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# NUTRACEUTICALS PRODUCTS IN COVID-19 MANAGEMENT AND REGULATORY ASPECTS IN INDIA, USA AND JAPAN

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**ABSTRACT:** In today's life, people believing more in "Prevention is better than cure." Since this is our overly processed food supply lacks the nutrients needed for maximum health is acknowledged by health care professionals. To overcome this problem, the best compounds came into our mind is "Nutraceuticals." Dairy products like milk and citrus fruits are a couple of examples of nutraceuticals. In order to prevent COVID-19 disease, several naturally occurring food ingredients have been investigated. Products like Bee propolis, Melatonin (N-acetyl-5-methoxytryptamine), Palmitoylethanolamide (PEA), *Camellia sinensis*, Quercetin, Vitamin C, Vitamin D, Probiotics etc are yet no direct evidence indicating the beneficial specifically against COVID-19 but reported benefits of these products in the ICU context suggest that it could be considered for patients. COVID-19 pandemic plays the role of catalyst to made nutraceuticals as emerging business. Government, to provide the best quality of nutraceuticals products to consumers, made Act & Rules for manufacturing, processing, selling, import-export, packaging & labelling of nutraceuticals product. Different countries have different authorities for nutraceuticals. In India, FSSAI is the working authority which control are the actions. FSSAI approved nutraceuticals product get a unique 14-digits number with symbol of FSSAI on product package. In USA, USFDA defines Nutraceuticals as Dietary Supplements under DSHEA & DSHEA is the working authority. DSHEA regulates all the regulatory requirements like product licensing, proof of safety and effectiveness, labelling, health claims, GMP, reporting of adverse reactions, and clinical trials. In Japan, MHLW defines Nutraceuticals as Food for Specified Health Use & takes all the necessary actions regarding their quality, safety & efficacy. The nutraceuticals products which are approved by MHLW get a symbol of FoSHU on their product package.

**KEYWORDS:** Nutraceuticals, COVID-19 disease, FSSAI, Dietary Supplements, Clinical trials.

# I. INTRODUCTION

1. **Nutraceuticals:** Nutraceuticals are those products which are made from food sources that advertise additional health advantages over and above the fundamental nutritional value of the food they are produced from. Products may make claims to postpone the ageing process, extend life expectancy, sustaining the body's structure or function & prevent chronic diseases, depending on administration.(1)

**1.1 Classification of Nutraceuticals:** Nutraceuticals products are of different types. The classification of nutraceuticals is based on foods available in the market. These products are briefly listed in figure 1.

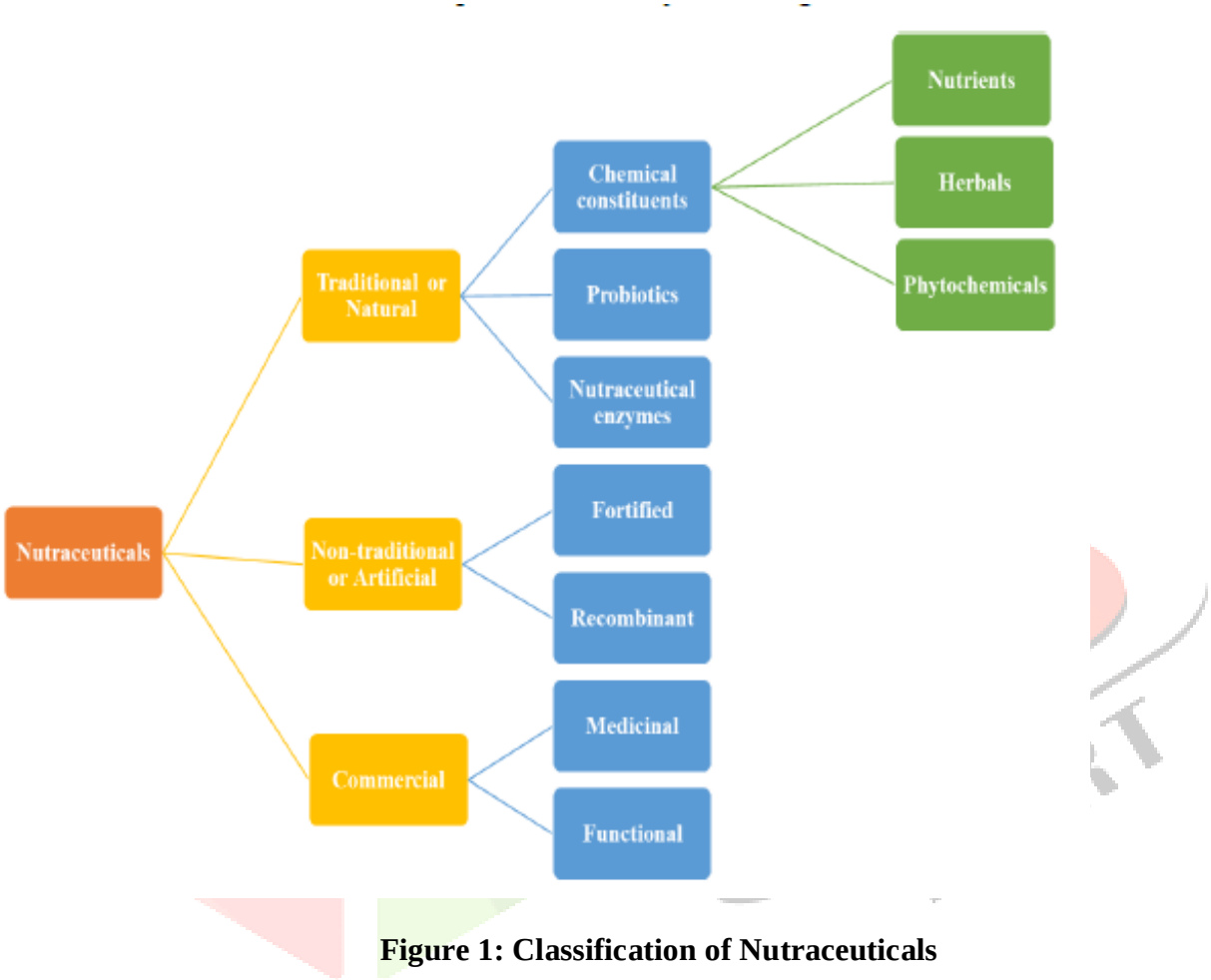



**Figure 1: Classification of Nutraceuticals**

**1.2 Traditional or Natural nutraceuticals:** Traditional nutraceuticals are entirely natural and the food is unaltered. In addition to providing basic nourishment, food contains a number of naturally occurring substances, such as lycopene in tomatoes, saponins in soy and omega-3 fatty acids in salmon.

**1.2.1 Nutrients:** Substances with well-known nutritional benefits, such as fatty acids, vitamins, minerals and amino acids. Vitamins can be used to treat heart disease, stroke, cataracts, osteoporosis, diabetes and cancer. They are found in most vegetables, wholegrain cereals, dairy products, fruits and meat and poultry.

**1.2.2 Herbals:** When used in conjunction with natural treatments, nutraceuticals have a tremendous deal of potential for enhancing health and preventing serious illnesses. As an illustration, an excellent example is willow bark (Salix nigra), which contains salicin, an active ingredient having anti-inflammatory, analgesic, antipyretic, astringent, and antiarthritic properties. *Petroselinum crispum* (Parsley) is diuretic, carminative and antipyretic in addition to containing flavonoids (apiol, psoralen). Menthol, an active ingredient in peppermint (*Mentha piperita*), is used to treat colds and the flu. The tannin found in lavender (*Lavandula angustifolia*) is beneficial for treating asthma, colds, coughs, stress, depression and hypertension.

**1.2.3 Phytochemicals:** Based on the chemical name assigned in accordance with their phytochemical characteristics, they are categorized into many categories. Carotenoids (isoprenoids), which are present in many fruits, vegetables and egg yolks.(2)

**1.3 Non-traditional or Artificial nutraceuticals:** They are biotechnology-aided foods created artificially. Bioactive ingredients found in food samples are used to create products for human wellness. They are positioned in nutrients.

**1.4 Recombinant Nutraceuticals:** Energy-giving foods including vinegar, bread, cheese, wine, fermented starches, yoghurt and others are produced using biotechnology. Production of probiotics, extraction of biologically active elements using enzymes and fermentation and genetic engineering are all made possible by biotechnology**.**(3)

**1.5 Commercial Nutraceuticals:** Nowadays, discovering new compounds is more costly, risky and difficult than ever. Nutraceuticals have an undeniably sizable and growing market, which is why numerous pharmaceutical companies are now seeking to manufacture them. Nutraceuticals are used to treat a wide range of medical conditions, including arthritis, flu and cold, digestive problems, insomnia, osteoporosis, the prevention of some cancers, diabetes, blood pressure, cholesterol management, pain relief and depression.

**1.5.1 Medicinal food:** Based on acknowledged scientific principles, a food designed to specifically manage the diet of a sickness or condition with special nutritional needs contain a specific nutrient that the body cannot naturally generate owing to a certain problem and are determined by medical examination without any ingredients that increase illness state is referred to as a medicinal food.

**1.5.2 Dosage Form:** The substance that is given to patients in order for them to obtain an efficient dosage of a drug is known as a pharmaceutical dosage form. Pharmaceutical dosage forms are required to provide the framework for the secure and practical administration of precise dosage . There are different types of dosage form of nutraceuticals which are based on the compounds sold in market are shown in figure2. (4)

**1.5.3 Functional foods:** They are defined as "any food or food ingredient that may provide a health advantage beyond the traditional nutrients it provides" in accordance with their generally recognized definition. Instead, then taking nutritional supplements that are produced in liquid or capsule form, functional foods are intended to allow consumers to eat enriched meals that are near to their original state. Nutrification is the process of enhancing or fortifying functional foods. By using this technique, the nutritional content of a product is returned to levels that were there before the food was processed. In some cases, complimentary extra nutrients are given,like vitamin D to milk

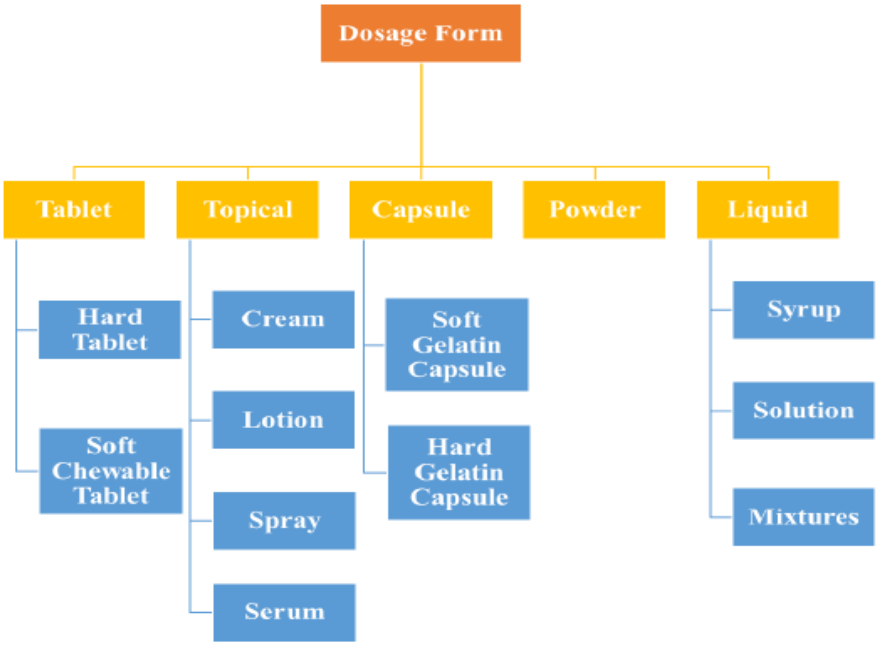



**Figure 2: Type of Dosage Forms of Nutraceuticals products**

## II. COVID-19

COVID-19 is also known as novel corona virus, a pandemic, which is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The first novel virus identified in Wuhan, China in December 2019 and spread worldwide. On January 30, 2020, World Health Organization (WHO) declared a Public Health Emergency of International Concern & a pandemic on March 11, 2020**.** As of August 26, 2022, a deadliest history inaugurated by COVID-19 due to about 59,68,73,121 cases & about 6,459,684 deaths. When a person speaks, sings, sneezes or coughs, the virus can be transferred from their lips or nose in minute liquid particles. From larger respiratory droplets to tiny aerosols, these particles come in a variety of sizes. Most virus-infected individuals will experience a mild to severe respiratory disease, but will recover without the need for special care. However, some people will get serious illnesses and need medical care. Serious illness is more likely to affect the elderly and persons with underlying medical disorders including cancer, diabetes, cardiovascular disease or persistent respiratory issues. At any age, COVID- 19 has the potential to seriously harm or kill anyon**.** During COVID-19 disease outbreak, the marketing of nutraceuticals increased because of its immune boosting power but its efficacy is little known against severe acute respiratory syndrome corona virus 2 [SARS-CoV-2]**.**(3)

**2.1 Structure of corona virus:** Corona, which meaning crown, refers to the appearance corona viruses have proteins that emerge from them and act as spikes. These spike proteins are essential to the biology of this virus. A human cell gets infected by the virus when it connects to the spike protein, which enables the virus to reproduce inside the infected cell and spread to additional cells. Some anti-spike protein antibodies can shield you from SARS-CoV-2 as depicted in figure 1.4. Because of the significance of this specific region of the virus, scientists who sequence it for research routinely spot mutations that alter the spike protein using a mechanism called genomic surveillance. As the SARS-CoV-2 virus undergoes genetic changes over time, genetic lineages start to take shape. Like a family has its own family tree, the SARS-CoV-2 virus can be further mapped out. Occasionally branches of that tree have one-of-a-kind characteristics that alter the virus's ability to propagate quickly, the severity of the illnesses it causes, or the efficacy of its ability to be treated. The modified viruses are referred to as "versions" by scientists. Despite the fact that they may be SARS-CoV-2, they could nevertheless behave differently**.**(4,5)

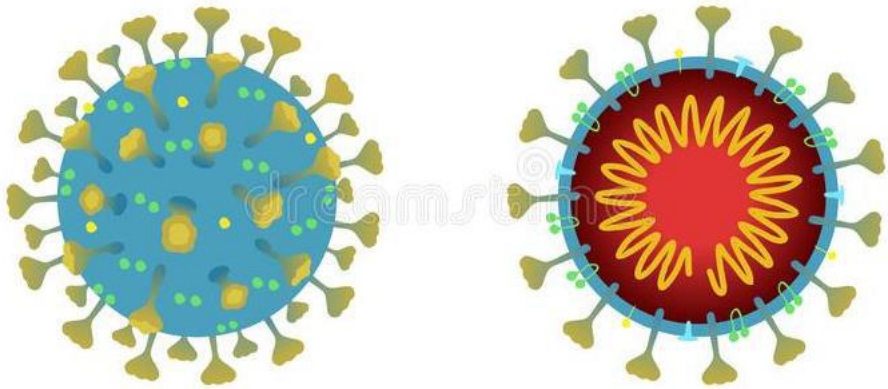


**Figure 3: Structure of Corona Virus**

## III. REGULATORY GUIDELINES OF NUTRACEUTICALS IN INDIA

**3.1 Food Safety & Standards Authority of India:** The Government of India's Ministry of Health & Family Welfare founded the FSSAI. It is in charge of regulating and overseeing food safety in order to safeguard and promote public health. In addition to the 14 referral laboratories, FSSAI also notified 112 NABL-accredited private laboratories and 72 state/UT laboratories spread across India. It is responsible for regulating food business operators' (FBO) licensing and registration in India. FSSAI's headquarters are in New Delhi. Additionally, the organization has six regional offices situated throughout.(6)

i. Northern Region - New Delhi (Head office)
ii. Eastern Region - Kolkata
iii. North-Eastern Region - Guwahati
iv. Western region - Mumbai
v. Southern Region - Chennai

**3.2 FSSAI Logo:** FSSAI approved product gets a 14-digit number. A registered food business operator's (FBO's) 14-digit FSSAI license number has five sections, each of which contains a separate piece of information about the FBO. The aforementioned indicator must be attached to the food product's packaging along with the FSSAI logo as represented in figure 4.

**Figure 4: Logo of FSSAI**

**3.3 Regulations**

• Food products standards and food additives
• Licensing and Registration of Food Businesses
• Sales Prohibition and Restriction
• Labeling and packaging
• Residues, toxins and contaminants
• Sampling and Laboratory Analysis
• Transaction of Business at its Meetings
• Procedure for Transaction of Business of the Central Advisory Committee
• Salary, Allowances and Other Conditions of Service of Officers and Employees
• Appointment & recruitment (7)

**3.4 FSSAI Registration**

Each and every food business operator who engages in the production, handling, distribution and sale of food items is required to obtain an FSSAI Registration or License. FBO should obtain the proper registration or permission in accordance with the size and nature of their operation; this is where FSSAI Registration and

FSSAI License diverge. A 14-digit registration or license number is placed on every food package. Information regarding the producer's permit and the assembling state is provided via the 14-digit registration number.

**3.5 Food Business Operators (FBOs):**Require FSSAI Registration are-

- Small-scale stores and retail establishments such a grocery store, candy store, bakery, etc.
- Food establishments that manufacture, deliver, store, and sale food items, such as Gol Gappas, Chats, Fruit and Vegetable Vendors, Tea Vendors, Snack Vendors, Bread Pakoda Vendors, Samosa Vendors, Chinese Food Vendors, South Indian Food Vendors, Sweet Vendors, Juice Vendors, etc.
- Cuisine vendors those move from one area to another (often on foot or in mobile carts) to offer prepackaged or freshly prepared food.
- Dairy businesses such as milk vendors, petty milkmen and milk chilling businesses.
- Machines for processing vegetable oil.
- Slaughterhouses, including those that sell lamb, mutton, poultry and other meats.
- Facilities for processing fish and meat.
- All food manufacturing and processing facilities that perform food repackaging.
- Novel and proprietary foods.
- A facility for cold or refrigerated storage.
- A company that transports food goods using a variety of specialized vehicles, such as milk tankers, food wagons, food trucks and insulated refrigerated vans and wagons.
- Food product wholesaler, supplier, distributor, and marketer.
- Inns, eateries and bars.
- Cafeterias and canteens, including those for midday meals.
- Food service providers and caterers.
- Dhabas, PGs that serve food, party halls that offer food catering services, home-based pantries and food booths at religious festivals.
- Companies that import and export food products, especially food ingredients.
- Online food vendors, such as cloud kitchens.(8,9)

**3.6 FSSAI Registration License**

There are mainly three types of FSSAI Registration Licenses. The maximum time period for the validity of these three licenses is 5 years and the minimum is 1 year.

**3.7 Procedure for obtaining FSSAI Registration Online**

- FBOs can receive FSSAI registration online by completing and submitting Form A or Form B) on the Focus site.
- The required documentation must be submitted with the FSSAI registration form. By sending Form A or Form B to the Food and Safety Department, FBOs may also register offline. When completing the application on the Focus website, the documents must be delivered physically or electronically to the Food and Safety Department.
- Within seven days of receiving an application electronically or physically through the portal of Focus, the Department may approve or reject the FSSAI registration form.
- If the application is denied, the applicant must be informed in writing.
- Before issuing the FSSAI registration certificate, the Department will review the provided documentation and, if necessary, may perform an inspection of the food facilities.
- If the Department determines that the FBO complies with all standards, it will issue an
- FSSAI certificate of registration with the registration plate, the applicant's photo, and their email address. The applicant may download the FSSAI registration certificate by logging into the Focus portal.
- During business hours, FBO must clearly display the FSSAI registration certificate on the premises.

**3.8 Documents Required**

- Photographic identification of owners of food businesses.
- A certificate of business constitution, such as a partnership deed, an incorporation certificate, a license for a store or other establishment or another proof of business registration.
- Documentation proving ownership of the business space such as a rental agreement, an owner's no-objection certificate, utility bills, etc.
- The management system plan for food safety.
- A list of manufactured or processed food items.
- Details about bank accounts.
- Supporting documentation (if needed), such as a copy of the manufacturer's license, a municipal or panchayat NOC or a health NOC.(10,11)

3.9 **FSSAI Registration Fees:** The following are the different types of registration's associated FSSAI registration fees:

- Rs. 100 for FSSAI Basic Registration
- Fees for the FSSAI State License range from Rs. 2,500 to Rs. 5,000
- The FSSAI Central License costs Rs. 7,500 rupees**.**

**3.10 Registration Form:** There are three types of forms which are filed during the registration of nutraceuticals products. These three forms are based on the type of business or annual turnover.

i. **Form A:** Form A is filed for those small businesses whose annual turnover is less than ₹ 12 lakh.
ii. **Form B:** Form B is filed for those food units whose revenue is less than ₹20 crore and if the business is restricted to the State.
iii. **Form C:** Form C is filed to report any changes in the business.

**3.11 Registration Process**

- Visit https://foodlicenceonline.com/ website.
- Add the necessary information to the draught specified.
- Send your submissions via email.
- Within 2 working days, all questions will be answered and documents will be checked.
- The paperwork will be delivered to the applicant in 7 business days.
- A brief registration process is shown in figure 5.(11,12)

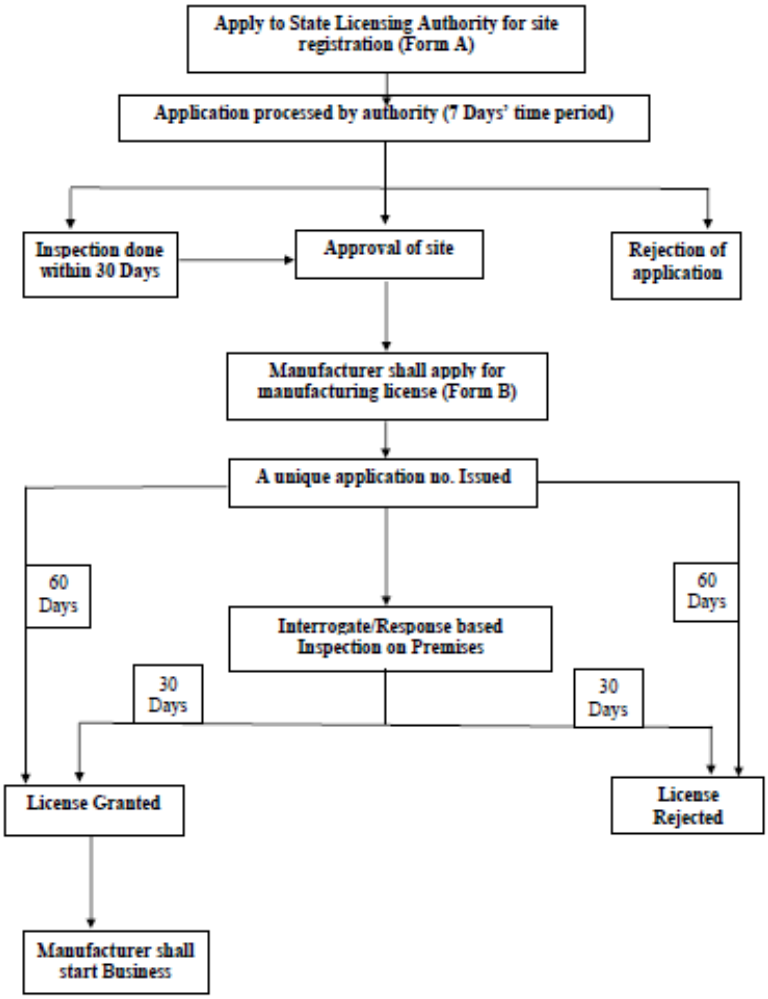



**Figure 5: Nutraceuticals Process for Registration in India**

## IV. REGULATORY GUIDELINES OF NUTRACEUTICALS IN USA

**4.1 Dietary Supplement & Health Education Act [DSHEA]** Dietary components and final dietary supplement products are also subject to FDA regulation. Dietary supplements are subject to a specific set of regulations issued by the FDA than "ordinary" food and medication items. In accordance with the 1994 Dietary Supplement Health and Education Act (DSHEA): • It is forbidden for producers and sellers of dietary components and supplements to advertise tainted or falsely labeled goods. This implies that before putting their products on the market, these companies must assess the safety and labeling of their products to make sure they comply with all DSHEA and FDA rules. FDA is not allowed to assess dietary supplement products for safety and efficacy before they are marketed. FDA is responsible for taking enforcement action against any adulterated or misbranded dietary supplement product after it enters the market**.** Dietary supplements are defined and governed by the Dietary Supplement Health and Education Act (DSHEA), a United States federal statute from 1994. The FDA is mandated by law to oversee supplements for Good Manufacturing Practices under 21 CFR Part 111. The main source of nutrients that keep us fed and healthy is food. To address the poor and unhealthy diets linked to the rise in various non-communicable diseases (NCDs), a food-based strategy is needed. The abundance of food goods in India, particularly medicinal-type products like health supplements that contain plants, herbs, or innovative components, adds a new layer of regulatory complexity. Several of these chemicals may conflict with medication rules because they are pharmacologically active substances.(12)

**4.2 Prior to DSHEA**

- Prior to the DSHEA of 1994, dietary supplements had to adhere to the same FFDCA (Federal Food, Drug and Cosmetic Act) regulations as conventional food ingredients (same regulatory scrutiny as food additives).

- Manufacturers are responsible for guaranteeing quality (within a reasonable degree of safety), safety, correct labelling and efficacy (contrast scenario of FDA regulatory role with food additives & drugs).
- The FDA now has the burden of providing adequate evidence to support the claim that the supplement is dangerous.

**4.3 Health Claims:** Three different categories of health claims exist:
a) Structural/functional claims
b) Nutrient content claims
c) Health claims

**a) Health claims:** Health claims were permitted by 1990 NLEA (Nutrition Labeling and Education Act). Medical claims explain a connection between a food, food component or component of a dietary supplement and decreasing risk of a sickness or health issue.

**b) Nutrient Content Claims:** These refer to the amount of specific nutrients or substances present in a food, such as an excellent source of calcium or low fat and they are used to indicate how much of a nutrient is present in a product in relation to the recommended daily intake.

**c) Function/Structure Claims:** Dietary Supplement Health and Education Act of 1994 permitted this claim. These assertions include making a favorable impact on health, enhancing a function or altering/ maintaining health.(13,14)

**4.4 National Health and Nutrition Examination Survey (NHANES)**

The National Center for Health Statistics (NCHS) conducts the National Health and Nutrition Examination Survey (NHANES), a survey research program, to evaluate the health and nutritional status of adults and children in the United States and to monitor changes over time. Interviews, physical examinations and laboratory tests are all included in the survey. Questions about demographics, socioeconomics, diet and health are all part of the NHANES interview. Medical professionals conduct laboratory tests as well as physical, dental and physiological assessments as part of the examination process. First NHANES was carried out in 1971 and the surveys were made annual in 1999. The first study on the subject was released in 2001. Estimating the prevalence of major diseases and disease risk factors is done using NHANES data. Information is used to assess a person's nutritional status and how it relates to preventing illness and promoting health. NHANES data are also used to develop national standards for parameters like height, weight, and blood pressure. NHANES data are utilized in epidemiological studies and health sciences research to develop efficient public health policies, direct and build health programs and services, enhance health knowledge and lengthen health span and longevity (including biomarkers of ageing). Following-up studies using NHANES data were made possible by linking mortality files and files with Medicare and Medicaid data.

**4.5 Dietary Supplements Regulatory Information & Guidance Documents Current Good Manufacturing Practice (CGMP)**

- **Small Entity Compliance Guide:** Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling or Holding Operations for Dietary Supplements.
- **Final Rule:** Current Good Manufacturing Practice in Manufacturing, Packing, Labeling or Holding Operations for Dietary Supplements Fact Sheet: Dietary Supplement Current Good Manufacturing Practices (CGMPs) and Interim Final Rule (IFR) Facts.
- **Proposed Rule:** Current Good Manufacturing Practice in manufacturing, packing or Holding Dietary Ingredients and Dietary Supplements Guidance for Small Businesses: Submission of Comments for CFSAN Rule making.
- **Advance Notice of Proposed Rule:** Current Good Manufacturing Practice in Manufacturing, Packaging and Holding of Dietary Supplements New Dietary Ingredients.(15,16)

**4.5.2 Special Issues:** Bovine spongiform encephalopathy (BSE)

- Direct Final Rule Withdrawn: Food Labeling: Ingredient Labeling of Dietary Supplements that Contain Botanicals.
- Direct Final Rule: Food Labeling: Ingredient Labeling of Dietary Supplements that Contain Botanicals.
- Proposed Rule: Food Labeling: Ingredient Labeling of Dietary Supplements that Contain Botanicals.

**Ephedrine Alkaloids**

- Final Rule: Declaring dietary supplements containing ephedrine alkaloids adulterated because they present an unreasonable risk.
- Proposed Rule; Withdrawal in Part: Dietary Supplements Containing Ephedrine Alkaloids
- Proposed Rule: Dietary Supplements Containing Ephedrine Alkaloids

**Warnings and Safety Information:** Dietary Supplement Alerts and Safety Information (consumer advisories on specific supplements. How to report problems; and other safety information)(17)

### 4.4.4 Labeling and Regulation

- **Labeling:** Draft Guidance for Industry: Policy Regarding Quantitative Labeling of Dietary Supplements containing Live Microbials.
- **Pure or Highly Concentrated Caffeine:** Highly Concentrated Caffeine in Dietary Supplements.
- **Liquid Dietary Supplements:** Guidance for Industry: Distinguishing Liquid Dietary Supplements from Beverages.
- **Substances added to Foods and Beverages:** Guidance for industry: considerations regarding substances added to foods, including beverages and dietary supplements.
- **New Dietary Ingredients (NDI):** New Dietary Ingredient Notifications and Related Issues.
- **Liquid Dietary Supplements:** FDA Letter to Industry Concerning Liquid Vitamin D Dietary Supplements.
- **Liquid Dietary Supplements:** FDA Letter to Industry: Factors that Distinguish Liquid Dietary Supplements from Beverages.
- **Liquid Dietary Supplements:** Draft Guidance for Industry: Factors that Distinguish Liquid Dietary Supplements from Beverages, Considerations Regarding Novel Ingredients, and Labeling for Beverages and Other Conventional Foods. A dietary supplement labeling guide and regulations & laws about dietary supplements.
- **Labeling:** Questions and Answers Regarding the Labeling of Dietary Supplements asn Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act.
- **Ephedrine Alkaloids:** Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because they present an Unreasonable Risk.
- **Label Warning Statements:** Iron-Containing Supplements and Drugs: Label Warning Statements: Small Entity Compliance Guide.
- **Labeling:** Statement of Identity, Nutrition Labeling, and Ingredient Labeling of Dietary Supplements Small Entity Compliance Guide.
- **Nutrient Content Claims:** Food Labeling; Nutrient Content Claims; Definition for "High Potency" and Definition for "Antioxidant" for Use in Nutrient Content Claims for Dietary Supplements and Conventional Foods Small Entity Compliance Guide.
- **Structure/Function Claims:** Small Entity Compliance Guide.
- **Substantiation for Claims:** Substantiation for Dietary Supplement Claims Made. Under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act.(18,19)

### 4.4.5 General Compliance and Inspection Information for Industry

- Inspections, Compliance, Enforcement and Recalls.
- FDA Compliance References (Compliance Policy Guides and Regulatory Procedure Manual)
- FDA Recalls and Safety Alerts (Policies, Enforcement Reports, Safety Alerts).
- FDA Federal Register Documents, Code of Federal Regulations & Food, Drug, and Cosmetic Act.
- Hazard Analysis Critical Control Point (HACCP)

**4.5 Codex Alimentarius:** The Latin word "Codex Alimentations" means "meal code." The Joint FAO/WHO Food Standards Program established the Codex Alimentations Commission (commonly known as Codex) to create food standards. The goal of Codex is to create global food standards that will protect consumer health and promote ethical behavior in the food industry. Currently, there are 189 Codex Members in the Codex Alimentations Commission, consisting of 188 Member Countries and 1 Member Organization (The European Union)**.**

**4.6 Registration Form to FDA**

FDA provides both online (electronic) & offline (by filling form 3537) methods. FDA strongly recommends for electronic registration by using internet because it is more convenient than offline process.

**4.7 Registration Process**

- Visit https://foodlicenceonline.com/ website.
- Add the necessary information to the aforementioned draught.
- Update all the appropriate documents along with this form.
- Authority members will verify the documents and answer any questions.
- Step by step brief registration process is shown in figure 6.(20)

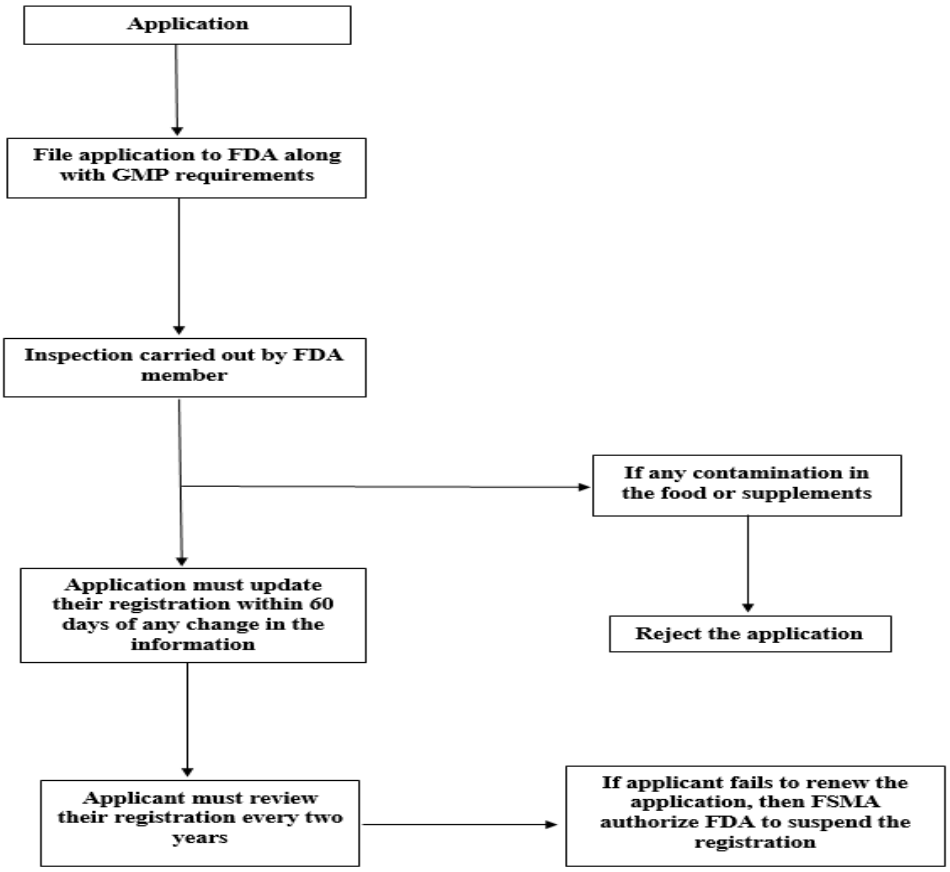



**Figure 6: Dietary Supplements Registration process in USA**

## V. REGULATORY GUIDELINES OF NUTRACEUTICALS IN JAPAN

**5.1 Introduction** Foods with physiological effects on the human body that are officially recognized as having health benefits are referred to as Food for Specified Health Use (FOSHU). This is meant to be ingested by those who want to manage certain medical disorders, such as high blood pressure or high cholesterol, or for special health applications**.** Nutraceuticals are classified as "Foods in General" or "Food with Health Claims" in Japan. There are three different categories listed under: 1. Food with nutrient claims (FNFC) that are mostly

made for minerals & vitamins. 2. For other functions- Food for Specified Health Uses (FOSHU). 3. Foods with Function Claims (FFC).

**5.2 FOSHU logo:** Ministry of Health, Labor and Welfare (MHLW) approved the dietary products. Those products which are approved by the MHLW have FOSHU symbol/logo as depicted in figure 6.1.


**Figure 7: Logo of FOSHU**

**5.3 Regulatory authority**

The primary oversight body for all medications and dietary supplements is the Ministry of Health, Labor, and Welfare. The MHLW seeks to enforce strict regulations for over-the counter medicines and nutritional supplements. Japan became the first nation to enact dietary supplement regulation when it passed the Food for Specified Health Use legislation (FOSHU). As a system of control to authenticate statements regarding how food affects the human body, it was created in 1991. When items bear the FOSHU designation, they have undergone extensive clinical testing and have proven to be efficient and safe for consumption, allowing them to make health claims on their labels. Even if a health promoting action is not backed by research but still satisfies FOSHU's safety requirements, the component may be approved. All things categorized as medications are governed by the Pharmaceutical Affairs Act (1960 to the last amendment in 2013).

**5.4 FOSHU Application Requirements**

i. Name and address of applicant (representative).
ii. Name and location of the manufacturing and head office.
iii. Brand name
iv. Life span
v. Content
vi. Justification for requesting approval and how the consumption contributes to a person's diet improvement and the maintenance or improvement of the general public's health.
vii. The applicant wants to get permission for certain health claims.
viii. Ingredients list and % breakdown.
ix. Precautions and considerations during ingestion.
x. Instructions for using, storing or consuming the product.
xi. Sample of the product.
xii. An illustration of the full packaging, including the labels and health claims.
xiii. Documentation demonstrating the product's beneficial effects for maintaining health, as demonstrated by clinical and dietary evidence.
xiv. Documentation demonstrating clinical and dietary evidence of the dosage of the product or its active ingredients.
xv. Additional human research on the eating experience is included in the documentation addressing the product's functionality and safety.(21,22)

**5.5Assessment:** The MHLW must give permission or approval before a food can be used to demonstrate any of the above-mentioned special dietary purposes (under the law of Health Promotion, Article 26).

**5.6 Labeling Requirement:** According to the requirements of the Ministerial Ordinance under the law of Health Promotion, FOSHU must bear information listed below on its packaging.

- Name of compound
- Date of min. durability
- Preservation methods
- Manufacturers' address and name
- Declared sanction
- Permitted phrase for display
- Amount of nutrient in the food
- Name of additives & food stuff
- If necessary, instructions for eating, preparation, and preservation
- If a manufacturer is not one of those who were approved, the name of the approved
- organization and its address should be provided.

**5.7 Registration Process**

Applicants from abroad submit their applications directly to the MHLW. There are four quarters in the calendar. Applications are accepted three times per year (usually March, June, September and December. It states that details regarding processing, safety, effectiveness, formulation, analytical procedure, physical analysis, and chemical analysis, among other things, must be disclosed. The application must be submitted with proposed labels and product samples that include suggested claims. All submitted information must be in Japanese. Japanese individual's have-to is used in at least some of the clinical data from Japan. Information must also be published in a Japanese scientific publication**.** In a hearing, MHLW examines the application and determines whether to move forward with the case. If the application is approved, MHLW distributes the application and product samples to the following three organizations:

i. Council of Pharmaceutical Affairs
ii. National Institute of Health and Nutrition
iii. Food Safety Commission

The Food Safety Commission determines the product's safety, while the Council of Pharmaceutical Affairs reviews the product's effectiveness**.** An application falling under this category of standardized FOSHU is exempt from the effectiveness and safety consultation stages**.** The analytical technique for determining the active component is approved by the National Institute of Health and Nutrition**.** The MHLW receives the reports from each group. The MHLW then establishes a committee of knowledgeable authorities in the disciplines of medicine, nutrition, food safety and pharmaceuticals, whose members are often picked from the Japanese academic community. The petition is given to the suitable committee for assessment and comment based on the health benefit claimed for the product. Following that, the committee determines if more information is required or whether the petition can be sent to MHLW with an advice of acceptance**.** After the procedure is finished, the MHLW decides whether to approve the product under FOSHU. The MHLW office has the right to request more information and changes during the evaluation process. The application may use the FOSHU mark on its label if clearance is granted. This represents "leaping for health."(23,24)

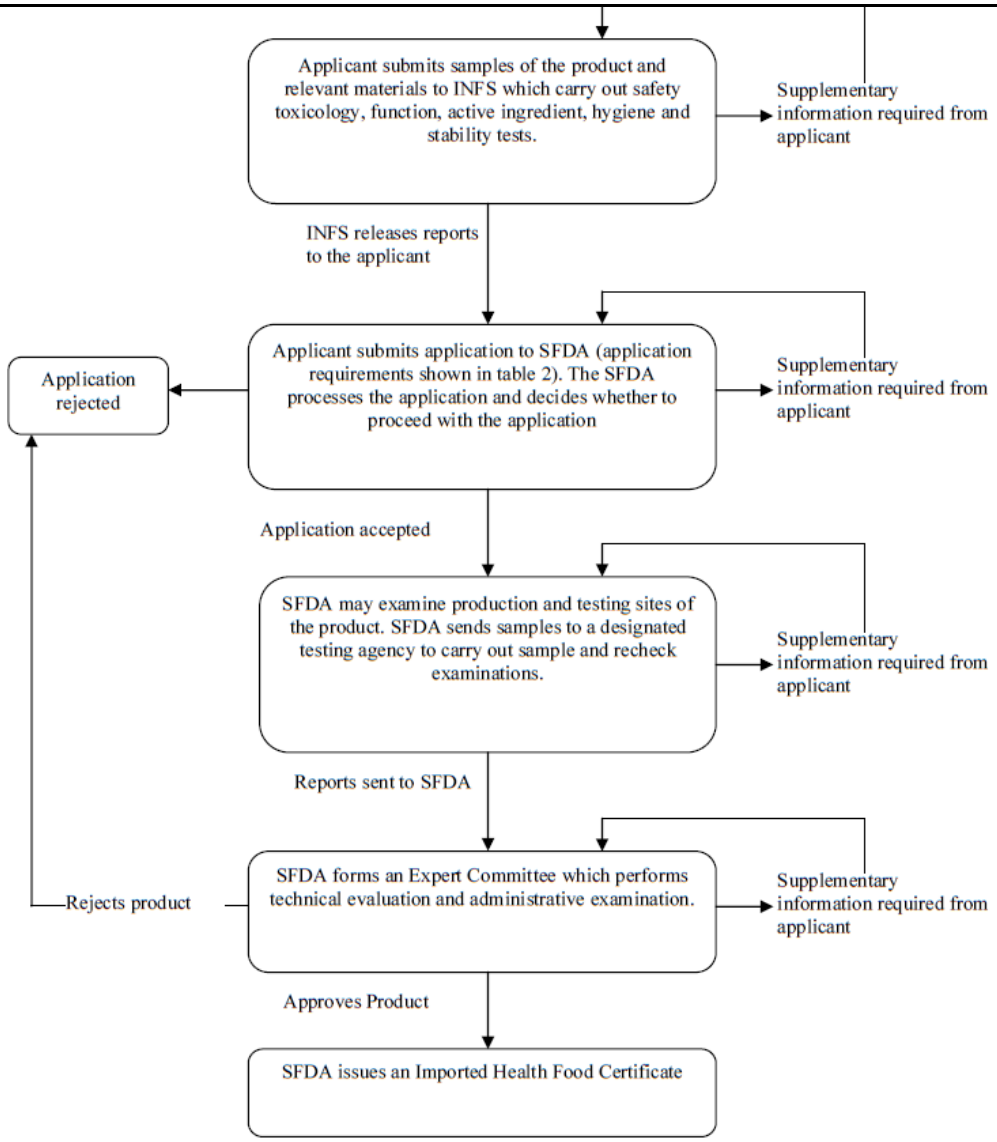



**Figure 8: Registration process of Food for Specified Health Use in Japan**

## VI. NUTRACEUTICALS PRODUCTS IN COVID-19 MANAGEMENT

- **Melatonin: (*N*-acetyl-5-methoxytryptamine)** Melatonin produced when it is dark by the pineal gland. Melatonin's primary function is to maintain the circadian rhythm. Additionally, melatonin controls HGH levels, seasonal depression, ocular health and sleep**..** Melatonin has a high security out-line because of beneficial effects as supportive use in COVID-19 in immune response, anti-oxidation, ant inflammation regulation has been frequently exhibited in respiratory disorder induced by infections and associated complications.(25)

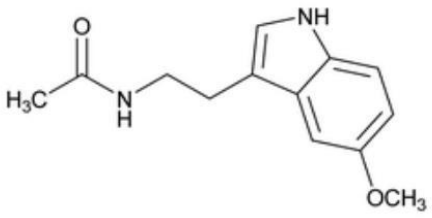



**Figure 9: Molecular Structure of Melatonin**

- **Palmitoylethanolamide (PEA):**PEA is an endogenous fatty acid. It belongs to nuclear factor agonist class. In-vivo and in-vitro studies of PEA gives evidence of binding ability to nuclear receptor by which it shows various types of biological effects like chronic inflammation and pain**.**(26)

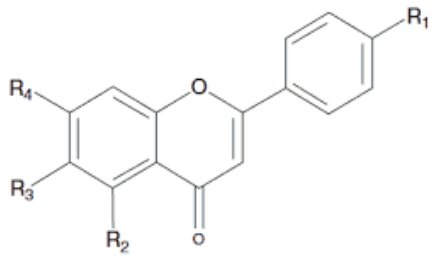
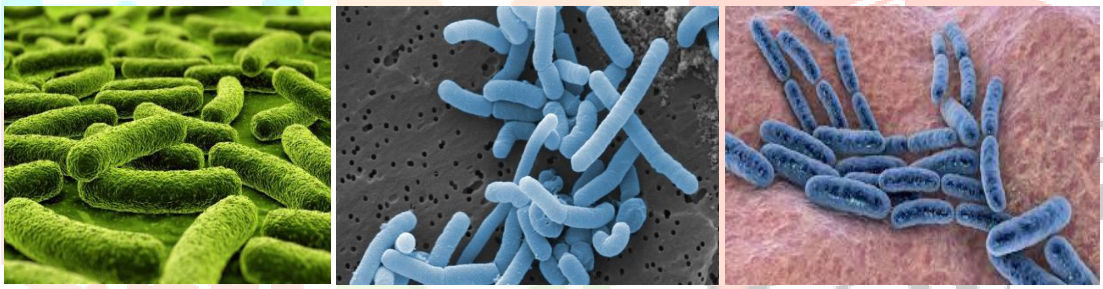



**Figure 10: Molecular Structure of Bee Propolis**

- **Vitamin D:** It is suggested that vitamin D can actively reduce the inflammatory response and have an immunological response to respiratory infections. For controlling the illness during the COVID-19 pandemic, many treatments are being investigated. Consequently, it has been proposed that vitamin D might enhance results in persons with proven COVID-19.(27)

- **Probiotics:** The intake of probiotics is taken for relieve COVID-19 signs and symptoms for boosting and enhancing the immune host response and enhancing gut micro biota**.** The use of probiotics may suggest its potential to work against SARS-CoV-2 or its correlated signs and symptoms via evaluation of anti-viral & anti-inflammatory robotic effects, *invitro, in-vivo* and clinically**.**(28)



**(A) (B) (C)**

**Figure 11: L-containing Probiotics- (A) *L. fermentum*; (B) *L. paracasei; (C) L. casei***

An assessment recommended that enhancement of intestinal micro biota contour by with the adaptation of weight loss program and supplementation, especially with probiotics, enhance the immune system for opposing COVID-19**.** Given important relationship among probiotics, micro biota and COVID-19, various researchers did targeted probiotics without any delay which have high anti-viral impact. Dannelly *et al.*, executed a doubleblind, placebo-controlled trial of an L-containing probiotic compound *L. fermentum*, *L. paracasei* & *L. casei* in affected patients with diseases such as flu. In this study, out of 136 registered subjects, 68 subjects were given a probiotic combination and remaining 68 were kept on placebo every day for 12 weeks. In comparison to the placebo group, the probiotic combination reduced the frequency of cold and flu-like symptoms by 50% to 60%. In the probiotic-treated group, the participants also showed elevated serum and intestinal IgA levels of interferon-gamma (IFN-). Increased IFN- levels can activate macrophages and cause a variety of immune responses, which may be responsible for lessening flu-like symptoms. Overall, this study found no negative effects, indicating that probiotics are secure and successful in treating upper respiratory infections. In another study, six completed scientific trials studied gave outcomes of probiotics on COVID-19 have been stated. A clinical examination of SARS-CoV-2 affected subjects with extreme symptoms, handled with a collective of probiotics inclusive of *Lactobacillus acidophilus* and *Bifidobacterium infantis*, confirmed clinical proof that probiotics may want to moderate immune feature and reduce secondary infections**.**

**Table 1: Nutraceuticals products in COVID-19 management with their Intervention and Phase of Clinical trial**

| Nutraceutical | Study Description | Dose Per Day | Mediation/Intervention | Phase of Clinical Trial |
|---|---|---|---|---|
| **Melatonin** | Used in COVID-19 as a potential supportive | 5 mg/ kg/day | In high doses, when administered intravenously to COVID-19 ICU patients, melatonin might reach at enough blood level, able to inhibit the sepsis and free radical production, leads to reducing mortality as well as hospital stay. | 2 |
| **Palmitoylethanolamide (PEA)** | Efficacy in RTI during COVID-19 | mPEA 300 mg + umPEA 600 mg | Restore tissue homeostasis, can control mast cells as well as microglia uncontrolled activation. | 4 |
| **Bee propolis** | Used to cure COVID-19 | 250 mg/ 10 kg | It blocks pro-inflammatory PAK-I (A kinase highly expressed in COVID-19 patients) | N/A |
| **Quercetin** | Used to cure COVID-19 | 400 mg | It is an antioxidant and having anti-inflammatory as well as immunomodulatory property. | 3 & 4 |
| **Vitamin D** | Trial to cure COVID-19 | 50,000 IU | Vitamin-D has direct effect on proliferation of immune cell and on their activity. | 3 |
| **Probiotics** | Influenza & syncytial virus | 2 strains 10x10^9 UFC | Probiotics help in reducing diarrhea associated with antibiotics and clostridium difficile. | N/A |

## VII. Comparison Of Regulatory Guidelines Of Nutraceuticals In India, USA & Japan

Both consumers, in developed and emerging nations, now view nutraceuticals as essential. Functional components like fatty acids, vitamins, probiotics, amino acids and minerals have also entered this area as a result of changing lifestyles and diseases that are associated to them. These items are intended for human consumption, regulatory bodies worldwide are concentrating on the product quality and safety. Food for Specified Health Use in Japan. With standardized technical requirements for registration of nutraceutical products in this market, it primarily focuses on the similarities and differences of the regulatory plan and structure for nutraceuticals in India, USA and Japan as depicted in table 2.(29,30)

**Table 2: Regulatory guidelines comparison of nutraceuticals products in India, USA and Japan**

| | **INDIA** | **USA** | **JAPAN** |
|---|---|---|---|
| **Regulation for licensing & Registration** | FSSAI | USFDA | MHLW |
| **Definition** | FSSAI give term Nutraceuticals as food for special dietary use | USFDA give term Dietary Supplements under DSHEA | MHLW give term Food for Specified Health Use |
| **Regulatory requirements for registration** | Product assessments, licenses, health information and label claims | Product licensing, proof of safety and effectiveness, labelling, health claims, GMP, reporting of adverse reactions, and clinical trials | Health claim, label claim, clinical trials, efficacy & safety of product, J-GMP and evaluation of product |
| **Stages of Registration Process** | It contains about 7-9 Stages | It contains about 6-8 stages | It contains about 7-8 Stages |
| **Registration Time** | Approx. 67 days | Approx. 60 days | Approx. 18 months |
| **Registration cost** | ₹1000 for license & ₹100 for registration | No fee | $1600 for application & tests |
| **Claims** | Label claims & Health Claims | Label claims & Health Claims | Disease risk claims & function claims |

## VIII. CONCLUSION:

According to statistics of India, about 14-15% of Indian citizens are malnourished or undernutrition. Nutraceuticals play a vital role in suppressing the malnutrition and act as a bond between Indian population and government efforts. Approximately USD 12 billion in GDP is invested in malnourishment. India's nutraceuticals business probably holds at least 3.5% of global market share by 2023. By the end of 2025, market or business of nutraceuticals probably grow from USD 4 billion to USD 18 (estimated). Covid-19 increased India's nutraceutical industry's growth rate from 10% to 22%, which has now stabilized at 16% annually. According to Amit Srivastava, India can continue to expand at a sustainable 20% annual rate till 2030. (Chief Catalyst, Nutrify Today). In 2020, nutraceuticals business is valued approximately at USD

3924.50 m and in 2026, it probably will reach at USD 10198.60 m. There is a need to establish well informative regulatory guidelines for nutraceuticals, dietary supplements or food for specified health use.

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