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Peel Extracted Antioxidant Nanoparticles: A New Green Therapy for Chronic Degenerative Disease

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ABSTRACT

Chronic Degenerative Disease is a major concern on various age groups of people including pediatric to geriatric patients, since CDD is related to cancer, cardiovascular disease (hypertension and hypotension), and obesity they are intimately related to oxidative stress (OS) which produces the formation of free radicals and reactive species of oxygen and nitrogen. This is combat by antioxidants. Synthetic antioxidants used in diet are not well absorbed and also possess a later effect on lifestyle disease. This can be avoided by incorporating organic antioxidants but because of high degradability in GIT, low bioavailability poses drawbacks. This can be overcome by giving them a sustained release in the aqueous system and provide stability in an acid environment. To achieve this point we have hypothesized encapsulating organic antioxidants obtained from peels of Citrus reticulata into soy protein an organic matrix for nanotechnology which will provide a sustained stability and control release and eventually increase bioavailability. In this review, we will review green therapy of organic nanoparticles with organic antioxidants as a new potential of CDD therapy.

INTRODUCTION:

Antioxidants are compounds that inhibit oxidation. Oxidation is a chemical reaction that can produce free radicals, thereby leading to chain reactions that may damage the cells of organisms. Antioxidant reacts with these free radicals and terminates this chain reaction by removing free radical intermediates and inhibits other oxidation reactions by oxidizing themselves. Oxygen is essential for the life of aerobic organisms but it may become toxic if supplied at higher concentrations. Dioxide in its ground state is relatively unreactive; its partial reduction gives rise to active oxygen species (AOS) such as singlet oxygen, superoxide radical anion, hydrogen peroxide, etc. This is partly due to the oxidative stress that is the adverse effect of oxidant on physiological function. Free oxygen radicals play a cardinal role in the etiology of several diseases like arthritis, cancer, atherosclerosis, etc. The oxidative damage to DNA may play a vital role in aging [1]and the presence of intracellular oxygen also can be responsible to initiate a chain of inadvertent reactions at the cellular level and these reactions cause damage to critical cell biomolecules. These radicals are highly toxic and thus generate oxidative stress in plants. Plants and other organisms have built a wide range of mechanisms to combat these Free Radical problems. Free radicals are an atom or molecule that bears an unpaired electron and is extremely reactive, capable of engaging in rapid change reactions that destabilize other molecules and generate many more free radicals. In plants and animals, these free radicals are deactivated by antioxidants. These antioxidants act as an inhibitor of the process of oxidation, even at relatively small concentrations, and thus have a diverse physiological role in the body.

TYPES OF ANTIOXIDANTS:

Antioxidants can be classified into two major types based on their source, i.e., natural and synthetic antioxidants.

Based on their solubility, antioxidants are broadly categorized into two groups: water-soluble and lipid-soluble.

Another commonly used classification is based on their mechanism of action, i.e., primary or chain-breaking antioxidants and secondary or preventive antioxidants.

Natural Antioxidants

Natural antioxidants either are synthesized in the human body through metabolic processes or are supplemented from other natural sources, and their activity very much depends upon their physical and chemical properties and mechanism of action. This can be further divided into two categories, i.e., enzymatic antioxidants and non-enzymatic antioxidants.

Enzymatic Antioxidants

Enzymatic antioxidants are uniquely produced in the human body and can be subdivided into primary and secondary antioxidants.

Primary Antioxidants

Primary antioxidants mainly include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).

Superoxide Dismutase Superoxide dismutase (SOD) enzyme is found in both the dermis and the epidermis. It removes the superoxide radical ($O2.^{-}$) and repairs the body cells damaged by free radical.

Catalase enzyme (CAT) is found in the blood and most of the living cells and decomposes H_2O_2 into water and oxygen.

Glutathione Peroxidase Glutathione peroxidase (GPx) is a group of selenium-dependent enzymes, and it consists of cytosolic, plasma, phospholipid hydroperoxide, and gastrointestinal glutathione peroxidase.

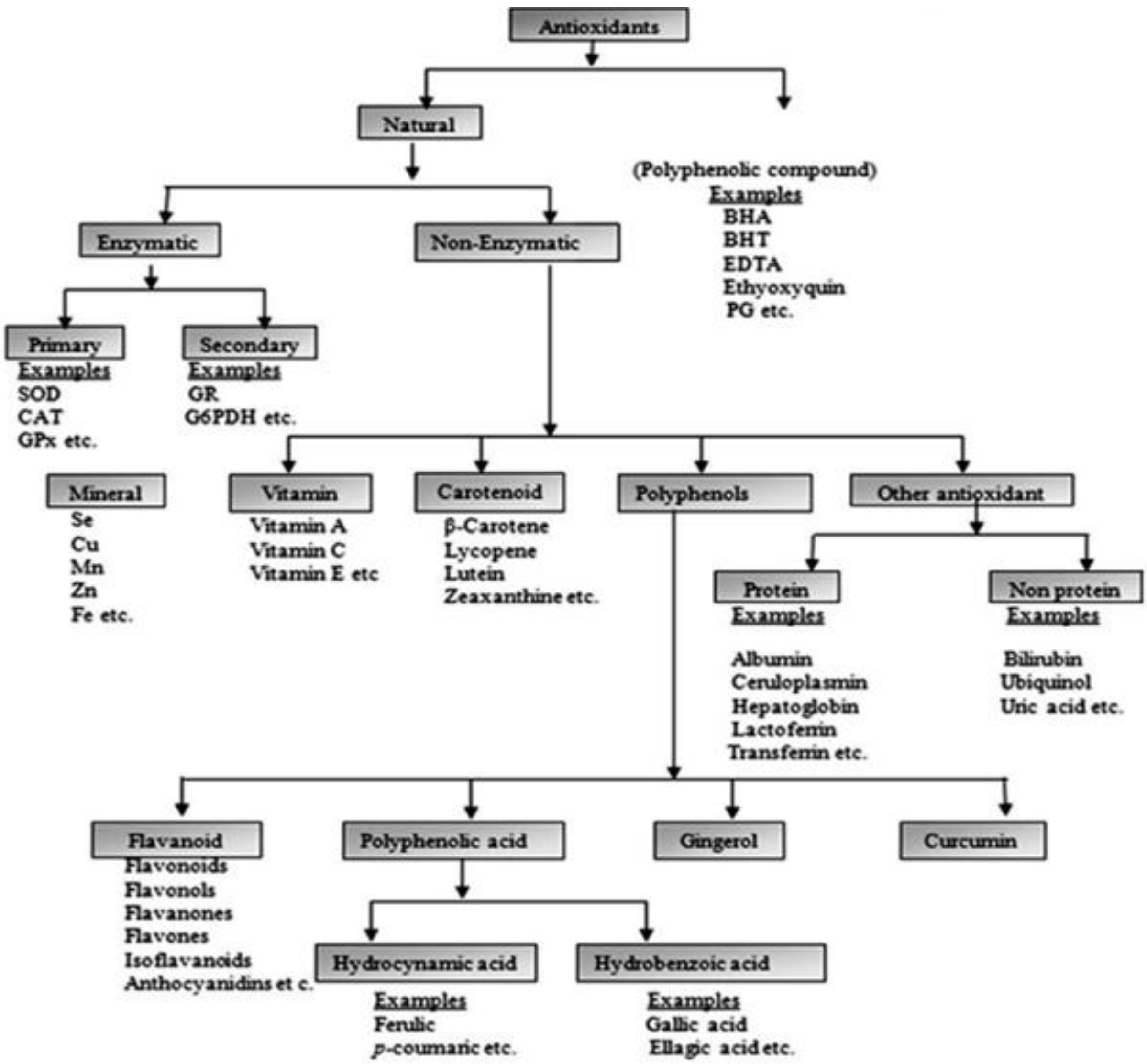

Figure No. 1: Types of antioxidant

Secondary Antioxidant

Secondary antioxidants include glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G6PDH). G6PDH generates NADPH. GR is required to recycle the reduced glutathione (GSH) using secondary enzymes GR and NNADP.

Nonenzymatic Antioxidants

They are a class of antioxidants that are not found in the body naturally but are required to be supplemented for the proper metabolism (Raygani et al. 2007). Some of the known nonenzymatic antioxidants are minerals, vitamins, carotenoids, polyphenols, and other antioxidants as listed below.

Minerals

Minerals are required in the body cells for the proper functioning of the enzymes. Their absence is known to affect the metabolism of many macromolecules. They include selenium, copper, iron, zinc, and manganese. They act as cofactors for the enzymatic antioxidants.

Iron (Fe) Iron is the most abundant trace metal found to be bound with protein in the biological system. Normally the concentration of free iron is very low and the low concentrations of iron-binding proteins promote ROS production, lipid peroxidation, and oxidative stress (Dabbagh et al. 1984).

Magnesium (Mg) Magnesium is a cofactor for glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) involved in the pentose cycle which catalyzes the production of NADPH from NADP during the glucose metabolism and hence maintains the normal ratio of GSH to GSSG and a normal redox state in cells (Fang et al. 2002).

Selenium (Se) Selenium is also a very important component of enzymatic antioxidants. In the presence of selenium (Se), glutathione peroxidase (GPx) plays a protective role against oxidation of lipids and protects the cell membrane, and takes part in H2O2 and lipids' hydroxy peroxide metabolism. Hence, Se behaves like vitamin E and can be substituted in place of vitamin E and is used to prevent the risk of cancer and cardiovascular diseases (Sikora et al. 2008).

Copper (Cu), Zinc (Zn), and Manganese (Mn) SOD is a class of enzymes that consists of different types of SODs, depending upon their metal cofactors such as Cu–Zn and Mn. These metals are responsible for SOD's antioxidant activities.

Vitamins

Vitamins form the class of micronutrients required for the proper functioning of the body's antioxidant enzyme system, such as vitamin A, vitamin C, vitamin E, and vitamin B. They cannot be synthesized in our body and hence need to be supplemented in the diet.

Vitamin A: Vitamin A is helpful in night vision and maintenance of epithelial cells in mucus membranes and skin. Because of its antioxidant properties, it assists the immune system also and is found in three main forms: retinol, 3, 4-didehydroretinol, and 3-hydroxy retinol.

Vitamin C Vitamin C is water-soluble and is also called ascorbic acid. It is found in fruits (mainly citrus), vegetables, cereals, beef, poultry, fish, etc. It helps prevent some of the DNA damage caused by free radicals, which may contribute to the aging process and the development of diseases, such as cancer, heart disease, and arthritis.

Antioxidants from C. reticulata peels:

The citrus genus is one of the most economically relevant fruit crops in the world. It includes about 17 species of citrus fruits such as Citrusreticulata Blanco (mandarin orange, tangerine), Citrus sinensis L. (sweet orange), Citrus aurantium L. (bitter orange), Citrus lemon L. (lemon), Citrus paradise M. (grapefruit) (Chutia et al., 2009). These crops of Asian origin, are nowadays distributed throughout the world, mainly in the tropical, subtropical, and temperate regions, like Brazil, Portugal, Spain, Italy, Greece, Morocco, Turkey, and Egypt (Boluda-Aguilar et al., 2010; Chutia et al., 2009). Their worldwide annual production is near 88 million tons (Negro et al., 2016). The industrial processing of citrus fruits generates millions of tons of organic waste residues such as peels, seeds, pulp, and membranes (Boluda-Aguilar et al., 2010; Hiasa et al.,2016; Negro et al., 2016). These industrial by-products are an environmental problem and a product waste. Increased awareness of food industries of the economic and environmental impacts of waste generation and disposal are calling for the transition towards more sustainable practices and the adoption of the circular economy concepts (Jurgilevich et al., 2016).

POMELO

It is a natural, i.e. nonhybrid, citrus fruit, native to Southeast Asia. Similar in taste to a large, sweet grapefruit, the pomelo is commonly consumed and used for festive occasions throughout Southeast Asia. The fruit is also known as jabong in Hawaii and jambola in varieties of English spoken in South Asia.

Scientific name: Citrus maxima

Higher Classification: Citrus

Figure No. 2: Pomelo

Family: Rutaceae

Order: Sapindales

CITRON

The citron is a large fragrant citrus fruit with a thick rind. It is one of the three original citrus fruits from which all other citrus types developed through natural hybrid speciation or artificial hybridization. It is used widely in Asian cuisine, and also in traditional medicines, perfume, and for religious rituals and offerings. Hybrids of citrons with other citrus are commercially prominent, notably lemons and many limes.

Figure No. 3: Citron

Scientific name: Citrus medica.

Higher Classification: Citrus.

Family: Rutaceae

Order: Sapindales

GRAPEFRUIT

The grapefruit is a subtropical citrus tree known for its relatively large sour to semisweet, somewhat bitter fruit. The interior flesh is segmented and varies in color from white to yellow to pink to red.

Figure No. 4: Grapefruit

Scientific name: Citrus × paradisi

Higher classification: Citrus

Family: Rutaceae

Order: Sapindales

FINGER LIME

The Australian finger lime or caviar lime is a thorny understorey shrub or small tree of lowland subtropical rainforest and rainforest in the coastal border region of Queensland and New South Wales, Australia. It has edible fruits that are under development as a commercial crop.

Scientific name: Citrus australasica

Higher classification: Citrus

Figure No. 5: Finger lime

Rank: Species

Family: Rutaceae

Higher classification: Citrus

Family: Rutaceae

Order: Sapindales

The mandarin orange, also known as the mandarin or mandarine, is a small citrus tree with fruit resembling other oranges, usually eaten plain or in fruit salads. Tangerine is a group of orange-colored citrus fruit consisting of hybrids of mandarin orange. (Wikipedia.et.al)

Figure No. 6: Citrus

Scientific name: Citrus reticulata

Higher classification: Citrus

Family: Rutaceae

Kingdom: Plantae

Order: Sapindales

Recycling of citrus by-products

has been mainly performed, fresh or after ensilage or dehydration, for cattle feed (Bampidis and Robinson, 2006; Caparra et al., 2007). Other potential re-uses of citrus fruit by-products include bioethanol production due to its high carbohydrate content (Boluda-Aguilar et al., 2010), essential oil production/recovery, mainly composed by D-limonene (Negro et al., 2016), as a substrate for multienzyme production(Mamma et al., 2008). Due to their high content of phenolic acids, polyphenols (e.g., polymethoxylated flavones, glycosylated flavanones, flavonoids, and limonoids), and carotenoids (Boluda-Aguilar et al.,2010; Hiasa et al., 2016; Ho and Lin, 2008; Huang and Ho, 2010; Moulehi et al., 2012), citrus peels can also constitute a source of potential pharmacological molecules. Citrus peel medicinal use is known for centuries, as dried peels of C. reticulata "Chen pi" have been used in the Traditional Chinese Medicine for treating indigestion, bronchitis, and asthma (Ho and Lin, 2008). Polymethoxylated flavones, such as tangeritin and nobiletin (Stuetz et al., 2010) have been reported to have anti-inflammatory (Zhang et al., 2016), antioxidant, anti-allergic, anti-proliferative, anti-atherogenic, antibacterial, antifungal, and antiviral activities (Ho and Lin, 2008; Liu et al., 2012; Manthey and Guthrie, 2002). Moreover, the flavonoids hesperidin and diosmin, play an important role in the prevention of atherosclerosis as they reduce total blood cholesterol, presenting also anti-hypertensive, hypolipidaemic, diuretic, and analgesic properties (Stuetz et al., 2010; Tounsiet al., 2011). Polyphenols may have potential uses as biobased phytosanitary products, able to control the incidence of crop diseases (Benouaret et al., 2014). The extraction of valuable polyphenols from by-product can reduce the environmental impact of some of these substances on the cultivated fields and on the irrigation water Kuppusamy et al., 2015; Seabra et al., 2010) and on the other hand can constitute a valuable source of natural phenolics for the pharmaceutical and cosmetic industries.

NANOPARTICLES:

Nanoparticles are the engineered materials having at least of its atomic dimension in the nano (10^{-9}) range.

NPs are tiny materials having sizes ranges from 1 to 100 nm. They can be classified into different classes based on their properties, shapes, or sizes. The different groups include fullerenes, metal NPs, ceramic NPs, and polymeric NPs. NPs possess unique physical and chemical properties due to their high surface area and nanoscale size. Their optical properties are reported to be dependent on the size, which imparts different colors due to absorption in the visible region. Their reactivity, toughness, and other properties are also dependent on their unique size, shape, and structure. Due to these characteristics, they are suitable candidates for various commercial and domestic applications, which include catalysis, imaging, medical applications, energy-based research, and environmental applications. Heavy metal NPs of lead, mercury, and tin are reported to be so rigid and stable than their degradation is not easily achievable, which can lead to many environmental toxicities.

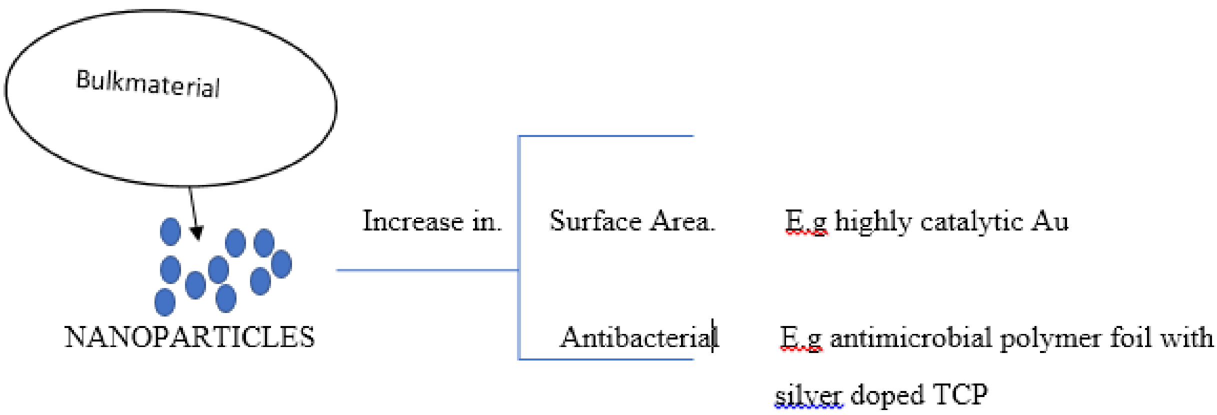

Figure No. 7: Nanoparticles

NPs are not simple molecules themselves and therefore composed of three layers i.e. (a) The surface layer, which may be functionalized with a variety of small molecules, metal ions, surfactants, and polymers. (b) The shell layer, which is a chemically different material from the core in all aspects, and (c) The core, which is essentially the central portion of the NP and usually refers to the NP itself (Shin et al., 2016). Owing to such exceptional characteristics, these materials got the immense interest of researchers in multidisciplinary fields.

Classification of NPs

NPs are broadly divided into various categories depending on their morphology, size, and chemical properties. Based on physical and chemical characteristics, some of the well-known classes of NPs are given below.

Carbon-based NPs

Fullerenes and carbon nanotubes (CNTs) represent two major classes of carbon-based NPs. Fullerenes contain nanomaterial that is made of globular hollow cage such as allotropic forms of carbon. They have created noteworthy commercial interest due to their electrical conductivity, high strength, structure, electron affinity, and versatility (Astefanei et al., 2015).

Metal NPs

Metal NPs are purely made of metal precursors. Due to well-known localized surface plasmon resonance (LSPR) characteristics, these NPs possess unique optoelectrical properties. NPs of the alkali and noble metals i.e. Cu, Ag, and Au have a broad absorption band in the visible zone of the electromagnetic solar spectrum. The facet, size, and shape-controlled synthesis of metal NPs are important in present-day cutting-edge materials (Dreaden et al., 2012). Due to their advanced optical properties, metal NPs find applications in many research areas. Gold NPs coating is widely used.

Ceramics NPs

Ceramics NPs are inorganic nonmetallic solids, synthesized via heat and successive cooling. They can be found in amorphous, polycrystalline, dense, porous, or hollow forms (Sigmund et al., 2006).

Therefore, these NPs are getting great attention from researchers due to their use in applications such as catalysis, photocatalysis, photodegradation of dyes, and imaging applications. (Thomas et al., 2015).

Semiconductor NPs

Semiconductor materials possess properties between metals and nonmetals and therefore they found various applications in the literature due to this property (Ali et al., 2017, Khan et al., 2017a). Semiconductor NPs possess wide bandgaps and therefore showed significant alteration in their properties with bandgap tuning. Therefore, they are very important materials in photocatalysis, photo optics, and electronic devices (Sun, 2000).

Polymeric NPs

These are normally organic-based NPs and in the literature, a special term polymer nanoparticle (PNP) collective is used for it. They are mostly nanospheres or nano capsular shaped (Mansha et al., 2017). The former are matrix particles whose overall mass is generally solid and the other molecules are adsorbed at the outer boundary of the spherical surface. In the latter case the solid mass is encapsulated within the particle completely (Rao and Geckeler, 2011).

Lipid-based NPs

These NPs contain lipid moieties and are effectively used in many biomedical applications. Generally, a lipid NP is characteristically spherical with a diameter ranging from 10 to 1000 nm. Like polymeric NPs, lipid NPs possess a solid core made of lipid and a matrix contains soluble lipophilic molecules. Surfactants or emulsifiers stabilized the external core of these NPs (Rawat et al., 2011). Lipid nanotechnology (Mashaghi et al., 2013) is a special field, which focuses on the designing and synthesis of lipid NPs for various applications such as drug carriers and delivery (Puri et al., 2009) and RNA release in cancer therapy (Gujrati et al., 2014).

Synthesis of nanoparticles

Various methods can be employed for the synthesis of NPs, but these methods are broadly divided into two main classes i.e. (1) Bottom-up approach and (2) Top-down approach (Wang and Xia, 2004) as shown in Scheme 1 (Iravani, 2011). These approaches further divide into various subclasses based on the operation, reaction condition, and adopted protocols.

Typical synthetic methods for NPs for the (a) top-down and (b) bottom-up approaches.

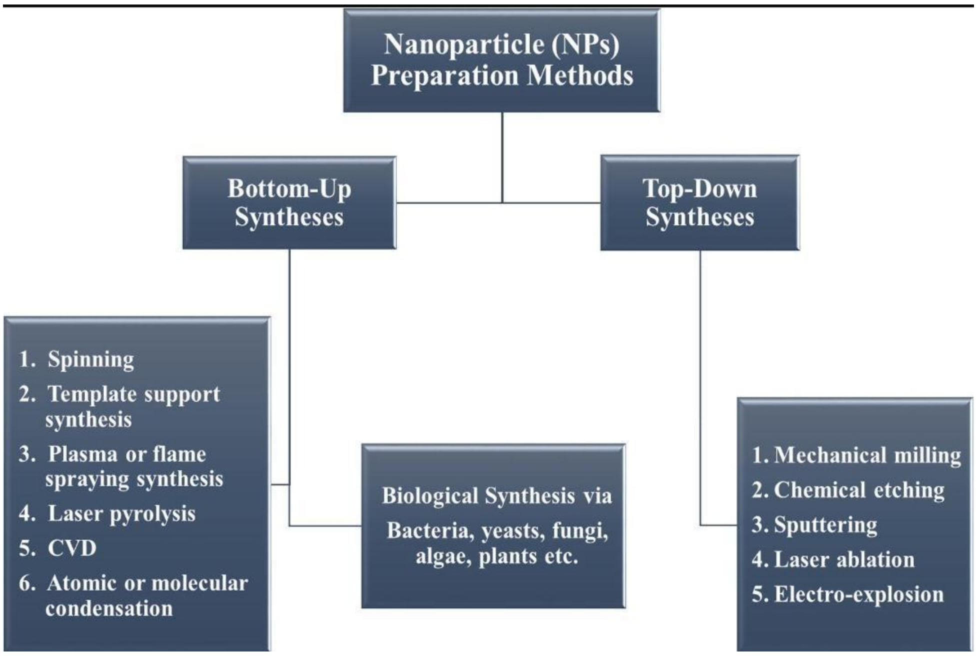

Figure No. 8: Methods of preparation of Nanoparticles

Top-down syntheses

In this method, a destructive approach is employed. Starting from larger molecules, which decompose into smaller units and then these units are converted into suitable NPs. Examples of this method are grinding/milling, CVD, physical vapor deposition (PVD), and other decomposition techniques (Iravani, 2011). This approach is used to synthesize coconut shell (CS) NPs. The milling method was employed for this purpose and the raw CS powders were finely milled for different intervals of times, with the help of ceramic balls and a well-known planetary mill. They showed the effect of milling time on the overall size of the NPs through different characterization techniques.

Bottom-up synthesis

This approach is employed in reverse as NPs are formed from relatively simpler substances, therefore this approach is also called the building up approach. Examples of this case are sedimentation and reduction techniques. It includes sol-gel, green synthesis, spinning, and biochemical synthesis. (Iravani, 2011). Mogilevsky et al. synthesized TiO_2 anatase NPs with graphene domains through this technique (Mogilevsky et al., 2014). They used alizarin and titanium isopropoxide precursors to synthesize the photoactive composite for photocatalytic degradation of methylene blue.

Characterization of NPs

Different characterization techniques have been practiced for the analysis of various physicochemical properties of NPs. These include techniques such as X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), infrared (IR), SEM, TEM, Brunauer–Emmett–Teller (BET), and particle size analysis.

Morphological characterizations

The morphological features of NPs always attain great interest since morphology always influences most of the properties of the NPs. There are different characterization techniques for morphological studies, but microscopic techniques such as polarized optical microscopy (POM), SEM, and TEM are the most important of these.

Structural characterizations

The structural characteristics are of the primary importance to study the composition and nature of bonding materials. It provides diverse information about the bulk properties of the subject material. XRD, energy dispersive X-ray (EDX), XPS, IR, Raman, BET, and Zieta size analyzer are the common techniques used to study structural properties of NPs.

Particle size and surface area characterization

Different techniques can be used to estimate the size of the NPs. These include SEM, TEM, XRD, AFM, and dynamic light scattering (DLS). SEM, TEM, XRD, and AFM can give a better idea about the particle size (Kestens et al., 2016), but the zeta potential size analyzer/DLS can be used to find the NPs size at an extremely low level.

Optical characterizations

Optical properties are of great concerned in photocatalytic applications and therefore, photo-chemists acquired a good knowledge of this technique to reveal the mechanism of their photochemical processes. These characterizations are based on the famous beer-lambert law and basic light principles (Swinehart, 1962). These techniques give information about the absorption, reflectance, luminescence, and phosphorescence properties of NPs. It is widely known that NPs especially metallic and semiconductor NPs possess different colors and therefore, best harmonized for photo-related applications.

Physicochemical properties of NPs

As discussed earlier, various physicochemical properties such as large surface area, mechanically strong, optically active, and chemically reactive make NPs unique and suitable applicants for various applications.

WHAT ARE ORGANIC NANOPARTICLES

Organic nanoparticles (NPs) are templated upon natural or synthetic organic molecules. Nature provides a wide range of examples of organic NPs such as protein aggregates, lipid bodies, milk emulsions, or more complex organized structures such as viruses, to name a few. Organic NPs also form part of many industrial products, mostly in food and cosmetics. Many food products such as creams, chocolate, and cakes present nanoemulsions in their formulation and that is also the case in the cosmetic industry. Organic NPs are also used in pharmaceutical formulations, that is, liposome vectors, polymersomes, polymer–protein, or polymer-drug conjugates.

One of the most important features of organic NPs is that they offer relatively simple routes for the encapsulation of materials. This together with the fact that the molecules used for the fabrication of the organic NPs can be biodegradable makes organic NPs the most appealing systems for drug delivery and biomedical applications.

WHY ORGANIC NANOPARTICLES

Organic NPs differ conceptually from inorganic NPs in terms of the principles of fabrication. Inorganic NPs are normally formed by the precipitation of inorganic salts, which are linked in a matrix. The nature of the bonding among atoms can be different: covalent, metallic, etc.

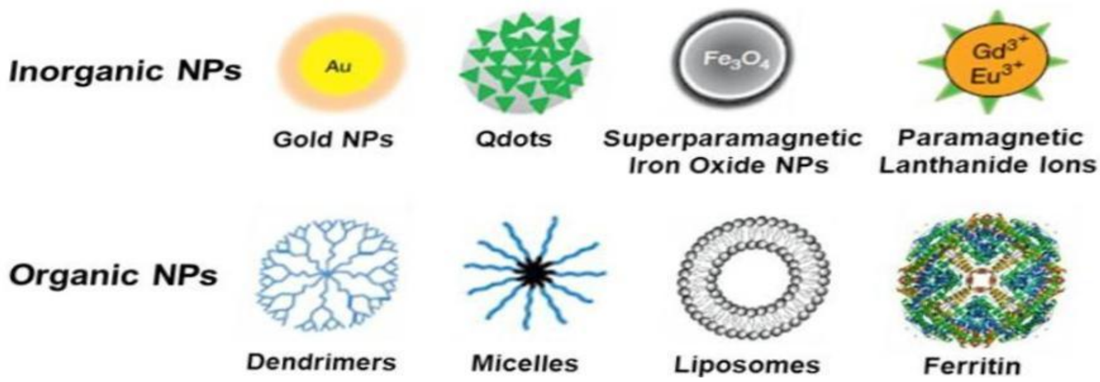

Figure No. 9: Organic and Inorganic Nanoparticles

Organic NPs can be fabricated both by "top-down" and by "bottom-up" approaches. In the "top-down" techniques, the most common is the mechanical milling,1 although, recently, other more complicated techniques involving microfluidics and lithography 2,3 have been used to produce organic nanomaterials.

In the "bottom-up" techniques, organic NPs are typically produced via precipitation and condensation methods,4,5 using synthetic methodologies6,7or applying self-assembly principles.

Organic nanoparticles have an upper edge in terms of biodegradability over inorganic nanoparticles, so they result in bio-nano composites when blended with a biodegradable polymer whereas the inorganic nanoparticles are extensively used as antimicrobial agents in food packaging systems.

Impact on various parameters after nanoparticle development.

Soy proteins as nanoparticles matrix:

The selection of nanoparticle materials is dependent on many factors including (a) the size of nanoparticles needed, (b) inherent properties of the drug such as aqueous solubility and stability, (c) drug release profile desired, (d) surface charge and hydrophobicity of nanoparticles, (e) biocompatibility and biodegradability of nanomaterials, and (f) antigenicity and toxicity of the product [9]. Biopolymer-based nanoparticles including protein nanoparticles have gained considerable interest in recent years due to their many desirable properties such as low toxicity and biodegradability [10]. They are actively being developed for both pharmaceutical and nutraceutical delivery.

Soybean (*Glycine max* L.) is currently one of the most abundant sources of plant proteins. The enriched form of soy protein, known as soy protein isolate (SPI), has been reported to have high nutritional values and ingredient functionalities. A wide range of applications of soy proteins as food ingredients has been well documented [39]. Also, SPI possesses a balanced composition of polar, nonpolar, and charged amino acids, allowing a variety of drugs to be incorporated. The major components of SPI are glycinin (MW = 360,000, ~60%) and β-conglycinin (MW = 180,000, ~40%) [40]. In an aqueous environment, these components exist as globular structures consisting of a hydrophilic shell and hydrophobic kernel, together with a certain amount of small water-soluble aggregates [41]. Upon addition of dissolvent or crosslinking agents, SPI molecules continue to aggregate and form various structures such as microspheres, hydrogels, and polymer blends [42,43]. Soy protein nanoparticles can be prepared either from a freshly prepared SPI by desolvation or from the glycinin fraction of defatted soy flour extraction using a simple coacervation method [43].

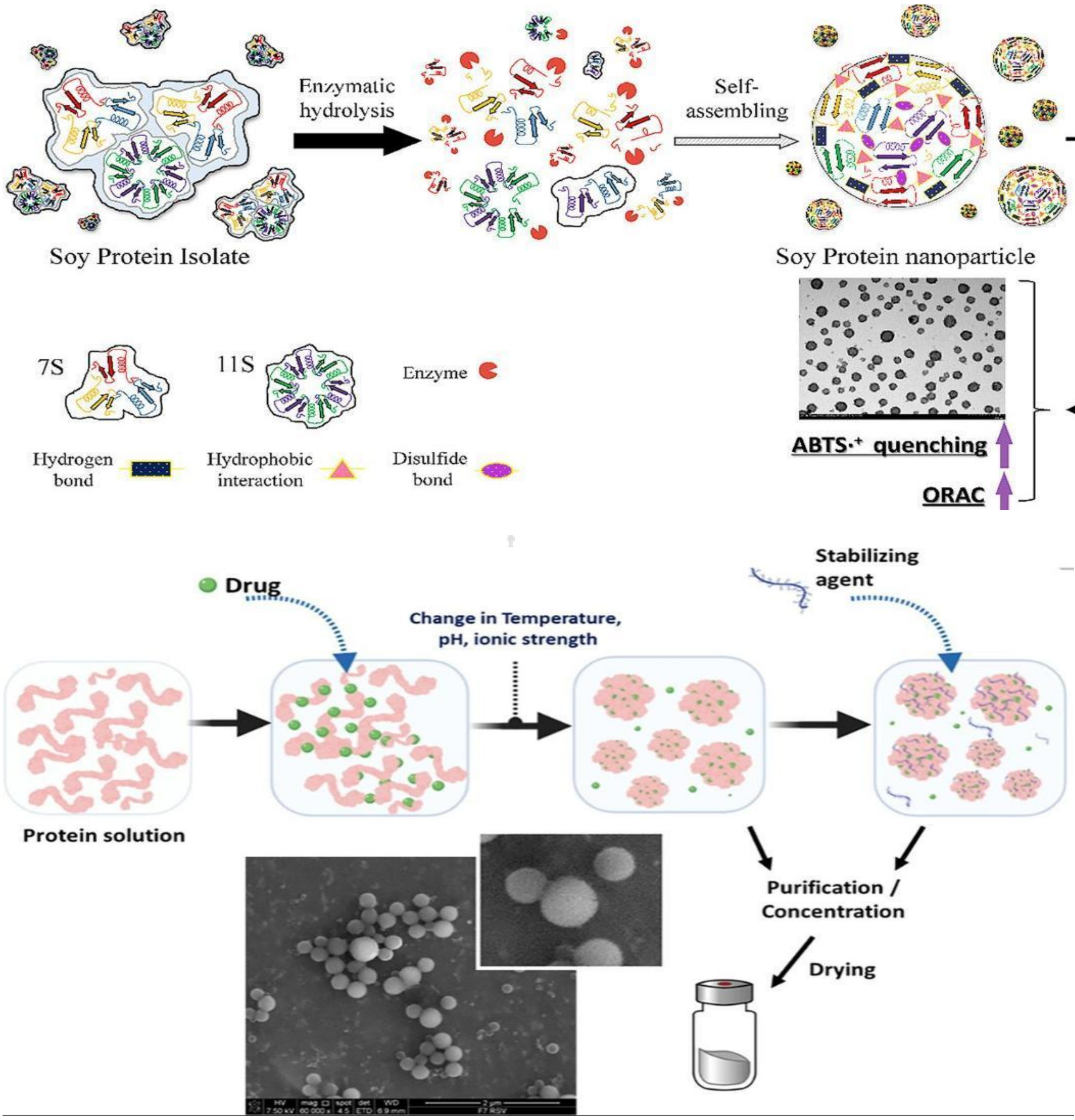

Figure No. 10: Synthesis of Nanoparticles from Soy protein

Nanoparticles were synthesized from soy protein, one of the most abundant and widely utilized plant proteins, for nutraceutical and drug encapsulation. The preparation process consisted of dispersion, desolvation, drug incorporation, cross-linking, and evaporation. The role of each procedure in the formation of nanoparticles was systematically investigated using particle size, size distribution, and zeta potential as well as morphology observation. These nanoparticles have promising properties like biodegradability, non-antigenicity, metabolizable, surface modifier, greater stability during *in vivo* during storage, and are relatively easy to prepare and monitor the size of the particles. These particles can attach covalently with drugs and ligands [3–5]. Protein nanoparticles can be used in various targeted therapies, namely, pulmonary delivery, cancer therapy, tumor therapy, and vaccines, in which protein nanoparticles can be incorporated into biodegradable polymers in the form of microspheres for controlled and sustained release. The major aim in designing nanoparticles as a drug delivery system is to control particle size, surface area, and surface properties so that the nanoparticles carrying required amounts of drug show desired pharmacological activity by releasing actives to achieve site-specific action.

CHRONIC DEGENERATIVE DISEASE:

A disease in which the function or structure of the affected tissues or organs changes for the worse over time. Osteoarthritis, osteoporosis, some cardiovascular diseases (e.g. atherosclerotic ones like coronary artery disease, aortic stenosis, etc hypotension, Obesity, and Alzheimer's disease are examples. Many degenerative diseases exist and some are related to aging. Normal bodily wear or lifestyle choices (such as exercise or eating habits) may worsen degenerative diseases, but this depends on the disease. Sometimes the main or partial cause behind such diseases is genetic.

Role of Antioxidants in CDD:

Normal cellular oxidative-metabolic reactions (endogenous) and other factors (exogenous) such as radiation, food constituents, tobacco smoke, and environmental pollutants from free radicals and other reactive Oxygen and Nitrogen Species (ROS and RNS). These reactive compounds are atoms or molecules that contain an unpaired electron in their outer orbital; therefore, they alter the structure and function of proteins, lipoproteins, carbohydrates, cell membranes, RNA, and DNA(Blomhoff et al., 2006). To avoid these damages, reactive compounds need to be quenched by antioxidants. However, when there is an imbalance between free radicals and antioxidants, OS is generated. Thus," a disturbance in the pro-oxidant/antioxidant systems in favor of the former may be denoted as oxidative stress".

The increase of ROS production deriving from endothelial dysfunction is commonly engaged in developing typical characteristics of Atherosclerosis, such as a Cardio Vascular Disease

(CVD). One of the critical steps in the development of atherosclerosis is when Low Density-Lipoprotein (LDL) that entered the arterial wall is oxidized by excessive ROS and scavenged by macrophages, forming lipid drops, which are characterized as foam cells, clogging the blood vessels On the other hand, ROS play an essential role in the initiation, development, and progression stages of some other CDD, such as cancer and diabetes. All aerobic organisms utilize a series of primary antioxidant defenses through enzymatic or non-enzymatic reactions in an attempt to protect themselves against oxidant damage (Davies, 2000). In this context, an antioxidant is defined as "a redox-active compound that limits oxidative stress by reacting non-enzymatically with a reactive oxidant", while an antioxidant enzyme is "a protein that limits oxidative stress by catalyzing a redox reaction with a reactive oxidant"(Blomhoff, 2005). Our cells utilize a series of antioxidant compounds that can be both endogenous and/or exogenous, such as enzymes [Super Oxide Dismutases (SOD), Glutathione Peroxidases (GPx), CATalases (CAT), Glutathione Reductase (GR)], vitamins (C and E), proteins (ferritin, ceruloplasmin, ubiquinone), uric acid, glutathione, carotenoids (beta carotene, beta-cryptoxanthin, lycopene, lutein, and zeaxanthin), and phenolic compounds (flavonoids and non-flavonoids) Exogenous antioxidants such as phenolic compounds are more usually studied for nanoencapsulation in different matrices to be used to prevent or decrease CDD. These compounds are considered the most potent exogenous antioxidants; hence, they exert several effects on human health and disease prevention.

Phenols act as antioxidants via different mechanisms, such as inhibition of oxidative enzymes, quenching of ROS, chelation of transition metals, the scavenging of free radicals, or due to interaction with biomembranes (Nirmala et al., 2014). Antioxidant molecules may react directly with the reactive radicals and destroy them, while they may become new free radicals that are less active, longer-lived, and less dangerous than the radicals that they have neutralized There is evidence that the consumption of polyphenols (having one or more aromatic rings bearing more than one hydroxyl group) enhances the activities of antioxidant enzymes such as CAT, SOD, GR, and GPx, preventing systemic or localized inflammation to prevent the development of CDD, consequently affecting the transcription factors of various genes encoding these enzymes (Kansanen et al., 2013). To protect against CVD, antioxidants decrease LDL oxidation, diminish blood pressure, inhibit platelet aggregation, improve endothelial functionality, reduce anti-inflammatory actions through the inhibition of cyclooxygenase and 5-LipoOxygenase (5-LO) pathways, and reduce the release of pro-inflammatory cytokines (Apostolidou et al., 2015; Magrone and Jirillo, 2010; Mohanty et al., 2015; Votruba et al., 2009). To protect against cancer, antioxidants such as flavonoids can restore to a normal state some altered cell-signaling pathways acting as carcino-preventive agents. For example, flavones and flavonols inhibit breast cancers (Doo and Maskarinec, 2014), flavones inhibit cancer-related to the upper aerodigestive tract (Woo and Kim, 2013), anthocyanins and flavonols inhibit colorectal cancer (Koosha et al.,2016), among others. In Diabetes Mellitus (DM) to avoid excessive glucose absorption or to suppress postprandial hyperglycemia, phenolic compounds can inhibit enzymes as α-glucosidase and α-amylase (Xia et al., 2017), as well as some glucose transporter, such as Sodium-dependent Glucose Transporter 1 (SGLT1) in the intestine (Johnston et al., 2005; Welsch et al., 1989). However, there is not sufficient information on polyphenols in glucose and insulin; hence, more studies must be conducted (Fernandes, Silva, et al., 2017; Fernandes, Pérez-Gregorio, et al., 2017) In general, the application of antioxidants to prevent or protect against CDD is not easy, due to that antioxidants present some disadvantages, including that they are labile to environmental factors (photosensitive, thermolabile, etc.) and body factors (such as pH and enzymes). Therefore, recently, research has focused on developing new technologies to maintain their bioactivity, as is the case of the nanoencapsulation in protein matrices such as soy protein.

CONCLUSION:

The changing lifestyle like depending on synthetic food materials and synthetic extracts attributes many lifestyle basis diseases like hypertension, hypotension, and obesity which affect a majority of groups and may affect the coming generation. To overcome this we need to find alternatives that may not only combat this but also provide an inbuilt sustained and greener therapy. Here we hypothesized a new therapy that not only boosts immunity but also is a greener therapy and environmentally friendly.

This protein nano encapsulated peel extracted antioxidants can play a major role in the prevention of Chronic Disease and may lead to many immunities boosting green therapies which are also potential for reducing waste from the majority food industry and helps in developing new pharmaceutical weapons to combat new lifestyle diseases.

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