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REVIEW ARTICLE

Nutraceuticals' Novel Formulations: The Good, the Bad, the Unknown and Patents Involved

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Abstract: Traditional nutraceuticals and cosmeceuticals hold pragmatic nature with respect to their definitions, claims, purposes and marketing strategies. Their definitions are not well established worldwide. They also have different regulatory definitions and registration regulatory processes in different parts of the world. Global prevalence of nutraceuticals and cosmeceuticals is noticeably high with large market share with minimal regulation compared to traditional drugs. The global market is flooded with nutraceuticals and cosmeceuticals claiming to be of natural origin and sold with a therapeutic claim by major online retail stores such as Amazon and eBay. Apart from the traditional formulations, many manufacturers and researchers use novel formulation technologies in nutraceutical and cosmeceutical formulations for different reasons and objectives. Manufacturers tend to differentiate their products with novel formulations to increase market appeal and sales. On the other hand, researchers use novel strategies to enhance nutraceuticals and cosmeceuticals activity and safety.

The objective of this review is to assess the current patents and research adopting novel formulation strategies in nutraceuticals and cosmeceuticals. Patents and research papers investigating nutraceutical and cosmeceutical novel formulations were surveyed for the past 15 years. Various nanosystems and advanced biotechnology systems have been introduced to improve the therapeutic efficacy, safety and market appeal of nutraceuticals and cosmeceuticals, including liposomes, polymeric micelles, quantum dots, nanoparticles, and dendrimers. This review provides an overview of nutraceuticals and cosmeceuticals current technologies, highlighting their pros, cons, misconceptions, regulatory definitions and market. This review also aims in separating the science from fiction in the nutraceuticals and cosmeceuticals development, research and marketing.

Keywords: Nutraceuticals, adulteration, counterfeiting, novel drug delivery, nanocarriers, fortified foods, toxicity, regulatory affairs.

1. INTRODUCTION

The famous Hippocrates' quote (400 BC), "Let food be thy medicine and medicine be thy food", represents that there has been a great interest in herbal products since decades [1]. There were many historical civilizations, such as ancient Egyptian, Greek, Roman and others that used herbal products and plants in treating and preventing diseases [2]. The oldest written document that included different 12 recipes of herbal medications was discovered on Sumerian clay tablet in Nagpur (around 5000 years ago) [3]. Dioscorides, the father of pharmacognosy, wrote "De Materia Medica" book in 77 AD, which included 657 plant originated medicines [3]. Hence, herbal products have been an interesting area along the human history.

There were many plants that were famous for their healing properties over the last millennia. For instance, ginseng had been used in China for treating and preventing different health problems [4]. Moreover, ancient Egyptians used many plants, including garlic, turmeric, thyme, cumin, juniper and others in medicine [3]. Cinnamon represented a great value

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in both Roman and antient Egyptian civilizations [2]. The Indian culture also used natural products in treating and preventing several diseases, such as Ayurveda [5]. Finally, honey was considered as one of the most well-known remedies in many ancient civilizations and was mentioned in religious books, such as the Holy Quran and Bible [2]. These findings have triggered a series of studies in nutraceuticals field [2].

There is a controversy over a specific definition and set of regulations to define the nutraceutical compounds [6]. The definition of nutraceuticals may not be well established worldwide [7]. However, nutraceutical compounds are health enhancing products that improve mental and physical activities of the body. They are commercialized to minimize the risk factors of various diseases [8]. Nutraceutical products are simply a hybrid between drug and food [9]. On the other hand, this terminology is a broader term that includes minerals, vitamins, amino-acids, botanicals or herbs [10]. Therefore, both dietary supplements and fortified foods can be classified as nutraceuticals [11]. The terminology of nutraceutical was defined by the foundation for innovation in medicine in (New York, USA) in 1989 [9]. Defelice's definition in 1995 was: "*A food or parts of food that provide medical or health benefits, including the prevention and/or treatment of disease* [12]". This term was originated from two terminologies: "nutrition" and "pharmaceutical" [9].

There were many trials to distinguish the differences between dietary supplements, fortified foods and nutraceuticals definitions because there is still a grey area between these terminologies [13]. It was claimed that the main difference between both fortified foods and nutraceuticals is the purpose of use [7]. The fortified foods are the foods that supply the body with essential amount of vitamins, minerals, carbohydrates, proteins and other required nutritional elements to improve the health status or treat and/or prevent anemia only while nutraceuticals are used to treat or/and prevent diseases except anemia [7].

Dietary supplement terminology was defined by The Dietary Supplement Health and Education Act (DSHEA) in 1994. The definition of DSHEA was: *"a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: A vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients".* Furthermore, DSHEA specified the supplements by different, main criteria. Firstly, the dietary supplements are represented by dosage formulas, such as tablets, capsules and liquid dosage forms. Secondly, dietary supplements could not be used as conventional foods or dietary sole items. Lastly, they should be labeled as a (dietary supplement) [7]. It was also proposed that there are two main distinguished differences between nutraceuticals and dietary supplements. First, nutraceuticals must treat or/and prevent health problems. Secondly, nutraceuticals could be used as conventional foods or dietary items [7].

The Food and Drug Administration (FDA) outlined some definitions to resolve the confusion between cosmetics, pharmaceutical products and herbal products terms. According to FDA, cosmetics were defined as "*articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance*" [13]. The terminology *"Cosmeceuticals"* has not been acknowledged yet under the law, according to The Federal Food, Drug, and Cosmetic Act (FD&C Act) [14]. Cosmeceutical products are marketed as a drug, a cosmetic or mixture of both [14]. According to the FD&C Act, the terminology for pharmaceutical drug was defined as "*articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals*" [13].

Nutraceuticals have many beneficial effects; hence, they have been used for treating and prevent many health problems, such as cancer, inflammation, hypertension, cardiovascular diseases, atherosclerosis, obesity, diabetes and others [6]. Some nutraceuticals, such as silymarin, curcumin, vitamin E, docosahexaenoic acid, choline and phosphatidylcholine are used in treating and preventing steatosis [15]. Additionally, many nutraceutical products, such as gallic acid, caffeine, curcumin and others act as anti-aging and antioxidant agents [16, 17]. PUFA[1]-rich fish oils reduce the risk of coronary cardiovascular diseases and enhance the brain functions [18]. Nutraceuticals are famous for their anticancer efficacy; hence, many nutraceutical ingredients, such as epigallocatechin gallate, curcumin, pomegranate and others, treat different types of cancer, such as breast cancer, prostate cancer and other types of cancer [19-21].

The global spread of nutraceutical products has dramatically increased recently. The main factor that lead to inflating the market share of these products, is that nutraceuticals have no strict regulations to control them [22]. On the other hand, pharmaceutical products are controlled by strict regulations and are closely monitored. Pharmaceutical products are also strictly regulated and have a governmental sanction [6]. Moreover, nutraceuticals have been advertised under the claim of being safe, effective and being a drug substitute. Additionally, it has been claimed that these products can be used in preventing and treating many health problems without any side effects [23]. The patients also have been concerned about the use of pharmaceutical products because of their high price and several side effects [22]. Therefore, the market share of nutraceuticals has been tremendously expanded [13]. Approximately 80% of global population preferred using dietary supplements and nutraceuticals [23]. Nutraceutical products now are the fastest growing market with an estimated worth of USD 117 billion globally in 2017 [24].

The extensive usage of these products should be supervised closely and regulated [25]. Some countries developed new regulatory bodies for monitoring these products. In the USA, nutraceuticals are regulated as "drugs, food ingredients and dietary supplements" due to the lack of a definite definition [6]. In contrast, in Europe, the European Food Safety Authority (EFSA) acknowledged the nutraceuticals termi-

[1] Polyunsaturated fatty acid

nology and outlined regulations to ensure their safety [25]. Moreover, DSHEA and Drug Administration Modernization Act are responsible for confirming the safety of nutraceuticals before commercializing them [25, 26]. According to FDA, the label of any nutraceuticals or dietary supplement products should state that "*This statement has not been evaluated by the FDA. This product is not intended to prevent, cure or treat any disease*" [10].

There are many approaches that have been adopted to classify nutraceuticals according to different parameters. First, it was classified based on their novelty into traditional and nontraditional nutraceuticals [24]. Secondly, nutraceuticals can also be categorized according to their chemical constituents into nutrients, herbals, dietary supplements, medical food and functional food [2, 24]. Thirdly, nutraceuticals were categorized into potential and established nutraceuticals based on their established efficacy and safety [2]. Fourthly, nutraceuticals were classified based on their structures into phytochemicals and herbals. Finally, there are other classifications that are based on other parameters, such as bioavailability, uses and others [2, 27].

Unfortunately, nutraceuticals are herbal products that suffer from different drawbacks and many limitations [28]. For example, nutraceuticals could suffer from ineffective targeting, poor solubility, low permeability, fast metabolism and other limitations [28, 29]. Hence, those drawbacks pushed researchers to discover and develop better methods for improving the bioavailability, pharmacokinetics and efficacy of these products [28]. Moreover, the Novel Drug Delivery Systems (NDDS) achieve many advantages. They enhance the stability of nutraceuticals by preventing physical and chemical degradation and prevent plasma concentration fluctuation. NDDS also provide sustained release formulations and prevent toxicity by targeting the active constituents to the site of action [30, 31].

Furthermore, NDDS introduce new strategies to enhance pharmacokinetics, pharmacodynamics, nonspecific toxicity, immunogenicity, biorecognition and efficacy of nutraceutical products [30]. NDDS can be administrated through different routes of administration, such as oral, sublingual, transdermal, transmucosal and others [30]. There are various novel systems, including liposomes, phytosomes, nanoparticles, emulsions, nanoemulsion, microspheres, dendrimers, conjugate systems, chitosan-based delivery systems, micelle-based delivery systems, nanoencapsulation, nanofibers and others, which have been used extensively in nutraceutical formulations [28, 30-32].

There are many challenges and concerns associated with nutraceuticals that should be taken into consideration. First, the presumed safety and efficacy of nutraceuticals need more study [25]. Secondly, The difficulty of establishing regulations to control nutraceuticals, is a big challenge due to the lack of globally shared regulations [25]. Thirdly, the *in-vivo* and *in-vitro* studies that prove the nutraceutical products claims have been neglected [13]. The scarcity of clinical trials is due to the difficulty of implementing a restricted dietary intervention [33]. The evaluation of diet efficacy is difficult because of different factors, such as certain expectation to a food, religious beliefs or cultural traditions and others [33].

2. CLASSIFICATION OF NUTRACEUTICALS

The variability of nutraceuticals and their different complex structures resulted in various categorizations [2]. The most common, recent classification of nutraceuticals is based on their novelty [34]:

1. Traditional Nutraceuticals
   - i. Chemical constituents
     - a. Nutrients
     - b. Herbals
     - c. Phytochemicals
     - d. Polyunsaturated Fatty Acids (PUFAs)
   - ii. Probiotics and prebiotics
   - iii. Nutraceutical enzymes
2. Non-traditional Nutraceuticals
     - a. Fortified nutraceuticals
     - b. Recombinant nutraceuticals

2.1. Traditional Nutraceuticals

Traditional nutraceuticals are the foods that are not subjected to any manual change [2]. They include three subcategories [34]. Both lycopene in tomatoes and omega 3 fatty acids in salmon are examples of traditional nutraceuticals [24].

2.1.1. Chemical Constituents

2.1.1.1. Nutrients

They were defined in 1996 by The Association of American Feed Control Officials "AAFCO". The definition of AAFCO is "*a feed constituent in a form and at a level that will help support the life of an animal* [24, 35]". There are many available nutrients, such as minerals, amino acids and fatty acids, but the most commonly used nutrients are vitamins and antioxidants [35, 36].

In 2018, Witham *et al*. [37] conducted a study to evaluate the use of omega-3 fatty acids or esters and maqui berry extract in the treatment of ocular disorders by using traditional and non-traditional systems (Table **1**). The active ingredients were loaded into soft gelatin capsules at different concentrations to evaluate their therapeutic effect [37]. It was claimed that this system was used in treating ocular diseases and other diseases, such as cancer, inflammation and heart disorders [37]. A clinical study was conducted on a group of volunteers who suffer from allergies, glaucoma, cataract, corneal disease and other ocular impairments to assess different parameters. First, tear osmolarity value was evaluated *via* conducting TearLab® Osmolarity System. Secondly, Matrix Metalloproteinase-9 (MMP-9) level was assessed by InflammaDry test. Thirdly, corneal staining was assessed by using Oxford staining scale [37].

Finally, other studies were conducted, such as questionnaire, Tear Break-Up Time (TBUT), and Schirmer's test were conducted [37]. Witham *et al*. concluded that an extract containing ratio of omega-3 fatty acids or esters to maqui berry (from 12:1 to 150:1) had high therapeutic activity [37].

It was claimed that this formulation showed a significant improvement in osmolarity scores and anti-inflammatory effect. Additionally, it attributed in up regulation of the lacrimal gland, but there was no improvement in corneal staining [37].

MacRedmond *et al*. [38] used Conjugated Linoleic Acid (CLA) to assess its efficacy and safety for mild asthma. CLA has been known for its biological regulatory effects [38]. A double blind, prospective, randomized clinical study was conducted on 28 overweight participants against a placebo group [38]. Different parameters were assessed *via* obtaining sputum samples, measuring inflammatory mediators, evaluating spirometry and Airway Hyper-Responsiveness (AHR) [38]. This study showed that CLA had a significant therapeutic effects on overweight mild asthmatic participants by improving Body Mass Index (BMI) and AHR [38].

2.1.1.2. Herbals

They are the oldest recognized form of nutraceuticals. So-called "Ayruveda" is the oldest written prescription of natural remedies, which was written by Indians [24]. Herbals are the products that consist of a whole, fresh plant or its part, such as dried leaf, fruit, roots, or concentrated extract [2, 24]. Nowadays there is an extensive demand on using herbals as nutraceuticals to promote health [2].

Bassino *et al*. [39] studied the effect of white Willow Bark (WWB) and 1,2-decanediol (DD) on acne vulgaris. Acne vulgaris is a skin disease, which is most common in adolescence. One of the main problem with acne is that it may lead to permanent scars [39]. The main causes of acne are the accumulation of *Propionibacterium acnes* and hyperkeratinization [39]. Bassino *et al*. [39] conducted *in-vitro* assessment by using human adult keratinocyte cell line (HaCaT). Enzyme Linked Immunosorbent Assay (ELISA) was performed to measure pro-inflammatory cytokines [39]. This study concluded that using WWB alone or in combination with DD had a positive effect on acne treatment [39].

Chang illustrated the use of Traditional Chinese Medicine (TCM) as an anticancer agent [40]. In this literature review, Chang stressed on the efficacy of polysaccharides class on cancer treatment and prevention [40]. Polysaccharides can be extracted from different plants such as *Silybum marianum L.* (milk thistle) [41]. Polysaccharides exert a significant antioxidant activity [41]. Chang showed the use of polysaccharides as immunomodulatory because of their β1,3 1,4 or 1,6 branch chains and their affinity to β-glucagon receptors [40]. Hence, polysaccharides have antitumor activity [40]. Moreover, more than 200 species showed antitumor activity whether fungi or plants [40]. *Basidiomycetes* family is one example that exhibits antitumor activity due to its polysaccharides [40]. It has been found that polysaccharides have better clinical outcome as an adjunctive therapy with chemotherapy and radiation in different types of cancer [40].

2.1.1.3. Phytochemicals

Phytochemicals are chemical constituents (secondary metabolites) that are extracted from plants. Phytochemicals exert specific biological effects [2, 42]. They may affect the metabolic activity or exert biochemical reactions [2]. They are classified according to their chemical structures into polyphenols, isoflavonoids, anthocyanidins, phytoestrogens, terpenoids, carotenoids, limonoids, phytosterols, glucosinolates and polysaccharides [36, 42]. Phytochemicals affect the body by different mechanisms [34]:

- They act as a substrate for different biochemical reactions.
- They act as a catalyst or cofactor in enzymatic reactions.
- They inhibit enzymatic reactions.
- They improve the absorption and stability of nutrients.
- They act as specific growth factors to improve the growth of beneficial bacteria.
- They inhibit harmful, intestinal bacteria.
- They eliminate toxins.
- They act as ligands that exhibit antagonistic or agonistic effect on cell receptors.

Eugenol (4-allyl-2-methoxyphenol) is a phytochemical compound, which is extracted from cloves [43]. Eugenol has been known for its anesthetic and local antiseptic effects [43]. In higher concentrations, it has an antioxidant, antimutagenic and anticancer effect [43]. Ghosh *et al*. [44] used eugenol in treatment of melanoma. Melanoma is one of the fastest growing tumors in developing countries that is resistant against chemotherapy, immunotherapy and vaccines [44]. Moreover, E2F is a protein, which is responsible for continuous proliferation of melanoma cells [44].

Ghosh *et al*. [44] designed *in-vitro* and *in-vivo* models to assess the efficacy of eugenol against melanoma [44]. Melanoma cell line was tested by using different concentrations of eugenol and isoeugenol [44]. *In-vivo* experiment was conducted on female mice that established B16 melanoma. Finally, Ghosh *et al*. concluded that eugenol down regulated E2F1, E2F2 and E2F3 proteins which have contributed in melanoma growth [43, 44]. Anchorage-dependence and anchorage-independence were inhibited to melanoma cell cultures [44]. Lastly, the tumor size was reduced by 40% after treatment with eugenol [44].

2.1.1.4. Polyunsaturated Fatty Acids (PUFAs)

Fatty acids have essential beneficial properties for any living organisms [45]. Fats can be classified according to their degree of saturation to saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids. Polyunsaturated Fatty Acids (PUFAs) have been categorized based on the position of the first double bond, located close to the terminal methyl group of the backbone chain. The most common and significant PUFAs are omega-3 and omega-6 PUFAs. Omega-3 PUFAs have been used as supplemental therapy for cardiovascular diseases, bipolar depression, asthma and diabetes. Additionally, omega-3 PUFAs reduce the level of lipid in serum so they have been defined as "essential fatty acids" [46].

PUFAs have been heavily used as nutraceuticals due to their beneficial effects; however, unfortunately, they have low chemical stability because of the presence of oxygen leading to oxidation [47]. Hence, their efficacy would be reduced along with toxic byproducts generation [47]. Subsequently, different novel delivery systems, such as, nanoe-

mulsion [47], emulsion [18] liposomes and nanoparticles [48] have been used to improve their stability.

Serini *et al*. [49] designed Solid Lipid Nanoparticles (SLN) to encapsulate omega-3 PUFAs into to treat or prevent colorectal cancer. The lipid matrix of SLNs had resveratrol that was esterified with stearic acid. The designed system enhanced the physicochemical properties and the delivery of omega-3 PUFAs. Moreover, SLNs prevented the degradation and oxidation of omega-3 PUFAs and improved their antineoplastic efficacy [49]. Throughout the systemic review of various novel nutraceuticals' carrier systems in this manuscript, multiple studies and patents discussing PUFAs applications as nutraceuticals would be reviewed.

2.2. Probiotics and Prebiotics

Lately, both prebiotics and probiotics are classified as nutraceuticals [2, 50]. Probiotics are a new term that was originated from the phrase "*for life*". They are live, beneficial microorganisms, which enhance health and prevent diseases [50, 51]. In the 90's, Metchnikoff proposed the idea of a beneficial bacteria for the human and suggested using it as treatment. Metchnikoff used *bifidobacteria* to treat infantile diarrhea. Afterwards, Havenaar and Huisint Veld introduced the modern definition of probiotics: "*as a viable mono or mixed culture of bacteria which, when applied to animal or man, affects the host beneficially by improving the properties of the indigenous flora*" [51]. *Bifidobacterium* and *Lactobacillus* are examples of the most commonly used bacterial species as probiotics [51, 52].

The intensive researches in the probiotics field lead to a discovery of a new field (prebiotics). Prebiotics were defined as nutrients that modify the microbial flora of GIT *via* stimulating the beneficial bacteria growth or inhibiting the deleterious bacterial growth [52, 53]. This definition was a subject of a debate because any carbohydrate or fermentable dietary fiber that is ingested by the host is accessible to the normal flora [52, 53]. This led to a new definition by the expert panel, which was defined as: "*a substrate that is selectively utilized by host microorganisms conferring a health benefit*" [53]. Moreover, the most commonly used prebiotics are galactose containing oligosaccharides, xylose-containing oligosaccharides, oligofructose, fructo-oligosaccharides and bifidogenic substrates [51].

Products that contain a combination of prebiotic and probiotic are called synbiotics [51]. Pre- and probiotics can enhance the human health by different mechanisms, such as competing with pathogenic organisms for nutrients, producing antitoxins or antibiotics against invasive pathogens, aiding in neutrophil migration and producing some useful enzymes, such as ß-galactosidase, which helps in alleviating the symptoms of lactose intolerance [42, 50].

Thilakarathna *et al*. [54] illustrated the potential use of probiotics and prebiotics in cancer prevention. Thilakarathna *et al*. explained how gut microbes can prevent cancer progression by demonstrating many mechanisms [54]. For instance, it was reported that probiotics have significant efficiency on reduction of toxins and carcinogens. Moreover, polymerized polyphenols, such as ellagitannins and proanthocyanidins, aid in cancer prevention and progression, but the complexity of their structure limited their absorption [54]. However, the probiotics have a significant role in catabolizing these polyphenols and improving their absorption [54]. Hence, phenol-based prebiotics showed positive results in cancer treatment. Finally, synbiotics have significant effect on treating cancer because they enhance the survival rate of probiotics [54].

Damaskos *et al*. [55] illustrated the use of prebiotics, probiotics and synbiotics in the treatment of Inflammatory Bowel Disease (IBD), which is known to be idiopathic [56]. Several hypotheses were introduced to explain the causes of IBD, such as genetic impairment, immune dysregulation, barrier dysfunction and microbial flora [55, 56]. Probiotics have different mechanisms of action to aid in preventing and treating IBD [55]. For example, *Lactobacillus* decreases translocation of normal flora bacteria. Probiotic also inhibits the production of Interleukin-6 (IL-6). Furthermore, *Bifidobaterium* inhibits distorted T-cell activation and increases interleukin-10 (IL-10) [55].

On the other hand, prebiotics have different mechanisms of action. Prebiotics regulate colonic mucosa physiology *via* the production of Short Chain Fatty Acid (SCFA) [55]. The most common prebiotics that are used in treatment of IBD include lactulose, inulin and lactosucrose [55]. Finally, synbiotics were being developed to achieve better effect, better compliance and cost effectiveness [55]. Different synbiotics were tested and showed better effect against IBS. For example, a study reported that a combination of *Bi. breve, Lactobacillus casei* and galacto-oligosaccharides improved bowel function in a girl with short bowel syndrome [57].

2.3. Nutraceutical Enzymes

Enzymes are main functional proteins in the body; the body will stop functioning without them [36, 42]. Enzymes are responsible for regulating body functions and alleviating health problems, such as hypoglycemia, hyperglycemia, digestive problems and obesity [36, 42].

Takabayashi *et al*. [58] aimed to treat chronic rhinosinusitis with nasal polyps (CRSwNP) with a nutraceutical enzyme called nattokinase (NK). NK is a fibrinolytic enzyme [58]. NK is produced from *Bacillus subtilis* [58]. Immunohistochemistry assay was conducted to assess the presence of nasal polyps. Moreover, clinical study was performed on patients with CRSwNP and asthma for 12 weeks to evaluate the mucus viscosity through different parameters, such as nasal discharge and sputum [58]. It was concluded that NK improved nasal polyps mass and reduced the mucus viscosity significantly [58].

2.4. Non-Traditional Nutraceuticals

2.4.1. Fortified Food

Fortified food was considered to be a part of nutraceuticals in some classifications. Fortified food, which is also known as "designer food", is a food that is fortified by nutrients, such as minerals, vitamins or/and other essential elements to maximize its efficacy [2, 59]. At the beginning, it was used in treating nutrient deficiencies [60]. The food fortification was started in USA in 1940s through the food fortification program, which aimed to enrich foods with neces-

sary nutritional elements. There have been successful trials of using these products to prevent diseases and improve health since decades. For instance, in 1924, salt was fortified with iodine to prevent goiter in USA [61]. Moreover, the milk was fortified by vitamin D *via* feeding cattle irradiated milk [62].

During the first and second world war, fortified food was utilized to alleviate nutrient deficiency among population [60]. In 1941, flour that was enriched with thiamin, niacin, riboflavin and iron was introduced and labeled "enriched" by FDA [62]. Food fortification was introduced into the Middle East in the late 1970s. For example, the Kingdom of Saudi Arabia (KSA) introduced enriched flour [60].

According to FDA, food fortification was classified into mandatory and discretionary. Mandatory fortified food should adhere with the specific standards of identity that were outlined *via* FDA [62]. There were two mandatory fortified foods: First, the flour that was fortified by nutrients: niacin, iron, riboflavin, thiamin and folic acid are considered to be mandatory fortified food. Secondly, the fortification of rice, breads, cereals, margarine, other grains and grain products have been also classified as a mandatory fortification by FDA. Hence, the mentioned nutrients should comply with the FDA standards [62]. The fortification of other forms of food were delineated as discretionary fortification by FDA [62].

Fortified food is the most effective treatment for micronutrient malnutrition for several reasons. First, fortified food can be accessible to large number of population by choosing the most attractive food form [63]. Secondly, it is socially acceptable because people prefer no change in food characteristics or food habits. Thirdly, fortified food can be introduced quickly, and its benefits are achieved quickly as well. Finally, most of people consider them safe and cost-effective [63].

Folic acid represents a prominently used fortifying nutrient. Folic acid is essential for DNA synthesis and repair. Folic acid deficiency has been correlated to various human diseases, such as megaloblastic anemia, neonatal neural tube defect and heart disease [64]. Hence, Canada obligated that cereals must be fortified with folic acid in 1998 [65]. Additionally, FDA approved fortified corn masa flour with folic acid in 2016 [66]. A study was conducted on 2446 participants in Canada to demonstrate the efficacy of folic acid fortification on reduction in neural-tube defects rate. It was reported that there was a 46% reduction in the rate of neural tube defect during a period of full-fortification [65].

Ruti, a flavonol glycoside, is a widely used fortifying nutrient. It has numerous pharmacological activities, such as anti-inflammatory, anticancer, antiviral, hypolipidemic and others. Rutin, which is naturally found in fruits and plants, has both free radical scavenging ability and antioxidant activity [67]. However, it suffers from low aqueous solubility which limits its bioavailability. Babazadeh *et al.* [68] encapsulated rutin in food grade Nanostructured Lipid Carriers (NLCs) to overcome its low solubility in aqueous phase and polarity. Three different food models namely; milk, apple juice and orange juice, were chosen to be fortified with the encapsulated rutin-NLC in this study. In this study, NLCs improved the bioavailability of encapsulated phyto-active compound.

Vitamin D is another broadly used fortifying nutrient. It is a fat-soluble vitamin that is highly sensitive to oxygen, light and high temperature. Hasanvand *et al.* [69] developed high amylose corn starch nanoparticles to encapsulate vitamin D_3. In this study, milk was used as a food model to be fortified. Vitamin D is insoluble in aqueous medium and forms granular texture in milk [70]. However, in case of fortified milk with loaded vitamin D nanoparticles, the taste, homogeneity, and total acceptance of fortified milk were improved, and the bioavailability of vitamin D was enhanced [69]. Livney *et al.* [71] developed charged nanoparticles *via* the interaction of oppositely charged β-lactoglobulin-polysaccharide and polysaccharide to form colloidal dispersion. The hydrophobic active compounds, such as Vitamin D and oil-soluble vitamins, were loaded into the nanoparticles. The novel vitamins' nanoparticulate carrier provided stability while maintaining transparency of beverage and food due to is nanosized dimensions. Furthermore, the novel system stabilized the loaded active compound against degradation by oxidation and other chemical and enzymatic reactions. In another study, Danino *et al.* [72] formulated beta-casein micelles or nanoencapsulator to encapsulate hydrophobic fortifying nutrients such vitamin D. Physical characterization, such as Transmission Electron Microscopy (TEM) analyses and stability studies were conducted. Casein micelles showed high stability profile at a very low pH range as low as 2 and wide temperature ranges. Furthermore, the nanoassembly provided small particles enough to keep transparency of clear beverages and food appearance. Per authors claims, the micellar system is considered a suitable and stable vehicle to deliver nutraceutical additives will maintaining beverages and other food products transparency.

Vitamin D deficiency has shown high prevalence rates in Europe and considered a pandemic problem [73]. Vitamin D deficiency causes metabolic bone diseases, such as rickets in children and osteomalacia and osteoporosis in adults [74]. Milk, dairy products and beverages that were fortified with vitamin D had a positive influence on the daily intake of vitamin D for adults in USA and Canada [75]. However, vitamin D fortification is unsuitable for individuals who suffer from milk allergy or lactose intolerance [76]. Thus, Tangpricha *et al*. [76] replaced milk with orange juice that was fortified with 1000 IU vitamin D. Moreover, 25-hydroxy vitamin D test revealed that the serum level of 25-hydroxycholecalciferol was increased by 150% [76].

Unfortunately, fortified food has drawbacks and adverse effects associated with its excessive consumption. Excessive intake of fat soluble vitamins can result in toxicity [62]. There is a risk of metabolism interference. For example, zinc reduces both copper and iron absorption [62]. It was reported that high intake of calcium causes prostate cancer and hip fracture in men and women, respectively [77, 78]. Additionally, it was reported that calcium supplements could lead to heart diseases, especially myocardial infarction [79].

2.4.2. Recombinant Nutraceuticals

Recombinant nutraceuticals were categorized as non-traditional nutraceuticals, which have been formulated by

using novel, biotechnological techniques, such as fermentation and genetic engineering [36]. Modifying the genetic material (DNA) of food alters its properties, which initiates allergy [80]. Genetically modified food is useful in controlling certain diseases [80]. However, the major drawbacks of genetically modified foods are the possible harmful effects, such as diseases, which have resistance against antibiotics. Furthermore, more studies should be done to evaluate the unknown, long term influence on human body [80].

Infants and adults mainly suffer from cow milk allergy due to the presence of β-lactoglobulin (BLG) [81]. Hence, Orcajo *et al*. [81] produced β-lactoglobulin free milk by generating DNA-free β-lactoglobulin gene in cow. Produced milk was more easily digested. It had lower binding affinity to Immunoglobulin E (IgE) than traditional milk [81]. For the same reason, enhancement of milk composition was performed through increasing casein milk concentration. Hence, Brophy *et al*. [82] introduced additional genes encoding bovine β- and κ-casein into fibroblast of bovine female. Thus, the produced milk showed higher β-casein and κ-casein levels [82].

3. NEW INSIGHT INTO THE WORLD OF NUTRACEUTICALS

Nutraceuticals formulations are hampered by many obstacles that negatively affect their efficacy [83]. Many natural active ingredients suffer from low solubility, poor permeability, fast metabolism, short half-life and others [83]. For instance, curcumin has low solubility, poor oral bioavailability, limited tissue distribution, short half-life and rapid metabolism [84]. Additionally, Epigallocatechin Gallate (EGCG) is a bioactive compound in green tea that has a vasculoprotective effect through its antioxidative and hypolipidemic effects [85]. However, EGCG uses are limited because of its fast degradation in the gut and low solubility [85]. These kinds of challenges that jeopardize the nutraceuticals existence push scientists and formulators to use different novel systems to maximize nutraceuticals safety and efficacy [83].

The process of entering an active, pharmaceutical ingredient into the body effectively and safely, is called drug delivery [86]. Introducing novel delivery systems to nutraceutical market was delayed due to its complex nature, high price and time consumption [86]. Hence, traditional forms have been used for many years, but, as it was mentioned before, they have many problems [15, 87]. Consequently, conventional herbal dosage formulas have been developed since many years. For example, permeation enhancers, surface modifiers, prodrug, colloidal lipid carriers and other novel carriers, have been developed [87]. There are many types of novel delivery systems. Herein, the most common novel systems are mentioned. Recent published research papers [15-20, 47, 85, 88-129] and patents [21, 37, 48, 130-166] adopting novel formulation strategies in ultraceuticals are summarized in Table **1** and Table **2** respectively.

3.1. Nanoparticles

Nanoparticle is a particle that has three nanoscale dimensions, which range approximately from 1 to 100 nanometer (nm) [167]. The new synthesized nanoparticles have completely different electrical, mechanical, physical and chemical properties [167]. Nanotechnology has gained extensive popularity in the field of drug delivery system. Nowadays, nanotechnology has been extensively applied in the field of nutraceuticals. Hence, the current market share of nanotechnology in the nutraceutical industry is around 1 billion dollars. It was also expected that the market share would reach over 20 billion dollars in the next decade [168]. Facchi *et al*. [92] synthesized encapsulated curcumin nanoparticles, which consisted of N, N-dimethyl chitosan, N,N,N-trimethyl chitosan and sodium tripolyphosphate in water-in-benzyl alcohol emulsion medium. This system overcame the low solubility, high crystallinity and poor oral bioavailability of curcumin. Additionally, the conducted *in-vivo* and *in-vitro* studies showed the enhanced anticancer properties of this system, as shown in Table **1** [92].

Semyonov *et al*. [94] enhanced the bioavailability and solubility of genistein by loading it into enzymatically developed dextran nanoparticles. Genistein is isoflavone and it has antioxidant and anti-inflammatory properties [94]. Wei *et al*. [138] designed nanoparticles, which were loaded with Chinese yams, radix astragal, rhizoma anemarrhenae, chicken's gizzard-membranes, radix puerariae, raw gypsum, rhizoma alismatis and/or others to treat or prevent many disease, such as diabetes, heart diseases and others [138].

3.2. Nanospheres and Nanocapsules

Both nanospheres and nanocapsules are polymeric nanoparticles, which have a diameter with less than 1 μm [169]. Nanocapsule has a vesicular structure which is surrounded by a polymeric membrane. The active ingredient is encapsulated into nanocapsule. Nanospheres have a dispersed polymeric matrix, which active ingredient is dispersed into [169]. Hu *et al* [103]. Made a polymeric nanoparticle and conjugated it with chitosan. This system was loaded by curcumin to be used as antioxidant. Moreover, Hu *et al*. characterized this polymeric system *via* Fourier-Transform Infrared spectroscopy (FTIR) and proton Nuclear Magnetic Resonance (^{1}H NMR) analysis. The particle size and Poly Disperse Index (PDI) were measured *via* Dynamic Light Scattering (DLS). Finally, zeta potential and the morphology of nanoparticles were determined *via* laser doppler microelectrophoresis and Transition Electron Microscopy (TEM), respectively (Table **1**) [103].

In a patent by Ortiz *et al*. [148], it was claimed that acylethanolamides could be loaded into nanocapsules polymeric system, besides other novel delivery systems. Acylethanolamides were used in prevention or treatment of alcohol dependence syndrome, alcohol poisoning and pathological intoxication. *In-vivo* study was conducted on rats to measure different parameters [148]. First, neuroinflammatory, which was induced by alcohol intoxication protocol, was evaluated by measuring blood ethanol level. Secondly, the signaling route of neuroimmune (Toll-Like Receptor 4 (TLR4), myeloid differentiation primary response 88 (MyD88), Nuclear Factor Kappa-light-chain-enhancer (NF-kB)) was evaluated after High Mobility Group Box 1 (HMGB1) activation alcohol. Lastly, the withdrawal behavior was observed *via* conducting elevated plus maze experiment [148], as shown in Table **2**.

3.3. Metal Nanoparticles

Metals, such as silver (Ag), iron (Fe), zinc oxide (ZnO), titanium oxide (TiO_2), are prepared in the nano size range. Metal nanoparticles have many advantages, including relatively large surface area, good biocompatibility and good catalytic activity [170]. Furthermore, superior selectivity, metal nanoparticles are usually isolable, dispersible and reusable catalysts [170]. Metal nanoparticles can be applied as metal or metal-oxide, such as nano-Ag, nano-ZnO, nano-Cu and nano-TiO_2. Each has its specific dimensions, homogeneousness and aggregative properties [171]. These different characteristics influence the compound's biological activity and toxicity [171].

Otunola *et al*. [172] conducted a study to analyze silver nanoparticles (AgNPs) biological activity (antimicrobial and antioxidant activity) in three different herbal species namely; garlic, ginger and cayenne pepper (Table **1**) [172]. Each active ingredient was encapsulated into AgNPs. These metallic nanoparticles had spherical shapes and average sizes of 3-6nm, 3-22nm and 3-18 nm for garlic, ginger and cayenne pepper, respectively [172]. It was concluded that AgNps exhibited more potent antibacterial activity against two gram−negative and two gram−positive bacterial strains [172]. Additionally, 1,1−diphenyl−2−picrylhydrazyl (DPPH) and 2,2−Azino−bis (3−ethylbenzthiazoline−6−sulfonic acid) (ABTS) assays showed that AgNps had better antioxidant activity [172].

In 2018, Bolisetty *et al*. [162] designed a novel, hybrid system, which consisted of amyloid fibrils that were covered by iron nanoparticles on its surface (Table **2**). The system was loaded with amyloid fibrils and minerals, such as iron oxides, calcium phosphates and others [162]. It was claimed that the synthesized formulation was used in treating or preventing iron deficiency anemia and diseases, which are associated with zinc deficiency. Hemoglobin repletion bioassay was performed on rats to assess the relative bioavailability of the hybrid system. As a result of that the bioavailability of the loaded ingredients was improved [162].

3.4. Composite Colloidal Nanoparticles

Composite nanoparticles are hybrid nanoparticles that consist of inorganic core (metal or metal oxide) and organic shell (polymerized monomer, organic molecule, chromophore, *etc*.) [173]. The first trial of composite nanoparticles synthesis was in late-90s *via* Vollath [174]. Composite nanoparticles have new electronic, magnetic, optical or biological characteristics [173]. There have been many trials to introduce nanocomposites into nutraceutical industry to enhance the efficacy of nutraceuticals. For instance, Jia *et al*. [21] coated pomegranate arils with both zinc oxide nanoparticles and carboxymethyl cellulose (Table **2**). This system enhanced the anticancer, anti-inflammatory and antioxidant activities of pomegranate. Jia and his team evaluated the antioxidant activity *via* conducting the DPPH radical scavenging technique [21].

Donsì and his team synthesized zein-based composite colloidal nanoparticles to encapsulate epigallocatechin-3-gallate (EGCG) within it (Table **1**) [111]. EGCG has hydrophobic nature and weak co-polymer interaction with zein. Hence, a colloidal stabilizer, sodium caseinate (NaCas), was used to enhance the encapsulation insufficiency. It was claimed that this system modulated the rate of fat digestion and enhanced antioxidant activities. Antioxidant activity of polyphenols was assessed *via* using ferric reducing antioxidant power [111].

Sun *et al*. [102] controlled the release of curcumin by encapsulating it into zein-shellac nanocomposite particles (Table **1**). Zein is the main storage protein in corn while shellac is a resin that is produced from lac beetle [102]. The formulated zein-shellac nanocomposite showed better encapsulation effectiveness, photochemical and thermal stability. Moreover, this study showed that zein to shellac ratio (1:1) is the most effective against curcumin degradation induced by thermal or ultra violet (UV) light exposure [102]. Zein-shellac nanocomposite had better stability in phosphate buffer saline (PBS) and simulated gastrointestinal conditions [102].

3.5. Self-Assembly Nanoparticles

Self-assembly technique is a powerful and cost efficient technique to control the self-organization of nanoparticles [175]. This technique depends on controlling the repulsive and attractive forces between particles to produce a variety of self-assembled structures of nanoparticles. Self-assembly alters the physical properties of the particles, such as optical, electronic and magnetic properties. It also enhances the bulk mechanical properties [175]. Various methods are used to enhance self-assembly, such as Langmuir-Blodgett technique, templating method and assisted self-assembly method [175].

Some compounds have the ability to form self-assembled nanoparticles, such as chitosan (CS) and polyaspartic acid (PAA) [85]. Self-assembled nanoparticles caught a great attention in the field of nutraceuticals due to their potential cost effectiveness, simple preparation and biocomptability [176]. For example, EGCG has a vasculoprotective effect through its antioxidative and hypolipidemic effect [85]. However, EGCG uses are limited because of their rapid degradation in the gut, (as it mentioned before). Thus, Hong *et al*. [85] encapsulated EGCG into self-assembled nanoparticles, which composed of chitosan and aspartic acid, as shown in Table **1**. *In-vivo* study was performed on male New Zealand white rabbits. The results of the *in-vivo* study reported that loaded EGCG had better activity against atherosclerosis [85].

3.6. pH Responsive Formulations

A pH responsive system is a delivery method that controls the release of active ingredients by specific pH change [177]. Different organs at the human body have different pH ranges, such as stomach (pH 1.5-3.5), small intestine (pH 5.5-6.8) and colon (pH 6.4-7.0). Moreover, the tumor has a specific pH value (around 7.4). Hence, pH responsive system represents an excellent candidate of site-specific targeting [177]. Therefore, this system has been dragged into the nutraceutical industry.

Table 1. Recent published research papers adopting novel formulation strategies in ultraceuticals.

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
***In vitro* assessment of nutraceutical compounds and novel nutraceutical formulations in a liver-steatosis-based model**	Three formulations (1, 2 and 3) consisted of mixture of six nutraceutical ingredients, which were solubilized in dimethyl sulfoxide (pure DMSO) solution. Formulation 1 consisted of all six natural ingredients, while formulations 2 and 3 did not have choline and phosphatidylcholine, respectively.	Silymarin Curcumin Vitamin E Docosahexaenoic acid Choline Phosphatidylcholine	Steatosis treatment	Traditional (Mixture)	Oil Red O Staining Colorimetric Assay: Steatosis level was assessed *via* qualitative and quantitative assessment of oil red O staining. Oxidative Stress Assay: Antioxidant activity was evaluated *via* the expression of SOD2[2] gene and protein. PPARα[3] and PPARγ[4] expressions were assessed by western blotting assay. lipid metabolism was evaluated by assessing the expression of LPL[5] mRNA. Lipid peroxidation assay was conducted to evaluate the effect of nutraceuticals on H_2O_2[6] oxidative stress.	MTT[7]	-	2018	[15]
Nanoscale delivery of resveratrol towards enhancement of supplements and nutraceuticals	The system consisted of resveratrol that was encapsulated in Solid Lipid Nanoparticles (SLNs) or Nanostructured Lipid Carriers (NLCs).	Resveratrol	Anticancer	Non-traditional	Entrapment efficiency was determined *via* UV-VIS spectrophotometer[8]. Protection efficacy of lipid nanoparticles against photodegradation was assessed *via* photostability studies by using UV-VIS spectrophotometer.	MTT	Particle size was determined *via* DLS[9]. Zeta potential was determined *via* Electrophoretic Light Scattering (ELS) Caco-2[10] cell permeability evaluation was conducted by HPLC[11].	2016	[88]
Effect of maillard conjugates on the physical stability of zein nanoparticles prepared by liquid antisolvent co-precipitation	Resveratrol was encapsulated within protein (zein) nanoparticles, which were coated *via* conjugated polysaccharides.	Resveratrol	-	Non-traditional	-	-	The efficacy of conjugation was assessed by measuring the decrease in free amino groups *via* the OPA[12] assay The concentration of resveratrol was determined *via* UV-VIS spectrophotometer.	2015	[89]

[2] Superoxide dismutase 2
[3] Peroxisome proliferator-activated receptor alpha
[4] Peroxisome proliferator-activated receptor gamma
[5] Lipoprotein lipase
[6] Hydrogen peroxide
[7] 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
[8] Ultraviolet–visible spectroscopy
[9] Dynamic light scattering
[10] Colorectal adenocarcinoma cells
[11] High Performance Liquid Chromatography
[12] o-Phthaldialdehyde

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
							Concentration of unreacted protein was measured by Lowry assay. High performance size exclusion chromatography was used to assess the conjugation products Mean particle size, PDI[13] and particle size distribution were measured by DLS[14]. The morphology of nanoparticles was evaluated *via* TEM[15]. Particle stability was evaluated by measuring particle size of the system at various environmental stress ($CaCl_2$, temperature and pH).		
Improving resveratrol bioaccessibility using biopolymer nanoparticles and complexes: Impact of protein-carbohydrate maillard conjugation	Biopolymer nanoparticles consisted of a caseinate or caseinate dextran shell, which was conjugated with resveratrol. Additionally, its core consisted of zein.	Resveratrol	-	Non-traditional	Bioaccessibility efficiency of the delivery system was assessed *via* using gastrointestinal model. The amount of the entrapped bioactive ingredient was measured *via* retention efficiency assay.	-	The efficacy of conjugation was assessed by measuring the decrease in free amino groups *via* the OPA assay The effect of stabilization of conjugated casein was evaluated *via* determining the decrease in turbidity of conjugated system. The encapsulated resveratrol level was measured using a UV-visible spectrophotometer. Mean particle size, PDI and particle size distribution were measured by DLS. The effect of UV[16] light on the stability of trans-resveratrol was evaluated by UV-light lamp and cabinet.	2015	[90]

[13] Polydispersity index
[14] Dynamic Light Scattering
[15] Transmission Electron Microscope
[16] Ultra violet

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Fabrication of resveratrol-loaded whey protein-dextran colloidal complex for the stabilization and delivery of β-carotene emulsions	Whey protein isolate was conjugated with dextran to form a nanocomplex, which was loaded with resveratrol in the form of emulsion.	Resveratrol	-	Non-traditional	-	-	The molecular weight of nanocomplex was measured *via* SDS-PAGE[17] technique. Circular Dichroism (CD) spectroscopy was used to evaluate the integrity of the nanocomplex due to the presence of dextran. OPA assay was used to assess the extent of glycation. The changes in the conformation and various interactions were evaluated *via* fluorescence spectroscopy. The particle size, PDI, and zeta-potential of nanocomplex system were measured by DLS. The morphology and size of nanocomplex were detected *via* TEM. The storage stability of nanocomplex was detected by UV-vis Spectrophotometer.	2018	[91]
Preparation and cytotoxicity of N-modified chitosan nanoparticles applied in curcumin delivery	Curcumin was encapsulated into nanoparticles, which consisted of N, N-dimethyl chitosan, N,N,N-trimethyl chitosan and sodium tripolyphosphate in water-in-benzyl alcohol emulsion medium.	Curcumin	Anticancer	Non-traditional	The studies of curcumin-controlled release were conducted in both simulated intestinal and gastric fluid.	MTT	The morphology and the size of nanoparticles were assessed *via* SEM and TEM. FTIR[18] analysis Thermogravimetric analysis Zeta Potential was measured *via* DLS. DSC[19] analysis The crystalline structure of the system was assessed *via* wide-angle X-ray scattering.	2016	[92]

[17] Sodium dodecyl sulphate-polyacrylamide gel electrophoresis
[18] Fourier-transform infrared spectroscopy
[19] Differential scanning calorimetry

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Enhancement of curcumin solubility by phase change from crystalline to amorphous in Cur-TPGS nanosuspension	Nanosuspension consisted of curcumin and d-α-Tocopherol Polyethylene Glycol 1000 Succinate (TPGS).	Curcumin	Antioxidant Anti-inflammatory Antimicrobial Anticancer Anti-Alzheimer Wound-healing	Non-traditional	-	-	The particle size, PDI, and zeta-potential of nanocomplex system were measured by DLS. The morphology and size of nanoparticles were assessed *via* Field Emission Scanning Electron Microscope (FE-SEM) and TEM. FTIR analysis. Thermogravimetric analysis DSC analysis X-Ray Diffraction (XRD) analysis	2016	[93]
Enzymatically synthesized dextran nanoparticles and their use as carriers for nutraceuticals.	Genistein was encapsulated within enzymatically developed dextran nanoparticles.	Genistein	-	Non-traditional	The complexation ability of freeze-dried dextran powder was evaluated *via* inclusion and complexation formation through decreasing pH and diluting DMSO[20] in water.	-	The particle size, PDI, and zeta-potential of nanocomplex system were measured by DLS. The morphology of nanocomplex was assessed *via* cryo-TEM. The crystalline structure of the system was assessed *via* wide-angle X-Ray scattering. The activity of the system was assessed *via* quantifying the concentration of released fructose and glucose by high-performance anion-exchange chromatography.	2014	[94]
Tangeretin-loaded protein nanoparticles fabricated from zein/ β-lactoglobulin: Preparation, characterization, and functional performance	Tangeretin was encapsulated within protein nanoparticles, which consisted of zein core and b-lactoglobulin shell.	Tangeretin	Anticancer Anti-inflammatory	Non-traditional	-	-	The quantification of tangeretin content was measured *via* HPLC. The morphology of protein nanoparticles was assessed *via* TEM. The particle size, PDI, and zeta-potential were measured by DLS.	2014	[95]

[20] Dimethyl sulfoxide

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
							The microstructure and appearance of protein nanoparticles were assessed *via* optical microscope and digital camera, respectively. The stability of protein nanoparticles was evaluated by measuring their particle sizes at various environmental conditions, including pH, temperature and salt solutions.		
Nanostructured Lipid Carrier (NLC) as a strategy for encapsulation of quercetin and linseed oil: Preparation and *In vitro* characterization studies	Quercetin and linseed oil were loaded within Nanostructured Lipid Carrier (NLC) *via* high pressure homogenization method.	Quercetin Linseed oil	Antioxidant Anticancer Antibacterial Anti-Inflammatory	Non-traditional	Entrapment efficiency was determined *via* UV-VIS spectrophotometer. *In vitro* antioxidant activity was assessed by UV-VIS spectrophotometer. The *in-vitro* release of quercetin was conducted *via* measuring the concentration of released quercetin by using UV-VIS spectrophotometer.	-	The particle size, PDI, and zeta-potential were measured by DLS. The morphology of NLC was assessed *via* TEM. Rheological analysis was conducted *via* a rotational rheometer. XRD analysis was conducted *via* using a D8 Discover X-ray diffractometer DSC analysis The storage stability analysis of NLC was conducted *via* evaluating the appearance, particle size, quercetin loading and entrapment efficiency for three months.	2017	[96]
Quercetin loaded biopolymeric colloidal particles prepared by simultaneous precipitation of quercetin with hydrophobic protein in aqueous medium	Composite colloidal nanoparticles consisted of quercetin and zein.	Quercetin	Antioxidant Anti-cancer Anti-viral	Non-traditional	The antioxidant efficacy of nanoparticles was measured *via* Ferric Reducing Antioxidant Power (FRAP) method.	-	The morphology of NLC was assessed *via* TEM. The particle size, PDI, and zeta-potential were measured by DLS and electrophoretic mobility data. The crystalline structure of the system was assessed *via* wide-angle X-ray scattering. FTIR analysis UV–Vis spectroscopy analysis	2012	[97]

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Chemical composition and antibacterial activity of Eugenia brejoensis essential oil nanoemulsions against Pseudomonas fluorescens	Nanoemulsions consisted of Eugenia brejoensis essential oil and tween 80.	Eugenia brejoensis essential oil	It is used as food preservative due to its antimicrobial activity.	Non-traditional	*In-vitro* antimicrobial activity was assessed by using agar diffusion technique through plate cavity. Inhibitory effect of the nanoemulsion was evaluated by using ham slices.	-	The volatile oils were quantified *via* Gas Chromatography coupled to Mass Spectrometry (GC/MS). The particle size, zeta potential and PDI were measured by DLS. Attenuated Total Reflectance Fourier-Transform Infrared spectroscopy (ATR-FTIR) was used to assess the different functional groups of *Eugenia brejoensis* essential oil.	2018	[98]
Nano-ZnO/carboxymethyl cellulose-based active coating impact on ready-touse pomegranate during cold storage	Pomegranate arils were coated with both Nano-ZnO[21] and carboxymethyl cellulose.	Pomegranate	Anti-carcinogenic Anti-inflammatory Antioxidant	Non-traditional	Antioxidant activity of the system was evaluated *via* the DPPH radical scavenging technique.	-	Microbiological evaluation was conducted *via* counting both total aerobic mesophilic bacteria, total yeasts and molds counts. Fruits quality evaluation: a) Soluble Solids Content (SSC) was measure by Atago Digital Refractometer. b) Titratable acidity was measured *via* titration technique. c) The pH of the pomegranate was measured *via* a pH meter. d) Weight Loss (WL) of the fruits was calculated in the term of the percentage of starting fresh pomegranate weight. e) The content of fruit juice was measured in the term of Juice Percent (JP). The pH differential method was conducted to measure the Total Anthocyanin Concentrations (TAC). Total Phenolic (TP) concentrations were assessed according to Folin–Ciocalteu procedure.	2017	[99]

[21] Zinc oxide

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Curcumin modulates macrophage polarization through the inhibition of the Toll-like receptor 4 expression and its signaling pathways	Curcumin solution	Curcumin	Atherosclerosis treatment	Traditional	The efficacy of curcumin to induce the growth inhibition was assessed *via* [^{3}H] thymidine (^{3}H-TdR) incorporation assay. Enzyme-Linked Immunosorbent Assay (ELISA) was conducted to assess the expression of Interleukin (IL-6), Tumor Necrosis Factor-a (TNF-α) and interleukin-12 subunit beta (IL-12B (p40)). The polarization and mechanism of macrophage were assessed *via* western blot and flow cytometry. The confirmation of curcumin molecular mechanism on the polarization of macrophage was conducted by inhibitors, including small interfering RNA, Toll-Like Receptor 4 (TLR4) and Mitogen-Activated Protein Kinase (MAPK).	None	-	2015	[100]
Loading of curcumin in macrophages using lipid-based nanoparticles	Curcumin was loaded within phospholipid vesicles or lipid-nanospheres (CmVe and CmLn).	Curcumin	Antioxidant Anti-inflammatory	Non-traditional	Reactive Oxygen Species (ROS) scavenge ability of systems was assessed *via* calculating the scavenging superoxide anion ($O_2^{\bullet-}$) *via* CmVe in the term of curcumin concentration. The superoxide, which was generated in xanthine oxidase and hypoxanthine anion system, was assessed *via* a chemiluminescence probe L-120. *In-vivo* study was conducted on male Wister rats. Moreover, confocal scanning analysis was used to examine its bone marrow, spleen, and liver after the formulation injections.	-	Phospholipid concentration was measured *via* a phospholipid assay kit. The diameter of systems was measured *via* a coulter submicron particle analyzer. The zeta potential was assessed *via* DLS. Confocal scanning microscope analysis The morphologies of CmVe and CmLn were assessed *via* TEM.	2008	[252]
Preparation, characterization and stability of curcumin-loaded zein-shellac composite colloidal particles	Zein-shellac nanocomplex was loaded within curcumin.	Curcumin	Anti-carcinogenic Anti-inflammatory Antioxidant	Non-traditional	Encapsulation efficiency was determined *via* UV-VIS spectrophotometer. *In vitro* kinetic release test of Cur was conducted under simulated gastrointestinal fluids.	-	Particle size, PDI and zeta potential were measured *via* DLS. DSC analysis FTIR analysis The morphology of system was assessed *via* Atomic Force Microscopy (AFM).	2017	[102]

Table (1) contd…..

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
							The physical stability of the colloidal dispersions was assessed *via* a Turbiscan Lab. Photochemical stability assessment Thermal stability assessment		
Biocompatible polymeric nanoparticles with exceptional gastrointestinal stability as oral delivery vehicles for lipophilic bioactives	Curcumin was loaded into polymeric nanoparticles, which was synthesized by sodium caseinate and stearic acid-conjugated chitosan.	Curcumin	Antioxidant	Non-traditional	The cellular uptake of FITC[22] labeled was evaluated *via* fluorescence microscope. Entrapment efficiency and loading efficiency were determined *via* UV-Vis spectrophotometer.	-	FTIR analysis ^{1}H NMR[23] analysis Particle size and PDI were measured *via* DLS. Zeta potential was determined *via* laser doppler microelectrophoresis. The morphology of nanoparticles was assessed *via* TEM and CCD camera.	2018	[103]
Fabrication of ovalbumin/κ-carrageenan complex nanoparticles as a novel carrier for curcumin delivery	Curcumin was loaded into nanoparticles, which consisted of ovalbumin and κ-carrageenan.	Curcumin	Anti-carcinogenic Anti-inflammatory Antioxidant	Non-traditional	Entrapment efficiency and loading efficiency were determined *via* HPLC. Antioxidant activity of the system was evaluated *via* the DPPH radical scavenging technique. The *in-vitro* release of curcumin was conducted *via* using UV-VIS spectrophotometer under simulated gastric and intestinal environments.	-	The optical densities were assessed *via* UV-Vis spectrophotometer. The content of curcumin was measured *via* HPLC. FTIR analysis Emulsifying properties were evaluated by measuring the absorbance after the formation of emulsion directly. Particle size, PDI and zeta potential were measured *via* DLS. The morphology of nanoparticles was assessed *via* SEM under simulated gastric and intestinal environments.	2019	[104]
A novel approach based on lipid nanoparticles (SLN®) for topical delivery of -lipoic acid	Alpha lipoic acid was encapsulated within solid lipid nanoparticles (SLN).	Alpha lipoic acid	Anti-aging	Non-traditional	-	-	The particle size and PDI were measured by DLS and Photon Correlation Spectroscopy (PCS). The crystalline structure of the system was assessed *via* Wide-angle X-ray scattering..	2005	[105]

[22] Fluorescein isothiocyanate
[23] Proton nuclear magnetic resonance

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
							DSC analysis UV–Vis spectroscopy analysis Rheological analysis was conducted *via* a rotational rheometer		
Quercetin-nanostructured lipid carriers: Characteristics and anti-breast cancer activities *In vitro*	Quercetin was encapsulated in biodegradable nanostructured lipid carriers (Q-NLC) *via* a phase inversion-based technique.	Quercetin	Anticancer	Non-traditional	Entrapment efficiency and loading capacity were determined *via* HPLC. *In vitro* release study was conducted *via* using HPLC. Cell apoptosis was assessed *via* using both annexin V binding and propidium iodide permeability techniques. The cellular uptake and localization of labeled Q-NLC were assessed *via* fluorescence microscopy.	MTT	The particle size, zeta potential and PDI were measured by DLS and TEM. DSC analysis The encapsulated system was evaluated *via* Raman spectroscopy. The crystalline structure of the system was assessed *via* X-ray diffraction.	2014	[106]
The binary complex based on zein and propylene glycol alginate for delivery of quercetagetin	Zein and propylene glycol alginate (PGA) formed a binary complex in a colloidal dispersion system. The quercetin was loaded in the binary complex by using anti-solvent co-precipitation method.	Quercetin	Antioxidant	Non-traditional	Entrapment efficiency and loading capacity were determined by UV-VIS spectrophotometer.	-	The particle size, zeta potential and PDI were measured by DLS and particle electrophoresis instrument. Fluorescence spectroscopy was used to assess the conformational structure of the system. The change in the secondary structure of zein was observed *via* circular dichroism spectroscopy. The crystalline structure of the system was analyzed by a wide-angle X-ray diffractometer (XRD) The interactions between quercetin, zein and PGA were assessed by using Small Angle X-Ray Scattering (SAXS). FTIR analysis A field emission scanning electron microscope (FE-SEM) was used to evaluate the micro-morphology of the system after lyophilization and heating. The physical stability of the system was evaluated *via* the LUMiSizer.	2016	[107]

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Nanochemoprevention by encapsulation of (-)-epigallocatechin-3-gallate with bioactive peptides/chitosan nanoparticles for enhancement of its bioavailability	Epigallocatechin-3-gallate (EGCG) was encapsulated inside cross linked nanoparticles, which consisted of chitosan (CS) and caseinophosphopeptides (CPPs).	Epigallocatechin-3-gallate	Chemo-preventive potential	Non-traditional	The *In vitro* absorption was mainly predicted from the apparent permeation rate (P_{app}) across the Caco-2 cell monolayers.	MTT	The particle size, zeta potential and PDI were measured by DLS and Atomic Force Microscopy (AFM). HPLC-MS analysis	2012	[108]
Cellular uptake and cytotoxicity of chitosan–caseinophosphopeptides nanocomplexes loaded with epigallocatechin gallate	Epigallocatechin gallate (EGCG) was loaded within nanocomplex particles, which consisted of caseinophosphopeptides (CPPs) and chitosan (CS).	Epigallocatechin gallate	Chemopreventive potential	Non-traditional	The cellular uptake of labeled nanoparticles was assessed *via* fluorescence microscopy. Intestinal permeability of the system was evaluated by using cell monolayer model (Caco-2).	MTT	The particle size, zeta potential and PDI were measured by DLS. Electrophoretic mobility was assessed *via* a Zetasizer Nano-ZS90. FTIR analysis The morphology of system was assessed *via* Atomic Force Microscopy (AFM).	2012	[19]
Improving effectiveness of (-)-epigallocatechin gallate (EGCG) against rabbit atherosclerosis by EGCG-loaded nanoparticles prepared from chitosan and polyaspartic acid	Epigallocatechin gallate (EGCG) was loaded in self-assembled nanoparticles, which consisted of chitosan and polyaspartic acid (PAA).	Epigallocatechin gallate	Atherosclerosis treatment	Non-traditional	Entrapment efficiency and loading capacity were determined *via* HPLC. The release study was conducted *via* using HPLC. *In-vivo* study was performed on male New Zealand white rabbits.	-	The particle size, zeta potential and PDI were measured by DLS. The morphology of the nanoparticles was assessed by TEM. The stability of nanoparticles was evaluated at different pH *via* measuring their particle size and zeta potential. *In-vitro* stability study was conducted at simulated gastric and intestinal conditions.	2014	[85]
Bioactive peptides/chitosan nanoparticles enhance cellular antioxidant activity of (-)-epigallocatechin-3-gallate.	Epigallocatechin gallate (EGCG) was loaded within nanocomplex particles, which consisted of caseinophosphopeptides (CPPs) and chitosan (CS).	Epigallocatechin-3-gallate	Antioxidant Anticancer	Non-traditional	Encapsulation efficiency and *in-vitro* release were assessed *via* using HPLC. Cellular antioxidant activity assay Cellular uptake of nanoparticles was evaluated by inverted fluorescence microscope.	-	The particle size, zeta potential and PDI were measured by DLS. The morphology of the nanoparticles was assessed by Atomic Force Microscopy (AFM).	2013	[109]
Antioxidant nanocomplexes for delivery of epigallocatechin-3-gallate	EGCG was encapsulated into polymeric nanocomplex, which consisted of phenolic acid grafting chitosan and caseinophosphopeptide.	Epigallocatechin-3-gallate (EGCG)	Antioxidant Anticancer	Non-traditional	The antioxidant activity of the nanoparticles was evaluated by DPPH[24] radical assay.	-	The particle size, zeta potential and PDI were measured by DLS. ^{1}H NMR[25] analysis	2016	[110]

[24] 2,2-Diphenyl-1-picrylhydrazyl
[25] Proton nuclear magnetic resonance

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
					The *In vitro* release of EGCG was quantified by HPLC under simulated gastric condition. The encapsulation efficiency of EGCG was assessed by dialysis technique *via* using HPLC. The stability of EGCG was evaluated *via* HPLC at neutral and alkaline pH.		UV-vis spectroscopy analysis FT-IR analysis The morphology of the nanoparticles was assessed by TEM. Phenolic acid was quantified by UV-vis spectrophotometer. The solubility of the system was evaluated in alkaline and neutral pH.		
Zein-based colloidal particles for encapsulation and delivery of epigallocatechin gallate	EGCG was loaded inside zein-based composite colloidal nanoparticles.	Epigallocatechin-3-gallate (EGCG)	-	Non-traditional	Antioxidant activity of polyphenols was assessed *via* using ferric reducing antioxidant power. Encapsulation efficiency was evaluated by UV-Vis spectrophotometer. The Cumulative of released EGCG was evaluated under simulated digestion condition. The efficiency of EGCG on lipolysis was evaluated during intestinal digestion.	-	The particle size, zeta potential and PDI were measured by DLS and electrophoretic mobility. The morphology of the nanoparticles was assessed by TEM.	2017	[111]
Epigallocatechin gallate-loaded polysaccharide nanoparticles for prostate cancer chemoprevention	Epigallocatechin-3-gallate was encapsulated into polysaccharide nanoparticles, which consisted of gum Arabic and maltodextrin.	Epigallocatechin-3-gallate	Chemo-preventive	Non-traditional	The *in-vitro* release of EGCG was quantified spectrophotometrically. Encapsulation efficiency was evaluated by UV-VIS spectrophotometer. The cytotoxic activity of nanoparticles was assessed *via* clonogenic assay and caspase-3 activation assay.	MTT	The particle size and PDI were measured by DLS. Zeta potential was measured by laser doppler velocimetry. The morphology of the nanoparticles was assessed by TEM.	2011	[112]
Anticancer activities of (_)-epigallocatechin-3-gallate encapsulated nanoliposomes in MCF7 breast cancer cells	EGCG was loaded inside nanoliposomes, which were coated with chitosan. The chitosan-coated nanoliposomes consisted of amphipathic phosphatidylcholine and hydrophobic cholesterol.	Epigallocatechin-3-gallate	Breast cancer treatment	Non-traditional	Entrapment efficiency and loading capacity were determined *via* HPLC. The release study was conducted *via* using HPLC Cellular uptake and fluorescent nanoliposome distribution were evaluated *via* fluorescence microscopy. Intracellular uptake was evaluated by measuring the total cellular protein concentrations *via* bicinchoninic acid (BCA) assay. The apoptosis efficacy of nanoliposomes was assessed *via* using a DeadEndTM colorimetric terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick and labeling (TUNEL) kit.	MTT	The size and morphology were assessed *via* SEM. The size and size distribution were measured by Brookhaven BI-MAS analyzer. Zeta potential was measured *via* DLS. EGCG was quantified by HPLC. The stability of nanoliposomes was assessed *via* measuring the changes in the concentration, particle size and zeta potential every 24 hrs.	2013	[113]

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Nanochemo-prevention: Sustained release of bioactive food components for cancer prevention	EGCG was loaded inside polylactic acid (PLA) and polyethylene glycol (PEG) nanoparticles.	Epigallocatechin-3-gallate (EGCG)	Chemo-preventive Anticancer	Non-traditional	The apoptosis efficacy of encapsulated EGCG on prostate carcinoma PC3 cells was evaluated *via* using apo-direct apoptosis kit. The angiogenesis efficacy was evaluated by using Ex ovo chick chorioallantoic membrane (CAM). *In-vivo* study was conducted on xenograft mouse model.	MTT	-	2010	[114]
Oral administration of naturally occurring chitosan-based nanoformulated green tea polyphenol EGCG effectively inhibits prostate cancer cell growth in a xenograft model	Epigallocatechin-3-gallate was encapsulated inside bioresponsive chitosan nanoparticles.	Epigallocatechin-3-gallate (EGCG)	Prostate cancer treatment	-	*In-vivo* study was conducted on xenograft nude athymic mice to assess the anticancer efficacy. Entrapment efficiency and loading capacity were determined by Liquid Chromatography/Mass Spectrometry (LC/MS). The cumulative of EGCG release was evaluated under simulated digestion condition. The antitumor activity of the system against prostatic tumor was evaluated by measuring the level of PSA[26] *via* ELISA assay. Immunohistochemical analysis, immunoblotting analysis and chemiluminescence detection were conducted to assess the anticancer activity of nanoparticles.	-	The particle size, PDI and morphology were measured by DLS and TEM.	2014	[20]
Tea polyphenols association to caseinate-stabilized oil-water interfaces	oil-in-water emulsion	Epigallocatechin-3-gallate (EGCG)	It acts as anti-proliferative and pro-apoptotic.	Traditional	-	-	Surface-weighted mean diameter, volume-weighted mean diameters, particle size distribution and total droplet surface area were measured *via* static light scattering. Zeta potential was measured *via* DLS. The interfacial dilatational elastic of emulsion was assessed *via* drop shape tensiometery.	2015	[115]

[26] Prostate-specific antigen

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Excellent anti-proliferative and pro-apoptotic effects of (-)-epigallocatechin-3-gallate encapsulated in chitosan nanoparticles on human melanoma cell growth both *In vitro* and *In vivo*	EGCG was loaded into chitosan nanoparticles.	Epigallocatechin-3-Gallate (EGCG)	-	Non-traditional	DNA cell cycle analysis was conducted to evaluate the apoptosis efficacy of nanoparticles. *In-vivo* study was conducted on xenograft male nude mouse model. Immunohistochemical and western blot analyses were conducted to assess the anticancer activity of nanoparticles.	MTT	-	2014	[116]
Beta-carotene encapsulated in food protein nanoparticles reduces peroxyl radical oxidation in Caco-2 cells	Beta-Carotene (BC) was loaded inside nanoparticles, which consisted of Whey Protein Isolate (WPI), Sodium Caseinate (SC), and Soybean Protein Isolate (SPI) *via* using homogenization-evaporation method.	Beta-Carotene (BC)	Antioxidant	Non-traditional	Chemical antioxidant efficacy was evaluated *via* measuring ferric reducing antioxidant power, DPPH radical scavenging activity, Cellular Antioxidant Activity (CAA) and hydroxyl radical scavenging activity. *In-vitro* release of BC was evaluated by using two proteases to simulated the gastric and intestinal conditions.	-	The particle size, zeta potential and PDI were measured by DLS. The crystalline structure of the system was assessed *via* X-ray diffraction. Attenuated Total Reflectance Fourier-Transform Infrared Spectroscopy (ATR-FTIR) was used to assess the different functional groups of nanoparticles. DSC analysis.	2015	[117]
Thermal degradation and isomerization of β-carotene in oil-in water nanoemulsions supplemented with natural antioxidants	β-Carotene (BC) was loaded into oil-in-water nanoemulsions in a combination with natural antioxidants, including α-tocopherol (AT) and L-Ascorbic Acid (AA).	Beta-Carotene (BC)	Antioxidant	Non-traditional	-	-	BC Isomers was evaluated *via* HPLC. The particle size, zeta potential and PDI were measured by DLS. Extraction and determination of BC was quantified *via* HPLC. The stability of nanoemulsions was assessed *via* measuring the changes in the concentration, particle size and zeta potential for 30 days.	2016	[253]
Fabrication of β-carotene nanoemulsion-based delivery systems using dualchannel microfluidization: Physical and chemical stability	β-Carotene was loaded into oil-in-water nanoemulsions by fabricating *via* using high-pressure dual-channel microfluidization.	Beta-Carotene (BC)	Antioxidant	Non-traditional	-	-	The particle size, zeta potential and PDI were measured by static light scattering. The microstructure of nanoemulsion was assessed by optical and confocal fluorescence microscopy.	2017	[119]

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
							The chemical and physical stability of nanoemulsions were assessed *via* measuring the changes in the concentration, particle size and zeta potential for 14 days at different thermal conditions.		
Eugenol improves physical and chemical stabilities of nanoemulsions loaded with β-carotene	β-carotene was encapsulated into nanoemulsions, which consisted of whey protein, lecithin, eugenol and soybean oil.	Beta-Carotene (BC)	Antioxidant	Non-traditional	Antioxidant efficacy was evaluated *via* DPPH and ABTS[27] assay.	-	The morphology of the nanoemulsion was assessed by Atomic Force Microscopy (AFM). The chemical and physical stability of nanoemulsions were assessed *via* measuring the changes in the concentration, particle size and zeta potential every 6 days at ambient temperature. The degradation kinetics of BC was assessed *via* UV-Vis spectrophotometer. The particle size, zeta potential and PDI were measured by *via* DLS. The portioning of eugenol between soybean oil and water was measured by HPLC.	2016	[120]
Fabrication of concentrated fish oil emulsions using dual-channel microfluidization: impact of droplet concentration on physical properties and lipid oxidation	Fish oil-in-water emulsions that contained high level of ω-3 Polyunsaturated Fatty Acids (PUFA) was prepared *via* dual-channel microfluidization technique.	PUFA-rich fish oils	It reduces the risk of coronary heart disease, hypertension, and enhances the brain functions.	Non-traditional	-	-	Interfacial tension was measured *via* a drop shape analysis instrument. The zeta potential was measured by particle electrophoresis. The surface-weighted mean particle diameter and PDI were determined *via* a static light scattering. The analysis of rheological properties of nanoemulsion was conducted *via* dynamic shear rheometer.	2016	[18]

[27] 2,2′Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
							The oxidative stability of nanoemulsions were assessed *via* measuring the concentration of lipid hydroperoxides every 3 days by spectrophotometer		
Physical stability, autoxidation, and photosensitized oxidation of ω-3 oils in nanoemulsions prepared with natural and synthetic surfactants	Omega-3 oil-in-water nanoemulsion was prepared *via* dual-channel microfluidization technique.	Omega-3 oil	It reduces the risk of coronary heart disease, inflammation, and enhances the brain functions.	Non-traditional	Antioxidant efficacy of surfactants was assessed *via* the Oxygen Radical Absorbance Capacity assay (ORAC). Lipid oxidation was evaluated *via* measuring hydroperoxides and propanal by UV–VIS spectrophotometer.	-	The particle size, zeta potential and PDI were assessed *via* a particle electrophoresis instrument. The stability of nanoemulsions was assessed *via* observing changes in the concentration, particle size and appearance (creaming or aggregation) at room temperature for 24 hours. The absorbance of each surfactant was assessed *via* UV-vis spectrophotometer.	2015	[47]
Controlled release of caffeine from tablets of spray-dried casein gels	Elastic controlled release of casein-caffeine tablet	Caffeine	Psychoactive natural substance stimulant	Non-traditional	-	-	Dynamic mechanical analyzer was used to evaluate mechanical properties and softness of the system. DSC scanning FTIR analysis The released caffeine was quantified *via* UV-Vis spectroscopy. The morphology of the system was assessed by SEM.	2019	[121]
***In vitro* digestion of lactoferrin-glycomacropeptide nanohydrogels incorporating bioactive compounds: Effect of a chitosan coating**	Curcumin or caffeine was loaded into chitosan coated nanohydrogel, which consisted of Lactoferrin (Lf) and Glycomacropeptide (GMP).	Caffeine or Curcumin	Antioxidant	Non-traditional	Antioxidant efficacy was evaluated *via* DPPH assay.	-	The particle size, zeta potential and PDI were assessed *via* DLS under gastric and intestinal conditions. Curcumin and caffeine were quantified *via* HPLC. Both Lf and GMP were quantified *via* reversed phase HPLC. The digestion process of nanohydrogels was assessed *via* TEM.	2018	[16]

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Effect of grafting method on the physical property and antioxidant potential of chitosan film functionalized with gallic acid	Gallic acid grafted chitosan (GA-g-CS) film	Gallic acid	Antioxidant	Non-traditional	Antioxidant efficacy was evaluated *via* DPPH assay.	-	Grafting ratio was assessed *via* Folin–Ciocalteu assay. UV-Vis spectroscopy analysis FT-IR analysis DSC analysis The crystalline structure of the GA-g-CS films was assessed *via* X-ray diffraction. The color of the synthesized GA-g-CS films was evaluated *via* SC-80C Colorimeter. The thickness of GA-g-CS films was assessed by Mitutoyo digital micrometer. The light transmittance and opacity of GA-g-CS films was assessed by UV-Vis spectroscopy. The water vapor permeability of the synthesized GA-g-CS films was evaluated *via* using test tube. Mechanical properties of GA-g-CS films, including elongation at break and tensile strength were assessed by TMS-Pro texture analyzer. The microstructure of the GA-g-CS films was assessed *via* SEM.	2019	[17]
Encapsulation of garlic extract using complex coacervation with whey protein isolate and chitosan as wall materials followed by spray drying	Garlic acid was encapsulated into coacervates, which consisted of whey protein isolate and microparticles.	Gallic acid	Anticancer Antimicrobial Antioxidant Hypolipidemic Anti-inflammatory Hypoglycemic Anticoagulant Antihy-pertensive	Non-traditional	Antioxidant efficacy was evaluated *via* DPPH and ABTS assay.	-	Zeta potential was measured *via* DLS. Rheological analysis was conducted *via* a rotational parallel plate rheometer. Spectrophotometric analysis The Folin–Ciocalteu was used to measure the Total Phenolic Content (TPC).	2019	[122]

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
							Different properties of microparticles were assessed, including solubility, hygroscopicity, water activity and moisture content. Microparticles morphology was evaluated *via* SEM. DSC analysis FTIR analysis		
Grafting of gallic acid onto chitosan enhances antioxidant activities and alters rheological properties of the copolymer	Gallic acid was grafted onto chitosan (GAg-CS).	Gallic acid	Antioxidant	Non-traditional	Antioxidant efficacy was evaluated *via* DPPH, ABTS, superoxide radicals, metal chelating ability, β-carotene-linoleic acid, lipid peroxidation inhibition and total antioxidant capacity assay.	-	Structural properties of GAg-CS were evaluated by NMR and UV−Vis spectrophotometer. Total Phenolic (TP) concentrations was assessed according to Folin–Ciocalteu procedure. Rheological analysis was conducted *via* a rotational rheometer.	2014	[123]
Preparation and characterization of antioxidant and pH-sensitive films based on chitosan and black soybean seed coat extract	Black soybean seed coat extract was loaded into pH-responsive chitosan film.	Black Soybean Seed Coat Extract (BSSCE)	Antioxidant pH-sensing food packaging materials	Non-traditional	Antioxidant activity of the system was evaluated *via* the DPPH assay. The change of the film color according to pH was evaluated by using digital camera and SC-80C colorimeter.	-	Anthocyanins were quantified *via* HPLC-MS. The color of the synthesized BSSCE films was evaluated *via* SC-80C Colorimeter. The thickness of BSSCE films was assessed by Mitutoyo digital micrometer. The water vapor permeability of the synthesized BSSCE films was evaluated *via* using test tube, which was covered with silica gel. Moisture content and water solubility were evaluated. The light transmittance and opacity of BSSCE films was assessed by UV-Vis spectroscopy Mechanical properties of BSSCE films, including elongation at break and tensile strength were assessed by TMS-Pro texture analyzer.	2019	[124]

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
							DSC analysis Microparticles morphology was evaluated *via* SEM. FTIR analysis XRD analysis		
Interpenetrating network gels composed of gelatin and soluble dietary fibers from tomato peels	Cross-linked, soluble dietary fibers consisted of gelatin chains and tomato peels.	Tomato peels	Enhancing food stability Improving food texture	Non-traditional	-	-	Rheological analysis was conducted *via* a rotational rheometer. Fibers morphology was evaluated *via* SEM. The texture profile analysis was performed *via* using TA-XT plus texture analyzer. Water holding capacity, freeze-thaw stability and swelling capacity were evaluated.	2019	[125]
Protocatechuic acid grafted onto chitosan: Characterization and antioxidant activity	Protocatechuic acid chitosan copolymer was grafted *via* carbodiimide mediated cross-linking reaction.	Protocatechuic acid	Antioxidant	Non-traditional	Antioxidant activity of the system was evaluated *via* the DPPH and reducing power assay.	-	Grafting ratio was assessed *via* Folin–Ciocalteu assay. UV–vis spectroscopy analysis FT-IR analysis ^{1}H NMR spectroscopy analysis CP-MAS[28] NMR spectroscopy analysis DSC analysis The morphology and size of nanoparticles were assessed *via* SEM. X-ray diffraction analysis	2016	[126]
Preparation, characterization and antioxidant activity of phenolic acids grafted carboxymethyl chitosan	Gallic acid, ferulic acid and caffeic acid were grafted onto N,O-carboxymethyl chitosan.	Gallic acid Ferulic acid Caffeic acid	Antioxidant	Non-traditional	Antioxidant activity of the system was evaluated *via*: 1- DPPH assay 2- Superoxide hydroxyl radical scavenging activities assay 3- Reducing power assay 4- Thiobarbituric acid reactive substances assay was used to evaluate the inhibition effect of lipid peroxidation.	-	Grafting ratio was assessed *via* Folin–Ciocalteu assay. UV–Vis spectroscopy analysis FT-IR analysis ^{1}H NMR spectroscopy analysis X-ray diffraction analysis	2013	[127]

[28] Cross polarization magic angle spinning

Table (1) contd….

Paper Title	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional/ Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
The effect of the molecular architecture on the antioxidant properties of chitosan gallate	Chitosan gallates copolymer was prepared *via* free radical grafting reaction.	Gallic acid	Antioxidant	Non-traditional	Antioxidant activity of the copolymer was evaluated *via* DPPH assay.	MTT	FT-IR analysis ^{1}H NMR spectroscopy analysis The crystallographic of copolymer was assessed *via* X-ray diffraction analysis.	2016	[128]
Pickering emulsions co-stabilized by composite protein/ polysaccharide particle-particle interfaces: Impact on *In vitro* gastric stability	Gastro-stabilized, sustained release Pickering oil-in-water emulsion was synthesized by using Lactoferrin nanogel particles (LFN) and leuconostoc citreum (INP).	-	-	Non-traditional	*In-vitro* release study was conducted to assess the effect of gastric digestion on the microstructure of Pickering emulsion.	-	The particle size, zeta potential and PDI were assessed *via* DLS. The morphology of prepared system was assessed *via* TEM. The microstructure of the emulsions was evaluated by optical light microscope. The gastric stability of Pickering emulsion was evaluated by observing the proteolysis patterns *via* SDS-PAGE[29] analyses.	2018	[129]

[29] Sodium dodecyl sulphate-polyacrylamide gel electrophoresis

Khan *et al*. [20] designed bioresponsive chitosan nanoparticles. These nanoparticles were loaded with EGCG, which released slowly at acidic, gastric condition and rapidly at alkaline, intestinal condition. Hence, the system protected EGCG against acidic degradation so that bioresponsive nano-EGCG was successfully administered orally. Additionally, *in-vivo* study was performed on xenograft nude athymic mice to evaluate the anticancer efficacy. As a result of that this system showed greater efficacy in treating prostate cancer, as shown in Table **1** [20].

Wang *et al*. [124] used pH responsive system in a different application (biodegradable food packaging). Chitosan has good mechanical strength and gas permeability. It is also edible and biodegradable [124]. Hence, Wang and his team loaded Black Soybean Seed Coat Extract (BSSCE) into pH-responsive chitosan film. BSSCE is a plant-derived phenolic compound that has antioxidant activity. The synthesized chitosan-BSSCE film that consisted of 15 wt% of BSSCE was the best food packaging and antioxidant. Finally, the system improved UV-vis light barrier characteristics, antioxidant activity, mechanical strength, thermal stability and other properties [124].

Tan *et al*. [121] designed a novel, controlled release matrix that consisted of casein gel to sustain the release of caffeine (Table **1**). Casein is a milk protein that is considered a good candidate for delivering and targeting [178]. Casein possesses excellent criteria as a delivery system, including high ion binding affinity, small size, water binding capacity, high stability and good emulsifying properties. It can also be used as a controlled delivery system due to its gel swelling property as a response to pH [178]. Additionally, caffeine is a natural ingredient that is mainly used in modulating cognitive brain functions [179].

3.7. Nanohydrogel

Nanohydrogel is a water-swellable, cross-liked polymeric system that does not dissolve in water [180]. It improves nutraceuticals bioavailability and selectivity [181]. Nanohydrogel is mostly prepared by two main steps. First, the polymeric system is synthesized. Secondly, the formed biopolymers are cross-linked. Hydrophilic nutraceutical ingredients are mixed with the formed biopolymer before synthesis of hydrogel system. In contrast, lipophilic nutraceutical ingredients are encapsulated into lipid droplets, such as emulsion or nano-emulsion. Nanohydrogel has three-dimensional structure, large surface area and hydrophilic nano-sized networks. Hence, this structure controls the release of active ingredient and enhances bioavailability and stability [180].

Bourbon *et al*. [16] synthesized chitosan coated nanohydrogel, which consisted of lactoferrin (Lf) and glycomacropeptide (GMP) (Table **1**). In this study, the effect of chitosan on active ingredient delivery was assessed. Hence, curcumin and caffeine were used to represent a lipophilic model and hydrophilic model, respectively [16]. Antioxidant efficacy was evaluated *via* conducting DPPH assay. The system increased the bioaccessibility of the lipophilic model

to 72%. Moreover, coated curcumin preserved 70% of its antioxidant activity under simulated gastric and intestinal condition. However, the free curcumin showed a loss of 68% of its antioxidant activity under the same conditions [16]. The bioaccessibility of coated caffeine and its free form were 63% and 59%, respectively [16].

3.8. Lipid Based Carriers

3.8.1. Liposomes

Liposome is traditional lipid-based carrier. It was prepared for the first time by Alec D Bangham in 1965 [182]. Liposomes are spherical vesicles that consist of a lipid bilayer membrane and an aqueous cavity. The coinage of liposome was originated from two Greek terms namely; lipid (fat) and soma (body). Liposomes have been classified based on their size, preparation and lamellarity. First, according to their size, they have been classified into small, intermediate and large. Secondly, according to preparation, they have been categorized into reverse-phase evaporation liposomes or vesicle extruded technique. Lastly, liposomes have been categorized into monolamellar, oligolamellar or multilamellar vesicles [183] based on their lamellarity.

Moreover, liposomes are able to protect active ingredients against enzymatic degradation. Moreover, they are flexible, biocompatible and non-toxic carriers. They have the merits of dual drug delivery by loading drugs with different physicochemical properties in their core and lipid bilayer [184]. For hydrophobic drugs, liposomes improve their solubility, stability and bioavailability [184]. However, liposomes suffer from some drawbacks, such as short half-life, poor stability, low loading capacity and high cost. Liposomes are removed rapidly *via* reticuloendothelial system.

Gao *et al*. [142] loaded natural ingredients into liposomal system. Moreover, it was claimed that the system could also be formulated in the form of sustained released tablets, gel powder, lotion and other dosage form (Table **2**). The natural ingredients were crocin, crocetin, green tea extract, curcumin, resveratrol, panax ginseng extract, α-lipoic and/or L-carnitine. The synthesized formulation was used in treating cancer and improving health [142]. In another patent, Underwood *et al*. [149] prepared nanoparticles of whole fruits (black chokeberries, cherries, plums, blueberries, pomegranates, raspberries, cranberries and/or black elderberries) and encapsulated them into emulsion and/or liposome. It was claimed that the prepared formulation was used in decreasing symptoms of arthritic pain, diabetes, gout and others [149] (Table **2**).

Moreover, Richard *et al*. [144] formulated pegylated or cationic liposomes or niosome to encapsulate the active ingredients into. It was claimed that the natural components were parts of natural plants, such as coffee bean, aloe vera, hazelnut oil, almond oil and others. Furthermore, Richard and his team claimed that their system had many uses such as rejuvenation of stratum corneum and epi-dermis, treatment of acne and anti-wrinkles. The morphology and size of vesicles were evaluated by TEM. Lastly, particle size, PDI and zeta potential were measured *via* DLS [144].

3.8.2. Solid Lipid Nanoparticles (SLNs) and Nanostructure Lipid Carriers (NLCs)

SLNs and NLCs have been introduced into the delivery systems since 1990 as substitutes of traditional liposomes, polymeric nanoparticles and emulsions [182].

3.8.2.1. Solid Lipid Nanoparticles (SLNs)

Solid Lipid Nanoparticles (SLNs) have spherical structure and nano-ranged size (around 40 to 1000 nm). SLNs consist of surfactant (0.1 to 30 % w/w) and solid fat (0.5 to 5%). They are solid at body and ambient temperature [182]. Furthermore, particle size, stability and drug loading depend on type of lipid and surfactant [185]. SLNs are considerably suitable for both hydrophilic and lipophilic drugs [186]. However, the drug loading capacity depends on drug lipophilicity [187]. Moreover, system instability during storage and high water content have been reported as disadvantages [187].

α-Lipoic acid is a natural antioxidant that is utilized in antiaging topical preparation. It has low irritation effect compared to other antiaging agents. Additionally, α-lipoic is useful for treating delicate areas (area around the eye) [105]. α-lipoic acid suffers from chemical degradation, which leads to bad odor in topical preparations. Souto *et al*. [105] solved such problem by incorporating α-lipoic acid into SLNs. Moreover, loaded α-lipoic acid showed higher occlusive effect. Hence, the system increased skin hydration and protection against UV irradiation [105].

Furthermore, Reyes *et al*. [165] claimed that both pharmaceutical or natural ingredients, such as ellagic acid dehydrate, vitamins and/or minerals can be loaded into solid nanoparticles, lipid-based carrier, lipid-containing nanoparticles, tablets, sealed conduit or others (Table **2**). It was also claimed that these systems were used in treating and preventing hyperglycemia, obesity, diabetes type I & II, gestational diabetes, latent auto-immune diabetes, metabolic syndrome, Alzheimer, liver disease, kidney disease, and others [165].

3.8.2.2. Nanostructure Lipid Carriers (NLCs)

Nanostructure Lipid Carriers (NLCs) are considered a modification of SLNs [182]. The main modification is that the lipids of NLCs are a mixture of both solid and liquid oils. Therefore, NLCs enhance stability and drug loading [181]. NLCs were introduced in 1999 to overcome SLNs drawbacks, such as low drug loading capacity and instability (drug expulsion) [187].

Resveratrol is a naturally occurring anticancer agent [188]. However, resveratrol suffers from photosensitivity, low solubility and oral bioavailability [189]. Neves *et al*. [88] utilized SLNs and NLCs to encapsulate resveratrol. Both systems enhanced trans-resveratrol protection against photodegradation. Furthermore, NLCs succeeded to improve resveratrol encapsulation. Additionally, NLCs prevented its rapid crystallization and release in GIT. Clearly, both systems enhanced resveratrol oral bioavailability for cancer treatment, as shown in Table **1** [88].

3.8.3. Nanoliposome

Nanoliposomes are lipid vesicles in nano-sized scale [168]. The reduction of liposomal system size leads to in-

creased surface area. Hence, the bioavailability of nanoliposomes is enhanced [168]. Therefore, nanoliposomes are used widely in nutraceuticals industry to maximize the safety and efficacy of these products. For example, EGCG has low stability in water and physiological fluid [190]. Therefore, de Pace *et al*. [113] loaded EGCG into nanoliposome, which composed of phosphatidylcholine and cholesterol to overcome this problem. Moreover, nanoliposomes were coated with chitosan to enhance the absorption, as shown in Table **1**.

3.8.4. Nanoemulsion

Nanoemulsion was invented for the first time in 1950. It is a single-phase and stable system. Nanoemulsion is a nano-sized emulsion with nano-sized droplets (20-600 nm) [191]. It generally consists of oil, water, surfactant and cosurfactant. Nanoemulsions were classified into three categories: water in oil, oil in water and bi-continuous nanoemulsions. Nanoemulsions are usually translucent dispersions due to their small droplet size which prevents flocculation. They are suitable for hydrophobic drugs delivery due to high solubilization capacity [191]. Nanoemulsion is utilized beneficially in drug delivery since it increases the loading capacity, stability and bioavailability of drugs [192]. Nanoemulsion can allow sustained or controlled release [193].

Gamay *et al*. [158] prepared nutraceutical formulation containing theobromine, caffeine, amino acids and other ingredients to modulate the cognitive brain functions, improve memory and enhance energy. Nanoemulsion was prepared *via* sodium alginate as encapsulant and cocoa protein as emulsifier. Nanoemulsion with stabilized fat droplet resulted in controlled release of the active ingredients (Table **2**) [158]. In another patent, acylethanolamides were encapsulated in nanoemulsion to treat or prevent alcohol dependence syndrome and alcohol intoxication, as shown in Table **2** [148].

β-Carotene has an important role in improving vision and treating vitamin A deficiency since it is the precursor of vitamin A [118]. β-carotene is a hydrophobic nutraceutical, which requires novel system for its delivery due to its limited solubility. Luo *et al*. [119] encapsulated β-carotene into oil-in-water nanoemulsions *via* high-pressure, dual-channel microfluidization. Moreover, its dispersibility in water and stability were enhanced by using quillaja saponins and whey protein isolate as emulsifiers. Luo and the rest of the team measured the particle size, zeta potential and PDI by static light scattering technique. Additionally, the microstructure of nanoemulsion was assessed by optical and confocal fluorescence microscopy, as shown in Table **1** [119].

Mendes *et al*. [98] formulated a nanoemulsion to encapsulate Eugenia brejoensis essential oil to use it as a food preservative. The synthesized nanoemulsion showed greater antimicrobial activity (Table **1**). Moreover, omega-3 polyunsaturated fatty acids have great efficiency to reduce risks of coronary heart diseases [194]. Thus, Uluata *et al*. [47] formulated oil-in-water nanoemulsion *via* dual-channel microfluidization technique to encapsulate omega-3 into it. It was reported that this formulation reduced the risk of coronary heart disease and inflammation. It also enhanced the brain functions (Table **1**) [47].

3.9. Dendrimers

Dendrimers are highly branched and nanoscaled polymeric macromolecules, which have a three-dimension structure. The term of dendrimer came from the Greek term 'dendron' [195]. Dendrimers were first introduced in 1978 by Vogtle [195]. Dendrimers have three basic components: core, repeated units (branches) and terminal functional group. The core of dendrimers consists of polymer, such as polyamidoamine (PAMAM), ethylene diamine (EDA), diaminobutyl (DAB), polypropylimine (PPI) and others. The branches of dendrimers are residues, such as carboxyl group, amino group and other groups, which are attached directly to the core. The size of dendrimers can be controlled by numbers of these added groups, which are coined as (generation).

Dendrimers are considered attractive drug delivery systems because they can be fully controlled [196]. The size, surface charge and architectural structure can be easily modified. The active ingredient can be encapsulated into their core or conjugated with their surface [196]. In contrast to traditional polymers, dendrimers are highly soluble, biocompatible and polyvalent with definite molecular weight [197]. Dendrimers have high entrapment efficiency, very small size up to 5 nm and low dispersity index [198]. Additionally, active component can be either attached to the surface or chemically reacted with the functional group [196].

However, the major drawback of dendrimers is their cytotoxicity, which is highly related to their cationic characteristics. These nanoparticles react strongly with the cell membrane causing cell lysis [199]. There were different trials using dendrimers to deliver natural ingredients. For example, Krueger *et al*. [136] claimed that they loaded ammonia oxidizing microorganisms into novel delivery systems, such as emulsion, nanocapsules, liposomes, dendrimers and others. It was also claimed that this system was able to treat neurological, nasal or sinus disorders, diabetes, bacterial vaginosis and dermal diseases [136].

3.10. Biopolymer Nanoparticles

Biopolymers are polymers of natural origin, including proteins, polysaccharides and nucleic acids [200]. Furthermore, they have been mostly classified based on their structure into inclusion, hydrogels and polyelectrolyte complexes [201]. Their particle size is considered to be a critical factor that affects the physicochemical characteristics, encapsulation, GIT stability and absorption of active ingredient [201]. Biopolymer nanoparticles are suitable for clinical application because they are biodegradable, non-toxic and biocompatible [200]. Moreover, proteins are highly stable and have good binding capacity. Thus, protein based nanoparticles are highly promising model as a drug carrier [200]. A wide range of proteins have been utilized to produce nanoparticles including casein, collagen, zein, elastin, silk fibroin and others [202].

Patel *et al*. [97] prepared zein-quercetin colloidal composite nanoparticles to overcome many quercetin problems, such as poor aqueous solubility, low bioavailability and extensive intestinal degradation (Table **1**). Quercetin is a natural flavone that exhibits anticancer, antiviral and antioxidant

Table 2. Recent patents adopting novel formulation strategies in ultraceuticals.

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Composition and method for dermal regeneration	**EP2229175A4**	Gel consisted of cross linked chitosan and glucomannan nanoparticles.	Glucomannan	Skin regeneration Wound healing	Non-traditional	Efficacy of nanoparticles on healing skin irritation was assessed *via* FLIM[1]. *In-vivo* study: a) Dermal irritation reduction was observed visually in injected rabbits. b) Proliferation and intradermal distension of collagen within dermis was assessed. c) The histology of lesions was observed *via* light microscopy.	-	The size of nanoparticles was measured *via* SEM[1].	2015	[130]
Microparticles for the encapsulation of probiotics, preparation and uses thereof	**EP2868206A2**	Probiotic bacteria were encapsulated into microparticles, which was consisted of chitosan and casein, which was cross-linked with calcium salts, vanillin or tripolyphosphate.	Probiotic bacteria	It was used in preventing and treating immune system impairment.	Non-traditional	*In-vivo* study: (mice) Immunophenotypic evaluation of peripheral lymphocytes was conducted. The resistance of probiotic bacteria was evaluated under gastric condition.	-	The size of nanoparticles was assessed *via* light microscopy and Colorview Soft Imaging Systems camera. The morphological structure of nanoparticles was measured *via* SEM. The survival rate of probiotic bacteria was evaluated. The bacterial count and death cycle were assessed. The storage stability was conducted at 25°C. The encapsulated bacteria were evaluated *via* fluorescence light microscopy.	2016	[131]
Nutraceutical co-crystal compositions	**US20100204204A1**	Co-crystals consisted of nutraceutical (epigallocatechin-3-gallate, quercetin, or hesperitin) and co-crystal former (caffeine, theobromine, or theophylline).	Quercetin	-	Non-traditional	-	-	DSC analysis The crystalline structure of the system was assessed *via* wide-angle X-ray diffraction. FTIR[1] analysis Raman spectroscopy analysis Thermogravimetric analysis Digital microscopic image of the system was taken. The solubility of quercetin was assessed *via* UV-VIS spectrophotometer[1].	2010	[132]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Composition comprising curcumin-captured ginsenoside and phospholipid-based lipid nanoparticle as effective ingredient for preventing or treating *Helicobacter pylori* infection	WO2018135912A2	Curcumin was encapsulated within controlled ginsenoside or phospholipid-based nanoparticles.	Curcumin	It was used in preventing and treating *Helicobacter pylori* infection.	Non-traditional	Antibacterial activity was assessed by MIC[1] *via* using agar dilution method.	-	Solubility was assessed *via* HPLC. Particle size, PDI and zeta potential were determined *via* DLS[1]. The morphological structure of nanoparticles was measured *via* light microscopy. The entrapment of curcumin was assessed *via* HPLC. Storage stability of nanoparticles was assessed by measuring their zeta potential for a year in refrigerator.	2018	[133]
Crystallized xylose isomerase in prevention of the development of non-alcoholic fatty liver disease	US20170056485A1	Enteric coated pellets consisted of crystalline xylose-isomerase, which co-crystallized with a magnesium salt or a bivalent metal salt.	Crystalline xylose-isomerase	It was used in preventing and treating non-alcoholic fatty liver and fructose-related disorders.	-	*In-vivo* study (rats): a) The body weight of each rat was measured. b) The levels of uric acid and iron were assessed for homogenized liver specimens. c) Cytokines and leptin were quantified. d) The quality control of clinical chemistry parameters was evaluated by the control serum Lyonorm Human N. e) Histopathological and pathogenic assessment were conducted. f) Different parameters, including TAG[1], ALT[1], AST[1], GMT, glucose, cholesterol, albumin, and insulin were measured.	-	Temperature stability of crystalline xylose-isomerase was assessed by measuring its activity. The pH-dependency of the system activity was assessed *via* measuring the level of fructose.	2017	[134]
Red propolis caseinates, process for producing red propolis caseinates, composition, use of the red propolis caseinates and use of the composition	WO2018126304A1	Red propolis caseinates were loaded into immediate released microcapsules, which were coated with a binary system (sodium casein and silicon dioxide).	The active ingredients were red propolis caseinates and other natural ingredients, such as green coffee, vitamins, espresso and others.	Antibacterial Anti-inflammatory Antioxidant	Non-traditional	Antioxidant activity was assessed *via* DPPH[1] test. Antibacterial activity was evaluated by disk diffusion method through using *Staphylococcus aureus* and *Pseudomonas aeruginosa.*	-	The morphological structure and size of nanoparticles were measured *via* SEM. DSC analysis FTIR-ATR analysis The dissolution of red propolis caseinates was assessed *via* UV-Vis spectrophotometer. Polyacrylamide gel electrophoresis was conducted to assess the integrity of protein encapsulating agent.	2018	[135]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Formulations containing omega-3 fatty acids or esters thereof and maqui berry extract and therapeutic uses thereof	US20180243253A1	The active ingredients were loaded into soft gel capsules. Additionally, it was claimed that the active ingredients could be loaded into nanoparticles and other sustained released, novel formulations.	Omega-3 fatty acids or esters Maqui berry extract	It was used in treating ocular diseases and other disease, such as cancer, inflammation and heart disorders.	Traditional/ non-traditional	Clinical Study a) Tear osmolarity value was measured *via* TearLab® Osmolarity System. b) Matrix metalloproteinase-9 (MMP-9) level was evaluated by conducting the InflammaDry test. c) Corneal staining was assessed by using Oxford staining scale. d) Questionnaire, TBUT[1], and Schirmer's Test were were conducted.	-	-	2018	[37]
Ammonia oxidizing microorganisms for use and delivery to the intranasal system	WO2018057710A1	It was claimed that the active ingredients were encapsulated into novel delivery systems, such as emulsion, nanocapsules, liposomes, dendrimers and others.	Ammonia oxidizing micro-organisms	Treatment of neurological, nasal or sinus disorders Anti-inflammatory Treatment of bacterial vaginosis Treatment of dermal diseases Treatment of diabetes	Traditional/ non-traditional	-	-	-	2018	[136]
Bioproduct based on selenium nanoparticles in a honey matrix for the treatment of complex injuries and dermatological infections	WO2018176168A1	The system consisted of selenium nanoparticles and honey matrix.	Selenium Honey	The formulation was used for treating different diseases such as, skin injuries, fungal infection, dermatophyte infection and other skin diseases, which have been caused by chronic diseases, such as diabetes.	Non-traditional	The antifungal activity of the system against Candida was assessed *via* measuring MIC[1] of candida albicans. Clinical study was conducted by applying the formulation on an 80-year patient and evaluating wound tissue reconstitution.	-	Particle size measurement	2018	[137]
Diabetes preventing and treating nutritional formula nanoparticles and preparing and processing method thereof	CN106174011A	The natural ingredients were loaded into nanoparticles.	The active ingredients were Chinese yams, *Radix astragal*, *Rhizoma anemarrhenae*, chicken's gizzard-membranes, *Radix puerariae*, raw gypsum, *Rhizoma alismatis* and/or others	The formulation was used to treat or prevent many disease, such as diabetes, heart diseases and others. It was used for Improving the immunity and salivation. It was used as antiaging.	Non-traditional	Clinical study was conducted on volunteers to evaluate the efficacy of the system by checking certain symptoms, such as fatigue, palpitation weight reduction, palpitation and others.	Acute toxicity was assessed on mice. Long term animals' toxicity test was conducted on animals. a) pathological examination was conducted on animals 'organs. b) Liver serum level was measured.	-	2016	[138]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Methods and compositions for the treatment of disease	WO2018129315A1	It was claimed that the active ingredients could be loaded into different delivery systems, such as nanoparticles, microemulsion (oil-in-water), film coated micro-crystals and others.	Th active ingredients were gingerol (*e.g.*, 6-gingerol) Or shogaol (*e.g.*, 6-shogaol) Or capsaicinoid (*e.g.*, capsaicin) or other natural/ pharmaceutical ingredients.	The formulation was used for treating or preventing different diseases, such as Charcot Marie tooth disease, myoclonic seizures, tardive dyskinesia, Friedrich's ataxia and side effects of cancer.	Non-traditional	-	-	Particle size measurement	2018	[139]
Compositions, methods, and medical compositions for treatment of and maintaining the health of the liver	US20170035829A1	The active ingredients were loaded into microsphere, liposome or other delivery systems. Additionally, it was also claimed that the active ingredients could be conjugated with monoclonal or polyclonal antibody.	Myristica extract Astragalus extract Poria extract	The system was used to prevent or treat hepatic disorders.	-	*In-vivo* study: (mice) Liver enzyme level was measured for acetaminophen-induced and CCl4 induced hepatotoxic model. GSH↓, SODs↓ and TG↑ were measured. *In vitro* histopathological scoring was conducted on ethanol-induced hepatotoxic models.	-	The content of the system was analyzed *via* HPLC. Particle size measurement	2017	[21]
Novel composition of *Nigella sativa* seeds to treat anxiety, stress and sleep disorders with significant memory enhancement properties and a process for producing the same	US20180125914A1	Free flowing powder	Black cumin extract Thymoquinone	Treatment of sleep disorders Enhancing the memory Anti-anxiety	-	The efficacy of anti-anxiety, learning ability and memory activity were evaluated *via* using elevated plus maze. The effect of the formulation on AchE↓ inhibitory assay was evaluated *via* using Ellman's method. The efficacy of the system on sleep quality was assessed *via* using sleep quality index (PSQI). The efficacy of the system on anxiety depression anxiety stress scales-21 (DASS-21). The effect of the system on U373-MG and IMR32 cell line were studied.	Toxicological study was conducted on Albino Wistar rats, and different vital parameters were assessed.	Thymoquinone was measured *via* HPLC. Black cumin oil (fatty acid) was evaluated *via* gas chromatography. The storage stability was assessed.	2018	[140]
Nutraceutical plant derived microRNA elements for treatment of cancer	EP3216869A1	Foods contained plant-derived miRNA. Additionally, it was claimed that other formulations could be a mixture of natural ingredients and pharmaceutical ingredients (ibuprofen and paracetamol).	Plant-functional microRNA or an extract	Anticancer	Non-traditional	The transfection efficiency of labeled plant-miRNA was assessed *via* flow cytometry analysis and trypan blue assay. The expression of SIRT1↑ and Bcl-2↓ was assessed.	Apoptosis was assessed *via* measuring the percentage of hypodiploid nuclei.	The alignment rate between every couple (human and plants) of miRNAs was assessed *via* using MirCompare algorithm.	2017	[141]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Compositions containing enriched natural crocin and/or crocetin, and their therapeutic or nutraceutical uses	US9211298B2	It was claimed that the natural ingredients could be loaded into liposomal system. Moreover, the system could also be formulated in the form of sustained released tablets, gel powder, lotion and other dosage form.	Crocin Crocetin Green tea extract Curcumin Resveratrol Panax ginseng extract α-lipoic L-carnitine	Anticancer Enhancing human health	Non-traditional	-	-	Crocin was quantified *via* HPLC and qNMR[1] analysis.	2015	[142]
Therapeutical methods, formulations and nutraceutical formulations	US20180071269A1	It was claimed that the active ingredients could be loaded into lipid nanoparticles, emulsion, micelles or other dosage formula.	*Rhizoma corydalis* extract Pure curcumin Curcuminoid extracted	Treatment of sexual dysfunction Antidepressant Anticancer Treatment of Alzheimer	Non-traditional	Clinical evaluation was conducted by using self-assessment of volunteers.	-	-	2018	[143]
Apparatus and method for preparing cosmeceutical ingredients containing epi-dermal delivery mechanisms	US 2017/0181940A1	Hydrophilic or hydrophobic active ingredients were encapsulated into liposome or niosome. The phospholipid was PEG-ylated or cationic. Moreover, the active ingredient could be unimolecular or multimolecular.	The active ingredients were parts of natural plants, such as coffee bean, aloe vera, hazelnut oil, almond oil and others.	It was used in rejuvenation of stratum corneum and epidermis. Treatment of acne Anti-wrinkles	Non-traditional	The distribution and penetration of hyaluronic acid were assessed *via* tape stripping method.	-	The morphology and size of vesicles were assessed *via* TEM. The particle size of niosome and liposome was determined *via* decompression rate. Particle size, PDI and zeta potential were determined *via* Brookhaven ZetaPlus.	2017	[144]
Combination of active agents for treating skin aging	WO2014191056A1	It was claimed that the active ingredients could be encapsulated into liposomes, polymeric vesicles, nanospheres, nanoemulsion and other dosage formula. Moreover, the formulation could be prepared in the form of ointment, cream, milk, powder and others.	Collagen Vitamin B3	The formulation was used in treating and preventing skin aging.	Non-traditional/ traditional	The efficacy of the system was evaluated by conducting a clinical study on 105 volunteers. Macrophotographs analysis was conducted.	-	-	2014	[145]
Exopolysaccharide for the treatment and/or care of the skin, culture media and compositions thereof	WO2015063240A1	Exopolysaccharide was loaded into lipid nanoparticles, microemulsion or liposomes. Moreover, the formulation could be prepared in the form of cream, gel cream, powder and others.	Exopolysaccharide was produced by Halomonas anticariensis bacterial species.	The formulation was used in treating or preventing skin aging and improving skin condition.	Non-traditional/ traditional	Nocturnin level was assessed *via* ELISA[1] test. Type I collagen was quantified by ELISA test. The total concentration of protein was assessed *via* BCA[1] Protein assay. The reduction in the level of lipid accumulation was assessed *via* measuring lipid content by fluorescent assay.	-	HPLC analysis. FTIR analysis	2016	[146]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
						In-vitro release of free glycerol was assessed *via* fluorometric assay. Clinical study was conducted on 21 female volunteers to assess the following parameters; a) Thigh contours reduction b) Smoothening effect c) Thermography of fat evenness d) Skin firmness e) Scoring of intensity of cellulite.				
Compositions and methods for treating skin conditions	US8728549B2	The active ingredients were loaded into liposomes. Moreover, the formulation could be prepared in the form of ointment, cream, skin patches and others.	Oenothera biennis oil Vitamin B12 Vitamin E	Eczema treatment	Non-traditional/ traditional	The efficacy of the system was evaluated by conducting a clinical study on volunteers. The reduction in eczema symptoms were assessed.	-	-	2014	[147]
Compositions for the prevention and/or treatment of alcohol use disorders	WO2017178682A1	The active ingredients were loaded into nanoemulsions, nanocapsules polymeric nanoparticles or other delivery systems.	Acylethanolamides	It was used in prevention or treatment of alcohol dependence syndrome, alcohol poisoning and pathological intoxication.	Traditional/ non-traditional	*In vivo* study (rats): a) Neuroinflammatory, which was induced by alcohol intoxication protocol, was assessed by measuring blood ethanol level. b) The signaling route of neuroimmune (TLR4↑, MyD88↑, NF-kB↑) was assessed after HMGB1↑ activation *via* alcohol. c) The withdrawal behavior was evaluated *via* conducting elevated plus maze experiment. The efficacy of the system was assessed by evaluating different parameters, such as proinflammatory mediator sand blood corticosterone, levels of TNF-α↑, I L-1 β↑ and others.	-	-	2017	[148]
Compositions comprising nanoparticles derived from whole fruit	WO2018048489A1	Nanoparticles were encapsulated into emulsion and/or liposome.	Whole fruits (black chokeberries, cherries, plums, blueberries, pomegranates, raspberries, cranberries and/or black elderberries)	Antioxidant Anti-inflammatory Antiaging It was used in decreasing symptoms of arthritic pain, diabetes, gout and others.	Non-traditional	-	-	Particle size measurement	2018	[149]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Nanoparticles comprising a vegetable hydrophobic protein and a water miscible non – volatile organic solvent and uses thereof	US9974753B2	The active ingredients were loaded into biodegradable nanoparticles, which consisted of hydrophobic protein (zein).	It was claimed that the active ingredients could be natural products such as curcumin, oil such as peppermint essential oil or drug such as chlorhexidine.	Antioxidant Anti-aging Fungicide It was claimed that it was used in treating and preventing other health problems.	Non-traditional	*Ex-vivo* bioadhesion study was conducted to assess the adherent concentration of nanoparticles in porcine buccal mucosa *via* fluorescently labeled nanoparticles. *In-vitro* release was quantified by using rhodamine dye under simulated saliva fluid and gastrointestinal condition.	-	The size of nanoparticle was evaluated by photon correlation spectroscopy. Zeta potential was determined by electrophoretic laser doppler anemometry. Nanoparticles morphology was assessed *via* TEM and light microscopy. The solubility of zein was studied by spectrophotometric monitoring the turbidity changes in zein solution. Encapsulation efficiency of zein nanoparticles was assessed by quantifying the concentration of encapsulated active ingredients spectro-fluorimetrically.	2013	[150]
Compound and method for reducing appetite, fatigue and pain	US20180169172A1	The active ingredients were loaded into liposomes. Moreover, the formulation could be prepared in the form of non-gelatin capsule, an HPMC[1] capsule, energy bar, carbonated drink, suppositories and others. The formula could have sustained, extended or immediate release.	*Mitragyna speciosa* plant extract or Synthesized mitragynine	The formulation was used in appetite suppressant and weight loss. It was also claimed that it reduced the pain, which was associated with chronic diseases, such as cancer, trauma and neurological diseases. It was also use in different diseases, such as Parkinson's disease, Wilson's disease, rheumatoid arthritis and others.	Non-traditional	*In-vitro* release study was conducted under simulated gastric and intestinal condition. The pharmacokinetic of the system was studied.	-	The active ingredients were analyzed *via* UV spectrophotometer and HPLC analysis.	2018	[151]
Pharmaceutical or nutraceutical composition with resistance against the influence of ethanol	US20180140556A1	The active ingredients were loaded into multi layered microcapsules, which consisted of water insoluble layer, anionic (meth)acrylate copolymer layer and alginic acid coat. The polymeric system was pH stimulated, sustained release system.	Natural or pharma-ceutical active ingredient	-	Non-traditional	*In-vitro* release of active ingredient was studied according to USP.	-	-	2017	[152]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Anti-aging formulation with stabilized Epigallo Catechin Gallate (ECGC)	US9901533B2	The active ingredients were loaded into polymeric structure.	The active ingredients were epigallo catechin gallate (EGCG), glucosamine, resveratrol, proteins vitamin A and/or others	Anti-acne Antiaging	Non-traditional	-	-	-	2018	[153]
Pharmaceutical and nutraceutical compositions of abscisic acid	US8536224B2	The active ingredients were encapsulated into liposomes, micelles, microemulsions or other delivery systems.	The active ingredients were abscisic acid, and/or salts, derivatives and analogs	Treatment of prostate enlargement Diabetes treatment	Non-traditional	*In-vivo* study: a) The efficacy of the system on reducing the weight of prostate was assessed. b) Serum glucose and triglyceride were measured. c) The weight gain of the tested offspring was measured. d) The mortality rate of offspring was evaluated. e) Neurotoxicity test was conducted.	Oral toxicity test on rodents Reproduc-tion toxicity test was assessed *via* two-generation study.	-	2013	[154]
Nutraceutical chocolate or compound chocolate product	WO2011107259A1	The active ingredients were carried or loaded into waxes, carbohydrates, gums, oils, proteins, fats and liposomes. The system was formulated in the form of chocolates or compound chocolate products.	Vitamin C, Vitamin E Zinc Copper Xanthophyll	The system was used in treating and preventing eye diseases, especially macular degeneration and cataract formation	Non-traditional	-	-	Particle size measurement Vitamin E was measured *via* fluorescence analysis and RP-HPLC[1]. Vitamin C was quantified by UV-spectroscopy and HPLC.	2013	[155]
Nanoparticle compositions and methods as carriers of nutraceutical factors across cell membranes and biological barriers	US20160263047A1	The active ingredients were encapsulated into nanoparticles, which consisted of phospholipid. Additionally, it was claimed that the dosage formula could be transdermal, periocular, intraoral or others.	It was claimed that the active ingredients could be antioxidant such as L-glutathione or lipoic acid, carotenoids such as cryptoxanthin, vitamins such as vitamin E or other natural ingredients.	-	-	Clinical study: tGSH[1] and GSSG[1] were assessed *via* Tietze's enzymatic method.	-	Size and particle size distribution were assessed *via* DLS.	2018	[156]
Compositions and methods for treatment of intestinal inflammation and colon cancer	WO2018098247A1	Broccoli-derived nanoparticles	Broccoli	It was used in treating intestinal inflammation and colon cancer.	Non-traditional	*In-vivo* study: a) The weight reduction and prevention of induced colitis were assessed. b) Histological scoring examination was conducted on colon. c) Immunohistochemistry analysis was conducted. d) ELISA analysis	-	Size distribution was determined by DLS and electron microscopy. Zeta potential was measured *via* DLS.	2018	[157]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
						e) Immunoblotting was conducted to assess cell lysates. f) RT-PCR analysis was conducted to assess the expression of genes in CD4+ T cells. g) Activation of T cell was evaluated *via* flow cytometry. h) IL-12[1] and TNF[1] levels were measured. k) Colon was imaged by confocal laser microscope. There were other different tests were conducted.				
Neuro-transmitter and brain modulating oral delivery system for enhancement of cognitive functions and energy	US20180236016A1	Nanoemulsion consisted of sodium alginate, polysaccharide (encapsulant) and cocoa protein (emulsifier). The system was also prepared in the form of emulsion system.	Theobromine Caffeine Amino acids Amino acid derivative (n acetyl l-tyrosine) Cocoa Carbohydrate Taurine Alpha-glyceryl phosphoryl choline Glucuronolactone	The system was used in modulating the cognitive brain functions. It was used in changing mood, enhancing energy and improving memory.	Traditional/ non-traditional	-	-	Viscosity measurement	2018	[158]
Site specific curcumin-polymer molecular complexes and methods of treating colon diseases and inflammation	US20180064821A1	Curcumin-polymer complex was encapsulated into nanoparticle or microparticles. Moreover, the system was prepared in the form of tablet, suspension, cream and others.	Curcuminoid components (curcumin, bisdemethoxy curcumin, demethoxycurcumin and others)	It was used in treating cancer, neurodegeneration, inflammation and immunod-eficiency.	Non-traditional	*In vitro* bioavailability of the system was assessed in mice *via* HPLC. The bioavailability of the system across the skin was assessed *via* HPLC. The stability was assessed *via* UV spectroscopy. The inhibitory efficacy of the system on activity of TLR-4[1] was evaluated. TNF-α[1] level was assessed *via* ELISA assay. *In-vitro* curcumin pH dependent intracellular delivery was evaluated *via* flow cytometer. The plasma centration of curcumin was assessed *via* HPLC in mice. The anticancer effect was assessed *via* MTT[1] assay	-	The active ingredients were measured *via* UV-spectrophotometry. FTIR analysis Particle size, size distribution and morphology were measured *via* SEM. DSC analysis Curcumin loading capacity was analyzed UV-Vis spectrophotometer. [1]HNMR analysis The crystalline structure was assessed *via* X-ray diffraction.	2018	[159]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Modified resveratrol composition and use thereof	WO2018042324A1	Resveratrol nanoparticles was coated with tree fat.	Resveratrol	It improved insulin resistance, cell longevity and dehydroepiandrosterone (DHEA) level by gene regulation. It was used in treating and preventing cardiovascular problems, metabolic syndrome, apoptosis, muscular dystrophy, stress resistance and others. Anticancer Anti-inflammatory Antiaging	Non-traditional	The bioavailability of the system was assessed. Gene expression was assessed *via* real-time PCR system. Clinical study: a) Clinical study was conducted to measure the serum glucose level (post-prandial sugar, fasting sugar, insulin fasting and insulin post prandial). b) Renal function was assessed *via* measuring serum creatinine, serum uric acid and Blood Urea Nitrogen (BUN). c) Lipid profile was assessed *via* measuring different parameters, such as HDL[1], VLDL[1], LDL[1] and others. e) Anti-Müllerian Hormone (AMH) level was measured. f) The bioavailability of the system was assessed by measuring resveratrol level in blood sample *via* LC-MS[1]. g) SIRT1 gene expression and TXNIP[1] gene downregulation were measured. e) Testosterone and dehydroepiandrosterone (DHEA) levels were measured.	-	The morphology and size of vesicles were assessed *via* TEM. Particle size, PDI and zeta potential were determined *via* DLS. Morphology was assessed *via* SEM.	2018	[160]
Green alga poly-saccharification nano-selenium and preparation method and application thereof	CN106539092A	Nano-green algae was encapsulated into polysaccharide nano-selenium particles.	Chlorella poly-saccharide	Inflammatory bowel disease treatment It was used in treating and preventing different diseases, such as hyperlipidemia, atherosclerosis, diabetes and other inflammation-related diseases.	Non-traditional	*In vivo* study (mice) a) Anti-inflammatory efficacy was assessed *via* measuring inflammatory markers such as IL-6 and TNF-α. b) Different symptoms, including diarrhea, fecal occult blood and others, were detected. c) Histopathological examination of the intestinal inflammation was conducted.	-	Particle size and morphology of nanoparticles were measured using TEM.	2017	[161]
Composite materials comprising amyloid fibrils and nanoparticulate nutritional minerals	WO2018166947A1	The hybrid system consisted of amyloid fibrils, which had iron nanoparticles on its surface.	Amyloid fibrils Minerals (iron oxides, calcium phosphates and others)	It was used in treating or preventing iron deficiency anemia and diseases, which were associated with zinc deficiency.	Non-traditional	Hemoglobin repletion bioassay was conducted in rats to assess the relative bioavailability of the system. The sensory performance of the system was evaluated and further confirmed *via* changing in color of food matrices. The digestion kinetics was assessed *via* conducting acidic dissolution and enzymatic hydrolysis tests to evaluate the ability of active ingredient delivery.	-	The morphology of nanoparticles was evaluated by TEM. Storage stability was assessed *via* changing in turbidity.	2018	[162]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Combination of bioenergy and nutra-epigenetic metabolic regulators, nutraceutical compounds in conventional and nanotechnology-based combinations, for reversing and preventing cellular senescence accelerated by chronic damage caused by diabetes and other complex chronic degenerative diseases	WO2017213486A2	Nanoparticles	Amino acids (glycine, arginine and cysteine) Resveratrol	The system was used in treating metabolic syndrome, such as obesity, hyperglycemia, gout, diabetes type 1 and 2 and others.	Non-traditional	Cell bioavailability and proliferation were assessed. The count of lymphocytes was evaluated *via* light microscope. The effect of the system on dsDNA was assessed by measuring the intact DNA *via* densitometric analysis. *In-vivo* study (rats): a) The serum level of aspartate aminotransferase (AST), transpeptidase transaminase glutamyl (GGT) and alanine aminotransferase (SGPT) were measured. b) Macroscopic examination of different organs was conducted. c) The serum levels of glucose, creatinine, uric acid and cholesterol were measured. *In-vivo* study (rats and rabbits) a) CBC test was performed. b) glucose, uric acid and cholesterol levels were measured. c) Weight gain of animals was observed. A clinical study was conducted on a 48-year old man and different parameters including body weight, LDL, HDL and others, were measured	MTT Toxicity was evaluated by determining mortality rate of brine shrimp (*Artemia salina* cyst). The acute and sub-chronic toxicity studies were conducted.	-	2017	[163]
Compositions and methods for treatment of alcohol induced liver injury	US20180140654A1	The active ingredients were loaded into nanoparticles, exosome-like nanoparticles or liposome-like nanoparticles.	Ginger or Grapefruit	Treatment of alcohol induced liver injury	Non-traditional	*In vivo* study (mice): a) The liver was examined *via* confocal microscopy after labeled formula administration. b) The cellular uptake of DiR[1] labeled ginger nanoparticles was assessed *via* using Kodak image station 4000MM Pro system. c) Western blot analysis was conducted to assess the nuclear translocation of Nrf2[1]. d) The concentration of ROS[1] was measured. e) The amount of labeled ginger derived-nanoparticles in the peripheral blood was measured *via* confocal microscopy. f) ALT and AST levels were measured. g) Histopathological examination of liver was conducted.	-	Nanoparticles were visualized *via* atomic force microscopy. Particle size, PDI and zeta potential were determined *via* DLS. HPLC analysis TLC[1] analysis *In-vitro* stability was assessed by measuring the particle size and surface charge of the system under gastric and intestinal conditions.	2018	[164]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Composition and method for improving cognitive function and brain bioavailability of ginseng and ginsenosides and treating neuro-degenerative disease and neurological disorders	WO2018148821A1	It was claimed that the active ingredients were loaded into phospholipid nanoparticles, nanoemulsion, micelle, or liposome.	The active ingredients were ginseng, ginsenoside, green tea, catechin and/or essential fatty acid.	It was used in treating neuro-degenerative disease and neurological disorders. It was also used in improving the cognition rejuvenation of the brain.	Non-traditional	Clinical study: a) Adverse effects such as persistent cold, nausea, vomiting and others, were observed. b) Mini-mental state exam (MMSE) was conducted to measure cognition. c) Attention and psychomotor speed were assessed *via* the digit symbol substitution test. d) Stroop test was conducted to evaluate the processing speed and parallel processing. e) Logical memory I and II were performed to measure immediate and delayed recall. f) MRI[1] scanning was conducted. g) Brain bioavailability was studied *via* determination of gensinsoide concentration in brain extract by LC-MS[1]. f) The brain activity was evaluated *via* blood oxygenation level dependent (BOLD) imaging.	-	-	2018	[48]
Use of ellagic acid dihydrate in food products and nutraceuticals	US20170367390A1	The active ingredients were loaded into solid nanoparticles, lipid-based carrier, lipid-containing nanoparticles, tablets, sealed conduit or others.	The active ingredients were pharmaceutical ingredients or natural ingredients, such as ellagic acid dehydrate, vitamins and/or minerals.	It was used in treating and preventing hyperglycemia, obesity, diabetes type I & II diabetes, gestational diabetes, latent auto-immune diabetes, metabolic syndrome, Alzheimer, liver disease, kidney disease, and others.	Traditional/ non-traditional	Cell membrane integrity was evaluated. The glucose uptake was determined in treated culture cells, including mouse myoblast C2C12[1] cells and MEF[1] cells *via* using fluorescently labeled glucose. Comparison between insulin treated culture cells and ellagic acid dehydrate treated culture cells, was conducted to evaluate the efficacy of both on glucose uptake. In-virto localization of glucose transporter (GLUT4) was assessed by confocal laser microscopy. *In-vitro* activation of AKT[1] and MAPK[1] pathways was imaged by using immunocytochemistry labeling. *In-vivo* study (mice): a) body weight and blood glucose level were measured. b) Gross locomotor activity was assessed in home cage *via* infrared motion detector.	*In-vitro* cytotoxicity test was assessed on mouse embryonic fibroblasts. The determination of cell proliferation rates was evaluated by flow cytometry.	-	2017	[165]

Table (2) contd….

Patent Title	Patent Number	System Description	Main Nutraceutical Ingredients	Therapeutic and other Uses	Traditional /Novel System	Efficacy Tests	Toxicity Tests	Characterization	Year	Refs.
Composition and method to alleviate joint pain using low molecular weight hyaluronic acid and astaxanthin	US9675635B2	Microdispersion or Nanodispersion	It was claimed that the active ingredients were glucosamine, type II collagen, docosahexaenoic acid, eicosapentaenoic acid, olive oil, astaxanthin, Pro-inflammatory low molecular weight microbial fermented sodium hyaluronate fragments and/or others.	The system was used in treating and alleviating joint pain symptoms.	Non-traditional	Clinical study: a) Physical examination b) X-ray c) Radiological investigations d) Matrix metalloproteinase 3 (MMP3) level was measured. e) Total health assessment was conducted on osteoarthritis patients. f) Osteoarthritis of the knee and lower extremity pain were assessed *via* Western Ontario McMaster (WOMAC). g) Pain parameters was measured *via* visual analog scale. h) Physical functions were evaluated by laquesne's index. k) The psychometric properties of medical outcomes study sleep scale were assessed.	-	-	2017	[166]

effects. This study showed that this system improved the molecular stability of quercetin against pH degradation and UV irradiation and high antioxidant activity [97].

In American patent, Salman *et al*. [150] formulated biodegradable nanoparticles, which consisted of hydrophobic protein (zein). Further, natural products, such as curcumin, oil (peppermint essential oil) or pharmaceutical drug, such as chlorhexidine was loaded into biodegradable nanoparticles. It was claimed that the system can be used as antioxidant, anti-aging and fungicidal agent. Salman *et al*. [150] conducted *ex-vivo* bioadhesion study to assess the adherent concentration of nanoparticles in porcine buccal mucosa *via* fluorescently labeled nanoparticles. Moreover, the size of nanoparticle was assessed by photon correlation spectroscopy. Zeta potential was also determined by electrophoretic laser doppler anemometry. Nanoparticles morphology was evaluated by TEM and light microscopy, as shown in Table **2** [150].

Biopolymers nanoparticles can be conjugated or cross linked to enhance their physical and chemical properties and improve their safety and efficacy.

3.11. Conjugated Biopolymer Nanoparticles

Biopolymers can be utilized in their natural form. However, physical, chemical or enzymatic modifications are performed to improve their properties [203]. For example, protein covalently bonded to polysaccharide showed better solubility and emulsifying properties [204]. Conjugation may be reversible (physical) or irreversible (chemical) [203]. The chemical conjugation has stronger and more permanent interaction [204]. Protein nanoparticles can be stabilized further *via* coating with conjugated polysaccharides [204].

Davidov-Pardo *et al*. [89] encapsulated resveratrol into protein (zein) nanoparticles, which were coated *via* conjugated polysaccharides by Maillard reaction. The efficacy of conjugation was assessed by measuring the decrease in free amino groups *via* the o-Phthaldialdehyde (OPA) assay [89]. As a result of that the limited water solubility, oral bioavailability and chemical instability of resveratrol were reduced. Furthermore, casein was adsorbed to hydrophobic particles. Additionally, dextran prevented aggregation *via* steric repulsion. Hence, coating with caseinate-dextran resulted in avoiding particle aggregation, as shown in Table **1** [89].

3.11.1. Cross-linked Biopolymer Nanoparticles

Cross-linking is the process of linking chains of a polymer by covalent or noncovalent bonding to form three dimensional structures [205]. Cross-linking is performed to enhance mechanical properties and aqueous stability of biopolymers [206].

Hu *et al*. [108] encapsulated EGCG, chemopreventive agent, into cross-linked nanoparticles of chitosan (CS) and caseinophosphopeptides (CPPs). Cross-linking CS with CPPs enhanced EGCG oral bioavailability and reduced CS cytotoxicity. In addition, crosslinking increased nanoparticles biocompatibility (Table **1**) [108].

Glucomannan polysaccharide stimulates fibroblast proliferation which aids in wound healing [207]. Hence, Heber

et al. [130] formulated cross-linked nanoparticles that were composed of chitosan and glucomannan to enhance wound healing and skin regeneration (Table **2**). Heber *et al*. [130] evaluated the efficacy of nanoparticles on healing skin irritation *via* Fluorescence Lifetime Image Microscopy (FLIM). Moreover, *in-vivo* study was conducted on rabbits to assess certain parameters. First, dermal irritation reduction was observed visually in injected rabbits. Secondly, proliferation and intradermal distension of collagen within dermis was assessed [130].

3.11.1.1. Nanosuspension

Nanosuspension is one of the novel approaches that solves low solubility of drugs [208]. Nanosuspension consists of a nanosized particle that is stabilized by surfactants [209]. In this dispersion, nanosized core is surrounded by surfactant molecules. Furthermore, nanosuspension enhances drug stability and ensures high drug loading [210]. Oral bioavailability is also improved as a function of solubility [208]. Another major advantage of nanosuspension is that it can encapsulate insoluble compounds [93]. Hence, many formulators have tried to use nanosuspension as a delivery system in nutraceutical industry [93].

Curcumin has beneficial effect on cancer and Alzheimer treatment [84]. However, the pharmacological application of curcumin has been limited due to its low solubility and poor oral bioavailability [84]. Thus, Shin *et al*. [93] fabricated nanosuspension of curcumin and α-Tocopherol Polyethylene Glycol 1000 Succinate (TPGS) by using ultrasonic homogenization technique. The prepared nanosuspension improved curcumin water solubility and dissolution rate. The particle size, PDI, and zeta-potential of nanocomplex system were measured by DLS [93]. Moreover, the morphology and size of nanoparticles were assessed *via* field emission scanning electron microscope (FE-SEM) and TEM. Different analyses were performed, such as Fourier-Transform Infrared Spectroscopy (FTIR) analysis, thermogravimetric analysis, differential scanning calorimetry (DSC) analysis and X-ray diffraction analysis, as shown in Table **1** [93].

3.11.1.2. Graft Copolymers

Graft copolymers are polymers of two or more different monomers. One monomer is the main chain (backbone), which is chemically bonded to side chains (branches). According to the synthetic techniques, the branches may be randomly or equally distributed along the backbone [211]. Grafting is usually performed to modify specific properties in polymers such as wettability, biocompatibility and mechanical properties [212]. Grafting can be done through different techniques, such as chemical grafting, living polymerization, photochemical grafting, enzymatic grafting, plasma radiation and radiation grafting [212].

Gallic acid is a natural triphenolic compound, which has strong antioxidant and apoptosis activities [213]. Hence, Wu *et al*. [128] developed chitosan gallates copolymer by free radical graft reaction (Table **1**). Gallic acid was encapsulated into the synthesized system to be used as antioxidant. Antioxidant activity of the copolymer was evaluated *via* DPPH assay. As a result of that the grafted copolymer showed enhanced antioxidant activity because of the increase in substitution degree and the reduction in molecular weight [128].

Moreover, protocatechuic acid is a natural phenolic compound with antioxidant activity. Protocatechuic acid was used in traditional Chinese medicines [126]. Therefore, Liu *et al*. [126] grafted protocatechuic acid onto chitosan by cross-linking reaction to enhance its antioxidant activity (Table **1**). Antioxidant activity of the grafted system was assessed *via* the DPPH and reducing power assay. Grafting ratio was evaluated by Folin–Ciocalteu assay. The morphology and size of nanoparticles were assessed *via* SEM [126].

3.11.1.3. Nutraceuticals Toxicity

The global consumption of nutraceuticals is dramatically increasing, which is driven by the mistaken assumption that they are safe because they are either a food or food derivative [214]. However, side effects and toxicity have been continuously reported not only due to ingestion of the nutraceutical itself but also owing to the possibility of contamination. Nutraceuticals could be contaminated with pesticides, other toxic plants, metals, fertilizers or even deliberate adulteration with chemical drugs [214]. Additionally, due to the complex nature of herbal products and the presence of many phytochemicals, many studies reported the incidence of drug-herbal interaction after co-administration [215]. Such interaction could result in over exposure to the drugs that elevate the incidence of toxicity and severe side effects. It could also lead to inhibition of the drug efficacy and lower therapeutic outcomes [215].

A remarkable number of commonly used nutraceuticals are associated with severe adverse effects and toxicity [34]. Ginkgo biloba extracts, are rich in flavonoids and are commonly recommended for the elderly patients to improve the peripheral circulation. *Ginkgo biloba* also is indicated for age associated dementia, alzheimer, schizophrenia and cerebral insufficiency [216]. However, it is reported that the exposure to high doses of Ginkgo biloba extracts over long periods of time is associated with spontaneous bleeding. Additionally, many animal studies showed the carcinogenicity of *Ginkgo biloba* [217].

Furthermore, green tea extracts contain catechins, which have anticancer properties. Green tea extracts are also used to prevent obesity and metabolic disorders [218], but over exposure could result in nephrotoxicity, hepatotoxicity and reproductive toxicity [219]. Moreover, it was reported that the ingestion of caffeine causes anxiety, tachycardia, osteoporosis and reproductive disorders, especially in early adulthood exposure [220]. Many other commonly consumed herbal products, such as cinnamon, aloe vera and St. John`s wort are associated with toxic side effects, including carcinoma, hepatotoxicity, genotoxicity and mutagenicity [219].

3.11.1.4. Nutraceutical Contaminants

The presence of nutraceutical contaminants represents one of the most threatening issues of using nutraceuticals. Pesticides are considered the most dangerous nutraceutical contaminants owing to the severe toxicity resulting from their ingestion. Toxicity may vary from mild skin rash to serious respiratory, neurological and reproductive disorders. However, the use of pesticides is necessary to maintain the quality of the medicinal herbs [214]. Thus, strict limits of residual contents of pesticides must be followed. Among the different classes of pesticides, organochlorines can persist in

the herbal product for longer duration and result in the most harmful toxic effect after chronic exposure [219].

Other important contaminants of nutraceuticals are heavy metals, including lead, cadmium, mercury and arsenic. The World Health Organization (WHO) has specified guidelines and limits for the presence of environmental contaminants, such as heavy metals in the final herbal product [221]. Heavy metals toxicity could result from acute exposure to high concentration of heavy metals or chronic exposure to low concentrations of heavy metals. The adverse effects of metal toxicity include cancer, cardiovascular toxicity, neurological disorders, hepatic and renal dysfunction [222].

Pyrrolizidine alkaloids are naturally occurring plant secondary metabolites, which induce developmental toxicity, genotoxicity, carcinogenicity and hepatotoxicity in animal studies [13]. Meanwhile, it was reported that their acute toxicity is manifested by liver damage [223]. These types of alkaloids exert the toxic action because of their strong alkylating nature. They react with cellular proteins and DNA causing cellular dysfunction and tissue necrosis [224]. Pyrrolizidine alkaloids are widespread in nearly 6000 species of plant. In Europe, Mulder *et al*. [225] analysed 1105 samples of food and food derivative products, which were collected from online websites and supermarkets. The study showed that 60% of the food supplement products were contaminated with pyrrolizidine alkaloids [225].

Finally, mycotoxins are fungal secondary metabolites that could be formed during plant cultivation or storage [226]. The ingestion of mycotoxins contaminated product causes severe adverse effects, such as carcinogenicity, hepatotoxicity, mutagenic and teratogenic disorders. Aflatoxins, ochratoxins and citrinin are among the most commonly detected mycotoxins in food supplements [226].

3.11.1.5. Nutraceuticals – Drug Interaction

Recently, many studies have reported numerous nutraceutical-drug interactions. The interaction nature may be through interfering with the metabolic pathway of the drug or affecting the drug transporters [227]. Owing to the complex nature and absence of pharmacokinetic, pharmacodynamics and safety studies for nutraceuticals, it is challenging to predict the incidence of nutraceutical-drug interactions [6].

Some of the reported interactions could be serious and life-threatening. For example, aspirin and some non-steroidal anti-inflammatory drugs interact with herbal products containing ginkgo, turmeric, ginger, ginseng, chamomile and garlic. Consequently, this reported interactions increased the risk of bleeding due to the inhibition of platelet aggregation ability [228].

The cytochrome P450 (CYP) enzymes are one of the mostly expressed metabolic enzymes in the liver and small intestine [229]. Additionally, they are involved in the metabolic pathways of many pharmaceutical drugs [230]. Saint John's Wort herbal extract is among the mostly reported nutraceuticals that induces wide range of CYP, including CYP1A2, CYP2C9, CYP2C19, CYP3A4 and CYP2E1. Induction of these enzymes results in accelerating the metabolism of the consumed drugs. Subsequently, the drug is eliminated from the body rapidly and it loses its activity [228]. It was also reported that Saint John's Wort included treatment failure of anti-depressant drugs and loss of oral contraceptive efficacy [228].

The bioavailability of fexofenadine, which is P-glycoprotein receptor substrate, is significantly improved when co-administrated with P-glycoprotein inhibitor phytochemicals [215]. Several phytochemical flavonoids, including naringenin, genistein and quercetin, are P-glycoprotein phytochemical inhibitors. Subsequently, the ingestion of nutraceuticals containing P-glycoprotein inhibitors with potent substrate drugs, such as irinotecan, digoxin or cyclosporine, could result in life-threatening toxicity [231].

Organic Anion Transporting Polypeptide receptor (OATP) is another key transporter in drug absorption and disposition [232]. Iijima *et al*. [233] conducted a study on 98 medical herbs commonly used in Japan to detect the interaction between some nutraceuticals and pharmaceutical drugs. It was found that 12 herbal species suppressed the function of the intestinal organic anion transporting polypeptide 2B1 (OATP2B1) receptor by less than 20% [233]. Additionally, seven herbal species enhanced the activity of the receptor by more than 150% [233].

Consequently, co-administration of these herbal products dramatically affects the absorption and bioavailability of substrate drugs, including bosentan, benzyl penicillin, aliskiren, fexofenadine, glibenclamide, unaprostone, statins, and other pharmaceutical medications [234].

3.11.1.6. Nutraceuticals Advanced Delivery Systems Toxicity

Recently, the incorporation of nutraceuticals into nano delivery systems is rapidly emerging. These advanced delivery systems are used to improve the absorption and bioavailability of nutraceuticals, provide targeted and controlled release profile and enhance the stability of phytochemicals, which are susceptible to degradation [235]. Nano-sized nutraceuticals improve the efficacy of nutraceuticals due to their unique, different chemical and physical properties after nanonization. However, the same advantageous, physicochemical properties of nano particles are the principle cause of human toxicity [235].

The safety of nano delivery system is questionable. Moreover, limited information and studies are available concerning the absorption, metabolism, distribution, excretion and toxicity of nano systems. Understanding the nano particles interaction with the biological systems at the molecular level is essential to predict their mechanism of action and safety [236]. Among the commonly reported adverse effects of nano particles are respiratory disorders, cardiovascular diseases, carcinogenicity and shorter life expectancy. It was also reported that most of these adverse effects are triggered by the oxidative stress and inflammation induced by the nano particles at the molecular level [235].

In a recent study, Zhang *et al*. [237] synthesized gold, silver, platinum and palladium nanoparticles to load three different dietary supplements, including vitamin C, (−)-epigallocatechin gallate and gallic acid. The hydroxyl radical scavenging activity of the synthesized systems were as-

sessed. Surprisingly, they found that the prepared nanoparticles decreased the hydroxyl radical scavenging ability of the antioxidant phytochemicals and generated a Reactive Oxygen Species (ROS). Hence, this system resulted in cellular damage and toxic effects in biological systems [237].

The European Food Safety Authority (EFSA) suggested an approach to assess the toxicity arising from the incorporation of nanotechnology in the food products and food derivatives. The guidelines titled: "*Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain*" recommended a set of physicochemical parameters to be evaluated for nanoparticles [238]. The EFSA list of parameters have included [238]:

- The identity and chemical of nanoparticles.
- The particle size of nanoparticles.
- The physical properties of nanoparticles.
- The morphology of nanoparticles.
- Particle and mass concentration.
- The specific surface area of nanoparticles.
- The surface chemistry of nanoparticles.
- The surface charge of nanoparticles.
- The redox potential of nanoparticles.
- Partition and solubility properties.
- Dustiness, viscosity, density and pour density.
- The chemical reactivity of nanoparticles.
- The photocatalytic activity of nanoparticles.

Recently, the focus is increasing on development of predictive models and high throughput approaches to aid in the early assessment of nano systems toxicity. This concept, which is known as "safety by design", will facilitate the process of nano delivery systems design and allow the manufacturing of safer systems. The implementation of safety by design concept in drug discovery helped to reduce the risk of drug withdrawal from the market for safety issues from 50% to only 20% [239].

4. NUTRACEUTICALS GLOBAL MARKET AND REGULATIONS

In 2016, the global market of nutraceutical was $198.7 billion and estimated to be $285 billion by 2021 with a compound annual growth rate (CAGR) of 7.5% [240]. By 2025, the market is expected to reach $578.23 billion with a CAGR of 8.8% [42]. Around 50% of the population in USA consumes dietary supplements [241]. The globally increased demand on nutraceuticals is driven by the emergence of healthy lifestyles, increased adverse effects associated with pharmaceutical drugs and the claims of nutraceutical safety and efficacy [242]. In contrast to the rapid growth of the market, the regulations of nutraceuticals are slowly evolving with unclear and variable definitions for the term "nutraceutical" all over the world. Hence, nutraceuticals are not regulated as pharmaceutical products in certain countries but as food supplements [13].

The absence of common global regulations and legalizations will be a major obstacle for nutraceutical market growth soon. WHO and the United Nations Food and Agricultural Organization (FAO) have released several guidelines regarding the safety and quality of food and food supplements with emphasis on herbal products [13]. Till now, many countries are following the "Codex Alimentarius" guidelines reported by FAO and WHO in 1992, as internationally recognized regulations for manufacturing and marketing of food and its derivatives [13]. The International Regulatory Cooperation for Herbal Medicines (IRCH) was formed in 2006 by 33 national and regional members with WHO support. The purpose of IRCH is to create international regulations for herbal medicinal products [243]. The creation of nutraceutical global regulation, with confined definition, quality parameters and safety aspects, is essential for the consumer health and nutraceutical industry growth [243].

According to the global market reports, United States nutraceutical market is the largest followed by Asia-Pacific [244]. According to the (DSHEA) and the Food and Drug Administration Modernization Act of 1997, manufacturers of nutraceuticals are responsible for the safety and labelling of the products. Moreover, the nutraceutical product must comply with current good manufacturing practice guidelines [25]. The Dietary Supplement and Non-prescription Drug Consumer Protection Act of 2006 obligated the manufacturers to report any adverse events associated with nutraceutical intake to the FDA [245]. Unlike pharmaceutical products, no FDA approval is required for manufacturing and selling of dietary supplements or nutraceuticals in the United States [25]. However, The Food Safety Modernization Act of 2011 mandates the FDA to detect and act against any safety threatening marketed products. In 2016, the FDA released a draft guidance titled "*Dietary Supplements: New Dietary Ingredients Notifications and Related Issues: Guidance for Industry*", which provides information on the procedures that are required for submitting new dietary ingredients and data that are needed for safety evaluation [245].

Japan is the largest nutraceutical market in Asia with a share of 70% and the second largest globally after the United States [2]. In Japan, the use of herbs for medication is traditional and known as "Kampo Medicine" [233]. The Japanese Ministry of Health, Labor and Welfare (MHLW) has established the Consumer Affairs Agency (CAA) to regulate the nutraceuticals labelling and to ensure credibility of its health claims and safety [242]. According to the CAA, nutraceutical products are classified either as Foods with Nutrient Functional Claims (FNFC) or as Foods for Specified Health Uses (FOSHU). The first type of nutraceuticals (FNFC) includes vitamins and minerals, for which the agency is only responsible for setting the standard minimum and maximum daily intakes. Meanwhile, the (FOSHU) includes nutraceuticals with labelled physiological effect for health enhancement. Further, a premarketing approval is needed for this category. It is also worthy to mention that any claim for disease risk reduction is not permitted [242].

The Chinese nutraceutical market share is the second in Asia-Pacific after Japan. However, it is estimated that China will be the largest nutraceuticals market by 2020 [244]. The

Chinese Health Care Association (CHCA) was created by the Ministry of Health to supervise and regulate the nutraceutical industry in China [242]. Similar to the United States FDA, the China`s State Food and Drug Administration (SFDA) is responsible for dietary supplements monitoring and registration. It is now known as China Food and Drug Administration (CFDA) [242]. The Indian nutraceutical market is one of the most evolving markets with 18% CAGR in the last three years [244]. Food supplements represent nearly 60% of the Indian market while vitamins and minerals account for 40% share of the market [242].

The Food Safety and Standards Authority of India (FSSAI) was founded by the Indian government in 2006 to act as a regulating authority for the food and food supplement products in India [246]. According to the FSSA, nutraceuticals are defined as "*food processed or formulated to satisfy particular dietary requirement for a physiological condition or specific disorder*" [246]. FSSAI monitors different processes, including manufacturing, packaging and labeling of nutraceuticals [247]. Additionally, FSSAI also puts restrictions on advertisements of nutraceuticals [247]. The Indian Pharmacopoeia Commission also plays a rule in standardization of the medicine's quality including the medicinal herbal products by publishing monographs in the Indian Pharmacopoeia [242].

The European Union nutraceutical market is the third largest after United states and Asia – Pacific with Germany and France contributing to nearly 50% of the market share [244]. In Germany, a federal commission known as Commission E, was responsible for creating monographs to describe the safety and efficacy of herbal products since 1978 [243]. In the United Kingdom, herbal products are not considered dietary supplement. They must also comply with the Traditional Herbal Registration (THR) regulations. Therefore, evidence of safety, quality and efficacy of the herbal product must be proven [243].

The European Food and Safety Authority (EFSA), which has been created according to the General Food Law Regulation of the European Parliament, is responsible for regulation of food and food supplements in Europe [248]. The EFSA responsibilities include assessment of the beneficial health claims and the associated adverse effects with food and supplements intake [13]. According to EFSA, a health claim is defined as " *any message or representation that states, suggest or implies that a relationship exists between a food category, a food or one of its constituents and health*" [1]. Consequently, a supplement is classified according to its health claims in one of the following categories; "general function claims", "new function claims" and "claims regarding disease risk reduction and child development or health" [1]. Moreover, Rapid Alert System for Food and Feed (RASFF) is reporting systems for monitoring and acting to detect any hazard regarding the food and food derivatives risk. RASFF was founded in the EU since 1979 [248].

Finally, some countries, such as Australia and China still classify and regulate nutraceuticals as food [13]. Furthermore, some countries, such as Argentina, Colombia and Brazil, follow a simplified registration-based way for nutraceutical regulations [249]. In contrast, other countries, such as China, Brazil and Taiwan, outlined strict regulations and require animals or human clinical trials before registration of nutraceuticals [250, 251].

CONCLUSION

The global consumption of nutraceuticals is rapidly growing, which is driven by its alleged safety and efficacy. Recently, the incorporation of advanced nanosized drug delivery system as a platform for nutraceutical formulation is gaining attention. This is influenced by the promising results obtained regarding the bioavailability, safety, targeting and stability of the nutraceuticals tested. Hence, various drug delivery systems were adopted, including nanoparticles, liposomes, dendrimers, phytosomes, nanoemulsion and others.

However, many challenges arise from nutraceutical formulation concerning their efficacy, safety and regulations. A global definition was not identified by concerned institutions. Regulatory bodies have not been implemented to control and regulate nutraceuticals worldwide. This review article provides a literature review of the most recent state-of-the-art technologies in nutraceuticals formulation and it discusses the prospective challenges and the different attempts to overcome it.

CURRENT & FUTURE DEVELOPEMENTS

The current status of nutraceuticals, cosmeceuticals and food supplements in the global market is alarming. The chaotic scene starts with the terminology and categorization, where these products are not considered medications. No uniform, consistent or standardized regulations govern the manufacturing, sales or marketing of such products. All of these products are sold with major therapeutic claims as natural safer substitutes to medications. Most of these products can be easily bought from online retail stores such as Amazon or eBay without any real regulations or controls [22]. Furthermore, many sellers use the novel carrier technologies as an attraction strategy to increase sales.

Finally, it is concluded that the term "nutraceutical" is poorly defined across the globe and from a regulatory perspective not clearly classified either as a category of food or pharmaceuticals. Subsequently, it is a challenging task for the regulatory authorities in the different parts of the world. However, clear and common regulations for nutraceuticals will be urgently needed in the near future to cope with rapidly emerging trends and demands in the global market.

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