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An Overview of the Nutraceuticals Industry: Demand, Challenges, Regulations and Clinical Evidence

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Abstract

Nutraceuticals, also popularly known as dietary supplements help in the prevention and treatment of diseases. In the past decade, India has witnessed an increase in the demand for nutraceuticals. Good quality clinical trials evaluating the efficacy and safety of nutraceuticals in different therapy areas will help in supporting claims, making policies, and implementing evidence-based healthcare. This review article highlights the regulations, current scenario, challenges, efficacy, and safety considerations of nutraceuticals. The practice of evidence-based nutraceuticals will increase confidence and awareness among healthcare professionals.

Keywords: ***Nutraceutical, Phytochemicals, Nutrition, Immunity, Clinical trials, Evidence-based Practice***

Introduction

Nutraceuticals are natural food substances or fortified food that provides necessary nutrients and supplementation which is needed for the body to prevent diseases. The word nutraceutical was first coined by Stephen DeFelice [1-3]. Nutraceuticals are being used for various diseases such as neurological disorders, cardiovascular diseases, obesity, cell damage, immunodeficiency, diabetes, osteoarthritis, osteoporosis, bone and joint health, anemia, Anti-inflammatory activities, allergy, etc. [4]. The main active ingredient includes carbohydrates, lipids, polyphenols, terpenes, steroids/ols, and alkaloids [5].

Classifications

Nutraceutical is a vast term for nutrition. It is important to classify nutraceuticals into further categories to understand the indication and uses of the products. Nutraceuticals are categorized into 2 ways; Traditional and Non-traditional.

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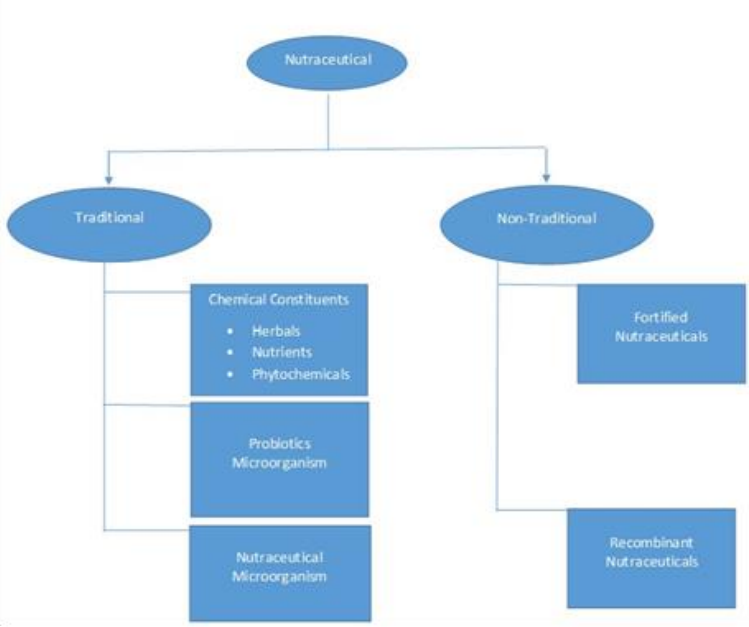

FIG. 1. **Classification of nutraceuticals.**

TABLE 1. **Food category and target groups with examples.**

Food Category	Target Group	Examples	Distribution channels
Functional foods and nutrition supplement	Healthy population to maintain well being	Probiotic yogurts Energy bars Sports drink Vitamin and mineral supplement	• Supermarkets • Online
Core nutraceuticals	People with common health problems	Cholesterol-lowering products Products to control diabetes, age-related muscle loss	• Supermarkets • Pharmacy • Online
Medical nutrition	Special nutrition need population	Specialized infant formulas nutrition for chronically ill patients	• Pharmacies with medical supervision

Need for legal distinction

The nutraceutical and botanical terms are often used by the lay press or for marketing purposes to describe health, beneficial food, food supplements, or herbs. However, there is no common definition of nutraceuticals or botanicals; moreover a lack of regulation that classifies this category. Concerning their health value, it is unclear if they belong to drugs or food. Currently, they fall into a legal limbo between both. This regulatory lack can lead to misuse of claims indicating a health benefit or the

misleading of the consumer. A universal definition and an internationally valid regulation to support the export and the import of food supplements are still missing.

Terminologies

The below table consists of terminologies related to nutrition or nutritional supplement. These terms are used differently in each country and their definitions differ from each of them. All the terms are related to nutrition, diet, and Foods.

TABLE 2. **Terminologies.**

Terminology	Definition
Food	Any item which is processed, partially processed or unprocessed is used for consumption for humans.
Nutraceutical	• As per DeFelice -'a food or part of a food, such as a dietary supplement, that has a medical or health benefit, including the prevention and treatment of disease'. • The European Nutraceutical Association
Functional food	A food substance containing biological or chemical additives to have physiological effects.
Fortified foods	Normal food that is enhanced with health promoting agents.
Dietary supplement	Any substance added to a diet which is often taken as a pharmaceutical formulation to treat and prevent disease.

TABLE 3. **Examples and therapeutic areas of the naturally occurring substances used as a nutrition.**

Naturally occurring substances	**Examples**	**Therapeutic area**
Dietary fibre Pectin, Polysaccharides cellulose, Gums, Lignin, Hemicellulose	Bananas, Rice, Carrot	Hyperlipidemia, Obesity, Diabetes, Hypertension
Probiotics Lactic acid bacteria,Lactobacillus plantarum, Lactobacillus brevis, Leuconostoc citreum, Lactobacillus acidophilus, Bifidobacterium bifidum.	Yogurt, fermented food, cheese	Gastrointestinal disorders, Immunity, Infections, Asthma
Prebiotics Fructo-oligosaccharides (FOS), Galactooligosaccharides (GOS), and Transgalacto-oligosaccharides (TOS)	Apple, Asparagus, Banana	Hyperlipidemia, GI Disorders
Polyunsaturated fats	Salmon Fish,	Cardiovascular disease, Diabetes,

Linoleic acid and alpha-linolenic acid, Linoleic, Omega 3 fatty acid, Omega 6 fatty acid.	Walnuts	Asthma
Antioxidant vitamins Vitamin C, Vitamin E, Carotenoids, Glutathione, Lipoic acid	Citrus Fruits, Bell peppers, Carrots	Degenerative Disease
Polyphenols Curcumin, condensed tannins, Theaflavin-3-gallate, Ellagic acid, Raspberry ellagitannin	Tea, Berries	Bacterial Infections, Diabetes, Neurodegenerative disease, Cardiovascular disease

Policy agenda for nutraceuticals

For the nutraceutical industry to develop effectively, there are few policies built to increase the use of nutraceuticals.

TABLE 4. **Policy agenda.**

Policy	Action to be taken
Address regulation	• Identify the new class of nutraceutical which can be alone or in combination • Combining ingredients for assessing the effect • Harmonization with international regulations
Encourage healthcare professional	Educate the healthcare professional about the advantages of prescribing nutraceuticals for disease prevention and management
Develop strong evidence	Conducting trials and studies to generate effective evidence to support the claims
Include authorities	Convince the government and public health authorities the use of nutraceuticals and that it is less expensive and safe than conventional drugs
Consumer awareness	Make the consumers aware of the use of nutraceuticals and their effectiveness and safety.

Growth of the nutraceutical industry

The demand for nutraceuticals is increasing all over the world. Every year the Compound Annual Growth Rate (CAGR) of nutraceuticals is increasing. CAGR was 4% in the year 2017 and currently, it has 8.31% and by 2022, CAGR is expected to grow to 10.01% [6].

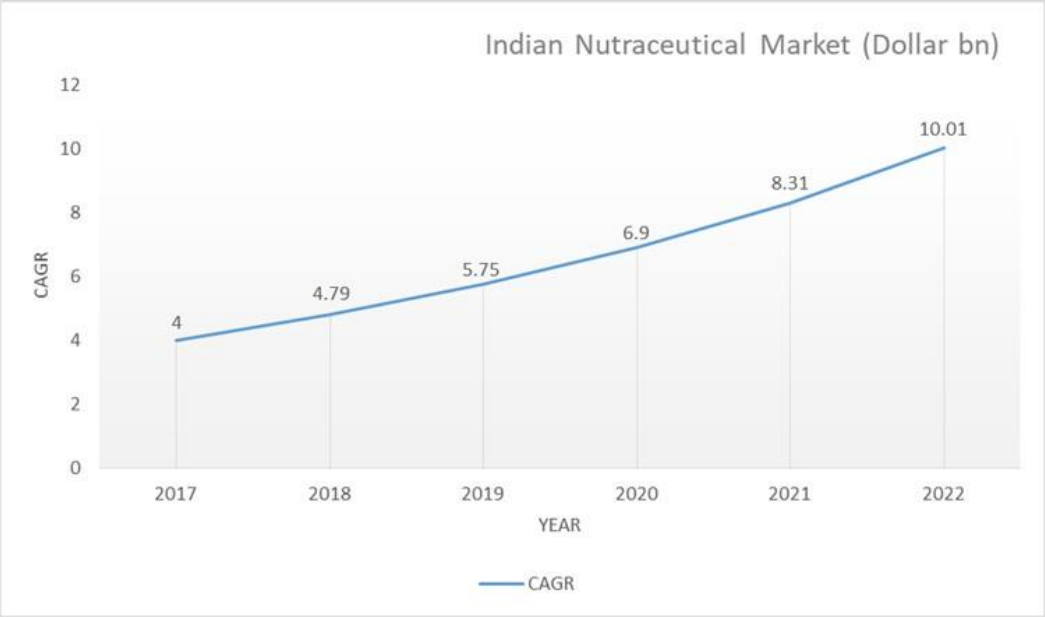

FIG. 2. **Indian nutraceutical market.**

Impacting factors

Increase in Awareness of health issues and well-being, Increase in Social Media Awareness, Increase in usage of Vitamins, Adoption of Fitness (need of multivitamins and proteins), Usage as a preventive option for improving health, Increasing incidence of chronic and degenerative diseases like diabetes, hypertension, cardiovascular disease, arthritis, osteoporosis, etc. [7].

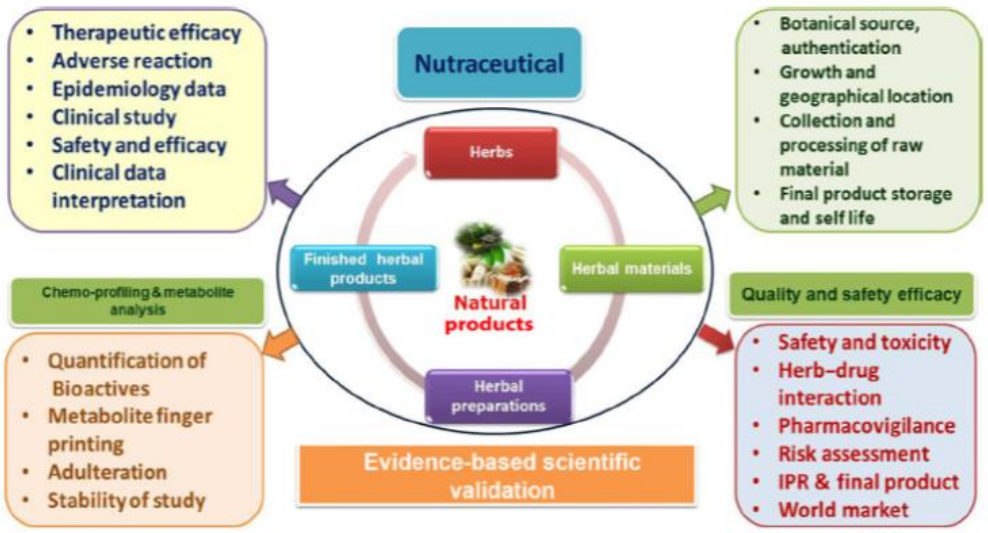

FIG. 3. **Evidence Based scientific validation.**

Regulations

Regulation is implemented to manage the complex system with the help of a certain set of rules and trends. The Food and Safety Standard Act (FSSA), 2006 has established the Food Safety Standard Authority of India (FSSAI) for regulating scientific standards and to supervise the food and nutraceutical industry. The ingredients used in the manufacturing of nutraceutical shall be categorized under schedule I, II, IV, VI, VII, or VII of the regulation. The amount allowed for each nutraceutical is decided by the Recommended Dietary Allowance provided by the ICMR.

These regulations are maintained to align with the international regulations, to produce products according to the scientific standards, clarity for novel findings [8].

TABLE 5. **Regulatory act of different country.**

Country	Regulatory Act	Regulatory Motive
Japan	Foods with Nutrient Function claim (FNFC) 2005	Restricted to specific nutrients with function claims in Food with Health claims (FHC)
China	State Council Legislative office (SCLO) 2009	Regulation of food with functional and health claims associated with their use.
India	Food Safety and Standard Authority of India (FSSAI), 2010	Nil
USA	Food Safety Modernization Act (FSMA),2011	Ensure safe US food supply by preventing contamination
European Union	Regulation (EU) No 383/2010	Authorize food that reduces disease risk and children's health
Brazil	National Sanitary Surveillance Agency, ANVISA,2002	Check natural or synthetic substances having a demonstrated and physiologic activity
Canada	Natural Health Product Directorate (NHPD), 2003	Defined Nutraceutical
Australia and New Zealand	New South Wales Government- Food Regulation, 2010	Regulation in food safety for food business

Formation of food safety and standard authority of India

Food regulation is aimed at protecting the consumer's health, increasing economic viability, harmonizing well-being, and engendering fair trade on foods within and between nations. For nutraceutical industries, two challenges are apparent; regulatory uncertainty and credibility of labeling claims. The food sector in India has been governed by multiple laws enacted at different points in time to complement and supplement each other. The multiplicity of ministries and administering

authorities at both the central and state level has resulted in a complex regulatory system that is not well integrated, which increases the burden on the food processing industry. Following pressure from the industries and stakeholders for a single regulatory body and an integrated modern food law, the Food Safety and Standards Act, 2006 (FSSA) was enacted by the Government [9].

Toxicity evaluation

Toxicity testing of nutraceuticals/herbal drugs is aimed at the toxicological measurement of herbs or herbal preparations to identify their adverse effects and to determine the limits of dose exposure at which such effects occur. Toxicity evaluation of nutraceutical is complex in comparison to the pharmaceutical because a plant source consists of more than one Phytochemical. Due to differences in geographic location, soil, the climate there would be changes in phytochemical constituents in plants. While growing plants, there would be the use of fertilizers and pesticides which can alter the phytochemicals. Some of the nutraceuticals can produce toxicity such as Aloe Vera, green tea extract, bitter melon, etc. There may be a presence of toxic contaminants/adulterants which causes toxicity in food or nutraceuticals such as phytotoxins, metals, pesticides, radiation, etc. To evaluate the safety and toxicity, Vertebrate and invertebrate species are used. Evaluation of invertebrate species is done by invasive or noninvasive approach [10].

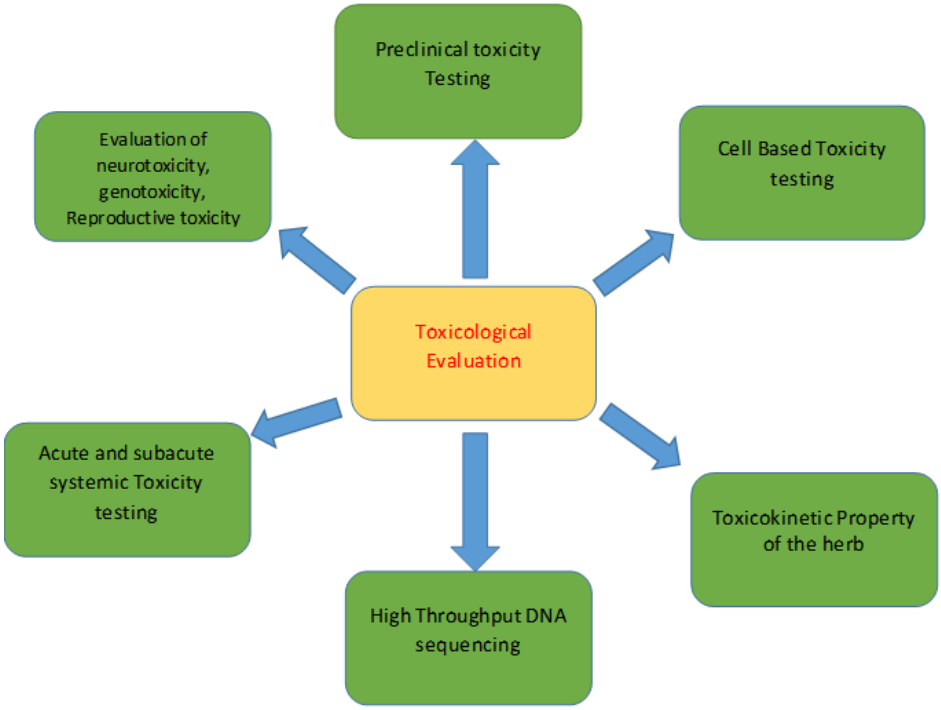

FIG. 4. **Toxicological evaluation.**

Challenges in the Nutraceutical Industry

- Minimal acceptance of the products: The level of acceptance of the nutraceutical product as a preventive or treatment product is less as it is derived from natural sources. People accept it as a diet rather than a medicine. There is minimal acceptance of the product as a curable medicine.

- Lack of awareness about the products: There is a wide range of products among nutraceuticals but the population is not aware of the variety. Nutraceutical is mostly considered as home remedies which are easily available at home but there is a need to create awareness about the wide range of products.

- Lack of optimal dose and dosage system: Unlike Pharmaceutical, Nutraceutical has limited doses for each indication. The doses are mostly unified making it common for most of the disease. There should be an optimal dose system for each indication. This can be achieved only by conducting more clinical research and studies.

- Lack of formulations other than oral and topical: Nutraceuticals are mostly found in tablets, capsules, patches. creams or syrups etc. There is a lack of new formulation which can provide faster action and increased efficacy. Formulations such as Injections, vials, sprays should be considered for innovation and clinical studies.

- Taste: The Indian population has variability in food preferences and so do their taste preference. So, the taste of the product can be a cause of concern for the administration of nutraceutical products.

- Expensive: The Indian Population is sensitive to pricing. if the prices would be high, only the urban population would be able to afford the products. The government can help the manufacturers by reducing the import cost and various other taxes. This would make the rural population have access to the nutraceutical product.

- Lack of strong evidence or clinical data: Clinical evidence is needed to implement Evidence-based practice among health professionals. To break the conventional practice and implement Evidence-based Practice, there is a need for convincing scientific evidence, clinical trial, and clinical studies to support the practice.

- Lack of data regarding metabolism or other Pharmacokinetic (PK) Data: Pharmacokinetic data such as half-life, metabolism, and excretion is not very well established. This would affect the prescribing pattern or the usage of nutraceutical during the practice. More studies to establish the pharmacokinetic data have to be conducted.

- Exact mechanism of action is not well established: Unlike Pharmaceutical products, Nutraceutical products do not have a well-defined Mechanism of action such as the receptor sites, target sites, the factors affecting the absorption, etc. These aspects need to be more emphasized and more clinical evidence has to be generated for the same.

- There are fewer Innovations in nutraceuticals compared to pharmaceuticals: Innovations are more performed in Pharmaceutical products than nutraceutical products. New delivery systems, new formulation, techniques to improve bioavailability, and efficacy are more discovered in the pharmaceutical industry. Similar innovations have to be made in the nutraceuticals industry to match up with the pharmaceutical industry.

- Route of administration is mostly orally and another route of administration is less established: The most common routes of administration for nutraceutical are oral and Topical. To increase the bioavailability and efficacy, there should be more discovery of other routes of administration for Humans. There are decreased use of IV, IM routes of administration among nutraceuticals

- Proper regulations for nutraceutical as pharmaceutical has been lacking: Regulating the products is a very important component. There are no standard books such as Indian Pharmacopoeia which can be taken as a standard or reference for safety and quality. The establishment of such resources can be helpful for researchers and other health professionals [11].

The purpose of this article is to highlight the evidence-based practice in nutraceuticals. This article includes information on the nutraceutical industry, growth, Regulations, and the challenges faced by the nutraceutical industry. Clinical trials and clinical evidence in nutraceuticals are also discussed. Innovations and prospects in the field of nutraceuticals are included.

Evidence-Based Practice

Need for clinical trials

Clinical trials are needed to be conducted in large numbers to generate appropriate clinical data. The safety and tolerability of the product are well known when trials are done on a large scale. To gain trust among the general public and medical community, the effectiveness and efficacy of the drug have to be well established. The pharmacodynamics data is clear for nutraceutical products, but it is unclear on how the product is eliminated or metabolized inside the body or information about any other pharmacokinetic data. More clinical evidence is needed to be generated to get information about the pharmacokinetics of the nutraceuticals by conducting more clinical studies. Optimal dose for nutraceutical is not well established. Most of the dosing is prepared commonly for all the disease conditions and populations. Nutraceuticals are mostly found in dosage forms like Oral dosages and Topical dosages. Due to decreased evidence on the stability and efficacy of other dosage forms, new formulations are not being produced. Marketing is the most reliable way to create awareness among the general public about Nutraceutical but without sufficient evidence and supporting clinical data it becomes a challenge for marketing the nutraceutical among the population.

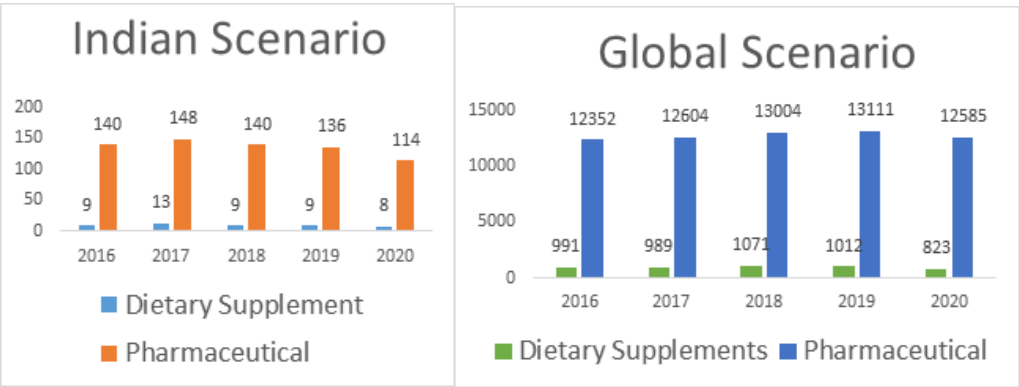

FIG. 5. **Indian and global scenario of Clinical Trials**

This comparison indicates that the clinical trials for pharmaceuticals are higher than Nutraceutical in both Indian and Global scenarios from the year 2016 to the year 2020. More trials and real-world experience are needed to establish the scientific evidence regarding the nutraceutical profile.

Pharmacokinetic, pharmacodynamics and clinical data are essential. It is hard to establish the uses and efficacy as the clinical trials conducted on nutraceuticals are very less compared to pharmaceuticals. The Real word evidence is needed to produce data for safety and tolerability of the products, to establish the efficacy and effectiveness, to produce data of Pharmacokinetic profile of the product, to try new formulation and delivery systems, to generate products for a specific area of therapy, and to establish evidence for creating awareness and for marketing the products. It will also show evidence related to variation in races, regions, and cultures.

Evidence based practice

Evidence-based Practice is an approach where clinical decisions taken by the health professional are based on clinical evidence about the drug/ product for individual patients. Evidence-based medicine is a mixture of Expert opinion, scientific literature, observations, and client point of view.

Benefits: There are various benefits of evidence-based practice. Effective patient care can be achieved through evidence-based practice which will eventually improve patient outcomes. EBP gives strong support to individualized treatment regimens. The quality of care provided to the patients by the clinicians is also improved through this approach. EBP helps the healthcare professional to be updated about recent trends and practices [12].

Challenges: A sudden shift from conventional medicinal practice to evidence-based nutraceutical practice can be a barrier to implementing it. There might be obstacles for new implementation from the management or colleagues. Approval from fellow teammates could be a challenge as there may be more than one health professional in managing a patient. Lack of time to educate about the evidence-based practice to all health professionals. Inadequate access to resources to be used in evidence-based practices can be a challenge to health professionals working in rural areas. Lack of Resources to find evidence about the nutraceutical to support the practice. Difficulties due to lack of teamwork can act as a barrier for nutraceutical evidence-based practice. Difficulty in accessing the nutraceutical evidence to support the practice.. Lack of time to study or research about the nutraceutical practice can be a challenge [13].

The principle of Evidence-based nutraceutical practice is based on five steps which are:-

1. Preparation of a question that is answerable
2. Generating clinical Evidence for the question
3. Critical appraisal of the evidence
4. Application of the evidence
5. Evaluating the Practice of Evidence-based medicine.

Research in nutraceuticals

- Development of Research plan for nutraceuticals

i. Developing a research question- The first step for a research plan development is preparing a question, this can be done by reviewing thoroughly through literature.

ii. Formation of the research team- To conduct research, there should be a team of expertise depending on whether the study is conducted on animals or humans. Searching for a company that can support the study is also considered.

- Information on preparation and characterization of the product- This includes characterization of each component and if not possible then the active ingredient present in the nutraceutical or nutritional supplement. Details about the preparation, temperature of the preparation, etc. should be included.
- Data on metabolism and mechanism of action of the nutraceutical: Pharmacodynamics and Pharmacokinetic data of the nutraceutical is important for the study design which includes the mechanism of action, half-life, metabolism, elimination, absorption, etc.
- Subject compliance: The adherence of the participant determines the success of the study. The researcher can check compliance personally by allowing the subject to take the product in the presence of the investigator or the researchers can send electronic reminders about the consumption of the product.
- Measuring the outcome of the study: Measuring the outcome of the study and the choice of the outcome is an important step in research. This will ensure that the study is a success or failure or whether it has met the needs of the study.
- Responder's *vs.* nonresponders: When the measurement of outcome is done, we can conclude whether the subject is responding or not responding to the needs of the study. Through this, the researcher can conclude about the factors affecting the study, the reason for not responding, etc.
- Use of animal data for a better human response- Animal data will be useful for human studies which have to be done in higher doses than the normal dose in foods. This would contribute as evidence for the efficacy of the nutraceutical. These data help in creating hypotheses for human studies and also help in investigating safety data.
- Publication of the high-quality data - Any high-quality data should be published irrespective of the results, this will help in further studies as clinical evidence [14].

Principles of pharmacologic research

i. Pharmacological active ingredients: The herbal extracts present in the herbal dietary supplement is a complex mixture of phytochemicals in which the pharmacologically active compounds often contain small parts. These minor constituents often give additive or synergistic effect to the main active ingredients. The main active ingredient includes carbohydrates, lipids, polyphenols, terpenes, steroids/ols, and alkaloids.

ii. Purity and Quality Check (QA, QC) of that active ingredient: Safety concerns about the use of dietary supplements are not raised only due to Pharmacological/toxicological properties, it is also caused by the quality of the product. The quality issues include Misidentification of the plant, contamination by microorganisms, pesticides, etc., and adulteration. Deliberate adulteration of nutraceutical products with prescription and over the counter drugs can disrupt the quality of the nutraceutical and can cause safety issues. So, there is a necessity for quality analysis and quality control check of the nutraceutical for each batch to ensure there is no decrease in the quality and safety of the nutraceutical.

iii. Adulteration: Adulteration of a product causes a decline in the quality and safety of the product. When prescription or OTC drugs are mixed with nutraceutical products, it is said to be adulterated. This is done to enhance or intensify the therapeutic effect of the nutraceutical. The USA FDA reported 572 cases of adulteration from 2007 to 2014, mainly in products claimed to enhance sexual performance (238 entries) and for weight loss (228 entries). The effect of adulterated nutraceutical includes stroke, acute liver injury, Kidney failure, and heart palpitation.

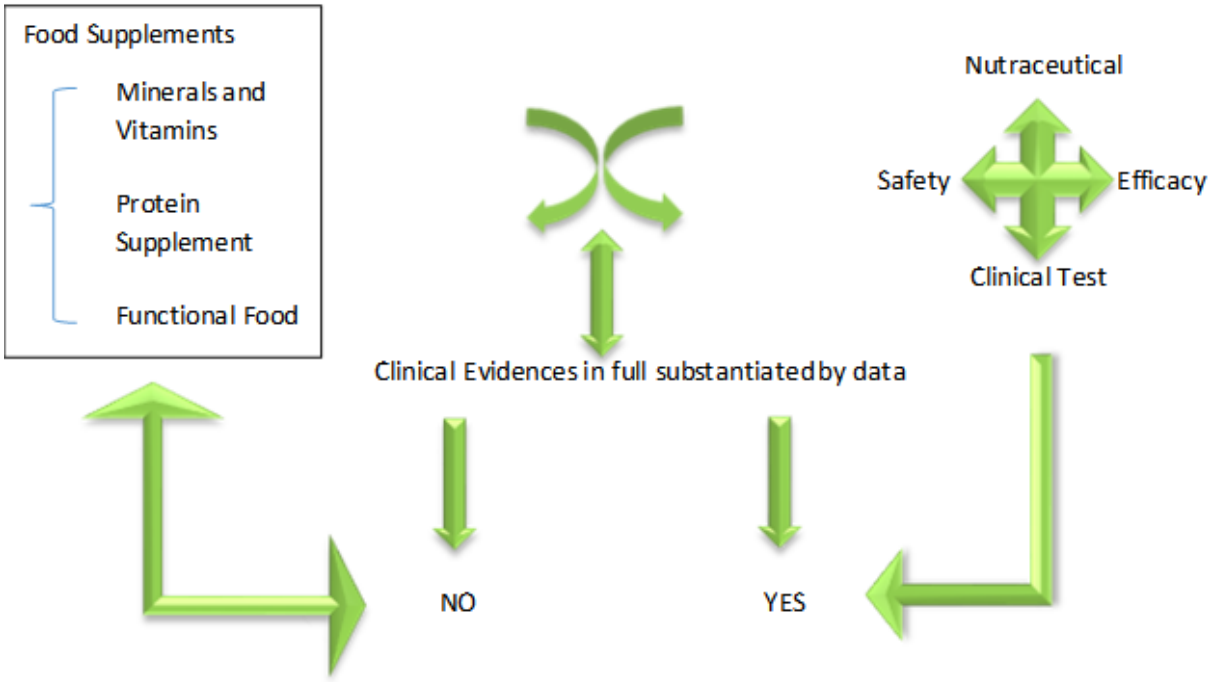

FIG. 6. **Food supplements and Nutraceutical**

Clinical Evidence

Meta-analysis is a statistical analysis where results from multiple scientific works of literature are gathered. Various articles on the same topic are searched from different sources like Pubmed, Cochrane, etc. All the articles are thoroughly studied and a meta-analysis is prepared. Another clinical evidence used is a systematic review which is a review of the evidence for a particular formulated question which is done in a systematic order by identifying, selecting, and critically appraising the evidence. Systematic review is considered high-quality evidence for practice.

Efficacy

Efficacy is defined as the ability of a nutraceutical product/ intervention to show its desired effect/results under certain conditions [15].

To determine efficacy, there should be certain endpoints/ parameters to be observed such as:

- Clinical Endpoints- e.g.: Decrease in blood pressure, etc.
- Pharmacokinetic Endpoint- e.g.: Serum concentration or half-life of the product.
- Pharmacodynamics Endpoint- e.g.: The nutraceutical product's ability to alter the disease mechanism.
- Laboratory parameter-e.g.: blood glucose level.
- Harbinger's sign- A warning or sign which indicates underlying condition/ effect.

The study design used to evaluate the efficacy of Nutraceuticals are:

i. Observational Studies
   - Cohort studies
   - Case-controlled studies

- Real-World Evidence

ii. Experimental studies

- Randomized controlled trials
- Comparative studies (Two Arm Trials)
- Patient-Reported Outcomes (PRO) [16].

Defined as a term which covers the health or clinical data which is reported by the patient regarding a product or studies such as a symptom, adherence to treatment, and satisfaction with the therapy. The source for PRO is solely the patient

TABLE 6. **Patient reported outcomes.**

PRO	Reference
Refractive error quality of life survey	Hays et al., 2003
The Medical outcomes study 36-item short-form questionnaire (SF-36)	Ware, Jr. and Sherbourne,1992
CLAU-S questionnaire	Marquis et al., 2001b
Social Phobia Inventory (SPIN) questionnaires applied to screen for phobic disorders	Connor et al., 2000, 2001

Component of Patient-Reported Outcomes: The components for Patient-Reported Outcomes include Physical Functioning, Social Functioning, Psychological Wellbeing, Pain, Vital signs, Disease-related symptoms, Treatment-related symptoms, Treatment satisfaction, and Treatment adherence. These components are considered during assessing a patient's reported outcomes [16].

Safety

Nutraceuticals also cause safety issues due to pharmacological alteration and also due to quality issues. Quality issues like misidentification of the plants, adulteration during manufacture, etc. Pharmacological issues like drug-food interaction, drug-drug interaction, nutraceutical-pharmaceutical interaction. Nutraceuticals have less or no side effects mostly. Side effects like constipation, diarrhea, vomiting are present. Since Nutraceutical preparation lacks proper regulation in comparison to pharmaceuticals, safety concerts are an issue. Pharmacological and toxicological studies of nutraceuticals are complex due to multiple phytochemicals present in one plant, use of fertilizers and pesticides. It is believed that since they are made from natural extracts, there are no considerable side effects. Since there is a chance of contamination of plants with other plant Alkaloids, metals, they may cause slight side effects such as GI disturbances like diarrhea, vomiting, etc. [17].

Green tea infusion and extracts are used around the world as a beverage, nutraceutical, and phytopharmaceutical. Kapetanovic et al. conducted a chronic toxicity study on fasted and non-fasted Beagle dogs which are 5 to 6 months old. They were given modified Green tea extract (64%). Dogs are given 0, 200, 500 and 1000 mg/kg/day. The study was terminated at 6.5 months and there were 16 deaths among 24 dogs. The liver lesions were described as Centro lobular

necrosis and chronic inflammation. Renal lesions were tubular epithelial necrosis, tubular dilation with granular or hyaline protein casts, epithelial regeneration, acute inflammatory exudate, and transitional hyperplasia [18]. Side effects of Green tea extract in humans are Bloating, Nausea, Heartburn, abdominal pain, dizziness, headache, muscle pain, and hepatotoxicity [19].

Side effects can be caused by other toxic contaminants/adulterants such as Phytotoxicants, metals, Mycotoxins, pesticides, radiation, drug abuse, and therapeutic drugs [20]. The most toxic component present in plant species is Pyrrolizidine Alkaloids (PAs). There are almost 150 PAs that have been identified. Similar toxic effects are seen in most of them, but there is variance in their potency due to their bio activation in the liver to the toxic metabolites called Pyrroles. These pyrroles which are powerful alkylating agents react with DNA and protein and cause tissue necrosis, cellular dysfunction [21]. Detection of Pyrrolizidine alkaloid in the biological system indicates the use of comfrey. The target organ for Comfrey is the Liver [22]. Nutraceutical specific biomarkers are not available but target organ-specific biomarkers are used to check the toxicity of the nutraceuticals. e.g.: SGOT, SGPT, Bilirubin for pyrrolizidine alkaloids. Recently, organ-specific microRNAs are useful biomarkers for organ toxicity since this biomarker can show early changes in comparison to other biomarkers [23].

Post marketing surveillance

Post Market Surveillance is the monitoring of the nutraceutical product in a larger population. The product is distributed on large scale to check the effect and to investigate the safety concerns in various populations. During this phase, the issues related to the product will be noted by the regulatory authority as evidence [24].

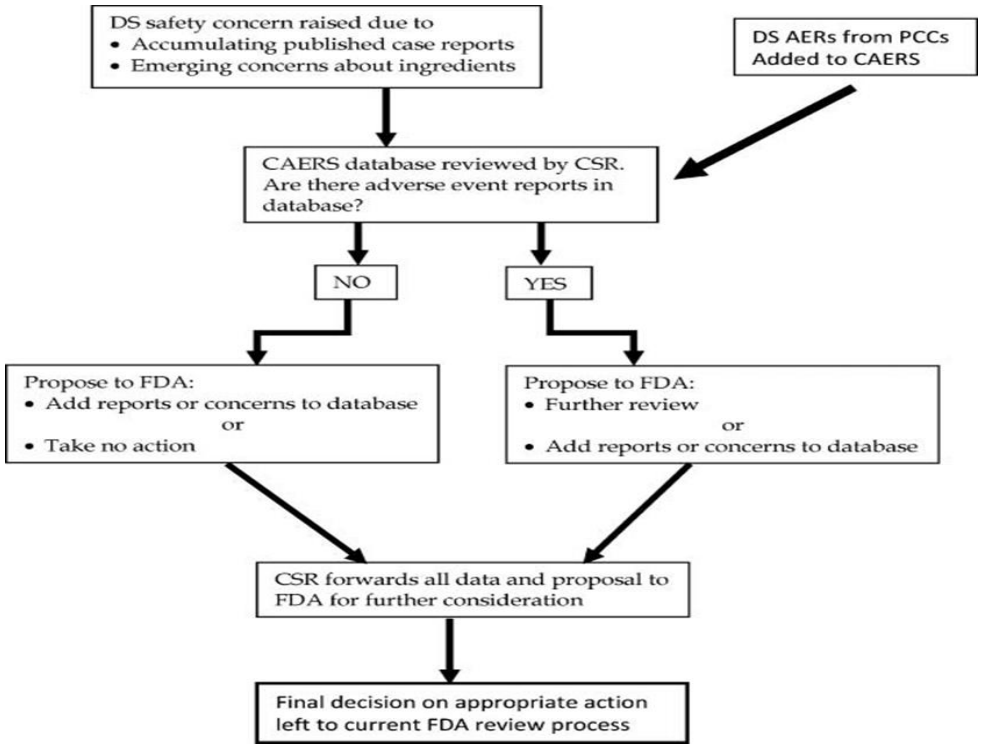

FIG. 7. **Post-marketing surveillance of Dietary supplements**

(DS- Dietary Supplement; AER- Adverse Event Report; PCC- Poison Control Centre; CAERS- Center for Food Safety and Applied Nutrition's Adverse Event Monitoring System; CSR- Contact Surveillance Researcher)

Reporting of adverse events

Reporting of the adverse event is important as it will make the regulatory official aware of the adverse event. If the adverse event is new to the database, it will act as evidence to support further events. The sponsor is responsible to report the event to the FDA. The IRB, FDA, Sponsor will use the safety information to make important decisions that can affect the clinical trials on humans [25]. The reporting of nutraceuticals or dietary supplements is limited because consumers assume that the products are safe and do not cause any adverse events. The consumers are not fully aware of the reporting system and that FDA regulates the nutraceutical/ dietary supplements [26]. Reporting by Consumers and healthcare professionals includes a). stopping the dietary supplement immediately b). Fill the safety report form through the safety portal of the FDA c). Log in as a guest d). Choose the "Dietary Supplement Report (voluntary)…" option e). Fill out the details. The consumers can report to the healthcare professional directly. Reporting by Industry includes a). Fill the safety report form through the safety portal of the FDA b). Log in as a guest c). Choose the "Dietary Supplement Report (mandatory)" option [27].

RWE and RWD

Real-World Evidence (RWE) is defined as the clinical evidence which is collected for supporting the usage and indicating the potential risk and benefits from Real-World Data (RWD). For example, clinical trials and observational studies. Benefits of Real-world evidence include Individual therapy for different patients, adequate evidence for the prevalence of the disease and can be used to monitor the safety and quality of nutraceuticals [28].

Real-World data is defined as are data collected related to the patient's health condition and the health care given to the patient from various validated sources. eg: Electronic health records, medical claims, data from registries of product or disease, or data generated from patients.

Benefits of Real-world data include Generation of hypotheses for RCT testing, drug development tool identification, and evidence generation for safety and effectiveness [29].

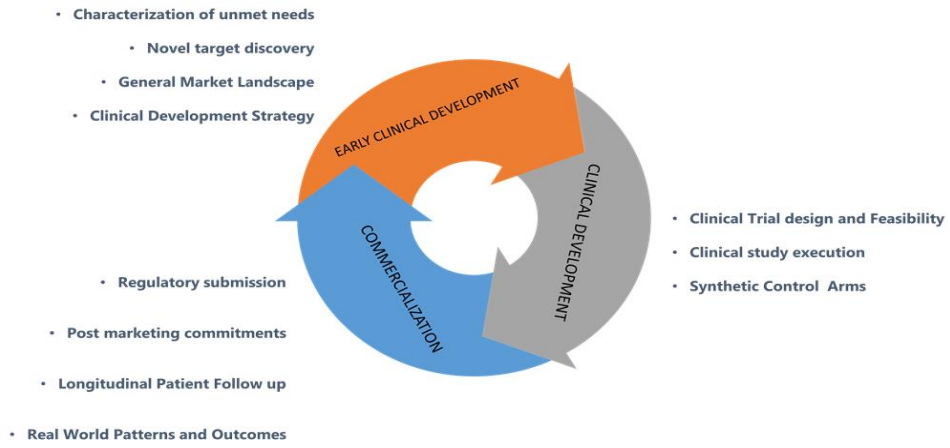

FIG. 8. **Real world evidence.**

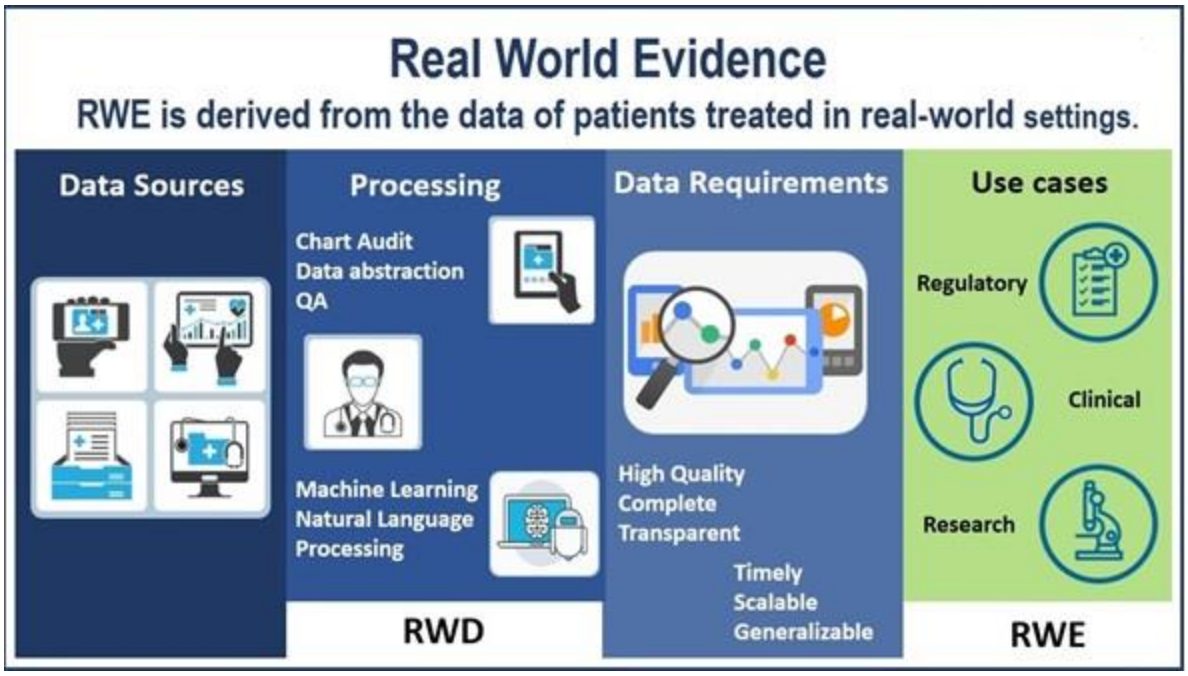

FIG. 9. **Real world data and real world evidence**

Current Scenario of Clinical Trials

The information used in this review article is extracted from Clinical Trials Registry- India by using the following keywords- "Nutraceutics", "Micronutrients"," Nutrients"," Vitamins", "Dietary Supplement", "Phytochemicals". Clinical trials conducted from 2019 to 2020 were reviewed.

The data for creating a ranking of the therapeutic area was extracted from Clinicaltrials.gov

TABLE 7. **Studies registered in CTRI.**

Sr. no	Nutraceutical/product	Indication	Study type	Sample size	Duration of treatment	Year
1	LI85008F	Resting metabolic rate	Interventional	60	6 month	2020
2	LN19184	Cognitive function	Interventional	100	1 Yr 3 months	2020
3	Venerg-UTM	Alcohol hangover	Interventional	20	2 months	2020
4	LN20189	Immunity	Interventional	40	6 month	2020

5	PICOVRID	COVID19	Interventional	70	2 months	2020
6	RV Forte Capsule	Immunomodulator	Interventional	60	1 month	2020
7	Natural Phytoconstituents Gargle	Inhibition transmission of respiratory virus	Interventional	24	6 month	2020
	Resveratrol and copper	Hematological malignancies	Interventional	20	1 yr	2020
8	LN18178	Male aging	Interventional	120	6 month	2019
9	CV-HFD01	Type 2 diabetes	Interventional	30	4 month	2019
10	CV-HFG01	Hyperuricemia	Interventional	30	4 month	2019
11	Neuroroj	Peripheral diabetic neuropathy	Interventional	50	3 month	2019
12	CV-HFU01	Recurrent UTI	Interventional	30	4 month	2019
13	Acculips	Evaluation of clinical condition	Interventional	200	1 yr	2019
14	CV-HFT01	Hypothyroidism	Interventional	30	4 month	2019
15	Nattokinase	Prevention of blood clot in Type 2 Diabetes patient	Interventional	50	10 month	2019
16	NRL/MW/201901	Erectile dysfunction	Interventional	100	3 month	2019
17	LI89034F2	Endothelial function in an	Interventional	75	1 yr	2019

		overweight adult with slightly elevated BP				
18	AquaLOX®	Post-exercise musculoskeletal function	Interventional	50	1 yr	2019
19	BioSOLVECurcuminTM	Rheumatoid arthritis	Interventional	24	3 month	2019
20	XanMax®(natural Lutein and Zeaxanthin) 80 crystals with rosemary extract powder	skin attributes like protection from UV radiation & skin moisturization	Interventional	100	9 month	2019
21	Erythropoiesis-relevant micronutrients in addition to Iron folic acid	Anemia	Interventional	1300	2 yr	2020
	Zinc	COVID 19	Interventional	100	1 month	2020
22	Iron drops	Iron deficiency	Interventional	230	2 yr	2019
23	Iron folic acid supplements	Anemia	Interventional	550	11 month	2019
24	Cinnamon	Type II Diabetes mellitus	Interventional	50	1 yr 1 month	2020
25	Cholecalciferol sachets and Calcium Tablets	Vitamin D deficiency and bone	Interventional	128	2 yr	2019
26	Probiotic supplementation	Prevention of neonatal sepsis	Interventional	6100	3 yr	2019

27	Vitamin C and Vitamin E, Omega-3 fatty acid, Spirulina 500 mg	Oral submucous fibrosis & oral cancer	Interventional	60	7 month	2020
28	Shitake mushroom extract (30% Polysaccharides-AHCC), Vitamin D3 (Cholecalciferol), Vitamin C (L-Ascorbic acid), Vitamin E (mixed tocopherols), Vitamin B6 (pyridoxine HCl), Zinc (as zinc sulfate), and Beta Carotene.	Immunity booster	Interventional	70	1 yr	2020
29	Micronutrients (zinc, vitamins B1, B2, B3, B5, B6, B12, A, C, E, and D) & iron-folic acid	Anemia	Interventional	1300	2 yr	2020
30	Vitamin D capsules and *Curcuma longa*	Lymphoma Patients	Interventional	80	4 yr 6 month	2020
31	Vitamin K2-7 100 mcg	Osteoporosis	Interventional	30	6 month	2020
32	BHC9619CP Turmeric extractin	Joint Health	Interventional	30	6 month	2020
33	Vitamin A	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity, and pharynx	Interventional	72	1 yr 6 month	2020
34	Probiotic blend of 2.5 billion cfu containing: *Bacillus clausii* (TBC034) 0.25 Bn., *Bifidobacterium bifidum* (TBB 037) 0.5 Bn., *Lactobacillus acidophilus* (TLA076)	Metabolic disorders	Interventional	60	4 month	2020

	0.25 Bn., *Lactobacillus plantarum* (TLP017) 0.5 Bn., *Saccharomyces boulardii* (TSB009) 0.5 Bn. and FOS-125 mg					
35	*Asparagus racemosus* & *Withania somnifera*	quality of life, and blood vessel function	Interventional	120	2 yr 1 month	2020
36	Curcumin 500 mg	Oral submucous fibrosis	Interventional	34	1 yr	2019
37	*Bacillus coagulans* MTCC 5856-2 × 10^9 cfu/capsule	Gastrointestinal disorders	Interventional	70	1 yr	2019
38	Uthever (NMN supplement)	Anti-aging and Work-Out Enhancer	Interventional	66	1 yr	2020
39	AquaLOX®	post-exercise musculoskeletal function recovery	Interventional	50	1 yr	2019
40	Upanahasweda	Pain management in osteoarthritis	Interventional	30	1 yr	2019
41	Obinil	Anti obesity	Interventional	120	1 yr	2019
42	Carica papaya leaf extract mouthwash, probiotics mouthwash, and kidodent	Antibacterial effect	Interventional	60	20 days	2020
43	*Divya swasari vati, Divya coronil, Divya anu taila*	Covid 19	Interventional	150	6 month	2020
44	Virowin, Energy Z	Covid 19	Interventional	60	3 months	2020

45	Tablet Pure Ashwagandha 500 mg, Tablet Pure Giloy Extract 1000 mg, Tablet Pure Tulsi Extract 500 mg, Anu Taila 4 drops BD, Powder Swasari Ras 2 gm	Covid 19	Interventional	120	2 month	2020
46	Mangosteen Fruit Gel	Gum Health	Interventional	25	3 months	2019

TABLE 8. **Studies registered in clinicaltrials.gov.**

Sr. no	**Product**	**Indication**	**Type of study**	**Sample size**	**Duration**	**Year**
1	Alpha- lipoic Acid	Migraine	Interventional	60	1 yr 6 months	2019
2	Alpha-lipoic acid	Non- alcoholic lipoic acid	Interventional	120	1 yr 4 months	2020
3	Lactoferrin	Iron deficiency anemia	Interventional	130	1 yr 11 month	2020
4	Vit. B12	Vit. B12 deficiency	Interventional	720	2 yr 8 months	2019
5	Vit. D3 and Zinc	Covid19	Interventional	700	1 Yr	2020
6	Vit. D	Chronic Urticaria	Interventional	262	5 months	2019
7	TK112690	Mucositis	Interventional	22	10 Months	2019
8	Topical melatonin	Oral Leukoplakia	Interventional	66	8 months	2020
9	VIRACIDE	Covid 19	Interventional	124	4 months	2020
10	Artemisinin (6 mg/ml), Curcumin (20 mg/ml), Frankincense (=Boswellia) (15 mg/ml) and vitamin C (60 mg/ml)	Covid 19	Interventional	50	8 months	2020

11	Ayurvedic Kadha	Covid 19	Interventional	52	1 month	2020
12	Oral zinc supplementation	Oral Lichen Planus	Interventional	50	8 months	2020
13	Branched Chain Amino Acids Supplementation	Chronic Liver Disease	Interventional	60	1 year 10 months	2020
14	Saturated Fat (Desi Ghee)	Alcoholic Hepatitis	Interventional	60	2 years 11 months	2019
15	Vitamin D	Aging PreDiabetes	Interventional	200	2 years 11 months	2019
16	Virgin Coconut Oil (VCO)	Dyslipidemia	Interventional	150	1 year 10 months	2019
17	Oxyjun	Obesity	Interventional	64	5 months	2020
18	Oral Nutritional Supplement	Poor Nutrition	Interventional	1500	1 year 5 months	2019

Nutrivigilance

Nutrivigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse events related to the use of food, dietary supplement, or medical food". People assume since dietary supplements are natural foods, they do not need any surveillance. But dietary supplements need to be monitored for quality, the active ingredient, purity. Any adverse event can only be reported by the health professional to nutrivigilance. For example, there were cases of adverse effects being reported regarding the consumption of food supplements containing Melatonin to the French Agency for Food, Environmental, and Occupational Health & Safety (ANSES). Reported side effects were headache, dizziness, drowsiness, irritability, tremors, migraine, nausea, vomiting, The ANSES recommended that population having Inflammatory, autoimmune disease, pregnant and lactating women, children should not consume food supplements with Melatonin.

Objectives of Nutrivigilance include a). Preventing Harm from Adverse Reaction in humans caused by nutraceutical or other dietary supplements b). Monitoring the safe and effective use of nutraceuticals c). Contribution towards the safety of the patient and public health [30].

Future Prospects

The current status of clinical evidence for nutraceuticals is less in comparison to pharmaceuticals. To implement Evidence-based practice for nutraceuticals, there is a need to generate more clinical evidence which includes Clinical trials, observational studies, Meta-analysis, and Real World Evidence studies. There is a need for multicenter trials to avoid bias as there would geographical variation, variation in the race, the difference in population. An increase in research trials can help innovate new formulation and their efficacy in humans. Even though Nutraceutical supplements are from natural sources,

there is a need to monitor the safety of the products which can be checked by the novel concept Nutrivigilance which is necessary to maintain quality standards, active ingredients, and purity of the products. Nutricosmetics, [31] Nutrigenetics, and Nutrigenomics are the new field of innovation in the nutraceutical industry. The current pandemic has created a lot of awareness regarding the need for immunity to fight against diseases and the need for immunity boosters has increased. Nowadays, Social Media is a very good platform for launching and creating awareness among the general public because of its easy accessibility.

Conclusion

The nutraceutical industry is gradually emerging and growing in India. Awareness has improved over the years has lead to higher consumption of nutraceutical products. Regulations have evolved and are now stricter than ever in terms of quality, claims, efficacy, and safety. Various challenges need to be resolved to stabilize the growth of the industry. Nutraceuticals, despite being nascent in some therapy areas, their innovation, conducting randomized clinical trials and real-world evidence studies must be encouraged. Although being derived from natural sources, surveillance and safety assessment of nutraceuticals is essential that is taken care of by “nutrivigilance”. Generating more clinical evidence is one of the many primary objectives. Good quality clinical trials evaluating the efficacy and safety of nutraceuticals in different therapy areas will help in supporting claims, making policies, and implementing evidence-based healthcare. By doing all this, the practice of evidence-based nutraceuticals will increase confidence and awareness among healthcare professionals.

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