World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

A REVIEW ON: NEW INSIGHT INTO THE WORLD OF NUTRACEUTICALS

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Article Received on 02/04/2022 **Article Revised on 22/04/2022** **Article Accepted on 12/05/2022**

ABSTRACT

Nutraceuticals have gotten a lot of press because of their presumed safety. This article can be used to stay up to date on the most recent developments in nutraceutical research. Traditional nutraceuticals and cosmeceuticals are pragmatic when it comes to definitions, claims, purposes, and marketing strategies. Their meanings aren't widely agreed upon. Furthermore, different regulatory definitions and registration regulatory processes exist in different parts of the world. Nutraceuticals and cosmeceuticals have a substantial market share and less regulation, compared to traditional medications. For a number of reasons and goals, many manufacturers and researchers use innovative formulation technologies in nutraceutical and cosmeceutical formulations in addition to traditional formulations. To improve market appeal and sales, manufacturers often use new formulas to differentiate their products. Researchers, on the other hand, employ novel strategies to improve the activity and safety of nutraceuticals and cosmeceuticals. The goal of this review is to examine the existing patents and research in nutraceuticals and cosmeceuticals that use innovative formulation methodologies. For the previous 15 years, patents and research papers on nutraceutical and cosmeceutical new formulations were analyzed. Liposomes, polymeric micelles, quantum dots, nanoparticles, and dendrimers are some of the nano systems and advanced biotechnology systems that have been created to increase the therapeutic efficacy, safety, and market appeal of nutraceuticals and cosmeceuticals. This analysis highlights the benefits, drawbacks, myths, regulatory definitions, and market for nutraceuticals and cosmeceuticals technology. This review also seeks to separate fact from fiction in the development, research, and marketing of nutraceuticals and cosmeceuticals.

KEYWORDS: Nutraceuticals, nanoparticles, lipid-based carriers, nanosuspension, novel drug delivery.

INTRODUCTION

"Natural foods and pharmaceuticals play an important part in public healthcare systems all over the world. The search for specific ingredients of plants, animals, minerals, and microbiological origin that are good to our general health has resulted in the coining of terms such functional food and nutraceuticals. The awareness of the link between food and health has led to the development of nutraceuticals".[1]

"Stephen L. Defelice, founder and chairman of the Foundation of Innovation Medicine, invented the term in 1989 as a combination of the words "nutrition" and "pharmaceutical." Nutraceuticals are food-derived products that are claimed to provide additional health advantages over and beyond the fundamental nutritional content of foods. Products may promise to prevent chronic diseases, promote health, slow the ageing process, extend life expectancy, or support the structure or function of the body, depending on the jurisdiction".[2]

"Functional foods that have components, or ingredients, added into them to provide a specific therapeutic or physiological advantage in addition to solely nutritional effects are known as functional foods. Many chronic diseases and maladies, such as cancer, diabetes, heart disease, hypertension, arthritis, and osteoporosis, have been linked to the use of nutraceuticals or functional foods in the prevention and/or treatment. The food business is responding to consumer desires for more healthful, nutrient-rich food products as the necessity of dietary adjustments to maximize health gains attention and acceptability".[1]

"Nutraceuticals provide a wide range of health benefits, and they've been used to cure and prevent diseases like

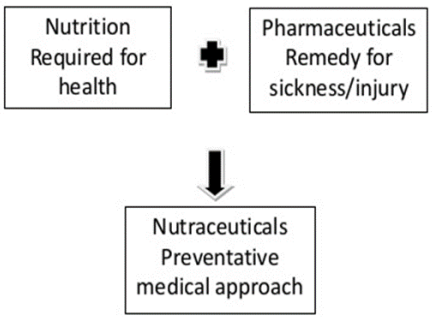
cancer, inflammation, hypertension, cardiovascular disease, atherosclerosis, obesity, diabetes, and others. Silymarin, curcumin, vitamin E, docosahexaenoic acid, choline, and phosphatidylcholine are some of the nutraceuticals used to treat and prevent steatosis. Many nutraceuticals, such as gallic acid, caffeine, curcumin, and others, also work as anti-aging and antioxidant agents. Fish oils high in PUFA1 lower the risk of coronary heart disease and improve cognitive function. Nutraceuticals are well-known for their anticancer properties; as a result, several nutraceutical substances, such as epigallocatechin gallate, curcumin, pomegranate, and others, are used to treat various cancers, including breast cancer, prostate cancer, and other types of cancer".[3]

"The cost of medical care has risen considerably as a result of growing demand for health care. As a result, patients have tried to improve their quality of life by eating more vegetables, fruits, and other plant foods, taking dietary supplements or nutraceuticals, or replacing chemotherapy or radiotherapy with nutritional therapy or phytotherapy. Manufacturers, marketers, and allied licensed professionals have expanded in response to the rising demand for nutraceuticals, phytonutrients, and therapeutic services".[4]

Clinical test findings from animal testing and studies are required in the pharmaceutical development process for verification of therapeutic effects. However, there was no verification procedure for foods in the prevention of diseases in the past. However, as the composition of food has been scientifically established to induce lifestyle-related disorders, it has become a social issue in recent years.[4]

"The health benefits of nutraceutical products include lowering the risk of cancer and heart disease, as well as preventing or treating hypertension, high cholesterol, excessive weight, osteoporosis, diabetes, arthritis, macular degeneration (which leads to irreversible blindness), cataracts, menopausal symptoms, insomnia, diminished memory and concentration, digestive upsets and constipation, and headaches; other products are marketed as cures for cancer and heart disease".[4]

"The concept of Nutraceuticals has started to be acknowledged as one of the measures for preventing diseases".[4]



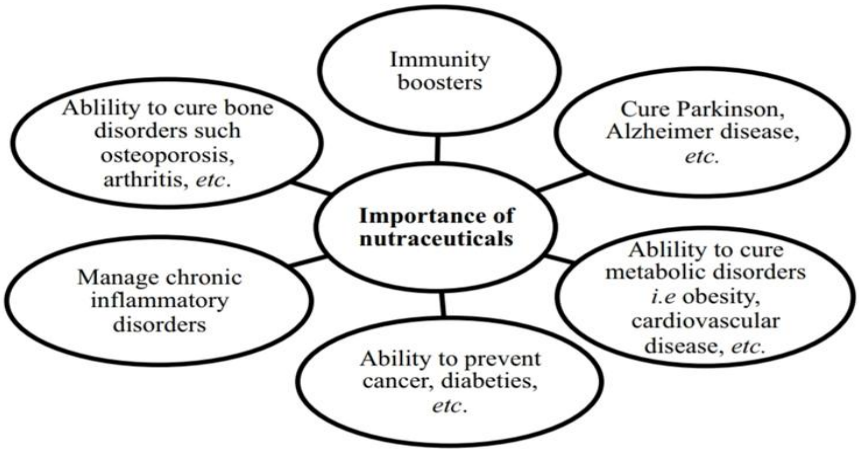
"Fig. 1: Concept of Nutraceuticals".[4]

Need and Objectives of Nutraceuticals

- "A growing percentage of people are concerned about rising healthcare expenditures.
- People who are dissatisfied with pharmaceuticals' ability to promote health are turning to nutraceuticals to help them enhance their health and avoid chronic disease.
- Health-care providers realize that our extensively processed food supply, which is derived from crops farmed with chemical fertilizers, pesticides, herbicides, and frequently genetically engineered seeds, lacks the nutrients required for optimal health.
- People who believe in prevention rather than cure.
- People with chronic diseases for which allopathic therapy has failed to provide a remedy.
- Patients who are financially disadvantaged". [2]
- "Improve overall health, boost energy, relieve anxiety
- Improve mental clarity, enhance sleep quality and quantity
- Prevent chronic diseases, reduce drug cravings
- Delay the aging process, increase life expectancy
- Support and regulate bodily functions" [5]
- "For many of us, getting appropriate nutrients from regular diet is impossible.
- Second, we live in a highly toxic environment, one that is rife with pollution and pesticides, disrupting our bodies' ability to manage it.
- Consider the slew of new diseases that are plaguing us: chronic fatigue, Epstein-Barr, this is a more rational method, rather than relying on antibiotics that have lost their potency, to improve our system or terrain.
- Because medications are not natural to the body, they often have adverse effects, however good quality supplementation that can be absorbed and utilized by the body can genuinely strengthen and provide vitality.
- Many diets are high in phenolics and are ingested on a daily basis by humans.
- They have very little side effects.
- They have a lengthy half-life and are quickly absorbed in the intestine upon intake.
- They are available without a prescription and do not require an appointment with a health care practitioner.

- Many people believe that this method is more natural than taking pharmaceutical medications. Dietary supplements, they believe, will make them feel stronger and healthier, offer them more energy, and help them avoid disease.
- When traditional treatments for their specific conditions fail, some people resort to these products". [4]

Role of Nutraceuticals in Various Diseases



"Fig. 2: Role of Nutraceuticals in various diseases".[6]

"Eating fruits and vegetables reduces the risk of diseases of the esophagus, stomach, lungs, endometrium, oral cavity, pancreas, throat, and colon, according to research." Among the most important phytochemicals are allium compounds, beta carotene, dietary fibers, flavonoids, folic acid, D-limonene, dithiolthiones, indole-3-carbinol, inositol hexaphosphate, isoflavones, isothiocyanates, lutein, lycopene, phytosterols, selenium, saponins, vitamin C, Fast-food intake adds to a high prevalence of lifestyle concerns such as obesity, atherosclerosis, and heart disease because the contemporary human diet is heavy in carbs and saturated fats.".[6]

"Cardiovascular disease (CVD) is a term used to describe a collection of disorders that affect the heart and blood vessels. Low consumption of fruits and vegetables has been linked to an increased risk of cardiovascular disease. A diet rich in vegetables and fruits has been shown in several trials to reduce the risk of cardiovascular disease. Nutraceuticals such as minerals, vitamins, dietary fiber, antioxidants, and omega-3 polyunsaturated fatty acids, as well as physical activity, are advised for the prevention and treatment of CVD. Flavonoids are also beneficial in the prevention of heart disease. By inhibiting angiotensin-converting enzyme and cyclooxygenase enzymes, they diminish platelet aggregation.".[6]

"Alzheimer's disease (AD) is a degenerative neurological disorder and the most common form of dementia. There is no cure for this illness, and it will eventually kill you. Turmeric, curcumin, lutein, lycopene, and carotene are examples of nutraceutical antioxidants that can help prevent disease by reducing oxidative stress."[6]

"Antioxidant qualities in carotenoids can help prevent cancer." Lycopene and other carotenoids play a role in cancer prevention. Lycopene-rich vegetables and fruits reduce oxidative stress and DNA damage, making them anti-cancer. Lycopene is found in tomatoes, pink grapefruit, guava, watermelon, and papaya. Pectin, a soluble fibre found in apples, has been demonstrated to aid in the prevention of prostate cancer by blocking cancer cells from adhering to other cells in the body."[6]

"Obesity is a global health problem that causes a variety of serious medical conditions, including congestive heart failure, hypertension, angina pectoris, hyperlipidemia, osteoarthritis, respiratory difficulties, cancer, and infertility." One of the primary causes of obesity is the consumption of high-fat foods. The potential of nutraceuticals in the treatment of obesity is now being investigated."[6]

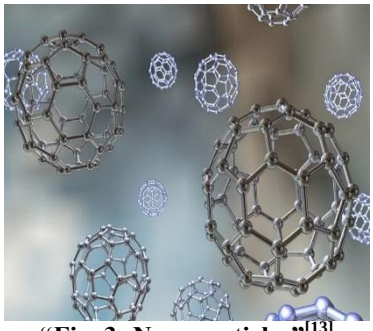
New Insight into the World of Nutraceuticals

"Formulations for nutraceuticals are limited by a number of issues that reduce their efficacy. Low solubility, poor permeability, rapid metabolism, short half-life, and other issues plague many natural active substances".[7] "Curcumin, for example, has a low solubility, poor oral bioavailability, limited tissue distribution, a short half-life, and a fast metabolism".[8] "Additionally, Epigallocatechin Gallate (EGCG) is a bioactive molecule found in green tea that possesses antioxidative and hypolipidemic properties, making it a vasculoprotective agent".[9] "However, due of its rapid breakdown in the gut and low solubility, EGCG's applications are limited".[9] "These kinds of obstacles, which put nutraceuticals' survival in jeopardy, drive scientists and formulators to develop new ways to improve nutraceutical safety and efficacy".[7]

"Drug delivery is the process of effectively and safely introducing an active medicinal ingredient into the body. Due to its complex nature, high price, and time commitment, the introduction of innovative delivery technologies to the nutraceutical industry has been delayed. As a result, traditional forms have been in use for many years, yet, as previously stated, they have numerous flaws".[3]

1. Nanoparticle

"A nanoparticle is a particle with three nanoscale dimensions ranging from one to one hundred nanometers (nm)".[10] "The electrical, mechanical, physical, and chemical properties of the newly produced nanoparticles are radically different". [10] "In the field of drug delivery, nanotechnology has acquired a lot of traction. Nanotechnology has become widely used in the field of nutraceuticals in recent years". [11] "In a water-in-benzyl alcohol emulsion medium, Facchi et al. produced encapsulated curcumin nanoparticles made of N, N-dimethyl chitosan, N, N, N-trimethyl chitosan, and sodium tripolyphosphate. This system overcame the low solubility, high crystallinity and poor oral bioavailability of curcumin. Semyonov et al. increased its bioavailability and solubility by putting genistein into enzymatically produced dextran nanoparticles, Genistein is an isoflavone with anti-inflammatory and antioxidant effects".[3]

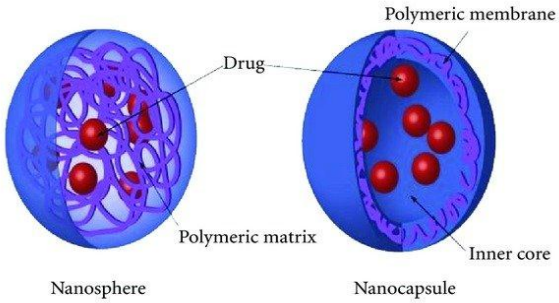


"Fig. 3: Nanoparticles"[13]

"Because NPs are not simple molecules, they are made up of three layers: (a) the surface layer, which can be functionalized with small molecules, metal ions, surfactants, and polymers. (b) The shell layer, which is chemically and physically distinct from the core, and (c) the core, which is the NP's central component and commonly refers to the NP itself (Shin et al., 2016). Due to their unique features, these materials have piqued the curiosity of researchers from various disciplines".[12]

2. Nanospheres and Nanocapsules

"Nanospheres and nanocapsules are both polymeric nanoparticles having a diameter of less than one mm. A polymeric membrane surrounds a vesicular structure in a nanocapsule. Nanocapsules are used to encapsulate the active substance. The active ingredient is disseminated into a dispersed polymeric matrix in nanospheres".[3]

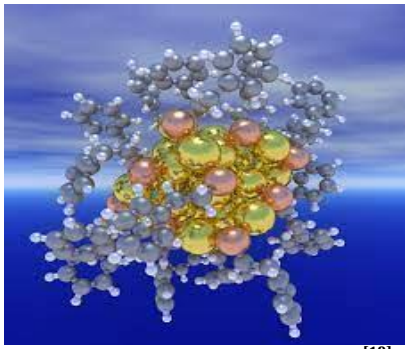


"Fig. 4: Nanosphere and Nanocapsule".[14]

"Hu et al. Made a polymeric nanoparticle using chitosan conjugation. Curcumin was placed into this system to serve as an antioxidant. Hu et al. also used Fourier-Transform Infrared spectroscopy (FTIR) and proton Nuclear Magnetic Resonance (1 H NMR) to analyze this polymeric system. Dynamic Light Scattering was used to determine particle size and the Poly Disperse Index (PDI) (DLS). Finally, using laser doppler microelectrophoresis and Transition Electron Microscopy (TEM), the zeta potential and shape of nanoparticles were assessed".[3]

3.Metal Nanoparticles

"In the nano size range, metals such as silver (Ag), iron (Fe), zinc oxide (ZnO), and titanium oxide (TiO2) are created. Metal nanoparticles provide a number of advantages, including a large surface area, biocompatibility, and catalytic activity". Furthermore, metal nanoparticles are frequently isolable, dispersible, and reusable catalysts,[15] "with greater selectivity. Metal nanoparticles, such as nano-Ag, nano-ZnO, nano-Cu, and nano-TiO2, can be used as metals or metal oxides. Each one has its own set of dimensions, homogeneity, and aggregative qualities. The biological activity and toxicity of the chemical are influenced by these distinct features".[16]



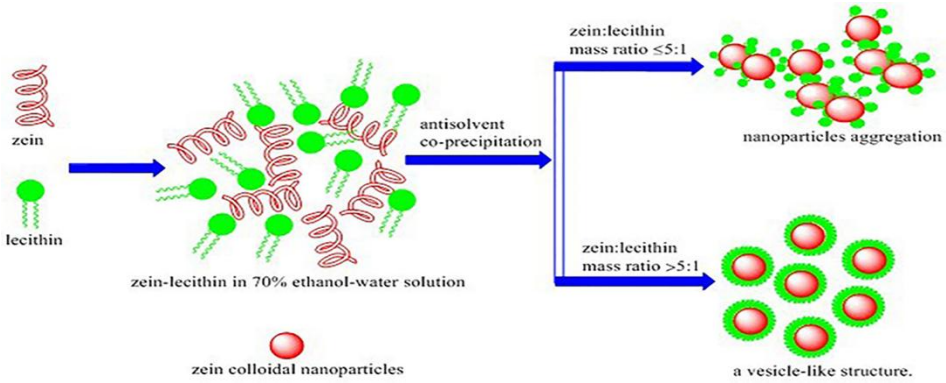
"Fig. 5: Metal Nanoparticles".[18]

"Otunola et al. investigated the biological activity (antimicrobial and antioxidant activity) of silver nanoparticles (AgNPs) in three different herbal species: garlic, ginger, and cayenne pepper. AgNPs were used to encapsulate each active component. For garlic, ginger, and cayenne pepper, these metallic nanoparticles had spherical forms with average diameters of 3-6nm, 3-

22nm, and 3-18 nm, respectively. Ag Nps had more strong antibacterial action against two gramnegative and two grampositive bacterial strains, according to the findings. In addition, antioxidant activity experiments using 1,1diphenyl2picrylhydrazyl (DPPH) and 2,2Azinobis (3ethylbenzthiazoline6sulfonic acid) (ABTS) indicated that AgNps had superior antioxidant activity".[17]

4. Composite Colloidal Nanoparticles

"Composite nanoparticles with an inorganic core (metal or metal oxide) and an organic shell are known as composite nanoparticles (polymerized monomer, organic molecule, chromophore, etc.). In the late 1990s, Vollath conducted the first trial of composite nanoparticle synthesis. Electronic, magnetic, optical, and biological properties of composite nanoparticles have been discovered. Many trials have been conducted to introduce nanocomposites into the nutraceutical business in order to improve nutraceutical efficacy. Jia et al., for example, used zinc oxide nanoparticles and carboxymethyl cellulose to coat pomegranate arils. Pomegranate's anticancer, anti-inflammatory, and antioxidant properties were increased by this approach. Jia and his colleagues used the DPPH radical scavenging technique to assess antioxidant activity".[3]

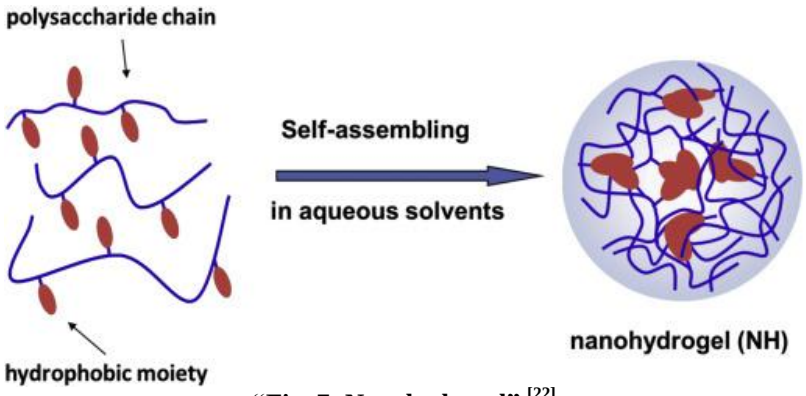


"Fig. 6: Composite colloidal nanoparticles".[20]

"Sun et al. used zein-shellac nanocomposite particles to encapsulate curcumin and control its release. Corn's major storage protein is zein, and shellac is a resin made by the lac beetle. The created zein-shellac nanocomposite performed better in terms of encapsulation, photochemical stability, and thermal stability. Furthermore, the zein to shellac ratio (1:1) was found to be the most efficient against curcumin degradation caused by thermal or UV radiation exposure. In phosphate buffer saline (PBS) and simulated gastrointestinal conditions, Zein shellac nanocomposite was more stable".[19]

5. Nanohydrogel

"Nanohydrogel is a cross-liked polymeric structure that swells in water but does not dissolve in it. It increases the bioavailability and selectivity of nutraceuticals. Nanohydrogel is typically made in two processes. The polymeric system is first created. Second, the biopolymers that are created are cross-linked. Before the synthesis of the hydrogel system, hydrophilic nutraceutical components are combined with the produced biopolymer. Lipophilic nutraceutical components, on the other hand, are encapsulated in lipid droplets like emulsion or nano-emulsion. Nanohydrogel is a three-dimensional material with a huge surface area and hydrophilic nanoscale networks. As a result, this structure regulates the release of the active ingredient while also improving bioavailability and stability".[3]



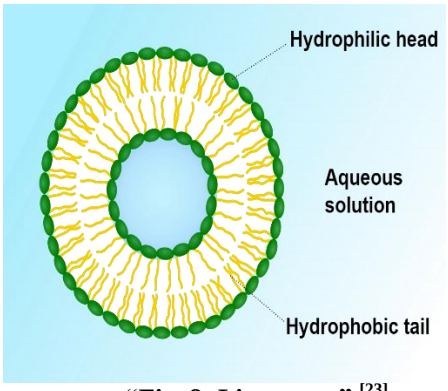
"Fig. 7: Nanohydrogel".[22]

"Bourbon et al. produced a chitosan-coated nanohydrogel containing lactoferrin and glycomacropeptide (GMP). The effect of chitosan on active component delivery was investigated in this study. Curcumin and caffeine, respectively, were employed to represent a lipophilic and hydrophilic model. The DPPH assay was used to assess antioxidant effectiveness. The system improved the lipophilic model Helal et al. bio-accessibilities by 72 %. Furthermore, under simulated stomach and intestinal conditions, coated curcumin maintained 70% of its antioxidant activity. Under the same conditions, however, free curcumin lost 68 percent of its antioxidant activity. Coated caffeine and its free form had bio-accessibility of 63 percent and 59 percent, respectively".[21]

6. Lipid Based Carriers

6.1 Liposomes

"The conventional lipid-based carrier is the liposome. Alec D Bangham prepared it for the first time in 1965. Liposomes are spherical vesicles with an aqueous cavity and a lipid bilayer membrane. The term liposome was coined from two Greek terms: lipid (fat) and soma (soma) (body). Liposomes are categorized according to their size, processing, and lamellarity. First, they were divided into three categories based on their size: small, moderate, and giant. Second, they were divided into two groups based on how they were made: reverse-phase evaporation liposomes and vesicle extruded approach. Finally, based on their lamellarity, liposomes have been classified as mono-lamellar, oligolamellar, or multilamellar vesicles".[3]

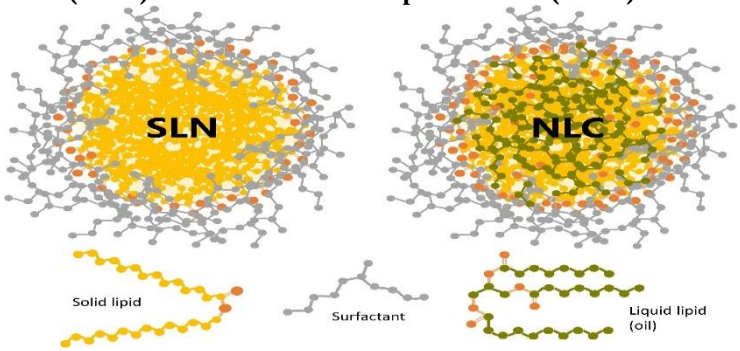


"Fig. 8: Liposomes".[23]

"Liposomes can shield active substances from breakdown by enzymes. They are also adaptable, biocompatible, and non-toxic carriers. By carrying pharmaceuticals with various physicochemical qualities in their core and lipid bilayer, they have the advantage of dual drug delivery. Liposomes improve the solubility, stability, and bioavailability of hydrophobic medicines. Liposomes, on the other hand, have some disadvantages, including a short half-life, poor stability, low loading capacity, and expensive cost. The reticuloendothelial system removes liposomes quickly".[3]

"Natural compounds were loaded into the liposomal system by Gao et al. Furthermore, the method might be made into sustained-release pills, gel powder, lotion, and other dosage forms, according to the patent. Crocin, crocetin, green tea extract, curcumin, resveratrol, panax ginseng extract, -lipoic acid, and/or L-carnitine were among the natural constituents. The developed composition was utilized to treat cancer and improve overall health. Underwood et al. created nanoparticles of entire fruits (black chokeberries, cherries, plums, blueberries, pomegranates, raspberries, cranberries, and/or black elderberries) and encapsulated them in emulsion and/or liposomes, according to another patent. It was stated that the created formulation could help with arthritic pain, diabetes, gout, and other ailments".[3]

6.2 Solid Lipid Nanoparticles (SLNs) and Nanostructure Lipid Carriers (NLCs)



"Fig. 9: Solid Lipid Nanoparticles (SLNs) & Nanostructure Lipid Carriers (NLCs)".[24]

6.2.1 Solid Lipid Nanoparticles (SLNs)

"Solid Lipid Nanoparticles (SLNs) are spherical lipid nanoparticles with a nanoscale size range (around 40 to 1000 nm). Surfactant (0.1 to 30% by weight) and solid fat make up SLNs (0.5 to 5 %). At body and ambient temperatures, they are solid. Furthermore, the type of lipid and surfactant affects particle size, stability, and drug loading. Both hydrophilic and lipophilic medicines

benefit greatly from SLNs. However, the drug loading capacity is determined by the lipophilicity of the drug. In addition, system instability during storage and a high-water content have been mentioned as drawbacks".[3]

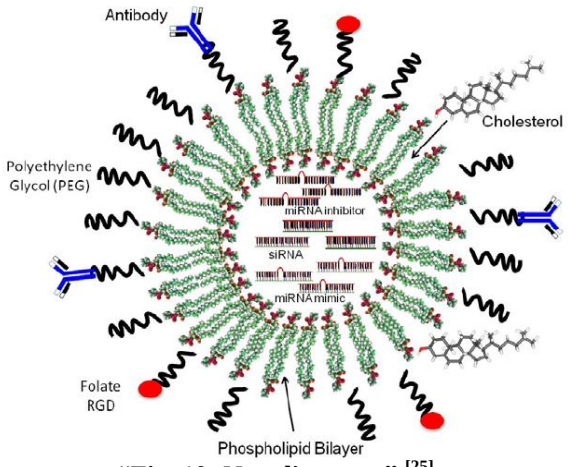
"α-Lipoic acid is a naturally occurring antioxidant that is used in anti-aging topicals. When compared to other antiaging medicines, it has a mild irritant effect. -lipoic acid is also useful for treating fragile areas (area around the eye). Chemical breakdown of -lipoic acid results in a foul odor in topical applications. By adding -lipoic acid into SLNs, Souto et al. were able to alleviate this problem. Furthermore, loaded-lipoic acid has a greater occlusive impact. As a result, the method improved skin hydration while also providing UV protection".[3]

6.2.2 Nanostructure Lipid Carriers (NLCs)

"NLCs (Nanostructure Lipid Carriers) are a variant of SLNs. The key difference is that NLCs' lipids are a combination of solid and liquid oils. As a result, NLCs improve medication loading and stability. NLCs were developed in 1999 to address the shortcomings of SLNs, such as poor drug loading capacity and instability (drug expulsion)".[3]

"Resveratrol is an anticancer substance found in nature. Resveratrol, on the other hand, has photosensitivity, low solubility, and low oral bioavailability. To encapsulate resveratrol, Neves et al. used SLNs and NLCs. Both technologies improved trans-resveratrol photodegradation protection. NLCs also succeeded in improving resveratrol encapsulation. NLCs also prevented fast crystallization and release in the GI tract. Both approaches clearly increased the oral bioavailability of resveratrol for cancer treatment".[3]

6.3 Nanoliposome

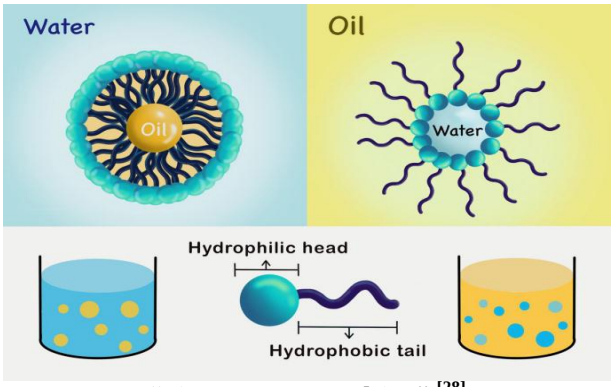


"Fig. 10: Nanoliposome".[25]

"Nanoliposomes are extremely small lipid vesicles. Increased surface area is achieved by shrinking the liposomal system. As a result, nanoliposome bioavailability is improved. Nanoliposomes are so are commonly utilized in the nutraceuticals business to improve product safety and efficacy. EGCG, for example, is unstable in water and physiological fluid. As a result, de Pace et al. injected EGCG into mice. To solve this problem, researchers developed nanoliposomes, which are made up of phosphatidylcholine and cholesterol. Nanoliposomes were also coated with chitosan to improve absorption".[3]

6.4 Nanoemulsion

"In 1950, the first nanoemulsion was developed. It is a stable, single-phase system. A nanoemulsion is an emulsion with nanoscale droplets (20-600 nm). Oil, water, surfactant, and cosurfactant are the most common components. There are three types of nanoemulsions: water in oil, oil in water, and bi-continuous nanoemulsions. Because of their small droplet size, nanoemulsions are usually translucent dispersions that do not flocculate. Because of their strong solubilization capability, they are ideal for delivering hydrophobic medicines. Nanoemulsions are useful in medication delivery because they increase drug loading capacity, stability, and bioavailability. Nanoemulsions can provide regulated or sustained release".[3]



"Fig. 11: Nanoemulsion".[28]

"Because it is the precursor of vitamin A, -carotene plays a significant function in improving vision and curing vitamin A deficiency".[26] "Because of its poor solubility, -carotene is a hydrophobic nutraceutical that requires a new delivery mechanism. Luo et al. used high-pressure, dual-channel microfluidization to encapsulate -carotene into oilin-water nanoemulsions. Furthermore, employing quillaja saponins and whey protein isolate as emulsifiers improved its water dispersibility and stability. The particle size, zeta potential, and PDI were measured using a static light scattering technique by Luo and the rest of the team. Optical and confocal fluorescence microscopy were also used to examine the microstructure of the nanoemulsion".[27]

7. Biopolymer Nanoparticles

"Biopolymers are natural-source polymers such as proteins, polysaccharides, and nucleic acids. Furthermore, they have been divided into inclusions, hydrogels, and polyelectrolyte complexes depending on their structure. Their particle size is thought to be a crucial component that influences physicochemical properties, encapsulation, GIT stability, and active

ingredient absorption. Biopolymer nanoparticles are biodegradable, non-toxic, and biocompatible, making them ideal for clinical use. Proteins are also extremely stable and have a high binding capability. As a result, protein-based nanoparticles offer a promising paradigm for medication delivery. Casein, collagen, zein, elastin, silk fibroin, and a variety of other proteins have been used to make nanoparticles".[3]

"Patel et al. created zein-quercetin colloidal composite nanoparticles to address many of the issues associated with quercetin, including poor water solubility, low bioavailability, and substantial intestinal degradation. Quercetin is a flavone found in nature that has anticancer, antiviral, and antioxidant properties. This research found that this approach increased quercetin's molecular stability against pH degradation and UV irradiation while also providing significant antioxidant activity. To increase their physical and chemical properties, as well as their safety and efficacy, biopolymer nanoparticles can be conjugated or cross linked".[3]

8. Conjugated Biopolymer Nanoparticles

"In their natural state, biopolymers can be used. To increase their qualities, however, physical, chemical, or enzymatic alterations are made. Proteins covalently bound to polysaccharides, for example, had higher solubility and emulsifying capabilities. Conjugation can be either reversible (physical) or irreversible (psychological) (chemical). The chemical conjugation has stronger and more permanent interaction. Coating protein nanoparticles with conjugated polysaccharides improves their stability".[3]

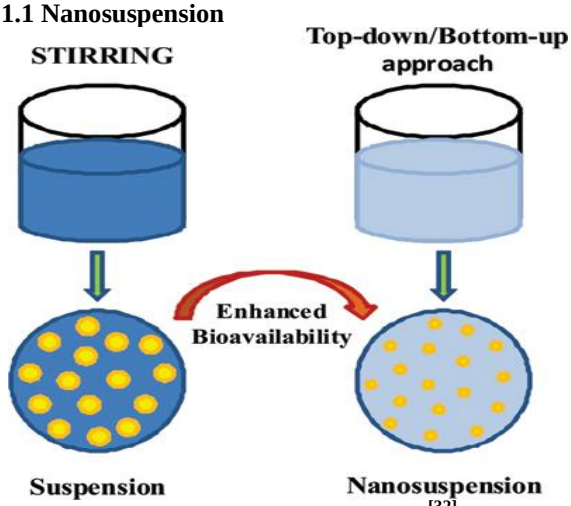
"Davidov-Pardo et al. encapsulated resveratrol in protein (zein) nanoparticles and coated them with conjugated polysaccharides via the Maillard reaction. The o-Phthaldialdehyde (OPA) assay was used to determine the efficiency of conjugation by evaluating the decrease in free amino groups. Resveratrol's poor water solubility, oral bioavailability, and chemical instability were reduced as a result. Casein was also adsorbed to hydrophobic particles. Dextran also inhibited aggregation through steric repulsion. As a consequence, coating with caseinate-dextran prevented particle aggregation".[3]

8.1 Cross-linked Biopolymer Nanoparticles

"Cross-linking is the process of covalent or noncovalently joining polymer chains together to generate three-dimensional structures. Biopolymers are cross-linked to improve mechanical characteristics and water stability. Hu et al. encapsulated EGCG, a chemo preventive drug, in chitosan (CS) and caseinophosphopeptides cross-linked nanoparticles (CPPs). The addition of CPPs to CS increased EGCG oral bioavailability while lowering CS cytotoxicity. Furthermore, crosslinking improved the biocompatibility of nanoparticles".[3]

"The polysaccharide glucomannan induces fibroblast proliferation, which helps wound healing. As a result, Heber et al. developed chitosan and glucomannan cross-linked nanoparticles to aid wound healing and skin regeneration. Heber et al. used Fluorescence Lifetime Image Microscopy to assess the efficiency of nanoparticles in treating skin irritation (FLIM). In addition, rabbits were used in an in-vivo investigation to evaluate key parameters. The reduction in cutaneous irritation was first seen in injected rabbits. Second, collagen growth and intradermal distension within the dermis were evaluated".[3]

8.1.1 Nanosuspension



"Fig. 12: Nanosuspension".[32]

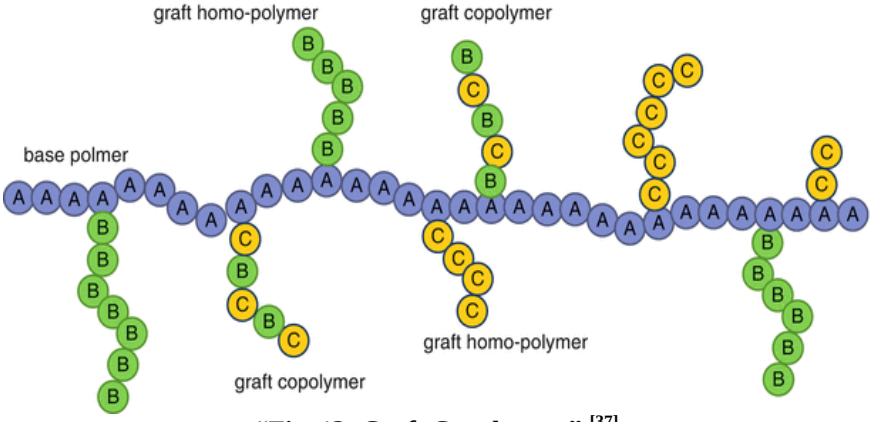
"Nanosuspension is a unique technique for addressing medication solubility issues".[29] "A nanosuspension is made up of nanosized particles stabilized by surfactants".[30] "Surfactant molecules surround the nanosized center in this dispersion. Nanosuspension also improves drug stability and provides maximum drug loading". [31] "Oral bioavailability improves with increasing solubility".[29] "Nanosuspension also has the capability of encapsulating insoluble substances. As a result, numerous formulators in the nutraceutical business have attempted to utilize nanosuspension as a delivery mechanism".[3]

"Curcumin possesses anti-cancer and anti-properties. Alzheimer's Curcumin's pharmacological potential has been limited due to its low solubility and poor oral bioavailability. Shin et al. used ultrasonic homogenization to create nanosuspension of curcumin and -Tocopherol Polyethylene Glycol 1000 Succinate (TPGS). Curcumin water solubility and dissolution rate were improved by the nanosuspension. DLS was used to determine the particle size, PDI, and zeta-potential of a nanocomplex system. The morphology and size of nanoparticles were also evaluated using a field emission scanning electron microscope (FE-SEM) and a transmission electron microscope (TEM). Fourier-Transform Infrared Spectroscopy (FTIR) analysis, thermogravimetric analysis, differential scanning

calorimetry (DSC) analysis, and X-ray diffraction analysis were all carried out".[3]

8.1.2 Graft Copolymers

"Graft copolymers are polymers made up of two or more monomers. The main chain (backbone) is one monomer that is chemically linked to side chains (branches). The branches may be arranged randomly or evenly throughout the backbone, depending on the synthetic procedures". [33] "Grafting is commonly used to change the properties of polymers such wettability, biocompatibility, and mechanical qualities. Grafting can be done using many procedures, such as chemical grafting, live polymerization, photochemical grafting, enzymatic grafting, plasma radiation and radiation grafting".[34]



"Fig. 13: Graft Copolymers".[37]

"Gallic acid is a naturally occurring triphenolic molecule with potent antioxidant and apoptotic properties. As a result, Wu et al. used a free radical graft reaction to create a chitosan gallates copolymer. Gallic acid was added to the manufactured system as an antioxidant. The DPPH assay was used to test the copolymer's antioxidant properties. As a result of the increased substitution degree and decreased molecular weight, the grafted copolymer demonstrated increased antioxidant activity".[3]

"Furthermore, protocatechuic acid is an antioxidant-active natural phenolic molecule. Traditional Chinese medications contained protocatechuic acid. To increase the antioxidant activity of chitosan, Liu et al. used a cross-linking procedure to graft protocatechuic acid onto it. The grafted system's antioxidant activity was measured using the DPPH and reducing power assays. Folin–Ciocalteu test was used to determine the grafting ratio. SEM was used to examine the morphology and size of nanoparticles".[3]

8.1.3 Nutraceutical Toxicity

"The erroneous belief that nutraceuticals are safe because they are either foods or food derivatives is driving growing global usage of nutraceuticals. However, negative effects and toxicity have been recorded repeatedly, not only as a result of ingesting the nutraceutical but also as a result of contamination. Pesticides, other poisonous plants, metals, fertilizers, or even deliberate adulteration with chemical medications could contaminate nutraceuticals".[35] "Furthermore, due to the complex structure of herbal products and the inclusion of several phytochemicals, many studies have reported the occurrence of drug-herb interactions following co-administration. Such an interaction could lead to excessive drug exposure, increasing the risk of toxicity and severe side effects. It may also cause inhibition of the drug efficacy and lower therapeutic outcomes".[36]

"Ginkgo biloba preparations are high in flavonoids and are often used to enhance peripheral circulation in elderly people. Ginkgo biloba is also used to treat dementia, Alzheimer's disease, schizophrenia, and cerebral insufficiency. However, it has been noted that long-term exposure to large doses of Ginkgo biloba extracts is linked to spontaneous bleeding. Ginkgo biloba has also been shown to be carcinogenic in numerous animal experiments".[3]

"Green tea extracts also include catechins, which are anticancer compounds. Green tea extracts are also used to treat obesity and metabolic problems, although excessive consumption can cause nephrotoxicity, hepatotoxicity, and reproductive toxicity. Furthermore, caffeine consumption has been linked to anxiety, tachycardia, osteoporosis, and reproductive problems, particularly in young adults. Many other regularly used herbal items, such as cinnamon, aloe vera, and St. John's wort, have been linked to cancer, hepatotoxicity, genotoxicity, and mutagenicity, among other things".[3]

8.1.4 Nutraceuticals – Drug Interaction

"Interfering with the drug's metabolic route or altering drug transporters could be the nature of the interaction. It is difficult to estimate the incidence of nutraceutical-drug interactions due to the complex nature of nutraceuticals and the lack of pharmacokinetic, pharmacodynamics, and safety investigations. Some of the described interactions may be dangerous and even fatal. Aspirin and some non-steroidal anti-inflammatory medicines, for

example, can interact with herbal remedies that contain ginkgo, turmeric, ginger, ginseng, chamomile, and garlic. As a result of the suppression of platelet aggregation ability, these identified interactions raised the risk of bleeding.

In the liver and small intestine, the cytochrome P450 (CYP) enzymes are one of the most often expressed metabolic enzymes. They also play a role in the metabolism of a variety of medicinal medicines. The herbal extract of Saint John's Wort is one of the most commonly reported nutraceuticals that activates a wide range of CYP, including CYP1A2, CYP2C9, CYP2C19, CYP3A4, and CYP2E1. The induction of these enzymes has the effect of speeding up the metabolism of the medicines eaten. As a result, the medicine is swiftly removed from the body and loses its effectiveness. Treatment failure of antidepressant medicines and loss of oral contraceptive function were also described as side effects of Saint John's Wort.

Another important transporter in drug absorption and disposition is the Organic Anion Transporting Polypeptide receptor (OATP). To discover the interaction between various nutraceuticals and pharmaceutical medications, Iijima et al. conducted a study on 98 medical herbs regularly used in Japan. The function of the intestinal organic anion transporting polypeptide 2B1 (OATP2B1) receptor was shown to be inhibited by less than 20% in 12 herbal species. In addition, seven herbal species increased the receptor's activation by more than 150 percent. As a result, using these herbal products together reduces the absorption and bioavailability of substrate drugs including bosentan, benzyl penicillin, aliskiren, fexofenadine, glibenclamide, unaprostone, statins, and other prescription drugs".[3]

8.1.5 Nutraceuticals Advanced Delivery Systems Toxicity

"Nutraceuticals have just begun to be incorporated into nano delivery systems. These sophisticated delivery systems are utilised to improve nutraceutical absorption and bioavailability, provide a targeted and controlled release profile, and improve the stability of phytochemicals that are easily degraded. Because of their distinct, varied chemical and physical properties after nanonization, nano-sized nutraceuticals boost the efficacy of nutraceuticals. The same favourable physicochemical features of nanoparticles, on the other hand, are the primary cause of human toxicity.

The nano delivery system's safety is debatable. Furthermore, there is a scarcity of knowledge and studies on nanosystem absorption, metabolism, distribution, excretion, and toxicity. Understanding the molecular interactions of nanoparticles with biological systems is critical for predicting their mechanism of action and safety. Respiratory illnesses, cardiovascular ailments, carcinogenicity, and lower life expectancy are all major side effects of nano particles. The majority of these negative effects are believed to be caused by oxidative stress and inflammation caused by nano particles at the molecular level".[38]

"The European Food Safety Authority (EFSA) has proposed a method for determining the toxicity of nanotechnology-based food items and food derivatives. A set of physicochemical parameters to be examined for nanoparticles was recommended in the guidelines titled "Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain." The EFSA's list of parameters included the following:

- Nanoparticles' chemical properties
- Nanoparticle particle size
- Nanoparticle physical properties.
- The nanoparticle morphology
- Mass and particle concentration
- Nanoparticles' particular surface area.
- The chemistry of nanoparticle surfaces.
- The charge on the surface of nanoparticles.
- A nanoparticle's redox potential.
- Solubility and partition characteristics
- Dustiness, viscosity, density, and pour density are all factors to consider.
- Nanoparticles' chemical reactivity.
- Nanoparticles' photocatalytic activity".[3]

CONCLUSION

Nutraceutical use is quickly increasing over the world, owing to their stated safety and efficacy. The use of sophisticated nanosized drug delivery systems as a platform for nutraceutical formulation has recently gained traction. The encouraging results gained in terms of bioavailability, safety, targeting, and stability of the nutraceuticals examined have affected this. Nanoparticles, liposomes, phytosomes, nanoemulsions, nanosuspension and other drug delivery methods were used as a result.

Nutraceutical formulation, on the other hand, poses numerous hurdles in terms of efficacy, safety, and regulatory compliance. Concerned institutions were unable to come up with a universal definition. Regulatory agencies to govern and regulate nutraceuticals have yet to be established worldwide. This article presents a literature overview of the most recent state-of-the-art technology in nutraceuticals formulation, as well as a discussion of the potential obstacles and various approaches to address them.

REFERENCES

1. N. Faisal, K. Sujit Varma, "Nutraceuticals and its impact on health care", B. Pharm Projects and Review Article, 2006; 1: 299-331. http://farmacists.blogspot.com/2009/05/nutraceuticals-and-its-impact-on-health.html.

2. Shilpa P. Chaudhari, Priyatama V. Powar and Mahesh N. Pratapwar, "NUTRACEUTICALS: A REVIEW", 2017; 6(8): 681-739.
3. Nada A. Helal, Heba A. Eassa, Ahmed M. Amer, Mohamed A. Eltokhy, Ivan Edafiogho and Mohamed I. Nounou, "Nutraceuticals' Novel Formulations: The Good, the Bad, the Unknown and Patents Involved", BENTHAM SCIENCE, Recent Patents on Drug Delivery & Formulation, 2019; 13:105-156.
4. S. Lakshmana Prabu1, T.N.K. SuriyaPrakash, C. Dinesh Kumar, S. Suresh Kumar and T. Ragavendran, "NUTRACEUTICALS: A REVIEW", Elixir Pharmacy, 2012; 46: 8372-8377.
5. The Powerful benefits of nutraceuticals On your overall health, jan 22, 2020. https://jbkwellnesslabs.com/blog/the-powerful-benefits-of-nutraceuticals-on-your-overall-health/
6. Vedant Sachdeva, Arpita Roy and Navneeta Bharadvaja, "Current Prospects of Nutraceuticals: A Review", BENTHAM SCIENCE, Current Pharmaceutical Biotechnology, 2020; 21: 884-896.
7. Zaki NM. Progress and problems in nutraceuticals delivery. J. Bioeq Bioavail, 2014; 6(3): 75.
8. Rakotoarisoa M, Angelova A. Amphiphilic nanocarrier systems for curcumin delivery in neurodegenerative disorders. Medicines (Basel), 2018; 5(4): E126.
9. Hong Z, Xu Y, Yin JF, Jin J, Jiang Y, Du Q. Improving the effectiveness of (-)-epigallocatechin gallate (EGCG) against rabbit atherosclerosis by EGCG-loaded nanoparticles prepared from chitosan and polyaspartic acid. J Agric Food Chem, 2014; 62(52): 12603-9.
10. Jeevanandam J, Barhoum A, Chan YS, Dufresne A, Danquah MK. Review on nanoparticles and nanostructured materials: History, sources, toxicity and regulations. Beilstein J Nanotechnol, 2018; 9: 1050-74.
11. Hadian Z. A Review of nanoliposomal delivery system for stabilization of bioactive omega-3 fatty acids. Elect Physician, 2016; 8(1): 1776-85.
12. Ibrahim Khan, Khalid Saeedb, Idrees Khanc, Nanoparticles: Properties, Applications and Toxicities, Arabian Journal of Chemistry, 2017; 1-8. doi: http://dx.doi.org/10.1016/j.arabjc.2017.05.011
13. Benedette Cuffari, How Safe are Nanoparticles for Our Environment?, 2017. https://www.azonano.com/article.aspx?ArticleID=4620
14. John B. Christoforidis, Susie Chang, Angela Jiang,2Jillian Wang, and Colleen M. Cebulla, Intravitreal Devices for the Treatment of Vitreous Inflammation, Hindawi Publishing Corporation, Mediators of Inflammation, 2012; 1-8.
15. Zahmakıran M, Özkar S. Metal nanoparticles in liquid phase catalysis: From recent advances to future goals. Nanoscale 2011; 3(9): 3462-81.
16. Bouwmeester H, Dekkers S, Noordam MY, et al. Review of health safety aspects of nanotechnologies in food production. Regul Toxicol Pharmacol 2009; 53(1): 52-62.
17. Otunola GA, Afolayan AJ, Ajayi EO, Odeyemi SW. Characterization, antibacterial and antioxidant properties of silver nanoparticles synthesized from aqueous extracts of Allium sativum, Zingiber officinale, and Capsicum frutescens. Pharmacogn Mag, 2017; 13(Suppl 2): S201.
18. Michael G. Taylor et al, How do you build a metal nanoparticle?, 10 July 2017.
19. https://phys.org/news/2017-07-metal-nanoparticle. htmlSun C, Xu C, Mao L, Wang D, Yang J, Gao Y. Preparation, characterization and stability of curcumin-loaded zein-shellac composite colloidal particles. Food Chem, 2017; 228: 656-67.
20. Lei Dai, Cuixia Sun, Di Wang, Yanxiang Gao, The Interaction between Zein and Lecithin in Ethanol-Water Solution and Characterization of Zein–Lecithin Composite Colloidal Nanoparticles, PLOS ONE, 2016: 1-20.
21. Bourbon AI, Pinheiro AC, Cerqueira MA, Vicente AA. In vitro digestion of lactoferrin-glycomacropeptide nanohydrogels incorporating bioactive compounds: Effect of a chitosan coating. Food Hydrocolloids, 2018; 84: 267-75.
22. Franco Alhaique, Pietro Matricardi, Chiara Di Meo, Tommasina Coviello, Elita Montanari, Polysaccharide-based self-assembling nanohydrogels: An overview on 25-years research on pullulan, Journal of Drug Delivery Science and Technology, Vol. 30, Part B, 2015; 300-309. https://en.wikipedia.org/wiki/Liposome.
23. Sebastián Scioli Montoto, Giuliana Muraca, María Esperanza Ruiz, Solid Lipid Nanoparticles for Drug Delivery: Pharmacological and Biopharmaceutical Aspects, frontiers in molecular bioscience, Oct 2020; 4. https://doi.org/10.3389/fmolb.2020.587997.
24. Monica Rivera, Pablo E Vivas-Mejia, Nanoparticles as Drug Delivery Systems in Cancer Medicine: Emphasis on RNAi-Containing Nanoliposomes, Pharmaceuticals, 6(11); 2013: 1361-1380.
25. Yi J, Fan Y, Yokoyama W, Zhang Y, Zhao L. Thermal degradation and Iisomerization of beta-carotene in oil-in-water nanoemulsions supplemented with natural antioxidants. J Agric Food Chem, 2016; 64(9): 1970-6.
26. Luo X, Zhou Y, Bai L, Liu F, Deng Y, McClements DJ. Fabrication of beta-carotene nanoemulsion-based delivery systems using dual-channel microfluidization: Physical and chemical stability. J Colloid Interface Sci., 2017; 490: 328-35.
27. Tolulope Joshua Ashaolu, Nanoemulsions for health, food, and cosmetics: a review, Environmental Chemistry Letters, 2021; 19: 3381–3395.
28. Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. J Adv Pharm Technol Res., 2011; 2(2): 81-7.
29. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov, 2004; 3(9): 785-96.

30. Wang Y, Zheng Y, Zhang L, Wang Q, Zhang D. Stability of nanosuspensions in drug delivery. J Control Release, 2013; 172(3): 1126-41.
31. Surya Goel, Vijay Agarwal, Monika Sachdeva, Development and Characterization of Oral Nanosuspension Using Esomeprazole Magnesium Trihydrate, 2020; 10(6): 909 – 917. http://dx.doi.org/10.2174/2210681209666191111113850
32. Rempp PF, Lutz PJ. 12 - Synthesis of graft copolymers. In: Allen G., Bevington J.C., editors. Comprehensive Polymer Science and Supplements. Amsterdam: Pergamon, 1989; 403-421.
33. Pillay V, Seedat A, Choonara YE, du Toit LC, Kumar P, Ndesendo VMK. A review of polymeric refabrication techniques to modify polymer properties for biomedical and drug delivery applications, AAPS Pharm Sci Tech, 2013; 14(2): 692-711.
34. Gil F, Hernández AF, Martín-Domingo MC. Toxic contamination of nutraceuticals and food ingredients. In: Gupta R.C., editor. Nutraceuticals: Academic Press, 2016; 825-837.
35. Yu J, Zhou Z, Tay-Sontheimer J, Levy RH, Ragueneau-Majlessi I. Intestinal drug interactions mediated by oatps: A systematic review of preclinical and clinical findings. J Pharm Sci., 2017; 106(9): 2312-25.
36. Tauqir A. Sherazi, Graft Polymerization, 31 August 2016. https://doi.org/10.1007/978-3-662-44324-8_274
37. Jain A, Ranjan S, Dasgupta N, Ramalingam C. Nanomaterials in food and agriculture: An overview on their safety concerns and regulatory issues. Crit Rev Food Sci Nutr, 2018; 58(2): 297-317.