Nephropathy)

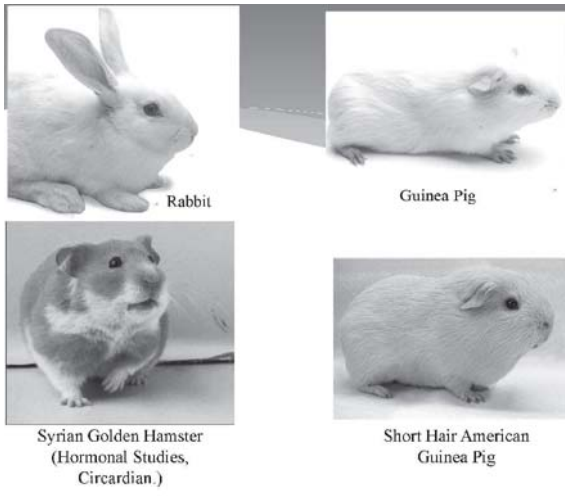


Fuzzy Rat

Swiss albino mice

Mutant Mice

KK Mice (Nephropathic and Diabetic studies)




**Conversion factor for Animals [Man to Animals]**

- 20g Mouse = Dose x 0.0026 = Xx50= Dose /Kg/Body wt.
- 200g Rat = Dose x 0.018 = Xx5 = Dose /Kg/Body wt.
- 400g Guinea pig =Dose x0.031 = Xx2.5= Dose/Kg/B. wt.
- 1.5 Kg Rabbit = Dose x 0.07 = Dose /1.5Kg/Body wt.

**Toxicity study**

- **Essential for any new compound** having biological activity.
- **Acute toxicity-** adverse effects occurring within a short time following administration of a single dose given within 24 hrs.
- **Sub- acute toxicity** - 6-8 weeks.
- **Chronic toxicity** - period of 1 year or more.
- **Special toxicity studies** - period of 2 years or more
  - •Carcinogenic
  - •Mutagenic
  - •Teratogenic
  - •Reproduction effect

**Important OECD guidelines**

| Guide line No. | Title of the study |
|---|---|
| 420 | Acute Oral Toxicity- fixed dose method |
| 423 | Acute Oral Toxicity- acute toxic class method |
| 425 | Acute Oral Toxicity- Up and Down method |
| 402 | Acute Dermal Toxicity |
| 404 | Acute Dermal Irritation/ Corrosion |
| 403 | Acute Inhalation Toxicity |
| 405 | Acute Eye Irritation / Corrosion |
| 406 | Skin Sensitization |
| 407 | 28days Repeated Oral Toxicity Studies in Rodents |

| Guide line No. | Title of the study |
|---|---|
| • 408 | 90days Repeated Oral Toxicity Studies in Rodents |
| • 409 | 90days Repeated Oral Toxicity Studies in Non-Rodents |
| • 410 | 90 days repeated Dermal Toxicity |
| • 411 | 90 days inhalation Toxicity study |
| • 412 | 28/14 days repeated dose inhalation Toxicity study |
| • 413 | 90 days repeated dose inhalation Toxicity study |
| • 414 | Prenatal Developmental Toxicity study |

| Guide line No. | Title of the study |
|---|---|
| • 415 | Reproduction / Development toxicity screening test |
| • 416 | Combined Repeated dose toxicity study with Reproduction / Developmental Toxicity screening test |
| • 417 | Neurotoxicity study in rodents |
| • 418 | Carcinogenicity studies |
| • 419 | Chronic Toxicity studies |
| • 420 | Combined chronic toxicity / carcinogenic studies |

**Acute Toxicity Studies**

- Single dose - Rat, Mouse (5/sex/dose), Dog, Monkey (1/sex/dose)
- 14 day observation
- In-life observations (body wt., food consumption, clinical observations)
- Necropsy


**Acute $LD_{50}$ Values vs Toxicity**

| Chemical | LD50 (mg/kg) | Toxicity |
|---|---|---|
| Sodium chloride | 4000 | Slightly toxic |
| DDT | 100 | Moderately toxic |
| Picrotoxin | 5 | Highly toxic |
| Strychnine | 2 | |
| Nicotine | 1 | |
| Dioxin | 0.001 | Super toxic |
| Botulinum toxin | 0.00001 | |

### Subchronic Toxicity

- **13 week study** +/- 4 wk recovery (3 doses and control)
- Species - Rat (10/sex/dose), Dog or Monkey (2/sex/dose)
- **In-life observations (+/- ophthamology)**
- Clinical pathology
- Necropsy
- Histopathology
- Used to set doses for carcinogenicity studies

### Chronic Toxicity

- 1 year study +/- 4-13 wk recovery (3 doses and control)
- Species - rat (10-15/sex/dose), dog or monkey (2-3 /sex/dose)
- In-life observations including ophthalmology
- Necropsy
- Histopathology

### Carcinogenicity Study

- 2 years (3 doses and control)
- Species - Rats and Mice (50/sex/dose)
- In-life observations
- Toxicokinetic studies
- Clinical pathology (rats, optional)
- Necropsy
- Histopathology

### Carcinogenicity Study Evaluation Issues

- Survival
- Body weight
- Variability of endpoints
- Pathology Working Group
- Maximum Tolerable Dose (MTD)
- Statistics vs Biology
- Dose-response
- Mechanistic factors

**OECD 423 (Acute toxic class method)**

**Principle**

- Based on a **stepwise procedure** with the use of a **minimum number of animals per step.**
- **Absence or presence of compounds related mortality** of the animals dosed at are step will determine the next step.
- **No further testing is needed.**
- Dosing of **three additional animals** with the same dose
- Dosing of **three additional animals with the next higher or the next lower dose level**

**Description of the method**

- **Preparation of the animals**
  Randomly selected animals are kept in their Cages for at least 5 days prior to start of the test to allow of acclimatization of the laboratory condition
- **Preparation of dose**
  Vehicles other than water , the toxic characteristics of vehicle should be known
- **Procedure**
  Three animals in each step
  Doses: 5,50,300,2000 mg/kg b/w

**Administration of Doses**

- **Rodents**-volume not to exceed 1ml /100gm b.w
- Aqueous solution 2 ml/100g b.w can be considered
- **Animals –**Fasted prior dosing
- **Rat-** Food but not water withhold overnight
- **Mouse**-Food but not water withhold 3-4 hrs
- Following the fasting weigh the animals and test drug administered. After administration food may be withheld for 3-4 hrs in rats and 2 hours in mice.

**Observation**

**14 days**

- Twice more on the day of dosing

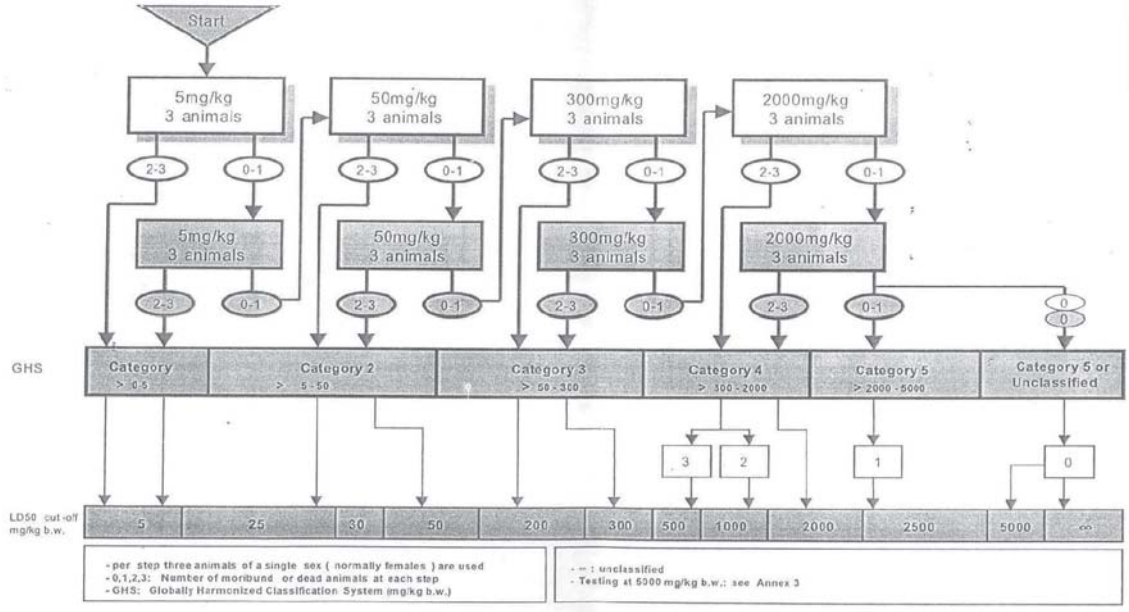
**At least once daily thereafter**

- Mortality
- Changes in skin, eyes, mucus
- Behavioural pattern changes
- Respiratory, Circulatory, ANS, CNS
- Observation of tremors, convulsions, salivation, diarrhea, sleep and coma

**Body weight – At least once in a week**

- Pathology – Microscopic examination

## OECD 423

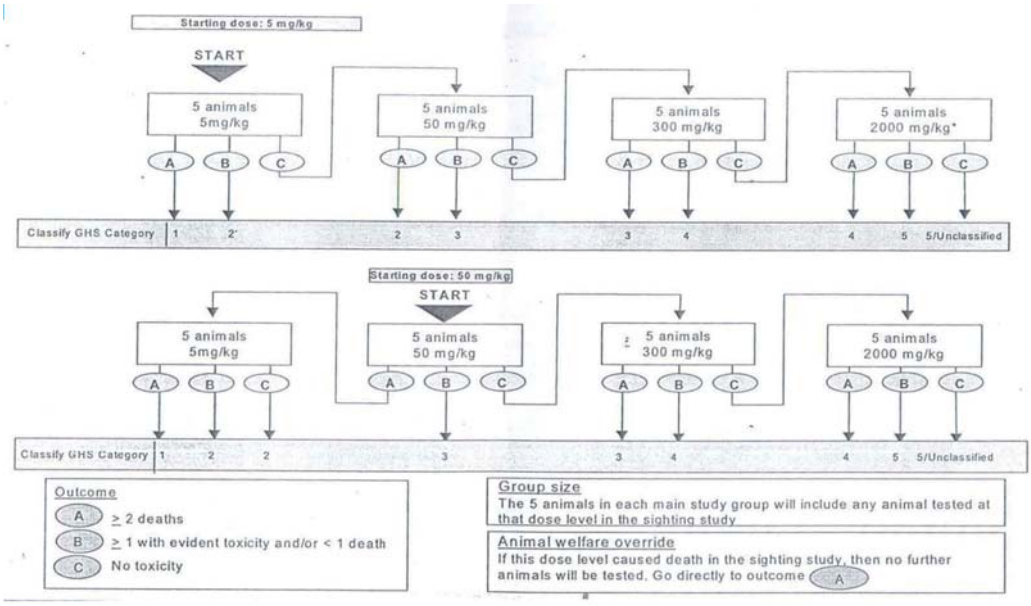



### OECD-420
### Acute Oral Toxicity – Fixed dose procedure

- **Fixed doses** –
  5, 50, 300, 2000, 5000 mg/g
- **Animal:** Rat **Sex:** Female preferable and 10-12 weeks old.
- **Number** : total of five animals used for each dose level
- **Dose:** single dose
  Rat overnight fasted
  Mice –3-4 hours fasted
- **Time interval between dosing:**
  Onset, Duration and Severity of toxic sign.
  Period of 3 or 4 days between dosing at each dose level is recommended.

- **Observation: 14 days**
  30 minutes periodically during the first, 24 hours (special attention during first 4 hours) daily thereafter for a total 14 days.
- **Body weight:** Individual weight of animals recorded before administration weekly thereafter.
- **Pathology:** Gross Pathological Changes recorded for each animals.

## OECD 420 Main Study




### OECD-425

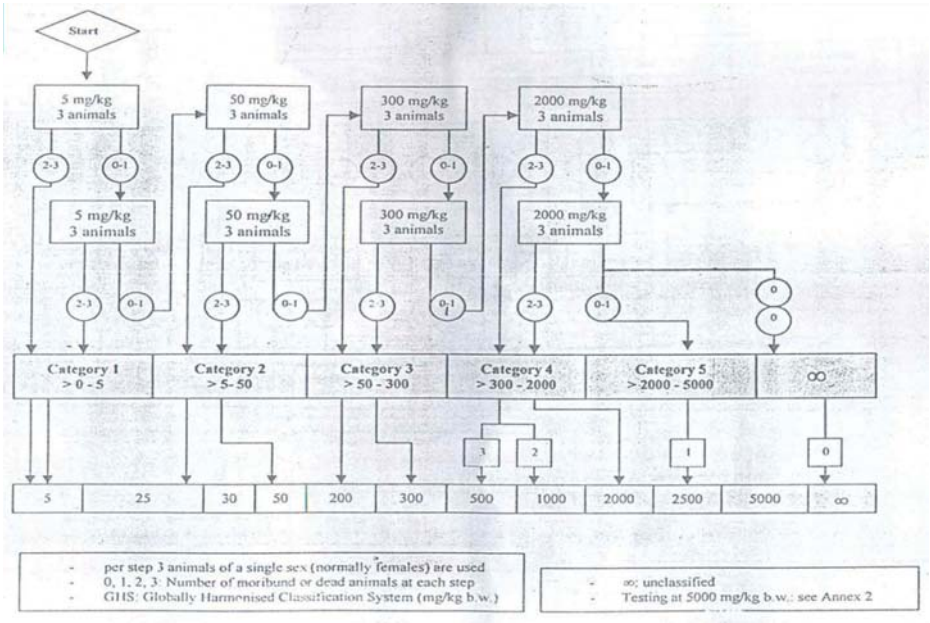
- This is an sequential test – uses a maximum of 5 animals dose 2000,5000 mg/kg.
- Limit test of 2000 mg/kg:
- Dose of animals at the test dose.
- Animal dies , conduct the main test to determine the $LD_{50}$ .
- Animal survives, dose four additional animal sequentially observe 14 days.

- The $LD_{50}$ less than the test dose (2000 mg/kg) when 3 or more animals die.
- $LD_{50}$ is greater than the test dose (2000 mg/kg) when 3 or more animal survive.

### Main test

- Single animals are dosed in sequence usually at 48 hour intervals (dosing is determined by the onset , duration and severity of toxic signs)
- The first animal is dosed below the best preliminary estimate of LD50. If the animal survives. The second animal receives a higher dose .
- If the first animal dies or appears morbid and the second animal receive a lower dose.
- Selected sequence dose 1.25, 5.5, 17.5, 55, 125, 550, 2000 (or) 1.25, 5.5, 17.5, 55, 175, 550, 1750, 5000 for specific regulatory needs
- Observation: 14 days.

## OECD 425




## OECD-407

**28 day repeated dose oral Toxicity study in Rodents: Animal species selection: Rat , Mice**

- Age : Nine weeks old.

**Housing condition:**

- Temperature: 220 c ± 30c
- Humidity: 50-60 %
- Lighting: 12 hr light 12 hr dark
- Feed : laboratory diet with water
- House : individually, small groups in same sex, not more than five/cage

- **Preparation of doses:**
  Administration by gavages or via the diet or drinking water Oral administration depend upon the physical / chemical properties of the best one materials

  Vehicles other than water the toxic properties of the vehicle is must be known.
- **Number and sex of animal:**
  10 animals -5 female and 5 male for each dose
- **Dosage:** 1000 mg/kg/day for 28 days daily
- **Volume:**
  1ml/100gm b.w – suspension
  2ml/100gm b.w – aqueous solution

- **Observation : 28 days**
  General clinical observation at least once a day.
- **Morbidity and mortality –** at least twice daily Changes in skin , eyes, mucous membrane, secretion and excretion and
- **ANS activity**- lacrimation, piloerection , pupil size, respiratory pattern Grip strength, motor activity assessment
- Body weight: Weekly
- Food consumption : Weekly
- Water consumption : Weekly

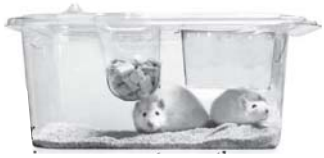
- **Haematology:** Haematocrit, Hb RBC, WBC, DC, platelet, clotting time.
- **Clinical Biochemistry:** Liver function test, kidney function test
- **Plasma or serum** – Na ,K+, glucose, total cholesterol, urea, creatinine, SGOT, SGPT, Total protein, Albumin, ALP, Gamma glutamyl transpeptidase
- **Urine analysis:** Last week of the study Volume, appearance , specific gravity, pH , protein glucose and blood cells.

**OECD-408**

- 90 day repeated dose oral Toxicity study in Rodents:
- Animal species selection: rat , mice
- Age : nine weeks old.

**Housing condition**

- Temperature: 220 c ± 30c
- Humidity: 50-60 %
- Lighting: 12 hr light 12 hr dark
- Feed : laboratory diet with water
- House: individually, small groups in same sex, not more than five/cage



- **Preparation of doses:**
  Administration by gavages or via the diet or drinking water Oral administration depend upon the physical / chemical properties of the best one materials

  Vehicles other than water the toxic properties of the vehicle is must be known.
- **Number and sex of animal:**
  20 animals - 10 female and 10 male for each dose
- **Dosage:** 1000 mg/kg/day for 90 days daily (3DOSE)
- **Volume:**
  1ml/100gm b.w – suspension
  2ml/100gm b.w – aqueous solution

- **Observation : 90 days** clinical observation at least once a day.
- **Morbidity and mortality –** at least twice daily Changes in skin , eyes, mucous membrane, secretion and excretion and
- **ANS activity**- lacrimation, piloerection , pupil size, respiratory pattern Grip strength, motor activity assessment
- Body weight: Weekly
- Food consumption : Weekly
- Water consumption : Weekly

**Parameters - Clinical Chemistry**

albumin
alkaline phosphatase
ALT (serum alanine aminotransferase)
AST (serum aspartate aminotransferase)
bilirubin (total)
calcium
chloride
cholesterol (total)
creatinine (blood)
CPK (creatine phosphokinase)
GGT (gamma-glutamyl transpeptidase)
globulin
glucose (blood)
LDH (lactate dehydrogenase)
phosphorus
potassium
protein (total)
sodium
SDH (succinate dehydrogenase)
triglycerides
urea nitrogen (blood)

**Parameters - Haematology**

clotting parameters (clotting time, prothrombin time)
erythrocyte count
haematocrit (packed cell volume)
haemoglobin
leucocyte differential count
leucocyte total count
platelet count
reticulocyte count
MCH (mean corpuscular haemoglobin)
MCHC (mean corpuscular haemoglobin concentration)
MCV (mean corpuscular volume)
blood smear

**Parameters - Urinalyses**

appearance
specific gravity
glucose
ketones
sediment (microscopic)
occult blood
pH
protein
volume
Bilirubin urobilinogen

**List of organs for organ weight determination and for Histopathological examinat**

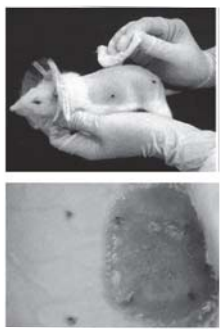
| Organs weighed | Tissues examined | | |
|---|---|---|---|
| adrenals*# | adrenals*# | heart*# | prostate*# |
| brain*# | accessory sex organs# | ileum* | rectum* |
| epididymides*# | aorta*# | intestines (small and large) # | salivary gland*# |
| heart*# | blood smear | jejunum* | seminal vesicle* |
| kidneys*# | bone* | kidneys*# | skin*# |
| liver*# | bone marrow*# | lacrimal gland | spinal cord (cervical thoracic, lumbar)*# |
| ovaries*# | brain (3 levels)*# | liver*# | spleen*# |
| spleen*# | cecum* | lungs*# | sternum |
| testes*# | colon* | lymph nodes*# | stomach*# |
| thymus*# | duodenum* | mammary gland*# | testes*# |
| thyroid (w/parathyroid) | epididymides* | muscle (smooth) | thymus*# |
| uterus*# | eyes# | muscle (skeletal)*# | thyroid (w/parathyroid)*# |
| | eyes (optic nerve)* | nerve (peripheral)*# | trachea*# |
| | gall bladder*# | oesophagus*# | urinary bladder*# |
| | Harderian glands | ovaries*# | uterus*# |
| | head - 3 sections (nasal cavity, para-nasal sinus, tongue, oral cavity, naso-pharynx, inner-ear) | pancreas*# | vagina |
| | | pituitary*# | Zymbal's gland |
| | | | gross lesions*# |

**OECD-452**

- 12 months repeated dose oral Toxicity study in Rodents
- Number and sex of animal:
  40 animals - 20 female and 20 male for each dose
  Hematology, clinical chemistry & Urine analysis
  3, 6 and 12 month

**OECD- 410**

- 21/28 –day Repeated Dose Dermal Toxicity study
- Prerequisites
  - solid or liquid
  - purity
  - solubility
  - pH
  - Stability, including stability in vehicle
  - Melting point/ boiling point



**Principle**

The test substances applied daily to the skin in graduated doses to several groups of experimental animals, one dose per group for 21/28 days.

- **Animals:**
  Adult rat -(200-300gm)
  Rabbits -(2-3 kg)
  Guinea pigs – (350-450g )

- **Number and sex:**
  10 animals (5 female and 5 male)

**Housing**

- --- Individual housing
- --- Temperature 220 C (±30 C)
- --- Relative humidity 30- 70%
- --- Lighting 12 hr light: 12 hr dark
- --- Ordinary diet + unlimited supply of drinking water

- **Dose level**
  At least three dose level with control

- **Limit test:**
  One dose level at least 1 gm/kg, b.w
  Test drug apply not less than 10% of the body surface area uniformly.
  Shaving may be exposed- At least 24 hr before the test.

- **Observation :**
  Sign and toxicity
  ANS , CNS, Behavior pattern, Food consumption weekly
  Weight variation weekly

**Clinical examination (all animals)**

- **Haematology:**
  Haemocrit, Hb, RBC, WBC, DC, Clotting time, Prothrombin time, Platelet count

- **Clinical Biochemistry:**
  Blood parameter of liver and kidney function, Na, K, Cl, Ca, fasting glucose

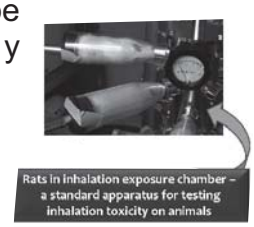
- P**athology**
  -- Gross necropsy
  -- Histopathology

**OECD- 412**

**"Repeated Dose Inhalation Toxicity"**
28day or 14 day study

- **Prerequisites:**

-- Gas , volatile material or aerosol/ particulate test substance
-- Chemical identification
-- Purity of the test substance
-- Liquid : vapour pressure, boiling point
-- Aerosol / particulate:
particle size, shape and density distribution
– Flash point
– Explosivity



Rats in inhalation exposure chamber – a standard apparatus for testing inhalation toxicity on animals

- **Animals:**
Rodents– preferred rats

- **Number:** 10 animals(5male and female) for each group

- **Equipment:**
Inhalation equipment
(air flow of 12-15 air changes/hr, adequate O2 content of 19 %)

- **Exposure concentration**
3 concentrations with control

- **Food and water** withheld during exposure

- **Exposure time:**
The duration of daily exposure should be 6 hrs after equilibration of the chamber concentrations

- **Observations:**
At least Once each day

- **Physical measurements:**
-- Rate of Air Flow
-- Temperature and Humidity
-- Particle Size Analysis
Clinical Examination
Sign of Toxicity

**Protocol form for research proposals submitted - IAEC**

- Title of the project work
- Chief investigator with address
- List of names under this proposal
- Funding source
- Duration of the project
- Study objective
- Animals required
  1) species
  2) age/weight
  3) gender
  4) number to be used.
- Rational for animal usage
- Description of procedures
- Methods of disposal post experimentation

Form B (per rule 8(a)*

**APPLICATION FOR PERMISSION FOR ANIMAL EXPERIMENTS**

Application to be submitted to the CPCSEA, New Delhi after approval of Institutional Animal Ethics Committee (IAEC)

Part A

1. Name and address of establishment

2. Registration number and date of registration.

3. Name, address and registration number of breeder from which animals acquired (or to be acquired) for experiments mentioned in parts B & C

4. Place where the animals are presently kept (or proposed to be kept).

5. Place where the experiment is to be performed (Please provide CPCSEA Reg. Number)

6. Date on which the experiment is to commence and duration of experiment.

7. Type of research involved (Basic Research / Educational/ Regulatory/ Contract Research )

Signature

Name and Designation of Investigator

Date:

Place:

*The filled in Form B having above information / details / supporting documents (1 original + 14 copies and 1 soft copy in CD) should be sent to: -

The Member Secretary,
CPCSEA, Ministry of Environment, Forests & Climate Change
5th Floor, Vayu Wing,
Indira Paryavaran Bhawan
Ali Ganj, Jor Bagh Road,
New Delhi-110 003

**PART B**

**Protocol from for research proposals to be submitted to the committee / Institutional Animal Ethics Committee, for new experiments or extensions of ongoing experiments using animals other than non-human primates.**

1. Project / Dissertation / Thesis Title:

2. Principal Investigator / Research Scholar / Research Guide / Advisor:

   a. Name
   b. Designation
   c. Dept / Div/ Lab
   d. Telephone No.
   e. Experience

3. List of names of all individuals authorized to conduct procedures under this proposal.

   Co-guides
   a. Name
   b. Address
   c. Experience

4. Funding source with complete address (Please attach the proof)

5. Duration of the project

   a. Number of months
   b. Date of initiation (Proposed)
   c. Date of completion (Proposed)

6. Detailed study plan may be given (Not more than one page)

7. Animals required

   a. Species / Common name
   b. Age/ weight/ size
   c. Gender
   d. Number to be used (Year-wise breakups and total figures needed to be given)
   e. Number of days each animal will be housed.
   f. Proposed source of animals.

8. Rationale for animal usage

   a. Why is animals usage necessary for these studies?
   b. Why are the particular species selected required?
   c. Why is the estimated number of animals essential?
   d. Are similar experiments conducted in the past? If so, the number of animals used and results obtained in brief.
   e. If yes, why new experiment is required?
   f. Have similar experiments been made by any other organization agency ? If so, their results in your knowledge.

9. Description the procedures to be used.

   List and describe all invasive and potentially stress full non-invasive procedures that animals will be subjected to in the course of the experiments.

   Furnish details of injections schedule
   Substances :
   Doses :
   Sites :
   Volumes :
   Blood withdrawal
   Volumes :
   Sites :
   Radiation (dosage and schedules):

10. Please provide brief descriptions of similar studies from invitro / invivo (from other animal models) on same / similar test component or line of research. If, enough information is available, justify the proposed reasons.

11. Does the protocol prohibit use of anesthetic or analgesic for the conduct of painful procedures (any which cause more pain than that associated with routine injection or blood withdrawal)? If Yes, explanation and justification.

12. Will survival surgery be done?

    If Yes, the following to be described.

    a. List and description of all such surgical procedures (including methods of asepsis)
    b. Names, qualifications and experience levels of operators
    c. Description of post-operative care
    d. Justification in major survival surgery is to be performed more than once on a single individual animals.

13. Methods of disposal post-experimentation

    a. Euthanasia (Specific method):

    b. Method of carcass disposal :

    c. Rehabilitation :

14. Animal transportation methods if extra-institutional transport is envisaged.

15. Use of hazardous agents (use of recombinant DNA-based agents or potential human pathogens requires documented approval of the Institutional Biosafety Committee (IBC). For each category, the agents and the biosafety level required, appropriate therapeutic measures and the mode of disposal of contaminated food, animal wastes and carcasses must be identified)

(a) Radionuclides
(b) Microorganisms / Biological infectious Agents
(c) Hazardous chemicals or drugs
(d) Recombinant DNA
(e) Any other (give name)

If, your project involved use of any of the above, attach copy of the minutes of IBC granting approval.

**Investigator's declaration.**

1. I certify that I have determined that the research proposal herein is not unnecessarily duplicative of previously reported research.
2. I certify that, I am qualified and have experience in the experimentation on animals.
3. For procedures listed under item 11, I certify that I have reviewed the pertinent scientific literature and have found no valid alternative to any procedure described herein which may cause less pain or distress.
4. I will obtain approval from the IAEC/ CPCSEA before initiating any significant changes in this study.
5. Certified that performance of experiment will be initiated only upon review and approval of scientific intent by appropriate expert body (Institutional Scientific Advisory Committee / funding agency / other body (to be named).
6. Institutional Biosafety Committee's (IBC) certification of review and concurrence will be taken (Required for studies utilizing DNA agents of human pathogens).
7. I shall maintain all the records as per format (Form D)
8. I certify that, I will not initiate the study unless approval from CPCSEA received in wiring. Further, I certify that I will follow the recommendations of CPCSEA.
9. I certify that I will ensure the rehabilitation policies are adopted.

Signature

Name of Investigator

Date:

**Certificate**

This is certify that the project title .....

.....

has been approved by the IAEC.

Name of Chairman/ Member Secretary IAEC: Name of CPCSEA nominee:

**Signature with date**

**Chairman/ Member Secretary of IAEC: CPCSEA nominee:**

(Kindly make sure that minutes of the meeting duly signed by all the participants are maintained by Office)

## Form C

### Record of Animals bred / acquired: (to be maintained by the Breeder/Establishment)

| Date of entry | No. of Animals (Specify species, sex and age) | No. of Animals acquired (Specify date of acquisition species, sex and age) | Name, Address and date & from whom acquired | No. of animals transferred (specify date, species, sex and voucher/bill no. ) | Name, address and registration No. of the Establishment to whom transferred | Signature |
|---|---|---|---|---|---|---|

**Form D**

**Record of Animals Acquired and Experiments performed: (to be maintained by the Investigator)**

| Date of entry | No. of animals acquired (specify species, sex and age | Name, address and registration No. of the breeder from whom acquired with voucher/bill no. | Date and particulars of order of grant of permission by the committee | Date/period of experiment | Name and address of the person authorizing the experiment | Certification of the investigator authorizing the experiment that all conditions specified for such an experiment have been complied with (Signature) |
|---|---|---|---|---|---|---|
| | | | | | | |

FORM- E

Record of animals sold

(to be maintained by the establishment)*

| Date | Species & number of animals sold | Name, address and Registration Number of the establishment to whom animals sold | Date & IAEC No. of the protocols against which animals sold |
|---|---|---|---|
| | | | |

# DEVELOPING GLOBALLY COMPLIANT PROPRIETARY HERBAL PRODUCTS: A BIRD'S EYE VIEW ON GENERAL REQUIREMENTS

by

**Dr. B.K. Ashok,**
Senior Research Scientist, R & D Himalaya Drug Company, Bangalore
(Lecture Delivered during the National Seminar on Modern Scientific Approach for Standardization of Medicinal Plants used in ASU & H Drugs on 25th & 26th March 2019)

## Surge in popularity.....!

REUTERS

**Future Trend of Herbal Medicine Market 2018 Scope | at a CAGR of ~ 7.2 % during 2017 to 2023 | Increasing Demand for Safe Therapies**

Global Herbal Medicine Market Information; By System (Ayurveda, Chinese, Western and Other), Application (Pharmaceutical, Personal Care and Other), By Source (Vegetable (Leaves and Fruit, Seeds, Roots, Bark and Other) and Animal (Oils, Bones, and Other)) – Forecast to 2023

FEATURED NEWS

1 Del Monte Philippines US$333 million IPO gets approval from SEC

The global herbal medicine market is expected to reach USD 117.02 billion by 2024

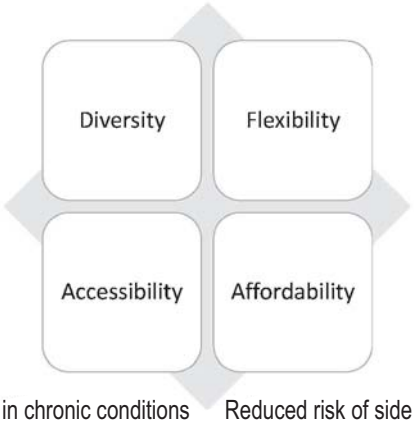
NEWS PROVIDED BY ReportBuyer → Oct 08, 2018, 19:00 ET

SHARE THIS ARTICLE

Himalaya SINCE 1930 Khush Raho, Khushaal Raho

9,493 licensed manufacturing units

## Advantages of TSM.....!



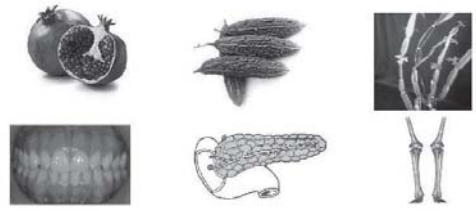

Effective in chronic conditions

Reduced risk of side effects

## Nature's Pharmacy....!!

अनेनोपदेशेन नानौषधिभूतं जगति किंचिद्द्रव्यमुपलभ्यते तां तां युक्तिमर्थं च तं तमभिप्रेत्य १२

There are no plants in this universe which are devoid of medicinal properties , but physician should know the proper usage of plants



**General classification as per D & C....**

**Classical Medicines**


**Proprietary Medicines**


**Major impediments for export.....**

- Lack of continuous supply of raw materials
- Non-availability of standardized raw material
- Ban on several herbs for exports
- Requirement of NOC from wildlife authority
- Shortage of buyers
- Delays in approval of formulations
- Lots of paper work required
- Adherence to the specifications related to packaging

**Major impediments for export contd.....**

- Medicines exported as food supplements
- No thorough information on the target customers
- High cost of registration charges abroad
- Adherence to the specifications related to packaging

**Issues with classical formulation for globalization....**

चन्द्रप्रभा वचा मुस्तं भूनिम्बामृतदारुकम्
हरिद्राऽतिविषा दार्वी पिप्पली मूलचित्रकौ
धान्यकं त्रिफला चव्यं विडङ्ग, गजपिप्पली
व्योषं माक्षिकधातुश्च द्वौ क्षारौ लवणत्रयम्
एतानि शाणमात्राणि प्रत्येकं कारयेद्बुधः
त्रिवृद्दन्ती पत्रकं च त्वगेला वंशरोचना
प्रत्येकं कर्षमात्रं च कुर्यादेतानि बुद्धिमान्
द्विकर्षं हतलोहं स्याच्चतुष्कर्षा सिता भवेत्
शिलाजत्वष्टकर्षं स्यादष्टौ कर्षास्तु गुग्गुलोः
एभिरेकत्र संक्षुण्णैः कर्तव्या गुटिका शुभा

Karpura | Berberis | Sweet Flag | Chitraka | Nut Grass | Vidanga | Tinospora | Lavana | Deodar | Trivrit | Shilajatu

## Bheshaja Pareeksha [The Basic Research] .....!?

| | |
|---|---|
| *Evam prakriti* | Authenticity |
| *Evam gunam* | Purity & Quality |
| *Evam prabhavam* | Efficacy |
| *Evam asmin deshe jatam* | Geographical source |
| *Asmin rutou* | Season of collection |
| *Evam gruheetam* | Method of collection |

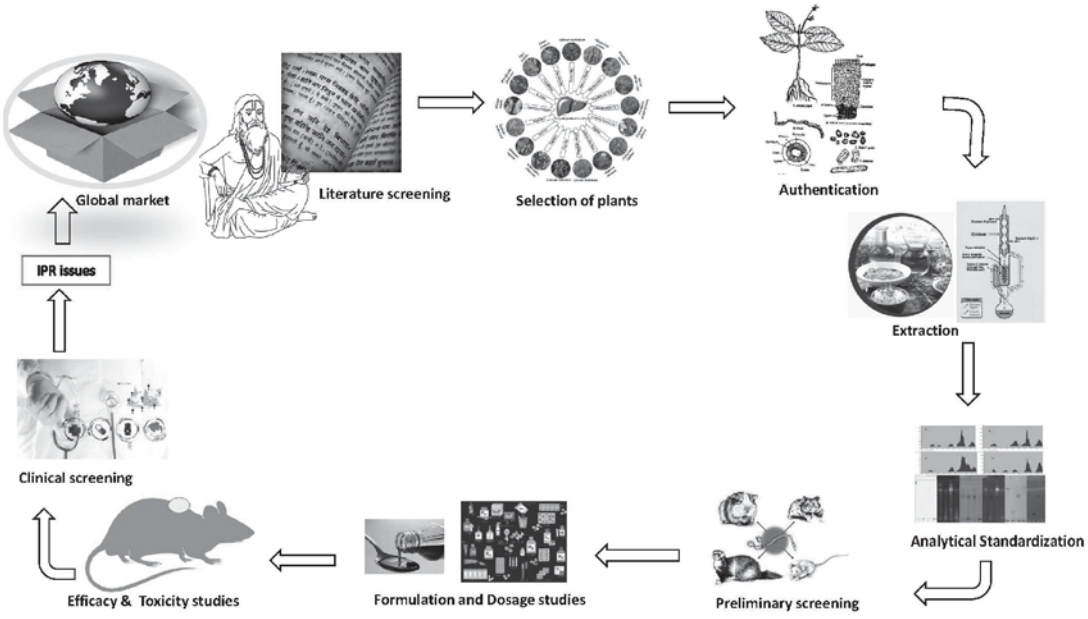
## Bheshaja Pareeksha cont.....

| | |
|---|---|
| *Evam nihitam* | Storage practice |
| *Evam upaskrutam* | F & D |
| *Evam maatram* | Suitable dosage |
| *Evam vyadhi* | Clinical condition |
| *Evam Vidham Purushasya* | Clinical trials |

## Qualities of Bheshaja vis-a-vis R & D.....

| | |
|---|---|
| *Bahukalpam* | Formulation development |
| *Bahugunam* | Quality |
| *Sampannam* | Authenticity & Purity |
| *Yogyam* | Safety & Efficacy |

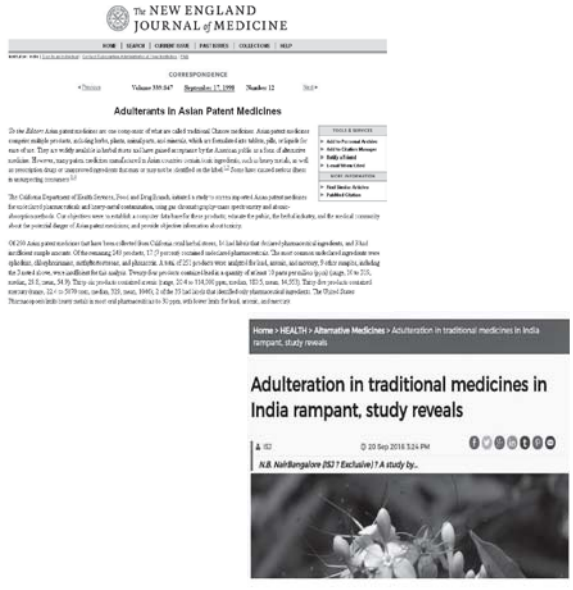
## Evidence Based Research…...




## Target identification - Holistic approach….

| | |
|---|---|
| ❖ Insulin secretagogue and insulinomimetic actions | Kataka |
| ❖ Antihyperglycemic action | Khadira |
| ❖ Alpha-glucosidase inhibitory action | Amalaki |
| ❖ Glucose utilization-stimulatory action | Ekanayaka |
| ❖ Inhibition of gluconeogenesis | Musta |
| ❖ β-cell repair/regenerative action | Haridra |
| ❖ Prevention of complications | Amra |
| ❖ Anti-hypercholesterolemic action | |

## Problems of adulteration & role of pharmacognosy….


The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Adulterants in Asian Patent Medicines

Home > HEALTH > Alternative Medicines > Adulteration in traditional medicines in India rampant, study reveals

Adulteration in traditional medicines in India rampant, study reveals

## Problems of adulteration, role of pharmacognosy contd….

Journal of Medicinal Plants Studies

Drug adulteration: A threat to efficacy of ayurveda medicine

Dr. Sreelekshmi M, Dr. Vimala KS, Dr. Railly P Paul, Dr. Nidhin Chandran, Dr. Priyanka A Shine and Dr. Nazneen A Salam

REVIEW

Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review

E. ERNST

DEPARTMENT OF BIOTECHNOLOGY
Ministry of Science & Technology

Study detects adulteration, suggests authentication for herbal medicine

Rapid Fire:

- High extent of adulteration found in herbal medicine made from Ashoka
- Stringent regulations to ensure quality of herbal products suggested
- DNA barcode & chemical fingerprinting techniques used to detect & quantify adulteration in the herbal item
- Authentication & certification system for herbal medicine suggested along with DNA barcoding

A new study has suggested stringent regulations to ensure quality of herbal products by authenticating them at various levels of the production.



Deaths due to tainted herbal medicine under-recorded

Date: October 25, 2019

Source: University of Adelaide

Summary: A forensic pathologist is warning that potentially harmful substances found in herbal medicines may be playing a bigger role in deaths of health tourists than previously thought.

Share.

RELATED TOPICS

Health & Medicine

- Alternative Medicine
- Dietary Supplements and Minerals
- Medical Topics

Mind & Brain

FULL STORY

A University of Adelaide forensic pathologist is warning that potentially harmful substances found in herbal medicines may be playing a bigger role in deaths of 'health tourists' than previously thought.

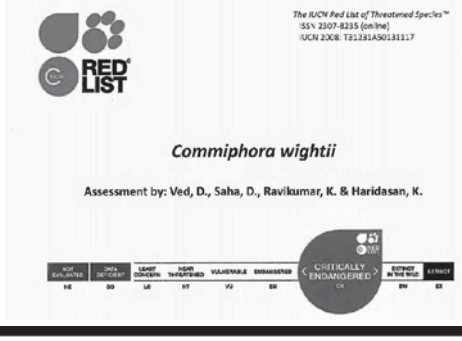
Professor Roger Byard is calling for closer checks during post-mortems for the presence of drugs and adulterants that originate from herbal remedies

### Commercially not viable…..!

- Asoka [Stem bark]
- Bilva [Stem bark]
- Agnimantha [Root]
- Karkatashringi [Galls]
- Asana [Heart wood]
- Chandana [Heart wood]
- Vidari Kanda [Tuber]
- Patala [Root]

### Import Source…..!

- Aquilaria agallocha [Wood]
- Commiphora wightii [Ole-oresin]
- Glycyrrhiza glabra [Roots]
- Quercus infectoria [ Galls]
- Piper chaba [Chavya]
- Ferula narthex [Exudate]
- Keshara [Crocus]
- Cinnamon bark



The IUCN Red List of Threatened Species™
ISSN 2307-8235 (online)
IUCN 2008: T31281A50131117

RED LIST

*Commiphora wightii*

Assessment by: Ved, D., Saha, D., Ravikumar, K. & Haridasan, K.

CRITICALLY ENDANGERED

## Substitution & Adulteration

*Hemidesmus indicus*

Substitution

*Decalepis hamiltonii*

Pepper

Adulteration

Papaya

*Crocus sativus*

Adulteration

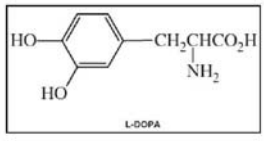
*Carthamus tinctorius*

## Case study: Identification Mucuna pruriens Market Samples

*Mucuna pruriens*

*Active constituent*

L-Dopa




*Mucuna deerigiana*

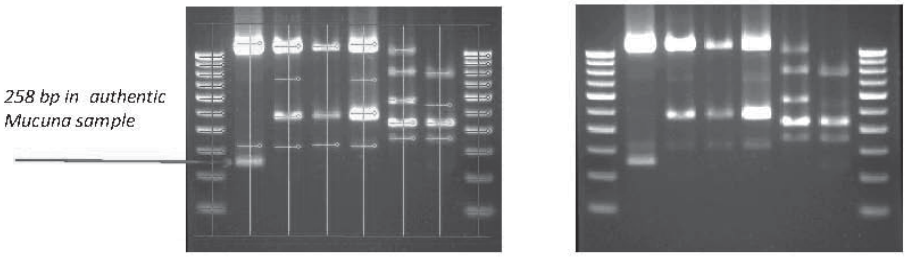
*M. utilis*

*M. cochinshinensis*

*Canavalia virosa*

*Canavalia ensiformis*

## RAPD fingerprinting.....




| Primer # 4 | Well # 1 | Well # 2 | Well # 3 | Well # 4 | Well # 5 | Well # 6 | Well # 7 | Well # 8 |
|---|---|---|---|---|---|---|---|---|
| Sl. No. | Ladder 100 bp | Mucuna pruriens | M. cochinchinensis | M.deeringeina | M.utilis | Canavalia enensiformis | C.virosa | Ladder 100 bp |
| | | 1180 | 1140 | 1140 | 1180 | 1100 | | |
| 1 | 1000 | | | | | | | 1000 |
| 2 | 900 | | | | | | | 900 |
| 3 | 800 | | | | | 830 | 820 | 800 |
| 4 | 700 | | 750 | | 750 | | | 700 |
| 5 | 600 | | | | | **590** | **540** | 600 |
| 6 | 500 | | 470 | 475 | 490 | 440 | 438 | 500 |
| 7 | 400 | | 315 | 325 | 325 | 355 | 355 | 400 |
| 8 | 300 | 320 | | | | | | 300 |
| 9 | 200 | **258** | | | | | | 200 |
| 10 | 100 | | | | | | | 100 |

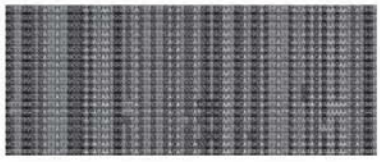
One primer produces a distinct band of 258 bp for the authentic plant, which is absence in adulterants

## DNA Barcoding....

- Himalaya is probably the first company in the world to have our 50 Herbs DNA Barcoded

.

- As a matter of pride, our scientists were invited by USP (United States Pharmacopeia) for a joint collaboration on developing monographs on botanicals



**The Director General of foreign Trade hereby prohibits the export of plants plant portions and their derivatives and extracts obtained from the wild….**

1. Aconitum species
2. Atropa species
3. Aristolochia species
4. Commiphora whightii
5. Coptis species
6. Gentiana kurroo
7. Gloriasa superba
8. Nardostachys jatamansi
9. Rheum emodi
10. Berberis aristata
11. Pterocarpus santalinus
12. Acorus species
13. Coscinium fenestratum
14. Costus speciousus
15. Didymocarpus pedicellata
16. Hydnocarpus species
17. Hyoscymus niger
18. Strychnos potatorum
19. Swertia chirata
20. Saussurea lappa
21. Rauvolifia serpentina
22 Taxus wallichiana

**List of species banned from export unless accompanied by Certificate of Origin from cultivation…..**

1. Rauvolfia serpentina
2. Aconitum species
3. Podophyllum hexandrum
4. Taxus wallichiana
5. Nardostachys jatamansi
6. Gentiana kurroa
7. Coptis teeta
8. Aquilaria malaccensis
9. Coscinium fenestratum
10. Pterocarpus santalinus
11. Picorrhizha kurroa
12. Swertia chirata
13. Kampheria galangal
14. Dioscorea deltoidea
15. Orchidaceae species
16. Saussurea costus

**Plants under Schedule E [Poisonous plants]……**

| No | Botanical name | Sanskrit name |
|---|---|---|
| 1 | Papaver somniferum | Ahiphena |
| 2 | Calotropis procera | Arka |
| 3 | Semecarpus anacardium | Bhallataka |
| 4 | Cannabis sativa | Bhanga |
| 5 | Baliospermum montanum | Danti |
| 6 | Datura metel | Dattura |
| 7 | Abrus precatorius | Gunja |
| 8 | Croton tiglium | Jayaphala |
| 9 | Nerium indicum | Karaveera |
| 10 | Gloriosa superba | Langali |
| 11 | Hyoscyamus niger | Paraseeka yavani |
| 12 | Aconitum ferox | Vatsanabha |

**CITES herbs [Ayurveda]……**

- Various Aloe species [Excluding Aloe vera]
- Picrorhiza kurroa
- Taxus wallichiana
- Kushta (Saussurea lappa)
- Orchis mascula (Tuber)
- Vanda roxburghii (Root)
-

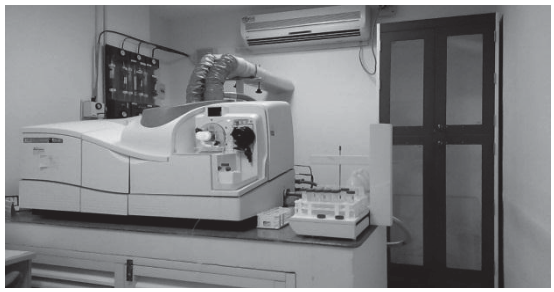
Convention on International Trade in Endangered Species of Wild Fauna and Flora

## Global Regulatory Compliance for some of the important herbs

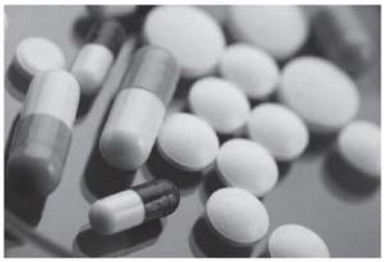
| Herbs | Plant part | Country | | | |
|---|---|---|---|---|---|
| | | US | SEA | EU | CIS |
| ***Terminalia chebula*** | Fruit | No restrictions | No restrictions | Belgium-Can be notified with dosage | No restrictions |
| ***Piper nigrum*** | Fruit | No restrictions | No restrictions | Belgium-Can be notified with dosage | No restrictions |
| ***Ocimum sanctum*** | Leaf | No restrictions | No restrictions | EFSA-(whole plant) | Restricted (all parts) |
| ***Withania somnifera*** | Roots | No Restriction | No restrictions | Withaferine A, Withanolides Piperidine alkaloids: | Prohibited in Foods & Feed Supplements |
| ***Tribulus terrestris*** | Fruit | No restrictions | No restrictions | No restrictions | Prohibited in Foods & Feed Supplements |
| ***Rauvolfia serpentina*** | Root | Ingredient is marketed as Drug in USA | Prohibited in Malaysia, ASEAN | EFSA – Whole Plant | No restriction |

## Analytical standardization ….

- Marker compound – standardization
- Heavy metals
- Pesticide residues
- Environmental pollutants
- Radioactive substances
- Mycotoxins/aflatoxins
- Microbial contamination
- Gluten



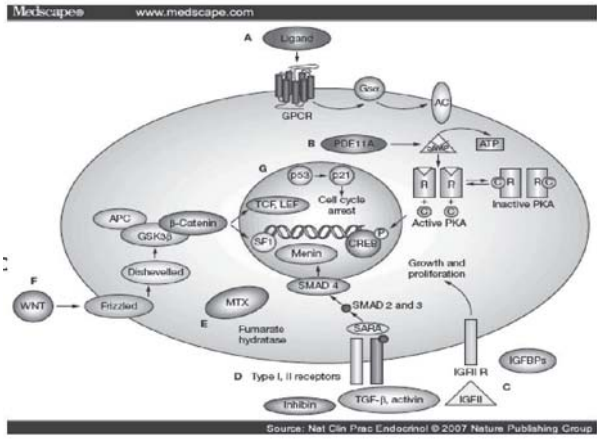
## Formulation development….



## Safety & Efficacy studies……

*In-vitro studies*

- Multiple biological assays
  - In vitro disease model assays
  - Enzymatic assays
  - Cellular models of skin and disease conditions
  - Advanced PCR assays
    - Amplify and simultaneously quantify a targeted DNA molecules
  - Molecular docking
- In-vitro studies……
  - Mice
  - Rats
  - Guinea pigs
  - Rabbits

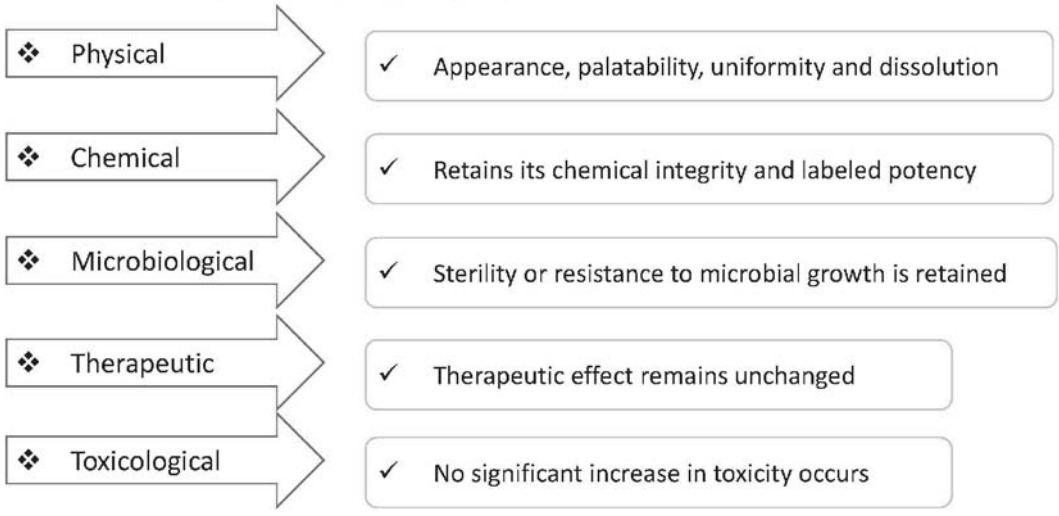


**Safety Studies…..**

- Systemic toxicity tests: Acute (24 hours)
- Long-term toxicity tests: – (2 weeks - 12 months)
- Local toxicity tests: - Skin sensitization tests
- Special toxicity tests: – Mutagenicity test
  – Carcinogenicity test
  – Reproductive and development toxicity test

**Saviryataa Avadhi aka Stability ….**

- The time lapse (period) during which drug to retains the same properties and characteristics to maintain its identity, strength, quality and purity



**Requirements of Advanced Clinical Research…..**

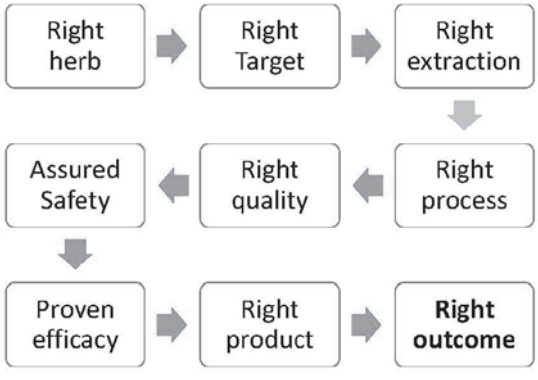
- Double blind placebo controlled multi-centric clinical trails
- Disease mechanisms and drug action
- ADME
- Pharmacokinetic and pharmacodynamic drug interactions
- Adverse Drug Reactions (ADRs)
- Pharmacovigilance

**Packaging development….**

The collection of different components which surround the pharmaceutical product from the time of production until its use

- Carry the correct information and identification of the product.
- Protect against physical damage
- Protect against all adverse external influences that can alter the properties of the product [Temp., light, moisture, etc].
- Protect against biological contamination

**Finally what should go behind the scene to Assure Right Outcome..!!??**




- TSM should be the main line of treatment rather than subsidiary [life style disorders etc].
- Robust evidences should be generated

**FSSAI to collaborate with Ayush ministry on Ayurvedic meals**

Ashwani Maindola, New Delhi

The apex food regulator is said to be working on standards for Ayurvedic meals, as a separate category, and is collaborating with the Ministry of Ayush for the same. According to Pawan Kumar Agarwal, chief executive officer, FSSAI, active discussions are on with the ministry for the project.

Speaking on the sidelines of an event hosted by the CII (Confederation of Indian Industry), he stated that both FSSAI and the Ministry of Ayush were exploring the possibilities of looking into the subject of standards for Ayurvedic food.

**Regulatory framework**

Agarwal added that discussions were going on between the authority and the ministry to dwell on the question whether there can be standards for Ayurvedic food as a separate category in the food supplements regulatory framework.

**Discussions were going on between the authority and the ministry to dwell on the question whether there can be standards for Ayurvedic food as a separate category**

"The decision of making it a separate category or keeping it in the existing food supplement regulations will be taken up at appropriate time," he said.

**Special medical purpose**

The proposal, according to sources, was made by the ministry itself, as FSSAI has already implemented a comprehensive regulation that prescribes standards for food and health supplements, nutraceuticals, foods for special dietary uses, for special medical purpose and functional and novel food in 2018.

Meanwhile, a working group has been constituted in January to draft a guideline on botanicals standards for Food Supplements under the Schedule IV of the Food Safety Standards (Health Supplements, Nutraceuticals, Foods For Special Dietary Uses, Special Medical Purpose, Functional and Novel Food) Regulations, 2018, which specifies the permitted levels of plant or botanical ingredients in supplements and nutraceuticals products.

New Column from Coming Issue
Ask Dr Deepa Bhajekar

# SHELF LIFE STUDIES OF ASU&H DRUGS

by

**Dr. R. Ilavarasan,**
Assistant Director (Scientist-4), Institute In-charge, CSMRADDI, Chennai
(Lecture Delivered during the National Seminar on Modern Scientific Approach for Standardization of Medicinal Plants used in ASU & H Drugs on 25th & 26th March 2019)

## Shelf life study

- To provide evidence of how the quality of drugs varies with time under the influence of a various environmental factors such as temperature, humidity and light.
- The period of time, from the date of manufacture,
- The drug product is expected to remain within its approved product specification while stored under defined conditions

## Shelf life study

- Shelf life is typically expressed in units of months i.e. 24 months, 36 months and maximum of 60 months
- To challenge the lifespan of either a new or commercial drug product
- The date of expiry of ASU & H drugs mandatory from Jan 2019

## Assessment and Monitoring of Stability

- Stability is one of the key features of all RMs (RM stands for Reference Materials)
- The value of each property can change over time for a variety of reasons, to different degrees and at different rates depending on the conditions
- Important conditions are
  - Conditions during long-term storage at the RM producers facilities
  - Conditions during transport to the user's premises
  - The Specified conditions of storage and use at the user's premises

## Assessment and Monitoring of Stability

- Accordingly, the RM producer is expected to manage material processing, storage, packaging, transport conditions, post-certification monitoring and advice to end users so that the risk of unexpected change is as small as reasonably possible.
- The assessment of stability may involve an experimental study to estimate the remaining degree of instability of RM after processing or to confirm the stability of the material.

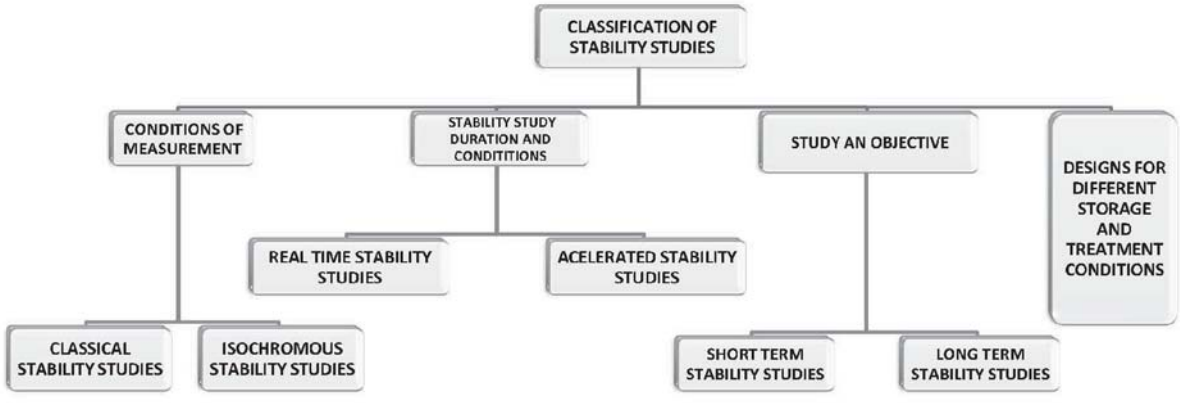
**Assessment of stability**

- Two types of (in) stability are;
  a)Long term stability
  b) Short term stability
- The long term stability is the stability of the material during the period of validity under specified storage condition
- The short term stability is the stability under reasonably expected conditions of transport
- Stability assessment should consideration of all the physical, chemical and biological properties

**Assessment of stability cont....**

of the material that might reasonably affect stability, . including the particular chemical or biological species certified

- Review of stability assessment or monitoring data on related materials
- Planned experiments, weather real-time or accelerated stability studies
- Experiments to test the effect of different storage arrangements, including container integrity and stabilization or preservation methods.



**Stability testing of ASU drugs**

1. "Shelf life testing" is also referred to as "Stability testing" According to duration and conditions of ASU drugs, Stability tests are:
   a) Accelerated
   b) Real time

2. In accelerated Stability tests, a product is stored at elevated stress conditions such as temperature, humidity and pH Temp: 40 ± 2 °C and Humidity: 75 ± 5% RH

**Stability testing of ASU drugs cont.....**

3. In real-time stability testing, a product is stored at recommended stored conditions and monitored until it fails the specification Temp: 30 ± 2°C and Humidity 65 ± 5 %RH

4. Received sample is stored at a temperature of 30°C ± 2°C, with humidity set at 65%RH ± 5%RH (RH-stands for Relative Humidity) for up to 60 months

**Stability testing**

5. Testing against the product's stability specification will take place at designated time points "Time points" reflect the duration of time that the product has been exposed in the set temperature / humidity storage condition

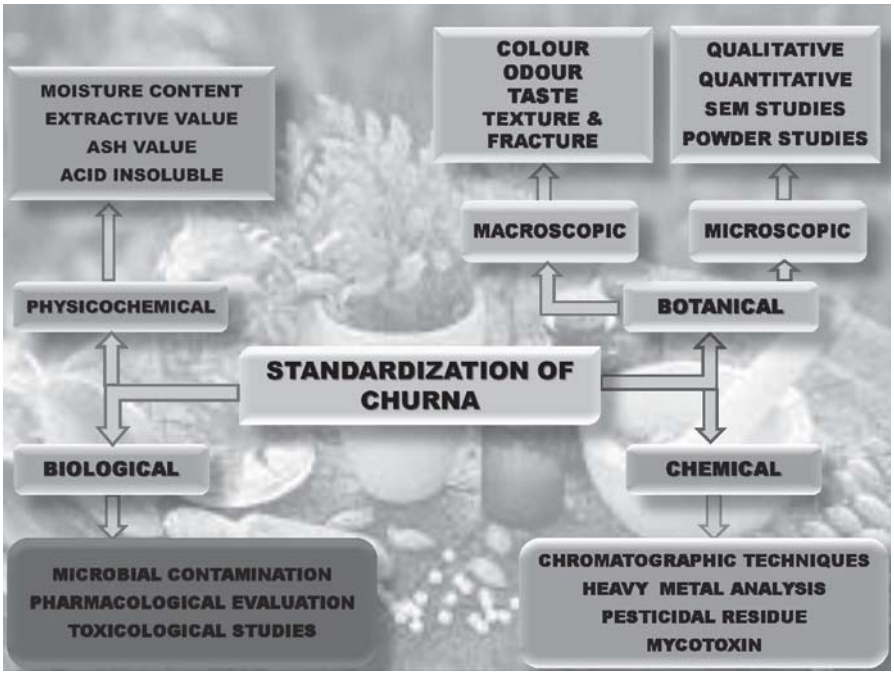
6. During the study, the samples are stored under same conditions as your normal production samples. If this is not possible the Samples should be stored at a known temperature and humidity.

**Stability testing cont.....**

7. These need to be checked and recorded regularly. Maximum storage times for quality and safety may not be the same.

8. To perform evaluation of drug quality at different quarters Till the target period completes.


Storage of
drugs in
Environmental
chamber


COLOUR
ODOUR
TASTE
TEXTURE &
FRACTURE
QUALITATIVE
QUANTITATIVE
SEM STUDIES
POWDER STUDIES
MOISTURE CONTENT
EXTRACTIVE VALUE
ASH VALUE
ACID INSOLUBLE
MACROSCOPIC
MICROSCOPIC
PHYSICOCHEMICAL
BOTANICAL
STANDARDIZATION OF
CHURNA
BIOLOGICAL
CHEMICAL
MICROBIAL CONTAMINATION
PHARMACOLOGICAL EVALUATION
TOXICOLOGICAL STUDIES
CHROMATOGRAPHIC TECHNIQUES
HEAVY METAL ANALYSIS
PESTICIDAL RESIDUE
MYCOTOXIN

## Microbial Contamination

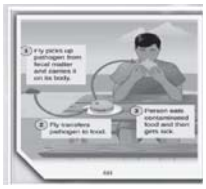
Microbial contamination refers to the non-intended or accidental introduction of microbes

1. Bacteria
2. Fungi
3. Yeast
4. Prions (Virus)
5. Protozoa etc.,

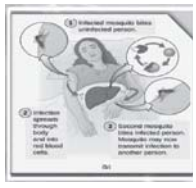
Microbial population

## Types of Microbial Contamination

**Direct contamination :**
Contamination by microbial components and poorly maintained heating, Ventilation and Air conditioning (HVAC) system.



**Cross contamination:**
Cross contamination is how microbes can spread.



## Source of Contaminants

- Passing of microorganisms other harmful substance indirectly
- From one sample to another through improper and unsterilized equipment's
- Some cells cross contaminated by cell of other species
  - Air Carrying dust
  - Outer skin of the Personnel
  - Persons walking will liberate 5000 bacteria/min
  - A singles sneeze will produce up to 1 million bacteria
  - Manufacturing process itself can generated contaminants

## Microbial contamination of pharmaceuticals

- A pharmaceutical raw material is an active or inactive substance used in the manufacture of a pharmaceutical dosage form.
- Non sterile pharmaceutical products with a high degree of water content may be contaminated with microorganisms.
- The contaminating microorganisms may cause spoilage of the product with loss of its therapeutic properties.

### Microbial Parameters

**Microbial contamination**

- Total Bacterial Count
- Total Fungal Count
- Enterobacteria count

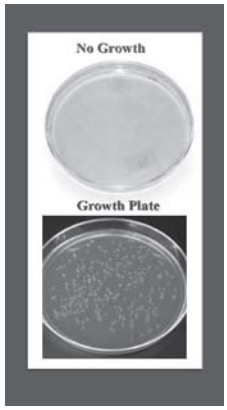
**For specific pathogen**

- E. coli
- Pseudomonas aeruginosa
- Salmonella sp.
- Staphylococcus aureus

### CFU Values

- Incubate all the plates at appropriate temperature.
- Observe plates for colonies growth
- Count the colonies and record the results

***Calculation formula:***
Calculate the number of colonies = No. of colonies X Dilution factor/dry weight of the sample = CFU



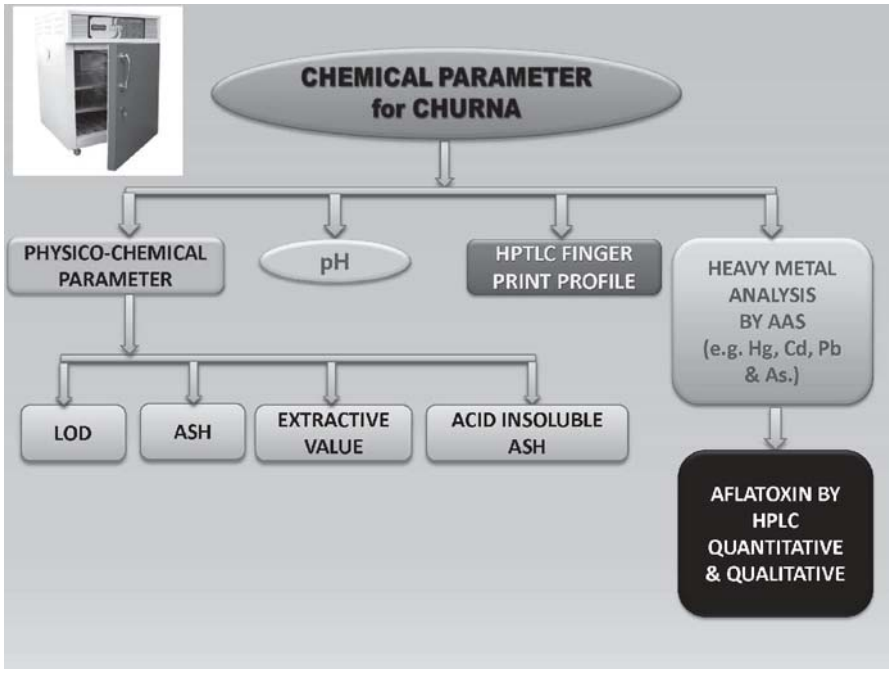

### Permissible Limits of Microbial Count

**As per the WHO/API guidelines for the contamination in Plant Material**

| S. No | Details of Study | For External Use | For Internal Use |
|---|---|---|---|
| 1 | Total Bacterial Count | $1x10^7$ per gram | $1x10^5$ per gram |
| 2 | Total Fungal Count | $1x10^4$ per gram | $1x10^3$ per gram |
| 3 | *Entero-bacteriaceae* | $1x10^4$ per gram | $1x10^3$ per gram |
| 4 | *Escherichia coli* | $1x10^2$per gram | $1x10^2$ per gram |
| 5 | *Salmonella spp* | Absent | Absent |
| 6 | *Staphylococcus aureus* | Absent | Absent |
| 7 | *Pseudomonas aeruginosa* | Absent | Absent |

## CASE study of Microbial Contamination of Churna

| S. No | Number of Quarters | Total Bacterial Count cfu/g | Total Fungal Count c fu/g | *Entero-bacteriaceae* | *E. coli* | *Salmonell spp.* | *Staphylococcus spp.* | *Pseudomonas aeruginosa* |
|---|---|---|---|---|---|---|---|---|
| 1 | 0 day | $1.0x10^4$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 2 | 1st Quarter | $1.0x10^4$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 3 | 2nd Quarter | $3.0x10^4$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 4 | 3rd Quarter | $5.5x10^3$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 5 | 4th Quarter | $1.0x10^4$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 6 | 5th Quarter | $1.0x10^4$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 7 | 6th Quarter | $5.5x10^3$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 8 | 7th Quarter | $1.0x10^3$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 9 | 8th Quarter | $<10^3$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 10 | 9th Quarter | $1.5x10^3$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 11 | 10th Quarter | $1.0x10^3$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |
| 12 | 11th Quarter | $1.5x10^3$ | $<10^3$ | Absent | Absent | Absent | Absent | Absent |

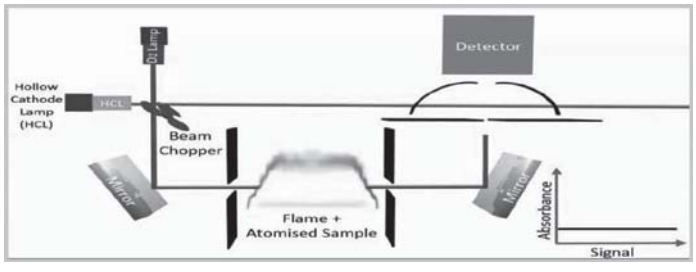


## Case study of churna for chemical pharameter

| S. No | Test parameters | LOD (%) | Ash (%) | Acid insoluble ash | Water soluble extractive | Alcohol soluble extractive | pH |
|---|---|---|---|---|---|---|---|
| 1 | Zero day | 11.01 | 7.23 | 3.64 | 52.73 | 29.38 | 4.34 |
| 2 | 1st Quarter | 11.06 | 7.36 | 4.12 | 52.32 | 29.26 | 4.33 |
| 3 | 2nd Quarter | 11.31 | 7.29 | 4.16 | 52.02 | 29.45 | 4.28 |
| 4 | 3rd Quarter | 11.69 | 7.37 | 4.21 | 51.85 | 28.01 | 4.39 |
| 5 | 4th Quarter | 11.06 | 7.32 | 4.23 | 51.73 | 28.53 | 4.53 |
| 6 | 5th Quarter | 12.70 | 7.31 | 4.28 | 51.23 | 27.02 | 4.56 |
| 7 | 6th Quarter | 12.50 | 7.29 | 4.01 | 50.98 | 256.8 | 4.51 |
| 8 | 7th Quarter | 11.82 | 7.26 | 4.16 | 51.23 | 25.98 | 4.53 |
| 9 | 8th Quarter | 11.60 | 7.34 | 3.93 | 50.86 | 25.80 | 4.67 |
| 10 | 9th Quarter | 12.01 | 7.36 | 4.25 | 50.12 | 25.68 | 4.60 |
| 11 | 10th Quarter | 11.66 | 7.28 | 4.19 | 50.23 | 25.01 | 4.58 |
| 12 | 11th Quarter | 11.53 | 7.32 | 4.24 | 50.24 | 24.98 | 4.52 |

## Permissible limits of Heavy Metals and Aflatoxins

### According to WHO guidelines




### Limits of Heavy Metal

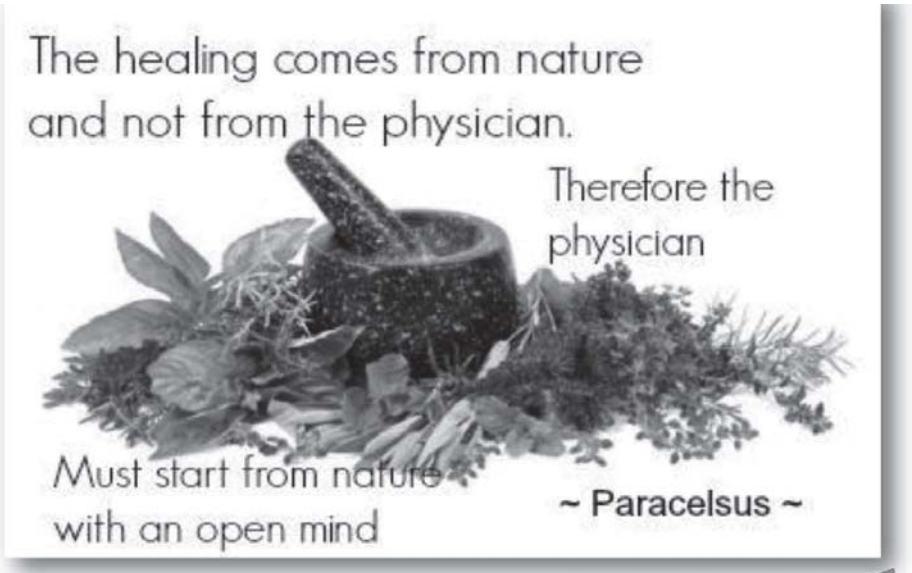
- Mercury – 1.0 ppm
- Lead – 10.0 ppm
- Cadmium – 0.3 ppm
- Arsenic – 3.0 ppm

### Limits of Pesticide residue

- DDT/ DDD – 1.00 ppm
- Hexachlorocyclohexane – 0.30 ppm
- Malathion – 0.10 ppm
- Parathion – 0.30 ppm
- Alderin/ Dieldrin – 0.05 ppm

### Limits of Aflatoxins

- Aflatoxins B1 – 0.5 ppb
- Aflatoxins B2 – 0.1 ppb
- Aflatoxins G1 – 0.5 ppb
- Aflatoxins G2 – 0.1 ppb




THANK YOU

# IMPORTANCE OF SAFETY AND EFFICACY STUDIES ON TRADITIONAL MEDICINES IN CONTEXT TO REVERSE PHARMACOLOGY

by

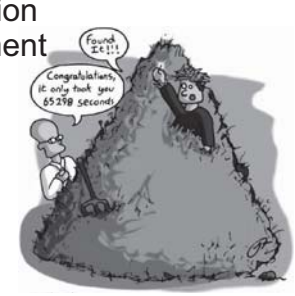
**Dr. Mukesh Kumar Nariya,**
Head Pharmacology, Institute of Post Graduate Teaching & Research in Ayurveda, Gujarat
(Lecture Delivered during the National Seminar on Modern Scientific Approach for Standardization of Medicinal Plants used in ASU & H Drugs on 25th & 26th March 2019)

## Drug Discovery

- Physiology based drug discovery
- Target oriented drug discovery
- Currently, all existing therapies hit only about 400 drug targets, as per review.
- At least 10 times as many potential drug targets that could be exploited for future drug therapy.

## New Drug Discovery and Development process:

- Target Discovery
- Target Validation
- Assay Development
- Screening and Hits to Leads
- Lead Optimization
- Drug Development




- Most research is carried out on diseases which afflict "first world" countries: (e.g. pain, inflammation, cardiovascular diseases, depression, diabetes, flu, migraine, obesity).
- Very few drug research on orphan diseases

## "Big Pharma" Drug Discovery in the 21st Century

- **The Problem:** The industry is short of new drugs.
- It is notoriously inefficient
- In the 2nd part of the 20th century, about 50-60 new drugs were approved by the FDA every year.

**"Big Pharma" Drug Discovery in the 21st Century**

- In contrast, in 2002, a historical low of 18 NCEs were approved. In 2001- 24 NCEs, in 2000- 27 NCEs, in 2003- 21 NCEs.
- Conversely, research costs for a new drug are estimated to be in the $1-1.5 Bi. range.
- Considering all high-profile failures in recent drug discovery, this figure is unlikely to drop substantially

**Clinical Trials**

- Very long & Expensive, 50 to 70% of the drug discovery and development cost.
- 90% percent of NCEs entering clinical trials fail. Forty percent of compounds fail in Phase 1,
- 62% of successful Phase 1 compounds fail in phase 2,
- 40% of successful Phase 2 compounds fail in Phase 3,
- and a surprising 23% of successful Phase 3 compounds fail at the registration stage, when the FDA denies approval.

**Clinical Trials—Overview**

- In 90's, the main reason for failure was problems in PK/bioavailability (40%), lack of efficacy (30%) and toxicology (12%).
- In 2000, the main reason for failure was lack of efficacy (27%), commercial and market reasons (21%) and toxicology (20%).

**Drug Failure- Ad-RTS-hIL-12**

- **Sponsor:** Ziopharm Oncology
- **Indication:** Glioblastoma (GBM)
- **Type of drug:** Viral gene therapy candidate for the controlled expression of interleukin 12 (IL-12)
- **How drug failed:** Three patients died in a Phase I study due to brain cancer. Two patient deaths at 6.7 months following a 20 mg dose, and the third, 3.9 months after treatment with a 40 mg dose.
- **Aftermath of failure:** The stock price slide 26%.

## Drug Failure- Birinapant

- **Sponsor:** TetraLogic Pharmaceuticals
- **Indication:** Myelodysplastic syndromes (MDS)
- **How drug failed:** Did not meet primary endpoint of response rate after four months of therapy in a Phase II study.
- Birinapant failed to show any clinical benefit over placebo. Company terminated the trial following an interim analysis of the first 62 patients.
- Aftermath of failure: Sparked a 76% plunge in share price. Company eliminated two-thirds of its workforce.

## Drug failure

| Drug (Indication) | Approved | Withdrawn Years | Delay | Reason Drug Is Pulled | |
|---|---|---|---|---|---|
| Fenfluramine (weight loss) | 1973 | 1997 | 24 | Pulmonary hypertension, heart valve disease | Wyeth-Ayerst |
| Vioxx (pain) | 1999 | 2004 | 5 | Heart attack, stroke | Merck |
| Rezulin (anti-diabetes) | 1997 | 2000 | 03 | Liver toxicity | Pfizer |
| Lotronex (IBD) | 2000 | 2000 | 09 | Ischemic colitis, constipation | Glaxo |

## Reverse Pharmacology

- Integrating documented clinical/experiential hits, into leads by trans disciplinary exploratory studies.
- Further, developing these into drug candidates by experimental and clinical research.
- The scope is to understand the mechanisms of action at multiple levels of biological organization.
- To optimize safety, efficacy and acceptability of the leads in natural products.

## Reverse Pharmacology

- The ancient medical science inspired reverse pharmacology.
- It relates to reversing the routine discovery pipeline from 'clinics to laboratories'.
- In this process 'safety' remains the most important starting point and the efficacy becomes a matter of validation.
- Reverse pharmacology offers a major paradigm shift in drug discovery.

## Examples of some important plant derived drugs

| Compounds | Species |
|---|---|
| Andrographolide | Andrographis paniculata |
| Berberine | Berberis spp. |
| Asiaticoside | Centella asiatica |
| Curcumin | Curcuma longa |
| Glycyrrhizin, Glycyrrhizinic acid | Glycyrrhiza glabra |
| Artemissine | Artemisia annua |
| Scopolamin | Datura sp. |
| Taxol | Taxus baccata |
| Diosgenin | Dioscorea spp. Costus spp. |
| Vinblastine, Vincristine | Catharanthus roseus |
| Quinine, Quinidine | Cinchona spp. |
| Sennosides A&B | Cassia angustifolia, C. acutifolia |

### During preclinical drug development

- Drug's Toxicity and Pharmacological Profile through HTS, in-vitro and in-vivo laboratory animal testing.
- Genotoxicity, Reproductive study and carcinogenicity screening
- Whether the product is reasonably safe for initial testing in humans.
- To understand the effects of drugs on the organism and to predict the drug's behavior in humans.
- The main models used are rodents including mouse and rat, but larger animals such as dogs, pigs, and, more rarely, monkeys are also used.

### During preclinical drug development

- They optimize the physicochemical properties of Drugs in terms of,
  1. minimal toxicity and side effects,
  2. maximum efficacy toward disease.
- The purity of the compound needs to be very high.
- PK/PD/ADME studies require analytical methods and sophisticated instrumentation.
- Mass spectroscopy, (whole-body) imaging, and chromatography technology (HPLC, LC-MS, LC-MS-MS).

## Safety aspects- Reverses Pharmacology

- Use of processed metals, minerals, mercurial, herbo-mineral formulations and herbal, as a medicine along with anupana has been an essential part of Ayurvedic practice in India.
- Unique procedures- Shodhana, Marana, Amritikaran etc. strictly as per traditional methods.
- Analysis of role of such procedure and Anupana concepts have to be designed in safety and efficacy.
- Most of the traditional methods are very teadious and lenghty
- Mass scale production by Pharmaceutical industry can full fill the requirement?
- JAMA article ?

## JAMA (Journal of American Medical Association) controversial drugs: Ayurvedic formulations were reported to be having heavy metals more than prescribed limit

Drugs were coded as **s, r, t, u and w** and tested for acute and chronic toxicological studies as per standard guideline

The effects of test drugs were assessed on ponderal, hematological parameters, biochemical, heavy metals in serum & organs and histopathological studies as per standard guideline.

Later drugs were decoded as,

- *Mahalaxmibilas Rasa with Gold*
- *Mahasudarshan Ghana Vati*
- *Mahayogaraja Guggulu,*
- *Navratna Rasa*
- *Swarn Mahayogaraja Guggulu*

- In acute toxicity study, LD50 value is higher than 2000 mg/kg by oral route hence, can be categorized as substances with low health hazard potential.
- The results of chronic toxicity showed that these drugs are absolutely safe even up to tenfold of therapeutically equivalent dose.

## Impact of Shodhana and Route of drug administration Role of Anupana

- Tamra bhasma prepared from Ashodhita Tamra showed severe hepatotoxicity, nephrotoxicity and testicular toxicity even in the dose of TED (5.5 mg/kg).
- In contrast Tamra bhasma prepared from Shodhita Tamra is safe even in five fold to TED (27.5 mg/kg).
- Tamra bhasma administration?
- Anupana for administration?

Research Paper

**Toxicological Studies of *Rasasindura*, an Ayurvedic Formulation**

R. A. GOKARN*, M. B. NARIYA1, B. J. PATGIRI2 AND P. K. PRAJAPATI2

Indian J Pharm Sci 2017;79(4):633-640

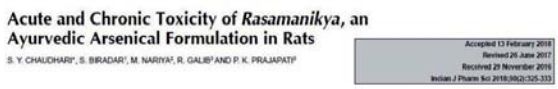
## Impact of Shodhana and Role of Anupana

Along with honey not toxic on acute administration at a maximum oral dose level of 2000 mg/kg in female rats as per OECD 425 guideline.

On chronic administration for 90 days, Rasasindura at TED has no any toxic potential in rats.

TED×10 dose level, for 90 days, produced mild to moderate adverse changes in the kidney, liver, intestine, and stomach of rats.

Rasasindura prepared as per customary method and administered with appropriate adjuvant as honey is safe to consume at therapeutic dose level.


Acute and Chronic Toxicity of *Rasamanikya*, an Ayurvedic Arsenical Formulation in Rats

S. Y. CHAUDHARI[1], S. BIRADAR[1], M. NARIYA[2], R. GALIB[3] AND P. K. PRAJAPATI[3]

Accepted 13 February 2018
Revised 26 June 2017
Received 29 November 2016
Indian J Pharm Sci 2019;80(2):325-333

## Impact of Shodhana and Role of Anupana

Rasamanikya processed in fruit juice of Benincasa hispida and administered along with honey and ghee.

Produced mild pathological changes after duration of 90 days at higher (TED×10) doses. The observed pathological changes were reverted after withdrawal of the drug.

RM should be administer in proper dose with a specified anupana (honey and ghee) for specified periods as mentioned in Ayurvedic classics.

## Role of classical procedure on safety aspects


Journal of Ayurveda and Integrative Medicine

Original research article (Experimental)

Acute and subchronic toxicity study of *Tamra Bhasma* (incinerated copper) prepared with and without *Amritikarana*

Swapnil Y. Chaudhari [a,*], Mukesh B. Nariya [b], R. Galib [a], Pradeep K. Prajapati [a]

Ld50 value may be higher than 2000 mg/kg by oral route. hence, can be categorized as substances with low health hazard potential.

Safe at TED in rats, however, at TEDx10 dose level, has prone to produce adverse changes in liver, kidney, and heart . With Amritikarana has low magnitude of adverse changes at higher dose.

Amritikarana is must for Tamra Bhasma, when prepared for internal administration.

## Genotoxicity studies in animals

- Rasamanikya
  (Arsenical formulation)
- Naga Bhasma
  (Calcined lead)

**Methods:**

- Sperm abnormality assessment
- Chromosomal aberration assay
- Micronuclei assay for assessment

Positive control- Cyclophosphamide, produced abnormal sperm (head & tail) abnormalities as well as high frequencies of chromosome breaks,

## Genotoxicity studies in animals

centric fusion, centric attenuation, deletion, fragmentation, end to end and polyploidy shape compared to control group.

Naga bhasma (30 and 60 puti) at both dose levels of TED and TEDx5 did not produce any adverse changes in sperm morphology and chromosomes extracted from bone marrow of albino rats.

Plate- 4.4. Photomicrographs of Sperm

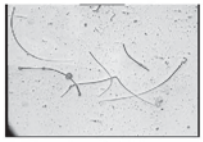


Fig. 4.4 (a)

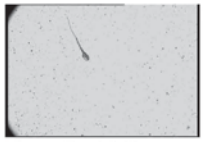


Fig. 4.4 (b)


Fig. 4.4 (c)

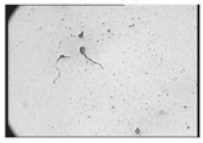


Fig. 4.4 (d)

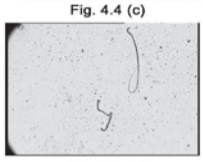


Fig. 4.4 (e)


Fig. 4.4 (f)

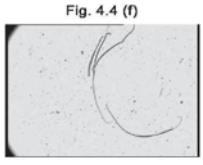


Plate- 4.5. Photomicrographs of Sperm


Fig. 4.5 (a)

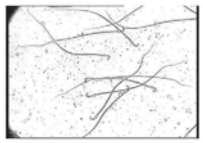


Fig. 4.5 (b)

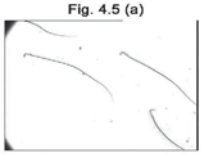


Fig. 4.5 (c)

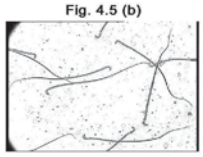


Fig. 4.5 (d)

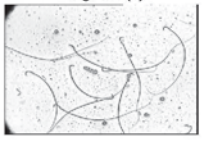


Fig. 4.5 (e)


Fig. 4.5 (f)


Fig. 4.5 (g)

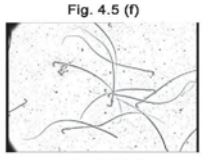


Fig. 4.5 (h)

Plate- 4.7. Photomicrographs of chromosomes

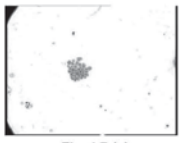


Fig. 4.7 (a)

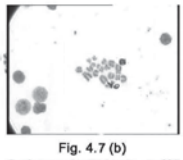


Fig. 4.7 (b)

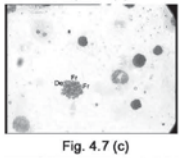


Fig. 4.7 (c)

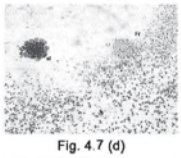


Fig. 4.7 (d)

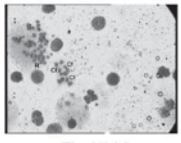


Fig. 4.7 (e)

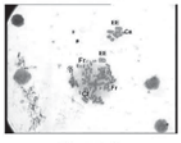


Fig. 4.7 (f)

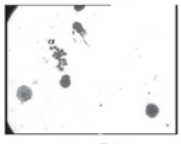


Fig. 4.7 (g)

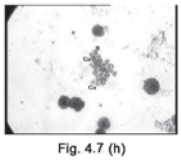


Fig. 4.7 (h)

Plate- 4.8. Photomicrographs of Chromosomes

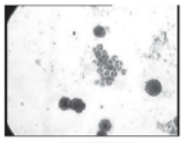


Fig. 4.8 (a)

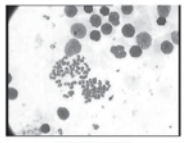


Fig. 4.8 (b)

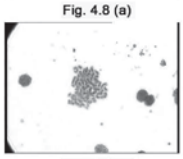


Fig. 4.8 (c)

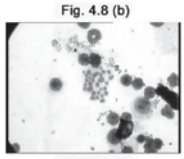


Fig. 4.8 (d)

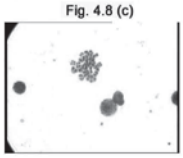


Fig. 4.8 (e)

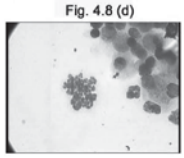


Fig. 4.8 (f)

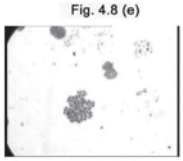


Fig. 4.8 (g)

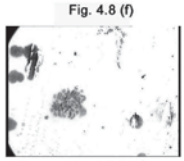


Fig. 4.8 (h)

## Safety of Ayurvedic formulations containing potential ingredients evaluated through Chronic toxicity studies in animals as per standard guidelines

| Bhasma (Calcined metal- minerals) | Kupipakwa (Mercurial and Arsenical formulations) | Single drug/Compound formulations |
|---|---|---|
| Naga (Lead) | Makaradhwaja (Gold containing) | Vatsanabha |
| Tamra (Copper) | Rasasindura | Tribhuvankirti rasa |
| Swarna makshika (Copper pyrite) | Malla sindura | Hridayarnava rasa |
| Rajata (Silver) | Sameera Pannaga Rasa | Bhallataka |
| Vanga (Tin) | Rasakarpura | Jayapala |
| Yashada (Zinc) | Rasamanikya | Vacha, Dhatura |

## Innovation in Diabetic wound healing

Leaves of *Securinega leucopyrus* (Willd.) Muell, Euphorbiaceae family.

Commonly known in Gujarat, India-"Humri/Thumari" and in Sri Lanka "Katupilla" is a plant used for the treatment of wounds.

J Ayurveda Integr Med. 2014 Jan-Mar; 5(1): 60–63. PMCID: PMC4012365
doi: 10.4103/0975-9476.128872 PMID: 24812478

*Katupila* (*Securinega leucopyrus*) as a potential option for diabetic wound management

Ahamed Shahan Ajmeer, Tukaram Sambhaji Dudhamal, Sanjay Kumar Gupta, and Vyasdeva Mahanta

Ayu. 2014 Apr; 35(2): 175–8. doi: 10.4103/0974-8520.146238.

**Topical application of Katupila (Securinega leucopyrus) in Dushta Vrana (chronic wound) showing excellent healing effect: A case study.**

Ajmeer AS[1], Dudhamal TS[2], Gupta SK[2], Mahanta V[2].

This miracle plant can save diabetes patients from going under the knife

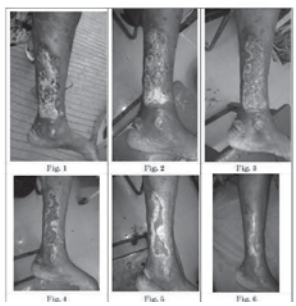
Nimesh.Khakhariya
@timesgroup.com

Rajkot: More than anything else, most diabetics shudder at the thought of foot amputation, the last resort when stubborn wounds or infections refuse to heal. But here is some sweet news for high-sugar patients.

Close to 100 diabetics have been saved from going under the knife, thanks to a medicinal plant named 'katupila' ficially studied and put to use by city-based Gujarat Ayurveda University

For all those patients, amputation was the only alternative left according to their doctors. In 2015, A S Ajmeer, a shalya tantra (surgery) student from Sri Lanka, got the plant named 'katupila' from his native country and a team began research on its medicinal properties. After getting encouraging results, they developed a paste from the crushed leaves of the plant and this was applied on wounds of diabetics.

►Continued on P 5



- Excision wound healing activity in rats
- Incision wound healing activity in rats
- Effects of test drugs on diabetic wound in rats

Paste of Secureniga leucopyrus leaves powder made in two liquid media i.e. sesame oil and water

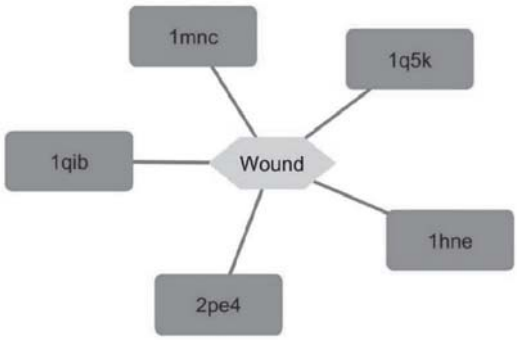
Significant results in rats treated in paste made in sesame oil .

The effects of drugs tested at molecular level, growth factors, cytokines and tensile strength of wounded skin.

**Network pharmacology**

- Novel concept creates a molecular network by integrating multidisciplinary biology including Biochemistry, Bioinformatics, and Systems Biology.
- It is based on multi targeting potentials of the effective drugs for therapeutic applications.
- Several diseases occur because it involves the interactions of multiple genes as well as functional proteins.
- Network pharmacology helps in detecting how and where in the disease network; one target inhibits or activates the disease phenotypes and assists in systematic characterization of the drug targets

**Targets involved in wound**




1hne: Human Neutrophil Elastase
1mnc: Human Neutrophil Collagenase
1q5k: Glycogen Synthase Kinase 3
1qib: Gelatinase
2pe4: Human Hyaluronidase

**Targets involved in wound**

LCMS analysis- 42 Phytoconstituents
GCMS analysis- 16 Phytoconstituents of S. leucopyrus leaves powder.

Only 39 chemical constituents of S. leucopyrus and 5 standards compounds, were proved for wound healing activity.

Ability to docked with total 5 target protein.

- 22 chemical constituents of S. leucopyrus docked with human neutrophil elastase
- 24 constituents docked with Human neutrophil collagenase
- 24 constituents docked with Glycogen synthase kinase
- 13 constituents docked with Gelatinase
- 18 constituents docked with Human Hyaluronidase.

Further, from binding energy and inhibition constant, it is concluded that,

Phytoconstituents present in S. leucopyrys leaves powder showed highest affinity towards the protein collagenase and glycogen synthase kinase followed by human neutrophil elastase, human hyaluronidase and gelatinase.

## Rasayana Effects


*Rasayana* effect of *Guduchi Churna* on the life span of *Drosophila melanogaster*

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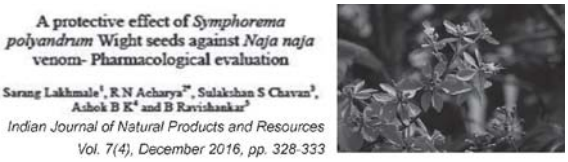
Official publication of Institute For Post Graduate Teaching & Research in Ayurveda, Jamnagar | Published by Wolters Kluwer - Medknow

Guduchi (Tinospora cordifolia) churna given in regular food media (0.25 to 0.70 g/100 ml) for 30 days to Drosophila melanogaster.

Guduchi churna increase the survival and enhances the life span of Drosophila melanogaster in both parent and F-1 generation.


A protective effect of *Symphorema polyandrum* Wight seeds against *Naja naja* venom- Pharmacological evaluation

Sarang Lakhmale[1], R N Acharya[2*], Sulakshan S Chavan[3], Ashok B K[4] and B Ravishankar[5]

*Indian Journal of Natural Products and Resources*
*Vol. 7(4), December 2016, pp. 328-333*

*Symphorema polyandrum* Wight (Family Verbenaceae) known as Badichang or Mahasindhu' - Used by tribal people of Odisha. Reported for snake bite, scorpion stings, cat and mad dog bite.

*S. Polyandrum* along with *P. nigrum* (130 mg/kg) as found to counteract an extent the venom action by increase the survival rate of animals.

**Role of Pippali**

## Role of Shodhana in efficacy

Evaluation of acute toxicity and intestinal transit time of *Croton tiglium* L. seeds

Shweta Vekariya[1*], Krushnkumar Taviad[2], Nidhi Rangpariya[3], Mukesh Nariya[4], Acharya R.N[5]
[1]Department of Dravyaguna, [2]Department of Rasa Shastra & Bhaishajya Kalpana,
[3]Department of Pharmacology, [4]Department of Pharmacology,

Indian Journal of Natural Products and Resources
Vol. 9(4), December 2018, pp 331-335

*Shodhana* of the seeds were carried out by *Swedana* (boiling) method with *Godugdha* (cow milk) for three hours and after *Swedana* of *Jayapala*, seeds were washed, air-dried and pulverized into fine powder. The fine powder was further subjected to *Bhavana* with *Nimbu swarasa* for three times[10]. These *Shodhita*

## Effects of formulation design in biological expression

PHYTOTHERAPY RESEARCH
*Phytother. Res.* (2009)
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/ptr.2744

**Comparison of Enteroprotective Efficacy of Triphala Formulations (Indian Herbal Drug) on Methotrexate-Induced Small Intestinal Damage in Rats**

Mukeshkumar Nariya[1], Vinay Shukla[2], Sunita Jain[1] and Basavaiah Ravishankar[2]*

## Age related changes and effects on biological expression

Anti-hyperlipidaemic activity of fresh and old *Guggulu* (*Commiphora wighiii* (Arn.) Bhandari) in experimental animals

Kruti Yagneshkumar Vyas, Mukeshkumar Nariya*, R Galib, Pradeep Kumar Prajapati
Department of Rasa Shastra and Bhaishajya Kalpana including Drug Research, [1]Pharmacology Laboratory, Institute for Post Graduate Teaching and Research in Ayurveda, Gujarat Ayurved University, Jamnagar, Gujarat, India



## Effects of route of drug administration- Reverse Pharmacology aspects

- Brahmi ghrita administered through Nasya route produced better bioavailability of biological marker and having pronounced memory and learning effect than administered through oral route.
- Triphala basti given through rectal route: The drug is well absorbed in systematic circulation in animal models.


Evaluation of the haematinic activity of *Opuntia elatior* Mill. fruit

Hemil Patel[1*], Shashikant Prajapati[1], Anagha Ranade[1], Rabinarayan Acharya[1] and Nariya Mukesh Kumar[2]
[1]Dravyaguna Department,[2]Pharmacology Laboratory, Institute for Postgraduate Teaching & Research in Ayurveda, Gujarat Ayurved University, Jamnagar - 361008, Gujarat, India

Indian Journal of Natural Products and Resources
Vol. 9 (1), March 2018, pp. 39-46

# THE LEADERSHIP CHALLENGES IN THE PHARMACEUTICAL SECTOR

by
**Mr. Bala Baskar. N**
Mother Theresa Post Graduate & Research Institute of health Sciences, Puducherry

Note: This article was awarded 2nd prize in the Essay Competition conducted by our Trust

## DEFINITION:

The Pharmaceutical sector or Pharmaceutical industry discovers, develops, produces and Markets drugs or Pharmaceutical drugs for use as medications. They are subject to variety of laws and regulations that govern the patenting, testing, safety, efficacy, and marketing of drugs. Some of Pharmaceutical companies are Cipla, Cadila Health care, Torrent Pharmaceuticals etc., under this we have to discuss about the Leadership challenges in the Pharmaceutical sector.

## INDIAN PHARMACEUTICAL SECTOR:

- India's cost of production is nearly 33 per cent lower than of the U.S
- Cost of efficiency continues to create opportunities for Indian companies in emerging markets & Africa.
- India has the 2nd largest number of USFDA - approved manufacturing plants outside the U.S
- Growing per capita sales of pharmaceuticals in India offers ample opportunities for the players in the market.
- Economic prosperity would improve affordability for generic drugs in the market & improve per capita sales of pharmaceuticals in India.

## IPORTANT SEGMENTS OF INDIAN PHARMACUTICAL SECTOR:

**ACTIVE PHARMACEUTICAL INGREDIENTS (APIs):** India became the third largest Global generic API merchant market in 2016, with a 7.2 per cent market share.

**FORMULATIONS:** Largest exporter of formulations in terms of volume, with 14 per cent market share and 12th in terms of export value. Drug formulations exports from India reached US$ 11.61 billion during April 2017 – February 2018.

**CONTRACT RESEARCH AND MANFACTURING SERVICES (CRAMS):** CRAMS Industry is estimated to reach US 18 billion in 2018 and expected to witness a strong growth at a CAGR of 18-20 per cent between 2013-18.

**BIOSIMLIARS:** The government plans to allocate US$ 70 million for local players to develop Biosimilars. These are the important segments of Indian pharmaceutical sectors.

**CHALLENGES IN PHARMACEUTICAL INDUSTRY:**

The challenges in pharmaceutical industry or sector are classified into:

- (PATENT) Effects of new products patent
- (FORMS) Regulatory reforms
- (QUALITY CONTROL FOR APPROVAL) Quality management
- (GLOBAL STANDARDS FOR CERTIFICATION) Conformance of global standards
- (BEST PRICE) PRICING ISSUES
- (R&D) R&D Spending
- (INFORMATION TECHNOLOGY) INFORMATIONS REGARDING PHARMA SECTOR

**1. EFFECTS OF NEW PATENT PRODUCT:** The product patent introduced in India in 2005. It is granted for period twenty years. This is helped to generate the new versions of generic drugs in pharmaceuticals. Thus earlier times, The Indian pharmaceutical industries produced generic drugs on mass level by using the process reverse engineering. This also threatens the supply of generic drugs due to heavily dependent countries along with the domestic market.

**2. REGULATORY REFORMS:** Any sector, on a monthly or yearly basis has deal with government or non government agencies like: 1. MIDC, 2. FDA, 3. Drug Controller General, 4. Excise state general, 5. Sales tax, 6. Customs and port, 7. Local political parties, 8. Transportation by local body, 9. Income tax.

**3. QUALITY MANAGEMNET AND CONFIRMANCE OF GLOBAL STANDARDS:** "WE ARE TAKING SWIFT ACTION TO PREVENT SUBSTANDARD QUALITY PRODUCTS FROM CONSUMERS"-US FDA. In this of some plants are banned because of its not proper in manufacturing practices and for some data integrity issues. For eg: RANBAXY have been banned some four plants are TOANSA, PAONTA, SAHIB, MOHALI DEWAS.

**4. PRICING ISSUES:** To ensure that vital drugs are available at affordable prices, the government Exercises control over the prices of certain drugs it defines as "essential". The Drug Pricing policy 2013 provides the framework through in which ceiling prices for these essential drugs are worked out under this act, DPCO, 74 drugs are subject to control. Thus, this gives less scope to the companies to invest in R&D.

**5. R&D SPENDING:** Indian manufacturers cannot fulfill their ambitions to become players on the world stage unless they make significant increases to their R&D expenditures at 2%. To promote the R&D in SMEs the government needs to come up with incentives and promotion programs. At present government is providing tax deduction to promote R&D, but according to industry Experts, this is not sufficient.

**6. INFORMATION TECHNOLOTY:** One of the main challenges faced by Pharma Software tools would help SMEs In computer aided drug designing but most players continues to under invest in IT systems and good accounting practices due to its over cost.

Some other challenges are the Ministry of Labour takes of care labour welfare and increasing competition from other low cost nations. These ae the some challenges in the pharmaceutical companies.

**CONCLUSION:**

Pharma organizations that survive and thrive will develop these important leadership competencies and will prepare their leadership team to handle the performance challenges inherent in the 21st trends the industry faces—from health care reform, a struggling economy, and global competition. I hope these useful informations are in this paper can help to facilitate for this leadership challenges in Pharmaceutical companies and help you determine how aligned your leaders are with the competencies vital to your current and future success.

# EVENTS

## CONVOCATION MEETING OF SRI RAMACHANDRA UNIVERSITY, CHENNAI



M/s. Sri Ramachandra Institute of Higher Education & Research, celebrated the convocation of various graduates who studied in that university held on 22nd April 2019. **Dr. S. Eswara Reddy**, Drug Controller General of India was the Chief guest of the convocation. Sri. V.R. Venkatachalam, Chancellor of the University and Sr. R.V. Sengutuvan and Dr. P.V. Vijayaraghavan, Vice Chancellors of the University participated in the convocation. The University has achieved 33rd rank, all India level, 11th rank in Medical Colleges and 20th rank in Pharmacy, amongst the Universities in India. The University is offering around 117 UG and PG programs in Medicine, Dental, Pharmacy and other health science programs. The University is also giving prominent importance in research and the research publications in high impact journals of repute.

**Dr. Eswara Reddy**, Drugs Controller General of India, in his convocation address hailed the University for attaining the leading research institutions in Medical & Healthcare. In his speech, he narrated the long history of Pharma industry and its regulation in India. He also said the promulgation of the Indian patent act, 1970 changed the Pharmaceutical industry scenario in our country, particularly, availability of quality and affordable prices of life saving drugs to the Indian population. He further said India is among the leading global producers of cost effective generic medicines and vaccines, supplying 20% of the total global demand by volume. He further narrated that out of 6500 domestic Pharmaceutical industries, many are approved for WHO GMP certification as well as Europe Certificate of Suitability and US FDA. He congratulated all the students who received a degree in the convocation ceremony particularly those who got Gold Medal in their academics.

# INFORMATION

## M. PHARM & PHARM D SCHOLARSHIPS 2018-19 AWARDED BY TNPSWT

Profile of 2nd Rank Projects

### *PHARMACEUTICS*

Name: Ms. Ranjitha. R

Project Title: Formulation and Evaluation of Lovastatin Loaded Nanosponges for Treatment of Hyperlipidemia

College: College of Pharmacy, Madras Medical College, Chennai

Guide's Name: Prof. K. Elango

### *PHARMACEUTICAL CHEMISTRY*

Name: Mr. Kathiravan. M

Project Title: Synthesis, Characterisation, Molecular Docking of Some Novel Benzofuran Derivatives and their Evaluation of Anti-microbial and Anticancer Activities.

College: College of Pharmacy, Madurai Medical College, Madurai

Guide's Name: Dr. G. Umarani

### *PHARMACEUTICAL ANALYSIS*

Name: Mr. Lingamallu Venkata Sai Krishna

Project Title: QbD Approach on Analytical Method Development and Validation for the Estimation of Febuxostat in their Formulations by LC-MS-MS

College: JSS College of Pharmacy, Ooty

Guide's Name: Dr. S.N. Meyyanathan

### *PHARMACOLOGY*

Name: Ms. V. Shanthi Priya

Project Title: Investigation of the Effect of Fenoprofen on Central MC Receptor for Central Mediated Regulation of Obesity and its complications.

College: Mother Theresa Post Graduate and Research Institute of Health Sciences, Puducherry

Guide's Name: Mr. J. Gopi Sudheer Kumar

## PHARMACOGNOSY

Name: Ms. Sumithra. S

Project Title: Formulation, Charaterization and Evaluation of Colon Targeted Tablets of Piperine for the Treatment of Colon Cancer.

College: College of Pharmacy, Madras Medical College, Chennai

Guide's Name: Dr. R. Vadivu

## PHARMACY PRACTICE

Name: Ms. Aparna. N

Project Title: Study on Anticoagulant Utilization Evaluation and Risk Score Assessment among Acute Coronary Syndrome.

College: College of Pharmacy, SRIPMS, Coimbatore

Guide's Name: Dr. V. Shivashankar

## PHARM D- PHARMACY PRACTICE

Name: Ms. Saumya Sam, Ms. Sreeshna. J

Project Title: Drug Drug Interactions of Cytochrome P450 3A4 substrates and their Management in the General Medicine Department

College: College of Pharmacy, SRIPMS, Coimbatore

Guide's Name: Dr. A. S. Manjula Devi

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# NOTIFICATION

## MINISTRY OF HEALTH AND FAMILY WELFARE

**(Department of Health and Family Welfare)**

**NOTIFICATION**

New Delhi, the 18th April, 2019

**G.S.R. 318 (E).**— The following draft of certain rules further to amend the Medical Device Rules, 2017, was published as required by sub-section (1) of section 12 and sub-section (1) of section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940) vide notification of the Government of India in the Ministry of Health and Family Welfare (Department of Health and Family Welfare) number G.S.R. 1187 (E), dated the 7th December, 2018, in the Gazette of India, Extraordinary, Part II, section 3, sub-section (I), inviting objections and suggestions from persons likely to be affected thereby, before the expiry of a period of thirty days from the date on which the copies of the Official Gazette containing the said notification were made available to the public;

And whereas copies of the Official Gazette were made available to the public on 8th December, 2018;

And whereas objections and suggestions received from the public on the said rules have been considered by the Central Government;

Now, therefore, in exercise of the powers conferred by section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules further to amend the Medical Devices Rules, 2017, namely:

1. (1) These rules may be called the Medical Devices (Third Amendment) Rules, 2019.

(2) They shall come into force on the date of their publication in the Official Gazette.

2. In the Medical Devices Rules, 2017(hereinafter referred to as the said rules), in rule 91, after the words “may apply to the Central Licensing Authority”, the words “for Class C and Class D medical devices and State Licensing Authority for Class A and Class B medical devices” shall be inserted.

3. In the said rules, in the Second Schedule, in the Table relating to “Fee payable for licence, permission and registration certificate”, against serial number 51, in column (3) for the word “distinct”, the words “category of” shall be substituted.

[F.No. X.11014/29/2018-DR]
Dr. MANDEEP K BHANDARI, Jt. Secy.

**Note:** The Medical Devices Rules, 2017 was published in the Official Gazette vide notification number 78 (E), dated 31st January, 2017 and last amended vide notification number G.S.R 224(E), dated the 18th March, 2019.

## NEWS

### Spiralling Input Costs Hit Production of Crucial Drugs

As several essential drugs get wiped off the shelves in government hospitals across the country, authorities say they are increasingly finding it difficult to find manufacturers to bid for tenders at existing cost. The cost of active pharmaceutical ingredients that are used as raw materials have gone up to nearly double for some drugs. Indian Drug Manufacturing Association says some companies may not survive the present crisis if the Centre does not allow them to increase the selling price.

If that happens, it is likely to cause a shortage of commonly-used drugs such as paracetamol, antibiotics like erythromycin, ofloxacin and azithromycin, and vitamins. At least 80% of the desi manufacturers depend on China for low cost active pharmaceutical ingredient (API). Over the last six months, the Chinese government enforced stricter environment laws and several factories shut down. Those that survived increased cost of APIs have more than doubled for several drugs. The fluctuations in rupee prices against dollar added to the increase.

For instance, the cost of one kilogram of paracetamol, which was 170 in March 2018, went up to 340 the next month and is now being sold at 395. Antibiotic azithromycin which was sold at 8250 per kilogram in June 2018 is now being sold at 9,100 and vitamin B12, which was sold 290 per gram is now being sold at 460 per gram.

"There is steep increase in prices of certain raw materials imported from China. Many companies are bearing the loss because margins have declined. Companies are absorbing the loss because they cannot pass on the price rise to consumers. The prices are fixed by government. Some may be compelled to cut or stop the production when increase is beyond limits. If the government does not allow manufactures to increase prices, some of them may find it difficult to survive," Indian Drug Manufacturers' Association (IDMA) past-president S V Veerramani, who is also the Managing Director, Fourrts India Laboratories.

At present, the National Pharmaceutical Pricing Authority, which regulates retail prices, fixed them for a year based on market prices. "It is done only once a year. Instead they should allow pro-rata increase if the cost of the active drug formulation goes beyond 20%," he said.

Some manufacturers say the increase the immediate impact of the rise in cost will been seen among those who supply generic drugs exclusively to government at very low profit margins. "Government may have no choice but to increase the cost when they call for retender. It will settle down and cost," said state IDMA president J Jayaseelan, also Managing Director of Saimirra Innopharm Pvt Ltd.

**Source:** *The Times of India,* 14th May 2019

## Almost 90% Slash in Prices of Nine Anti-cancer Drugs

In a major step to make cancer cure affordable for patients and their families, the retail prices of several anti-cancer drugs, including commonly used chemotherapy injections for lung cancer treatment, have been slashed by up to 87% by the drug price control authority.

After reviewing the data collected from drug manufacturers, the National Pharmaceutical Pricing Authority's May 15 memorandum has brought nine anti-cancer drugs in its price control framework. NPPA is an independent body of experts under the Union ministry of chemicals and fertilisers that monitors and controls drug prices in India.

As per the revised order, the maximum retail price of chemotherapy injection pemetrexed (500mg), sold under the brand name Pemxcel and used to treat lung cancer, has come down from Rs 22,000 to Rs 2,800. A 100mg dose of the same injection will henceforth cost Rs 800 against Rs 7,700 now

The retail price of another common chemo drug, epirubicin (brand name Epichlor), will be Rs 276.8 for a 10mg injection against Rs 561 and Rs 960 for a 50mg injection against Rs 2,662.

The price of erlotinib tablets, sold as Erlotaz, will cost Rs 1,840 for a pack of 10 of 100mg strength, against the old price of Rs 6,600, and Rs 2,400 for a 10-tablet pack of 150mg strength against the old price of Rs 8,800.

Similarly, the price of everolimus (brand name Lanolimus) of strengths 0.25mg and 0.5mg have been brought down to Rs 406 and Rs 739 from Rs 726 and Rs 1,452, respective

The price of leuprolide acetate hormonal therapy injection (brand name Leuprogon Depot), commonly administered to cancer patients, has come down to Rs 2,650 from Rs 3,990. “Most of these are commonly used in several cancer therapies. The cost cut will be extremely beneficial to patients, particularly those who spend out of their pocket,” said Apollo Specialty Hospital senior oncologist Dr T Raja.

This is the second time that the NPPA has announced a price cut on anti-cancer drugs since March. In February, it invoked extraordinary powers in public interest under the Drugs (Prices Control) Order, 2013 to bring 42 non-scheduled anti-cancer drugs under price control, capping trade margin at 30% through trade margin rationalisation. At least 72 formulations and more than 390 brands reduced costs following the order.

Though major drug manufacturers did not comment on the ramifications of the price cut, health industry spokespersons said the companies have been asked not to cut down on production volumes.

Patient groups and organisations are happy with the government order. “My doctor has told me that the reduction in medicine cost will bring down my chemo bills drastically. I will have to see my bills to know how much it will be,” said 56-year-old Arunachalam V, a banker. He has medical insurance but had exhausted the limit a few months ago after a surgery. “Any price cut is good for patients like me,” he said.

**Source:** *The Times of India,* 19th May 2019

## World's Rivers are Contaminated with Antibiotics

Rivers around the world are contaminated with dangerous levels of antibiotics, according to a major new study. Concentrations of antibiotics in some waterways exceed safe levels by 300 times, a global team of scientists led by the University of York found.

The Thames was contaminated with five antibiotics, including levels of ciprofloxacin — used to treat skin and urinary tract infections — that were three times what is considered safe.

Researchers looked at 14 commonly used antibiotics in rivers flowing through 72 countries and found antibiotics were in two-thirds of samples.

Scientists fear antibiotics in rivers cause bacteria to develop resistance meaning they can no longer be used in medicines for humans. The UN estimates that the rise in antibiotic resistance could kill 10 million people by 2050.

"A lot of the resistance genes we see in human pathogens originated from environmental bacteria," Professor William Gaze, a microbial ecologist at the University of Exeter who was not involved in the study, told The Guardian.

Drugs get into rivers via human and animal waste, as well as leaks from wastewater treatment and drug manufacturing sources.

In one site in Bangladesh, levels of metronidazole — which is used to treat mouth and skin infections — were 300 times greater than what is considered safe. The most common antibiotic was a urinary tract infection antibiotic called trimethoprim, which was present in 307 of 711 sites tested.

Researchers found Bangladesh, Kenya, Ghana, Pakistan and Nigeria were home to the most contaminated rivers. The team said that the safe limits were most frequently exceeded in Asia and Africa. However, sites in Europe, North America and South America also had high levels of contamination showing that antibiotic contamination was a "global problem".

Professor Alistair Boxall, from the York Environmental Sustainability Institute, said: "Solving the problem is going to be a mammoth challenge and will need investment in infrastructure for waste and wastewater treatment, tighter regulation and the cleaning up of already contaminated sites."

**Source:** *The Times of India,* 28th May 2019

## Patients Turn Litigants as New Rules Stall Therapy

**Licence required for stem cell treatment**

Several critically ill patients have been forced to line up at the Delhi High Court after they suddenly stopped getting their medication following the implementation of the Centre's 'New Drugs and Clinical Trials Rule 2019'.

The March 19 notification, issued by the Ministry of Health and Family Welfare, marked "stem cell derived products" under the definition of "new drug". It also mandated that such formulations are approved by the Central Drugs Standard Control Organisation. The new rules require clinics engaged in such 'new drug' therapy to acquire a marketing licence. But there is no provision for an interim arrangement for the period between an application being made to the Drug Controller and a decision being taken on the application.

While this process is likely to take few months, four patients with different ailments, have moved the High Court as their treatments has been discontinued.

One of the appellants, Krishna Tokas, in his plea filed through advocate Ajay Kohli, said he was suffering from a spinal injury and the notification of the new rules had resulted in stoppage of his Human Embryonic Stem Cell Therapy, which was required for his day-to-day sustenance of life and basic activities.

Mr Tokas said the clinic administering the treatment was now unable to function until it obtained a licence.

Another petition was filed by Ms Rita Devi suffering from Dilated Cardiomyopathy, who had also stopped receiving Human Embryonic Stem Cell Therapy.

**Interim order**

Taking note of the issue at hand, a Bench of Justice G.S. Sistani and Justice Jyoti Singh said the treatment being provided to the four patients should not be hindered. As an interim measure, and till such time as the clinics' application for a licence is processed, the Bench allowed patients to continue receiving therapy from their clinics.

It also said the clinics in question should submit all information on the treatment being afforded to the patients to the Central Drugs Standard Control Organisation (CDSO).

**Source:** *The Hindu,* 4th June 2019

## Drug-resistant Tuberculosis Reversed in Lab

Scientists have found a compound that prevents and even reverses resistance to a widely used antibiotic for treating tuberculosis -- the most lethal infectious disease worldwide. A growing rise in drug-resistant tuberculosis (TB) is a major obstacle to successfully treating the illness. About 1.5 million people died of TB in 2017, making it the most deadly infectious disease in the world.

Researchers at Washington University in the US and Umea University in Sweden reversed resistance to isoniazid, the most widely used antibiotic for treating TB.

The research, published in the journal Proceedings of the National Academy of Sciences, was conducted in bacteria growing in the lab, setting the stage for future studies in animals and people.

Using the compound in conjunction with isoniazid potentially could restore the antibiotic's effectiveness in people with drug-resistant tuberculosis.

The compound also may bolster the antibiotic's power to kill TB bacteria -- even those sensitive to drugs -- which means doctors could start thinking about cutting down the onerous six-month treatment regimen they prescribe today.

"It is very hard for people to comply with such a long regimen. It's four drugs. They have side effects," said Christina Stallings, an associate professor at the Washington University.

"The longer people have to be on antibiotics, the more issues with patient compliance you get, and that can lead to drug resistance and treatment failure," said Stallings.

"Here, we've found a compound that sensitizes bacteria to an antibiotic, prevents drug resistance from arising, and even reverses drug resistance -- at least in the lab," she said.

"If we can turn this compound into a drug for people, it could make our current therapies more effective and be really beneficial for fighting this pandemic," she said.

Tuberculosis is caused by the bacterium Mycobacterium tuberculosis. Once inside the body, the bacteria morph into a tougher form that can withstand more stress and is harder to kill.

Rather than look for new and better antibiotics, the researchers decided to look for compounds that prevent the bacteria from toughening up.

When put in a low-oxygen environment to mimic the stressful conditions TB bacteria encounter inside the body, the bacteria come together and form a thin film called a biofilm that

is resilient to not only low-oxygen conditions but also to antibiotics and other stressors.

The team screened 91 compounds that share a core chemical structure that inhibits biofilms in other bacterial species.

The researchers found one compound, called C10, that did not kill the TB bacteria but prevented them from forming a biofilm.

Further experiments showed that blocking biofilm formation with C10 made the bacteria easier to kill with antibiotics and even curbed the development of antibiotic resistance.

The researchers needed only a fraction of the amount of isoniazid to kill the TB bacteria when C10 was included than with isoniazid alone.

In addition, one out of one million TB bacteria spontaneously become resistant to isoniazid when grown under typical laboratory conditions.

However, when the researchers grew TB bacteria with isoniazid and the compound, the drug-resistant mutant bacteria never arose.

"By combining C10, or something like it, with isoniazid we could enhance the potency of the antibiotic and block the TB bacteria from developing drug resistance," Stallings said.

"That means we might be able to shorten the treatment regimen," she said. The compound is not ready to be used in people or even tested in animals, Stallings cautioned.

This study was conducted on bacteria growing in a lab. The researchers are still figuring out whether the compound is safe and how it might be processed by the body.

**Source:** *ET Healthworld,* 5th June 2019

## Nearly 10k Fake Antibiotic Vials Worth Rs 7 Lakh Recovered in Agra, 4 held

In a joint operation by drug safety department and Agra police of Nibohra, nearly 10,000 fake antibiotic vials of Amikacin injection worth Rs 7 lakh were recovered in Agra.

The consignment was recovered from Nibohra after an anonymous tip-off was shared with the drug safety department about a hatchback ferrying the fake antibiotic to Pinhat, Fatehabad and Rajasthan's rural areas. “As soon we received the tip-off on fake drugs being taken to rural areas from Kamla Nagar, we immediately alerted local police to cordon off Nibohra and conduct checking of

vehicles. Later, in the afternoon, four persons were nabbed with 9,924 vials of Amikacin injection from a hatchback," said drug inspector Brijesh Yadav.

The accused were identified as Ramhari Pramod Kumar, who is a history-sheeter in robbery and other criminal cases. He hails from Sahadpur village of Nibohra. Along with him, the teams nabbed his paramour Sital Sharma, who is in a live-in relationship with Ramhari since she left her husband. Two other men, identified as Santosh also from Nibohra and Abhimanyu Chauhan, who hails from Kamla Nagar, were also arrested.

"During interrogation, the accused claimed that they have been involved in the business for over half a decade. They would prepare fake antibiotics in Avita Vihar of Kamla Nagar area at Ambar Pratap Singh's property and would sell the drug in rural areas of Agra and the neighbouring state of Rajasthan," said officer Yadav.

He added, "We are now going to search and investigate Ambar Pratap Singh. Meanwhile, an FIR was lodged against four nabbed persons under IPC sections 274 (adulteration of drugs), 275 (sale of adulterated drugs), 276 (sale of drug as a different drug or preparation), 419 (punishment for cheating by personation), 420 (cheating and dishonestly inducing delivery of property), 467 (forgery of valuable security, will, etc) and 471 (using as genuine a forged document)."

In the market, 2ml of Amikacin Injection vial is worth Rs 95. After confiscating the fake drug consignment, four samples were sent to Lucknow-based government laboratory to test the drug. The fake drug was prepared under two different pharmaceutical brands, including one based in Delhi.

**Source:** *ET Healthworld,* 6th June 2019

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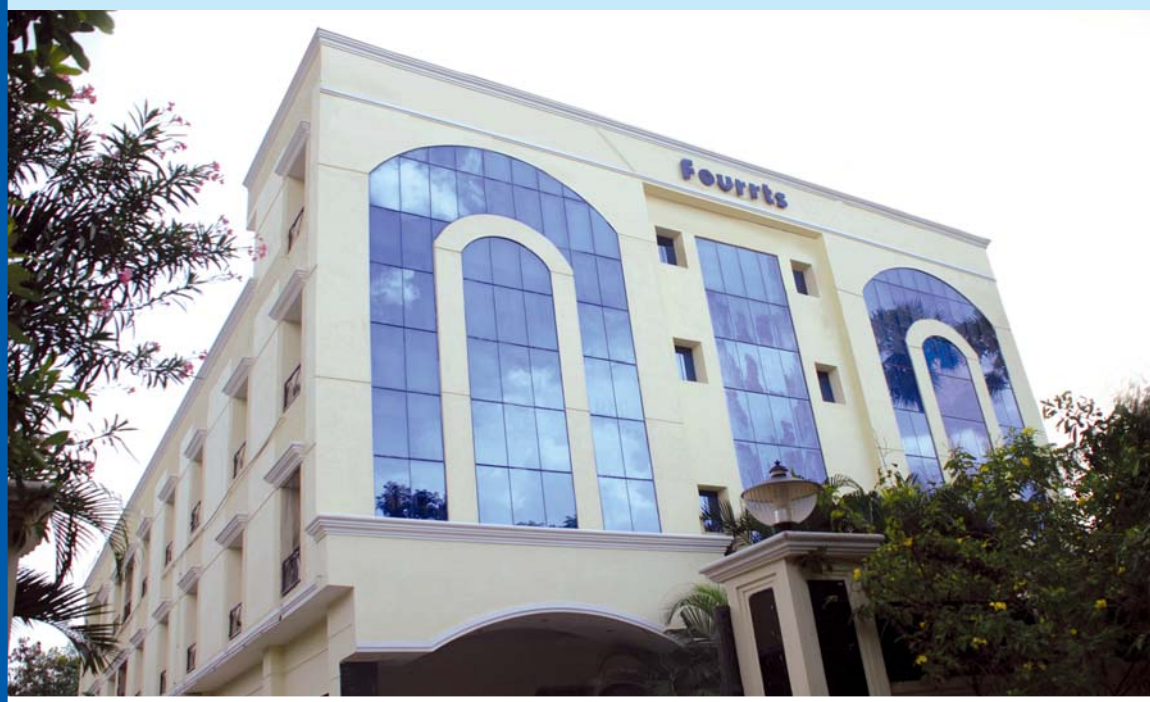


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