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Nutraceuticals and their Nanotechnology-Based Therapeutic Applications in Different Diseases

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Abstract

Nanotechnology today is growing very rapidly and has infinite applications in almost everything we do, in the medicine we take, food we eat, chemicals we use, car we drive and much more. Nanoparticles could help make more compelling clinical medicines. The point is to improve regions going from drug conveyance to the discovery of infections. One of the expected advantages of nanoparticles is the chance of creating focused on treatments, so that medications go precisely where they are required in the body Nutraceuticals, up today, today, don't have a particular definition unmistakable from those of other food-inferred classes, for example food supplements, natural items, pre and probiotics, useful nourishments, and so on They have, be that as it may, a pharmacological useful impact on wellbeing. Numerous investigations have been as of late routed to survey their wellbeing, adequacy, and guideline since they are getting developing consideration by market and examination, with the plan to clear the contrast among them and other market accessible food-determined items that guarantee gainful impact on wellbeing. Additionally, nutraceuticals have been widely explored for promoting overall health outcomes and in management of various diseases since they are considered to be neutral. They play a vital role in modifying and maintaining normal body physiological functions. Nonetheless, the bioactive mixes present in nutraceuticals can't accomplish their possible results because of restricted watery solvency prompting helpless bioavailability profile and collaboration with gastro-intestinal liquids. Greater part of traditional items in market are unable to show their therapeutic outcome. Nanotechnology has tremendous potential to revolutionize the nutraceutical market. Recent progress in field of nutraceutical delivery has incorporated nanotechnology to overcome the drawbacks accompanying nutraceuticals. This review focuses on issues associated with nutraceuticals and various nanoscale formulation approaches like liposomes, nano emulsions, nanocrystals, lipid and polymeric nanoparticles to obtain an insight to recent developments in nutraceuticals segment.

Keywords: Nanoparticles; Nutraceutical; Nutraceutical delivery; Dietary supplements

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Nutraceuticals

The term nutraceuticals arise from the combination of nutrition and pharmaceuticals. These are a piece of food or nourishments which offer wholesome and drug benefits, that is, offer supplements to the body, give obstruction against a few infections and furthermore help in relieving of certain sicknesses [1]. Nutraceuticals can be divided into three main categories-dietary supplements, functional foods and functional beverages. Further the dietary enhancements can be partitioned into nutrient and mineral, home grown enhancements, plant concentrates and protein supplements. Useful nourishments incorporate omega unsaturated fat nourishments and probiotics, though utilitarian refreshments can be sub segmented into caffeinated drinks, sports drinks and strengthened juices. Some common words related to nutraceuticals or used as synonym for nutraceuticals are functional food, multifunctional food, dietary supplements, etc. Functional foods are just the same as basic foods providing nutrition, incorporated with special and specific ingredients which provide health benefits to the body [2].

Nutraceuticals are also minor food elements which improve the body functioning by fighting against some persistent diseases [3]. Nutraceuticals are generally ordered into three general gatherings, for example, dietary enhancements (glucosamine, probiotics, and so on), herbals (spices or natural items), and supplements (nutrients, minerals, and so forth) Also, they are devoured every day by individuals as an option in contrast to current medication, along these lines advancing quality life and expanding future. They have proved to offer benefits such as acting as a natural antioxidant and immune booster, fewer side effects than drugs, improved bioavailability, and long half-life [4]. However, despite their widespread popularity, their therapeutic effects are inhibited by their[4]low bioavailability due to various physiological and physiochemical factors, and Kaur [4] quality control, which is an important step to determine the safety and authenticity of the nutraceutical on the global supply level. Consequently, extraordinary definition methodologies have been accounted for in writing to improve the medication measurements structure and conveyance of the bioactive compound to the ideal piece of the body.

Nutraceuticals Interaction

There are many considerations on delivery of nutraceuticals. There are many problems that prevent nutraceuticals to reach the target site. First, some products have the problem in absorption. Focusing on poor absorption, it might be due to labile and insolubility of the active ingredients. This problem can be seen in cases of vitamin supplementation. The vitamin is usually labile and the problem is in justification for the proper nutraceutical dosage [5]. The other widely known case is on calcium supplementation. It is no doubt that poor absorption is a basic problem in calcium supplementation. Second; the problem might be due to the interaction. The active ingredients within nutraceutical products might interact with other chemicals, which might be drugs or other nutraceuticals [5]. The interaction can either increase or decrease the desired therapeutic effect, or it might result in a new effect that might be dangerous and undesired [5].It was reported that “some foods and drugs, when taken simultaneously, can alter the body’s ability to utilize a particular food or drug, or cause serious side effects [5]. In clinical practice, there can be two ways of interactions. Drugs might affect nutritional status due to disturbance of nutrient absorption, metabolism, utilization or excretion. On the other hand, foods or nutraceutical supplements can alter absorption and reduce effectiveness of drugs [5]. Hence, the problem of interaction is very important. In fact, the interaction is an issue to be considered for nutraceutical supplementation. This issue is usually forgotten and can be dangerous in clinical practice [6]. Evaluation of the possible interaction is suggested for all nutraceutical products [7].

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Finally, it should be noted that the special concern must be made for the case with unhealthy background. In some patients with pathophysiological conditions, such as aging, hepatic dysfunction or renal impairment, the increased awareness of proper dosage and interaction of nutraceutical product is very important [8].

Nanotechnology delivery system of nutraceuticals

Nanotechnology has been broadly defined as the science and technology involved in the design, synthesis, characterization, and application of materials and devices with at least one of the dimensions on the nanoscale (usually in the range of 1-100 nm) [9]. Nanotechnology has vast applications in food industry. It deals with size range of 10^9 m and at this size particles exhibit unique properties which changes their pharmacokinetics. Nutraceuticals are products that provide essential components to the body and prevent disease. It is a requirement beyond the basic nutrition which we get from our daily meals. It may comprise of dietary supplements, products of plant origin, nutrients that are isolated from mixture, genetically engineered food and products which are processed like beverages, cereals and soups, etc [9], molecules and its subsequent effects. On the other hand, nutraceuticals are food products that have health and medical benefits, hence promoting their use in prevention and treatment of diseases. Recently, nutraceuticals have come to limelight because of current lifestyle trends which lead to improper nutrition thereby creating a need for food supplements. Due to improper systemic delivery and poor oral bioavailability, potential use of nutraceuticals is limited. Most of the nutraceuticals show difficulty in adsorption through intestinal epithelium due to the presence of bilayer lipid membrane. Other factors such as low solubility or stability of nutraceuticals under harsh gastric conditions limit their beneficial use in health industry [9].

Nanotechnology ensures better efficiency of nutraceuticals than the traditional products. Encapsulation of bio actives prevents them from degradation. Release of nutraceuticals is enhanced when delivered in nano sized form. Nanoencapsulation of nutraceuticals can improve their bioavailability thereby increasing health benefits. Recently there has been broad exploration on encapsulation of nutraceuticals into biodegradable nanocarriers to build their absorption and hence medical efficacy. Different materials have been utilized for arrangement of defensive shell of encapsulates. The material ought to be food-grade and biodegradable and must have the option to shield the inward stage from its environmental factors. Of the apparent multitude of materials of decision, most much of the time utilized are polysaccharides. Proteins and lipids are likewise encouraging possibility for proper exemplification. The capability of nanotechnology to conquer the different constraints with the nutraceuticals dependent on the ongoing improvements here are being reported [9].

Nanotechnology for delivery of nutraceuticals concept

Nanoscience is the newest scope of science dealing with the very small thing and phenomenon in “nano” scale. The nanoscience can be useful in numerous ways including its application for biomedical science. For healthful medication, the utilization of nanotechnology is conceivable. Using nanotechnology for improving the delivery of nutraceuticals is a new application in nutritional at present, many nutraceutical products have the problem in nutrient delivery for the best usage in vivo. Basically, nanotechnology can resolve the problem of unsuccessful drugs and nutraceuticals delivery [10]. The use of nanotechnology techniques can help solve the basic problems of nutraceutical delivery. Targeting to the focused site can be improved by nano-delivery systems [10]. With use of nano-delivery technique, “combining unique elements of size, surface activity and charge of

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nanostructures" of molecules can be derived [10]. The problems on absorption and solubility of the nutrients can be solved by the advanced nanotechnology. Hence, it is a hope for better improvement of present nutraceutical products. Using nanotechnology, there are many acquired useful properties. The derived properties can be useful in modifying the problematic biological process into desirable process. First, when size is reduced, the surface of molecules increases and this helps to increase the desired biological process. For example, when silymarin was reformulated into nano-liposome, the significant increase absorption can be derived [11]. Second, the modification of the nutraceutical molecules into nano molecule can get rid of unwanted biological effect. For example, the nanoencapsulation of vitamins and antioxidants can reduce gastrointestinal destroy after ingestion [12]. Hence, it can be concluded that the nano-delivery system can result in successful overcoming in vivo barriers. At present, the nano-delivery system is widely used in pharmaceutical science. The system has also been implemented into nutraceutical science for a few years. The design of new nano-delivery system usually focuses on coating and ligandin (complex formation). A proper coating can increase bio-compatible of the nutraceuticals [13]. Hence, the coating mainly deals with composition, electrical charge, permeability, absorption and responsiveness to digestion and release [14]. Meanwhile, a good ligandin, modifying of the original nutraceuticals, can help better match to the desired target [13]. Presently, the most widely used nano-delivery technique is lipid-based nanoparticle system. The lipid-based nanoparticle system can create the stable, circulating, tissue-targeted nanoparticles. Nano-liposomal formulations and solid-core micelles are the two most widely used lipid-based nanoparticles. Focusing on using nano-liposomal formulation in nutraceutical delivery, the good example is phosphatidylcholine nano-liposome complex that is specially designed for solving the problem of poor absorption of silymarin [15]. With use of the mentioned nano-liposomal formulation, the absorption increases to three time's normal [15]. The recently developed, soya-phosphatidylcholine-andrographolide complex, a kind of solid lipid nanoparticle, is a more advanced formulation. This formulation can help increase not only absorption but also hepato-protection property [16]. For using solid-core micelle; the main aim is increased target cell penetration and intracellular delivery. The assigned composition of lipid during the nano-micelle design is a key factor determent for anticancer drug delivery at present [17]. The designed particles usually contain vitamin B12 [17]. However, the application in nutraceuticals delivery is limited.

Potential uses of nanotechnology in nutraceuticals delivery for the prevention and treatment of diseases

Cancer is regarded as one of the most devastating diseases with more than 10 million new annual cases globally. Nutraceuticals are elective strong restorative operators utilized for the avoidance and therapy of different illnesses including malignant growth. Nutraceuticals having anticancer action incorporate, for example, curcumin, propolis, green tea, silymarin, and capascin. In spite of the phenomenal anticancer movement of numerous nutraceuticals, their clinical use is restricted because of their helpless solvency and short half-lives. The ongoing advances in nanotechnology have indicated a progressive effect on various parts of science, particularly biomedical science. For example, nanomaterials-based transporter frameworks have exhibited an incredible potential in consolidating regular items and taking care of their inalienable issues without bargaining their helpful exercises. Also, the upgraded penetrability and maintenance (EPR) impact of tumors upheld the controlled and focused on conveyance of the nanomaterials-stacked nutraceuticals. This audit traces the clinical significance with an accentuation on anticancer action of various nutraceuticals. The capability of nanotechnology and nanomaterials in the

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controlled conveyance of nutraceuticals for counteraction and therapy of malignant growth is likewise examined. The concept of nutraceuticals is widely used in clinical practice. At present, there are many nutraceutical products covering drugs, dietary supplements and food ingredients that can be applied for management of health disorders. For effective use of nutraceuticals in internal medicine, the delivery of nutraceuticals for body usage is very important. Based on the present advanced nanotechnology, many new techniques can be used for improving delivery of nutraceuticals. Drug has been known and used for managing of diseases for thousand years. Nevertheless, to get the good health, not only drug for treatment of disease but also food for health promotion is important. Food is accepted as the source of necessary nutrition for everyone. Nutrition from food passes basic biological process in human body and further help normalizing physiological process [18]. Within the recent years, the new concepts for applying and integrating the use of food as drug for fighting of diseases and promoting health are raised [18]. This is the origin of the nutraceuticals concept [18]. In fact, using food as drug can provide several advantages. Food is generally ingested and it has lower toxicity comparing to drug. In nutraceuticals, the food is accepted as the source of nutrition that can be further use for controlling and modifying of physiological process within human body. The concept of nutraceuticals is widely used in clinical practice. The focus is usually on the active ingredient within food that can be useful in medicine [19]. Similar to pharmaceuticals, good control and management of useful ingredients is very important in nutraceuticals [19]. In the current day, this is the significant point for making a decision about the nature of nutraceutical items. As of now, there are numerous nutraceutical items covering drugs, dietary enhancements and food fixings that can be applied for the executives of wellbeing issues. Based on the basic belief that nutraceutical supplements are "natural and safe, may prevent disease, may replace prescription medicines, or may make up for a poor diet," several nutraceutical products are in the market at present. The Office of Dietary Supplements points for the importance of continuous research on nutraceuticals as a way for continuous quality improvement [20]. For effective use of nutraceutical product in internal medicine, the delivery of nutraceuticals for body usage is very important. Based on the present advanced nanotechnology, many new techniques can be used for improving delivery of nutraceuticals. The updated information on delivery of nutraceuticals using nanotechnology will be summarized and presented in this brief article.

Chemo-preventive and antitumor approaches

It was reported that the antitumor effect of lycopene-enriched tomato extract (LycT) by affecting hypoxia-induced factor (HIF)-1α, VEGF, CD31, MMP-2andMMP-9, in the initial steps of liver carcinoma chemically induced in mice, providing evidence that prophylactic dietary supplementation with LycT may counteract HCC progression and/or protect against tumor onset [21]. Another interesting example of chemo preventive and therapeutic efficacy of a nutraceutical approach is represented by blueberry supplementation in animal carcinogenesis model which was reported to inhibit the development and progression of squamous cell carcinoma abroad at in gTGF-β and PI-3K/Akt pathways and downregulating MMPs and VEGF. Blueberry extract also inhibited migration and tube formation of cultured ECs [21]. The diet routine of Mediterranean Sea is a settled wholesome style with defensive adequacy against various metabolic issues. Among the eating regimen segments, additional virgin olive oil (EVOO) is an intriguing wellspring of dynamic principles. [21] From a chemical point of view, 98-99% of the total weight of EVOO is represented by fatty acids, especially monounsaturated fatty acids such as oleic acid. Tocopherols, polyphenols and other minor constituents represent the remaining 1-2%. Recently, the anticarcinogenic effects of olive oil phenolic

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alcohols and theirs ecoiridoid derivatives have been established by the use of different experimental models, demonstrating their capacity to inhibit proliferation and invasion of cancer cells, induce apoptosis, block tumor angiogenesis and regulate inflammatory response. In some cases the molecular mechanisms were not directly associated to their anti-oxidant effects. We have contributed to demonstrate that dihydroxyphenyl ethanol or hydroxytyrosol (HT), a product from olive oil, blocks microsomal prostaglandin-E synthase-1 and HIF-1α dependent VEGF expression, thus reducing tumor angiogenesis [22], and promotes epidermal growth factor receptor (EGFR) degradation in colon cancer tumor cells, thus sensitizing them to anticancer drugs [21]. Oleuropein (OL), the most abundant phenolic compound in olives, was demonstrated to inhibit progression of melanoma in mice exposed high-fat-diet (HFD)-induced obesity. OL suppressed HFD-induced tumor growth by reducing the expression of angiogenesis (CD31, VE-cadherin, VEGF-A, and VEGFR2), lymph angiogenesis (LYVE-1, VEGF-C, VEGF-D, and VEGFR3), and hypoxia markers (HIF-1α and GLUT-1). Additionally, OL directly inhibited in vitro tube formation of HUVECs and lymphatic ECs [23].Other plant derivatives recently described with antitumor and antiangiogenic efficacy in cellular and animal models were hydroxybenzoic acids, hydroxycinnamic acids and flavone groups from the aqueous extracts of *Basella alba* and *B. rubra* stems [24], methanol extract of wheat grass [25], bioactive compounds derived from Allium vegetables such as diallyl trisulfide (DATS) [26], and capsaicin [27], which act on multiple molecular targets associated with cancer progression and metastasis. Another interesting nutraceutical approach is the possibility to access to antiangiogenic proteins present in milk. Milk contains at least three proteins with modulatory effect on angiogenesis [21]. The antiangiogenic activity of milk lactoferrin, known from 1997, has been confirmed recently in experimental human colon cancer models, consistent with a significant down regulation of VEGFR2, VEGF-A, pPI-3K, pAkt, and pERK1/2 proteins [21]. This limited list of examples comes from epidemiologic studies which linked consumption of certain vegetables or foods to decreased incidence of cancer and pave the way for the development of defined products with high significance in the pharmaceutical and nutraceutical industries.

Nano formulation of natural compounds against neurodegeneration disease

The nanotechnology approach of disease treatment has gained a lot of interest over the past few decades. One of the greatest advantages of nano- drug delivery is to increase in the bioavailability and thereby maximizing the therapeutic index of the drug by specifically targeting particular cells or tissues. This helps to reduce the overall side effect of the drug [28]. The small drug molecules are encapsulated within the nanoparticles which transport them to desired location. Although there are various advantages in treating neurodegenerative diseases, the treatment strategy are only temporary satisfaction as the delivery of the drug to the brain is a challenge [28]. Recent advances in the field of nanotechnology are the use of nanoparticles for neurodegenerative diseases [28]. The size range of then nanoparticles helps it to cross various biological barriers within the body especially the blood brain barrier which is a very challenging question [28]. Various studies are carried out to produce nano formulation of natural compounds, but whether the compound which is nano-encapsulated possesses the same activity as raw remained a question. This has been answered by many studies. Table (1) summarizes the types of nano-formulation of herbal medicine and natural compounds. Curcumin an ancient ayurvedic medicine which is derived from an herb known as turmeric is known for its medicinal properties for many centuries. Some of the disadvantages of curcumin are its low solubility in water and poor bioavailability, so in order to overcome this issue Curcumin nanoparticles are used. One

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common method in the preparation of Curcumin nanoparticles is by wet-milling technique in which the Curcumin was sprayed into boiling water under sonication and stirring [29], had improved solubility, anti-bacterial, and anti-fungal activity when compared to raw Curcumin [30]. Other methods are also used to prepare nano Curcumin particles [31], prepared nanoparticles using emulsion-diffusion evaporation method which produced stable, spherical nanoparticles. The bioavailability of the molecule becomes drastically high (ninefold increase) when the nanoparticles were administered orally. Studies also suggest that nanocurcumin Another approach is nano-precipitation a method used to encapsulate Curcumin in polymer (PLGA-PEG) [28]. Similar to curcumin a number of research strategies have been proposed to increase the bioavailability of resveratrol. Studies suggest that solubility and transport across the plasma membrane of Resveratrol increases when the size is in nanoscale [28]. Some of the disadvantages of Resveratrol are its poor bioavailability, low solubility, and rapid metabolism of the compound [32]. Nano approach helps to overcome these disadvantages. Common method of preparation of Resveratrol nanoparticles is by high shear homogenization technique which produces microparticles and later ultra sound method is used to produce nanoparticles [32]. The tissue concentration in brain, liver and kidney improves when Resveratrol is loaded onto lipid core nanoparticles. Resveratrol incorporated in abio-degradable nanoparticle has been reported for its activity against glioma [33]. Khan et al. [34], suggested that nano-encapsulation of with aferin-A, an active constituent of *Withania somnifera* tend to increase the anxiolytic activity. Nano scaled Ginseng was created by utilizing high energy ball processing in which the Ginseng remove powder was ground at different time stretches. The cancer prevention agent limit and cell development capacity was tried and it was discovered to be strikingly high when contrasted with crude Ginseng powder extract. [35] Shinji et al. [36] analyzed the activity of silva nano sized ginkgo on brain cells. *G. bilobanano*p articles were pre-pared by a combinatorial method of both dry (gas phase grinding) and wet method (liquid phase grinding). Nano-sized Ginkgo boost the acetylcholine release from the cortical synapse of the brain cerebral hemispheres. Studies have also suggested that gold and silver nanoparticles are prepared from the leaf extract of natural herbs such as Bacopa Monnieri, Ashwagandha, Mucun apruriens Linn, Panax ginseng root [28]. Polymeric nano-micelles as novel delivery colloid systems which can be applied for nano-encapsulation of poorly water soluble and amphiphilic phenolics. They have a copolymer deblock structure with hydrophilic shell and hydrophobic core. Micelle formation occurs as a result of two forces. Attractive force that leads to the association of molecules and repulsive force prevents unlimited growth of the micelles to a distinct macroscopic phase. Micelle formation of amphiphilic block copolymers is accompanied with minimizing free energy; change in entropy is generally considered the most important factor to form stable polymeric micelles. The concentration of polymers in solutions is the most important factor during the process of the entropy-driven micelle formation. At very low concentrations, the polymers only exist as single chains. As the concentration increases to a specific value called critical micelle concentration (CMC), polymer chains start to associate to form micelles in such a way that the hydrophobic part of the copolymer is to avoid contact with the aqueous media in which the polymer is diluted [37]. Song et al. [38] successfully loaded anticancer us drug. curcumin into the MPEG-P (CL-co-PDO) micelles by a solid dispersion method with a high encapsulation efficiency ([95%). The curcumin-loaded micelles were mono disperse with a PDI less than 0.15 with small particle sizes of approximately 30 nm. Lu et al. [39] fabricated Resveratrol-loaded polymeric micelles based on amphiphilic block copolymer. The effect of Resveratrol-loaded polymeric micelles was studied on the viability and Ab protection of PC12 cells. The study suggest that Resveratrol-loaded nanoparticles did not show toxicity to cells, and protected

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PC12 cells from Ab-induced damage in a dose dependent manner (1-10lM) by attenuating intracellular oxidative stress and caspase-3 activity.

Table 1: Types nano formulation of herbal medicine and natural compounds.

System	Natural compounds	Activity	Methods	References
Nanoparticles	Bacopamonnieri	Brain tonic memory boosting	Gold NPs produced by UV cross linking of B. monnieri leaf extract	Babu et al [40].
	Panax ginseng	Enrich energy, vitality, immune ability and scavenge free radicals	High energy ball milling Gold and silver NPs by green synthesis from the root extract of ginseng	Lee et al [35].
	Mucunaprurien s Li Nn	Anti- Parkinsonism	M. pruriens gold NPs	Arulkumar and Sabesan, [41]
	Curcumin	Pro-inflammatory activity	Curcumin loaded PLGA particles by emulsion-diffusion-evaporation method. Curcumin encapsulated NPs by nanoprecipitation Curcumin encapsulated in alginate-chitosan-pluronic by ionotropic pre-gelation and polycationil cross linking Emulsion polymerization method.	Anand et al. [42], Duan et al. [31], Shaikh et al. [30], Yallapu et al [43].
	G. biloba	Brain cell activation	High Speed ball milling	Shinji et al [36].
	Ginsenoside	Immune booster	Ginsenoside NPs (ginsomes) prepared using ISCOM matrix Technology	Song et al [44].
	With aniasomnifera (Ashwagandha)	Withaferin A-antioxidant, adaptogenic, anti-inflammatory	Withaferin A- poly (lactic acid) NPs prepared by solvent evaporation method	Khan et al [34].
Polymeric Na Nomicelles	Curcumin	Improve Bioavailability	Solid dispersion method	Song et al [38].
	Resveratrol	Good drug loading Protect from b-amyloid peptide toxicity Difficult to scale up synthesis techniques	Nano-precipitation method Resveratrol loaded polymeric micelles	Lu et al [39].
Complex Polymers	Curcumin	Release control	Layer by Layer	Zheng et al [45].

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Use of nutraceuticals in Angiogenesis-Dependent Disorders

The term of angiogenesis alludes to the development of new vessels from previous present capillaries. The wonder is fundamental for physiological development, repair and working of our organs. While happening in a not directed way, it agrees to obsessive conditions as tumors, eye sicknesses, and persistent degenerative problems. On the opposite inadequate neovascularization or endothelial brokenness goes with ischemic and metabolic problems. In both the cases a provocative and oxidative condition exists in supporting angiogenesis liberation and endothelial brokenness. The utilization of nutraceuticals with cancer prevention agent and calming exercises can be a helpful alternative to keep up a satisfactory vascularization and endothelial cell appropriate working or to dull abnormal angiogenesis. A correction of the refreshed writing investigates nutraceuticals to direct endothelial cell wellbeing and to reestablish physiological tissue vascularization is the goal of this paper. The basic angles just as lacking information for human use will be investigated from a pharmacological perspective [21]. This part declares reports for recently portrayed nutraceuticals with antiangiogenic impact proposed both as prophylactic and the rape udic methods in various pathologies frequently joined by inflammatory process and an oxidative stress climate. A halfway rundown of food and their major nutraceutical segments appeared to have antiangiogenic properties is presented in Table 2 [21].

Table 2: Use of nutraceuticals in angiogenesis-dependent disorders.

Category	Food	Active principle
Beverages and drink	Green tea, red wine	Stilbenoids (resveratrol), flavanols (catechins)
Fruits	Strawberries, blackberries, raspberries, blueberries, cranberries, apple, pineapple, cherries, oranges, grapefruit, lemons, red grapes, pomegranate	Carotenoids (lycopene), The most part of flavonoids and in particular glycosides Of anthocynidins (anthocyanins), stilbenoids (resveratrol), flavanones (hesperetin)
Vegetables and Mushrooms	Artichokes, Soy beans, tomatoes, garlic, kale, broccoli, cauliflower, Brussels sprouts, bokchoy, lavender, maitake mushrooms, parsley, pumpkin	Flavones (apigenin), isoflavones (genistein), Flavonols (quercetin), Isothiocyanate (sulfurafane), glycosides Of anthocyanidins (anthocyanins)
Oils	Extra-virgin olive oil, grape seed oil	Oleic acid, Phenylethanoids (hydroxytyrosol)
Other	Dark chocolate, ginseng, licorice, turmeric, ginger, nutmeg, cinnamon, red propolis	Glycosides of Anthocyanidins (anthocyanins), ginsenoides, phenolic acids (curcumin)
Fish and meat	Tuna, sea cucumber	Omega-3 fatty acids, mucopolysaccharides, saponins

For average concentration of each active molecule and specific antiangiogenic Mechanism [5].

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Nutraceuticals and Ocular Disorders

Different eye illnesses are portrayed by reformist advancement joined by aggravation and oxidative pressure. Accordingly, they are the ideal objective for cell reinforcement and mitigating nutraceuticals. Age-related macular degeneration (AMD) is a reformist eye infection run of the mill of the older, influencing the macula, the focal district of the retina. In AMD patients, degeneration influences right off the bat the retinal shade epithelial cells and afterward the photoreceptors, prompting adjustment or incomplete loss of focal vision and visual impairment. Two types of AMD can be distinguished: the more successive atrophic-dry AMD and the less incessant neovascular-wet AMD portrayed by choroidal neovascularization (CNV). The pathogenesis of AMD is intricate and multifactorial. The perceived danger factors include: hereditary inclination, ecological determinants (i.e., serious light presentation) and way of life (i.e., smoking). The advancement of AMD is ordinarily joined by the atomic cycles of lipofuscino genesis, druso genesis and aggravation, while in wet AMD angiogenesis unbalance is normally found. Diabetic retinopathy (DR) is extensively perceived as a microvascular difficulty of diabetes. Clinically, DR can be ordered into non - proliferative DR (NPDR) and proliferative DR (PDR). NPDR is portrayed by the event of microaneurysms and little hemorrhages. Serious NPDR shows expanded retinal microvascular harm as confirmed by cotton fleece spots, venous beading and circles and variations from the norm in retinal vessels. Decreased perfusion and degeneration of the retinal vessels bring to a status of hypoxia and actuation of HIF-1α. Surely, whenever left untreated, PDR can create with irregular retinal neovascularization, retinal edema, glassy discharge and tractional retinal separation, till irreversible visual impairment in working age. With respect to AMD, oxidative pressure and aggravation are perceived functions happening in DR. Close to glycemia control, it is essential to safeguard microvascular working in the principal stage and afterward repress neovascularization in PDR. Since VEGF is an overwhelming proangiogenic factor in choroidal and retinal neovascular development, wet AMD and PDR are treated inside travitreous infusions of hostile to EGF operators, yet because of results and costs, successful and safe choices are required. Nutraceuticals can be a chemo preventive or correlative methodology [51]. Attention has been devoted to polyphenols (resveratrol, curcumin as example) and ω-3 polyunsaturated fatty acids. In particular, dietary long-chain ω-3 polyunsaturated fatty acids (LCω-3PUFAs) and lutein have been reported to protect against AMD [52]. It was demonstrated lower levels of various inflammatory modulators inherit in acrochordid mice fed withLCω-3PUFAs or lutein, without additive effects. On the contrary, the generation of reactive oxygen species (ROS) in experimental chorioretinal lesions, as well as the expression of NADPH oxidase 4 in the retina of mice was attenuated by LCω-3PUFAs and lutein in a synergistic manner. Similarly, curcumin decreases ROS generation and TNF-α release in human retinal endothelial cells and epithelial pigmented cells exposed to oxidative stress, and protects pericytes from high glucose induced damage [53]. Of note, supplementation of curcumin is right now under clinical assessment in patients with DR (NCT02984813 and NCT01646047 clinical preliminaries). These outcomes in this way show that beneficial oral dietary admission of LCω-3PUFAs, lutein and curcumin constrict visual sicknesses, including CNV and diabetic retinopathy. The defensive impacts appear to be to be added substance and related to down-guideline of fiery middle people and ROS [27].

Nutraceuticals and Pro-Endothelium Applications

In the following section we will report on some nutraceutical interventions in various angiogenesis disorders where endothelial integrity needs to be recovered or physiological angiogenesis promoted. A partial list of foods and their major nutraceutical components

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demonstrating to have proangiogenic and endothelial protective activities is reported in Table 2 [21].

Interventions for Endothelial Dysfunction

In the last few decades, numerous epidemiological studies, as well as interventional trials, confirmed cardioprotective properties of the Mediterranean diet [54] In this context, EVOO, the most representative component of this diet, seems to be relevant in lowering the incidence of cardiovascular events, including myocardial infarction and stroke. Oleic acid, tocopherols and polyphenols present in EVOO may potentially contribute to 'health maintenance [55]. Additionally, the preventive impact of nuts and apple bio actives on vascular oxidative stress and function of endothelial system has additionally been as of late documented [54]. Vitamine ought to be included for this paper. As of late, epidemiological investigations have distinguished a backwards connection between cardiovascular wellbeing and folic acid admission and plasma folate levels. Likewise, experimental evaluation considers were directed to clarify the mechanism(s) through which folic acid improves the function of vascular endothelial system capacity. These examinations confirmed that folic acid and its dynamic metabolite 5-methyltetrahydrofolate increment NO bioavailability by stimulating endothelial NO synthase (NOS) coupling and improving NO creation, just as by ROS scavenging effect [56]. By these effects, folic acid may prevent or improve endothelial cells capacity, subsequently preventing or switching the developmental issues of cardiovascular disease in patients with plain sickness or at raised danger. These findings encouraged a number of clinical studies on folic acid supplementation to potentially reverse endothelial dysfunction in patients with cardiovascular pathologies, which are ongoing with positive outcomes [57]. The same evidence seems not so clear for vitamin D, C and E. In normotensive subjects, reduced levels of 25-hydroxyvitamin D (25[OH] D) have been associated with an increased risk of hypertension, while deficiency of vitamin has been correlated with endothelial dysfunction. Nevertheless, the effect of vitamin D supplementation on endothelial dysfunction in normotensive subjects has not been evaluated rigorously. Results from a recent clinical trial documented however no improvement in endo the lia function after administration of vitamin in over weight/ obese normotensive peoples [58]. Vitamins C and E demonstrated negative results on clinical trials, and the preventive efficacy in people at cardiovascular risk is still debated in the literature [59]. Nutraceutical Approaches for Diabetes Mellitus Diabetes mellitus (DM) is characterized by chronic damage to endothelium, especially of micro vessels, due to hyperglycemia. The damage to endothelium causes endothelial dysfunction, thuspredisposingpatientstoaseriesofvascularan dneurovascularpathologies, in which the vascular wall is characterized by a persistent condition of inflammation and oxidative stress. One of the consequences is impairment of wound healing and tissue regeneration [21] Endothelial progenitor cells (EPCs), present in bone marrow and peripheral blood, as well as other mesenchymal stem cells, are involved both in the repair of damaged vessels and in neovascularization. Their activity should be improved in DM patients with vascular complications since the advanced glycation end products (AGEs) generated in DM subjects affect the number and the function of EPCs. Thus, the availability of compounds with anti-oxidant, anti-inflammatory and pro-survival or proangiogenic properties is crucial to limit vascular complications in DM patients. Lycopene (Lyc) is an identified natural antioxidant that protects EPCs. from damage due to micro- environmental AGEs. However, the underlying mechanism remain. ns to be defined. Recently, Zeng and coworkers demonstrated that Lyc improved EPC proliferation and reduced cytotoxicity due to AGEs in type 2 diabetes mellitus rats. In particular, activation of cell cycle reduced apoptosis and decreased autophagic reaction

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including ROS and mitochondrial membrane potential was found in Lyc exposed EPCs [60]. By promoting EPCs survival and protecting EPCs from apoptosis and oxidative autophagy induced by AGEs, Lyc supports the number and function of EPCs, suggesting being a new potential therapeutic option for DM vascular complications. Another interesting approach is represented by polyunsaturated fatty acids (PUFAs), specifically theω-3, which is essential for grow and development, as during pregnancy. Mathew and coworkers treated placenta-derived mesenchymal stromal cells with ω-3 fatty acids docosahexaenoic acid (DHA) and eicosatetraenoic acid (EPA), testing their angiogenic potential. They reported an upregulation of both FGF-2 and VEGF-A and enhanced in vitro angiogenesis with DHA: EPA, also in culture experiments with mature ECs. Their findings supports the supplementation with low doses of PUFAs in enhancing the angiogenic potential of placenta derived mesenchymal stromal cells [61]. making them appealing as cellular therapy to favor wound healing in chronic metabolic disorders characterized by poor recovery of tissue integrity [62].

Pharmacological Issues to Be Solved

A progression of basic issues needs anyway to be considered before the presentation of nutraceuticals in human use for sickness treatment. A first issue is identified with the drug arrangement. While characteristic items appear to be a decent alternative, their fixation, fine structure and bioactivity are extremely subject to irregularity, climate and development conditions. Ceutical inside food staff or concentrates. Subsequently, the consistency of helpful arrangements ought to be guaranteed from numerous groups of items with fitting quality control or on the other hand, by synthetic union of the compound of intrigue. Following preclinical approval of viability and disclosure of the component of activity, explicitly planned clinical preliminaries ought to be raced to get data on the best source and detailing of nutraceuticals (food as well as refreshments, extricated phytocomplexes, disconnected nutraceuticals, engineered analogs or metabolites). In fact, as announced in Table 1 clinical preliminaries are running on all these various arrangements. Suitable details ought to be intended to advance measurement and arrangement of nutraceuticals for the proposed course of organization. Appropriate formulations should be designed to optimize dosage and preparation of nutraceuticals for the proposed route of administration. Of note, various nutraceuticals combination just as the expansion to regular medications ought to be surveyed, particularly considering conceivable pharmacokinetic or pharmacodynamic co-operations. As indicated by rules, legitimate toxicological investigations are important to show the security of novel nutraceuticals to be proposed in the market. Once in use, an active pharmaco-vigilance should be conducted by healthcare professionals in order to detect possible adverse reactions, especially when supplementary strategies are given in combination with prescription drugs. One of the major concerns of nutraceuticals is the extremely low bioavailability due to scarce water solubility and low absorption rate. As a consequence, only negligible levels of the compounds can be found in the circulation and can reach to diseased tissue [63]. Accordingly, there is a great effort to improve nutraceuticals bioavailability, as the use of nano-carriers [64] or hydrophilic carriers [65]. Natural compounds can be packaged into biodegradable polymeric nanoparticles for solid or liquid formulations. Due to the better pharmacokinetic profile of nano-formulations, these preparations demonstrate to retain the activity of the native molecules and to facilitate their targeting to the tissue of interest [64]. For example, EGCG encapsulated in nano-carriers has the same pro-apoptotic and anti-angiogenic effects exerted by the native compound, but with the advantage of a 10-fold lower dose [64], and nano-encapsulated curcumin, kaempferol and berberine have improved in vivo antiangiogenic and anti-tumor effects compared to the free forms [66]. For curcumin, several oral formulations with hydrophilic carriers are

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available, and recently, their pharmacokinetic profiles have been investigated in view of use in ocular disorders [65]. However, once designed, the safety and clinical validation of these novel formulations remain to be established [67]. Another concern related to nutraceuticals is the information about the circulating metabolites and their expected biological activities. Indeed, it is not excluded that circulating metabolites can exert the same or opposite biological activities, as seen in one of our previous paper on the dual angiogenic properties of quercetin metabolites [21].

The final result of inhibition or activation of angiogenesis is thus finely dependent on in vivo metabolism by metabolites, as well as by the inflammatory/oxidative microenvironment in which the metabolites are coopted to work. This aspect should be taken into consideration when designing therapeutic or preventive strategies based on food derivatives. The combination of these two latter aspects of nutraceuticals, nano formulation and use of active metabolites, has been considered in the study of Bhatt et al [68]. where nano nutraceuticals were designed using the metabolites resulting from the solid phase fermentation of soybean with *Bacillus substilis*. The efficacy of these novel formulations has been validated for the antioxidant activity and beneficial impact on cognitive defects in an experimental model of Alzheimer's disease [68].

Future trends and considerations

It seems that the application of nanotechnology for delivery of nutraceuticals will be worldwide used in the future. There will be many new innovations of nano-based nutraceutical technologies, especially for the novel patents on a number of applications. The trend will be the development of new eco-favorable systems with increased quality, safety, stability, and efficiency of nutraceuticals [69].Also, the application on nanotechnology will be the tool for quality control and management of the nutraceutical products. This will be the great improvement in nutraceutical medicine. Nevertheless, the consideration on the possible adverse effect of nano-delivery system should be raised. The nanotoxicity of the applied nanomaterials has to be continuously monitored [70]. Hence, good delivery of nutraceuticals is an important step for increased effectiveness of nutraceuticals use. Advanced nanotechnology can be useful in improving delivery of nutraceuticals. Many new techniques are presently available for improvement of absorption and distribution of nutraceuticals. In fact, the quality control of quality control of the present nutraceuticals is a big issue to be considered. Low solubility and poor adsorption of bioactive compounds would be also closely related to the low oral bioavailability due to lower stability of compounds and poor hepatic first pass metabolism [69-71]. Nanotechnology application in nutrition and food industry is to fabricate or formulate food ingredients with novelty which has marked enhancement in its solubility, stability towards heat and light, better oral bioavailability and much pronounced physiological performance. Nano-carrier systems utilizes cores that may be liquid (emulsions and microemulsions), solid (solid lipid nanoparticles-SLNs), or a mix of solid and liquid domains (nanostructured lipid carriers-NLCs). Particles for encapsulation of hydrophilic ones are composed of an aqueous core, delineated from the surrounding continuous phase by a shell. These include nanohydrogels, liposomes and colloidosomes. In both categories, the nanocarriers are stabilized by either emulsifying molecules (emulsions) or by colloidal particles (Pickering emulsions) [69] All these have been widely exploited for effective delivery of lipophilic agents. Due to their extremely small size, nanocarriers have shown many advantages such as improvement of the aqueous solubility, enhancement of residence time in gastrointestinal (GI) tract regions, better physicochemical stability in GI tract, increase the intestinal permeation, controlled release in GI tract, intracellular delivery, and transcellular delivery [69].

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Conclusions

A large number of nutraceutical compounds are integral part of the healthy diet and in the past decades a great number of reports support their beneficial properties in human health, by acting in different signaling pathways of various cell types. Diet components and selected nutraceuticals have been demonstrated to maintain vascular structure and function or ultimately to induce the formation of capillary-like structures (by inducing endothelial cell growth, migration, and invasiveness). Then again, numerous nutraceuticals generally got from plants, can repress the means of angiogenesis prompting the restraint/relapse of vascular turn of events. It must be noticed that similar mixes or classes of nutraceuticals, exhibit both favorable to and antiangiogenic properties. This obvious Catch 22 can be clarified by considering the setting wherein the dynamic metabolites work, in particular a climate where aggravation and oxidative species are available and agree to infection advancement along with angiogenesis liberation. Indeed, most of the nutraceuticals so far studied exert anti-inflammatory and/or anti-oxidative properties. As discussed earlier, the dual activity on angiogenesis by the same nutraceutical seems concentration or dose related: i.e., for red wine polyphenols low doses have been reported to promote angiogenesis, while high doses were antiangiogenic, acting on different cellular and molecular mechanisms. A viewpoint unmistakably missing from the writing about the impact of nutraceutical subsidiaries on angiogenesis, is vessel standardization. Both in angio-hindrance and in advancement of angiogenesis it is essential to acquire physiological or develop vessels, staying away from variant neovascularization and profoundly penetrable/broken vessels. Just a single trial report zeroed in on the impact of nutraceuticals on this component the pretreatment with neem leaf glycoprotein brought about vascular standardization in melanoma and carcinoma bearing mice, giving ascent additionally to immunomodulation. This element benefits to be investigated in a more predictable way. Taking everything into account, dietary dynamic segments can be created as promising interventional devices albeit significant perspectives stay to be inspected, reinforcing the information on their focus interceded impacts, assessing the effect(s) of specific active molecules and circulating metabolites, designing appropriate formulations and finally establishing their effective usefulness against different disorders tools to be used alone or in association with drugs.

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