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Plants as a Source of Potential Antioxidants and Their Effective Nanoformulations

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Abstract: **Antioxidants act as weapons to neutralize the damaging effects of free radicals that are produced in the living systems during cellular activities and are responsible for a number of diseases. Plants are the major source of antioxidants in the form of enzymatic as well as non-enzymatic which is proved by several pieces of research on various natural products that have the potent capability to mimic the deleterious effects of free radicals. Among several antioxidants, the non-enzymatic antioxidants such as polyphenols, vitamins, carotenoids, glutathione, etc. have been isolated and screened for anti-oxidant properties from several food sources. Unfortunately, the effects of these natural antioxidants are limited due to their reduced absorption, hindrance in crossing the cell membranes and its degradation in the pathway during delivery, etc. To overcome these troubles and for effective, targeted delivery of antioxidants, its gradual and sustained release, nanoformulations of natural antioxidants are the key players in the enhancement of effectiveness and their release at the specific targeted site in the treatment of several diseases. This review focuses on the current advancements in the field of natural antioxidants and their nanoformulations with potent and enhanced action in minimizing the damaging effects of free radicals.**

Index Terms: **Antioxidant, free radicals, reactive oxygen species, nanoformulation, nanoparticles.**

I. INTRODUCTION

Free radicals are molecular species containing unpaired an electron capable of independent existence (Lobo et al., 2010). The presence of the unpaired electron in the atomic orbital of free radicals makes them highly unstable and reactive, which facilitates them to donate or accept electrons and act as either oxidant or reductant (Young et al., 2001). The presence of the unpaired electron in the atomic orbital of free radicals makes them highly unstable and reactive, which facilitates them to donate or accept electrons and act as either oxidant or reductant (Young et al., 2001). The major free radicals associated with health disorders are reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive sulphur species (RSS) e.g. oxygen singlets, superoxides, hypochlorite, hydrogen peroxide, hydroxyl radical, nitric oxide, and peroxynitrite radicals (Lobo et al., 2010). Free radicals play an essential role in various biological activities like a non-specific host defence mediators, cell signalling, killing of tumour cells. However, their excess damages biologically relevant molecules such as carbohydrates, proteins, lipids and nucleic acids (Young et al., 2001; Pham-Huy et al., 2008) resulting in cellular damage and homeostatic disruption. Free radicals are generated during the normal essential metabolic processes in the human system as a by-product of both enzymatic and non-enzymatic reactions, however, exposure to physical agents such as X-rays, ozone, nicotine, air pollutants and certain industrial chemicals (Bagchi and Puri, 1998; Devasagayam et al., 2004). The endogenous production of free radicals takes place through enzymatic and non-enzymatic reactions of respiratory chain, cytochrome P-450 system, prostaglandin synthesis, mitochondria, peroxisomes, xanthine oxidase, arachidonate pathway etc. (Lobo et al., 2010; Phaniendra et al., 2015; Uttara et al., 2009). The free radicals produced generally leads to damage of cellular membranes, subcellular organelles, and biomolecules leading to impairment of normal cellular functioning (Phaniendra et al., 2015). At the systematic level free radicals induced oxidative stress results in the hastening and development of several health disorders including Alzheimer, Parkinson, acute renal failure, cancer, radiation injury, diabetes, cardiovascular diseases and even ageing (Koltover, 2010; Gupta et al., 2015).

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Antioxidants are substances, present at low concentration, capable of delaying or inhibiting the negative impact of free radicals. As a consequence of action of antioxidants against free radicals, the cellular components are prevented from damage (Lobo et al., 2010). Antioxidants function as scavengers of the free radical, thereby minimizing the deleterious effects of free radicals on organisms. Antioxidants have been the major area of research because of their production as a pathophysiological response at the time of oxidant and anti-oxidant counteraction imbalance. Nearly all the organisms possess endogenous enzymatic and non-enzymatic antioxidant defence and repair system, however, in extreme stress conditions these systems are inadequately efficient in combating the oxidative damage (Simic, 1988), hence, exogenous supplementation of antioxidants are recommended to meet the adequate requirement of the human body(Taghvaei and Jafari, 2015). The antioxidant activity can be observed in two ways: (a) prevention of free radical (ROS/RNS/RSS) formation and (b) scavenging of free radicals; however, in some cases, especially the enzymatic antioxidants, the free radicals decomposition to fewer harmful or neutral products can also be observed (Pellegrini et al., 2003; Sharpe et al., 2011).

Since ancient time medicinal plants are being used for the maintenance of health. Sumerian clay slab with 12 recipes for the preparation of drugs is the oldest (5000 years old) written evidence which states about the preparation of drugs from medicinal plants (Khan et al., 2019; Petrovska, 2012). About 35000-70000 species of plants have been assayed for medicinal use so far (Veeresham, 2012). Studies have shown that plants, with their different parts, are rich in phytochemicals like phenolic acids and flavonoids that have therapeutic potentials such as antimicrobial, anti-carcinogenic and antioxidant potential (Skala et al., 2016; Wang et al., 2017). These plants are available in the form of vegetables, fruits, cereals, beverages, mushrooms, flowers, spices, herbs and traditional medicinal plants. The main components of plants that act as antioxidants are carotenoids, phenolics (flavonoids, lignans, phenolic acids), and vitamins (Yashin et al., 2017). A number of chemical compounds exogenously or endogenously produced (based on origin source) by plants have been evaluated for their antioxidant properties, of which the majority are obtained from human diet (Khan and Giridhar, 2011). The naturally occurring antioxidants such as ascorbic acid, carotenoids, polyphenols, metabolic sensitizers (methyl selenocysteine), gallic acid, and other bioactive compounds were found to potentially modulate the oxidative stress in humans by their free radical scavenging activity, reduction of lipid peroxidation, and inhibition of nitrosation reactions (Medhe et al., 2014; Fleuriet and Macheix, 2003; Lim, 2007; Anagnostopoulou et al., 2006; Li et al., 2005; Tułodziecka and Szydłowska-Czernia, 2016). Due to the inadequacy of natural antioxidant activity during severe stress, synthetic antioxidants like butylatedhydroxytoluene (BHT) tert-butyl hydroquinone (TBHQ), gallates, and butylatedhydroxy anisole (BHA) are used exogenously to suppress the effects of free radicals (Pratt and Hudson, 1990; Yehye et al., 2012). These antioxidants have several negative effects with their therapeutic potentials, for example, it is tested that BHA and BHT had carcinogenic effects on kidneys and liver of rats. Some studies have remarked that synthetic antioxidants do not exert any negative effect on humans rather produce some other beneficial effects. The use of synthetic antioxidants has become a controversial discussion because of its differential therapeutic effects and different regulation of usage levels in different countries has forced researchers to find some other alternatives of synthetic antioxidants with less or no harmful effects (Taghvaei and Jafari, 2015).

The cellular transport, uptake and efficiency of antioxidants to target tissues and organs have been a major setback in treatment of oxidative stress induced health disorders. Nanotechnology provides potential solutions to these problems, specifically in targeting dietary antioxidants to diseased cells and tissues. The delivery systems based on nanoformulations prevents the degradation of antioxidants, enhances their transport across membranes and bio-availability (Fernandes et al., 2014). The present review is an attempt to summarize the antioxidant potential of medicinal plants, their role in disease treatment, antioxidant activity assay methods and role of nanotechnology in antioxidant delivery and bioavailability.

II. FREE RADICALS AND ANTIOXIDANTS

Free radicals are the atoms or molecules that are produced by normal cellular metabolism with one or more than one unpaired electrons in its valency shell or outer orbit. There are two broad categories of the damaging free radicals: the ROS and the RNS. Oxygen molecules containing unpaired electrons and radicals acting as oxidizing agents (which may be converted to radicals) are included in ROS. RNS also includes both radicals (such as nitrogen dioxide and nitric oxide) and non-radicals (like N_2O_3, $ONOO^-$ and nitrous acid). Free radicals are produced internally in mitochondria during the respiratory chain, during phagocytosis in phagocytes, in the peroxisome, through arachidonate pathways, during exercise and through inflammation. Radiations, tobacco smoke, certain drugs, environmental pollutants and industrial solvents are the external sources that can induce free radical production (Phaniendra et al., 2015; Sharma et al., 2018) **(Fig. 1).**

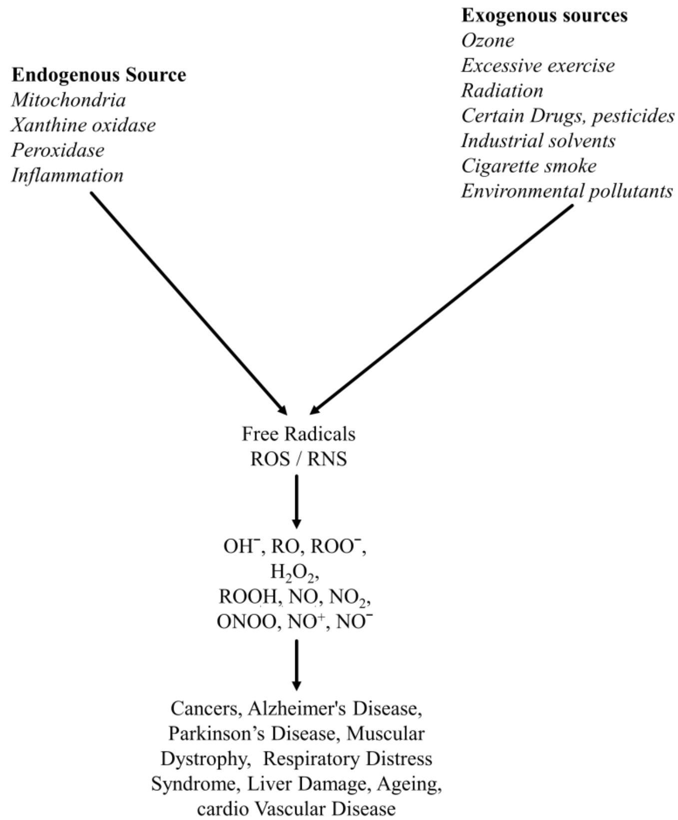

Figure 1: Sources of free radicals and their ill effects on human.

Free radicals at moderate concentration are very important for normal cellular activities and participate in the defense system of the body. Immune system cells like neutrophils, macrophages, monocytes destroy invading pathogens by releasing free radicals. The NADPH oxidase system bound to the membrane is defected in patients affected with granulomatous disease, due to which the patients are not able to produce superoxide anion radical ($O_2^{\bullet-}$) and thereby becoming susceptible to multiple and persistent infections. Nitric oxide synthase synthesizes nitric oxide ($O_2^{\bullet-}$) from an L-arginine's terminal guanido nitrogen atom. Inducible synthase (an isoform of nitric oxide synthase) is expressed in immune cells and continuously produce a large amount of nitric oxide and is responsible for the toxicity of the immune cells (neutrophils, macrophages, mast cells, endothelial and vascular smooth muscle cells). Although the nitric oxides are not very toxic, but the reaction of nitric oxides and superoxide that produce peroxynitrite, increases its toxicity at a greater extent (Pham-Huy et al., 2008; Knight, 2000).

ROS are also involved also in programmed cell death. Apoptosis is a special type of programmed cell death in which cells with unusual activity or cells during embryonic development are directed for destruction in multicellular organisms. TNF-α in leukocytes and fibroblasts induces the release of super oxide by NADPH oxidase in mitochondria and depending on the cell condition producing ROS and super oxide, induction of cell proliferation or cell death takes place (Droge, 2002). Free radicals also play a significant role in the intracellular signaling pathways, for example, nitric oxide (NO), an intracellular messenger in non-phagocytic cells such as endothelial cells, fibroblasts, cardiac monocytes, and thyroid tissues regulates intracellular signaling (Pham-Huy et al., 2008).

When produced in excess free radicals can damage cellular components as well as biomolecules. Hydroperoxyl ($HO^{\bullet}_2$) and hydroxyl radicals ($HO^{\bullet}$) are the two main ROS that are extremely involved in the peroxidation of the lipids (Ayala et al., 2014). ROS/RNS can also damage DNA, proteins and lipids which lead to serious consequences like carcinogenesis, ageing, diabetes, neurological disease and development of cardiovascular diseases (Valko et al., 2007). Free radicals, if not balanced with antioxidants induce oxidative stress, which is implicated in the development of certain disease such as Parkinson's and Alzheimer's disease, cancer, atherosclerosis, diabetes mellitus, inflammatory disease as well as aging and psychological diseases (Pizzino et al., 2017).

Antioxidants prevent oxidative damage by neutralizing free radicals. These antioxidants are produced either in the living system or they are provided through the diet (Salehi et al., 2018). In plants and animals catalase, peroxidase, superoxide dismutase, vitamin C and E etc. are some antioxidants that counter the deleterious effect of the free radicals (Kurutas, 2016). The neutralizing mechanisms of antioxidants include prevention, repair or interception. Those enzymes which act by prevention mechanism include SOD and catalase. SOD and catalase try to inhibit the formation of ROS. SOD converts superoxide to H_2O_2 and catalase convert H_2O_2 to water. Interceptors are also known as free radical scavengers. Repairing enzymes are involved at the level of repairing (Devasagayam, 2004).

Non-enzymatic antioxidants include vitamins (A, C, E, and K), uric acids, polyphenols, carotenoids and glutathione (Gomeset al. 2012; Ramana et al., 2018; Palace et al., 1999; Vervoort et al., 1997). Ascorbic acid reduce membrane bound oxidized tocopherol and generate active tocopherol that are able to scavenge free radicals (Pisoschi and Pop, 2015). Natural antioxidants have strong potential to eliminate oxidative stress and maintain cellular homeostasis by free radicals scavenging, breaking the chain reactions mediated by free radicals, prevention of lipid peroxidation and inhibiting free radical formation (Gomes et al., 2012; Ramana et al., 2018).

III. ANTIOXIDANT POTENTIAL OF MEDICINAL PLANTS

Recent researches have indicated that the use of traditional medicinal plants accounts for the lower incidence of the disease that occurs in human beings. Several plants have been investigated with potent antioxidant activity (Ozkan et al., 2016). The alcoholic and aqueous extracts of *Ficus beecheyana* roots have shown to contain the major phenolic compounds like gallic acid, protocatechuic acid (only aqueous root extract of *F.*

beecheyana) epicatechin (only ethanolic extract of roots of *F. beecheyana*) p-hydroxybenzoic acid, chlorogenic acid, caffeic acid, rutin, and p-coumaric acid. These phenolic compounds are responsible for the antioxidant activity of the *F. beecheyana* (Yen et al., 2018). Traditionally used for oral hygiene, methanolic extract of *Salvadora* fruit pulp have shown potential antioxidant activity (Kumari et al., 2017).

IV. CLASSIFICATION OF ANTIOXIDANT COMPOUNDS

The whole system of the antioxidant is mainly divided into two categories; synthetic antioxidant system and the natural antioxidant system. The natural antioxidant system of the body is further subdivided into two groups consists of enzymatic and the non-enzymatic system of antioxidants (Lourenço et al., 2019) **(Fig.2)**.

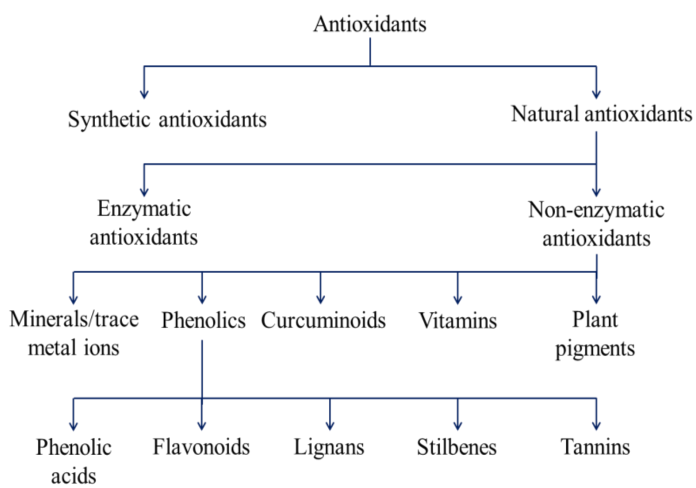

Figure 2: Classification of antioxidants. They are broadly classified into synthetic and natural antioxidants. Natural antioxidants are further categorised into enzymatic and non-enzymatic ones. Non-enzymatic antioxidants are classified into minerals, phenolics, curcuminoids, vitamins, and plant pigments. Phenolic antioxidants include phenolic acids, flavonoids, lignans, stilbenes and tannins.

A. Synthetic Antioxidants

To compare the antioxidant activity of the natural antioxidants and to incorporate antioxidants in foods, development of synthetic antioxidants was needed. Synthetic antioxidants are divided into various classes which include nitroxides, Mn-porphyrin superoxide dismutase mimics (like M40403 and M40419, AEOL-10113 and AEOL-10150), spin traps, salens (e.g. EUK134), GPX mimetics (ebselen, BXT- 51072), coenzyme Q analogues (e.g. ibedenone) or aminosterols (lazaroids) (Augustyniak et al., 2010). Synthetic antioxidants present in the foods increase the shelf life of the foods. Studies show that the synthetic antioxidants incorporated in the foods are safe but some time they are harmful. Butylatedhydroxytoluene (BHT) and butylatedhydroxyanisole (BHA) are the most commonly employed chemical antioxidants. European food safety authority (EFSA) has recommended the daily intake of 0.25mg/kg bw/day for BHT and 1.0 mg/kg bw/day for BHA. TBHQ contributes to the stability of food components and preserves the nutritive value, freshness, color and flavor of food products to be used by animals (Carocho and Ferreira, 2013).

N-Acetylcysteine (NAC) is a synthetic antioxidant in which acetyl group is attached to the amino group and also contain an amino acid L-cysyteine. Sulfhydryl group of the NAC is responsible for the scavenging activity of free radical e.g. hydrogen peroxide, hydroxyl and superoxide radical. L-cysteine is also involved in antioxidant activity indirectly by acting as precursor of reduced GSH. Therefore, NAC restores the redox homeostasis (Radomska-Lesniewska et al., 2016).

B. Natural Antioxidants - Bioactive compounds from medicinal plants as antioxidants

Natural antioxidant system of the body is consisting of enzymatic and non-enzymatic antioxidants.

1) Enzymatic Antioxidant

The enzymatic antioxidants include SOD, catalase, and glutathione (GSH) peroxidase (primary enzyme) and glutathione reductase, glucose-6-phosphatase dehydrogenase (secondary enzyme). SODs are present at different site with different configuration in almost all cells respiring in the presence of oxygen and extracellular fluids. SODs convert superoxide free radical into oxygen and hydrogen peroxides. SODs use different metals (Cu, Zn or Mn) for the antioxidant activities in different part of the cells (H_2O_2). Catalase found in peroxisomes breaks down the H_2O_2 into H_2O and O_2. Glutathione peroxidase (GPx) helps the decomposition of H_2O_2 and organic peroxide into H_2O with the simultaneous oxidation of glutathione (GSH) into oxidised GSH as GSSG. Glutathione reductase (GR) reduces oxidised forms (GSSG) of glutathione into GSH for its further utilisation by GPx. Reduction reaction catalysed by GR is assisted by simultaneous oxidation of $NADP^+$ into NADPH. Another enzyme glucose-6-phosphatase dehydrogenase (G6PDH) further regenerates $NADP^+$ in the system from accumulated NADPH. Reduced coenzyme Q ($CoQH_2$) coverts both the superoxide radical ($O_2^{-\bullet}$) and the perferryl radical (Fe^{3+}) to H_2O_2 which is subsequently converted to H_2O by catalase (**Fig. 3A-D**). Ascorbic acid in combination with tocopherol removes lipid peroxide radicals (Pisoschiand Pop, 2015).

2) Non-enzymatic antioxidants

a) Minerals as antioxidants

Antioxidant system involvesa number of enzymatic antioxidants such as GPx, CAT, SOD and GST. GPx, CAT and SOD use unique metals in their active sites as cofactors. Among these enzymes, GPx uses selenium (Se), CAT useiron (Fe) along with haeme protein, and SOD uses copper (Cu) and Zinc (Zn) as cofactors. These trace elements help enzymatic antioxidants to maintain redox homeostasis and to prevent many disorders due to oxidative stress or aging. Along with being cofactors of enzymes, zinc also protect depletion of vitamin E, stabilize membrane structure, maintain the concentration of metallothioneins in the tissues and scavenge free radicals. Copper plays crucial roles in growth, development, immune functions and also participate in wound healing (Sabuncuoglu et al., 2015; Sfar et al., 2009).

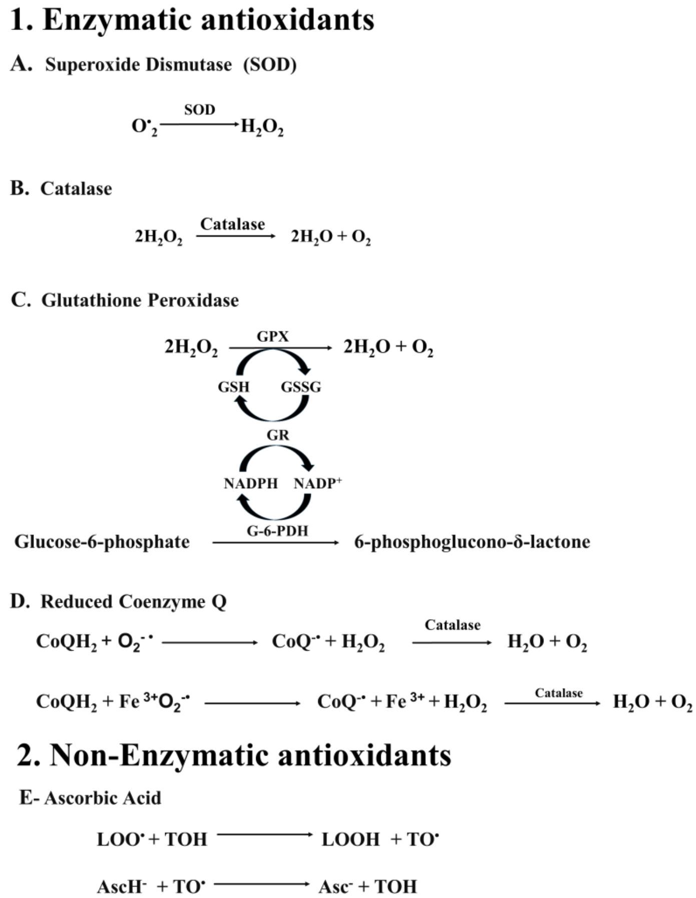

Figure 3: Mechanism of action of different antioxidants. 1-Enzymatic – (A) Super oxide dismutase (SOD) converts superoxide radical anions to H_2O_2 (hydrogen peroxide); (B) Catalase enzyme converts H_2O_2 to H_2O; (C) Glutathione peroxidase catalyses reduction of H_2O_2 to H_2O; (D) Reduced coenzyme Q catalyses conversion of both the superoxide radical ($O_2^{-\bullet}$) and the perferryl radical (Fe^{3+}-$O_2^{-\bullet}$) to H_2O_2 which then converted to H_2O by catalase enzyme. 2-Non-Enzymatic – (E) Ascorbic acid converts tocopheroxyl ($TO^{\bullet-}$) radical to active tocopherol (TOH) which acts as antioxidants. Tocopheroxyl ($TO^{\bullet}$) radical is produced by reaction of tocopherol (TOH) with peroxyl radical $LOO^{\bullet}$.

Selenium is one of the trace elements that plays important role in human health. Deficiency of Selenium may result in several pathological conditions such as muscular, cardiac and immune disturbances. Selenium with glutathione peroxidase (GPx) acts as second line of defense where enzyme destroys hydrogen peroxides and peroxides. Different and/or multiple isoforms of GPx are present in different tissues due to their formation by different genes, and therefore, they act in cooperation with each other to protect different tissues by their antioxidant activity (Kiełczykowska et al., 2018; Lee et al., 2007).

Selenium exerts its antioxidant activity via selenoproteins. The number of selenoproteins in mammal ranges up to hundred. Glutathione peroxidase enzymes are one of those enzymes which is synthesized by amino acid selenocysteine. Since antioxidant activity is associated with antioxidant activity, therefore low or suboptimum level of selenium intake could be associated with the development of various diseases (Braciela et al., 2008). According to one hypothesis high selenium as antioxidant reduces atherogenesis in heart disease because Se reduces oxidation of the low density lipoprotein (LDL) (Tinggi, 2008).

Zinc present as cofactor of SOD enzyme and by catalyzing the dismutation of superoxide radicals into less toxic oxygen and hydrogen peroxide. It has been proven that zinc also upregulate the genes that encode the SOD as well as GSH, GST, HO-1 and nuclear factor erythroid 2-related factor 2 (Nrf2). Zinc exposure induces some other ultimate antioxidants like metallothioneins (MTs). Deficiency of zinc alters the activity of the MTs and makes the organisms susceptible to oxidative stress. In another mechanism, zinc stabilizes protein sulfhydrils which is involved in oxidation process (Jarosz et al., 2017).

b) Phenolics

i) Phenolic Acids

Phenolic acids are one group of secondary metabolites that occur naturally majorly in cereal grains. Phenolic acids account for the color, antioxidant property, and sensory quality of the plants and organoleptic properties of foods.

Phenolic acids (ferulic and caffeic acids) are produced in plants and are used as a protective agent against UV light, viruses, bacteria and insects. Plants use either L-phenylalanine or L-tyrosine amino acid for the synthesis of phenolic acids from the shikimate pathway. The presences of phenolic hydroxyl groups connected to ring structure are responsible for the antioxidant properties of phenolic acids. Phenolic acids exhibit antioxidant properties by donating hydrogen, quenching singlet oxygen, and scavenging superoxide radicals. They also act as metal ion chelators over proxyl and hydroxyl radicals, peroxynitrites and superoxide anions (Robbins, 2003; Heleno et al., 2015).

ii) Flavonoids

Flavonoids are biological phenolic compounds that are produced universally by all plants. The antioxidant activity exhibited by flavonoids is used for medication of various diseases such as atherosclerosis, cancer, alzheimer's disease. The part of the plant body in which flavonoids are produced includes flowers, fruits, leaves, etc. Flavones, isoflavones and flavonols are some of the subgroups of the flavonoids that are produced by the unique sources. In plants, flavonoids acts against abiotic and biotic stresses and also serve to attract pollinators, so that dispersal of seeds could be accomplished very easily (Panche et al., 2016).

The antioxidant activities for example ROS and RNS scavenging, of flavonoids are dependent upon the functional groups that are optimally arranged to accomplish the task. The combination of free radical scavenging activity and inhibition of ROS generating enzymes such as NADH oxidase, mitochondrial succinoxidase, microsomal monooxygenase and glutathione S-transferase are responsible for the antioxidant activity of flavonoids (Prochazkova et al., 2011).

iii) Lignans

Lignans are natural polyphenolic compounds. Lignans behave like estrogen as well as exhibit other activities effective on the living system such as anti-inflammatory activities, anti-carcinogenic activities and anti-oxidant activities. Because of their health benefits, the consumption of the lignin rich diet is being promoted. Flaxseed, fruits, vegetables, and beverages like tea, coffee and wine are a good source of lignans

(Idehen et al., 2017; Brito and Zang, 2019).

Aryltetralin, arylnaphthalene, divenzylbutane, dibenzylbutyrolactol, dibenzocyclooctadiene, divenzylbutyrolactone, furofuran and furan are the eight groups of lignans classified on the basis of the pattern of the structure which includes carbon skeleton, the way of incorporation of oxygen in the skeletons, and the pattern of cyclization (Teponno et al., 2016). According to the study, different types of ligands have different radical scavenging activity depending on the structural feature (phenolic hydroxyl moiety) of that particular lignan molecule (Eklund et al., 2005).

iv) Stilbenes

Various families of the plant kingdom produce stilbenes as phenolic compounds. The compounds participate in the defence mechanism when plants are encountered with pathogens. Many compounds have been identified as stilbene derivatives with different structures. Resveratrol is a stilbene that has been comprehensively studied because of their significant biological activities (antidiabetic, chemopreventive, and neuroprotective). Grapes, peanuts, some berries and red wine are some limited sources of stilbene (Reinisalo et al., 2015). Stilbenes are synthesized via the phenyl-propanoid pathway.

Stilbenes are organic compounds that contain two phenolic rings. The backbone of resveratrol is synthesized with the help of stilbene synthase by condensing one molecule of coumaroyl-CoA with three molecules of malonyl-CoA or one molecule of cinnamoyl-CoA in place of coumaroyl-CoA (Kiselev et al., 2016). Melatonin derived from serotonin can act as free radical scavengers in the eye and serotonin is synthesized with the help of BH4. BH4 is an enzyme cofactor of which bioavailability is restored by stilbene. Therefore, it could be concluded that stilbene can be used as a remedy for obesity, type 2 diabetes, neurodegenerative disease and Alzheimer's disease (Reinisalo et al., 2015).

v) Tannins

Tannins are named because of its use in tanning of leather, it is a plant compound. Tannins are classified into hydrolysable and non-hydrolysable tannins having molecular weight between 500 and 3000 Da. Non hydrolysable tannins are also known as condensed tannins, flavolans or proanthocyanidins. Hydrolysable tannins consist of esters of polyols such as glucose and phenolic acids. If the phenolic acid is gallic acid then it is called gallotannins or it is called ellagitannins if it is derived from galloyl residues. Condensed tannins are composed of flavan-3-ols and/ or flavan-3,4-diols. When condensed tannins are heated, they yield anthocyanidins because of that, condensed tannins are called proanthocyanidins (Madsen and Brinch-Pedersen, 2016). Hydrolysable tannins include three subclasses the simple gallic acid derivatives, gallotannins (GTs) and ellagitannins (ETs).

Free radical scavenging property of tannins is due to electron donating capability to free radicals converting these radicals into more stable and less harmful forms. The high degree of hydroxylation of aromatic rings and high molecular weight of the tannins are responsible for their antioxidant activity. When tested by ABTS scavenging assay, hypochlorous scavenging assay or by FRAP assay, dimericprocyanidins were shown to have most reducing power than other polyphenols. In vitro studies have confirmed that tannins act as metal ion chelaters and exhibit antioxidant activity. Tannins also interfere with the enzymes that are involved in production of oxidative stress. Tannins inhibit nitric acid synthases so that the formation of NO decreased. Ellagitannins isolated from *Cunoniemacrophylla* inhibited xanthine oxidase, phlorotannins isolated from *Eiseniabicyclis* inhibited lipooxygenase (LOX), and epichatechin significantly inhibited recombinant human 5-LOX activity. Xanthine oxidase, LOX and 5-LOX are considered as pro-oxidant enzymes. Lipid peroxidation oxidizes low-density lipoproteins (LDL) that lead to the atherosclerosis formation. Tannins have been shown to protect oxidation of LDL. The possible mechanism behind the inhibition of oxidation of LDL by tannins involves the quenching of the radical or the oxidative products that are already formed. This shows that tannins also act as antioxidant by inhibiting lipid peroxidation (Koleckar et al., 2008; Gulcin, 2020).

c) Curcuminoids

Curcuminoids are the member of a group of phenolic compounds known as diarylheptanoids. Curcumin, dimethoxycurcumin and bis-demethoxycurcumin are few examples of curcuminoids isolated from *Curcuma longa*. Curcuminoids have reported to exhibit antioxidant, anti-nflammatory and anticancer activities. Curcuminoids have a long history of using as traditional medicine as evidenced by scientific studies.Antioxidant activity of the curcumin was evaluated by hydrogen atom transfer method which shows curcumin exhibit larger antioxidant activity than α–tocopherol. Curcuminoids are therefore able to inhibit reactive oxygen species (superoxide anions, hydroxyl radicals, peroxides and nitrite radicals), and therefore prevent DNA damage that may be initiated by singlet oxygen and lipid peroxides. (Sandur et al., 2007; Amalraj et al., 2016).

About two centuries ago, Vogel and Pelletier defined curcumin as yellow colour giving substance. The chemical formula of curcumin is $C_{21}H_{20}O_6$ and is chemically denoted by 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione or dipheruloylmethane. Curcumin is insoluble in water at neutral and acidic pH, sensitive to light. The bioavailability of the curcumin in the body is low which can be modulated by using piperine with curcumin. Curcumin is a polyphenolic compound with small molecular weight and is lipophilic in nature. The fat soluble nature of the curcumin makes it insoluble in water but it is soluble in ethanol and other organic solvents (Llano et al., 2019; Kocaadamand Şanlier, 2017; Rathore et al., 2020).

Among the antioxidants, curcumin possesses different kind of functional groups for example carbon-carbon double bonds, β-diketo group, and phenyl rings. These phenyl rings contain variety of hydroxyl and methoxy substituents. Free radical scavenging activity of curcumin has been found to be contributed by hydrogen-atom donating central methylene group and the phenolic group. The hydrogen atom from the phenolic group can be abstracted easily as diketo form is less stable than the enol form of the curcumin and the bond dissociation enthalpy of the central O:H bond is higher than the bond dissociation enthalpy of the phenolic O:H bond. The activity of the reaction medium and the attacking radical decides the relative antioxidant activity of central methylene group and phenolic group (Menon and Sudheer, 2007).

Curcumin also modulate the activity of catalase, GSH and SOD enzymes, which are responsible for elimination of activity of free radicals. Curcumin also inhibits the enzymes (xanthine hydroxygenase/oxidase and lipoxygenase/cyclooxygenase) that involved in the production of reactive oxygen species and because of its lipophilic nature it can efficiently scavenge peroxyl radicals (Rathore et al., 2020).

d) Vitamins as antioxidants

i) Vitamin A

Vitamin A is one of the fat-soluble vitamin also called retinoic acid. It was first identified as fat soluble fraction A and later it was found that beta carotene is converted into the vitamin A in the intestine. Monaghan and Schmitt first demonstrated the antioxidant potential of the vitamin A and reported that vitamin A and carotenoids can protect degradation of lipids. At present, more than 600 carotenoids have been discovered (Palace et al., 1999).Vitamins A prevent lipid peroxidation by combining with peroxylradicals. It is also found that retinoic acid derived from Vitamin A upregulates the genes encoding for intrinsic antioxidant enzymes. Retinol also augments the activity of antioxidant enzymes such as glutathione transferase and superoxide dismutase. The evidences suggest that Vitamin A could play a role of potential antioxidant (Dao et al., 2017; Milisav et al., 2018).

ii) Vitamin C

Vitamin C or ascorbic acid is a micronutrient (water soluble) naturally found in foods. It has several biological functions that include enzyme cofactors, hydroxylation of glycine, lysine, and proline, and the formation of bile from cholesterol and activation of the vitamin B. Along with all these activities, vitamin C also acts as a natural antioxidant with free radicals scavenging property and thus constitutes the defence system of the body (Chambial et al., 2013; Montecinos et al., 2007).

Oxidative degradation of the membrane lipids is one from many of the deleterious effects produced by free radicals. Because ROS producing enzymes fixed deeply in the lipid bilayer of the membrane, so the chance of attack by ROS radicals is increased. Once produced lipid radicals initiate the propagation reaction of radicals if it is not neutralized by α-tocopherol, present in the membrane and causes the production of different LPO products (malondialdehyde, 2-alkenals and epoxides). Vitamin C can protect the membrane lipid from its peroxidation by scavenging ROS and reducing the lipid hydroxyl radicals (**Fig. 3E**). *In vivo* experiments have provided sufficient result that indicates the vitamin C could be used to suppress the effect of LPO (Traber and Stevens, 2011).

iii) Vitamin E

Vitamin E is a micronutrient (fat soluble) found in fat rich diets. Coconut oils, maize (corn) oils, palm oils, olive oils, etc are the best source of vitamin. The derivatives tocol and tocotrienol are divided into tocotrienols and tocopherols which are collectively termed as tocochromanols (the vitamin E group). Vitamin E that occurs naturally has eight forms – α, β, γ and δ, and four from each tocochromonols. Vitamin E with its all forms is synthesized in plants from homogentisic acid. Among all the forms of vitamin E, α and γ-tocopherols are two major forms with their occurrence in red blood cells and serum. Vitamin E is primarily located in the membranes of cells and organelles, and is able to protect the membrane at very low concentration. Vitamin E protects cellular components by inhibiting new free radical production or by neutralizing the existing free radicals or by acting as a potent chain-breaker. Since unbalanced free radicals production is associated with the development of numerous medical conditions. Thus, the vitamin E might be used to prevent or delay the medical conditions associated with free radicals. In comparison to tocopherol alone, a mixture of tocopherol can have a powerful inhibitory effect (Rizvi et al., 2014; Niki, 2015).

iv) Vitamin K

Vitamin K is a lipid soluble micronutrient. There are three types of vitamin K vitamin K1 (phylloquinone), K2 (menaquinone) and K3 (menadione). Phylloquinone is produced by dark green leafy plants and seeds. In contrast, menaquinone is obtained from conversion of phylloquinone or from the gut of bacteria, meat eggs and fermented cheese. The most abundant form of the vitamin K is menaquinone found in animal tissues. It has been reported that vitamin K blocks the activation of lipoxygenase and thereby inhibits the arachidonic acid-induced oxidative injury. Glutathione depletion induces generation of ROS and oxidative injury which lead to the development of oligodendrocytes and immature neurons which could be prevented by K1 and menaquinone (Mozos et al., 2017).

e) Coenzyme Q10as antioxidant

Coenzyme Q10 (CoQ10) or ubiquinone (UQ10) is another lipid soluble isoprenoid antioxidant which is primarily present in inner mitochondrial membrane (Saini, 2011). In mitochondria, it takes part as mobile electron carrier in electron transport system mobilising electrons from complex I and II to complex III. Its reduced form ($UQ10H_2$) has potent antioxidant propertyby directly neutralizing free radicals and by preventing their generation. In addition, CoQ10 is reported to regenerate other antioxidants such as vitamin E and C (Navas et al., 2007). It also prevents lipid peroxidation and oxidation of low density lipoproteins (Ernster and Dallner, 1995). Ubiquinone is one of the endogenous cellular antioxidants that are produced by wide variety of organisms ranging from microbes to human. Although animal based products e.g. beef, herring, rainbow trout, chicken are the rich sources of this factor, some important herbal dietary sources are soybean oil, canola oil, peanuts, sesame seeds, pistachio, broccoli, cauliflower and strawberries (Mattila and Kumpulainen, 2001).

f) Plant pigments as antioxidants

Plant pigments are important group of antioxidants having ROS and free radical scavenging properties. Major plant pigments are chlorophylls, carotenoids and anthocyanin wherein former has principal photosynthetic role and later two assist. Carotenoids and anthocyanins are secondary metabolites and their nutritional and health benefits have been reviewed previously (Chen, 2015).

Carotenoids responsible for yellow, orange or red pigmentation exhibit greater extent of structural and functional diversity with more widespread occurrence (Scheer, 2013) which make it an excellent food derived antioxidant candidate. Chemically, carotenoids are isoprenoid compounds having long hydrocarbon backbone with a series of conjugated carbon double (C=C) bonds. These are water insoluble and lipid soluble antioxidants that are easily extracted by using organic solvents e.g. methanol, hexane, acetone, ethylacetate etc. Antioxidant properties of these pigments are due to polyene backbone which reacts with and thereby scavenge singlet oxygen and free radicals protecting cells from oxidative damages (Young and Lowe, 2018). Important dietary carotenoids are α-carotene, β-carotene, and β-cryptoxanthin, zeaxanthin, lutein, and lycopene. Several fruits and vegetables of red, yellow, orange, and dark green colourations are rich sources of carotenoids. Important examples are carrots, papayas, spinach, apricots, beetroot, sweet potatoes etc. Dietary β-carotene, α-carotene and β-cryptoxanthin are considered provitamin-A as they are converted into the vitamin A or retinol in animal's system. Accumulation of lutein and zeaxanthin in retinal macula (yellow spot) has been associated with their protective function (Gong et al., 2017).

Anthocyanins are water soluble pigments that contribute to red, blue, purple, and violet colourations of several vegetables and fruits. These are a subtype of polyphenolic flavonoids that are commonly found in red wines, some cereals, darkly coloured vegetables, roots and fruits. Chemically, anthocyanins are glycosides or glycones (glycosylated with sugars) of aglycones (not glycosylated) called anthocyanidins. In general, these compounds are composed of polyhydroxy or polymethoxy groups which along with phenolic rings or conjugated double bonds contribute to their antioxidant properties (Brewer, 2011). Naturally occurring anthocyanins are the glycosylated derivatives of six common anthocyanidins e.g. cyanidin, delphinidin, pelargonidin, malvidin, peonidin and petudinin. In addition to colouring and physiological roles in plants, anthocyanins are important dietary antioxidants more potent than other related phytochemicals.They strongly inhibit peroxidation of membrane lipids by scavenging peroxyl radicals (Mattioli et al., 2020; Mbah et al., 2019).

V. NANOFORMULATION OF ANTIOXIDANTS

Nanoformulation significantly improves the effects of natural antioxidants. Nanoformulation of a drug is encapsulation of the drug in a suitable nanoparticle (1 to 100 nm) to enhance the effectiveness of the drug concerning its solubility, bioavailability, stability, and target efficiency along with reducing the cytotoxicity of the drugs (Srivastava et al., 2018; Zobeiriet., 2018).For nanoformulation of the antioxidants, crude extract is made from different parts of the plant and specific antioxidants are then subsequently identified with help of different technical tools. The constructed antioxidants are then used for the treatment of different disease (**Fig. 4**). Nanoformulated antioxidants showed significant therapeutic effects when tested for the antioxidant activity or when used for the treatment of the disease caused by the imbalance of the redox stability. The effectiveness of the antioxidants depends on the size and surface properties of the nanoparticles. Nanoformulation of natural antioxidants enhances the effect of antioxidants derived from plants, which are unable to produce the effects of the same potential in the free form. These antioxidants encapsulated in nanoparticles are now delivered and released efficiently at the target site and the amount of required antioxidants is also reduced (Yen et al., 2010;Cartiera et al., 2010; Mukerjee and Vishwanatha, 2009). There are different ways of formulating nanoantioxidants that are briefly discussed in the following sections.

A) Inorganic nanoparticles or metal/inorganic nanoparticles with inherent antioxidant activity

In vitro as well as in vivo studies have demonstrated that inorganic nanoparticles such as metal (platinum and gold) and metal oxides (e.g. iron, ceria oxides) possess antioxidant activity by scavenging ROS and RNS that efficiently reduce and decrease them. These inorganic nanoparticles are able to reduce the oxidative stress and diminish the likelihood of development of the disease associated with oxidative stress because of their electrochemical and physical properties like redox and catalytic properties, high surface to volume ratio, electronic configuration and biocompatibility (Erica et al., 2011).

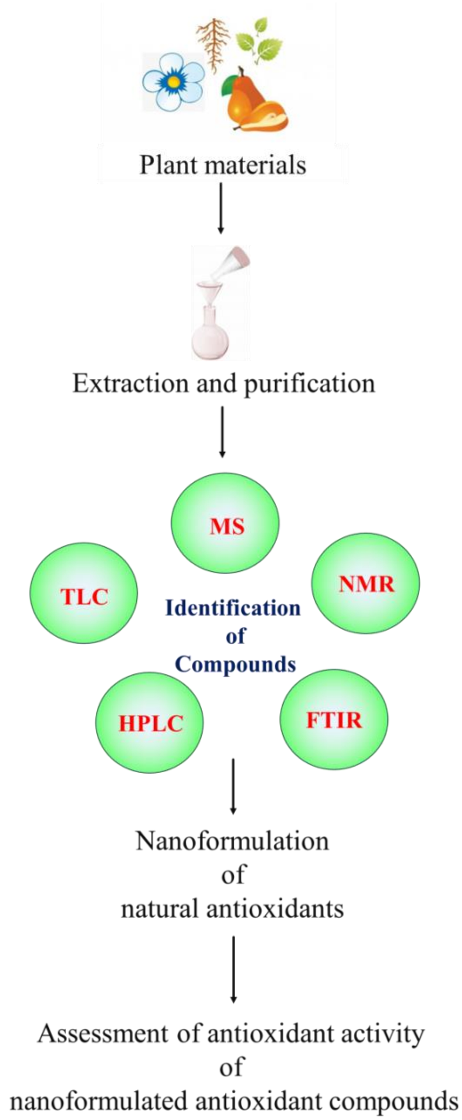

Figure 4: Nanoformulation of different types of compounds extracted from different materials of the plants and their assessment of antioxidant activity. This figure represents nanoformulation of antioxidants derived from different parts of the plants. It shows the extraction of different plant materials, purification and identification of compounds with the help of different modern techniques like TLC (thin layer chromatography), NMR (nuclear magnetic resonance spectroscopy), HPLC (high performance liquid chromatography), MS (mass spectroscopy) and FTIR (fourier-transform infrared spectroscopy). The identified compounds are further formulated into different types of nanoparticles. These nanoparticles are subsequently are assessed for their antioxidant activity with different methods.

The ceria oxide exhibit mixed valence states of Ce^{3+} and Ce^{4+} and this state enable the ceria oxide to mimic like the SOD. Cerium oxide nanoparticles (CNPs) have been shown to protect liver from ROS (Lin et al., 2013). Gold NPs (AuNPs) has good radical scavenging capacity when tested with DPPH assay. The percent inhibition was 72.63 ± 0.567% for AuNPs without any stabilizer, 73.51 ± 0.221% for AuNPs using Gum Arabic as a stabilizer and 74.39 ± 0.255% for AuNPs using Gum Arabic as both a stabilizer and reductant. The destabilized AuNPs exhibited decreased DPPH percent inhibition because of the reduced surface area of NPs available the reduction of DPPH radicals. This reduced inhibition could likely be resulted from the reduced particle surface area due to the presence of large clusters, available to scavenge the DPPH radicals (Djajadisastra et al., 2014).

The application of metal oxide nanoparticles has drawn attention of the researchers in biomedical fields. The iron oxide was able to scavenge the DPPH free radicals in a concentration dependent manner. As the size of iron-oxide particles decreased the antioxidant capacity of the iron-oxide increased that is the antioxidant activity of the iron-oxide depends on the size of the iron-oxide particles. The scavenging capacity of the DPPH free radicals might be possible because of the transfer of the electrons (Paul et al., 2009).

Recent data support that in cigarette smokers pulmonary inflammation occurs because of the increased oxidative stress. Cigarette smoke contains ROS and also capable of generating huge amount of ROS. These ROS can induce pulmonary inflammation and may cause occurrence of cigarette smoke inflammatory lung disease like chronic obstructive pulmonary disease. Since here ROS are responsible for eliciting inflammatory lung disease antioxidants could be effective in treating such disease. The studies validate that polyacrylate stabilized platinum nanoparticles (PAA-Pt) acts as antioxidants that efficiently quench ROS. In vivo study, where the PAA-Pt nanoparticles administered to mice prior to cigarette smoke, shows an stability in the antioxidant capacity and activation of $NF_k\beta$. Whereas the mice not treated with PAA-Pt nanoparticles shows depletion of antioxidant activity, activation of $NF_k\beta$ and inhibits neutrophilic inflammation in the lungs of mice. In vitro experiments performed on alveolar – type-II-like A549 cells also supports that the platinum nanoparticles works as antioxidant (Onizawa et al., 2009).

The AgNPs functionalized with the *Clerodendrum phlomidis* leaf extract have shown higher ferric reducing power as compared to extract alone. The DPPH radical scavenging activity of the extract functionalized AgNPs have shown greater inhibition as compared to extract alone which was dose dependent. AgNPs made from *Morus alba* leaves extract have shown to increase the antioxidant activity to 47.81 % by scavenging DPPH in the same experiment where the ascorbic acid shown ~56% DPPH scavenging activity at the same concentration. When $ABTS^+$ scavenging activity of plant extract functionalized AgNPs was compared to BTH standard both of the showed equal activity i.e. 95.08% at 100µg/mL. Along with DPPH and ABTS scavenging activity AgNPs exhibited nitric oxide scavenging activity 64.04 % that was comparable to plant extract (45.72%) and gallic acid standard (88.62%) at 100µg/mL (Kumar et al., 2020; Nagaich et al., 2016).

In addition to these nanoparticles, selenium nanoparticles (SeNPs) are also drawing attention of scientists because of their scaled properties like photoelectrical, semi-conduction, photoconduction, catalytic, etc., and their possible capability in electronic and optical instruments. SeNPs are less toxic than selenium compounds and show various therapeutic properties there they can be used in medical practices. A number of researchers succeeded successfully in forming SeNPs using different material like *Streptomyces minutiscleroticus* M10A62 that was obtained from magnesite mine, *Pantoea agglomerans* isolated from the Camarones River, Trolox with potential antioxidant activity. Furthermore, Se@Trolox (surface-functionalized selenium nanoparticles) have shown to block the accumulation of (ROS) induced by cisplatin, activation of the MAPK and AKT signaling pathway, and damage of DNA mediated by p53 phosphorylation in HK-2 cells (Kumar et al., 2020; Khurana et al., 2019; Hosnedlova et al., 2018; Almurshidi, 2020).

B) Antioxidant functionalized dual nanoparticles

As single nanoparticles are formed by attaching antioxidants with the dual nanoparticles are formed in the same way so that high antioxidant properties can be attained. Bimetallic nanoparticle based on Ag and Se was synthesized by using quercetin and gallic acid and stabilized. The NPs were tested in vitro for their antioxidant activity using DPPH, ABTS and MTT assay and showed antioxidant activity in the range of 59-62 %. The redox potential of the quercetin and the gallic acid present on the surface of the bimetallic nanoparticles are responsible for the antioxidant potential of the nanoparticles. On the surface quercetin and gallic acid donate H^+ and scavenge $^1O_2$ and justify the antioxidant potentiality of the composite nanoparticles (Khalil et al., 2019). In a study, bimetallic nanoparticles composed of silver and platinum were synthesized using ethanolic extract of the plant – *Vernonia mespilifolia* exhibiting potential antioxidant activity. The AgPtNPs exhibited a higher ability to scavenge free radicals, especially ABTS and DPPH (IC50 21.6 and 19.5 µg/mL) respectively as compared with AgNPs and ascorbic acid. Moreover, the AgPtNPs showed greater FRAP activity (44.1 mg GAE/g) as compared to AgNPs (18.5 mg GAE/g). These interesting bioactivities exhibited by the AgPtNPs suggest that they could be applied in biomedical practices (Unuofin et al., 2020).

C) Lipid based nanoparticles

Because of the cellular resemblance, liposome could be the best option for delivering the drugs to the specific target site. They are composed of special types of lipids called phospholipids containing one hydrophobic and one hydrophilic group that have specific advantages. The biosynthetic methods, size and the lamellarity of the liposomal vesicles are the main criteria of the liposome classification that may influence the efficiency of the liposomes (Bozzuto and Molinari, 2015).

Liposomes are biodegradable and biocompatible so they are most studied nanoparticles. Liposomes are composed of amphipathic lipids and because of this dual nature of the lipid molecules are organized in to lipid bilayer and in the presence of water form vesicles so that they are capable of encapsulating both hydrophilic and hydrophobic drugs. Fluidity of the lipid membrane determines its stability in the blood. Cholesterol molecules are added to the lipid bilayer that decrease the fluidity of the membrane and increase the stability of the liposome in the blood and also increase the permeability of the hydrophobic drugs. Addition of cholesterol molecule into the liposome increases the number of bilayer in the liposome with Liposomes are loaded with the drugs and the ligand that can bind with the target site specifically because of the presence of the receptors present on the cells. Nanoformulation of the antioxidants with liposome increases the stability, enhances the activity, solubility and skin penetration capability of the antioxidants (Tran et al., 2019).Antioxidants such as curcumin and resveratrol face several challenges because of their physiochemical properties which make them unstable in free form. Encapsulation of curcumin and resveratrol simultaneously in the liposome produce nanoparticles of lowest particle size (77.50 nm), with highest encapsulation efficiency (reaching 80.42 ± 2.12%), lowest polydispersity index (0.193) and highest LPO inhibition and strongest DPPH scavenging activity (Huang et al., 2019).

Solid lipid nanoparticles protect the encapsulated drug from degradation thereby increase the stability of the drug and allow slow release of the drug at specific target site (Garces et al., 2017; Garcia-Pinel et al., 2019). Solid lipid nanoparticles loaded with resveratrol Improves the insulin resistance in adipose and muscle cells by affecting the three protein components of the SNARE protein in rats with type 2 diabetes (Mohseni et al., 2019).

D) Dendrimers

Dendrimers are known for their characteristic properties such as their shape and size. They are highly branched polymeric molecules of sequentially arranged layers of monomers and have a central core, repetitive branching units and terminal groups including anionic carboxyls, cationic amines, or neutral hydroxyl groups. Further, these groups are attached to the modifiable surface of the dendrimer. There are different methods of synthesizing dendrimers that have their own advantages. Polyamidoamine (PAMAM), poly (propylene imine), poly-L-lysine (PLL) are a few examples of dendrimers used for nanoformulation (Palmerston Mendes et al., 2017; Srinageshwar et al., 2017). Dendrimers perform the job of drug targeting, solubilization, making bioavailability of drugs, dissolution, making a drug stable etc (Madaan et al., 2014).

E.) Carbohydrate based nanoparticles

Cyclodextrin, alginate, chitosan, etc. are the common polysaccharides that can be used for the preparation of nanoparticles. They are safe, non-toxic and degradable. There are several evidences which support that carbohydrate-based nanoparticles could enhance the antioxidant activity of epigallocatechin gallate (EGCG) (Yang et al., 2019).Carbohydrates ensure the targeted delivery because they are degraded by specific enzymes at a specific place (Sampathkumar and Loo, 2018).

There are several forms of carbohydrates such as monosaccharides, oligosaccharides and polysaccharides that are used to create nanoparticles because they have ability to entrap bioactive compounds. Alginate is derived from some natural sources can and because of their availability, biocompatibility, low cost and simple formulation alginate can be used as nanoparticles. Alginate based nanoparticles loaded with epicatechin tested on ex vivo skin model and these experiments demonstrated the excellent release of the antioxidant on skin surface with full antioxidant activity (Silva et al., 2020). Chitosan solely or in combination with other materials are used to produce nanoparticles. Chitosan has the mucoadhesive property which can be used for targeted delivery of the drugs in mucosal surface. Nanoformulation of chitosan loading antioxidants such as Ascorbic acid, catechol and vitamin E has increased the encapsulation efficiency by 76 %, stability as well as target delivery to the breast cancer cells where it can efficiently scavenge free radicals when compared free form of these antioxidants. Investigations have shown that the chitosan nanoparticles simultaneously loaded with catechin and quericitin had high antioxidant potential when measured with DPPH< $ABTS^+$, O_2, and OH radical scavenging activity compared to native drugs. The nanoparticle was prepared by ionic gelation reaction between sodium tripolyphosphate and chitosan which was subsequently modification by genipin (Li et al., 2018).

F) Protein based nanoparticles

Proteins can also be used for the encapsulation of antioxidants and the common proteins which can be used for the formation of nanoparticles include lactoglobulin, albumin, casein, etc. Nanoparticles prepared from proteins can enhance the level of absorption of the loaded antioxidants. For example Epigalloctechingallate-β-lactoglobulin nanoparticles (size less than 50 NM) prepared by self-combining Epigalloctechin gallate (EGCG) and β-lactoglobulin under optimal heat treatment conditions decrease the initial degradation of the EGCG- β-lactoglobulin nanoparticles by 33 times when compared to free EGCG. This property of EGCG-β-lactoglobulin increase the concentration of antioxidant EGCG molecule in the nanoparticles and slow release of the antioxidant increase the bioavailability of the EGCG in the gastro intestinal tract. The EGCG nanoparticles prepared from gelatin electro spraying have shown to prolong the antioxidant activity of the phytochemicals (Yang et al., 2019; Chang et al., 2019). Albumin is one of the most used protein based nanoparticles because of its electro physical properties. Quercetin loaded in the in the protein nanoparticles made up of BSA by hydrophobic interaction have shown promote stability of the quercetin while maintaining its antioxidant activity. Encapsulation of rutin (flavonoid that occur naturally in buckwheat and *Sophora japonica L* fruit peels of citrus plants) in serum albumin based nanoparticles have shown two fold ABTS radical scavenging activity as compared to free form of rutin. The NPs was prepared by the nano spray drying method and showed adequate physiological properties of efficient delivery of the nanoparticles (Regiellen et al., 2020; Khalil et al., 2019; Chang et. al., 2019; Yadav et al., 2014).

Gelatin is a solid shaped, colorless gelatin derived from collagen is also a protein based nanoparticle used to deliver the natural antioxidants such as tannic acid, epigallocatechingallate, and tea Flavin and curcumin (Azizian et al., 2018; Khalil et al., 2019).Other protein based nanoparticles includes silk proteins, soy proteins, milk proteins such as beta-lactoglobulin and casein that deliver antioxidants efficiently. These nanoparticles have structures that provide features like self-assembling ability, processing flexibility, mechanical strength, biodegradability and bioavailability (Khalil et al., 2019; Shuangquan et al., 2019; Malekhosseini et al., 2019; Jin et al., 2019).

CONCLUSION

Synthetic antioxidants are less efficient when used for the treatment of disease. Along with low efficiency, they also produce side effects. Now it has become a need to search for those antioxidants that will produce significant effect with low or no side effects. It has been estimated that the medicinal plants and foods are the great source of antioxidants that have given satisfactory results when used for the suppression of the effects induced by free radicals. The nanoformulation of these antioxidants can overcome the limitations associated with the use of natural antioxidants in free form. The efficiency of the crude extracts from the different parts of the plant and the nanoformulated compounds as an antioxidants can be determined by different methods like DPPH method, DNA nicking assay, ORAC, TEAC assay, FRAP, and spot assay.

CONFLICT OF INTEREST

Authors declare no conflict.

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REFERENCES

Almurshidi B. (2020). Selenium, platinum and cerium oxide nanoparticles' applications to cancer and fibrotic diseases in medicine.*(Doctoral dissertation)*. Retrieved from https://scholarcommons.sc.edu/etd/5686

Amalraj A., Pius A., Gopi S. & Gopi S. (2016). Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives - A review. *J.Tradit. Complement. Med.*, 7(2):205-233.

Anagnostopoulou M.A., Kefalas P., Papageorgiou V.P., Assimopoulou A.N. & Boskou D. (2006). Radical scavenging activity of various extracts and fractions of sweet orange peel *(Citrus sinensis*). *Food Chem.*, 94(1): 19–25.

Augustyniak A., Bartosz G., Cipak A., Duburs G., Horakova L., Luczaj W., Majekova M., Odysseos A.D., Rackova L., Skrzydlewska E., Stefek M., Strosova M., Tirzitis G., Venskutonis P.R., Viskupicova J., Vraka P.S., & Zarkovic N. (2010). Natural and synthetic antioxidants: an updated overview. *Free Radic. Res*., 44(10):1216-1262.

Ayala A., Munoz M.F. & Arguelles S. (2014). Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid. Med. Cell Longe.,* 2014:360438.doi: 10.1155/2014/360438.

Azizian S., Hadjizadeh A. & Niknejad H. (2018). Chitosan-gelatin porous scaffold incorporated with Chitosan nanoparticles for growth factor delivery in tissue engineering. *Carbohydr.Polym.,* 202:315-322.

Bagchi K. & Puri S. (1998). Free radicals and antioxidants in health and disease. *East Mediterranean Health Jr*., 4:350–360.

Bozzuto G. & Molinari A. (2015). Liposomes as nanomedical devices. *Int. J. Nanomed.*, 10: 975-999.

Braciela J., Herrero C., Garcia-Martin S., &Pena R.M. (2008).A brief study of the role of Selenium as antioxidant.*Electronic J. Environ.Agricult. Food Chem.*,7(8):3151-3155

Brewer M.S. (2011). Natural antioxidants: sources, compounds, mechanisms of action, and potential applications. *Comprehen. Rev. Food Sci. Food Safet.*, 10: 221-247.

BritoA. F. & Zang Y. (2019). A review of lignan metabolism, milk enterolactone concentration, and antioxidant status of dairy cows fed flaxseed. *Molecules*,24(1): 41. doi: 10.3390/molecules2401004

Carocho M. & Ferreira I.C. (2013). A review on antioxidants, prooxidants and related controversy: natural and synthetic compounds, screening and analysis methodologies and future perspectives.*Food Chem.Toxicol.*, 51: 15-25.

Cartiera MS., Ferreira E.C., Caputo C., Egan M.E., Caplan M.J., & Saltzman W.M. (2010). Partial correction of cystic fibrosis defects with PLGA nanop articles encapsulating curcumin. *Mol. Pharm*., 7(1): 86-93.

Chambial S., Dwivedi S., Shukla K.K., Jhon P.J., & Sharma P. (2013). Vitamin C in Disease Prevention and Cure: An Overview. *Ind. J. Clin.Biochem*., 28(4):314–328.

Chang C., Meikle T.G., Su Y., Wang X., Dekiwadia C., Drummond C.J., Conn C.E., & Yang Y. (2019). Encapsulation in egg white protein nanoparticles protects anti-oxidant activity of curcumin. *Food Chem*., 280:65-72.

Chen C. (2015). Overview of plant pigments. In: Chen C. (Ed.), Pigments in fruits and vegetables. Springer, New York, USA, pp. 1–8.

Devasagayam T.P.A., Tilak J.C., Boloor K.K., Sane K.S., Ghaskadbi S.S., & Lele R.D. (2004).Free radicals and antioxidants in human health: curren t status and future prospects. *J. Assoc. Physicians India*. 52:794-804.

Djajadisastra J., Sutriyo., Purnamasari P., & Pujiyanto A. (2014).Antioxidant activit of gold nanoparticles using gum arabic as a stabilizing agent.*Int. J. Pharm. Pharm. Sci*. 6(7): 462-465.

Droge W. (2002). Free radicals in the physiological control of cell function. *Physiol. Rev.* 82 (1):47-95.

Eklund PC., Langvik OK., Warna JP., Salmi TO., Willfor SM., & Sjoholm RE. (2005). Chemical studies on antioxidant mechanisms and freeradical scavenging properties of lignans. *Org Biomol Chem*. 3(18):3336-47.

Erica S., Daniel A., & Silvana A. (2011). Artificial Nanoparticle Antioxidants. *ACS Symposium Series* 1083:235-253. DOI: 10.1021/bk-2011-1083.ch008.

ErnsterL., & Dallner G. (1995). Biochemical, physiological and medical aspects of ubiquinone function. *Biochim.Biophys. Acta*, 1271 (1): 195-204.

Fernandes C., Oliveira C., Benfeito S., Soares P., Garrido J., & Borges F. (2014). Nanotechnology and antioxidant therapy: an emerging approach for neurodegenerative diseases.*Curr. Med. Chem.*, 21(38):4311-27.

FleurietA., & Macheix J.J. (2003). Phenolic acids in fruits and vegetables. *Flavonoids Health Dis.*, 1: 17–20.

Garces A., Amaral M.H., Sousa Lobo J.M., &Silva A.C. (2017). Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review. *Eur. J. Pharm Sci*. 112:159-167.

García-Pinel B., Porras-Alcala C., Ortega-Rodríguez A., et al. (2019). Lipid-based nanoparticles: application and recent advances in cancer treatment. *Nanomaterials (Basel)*. 9(4):638. doi:10.3390/nano9040638

Gomes E.C., Silva A.N. & de Oliveira M.R. (2012). Oxidants, antioxidants, and the beneficial roles of exercise-induced production of reactive species. *Oxid. Med. Cell Longev*.; 2012: 1-12.doi: 10.1155/2012/756132.

Gong X., Draper C., Allison G.,Marisiddaiah R., & Rubin L. (2017). Effects of the macular carotenoid lutein inhuman retinal pigment epithelial cells. *Antioxidants.* 6(4): 1-13. doi: 10.3390/antiox6040100.

Gulcin I. (2020). Antioxidants and antioxidant methods: an updated overview. *Arch.Toxicol*., 94(3): 651-715.

Gupta P., Authimoolam S.P., Hilt J.Z.,&Dziubla T.D. (2015).Quercetin conjugated poly (β-amino esters) nanogels for the treatment of cellular oxidative stress. *ActaBiomate.* 27, 194–204.

Heleno S.A., Martins A., Queiroz,& Ferreira I.C. (2015). Bioactivity of phenolic acids: metabolites versus parent compounds: a review. *Food Chem*. 173:501-513.

Hosnedlova B., Kepinska M., Skalickova S., Fernandez C., Ruttkay-Nedecky B., Peng Q., Baron M., Melcova M., Opatrilova R., Zidkova J., Bjørklund G., Sochor J., & Kizek R. (2018). Nano-selenium and its nanomedicine applications: a critical review. *Int. J.Nanomed*., 13:2107-2128.

Huang M., Liang C., Tan C., Huang S., Ying R., Wang Y., Wang Z., &Zhang Y. (2019). Liposome co-encapsulation as a strategy for the delivery of curcumin and resveratrol.*Food Funct*., 10(10):6447-6458.

Idehen E., Tang Y., &Sang S. (2017). Bioactive phytochemicals in barley. *J Food Drug Anal*., 25(1):148-161.

Jarosz M., Olbert M., Wyszogrodzka G., Młyniec K., & Librowski T. (2017).Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. *Inflammopharmacology*. 25(1):11-24.

Jin B., Zhou X., Zhou S., Liu Y., Zheng Z., Liang Y., & Chen S. (2019). Nano-encapsulation of curcumin using soy protein hydrolysates - tannic acid complexes regulated by photocatalysis: a study on the storage stability and *in vitro* release. *J Microencapsul*., 36(4): 385-398.

Khalil I., Yehye WA., Etxeberria AE., Alhadi AA., Dezfooli SM., Julkapli NBM., Basirun WJ., & Seyfoddin A. (2019). Nanoantioxidants: Recent Trends in Antioxidant Delivery Applications. *Antioxidants (Basel)*. 9(1): 24. doi: 10.3390/antiox9010024.

Khan A. W., Khan A.U., Shah S.M.M., Ullah A., Faheem M., & Saleem M. (2019). An updated list of neuromedicinal plants of Pakistan**,** their uses, and phytochemistry. *Evid Based Complement. Altern Med*., 2019: 6191505. doi: 10.1155/2019/6191505.

Khan M.I., & Giridhar P. (2011). Dietary antioxidants: The insurer of health. *Everyman's Sci.46*, 214–218.

Khoo H.E., Azlan A., Tang S.T., & Lim S.M. (2017). Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food Nutrit.Res.*, *61*(1), 1361779.

Khurana A., Tekula S., Saifi M.A., Venkatesh P., &Godugu C. (2019). Therapeutic applications of selenium nanoparticles. *Biomed.Pharmacother*., 111: 802-812.

Kiełczykowska M., Kocot J., Pazdzior M.,&Musik I. (2018). Selenium - a fascinating antioxidant of protective properties. *Adv. Clinic.Exp Med*. 27(2):245-255.

Kiselev K.V., Grigorchuk V.P., Ogneva Z.V., Suprun A.R.,&Dubrovina A.S.(2016). Stilbene biosynthesis in the needles of spruce *Piceajezoensis.Phytochem*.,131:57-67.

Knight J.A. (2000). Review: Free radicals, antioxidants, and the immune system. *Ann.Clin. Lab. Sci*., 30(2):145-58.

KocaadamB.,&Şanlier N. (2017). Curcumin, an active component of turmeric (*Curcuma longa*), and its effects on health.*Crit. Rev. Food Sci.Nutr*.,57(13):2889-2895.

Koleckar V., Kubikova K., Rehakova Z., Kuca K., Jun D., Jahodar L., & Opletal L. (2008). Condensed and hydrolysable tannins as antioxidants influencing the health. *Mini Rev. Med. Chem*., 8(5):436-447.

Koltover V. (2010). Antioxidant biomedicine: From free radical chemistry to systems biology mechanisms. *Russ. Chem. Bull.*, 59: 37–42.

Kumar H., Bhardwaj K., Nepovimova E., Kuca K., Dhanjal DS., Bhardwaj S., Bhatia SK., Verma R., & Kumar D. (2020). Antioxidant Functionalized Nanoparticles: A Combat against Oxidative Stress. *Nanomaterials (Basel)*, 10(7):E1334. doi: 10.3390/nano10071334.

Kumari A., Panda A., Parida A.K., & Rangani J. (2017). Antioxidant activities, metabolic profiling, proximate analysis, mineral nutrient composition of *Salvadorapersica* Fruit unravel a potential functional food and a natural source of pharmaceuticals. *Front. Pharmacol*., 8:61. doi: 10.3389/fphar.2017.00061.

Kurutas E.B. (2016). The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutr.J*., 15(1):71.doi: 10.1186/s12937-016-0186-5.

McDowell L.R.,Wilkinson N., Madison R.,&Felix T. (2007).Vitamins and minerals functioning as antioxidants with supplementation considerations.*Florida Ruminant Nutrition Symposium*, Best Western Gateway Grand, Gainesville, FL

Li F., Jin H., Xiao J., Yin X., Liu X., Li D., & Huang Q. (2018). The simultaneous loading of catechin and quercetin on chitosan-based nanoparticles as effective antioxidant and antibacterial agent. *Food Res. Int*. 111:351-360.

Li L., Ng T., Gao W., Li W., Fu M.,Niu S., Zhao L., Chen R.,&Liu F. (2005). Antioxidant activity of gallic acid from rose flowers in senescence accelerated mice. *Life Sci.*, 77:230–240.

Lim Y., Lim T., &Tee J. (2007). Antioxidant properties of several tropical fruits: A comparative study. *Food Chem.*, 103:1003–1008.

Lin C.H., Al-Suwayeh S.A., Hung C.F., Chen C.C., &Fang J.Y. (2013).Camptothecin-Loaded Liposomes with α-Melanocyte-Stimulating Hormone Enhance Cytotoxicity Toward and Cellular Uptake by Melanomas: An Application of Nanomedicine on Natural Product. *J.Tradit. Complement. Med*., 3(2): 102-9.

Llano S., Gomez S., Londoño J., &Restrepo A. (2019).Antioxidant activity of curcuminoids.*Phys. Chem. Chem. Phys*., 21(7):3752-3760.

Lobo V., Patil A., Phatak A.,& Chandra N. (2010). Free radicals, antioxidants and functional foods: Impact on human health. *Pharmacogn Rev.*, 4(8):118–126.

Lourenço S.C., Moldao-Martins M., &Alves V.D. (2019). Antioxidants of natural plant origins: from sources to food industry applications. *Molecules*, 24(22):1-25.

Madaan K., Kumar S., Poonia N., Lather V., &Pandita D. (2014). Dendrimers for Drug Delivery. *J. Pharm.Bioallied. Sci.*, 6(3): 139-150.

MadsenC.,&Brinch-Pedersen H. (2016). The Antinutritional Components of Grains.*Encyclopedia of Food Grains*. 10.1016/B978-0-12-394437-5.00111-X.

Malekhosseini P., Alami M., Khomeiri M., Esteghlal S., Nekoei A.R., & Hosseini S.M.H. (2019). Development of casein-based nanoencapsulation systems for delivery of epigallocatechingallate and folic acid. *Food Sci.Nutr*., 7(2):519-527.

Mattila P., & Kumpulainen J. (2001). Coenczyme Q9 and Q10: Contents in foods and dietary intake. *J. Food. Comp. Anal.*, 14(4): 409-417.

Mattioli R., Francioso A., Mosca L., &Silva P. (2020). Anthocyanins: A Comprehensive Review of Their Chemical Properties and Health Effects on Cardiovascular and Neurodegenerative Diseases. Molecules. 25(17):3809. doi: 10.3390/molecules25173809.

Mbah C.J., Orabueze I., &Okorie N.H. (2019). Antioxidants properties of natural and synthetic chemical compounds: Therapeutic effects on biological system. *ActaSci. Pharm. Sci*.,3(6): 28-42.

Medhe S., Bansal P., &Srivastava M.M. (2014). Enhanced antioxidant activity of gold nanoparticle embedded 3, 6-dihydroxyflavone: A combinational study. *Appl. Nanosci.*, 4: 153–161.

MenonV..P.,&Sudheer A.R. (2007). Antioxidant and anti-inflammatory properties of curcumin.*Adv. Exp. Med. Biol*.,595:105-125.

Milisav, I., Ribaric, S., & Poljsak, B. (2018). Antioxidant Vitamins and Ageing.In: Harris J., &Korolchuk V. (eds) Biochemistry and Cell Biology of Ageing: Part I Biomedical Science. Subcellular Biochemistry, vol 90, Springer, Singapore, pp.1–23.

Mohseni R., ArabSadeghabadi Z., Ziamajidi N., Abbasalipourkabir R., & RezaeiFarimani A. (2019). Oral

Administration of Resveratrol-Loaded Solid Lipid Nanoparticle Improves Insulin Resistance Through Targeting Expression of SNARE Proteins in Adipose and Muscle Tissue in Rats with Type 2 Diabetes. *Nanoscale Res.Lett*., 14(1):227. doi:10.1186/s11671-019-3042-7

Montecinos V., Guzman P., Barra V., Villagran M., Munoz-Montesino C., Sotomayor K., Escobar E., Godoy A., Mardones .L, Sotomayor P., Guzman C., Vasquez O., Gallardo V., van Zundert B., Bono MR., Onate SA., Bustamante M., Carcamo JG., Rivas CI., & Vera JC. (2007). Vitamin C is an essential antioxidant that enhances survival of oxidatively stressed human vascular endothelial cells in the presence of a vast molar excess of glutathione. *J. Biol. Chem*., 282(21):15506-15515.

Mozos I., Stoian D., &Luca C.T. (2017).Crosstalk between Vitamins A, B12, D, K, C, and E Status and Arterial Stiffness.*Dis Markers*. 2017, Article ID:8784971.https://doi.org/10.1155/2017/8784971

Mukerjee A., & Vishwanatha J.K.(2009). Formulation, characterization and evaluation of curcumin-loaded PLGA nanospheres for cancer therapy.*Anticancer Res.,* 29(10): 3867-75.

Nagaich U., Gulati N., &Chauhan S. (2016). Antioxidant and antibacterial potential of silver nanoparticles: biogenic synthesis utilizing apple extract. *J. Pharm.,* 2016: Article ID 7141523. https://doi.org/10.1155/2016/7141523

Navas P., Villalba J.M., &de Cado R. (2007).The importance of plasma membrane coenzyme Q in aging and stress management.*Mitochondrion*. 7 Suppl: S34-40.

Niki E. (2015). Evidence for beneficial effects of vitamin E. Korean.*J. Intern. Med*., 30(5):571-579.

Dao DQ, Ngo TC, Thong NM, Nam PC. (2017). Is Vitamin A an Antioxidant or a Pro-oxidant? J Phys Chem B., 121(40):9348-9357.

Onizawa S., Aoshiba K., Kajita M., Miyamoto Y., & Nagai A. (2009). Platinum nanoparticle antioxidants inhibit pulmonary inflammation in mice exposed to cigarette smoke. *Pulm.Pharmacol.Ther.*, *22*(4): 340–349

Ozkan G., Kamiloglu S., Ozdal T., Boyacioglu D., &Capanoglu E.(2016). Potential use of turkish medicinal plants in the treatment of various diseases.*Molecules*, 21(3):257.

Palace V.P., Khaper N., Qin Q., &Singal P.K. (1999).Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. *Free Radic. Biol. Med*.,26(5-6):746-761.

Mendes L.P., Pan J., &Torchilin V.P. (2017).Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy. *Molecules*,22(9):1401.doi:10.3390/molecules22091401.

Panche A.N., Diwan A.D., &Chandra S.R. (2016). Flavonoids: an overview. *J.Nutr. Sci*., 5:e47.

Paul S., Saikia J.P., Samdarshio S.K., & Konwar B.K. (2009). Investigation of antioxidant property of iron oxide particlesby 1′-1′diphenylpicryl-hydrazyle (DPPH) method. *J. Magn. Magn.Mater*.,321(21): 3621–362.

Pellegrini N., Serafini M., Colombi B., Del Rio D., Salvatore S., Bianchi M., & Brighenti F. (2003). Total antioxidant capacity of plant foods, beverages and oils consumed in Italy assessed by three different in vitro assays. *J. Nutr*., 133*:* 2812–2819.

Petrovska B.B. (2012). Historical review of medicinal plants' usage. *Pharmacogn Rev*., 6(11): 1–5.

Pham-Huy L.A., He., & Pham-Huy C. (2008). Free radicals, antioxidants in disease and health.*Int. J. Biomed. Sci*.,4(2):89–96.

Phaniendra A., Jestadi D.B.,&Periyasamy L. (2015). Free radicals: properties, sources, targets, and their implication in various diseases. *Indian J.Clin.Biochem.*,30(1):11–26.

Pisoschi A.M., &Pop A. (2015). The role of antioxidants in the chemistry of oxidative stress: A review. *Eur. J. Med. Chem*.,97:55-74.

Pizzino G., Irrera N., Cucinotta M., Pallio G., Mannino F., Arcoraci V., Squadrito F., Altavilla D., & Bitto A. (2017). Oxidative Stress: harms and benefits for human health. *Oxid. Med. Cell Longev*.,2017 (3): 1-13.

Pratt D.E., & Hudson B.J.F. (1990).Natural antioxidants not exploited commercially in food antioxidants. In: Hudson B.J.F. (Ed.), In *Food Antioxidants*. Elsevier Applied Science, London, 1990, pp. 171-191.

Prochazkova D., Bousova I., &Wilhelmova N. (2011).Antioxidant and prooxidant properties of flavonoids.*Fitoterapia*, 82(4):513-23.

Radomska-Lesniewska DM., Hevelke A., Skopinski P., Bałan B., Jozwiak J., Rokicki D., Skopinska-Rozewska E., & Białoszewska A. (2016). Reactive oxygen species and synthetic antioxidants as angiogenesis modulators: Clinical implications. *Pharmacol Rep.,* 68(2):462-471.

Ramana K.V., Reddy A.B.M., Majeti N.V.R.K., & Singhal SS.(2018). Therapeutic potential of natural antioxidants. *Oxid.Med.CellLongev*. 2018:9471051. doi: 10.1155/2018/9471051.

Rathore S., Mukim M., Sharma P., Devi S., Nagar JC., & Khalid M. (2020). Curcumin: A Review for Health Benefits. *Int. J. Res. Rev.,* 7(1): 273-290).

PedrozoR.C., Antonio E., Khalil N.M., & Mainardes R.M. (2020). Bovine serum albumin-based nanoparticles containing the flavonoid rutin produced by nano spray drying.*Braz. J. Pharm. Sci*. 56: 1-8. doi.org/10.1590/s2175-97902019000317692

Reinisalo M., Karlund A., Koskela A., Kaarniranta K., & KarjalainenR.O. (2015). Polyphenol Stilbenes: Molecular Mechanisms of Defence against Oxidative Stress and Aging-Related Diseases. *Oxid. Med. Cell Longev*., 2015:340520.

Rizvi S., Raza S.T., Ahmed F., Ahmad A., Abbas S., &Mahdi F.(2014).The role of vitamine in human health and some diseases. *Sultan Qaboos Univ. Med. J.*,14(2):e157-65.

Robbins R.J. (2003). Phenolic acids in foods: an overview of analytical methodology. *J.Agric. Food Chem*., 51(10):2866-2887.

Sabuncuoglu S., Eken A., Aydin A., Ozgunes H., &Orhan H. (2015). Cofactor metals and antioxidant enzymes in cisplatin-treated rats: effect of antioxidant intervention. *Drug Chem.Toxicol*., 38(4):375-382.

Saini R. (2011). Cenzyme Q10: The essential nutrient. *J. Pharm.Bioallied Sci*., 3(3): 466-467.

Salehi B., Martorell M., Arbiser JL., Sureda A., Martins N., Maurya PK., Sharifi-Rad M., Kumar P., & Sharifi-Rad J. (2018). Antioxidants: positive or negative actors. *Biomolecules*, 8(4):114-124.

Sampathkumar K.,& Loo S.C.J. (2018). Targeted Gastrointestinal delivery of nutraceuticals with polysaccharide-based coatings. *Macromol. Biosci.* 18(4): e1700363.

Sandur S.K., Pandey M.K., Sung B., Ahn K.S., Murakami A., Sethi G., Limtrakul P., Badmaev V., & Aggarwal B.B. (2007). Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. *Carcinogenesis*, 28(8):1765-73.

Scheer H. (2013). Chlorophylls and carotenoids. In: Lennarz W.J., Lane M.D. (Eds.), *Encyclopedia of Biological Chemistry. Elsevier,* Amsterdam, Netherland, pp. 498–505.

Sfar S., Jawed A., Braham H., Amor S., Laporte F., &Kerkeni A. (2009).Zinc, copper and antioxidant enzyme activities in healthy elderly Tunisian subjects.*Exp.Gerontol.*,44(12):812-817.

Sharma G.N., Gupta G., &Sharma P.A. (2018).Comprehensive review of free radicals, antioxidants, and their relationship with human ailments. *Crit. Rev.Eukaryot. Gene Expr*., 28(2):139-154.

Sharpe E., Andreescu D., & Andreescu S. (2011). Artificial nanoparticle antioxidants.*In* Andreescu S., &Hepel M., *Oxidative stress: diagnostics, prevention and therapy*. vol. 1083.ACS Publications: Washington, DC, USA., 235–253.

Gou S., Huang Y., Sung J., Xiao B., & Merlin D. (2019). Silk fibroin-based nanotherapeutics: application in the treatment of colonic diseases. *Nanomedicine*. 14: 2373.

Silva J.,Vanat P., Marques-da-Silva D., Rodrigues J.R., &Lagoa R. (2020). Metal alginates for polyphenol delivery systems: Studies on crosslinking ions and easy-to-use patches for release of protective flavonoids in skin. *Bioactive.Mater.*,5(3):447-457.

Simic M.G. (1998).Mechanisms of inhibition of free-radical processes in mutagenesis and carcinogenesis. *Mut. Res./Fundam. Mol. Mech. Mutagen.*,202: 377–386.

Sinbad O.O., FolorunshoA.A., Olabasi O.L., Ayooda A.A., &Temitope E.J. (2019).Vitamin as antioxidants.*J. Food Sci.Nutr. Res.*, 2 (3): 214-235

Singh K., & Mishra A. (2014). Gelatin nanoparticle: prepration, characterization and application in drug delivery. *Int. J. Pharm. Sci. Res*., 5(6): 2149-57.

Skała E., Sitarek P., Rozalski M., Krajewska U., Szemraj J., Wysokinska H., & Sliwinski T. (2016). Antioxidant and DNA repair stimulating effect of extracts from transformed and normal roots of rhaponticum carthamoides against induced oxidative stress and DNA damage in CHO cells. *Oxid Med. Cell Longev.,* (1): 1-11. doi: 10.1155/2016/5753139

Srinageshwar B., Peruzzaro S., Andrews M., Johnson K., Hietpas A., Clark B., McGuire C., Petersen E., Kippe J., Stewart A., Lossia O., Al-Gharaibeh A., Antcliff A., Culver R., Swanson D., Dunbar G., Sharma A., &Rossignol J. (2017). PAMAM Dendrimerscross the blood-brain barrier when administered through the carotid artery in C57BL/6J mice. *Int. J. Mol. Sci.*, 18(3):628.

Srivastava S., Mohammad S., Gupta S., Mahdi AA., Dixit RK., Singh V., & Samadi FM. (2018). Chemoprotective effect of nanocurcumin on 5-fluorouracil-induced-toxicity toward oral cancer treatment. *Natl. J.Maxillofac. Surg*., 9(2): 160-166.

Taghvaei M., & Jafari S.M. (2015). Application and stability of natural antioxidants in edible oils in order to substitute synthetic additives. *J. Food Sci. Technol*., 52(3):1272–1282.

Teponno R.B., Kusari S., &Spiteller M. (2016). Recent advances in research on lignans and neolignans. *Nat. Prod. Rep*., 33(9):1044-92.

Tinggi U. (2008). Selenium: its role as antioxidant in human health. *Environ. Health Prev. Med*.,13(2):102-108.

TraberM.G., & Stevens J.F. (2011). Vitamins C and E: beneficial effects from a mechanistic perspective. *Free Radic. Biol. Med*., 51(5):1000-13.

Tran V.V., Moon J.-Y., &Lee Y.-C. (2019). Liposomes for delivery of antioxidants in cosmeceuticals: Challenges and development strategies.*J. Contr. Rel*., 300:114-140. doi: 10.1016/j.jconrel.2019.03.003.

TułodzieckaA.,&Szydłowska-Czerniak A. (2016). Development of a novel gold nanoparticle-based method to determine antioxidant capacity of Brassica oilseeds, white flakes and meal.*Food Chem.*, 208:142-149. doi: 10.1016/j.foodchem.2016.03.105.

Unuofin J.O., Oladipo A.O,Msagati T.A.M., Lebelo S.L.,Meddows-Taylor S., & More G.K. (2020). Novel silver-platinum bimetallic nanoalloy synthesized from *Vernoniames pilifolia* extract: antioxidant, antimicrobial, and cytotoxic activities. *Arabian J. Chem.*, 13(8): 6639-6648

Uttara B., Singh A.V., Zamboni P., &Mahajan R.T. (2009). Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr. Neuropharmacol.*, 7(1): 65-74.

Valko M., Leibfritz D., Moncol J., Cronin MT., Mazur M., & Telser J. (2007). Free readicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol*., 39(1):44-84.

Veeresham C. (2012). Natural products derived from plants as a source of drugs. *J. Adv. Pharm. Technol. Res*., 3(4):200-201.

Vervoort L.M., Ronden J.E., &Thijssen H.H. (1997).The potent antioxidant activity of the vitamin K cycle in microsomal lipid peroxidation. *Biochem.Pharmacol*., 54(8):871-876.

Wang R., Xiao S., &Niu Z. (2017).Anti-cancer activity of *Aster tataricus*on ON SCC-9 human oral squamous carcinoma. *Afr. J.Tradit.Complementary Altern. Med.*,14(2):142–147.

Yadav R., Kumar D., Kumari A., &Yadav S.K. (2014). Encapsulation of catechin and epicatechin on BSA NPS improved their stability and antioxidant potential. *Excli. J.*,13:331-346.

Yang Q.Q., Wei X.L., Fang Y.P., Gan R.Y., Wang M., Ge Y.Y., Zhang D., Cheng L.Z., &Corke H. (2020). Nanochemoprevention with therapeutic benefits: An updated review focused on epigallocatechingallate delivery. *Crit. Rev. Food Sci.Nutr*., 60(8): 1243-1264.

Yashin A., Yashin Y., Xia X., &Nemzer B. (2017). Antioxidant activity of spices and their impact on human health: A Review. *Antioxidants (Basel).*, 6(3). Pii: E70.

Yehye WA., Abdul Rahman N., Alhadi AA., Khaledi H., Weng NS., & Ariffin A. (2012). Butylated hydroxytoluene analogs: Synthesis and evaluation of their multipotent antioxidant activities. *Molecules*, 17:7645–7665.

Yen F.L., Wu T.H., Tzeng C.W., Lin L.T., & Lin C.C. (2010). Curcumin nanoparticles improve the physicochemical properties of curcumin and effectively enhance its antioxidant and antihepatoma activities. *J. Agric. Food Chem*., 58(12): 7376-7382.

Yen GC, Chen CS, Chang WT, Wu MF, Cheng FT, Shiau DK, Hsu CL. (2018). Antioxidant activity and anticancer effect of ethanolic and aqueous extracts of the roots of *Ficus beecheyana* and their phenolic components. *J. Food Drug Anal*., 26(1):182-192.

Young A.J., &Lowe G.L. (2018). Carotenoids – antioxidant properties. *Antioxidants*, 7 (28): 1-4.

Young I.S.,&Woodside J.V. (2001). Antioxidants in health and disease.*J Clin.Pathol*., 54(3):176-186.

Zobeiri M., Belwal T., Parvizi F., Naseri R., Farzaei M.H., Nabavi S.F., Sureda A., & Nabavi S.M. (2018). Naringenin and its nano-formulations for fatty liver: cellular modes of action and clinical perspective. *Curr. Pharm.Biotechnol.* 19(3):196-205.

Zou L., Wang D., Hu Y., Fu C., Li W., &Dai L. (2017). Drug resistance reversal in ovarian cancer cells of paclitaxel and borneol combination therapy mediated by PEG-PAMAM nanoparticles. *Oncotarget*, 8(36): 60453-60468.

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