Pre-Clinical Studies – Role of Regulators, FBOs and CROs

"Clinical Evaluation/Intervention Studies for New Foods & Food Ingredients"

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CAN NUTRACEUTICALS REPLACE MODERN DRUGS ?

Health foods

Food Medicine

Function Foods

Dietary supplements

Designer food

Herbal products

Processed foods

↑ Chronic diseases
Expensive high tech.
Disease treatment approach

?

Alternatives

1. Increase the health value of our diet.
2. Facilitate for live longer.
3. Postpone particular medical conditions.
4. Psychological benefit.
5. Natural than traditional medicine with minimum unpleasant side- effects.
6. Food for populations with special needs (e.g. nutrient-dense foods for the elderly).

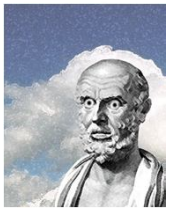
- Beneficial products
- Health promoting, disease preventing

DESTINATION

Nutraceuticals	Pharmaceuticals
Low potency	High potency
Weak interaction with targets	Strong interaction with targets
Pleiotropic intervention with physiology mechanisms	More specific intervention with physiology mechanisms
Inhibition of disease	Treatment of disease
Long term application/effects	Short term application/effects
Empirical, low causal evidence	Empirical, often causal evidence

LET FOOD BE THY MEDICINE AND MEDICINE BE THY FOOD?

Hippocrates, c. 500 BC

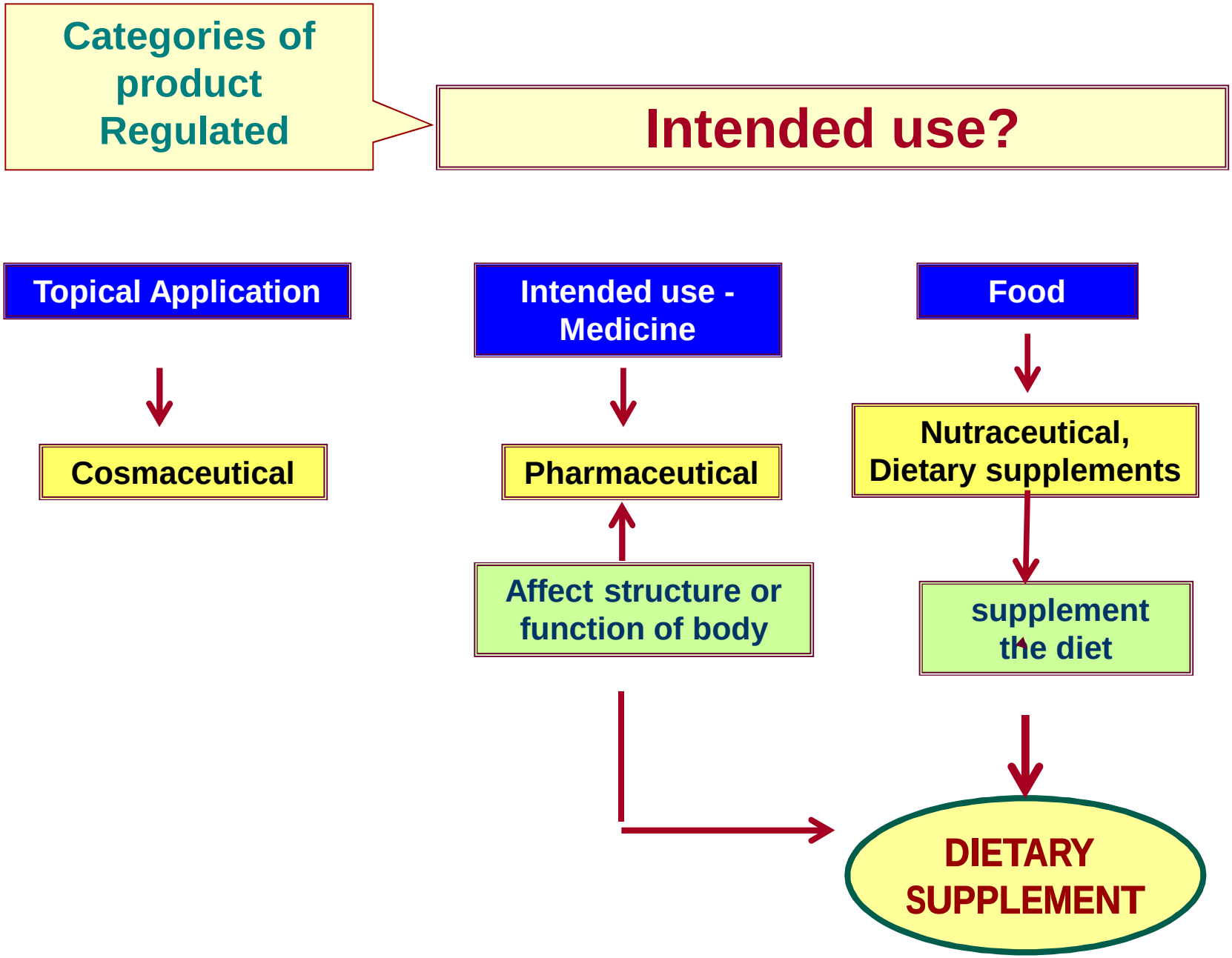


Mahabhaishajya (Super

भेषजेनोपपन्नोऽपि निराहारो न शक्यते ।तस्माद्भिषग्भिराहारो महाभैषज्यमुच्यते ।।

Ref.*Kasyapa samhita.Khi*

100 BCE and 200 CE


Categories of product Regulated
Intended use?
Topical Application
Cosmaceutical
Intended use - Medicine
Pharmaceutical
Affect structure or function of body
Food
Nutraceutical, Dietary supplements
supplement the diet
DIETARY SUPPLEMENT

FSSAI- Categories of Products for Regulatory Approvals

I. Food or Health Supplements

II. Nutraceuticals

III. Foods for Special Dietary Uses (FSDU) Other than infants and those intended to be taken under medical advice

IV. Foods for special Medical Purposes (FSMP)

V. Foods with added Probiotic ingredients

VI. Foods with added Prebiotic ingredients

VII. Specialty Foods containing plant/botanical ingredients with known history of Safe use in India

VIII. Novel foods

‘?’ MARKETING / CLAIMER / COMPLAINCE

Burning **‘?’**

- **Ayu-ceuticals**
- **Herba-ceuticals**
- **Nutra-ceuticals**
- **Pharmaceuticals**

- **Who Certify**
- **How Validate**
- **? Safety Concern**
- **Market Vigilance**

The Doughnut Corporation sought endorsement from the Nutrition Division of the War Food Administration for its Vitamin Doughnuts campaign .National Archives,

भारत का राजपत्र
The Gazette of India
असाधारण
EXTRAORDINARY
भाग III—खण्ड 4
PART III—Section 4

REGD. NO. D. L.-33004/99, F. No. 12/PA Regulation/Dir (PA)/FSSAI-2016 /2017
FSSAI (**Nutra) Regulations, 2022**]- Letter 29th march 2022; Effective from 1st April 2022

FORM – I (*See* sub-regulation (1) of regulation 4)
(Application for approval of non-specified food and food ingredient)

2/18 **Regulatory Status** : (Mention the countries where the product is permitted for direct or indirect human consumption as food. If so, provide the level and purpose of consumption by the consumers with the relevant regulations along with the documentary evidence.)

2/20 Safety Information (Documents on risk assessment or toxicity studies)

(a) The information shall be based on safety or risk assessment review from published studies and safety studies conducted on the ingredient and food product by the applicant

(b) Provide evidence to demonstrate that the proposed product or the ingredient will not adversely affect any specific population groups that is pregnant women, lactating mothers, children, elderly or any other vulnerable group

FORM – I (*See* sub-regulation (1) of regulation 4)….

3. Additional specific information: …

(a) Novel food or novel food Ingredients or food processed with the use of novel technology:-

3 a 1. The target group for the said proposed food, if any

3.a.4. Safety Information (Documents on risk assessment or toxicity studies to be attached)

(a) Information on human studies including dietary exposure, nutritional impact and potential impact on the consumer if any

(b) Toxicological studies including results of Ame's tests to test mutagenecity, chromosomal aberration tests, studies for reproductive toxicity, prenatal developmental toxicity studies

(c) Allergenicity (published or unpublished reports of allergenicity or other adverse effects in humans associated with the food consumption; may include reports prepared by World Health Organisation or by other national or international agencies responsible for food safety or public health)

3.a.5. History of consumption of food product/food ingredient, (attach supporting documents)

(a) Geographical area of use (with established history of safe use in at least two countries, with well-established regulatory status)

(b) Quantity of consumption

(c) Duration of consumption (in years)

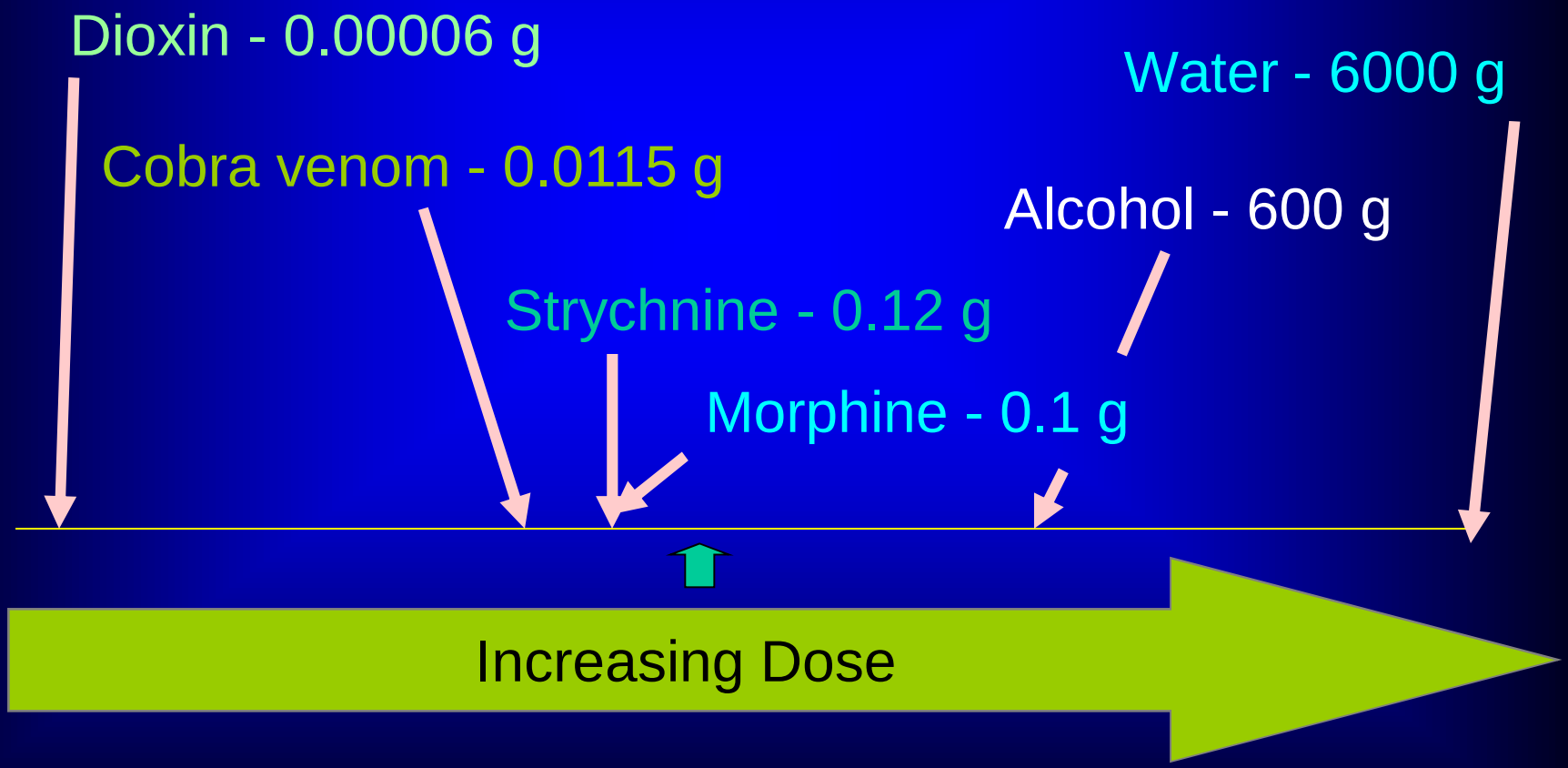
65. If no safety and efficacy data available in the Indian population, then what to do?

Unlike drugs, food is consumed by the common man with no supervision in most instances. Thus, it is important to provide safety data of use of the product in human population. To approve the product as 'food' in India, the history of safe use for 15 years in India and 30 years in the country of origin is a requirement as per the Nutraceutical regulations and in addition the safety data from Indian population if available is preferred. However, if the safety data from Indian population is not available, the applicant can submit relevant safety studies available on south east Asian population for consideration. In case of novel foods and new ingredients where the safety data from Indian population will not be available, the FBO shall have to conduct the clinical trial in consonance with the guidelines stipulated in the ICMR including ethical clearance, and where the product is to be imported the FBO shall import the ingredient/product for the purpose of R & D as stated in the FSS (Import) Regulations,2017 to conduct the clinical trials to generate the safety data for approval of the product / ingredient

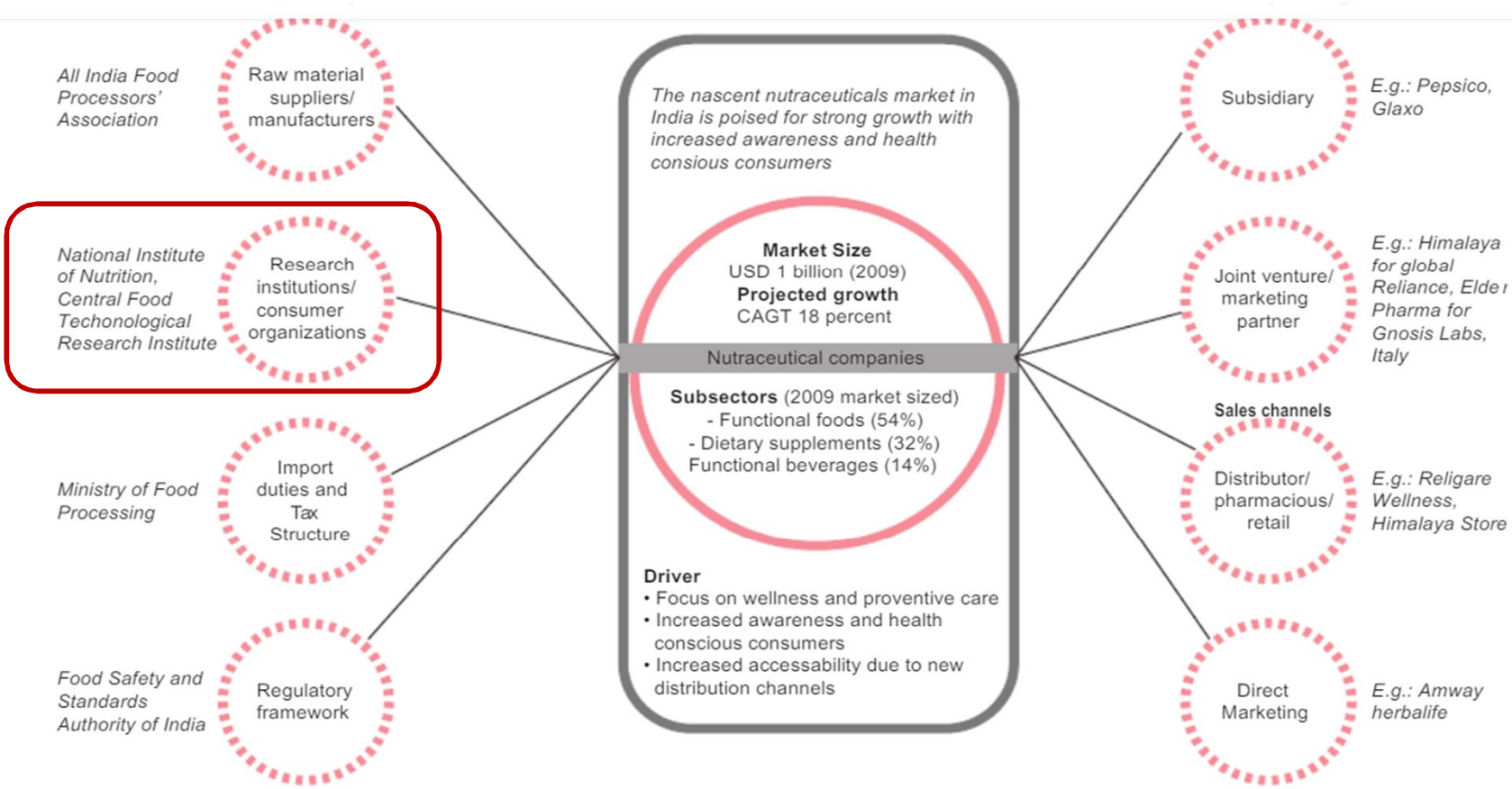
Toxicology 101

"All things are toxic, it is only a matter of dose"

Paracelsus, c. 1530

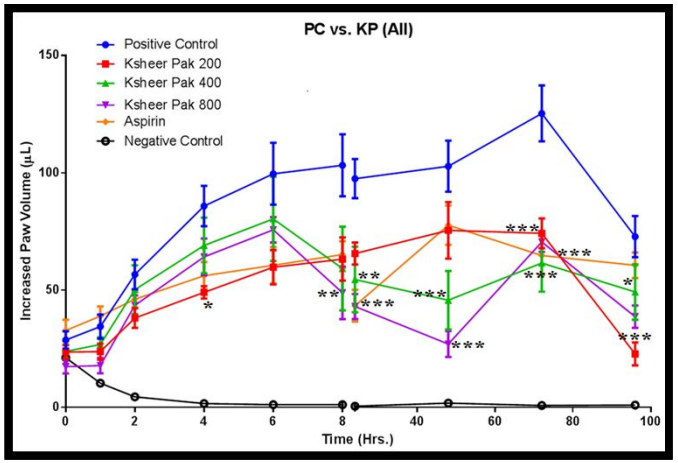


INDIAN NUTRACEUTICAL MARKET SCENARIO



Case Studies –ICMR-NIN

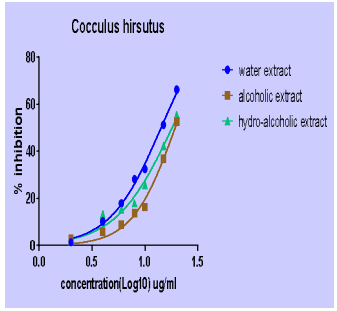
Arjuna Ksheer pak

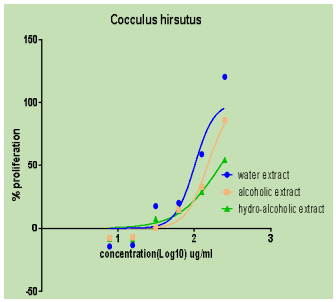


- Poor Antioxidant in-vitro
- Strong anti inflammatory

Nivedita Dube, & Dinesh Kumar Journal of Traditional and Complementary Medicine xxx (2016) 1-7

Cocculus hirsutus





Water extract

- Potential anti-inflammatory
- immune modulator

Anita Singh, Vandana Singh, Dinesh Kumar J Ayurveda Integr Med . 2022 .13(1):100537.

ED-50, ??? safety dose

Case Studies… ICMR-NIN

Poly Herbal Formulation for Pre-biotic potential & Immunomodulator

Zingiber officinale

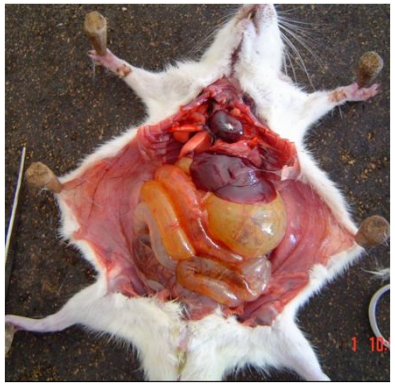
Piper nigrum

Ocimum sanctum

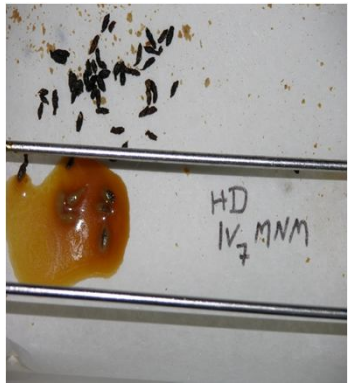
Immunomodulator

Source:
Narendra , Hemlatha, Dinesh

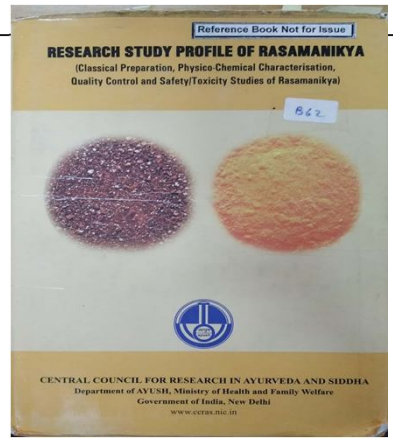
- ✓ *American Journal of Biochemistry and Molecular Biology 1-11-2012*
- ✓ *Trends in Medical Research, 6 (1): 23-31-2011*



CODED

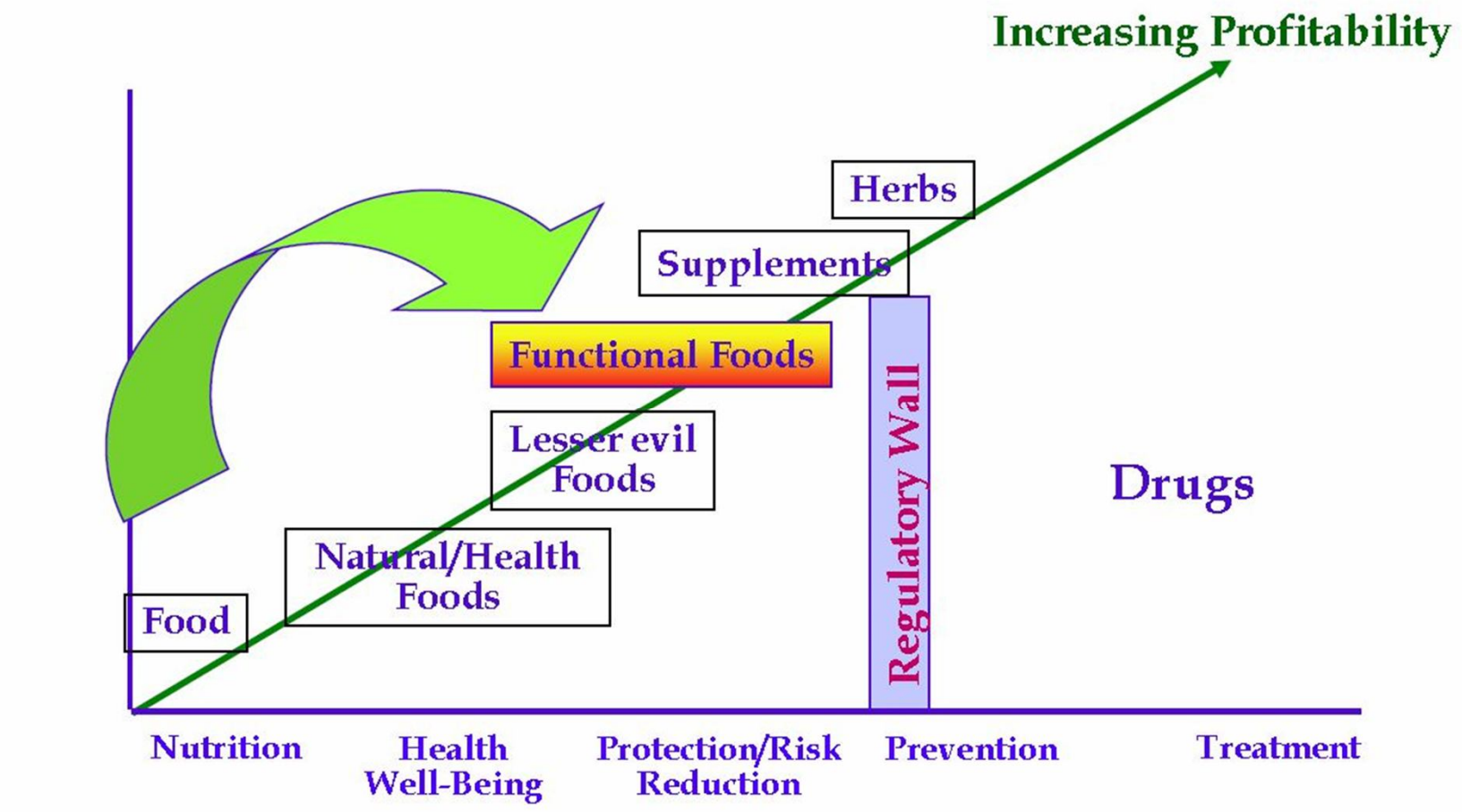


HERBO MINERAL



MONOGRAGH

Food and drug –Regulatory walls



Investigations for Safety Profile

Test Details	Brief
1. Compositional analysis	
Compositional analysis of key component	Compositional analysis of key components in transgenic Test material which are present in edible part.
2. Allergencity studies	
Bioinformatics Analysis of proteins	Bioinformatic analysis of recombinant proteins expressed in transgenic Test material to assess potential allergenic-cross-reactivity to known allergens.
Pepsin Digestibility Assay	Assessment of Allergenicity of Recombinant Proteins Expressed in Transgenic Test material by *in vitro* Pepsin Digestibility Assay in Stimulated Gastric Fluid.
Thermal Stability	Assessment of Allergenicity of Recombinant Proteins Expressed in Transgenic Test material by Thermal Stability Assay *in vitro*

Transgenic – in case of recombinant protein

Investigations for Safety Profile Contd…

Study Details	Duration	Parameters
Acute Toxicity Study single / multiple exposures within 24 hours (MTD)	**14 -D** Post Exposure Pure Protein	✓ Cage side Observation (Daily) ✓ Recording of body weights (Twice a week) ✓ Physical Examination (Twice a week) ✓ Neurological Examination (Twice a week) ✓ Lethality (Daily)
Sub-Chronic study of test material for comparison of transgenic to their non–transgenic counterparts.	**90- D**	✓ Cage side observation (Daily), ✓ Physical Examination (Twice a week) Recording of body weights (Twice a week) ✓ Recording of Feed intake (Daily) ✓ Neurological Examination (Twice a week) ✓ Urine analysis qualitative (Before & after exposure to the test material) ✓ Biochemistry, Hematology, Necropsy and Histopathology of vital organs (End of the euthanization)

Species preferred

RAT'S AGE VERSUS HUMAN'S AGE: WHAT IS THE RELATIONSHIP?

Rat's age in months	Human's age in years
6 months	**18 years**
12 months	**30 years**
18 months	**45 years**
24 months	**60 years**
30 months	**75 years**
36 months	**90 years**
42 months	**105 years**
45 months	**113 years**
48 months	**120 years**

Total lifespan:	13.8 rat days	= 1 human year
Nursing Period:	42.4 rat days	
Prepubescent Period:	4.3 rat days	
Adolescent Period:	10.5 rat days	
Adult Phase:	11.8 rat days	
Aged Phase:	17.1 rat days	
Average:	16.7 rat days	

Source: ABCD Arq Bras Cir Dig Review Article 2012;25(1):

? Preclinical predictors of Clinical Safety

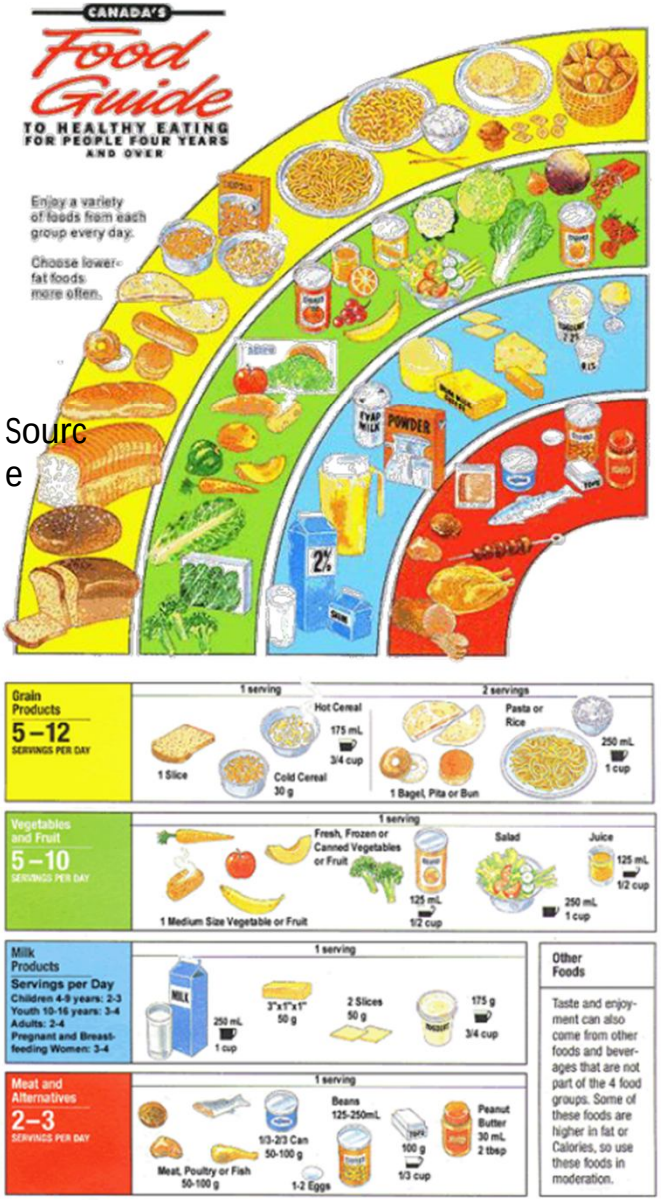
OR

Opportunities For Improvement

150-COMPOUNDS DATA PREDICTS

RODENT TOXICOLOGY	– 43%- HUMAN TOXICITIES
NON-RODENT TOXICOLOGY	– 63%- HUMAN TOXICITIES
TOGETHER	– 71%- HUMAN TOXICITIES

Source: CPT, 2007, 82, 211-214



Source

Nutrition and health

5-10 servings of fruits and vegetables

How do we eat them?

Does it affect the availability of the target nutrient?

If we fortify our food, any food or all foods, do we have the toxicological studies to ensure long term safety?

FREQUENTLY ASKED ????? & CRO /FBO

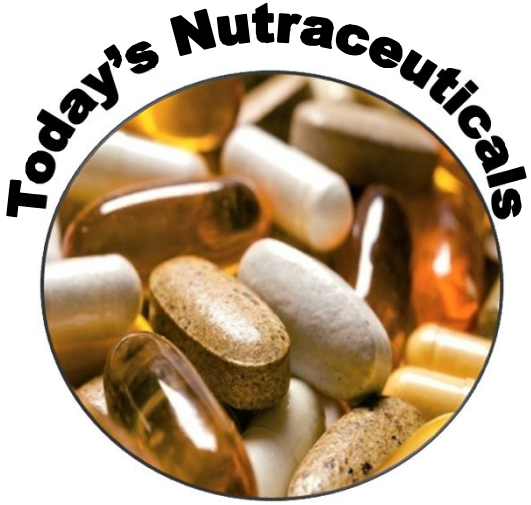
65. If no safety and efficacy data available in the Indian population, then what to do?

Unlike drugs, food is consumed by the common man with no supervision in most instances. Thus, it is important to provide safety data of use of the product in human population. To approve the product as 'food' in India, the history of safe use for 15 years in India and 30 years in the country of origin is a requirement as per the Nutraceutical regulations and in addition the safety data from Indian population if available is preferred. However, if the safety data from Indian population is not available, the applicant can submit relevant safety studies available on south east Asian population for consideration. In case of novel foods and new ingredients where the safety data from Indian population will not be available, the FBO shall have to conduct the clinical trial in consonance with the guidelines stipulated in the ICMR including ethical clearance, and where the product is to be imported the FBO shall import the ingredient/product for the purpose of R & D as stated in the FSS (Import) Regulations,2017 to conduct the clinical trials to generate the safety data for approval of the product / ingredient

FREQUENTLY ASKED ????? & CRO /FBO Cont….

66. Does the FBO need to provide a declaration that the Product or ingredient will not have an adverse effect on the vulnerable population?

The FBO shall provide a declaration on the Product or ingredient that it will not have an adverse effect on the vulnerable population (infants, pregnant & lactating mothers and elderly population) especially if the product is intended to be used by the population of all age group and specified physiological conditions.



TODAY & ????

ALSO….

9 Reasons why An Apple a Day Really Keeps the Doctor away ?

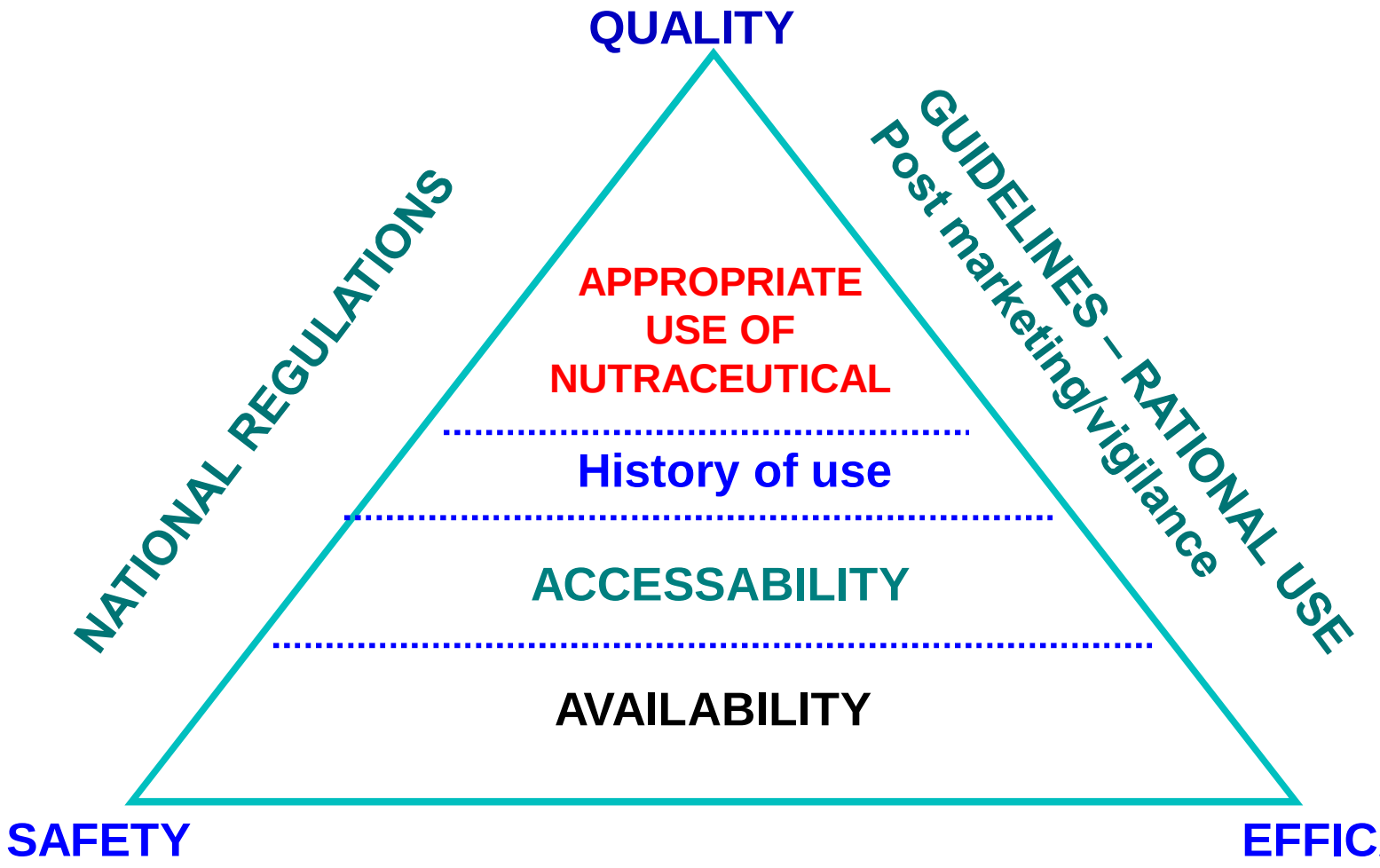
MYTH BUSTED

Five Apples a day
brings Dentist closer ?

Eating regularly 4 times damages 2mm surface enamel of teeth

Regulatory science under appreciated but has to be implemented..

THREE PILLARS OF IDEAL NUTRACEUTICALS AND THEIR RATIONAL USE



To achieve a through understanding, collaborative studies are required, combining expertise in food chemistry, Pharmacologist, Biochemistry, Plant Physiology, Nutrition, Medicine, Engineering, CRO/FBO etc.,

Way Forward…..

THE HINDU BENGALURU
SUNDAY, OCTOBER 1, 2017

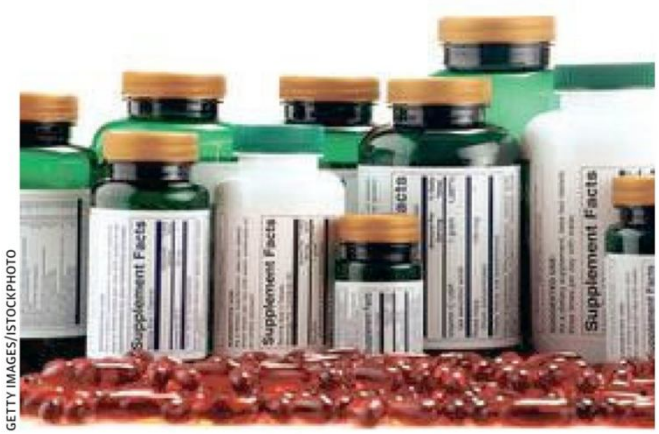
Good food or bad drugs?

Guidelines to regulate the 'nutraceutical' industry have led to mixed reactions

ROHIT P.S.

A doctor at a public hospital in Hyderabad became concerned when a middle-aged man being treated for jaundice reported puffiness of the face during treatment.

The doctor noticed that the patient had been taking a branded herbal preparation for months, given to him under the guise of it being a food supplement for general well-being. Suspicious, the hospital's clinician sent a sample of the supplement for testing at the National Institute for Nutrition (NIN), Hyderabad. Scientists at the premier facility's drug toxicology labs were not surprised to find lead in the formulation. The patient was then treated for heavy metal poisoning.



GETTY IMAGES/ISTOCKPHOTO

Varied claims

Reports of patients experiencing adverse events during the course of medical treatment, accompanied by samples for testing, often land at the NIN's doorstep. Obesity pills, diet regimens and shakes sold with exaggerated benefits, as well as preparations – often adulterated with corticosteroids –that promise anything ranging from enabling pain relief to easing chronic conditions such as arthritis – are frequent suspects. Supplements sold to improve sexual potency are another group of products frequently assessed by scientists when an adverse reaction is reported.

New directions

Until recently, a system to verify and notify adverse reactions from products other than those recognised as 'drugs', under the Drugs and Cosmetics Act, did not exist. With the framing last year, of guidelines by the Food Safety and Standards Authority of India (FSSAI) to regulate products recognised as 'nutraceuticals' – or supplements and foods that aren't drugs but purported to contain ingredients essential to well-being, the need to report adverse reactions was felt and the Hyderabad-based NIN was selected to run the centre.

"It was set up earlier this month. We plan to start functioning by carrying out [a] sensitisation campaign for doctors practising all systems of medicine, to report adverse events in a prescribed format," says B. Dinesh Kumar, who heads the Drug Toxicology Division at NIN and is a coordinator for the recently-inaugurated facility. Called the 'National Coordination Centre - Pharmacovigilance Programme of India, the body's mandate also involves monitoring advertised and marketed claims of products classified as 'foods', adds Dr. Kumar.

Reporting mechanism

On receiving reports of adverse reactions, the NIN centre will discuss with reporting clinicians the specific case to make an assessment. The adverse event is then tagged to the Indian Pharmacopoeia Commission (IPC) for notification to the product manufacturer.

The centre has been envisaged as a part of India's larger efforts to regulate 'nutraceuticals,' a category that didn't exist until recently. In a 2017 report, the Associated Chambers of Commerce and Industry of India estimated the global nutraceutical industry to be growing by about $15 billion annually. In India alone, it says the industry is worth more than $2 billion.

The new rules formulated by FSSAI are set to become effective in January next year. Though exhaustive, there is scepticism – mostly legal – in the food and drug industry over whether the new set of rules can effectively regulate nutraceuticals.

The Indian Council of Medical Research has recommended that dietary supplements such as multivitamins can remain out of the ambit of the Drugs and Cosmetics Act if they are within the recommended dietary allowance in a product. Recently, the government's reported attempts to amend the Drugs and Cosmetics Act to make a distinction between drugs and dietary supplements has seen the industry aver that vitamins should have the benefit of being defined as both a drug and food.

Reactions

Scientists at the IPC caution that the NIN's role should not be interpreted as an assault on an industry. On the contrary, they suggest that adverse reactions, as in the case of drugs, can often result unexpectedly and be specific to a small group of individuals, without necessarily being a result of nutraceutical intake.

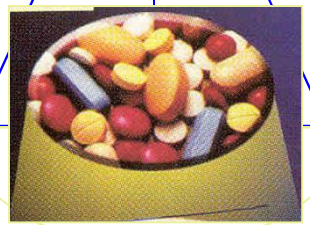
"A person's genetic make-up or the conditions under which a substance is taken can lead an individual to experience an adverse reaction while another may not. Additionally if a person takes two substances together despite being explicitly told not to, an adverse reaction can occur," a senior scientist at IPC said, asking not to be named.

rohit.ps@thehindu.co.in

THE UNBEATABLES

THANK YOU

HEALTH CANNOT BE BUILT AT PHARMACY COUNTER



ECONOMICAL, FRESH, TASTY, BETTER ABSORBED AND RETAINED. AVAILABLE IN NATURAL FORM AND RICH IN FIBER.

EXPENSIVE, SYNTHETIC, HAZARDOUS IF TAKEN IMPROPERLY / IN EXCESS PRODUCE UNWANTED SIDE EFFECTS.

Concept (1994); Dinesh Kumar &Kamla Krisnaswamy