

ADVANCED APPLICATIONS OF PHYTONANOTECHNOLOGY IN FOOD, AGRICULTURE, AND MEDICINE AND ASSOCIATED CHALLENGES TO OVERCOME

Abstract

Nanotechnology, one of the most exciting fields of research have emerged among various areas of science and has contributed to the benefit of mankind. However, there was a pause in the use of these NPs as the chemical and physical methods of their preparation were found toxic to humans. Thus, the world of nanotechnology has taken a deviation from the conventional to the eco-friendly concept of green NPs. With a long-known fact that plants can reduce metal ions, plant derived compounds have been exploited to synthesize diverse innocuous green NPs. This review is dedicated to highlight the importance of the use of plant derived NPs in three major fields such as food industry, biomedicine and agriculture that are directly connected to humans. Here we explore and detail the use of plant-based NPs in food preservation, biomedical applications, and their use in agriculture methods of crop development and protection. Furthermore, their mechanism of action and challenges faced are discussed.

Keywords: Plant-derived nanoparticles, food industry, biomedicine, agriculture, mechanism

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I. INTRODUCTION

Nanotechnology is one of the most exciting field of research that have emerged among various areas of science. For its contribution to various advances in technology and science, nanotechnology has become extremely important as it has benefited the mankind (Singh *et al.* 2002). Though nanotechnology depends on the synthesis and modulation of nanoparticles (NPs), it was unknowingly used for thousands of years; for example, gold nanoparticles that were used for staining glasses have cured several diseases. From then, scientists have studied the properties of various nanoparticles using advanced techniques and have utilized for various purposes such as biomedical, agricultural, environmental, catalysis, chemical industries, cosmetics, drug delivery, electronics, environment, energy science, food and feed, health care, mechanics, optics, space industries, non-linear optical devices, single-electron transistors, and photo-electrochemical applications. (Giljohannet *al.* 2010, Abbasi *et al.* 2014, Rai *et al.* 2015, Rao *et al.* 2015, Zhang *et al.* 2020). Due to these widespread applications, the global market of the nanotechnology has grown tremendously over the past years. However, there was a pause in the use of the NPs synthesized through physical approaches due to disadvantages like the generation of toxic waste as evidenced in chemical synthesis due to involvement of toxic chemicals and also require extravagant energy resources to comply (Khan *et al.* 2018). Thus, the world of nanotechnology had taken a deviation for the novel, affordable, and safer methods to synthesize nanoparticles culminating in the sustainable and eco-friendly concepts such as green NPs (Oviaset *al.* 2018).

There are numerous methods that were introduced for the synthesis of metallic nanoparticles (MNPs) which include the physiochemical approaches such as aerosol technologies, laser ablation, ultraviolet irradiation, lithography, photochemical reduction, and ultrasonic. These procedures require the practice of reactive and toxic chemicals causing disruptive effects of the ecosystem (Ahmad *et al.* 2019). Consequently, the scientific community has been continuously striving for the development of NPs that are safe, cost-efficient, and straightforward biological processes for the synthesis of MNPs. The green NP approach utilize the natural resources such as plants and other microorganisms for the synthesis of energy-fit, and safer bio metallic nanoparticles by using their phytochemicals such as polyphenols, flavonoids, terpenoids, and high-low molecular weight proteins involved in the complex redox mediated processes. Generally, there are two approaches that are used in the manufacture of the MNPs, such as the bottom-up and top-down approaches. The former uses the atoms and molecules assemble to form the nanostructures while the later utilizes the breakdown of bulk material to nano-sizes particles. In the biological synthesis, the bottom-up approach is practiced.

II. NPS AND MECHANISM OF PLANT BIO-REDUCTION OF METAL IONS DURING NP PREPARATION

NPs are extremely small sized elements that are either naturally occurring or engineered which exhibit unique and valuable physical and chemical properties. At the size of nanoscale, particles display improved catalytic, magnetic, electrical, optical, chemical, and biological properties (Letchumanan *et al.* 2021). Due to these unique physiochemical properties, NPs show versatile scaffolds for functionalization with biomolecules. Certain NPs, such as gold and magnetic NPs, respond to external stimuli achieving a spatiotemporal controlled release of macromolecules. For these additional reasons, NPs from the last two

decades successfully tested and applied in medicine and pharmacology, especially for diagnostic or therapeutic purposes (Sanzari *et al.* 2019). Generally, NPs are prepared using commercial physical and chemical methods. The chemical methods such as electrochemical, precipitation, sonochemical route, sol-gel, the hydrothermal approach, chemical bath deposition, chemical reduction, chemical vapor deposition use harsh reducing agents, toxic chemicals, organic solvents and dangerous by-products. The use of harmful chemicals as reducing agents leads to the absorption of noxious chemical and subsequently causing the NPs to be toxic (Letchumanan *et al.* 2021).

With a long-known fact that plants can reduce metal ions on their surface and in various organs, studies have unveiled the mechanism of plant-derived molecules that can bind and reduce the metals during the preparation of NPs. Compounds such as terpenoids, polyphenols, sugars, alkaloids, phenolic acids, and proteins derived from plants were found to play a pivotal role in the bio-reduction of metal ions and may vary in their concentrations in plants. This can partially explain the morphological diversity of NPs with various forms such as triangles, hexagons, pentagons, cubes, spheres, ellipsoids, nanowires, and nanorods (Makarov *et al.* 2014).

Figure 1 depicts the mechanism of metal ion reduction by plant derived compounds. Overall, the mechanism of NP formation in plants and plant extracts takes place in three steps. 1) the activation stage where the reduction and nucleation of the metal ions and atoms takes place and 2) the growth stage during which the small NPs amalgamate into large particles by means of heterogeneous nucleation and growth followed by further reduction; a process referred to as Ostwald ripening accompanied by the thermodynamic stability of NPs and 3) finally the termination stage where the shape of NPs is determined (Glusker *et al.* 1999, Si and Mandal 2007). Among the several mechanisms of reduction of metal NPs by plants, antioxidant activity is one major device employed by plants compounds for the conversion of metals from noxious to innocuous NPs. Natural polymers derived from plant such as terpenoids are the five-carbon isoprene units that have strong antioxidant activity. Eugenol, the main terpenoid of *Cinnamomum zeylanisum*(cinnamon) extracts was found to reduce metal ions (HAuCl_4 and AgNO_3) through antioxidant activity. Dissociation of a proton of the eugenol OH-group results in the formation of resonance structures capable of further oxidation. The reduction of metal ions through flavonoids were found to occur during their tautomeric transformations from the enol-form to the keto-form during which they release the reactive hydrogen atom that can reduce metal ions to form nanoparticles. Example of such mechanism include the *Ocimum basilicum*(sweet basil) extracts where the flavonoids luteolin and rosmarinic acid when transform from the enol- to the keto-form plays a crucial role in formation of silver nanoparticles from Ag ions (Ahmed *et al.* 2010). In addition to reduction, flavonoids such as quercetin can chelate the metal ions with their carbonyl groups or π -electrons.

Studies have shown that monomers (linear or that contain aldehyde groups) of plant sugars were found to be good reducing agents of metal ions. Monosaccharides like fructose that comprise a keto-group can be active as antioxidants only when they undergo a series of tautomeric transformations from a ketone to an aldehyde. The disaccharides and polysaccharides also can have antioxidant activity provided that the monomer present can adapt to an open chain form to provide access to an aldehyde group. It is now believed that the mechanism involved here is the that the sugar aldehyde group is oxidized that leads to the

reduction of metal ions in the synthesis of NPs. Next to plant derived sugars, amino acids were found to have reduced capability of metal ions. Although a variation in the extent of reduction exists among individual amino acids, all the naturally occurring α -amino acids were found to reduce metal ions during the formation of NPs (Tan *et al.* 2010). Amino acids can bind to metal ions through the amino and carbonyl groups of the main chain or through side chains or through nitrogen atom. Other side chains binding metal ions include the thiol (cysteine), thioether (methionine), hydroxyl (serine, threonine, and tyrosine), and carbonyl groups (asparagine and glutamine) (Gluskaret *al.* 2014; Makarov *et al.* 2014). In addition to individual amino acids, peptides and proteins were found to be used in the synthesis of NPs where the reducing capability depends on the free amino acids present in the peptide or protein molecules. Above all, pH and temperature of the plant extracts were found to influence the extent of reduction of the metal ions (Makarov *et al.* 2014).

III. APPLICATION OF PLANT DERIVED NANOPARTICLES

Plant derived nanoparticles have wide range of application. Figure 2 shows the pictorial representation of various fields, where these NPs are applied.

IV. NANOTECHNOLOGY IN FOOD INDUSTRY

Food processing transforms raw food ingredients into a palatable form with long shelf-life and in turn, ensure efficient marketing and distribution systems for the enterprise. Importantly on the other hand, fresh foods, like the vegetable and fruits require robust logistics for their transportation from source to consumer. The major challenge that the food processing industries face is in the development and implementing systems to provide high quality food, nutritious and safe and hygienic, environmentally acceptable, and sustainable food (Neethirajan and Jayas 2011, Dikshith *et al.* 2021). One single solution to many challenges is introduction of nanotechnology in food industries. As witnessed in the previous years, nanotechnology has made tremendous contributions in food technology and improved production processes to provide products with better characteristics and new functionalities in the food and bioprocessing industries. Nanoparticles (NPs), nanocomposites (NCs), nanoclays (NCs), nanoemulsions (NEs), nanosensors (NSs), and nanostructures (NSTs) are some of the important nanomaterials that have been used in food packaging and preservation (Agriopoulou *et al.* 2020). Since there are several toxicological risks involved with the use of NPs in food system, we emphasize on the use and development of plant derived NPs concerning the human health.

1. Plant-Based Nanoparticles in Food Preservation and Packaging: The main goal of food packaging is preservation and safety, environmental concerns and tamper proofing. There are different technologies that have emerged in recent years and are named as active and smart packaging that improve the shelf-life quality of the food products. Food preservation systems with antimicrobial materials provide advanced barrier properties to the food. NPs made of materials such as starch and sorbic acid-based films are being utilized as packaging materials to inhibit the growth of microbes and are also effective due to their high surface-to-volume as well as enhanced surface reactivity. Next to these, metal and metal oxide nanoparticles that are commonly used in food packaging applications include silver (Ag), zinc oxide (ZnO), titanium dioxide (TiO₂), and aluminium oxide (Al₂O₃) nanoparticles. The common selective usage of these inorganic

metal-based NPs in food packaging is due to their improved tensile strength, gas and UV barrier properties, ethylene-scavenging, and antimicrobial activities. The method of green synthesis of inorganic nanoparticles is preferred for their application in food as physical and chemical synthesis involve toxic chemicals and extreme reaction conditions (Reviewed in Shabnam *et al.* 2020, Dikshit *et al.* 2021)

Zinc oxide (ZnO) is one of the most suitable nanomaterials for food application as they have achieved the generally regarded as safe (GRAS) status and possess antimicrobial properties. Usually, ZnO NPs are synthesized by hydrothermal or sol-gel processes and the green synthesis by reducing the zinc salt using plant extracts that is inexpensive. Kumar *et al.* (2020) have prepared the chitosan and gelatin nanocomposite hybrid films containing green synthesized ZnO NPs using the fruit extracts of *Cassia fistula*. The synthesized polyhedral ZnO NPs size ranged from 20–40 nm was found to have significant antimicrobial activity against *E. coli*. The study claimed that the developed hybrid nanocomposite has potential to be used as biodegradable alternative for postharvest packaging of fresh fruits and vegetables.

Among the trace elements required for the human body, Selenium is an essential trace mineral involved in the maintenance of health and growth and has various physiological roles. NPs that are derived from selenium have a potential application as biocide in biopolymers due to their less toxicological roles, protection of cells from free radicals and increased biological and satisfactory bioavailability compared to the selenium element. Since the preparatory methods of SeNPs require the use of acidic pH, high temperatures as well as strong chemicals, these NPs are not suitable for their use in food industry (Wadhvani *et al.* 2016, Ndwandwe *et al.* 2020). Although methods for green synthesis of Se NPs with microorganisms is available, the disadvantages with the use of microbes in the synthesis of SeNPs include pathogenicity of bacteria, longer process times and elaborate post-harvest steps (Shah *et al.* 2015, Ahmed *et al.* 2016). Thus, the synthesis of SeNPs using plant extracts is more feasible and thus has an advantage of no culturing and maintenance of cells, cost effective and are environmentally friendly (Reviewed in Ndwandwe *et al.* 2020).

Although SeNPs have been utilized in therapeutic aspects, in recent years they have been promoted for their use in food preservation through food active packaging. Veral *et al.* (2016) have demonstrated that SeNPs synthesis using a solution-phase approach based on the reduction of selenite with ascorbic acid in the presence of different stabilizers such as chitosan, a poly(D-glucosamine) or an ethoxylated non-ionic surfactant (Triton X-100 (toctylphenoxyethoxy-ethanol)), isotridecanol ethoxylate, and/or 2,4,7,9-tetramethyl-5decyne-4,7-diol ethoxylate that had high antioxidant activity when used in meat and shelf life of hazel nuts. Jamróz, Kopel, *et al.* (2019) evaluated nanocomposite films of furcellaran and gelatin loaded with different concentrations of SeNPs and reported the preservative effect of fresh kiwis.

AgNPs that have found applications extensively in various fields and can find a profound position in food sector. *In vitro* antioxidant and antibacterial activities of green AgNPs synthesized from *Dillenia indica*, *Morinda pubescens*, *Ceropegia thwaitesii*, *Helicteres isora* root extract (Inbathamizhet *et al.* 2013, Singh *et al.* 2013, Bhakya *et al.* 2015, Muthukrishnan *et al.* 2015). AgNPs synthesized from *Argyrea nervosa* showed

antibacterial and antifungal activity of silver nanoparticles was assessed against *Staphylococcus aureus*, *Bacillus subtilis*, *Aspergillus niger*, *Escherichia coli* and *Pichia pastoris* (Thombre *et al.* 2014). Similar work carried out by Niraimathi *et al.* (2013) showed that AgNPs from aqueous extract of *Alternanthera sessilis* Linn. showed antibacterial and antioxidant activity. The work attributed that phytochemical such as alkaloid, tannins, ascorbic acid, carbohydrates, and proteins present in the extract serve as effective reducing and capping agents for converting silver nitrate into NPs. The work carried out by Mohanta *et al.* (2017) reported the biosynthesis of AgNPs from leaf extract of plant *Protium serratum* which had potential antibacterial activity against food borne pathogens such as *Pseudomonas aeruginosa*, *Escherichia coli* and *Bacillus subtilis* and claimed that these NPs can find specifically as antibacterial agent in food packaging and preservation to combat against various food borne pathogenic bacteria. Such antibacterial activity was also found against food pathogens of AgNPs that were derived from *Cinnamom zeylanicum* bark Extract (Satishkumar *et al.* 2009) and antioxidant acidity of those derived from *Sambucus nigra* L. fruits extract (Moldovan *et al.* 2016).

In addition to Ag, AuNPs were also evaluated for the preservative properties by various researchers. The green synthesis using *Indigofera tinctoria* leaf extract mediated of silver and gold nanoparticles were shown to have anticancer, antimicrobial, antioxidant, and catalytic properties as evaluated by Vijayan *et al.* (2018) and antibacterial activity of Ag and AuNPs extracted from root extract of *Zingiber officinale* (Velmurugan *et al.* 2014). Patra *et al.* (2015) has shown proteasome inhibitory activity, antibacterial, and antioxidant potential of AuNPs extracted from *Citrullus lanatus* rind.

- 2. Mechanism of NP Activity in Food Preservation:** Food security or protection means that public of a country, city, village, or family should have physical and inexpensive access to adequate, safe, and nutritious food for a healthy life. With the steeping increase in population, ensuring an abundant and safe food call for a new initiative. Technology development is required not only for intelligent farming but also to reduce food waste as well as provide safety to the food product. With the advancement in nanotechnology, nanotechnological applications are now not limited to the production level but have been extended to all the food attributes such as product quality, consumer acceptance and resource use efficiency.

In the interest of protection of food during packing and storage, smart nano-packing is efficient in detecting food spoilage and extending the shelf life by releasing the nano-antimicrobes. The functionalized engineered NPs (FEN) used in packing generally bind to the matrix and provide mechanical strength and also act as barrier towards the movement of gases, volatile compounds or moisture. They also provide heat resistance to the food material while providing barriers against oxygen, carbon dioxide, UV radiation, and volatile substances (Sekhon 2010). Next to FEN, nanolaminates are thin food-grade films that are physically and chemically bonded and are used for packing fruits, vegetables, chocolates, candies and baked food. The foods are coated with these nanoaminates either by dipping or spraying and are absorbed either by electrostatic attraction between the food and the adsorbing substance. These laminates protect the food from moisture, lipids, and gases and improve texture by serving as carriers of color,

flavour, antioxidants, nutrients and antimicrobials (Cagri *et al.* 2004, Cha and Chinnan 2004, Shrivastava and Dash 2012, Shabnam *et al.* 2020).

Keeping in mind the environmental concerns, safety and tamper proofing, the role of packaging is not just confined to preservation and thus various technologies have emerged for packing such as smart and active packing that improves the shelf life and quality of food products. Active packaging is defined as a packaging food product so that the food, packing material and the environment are in continuous contact with each other and the shelf life is enhanced while maintaining the quality of the food product. The main role of NPs in active packaging is their antimicrobial effects along with other effects such as oxygen scavenger, ethanol generating system, ethylene remover, carbon dioxide generator, etc (Shabnam *et al.* 2020). The antimicrobial effect of the NPs used in food packing produce reactive oxygen species (ROS) thus damaging the microbes on the surface of the food and the packing material. AgNPs work by attaching to the surface of the bacterial cell, degrade the lipopolysaccharides (LPS) of the membrane and damage the DNA. The Ag⁺ ions bind to the binds to the electron donor group such as sulfur, oxygen and nitrogen and this inhibits the ATP synthesis and DNA replication and leads to bacterial cell death (Li *et al.* 2008; Karimi *et al.* 2018). In addition, the NPs with TiO₂ acts as photocatalytic disinfecting agent causing peroxidation of the phospholipids of the cell membranes of microbes (Maness *et al.* 1999; Chawengkijwanichet *et al.* 2008).

- 3. Current Strategies of Using NPs for Food Quality, Processing and as Sensors:** Although the food preservation is the major concern for the food sector, maintaining/improving the quality of the food is the next greatest challenge for food bioprocessing industries. With the advent in nanotechnology, the detection or indications of food spoilage is now possible with the incorporation of NPs, to detect the spoilage of food components, control the quality and for the detection of the abuse at the source or during the production (Lu and Bowels 2012).

The use of the conducting polymer NPs are being used as sensors as they respond to analytes and volatiles in the food storage environment and thus detect the spoilage of the product. These NPs based biosensors can participate in combining the fields of material science, molecular engineering, chemistry, and biotechnology and can increase the sensitivity and specificity of biomolecule detection (Reviewed in Shabnam *et al.* 2020). As the main aim of the nanosensors in food technology is the reduction in time pathogen detection, the biosensors can be directly place in the food to detect the release of chemicals, respond to changes in the temperature, humidity in storage rooms and oxygen exposure level, microbial contamination, or food degradation (Bouwemeester *et al.* 2009)

In addition to use of NPs in maintain or sense the quality of the food product, the current applications of NPs in food industry include their use as nano-emulsions, surfactant micelles, emulsion bilayers, and reverse micelles for developing the texture or nutrients of the food. “Nanococleates” meaning a “snail with a spiral shell” derived by adding calcium ions to small phosphatidylserine vesicles to influence the formation of discs which are then fused to large sheets of lipid molecules and finally rolled up into nanocrystals. These are designed to protect micronutrients and antioxidants from degradation during processing and storage. In addition, nanoencapsulation is another area essentially used in delivering of susceptible foods. It can be used to mask the taste and

odour of tuna fish oil to its rich omega-3 fatty acid content or deliver live probiotic microbes for healthy metabolic function.

- 4. Challenges that Demand for Plant Derived NPs in Food Industry:** In the food industry, the application of nanomaterials is broadly classified as food packaging, food processing and nano sensors. In food packaging, the toxicological risk involved is the phenomenon of migration, as well as the occurrence of toxic effects on the exposed human body. In food processing the nanostructures are used as food additives which are the carriers of nutrients, anticaking agents, antimicrobial agents, fillers for improving the mechanical strength and durability of the packaging material, etc. In addition, the nano sensing can be applied to achieve better food quality, safety, and the detection of pathogens.

Nanotechnology is proven impactful at every stage of food manufacturing, enhancing shelf-life, nutrition, quality control, and smart packaging. However, the unregulated applications of NPs can pose potential risks to human health and environment. Numerous studies have demonstrated the toxicological effects of NPs on biological systems. For the increased use of NPs in food industry there is a great concern for the development of biocompatible, safe, and nontoxic nanostructures. This is because long-term exposure to nanoparticles can cause oxidative stress in human cells, kidney and liver damage, and DNA damage. Phyto nanotechnology uses simple, green, and cost-effective protocols to synthesize nanomaterials from plants/plant extracts. The method is economical and can be scaled up easily to meet large-scale demand. Soon, nanomaterials obtained from plants should be exploited more and more for the food processing industry (Agriopoulou *et al.* 2020, Shabnam *et al.* 2020, Dikshit *et al.* 2021)

V. ADVANCED TREATMENT IN CANCER USING PLANT-BASED NANOPARTICLES.

Next to heart diseases, cancer is the second leading cause of death of all ages. There are various ways to treat cancer such as surgery, radiotherapy, usage of drugs and any combination of these treatments (DeVita and Chu 2008, Przystupski *et al.* 2019). Among these, conventional chemotherapy remains the foremost form of treatment even for the advanced cancers. However, there remains challenges with chemotherapy which includes the toxicity of the drugs, low selectivity of the cells of target, various side effects of the drugs and due to the development of resistance to the drugs. Thus, there is a dire need to improve the delivery strategies of the drugs for a possible therapeutic response.

With the persistence of the above-mentioned challenges of chemotherapeutic drugs, researchers have been looking for alternatives for drugs that are less toxic and have the same potential in treating cancer as the conventional cancer drugs. The best possible replacements were the phytochemicals from plants that have shown to regulate the cellular and molecular events including apoptosis, cell proliferation, cell cycle, DNA repair, differentiation, and metastasis (DiMarco-Crook *et al.* 2015, Lall *et al.* 2015, Baena *et al.* 2016). Despite these incredible exertions in preclinical settings, the use of the phytochemicals in cancer has been only a limited success. Reasons include the inefficient delivery of the natural agents to the target cells due to their poor watersolubility, their chemical instability in the biological environment, poor pharmacokinetic characteristics of certain phenolic compounds arising

from rapid metabolism, toxicity due to poor solubility and stability, inefficacy, and low tissue distribution. Hence, it has been imperative in cancer treatment to develop novel strategies that can ameliorate these setbacks of the potential plant phytochemicals (Wei *et al.* 2019). In this scenario, the development of inorganic nanoparticles has created new formulations to maximize the potential use of phytochemicals. In several studies the synthetic nanoparticles were utilized as delivery vehicles as these are comprised of siRNAs, proteins, and pharmaceutical agents (Cho *et al.* 2008, Laroui *et al.* 2014). Although these nanoparticles have been proposed and used in drug delivery, nanoparticles have suffered from limitations including their toxicity, insufficient tissue distribution, little oral bioavailability and large-scale problems have hindered and limited their use in clinical applications (Cho *et al.* 2008, Wang *et al.* 2013). To overcome these barriers, studies have looked towards the development of plant-based nanoparticles (Zhang *et al.* 2017).

1. Phyto-Engineered Synthetic Nanoparticles for Cancer Treatment: Among several inorganic metals, gold (Au) and silver (Ag) have been used in infection treatment as they possess antibacterial, antimicrobial, and anticancer activities and also possess low cytotoxicity, high surface area to volume ratio and stability that support them for a better candidate for chemotherapy and immunotherapy in cancer treatment (Sindhu *et al.* 2011, Mousavi *et al.* 2018). Since the initial Au and Ag NPs that were synthesized using the chemicals and solvents that has a negative consequence on environment and human health, simpler synthesis via green chemistry has become the foremost importance. AuNPs synthesized using Curcumin (Cur-AuNPs) are the most studied Phyto fabricated synthetic NPs and it was found that Cur is the well performing reducing agent to produce functional AuNPs (Singh *et al.* 2013; Singh *et al.* 2017). It was found that Cur-AuNPs are potential in inducing apoptosis in colon (HCT-116) and breast (MCF-7) cancer cell lines (Elbialy *et al.* 2019, Vemuri *et al.* 2019). In addition to curcumin, quercetin reduced Au NPs (Qc-NPs) were found to inhibit epithelial-mesenchymal-transition (EMT), angiogenesis, invasion via epidermal growth factor receptor (EGFR)/vascular epidermal growth factor receptor (VEGFR)-2-mediated pathway and induce apoptosis via inhibiting EGFR/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)-mediated pathway in breast cancer cell lines (MCF-7 and MDA-MB 231) (Balakrishna *et al.* 2016, Balakrishna *et al.* 2017). Similar to AuNPs, AgNPs that were produced with green synthesis are cost effective, biocompatible and eco-friendly. Unlike in the synthesis of AgNPs, thought the reducing bioactive compound is not known, AgNPs treated with the plant extract (*Piper longum*) were found to have anticancer effect of Hep-2- cell lines (Jacob *et al.* 2012). Further, the Cur and EGCG-coated AgNPs conjugated on serum proteins were found to be stable and potential biosensors where each of the element in this complex showed anticancer ability (Abraham *et al.* 2018).

Next to Au and Ag NPs, copper (Cu) and copper oxide (CuO) NPs were reported to be employed as anticancer agents apart from antimicrobial, antifungal, and anti-inflammatory agents, and therapeutic agents for wound healing. Since the Cu free ions are toxic to humans, plant based green synthesis of Cu and CuO NPs were generated using different parts of the plants. Given the advantages of plant-based Cu/CuO NPs in the ease of production and eco-friendly, the plant-based CuNPs were found to be more efficient in suppressing various cancers compared to commercial Cu NPs (Detailed review by Letchumanan *et al.* 2021). Apart from conventional Cu based NPs, several studies have reported the anticancer effect of plant-based Cu NPs particularly, breast, cervical, colon,

skin, gastric, liver, blood, lung, ovarian, etc (Letchumanan *et al.*2021). Based on the studies conducted, the antioxidant property of Cu NPs and CuO NPs produced from *Matricaria chamomilla* flower extract, leaves of *Azadirachta indica*, *Hibiscus rosa-sinensis*, *Murrayakoenigii*, *Moringa oleifera*, *Tamarindusindica*, *Eclipta prostrate*, and *O. europaea*.

- 2. Mechanism of Action of NPs in Tackling Cancer:** The advantages of the NPs due to their small size, variety of physiochemical properties are employed to bind and carry either the genes or drugs to the site of target in treating human diseases. However, today we find that NPs themselves serve as anti-cancerous agents where they not only enter the cell at the site of injection but also reach distant sites in the human body through various mechanisms (Connor *et al.*2005). NPs from many different compositions such as metals, metal oxides, carbons, and quantum dots and etc show cytotoxicity in biological systems and this is in turn dependent on the NP composition, concentration, size and surface charge, surface area, functionalization, and other factors (Mohammadinejad *et al.*2019). There is numerous study that report the effect of plant mediated Cu/CuO NPs to have anti-cancerous effects particularly towards breast, cervical, colon, gastric, blood, liver, lung and ovarian cancer (Reviewed by Letchumanan *et al.*2020). One of the studies conducted by Rehana *et al.*(2017) analysed the plant derived CuNPs from various plants sources such as *Azadirachta indica*, *Hibiscus rosa-sinensis*, *Murrayakoenigii*, *Moringa oleifera*, and *Tamarindus indica* demonstrated different levels of cytotoxic effects on various cancer cells (MCF-7, HeLa, Hep-2, and A549). The study found that the cytotoxicity was dependent on the contents of proteins, amino acids, carbohydrates, higher flavonoids, glycosides, phenolic compounds, saponins, and tannins. This explains the difference of varied effect of NPs. A plethora of studies have demonstrated the anti-cancerous activities of several inorganic of plant derived NPs. However, we are still far in understanding the mechanism of the mode of action of NPs in treating cancers. Based on the available data, we present here the various mechanisms that were shown by different authors.

Programmed cell death is defined as any form of cellular suicide governed by intracellular programs that induce apoptosis, necroptosis, autophagic cell death and ferroptosis. In general, PCD works as an intrinsic strategy to balance cell survival and cell death and are strictly followed in normal/ healthy cells. However, the rules of the PCD pathways are irregular in cancer cells which help to circumvent cell death and leads to uncontrolled cell proliferation named cancer. Understanding these pathways is interesting and developing strategies to stop the uncontrolled growth is vital that helps to develop anti-cancerous agents to combat cancer. Although there are several tactics developed by various studies, one of the interesting features is NPs which can exhibit anticancer characteristics on their own by inducing cytotoxicity in cancer cells by triggering different forms of PCD through generation of ROS.

- 3. Mechanism of NPs Triggering Necroptosis:** Necroptosis is a regulated process of cell death that involves ligand binding to TNF (tumor necrosis factor) death domain receptors. Targeting necroptotic cell death in cancer cells has possible therapeutic benefits and it is a proinflammatory form of PCD. The inflammatory responses induced by necroptosis can boost immune-mediated anticancer effects (Mohammadinejad *et al.*2019, Sepand *et al.*2020). NPs could trigger necroptosis and among the various mechanisms, the dominant pathway is the involvement of ROS that could cause the reduced mitochondrial

membrane potential and DNA damage and leads to cellular fate towards the necrotic cell death of cancer cells (Lu *et al.*2015). There are other mechanisms where NPs could induce necroptosis in cells. One of these include the germanium NPs that elevate calcium levels in the cell leading to ROS generation and subsequently leading to necroptotic cell death (Ma *et al.*2011). Silica NPs through ROS production trigger apoptosis and necroptosis by the elevation of expression of Fas/FasL/RIPK1/FADD/caspase-8/caspase-3 and RIPK3/MLKL via the induction of necroptosis (Ren *et al.*2016). Another mechanism in NP-mediated necrosis is via disintegration of lysosome structure, cytoskeletal collapse, significant changes in actin and tubulin structure, that leads to the leakage of toxic substances into the cytosol or trigger necroptosis that ultimately leads to cell death (Reviewed by Sepand *et al.*2020).

- 4. NP Induced Mechanism of Apoptosis:** Apoptosis is first introduced to describe the cell death in hepatocytes which involves the physiological changes such as membrane blebbing, cell shrinking, chromatin condensation and inter-nucleosomal DNA fragmentation, and formation of small vesicles named apoptotic bodies. Apoptosis was found to occur in 3 different pathways, involving death receptors, mitochondria, or the endoplasmic reticulum (ER). While the extrinsic pathways for apoptosis induction includes the extrinsic apoptotic pathway, the superfamily of death receptor transmembrane proteins, including TNFRSF1A/TNFR1 (TNF receptor superfamily member 1A), FAS/CD95 (Fas cell surface death receptor), TNFRSF10A/TRAILR-1 (TNF receptor superfamily member), the intrinsic pathway of apoptosis is initiated by mitochondrial membrane permeabilization, various types of oxidative stress including hypoxia, DNA damage, and growth-factor deprivation. The third pathway of apoptosis is activated by various injuries from ER stressor. It has become evident that there is complex and close association of the cross talk between different apoptotic pathways where the extrinsic pathway can activate the mitochondrial pathway, and alternatively the cell death receptor pathway may activate the intrinsic pathway of apoptosis. Among the wide variety of signals that can induce apoptotic pathways, NPs can induce apoptosis via organelle dysfunction, ROS generation, ER stress and DNA damage (Reviewed in Mohammadinejad *et al.*2019).
- 5. Mechanism of Autophagy Induction by NPs:** Autophagy is an adaptive process in cells, serving a cytoprotective function that helps in survival during nutrient starvation and ATP deficiency. Under stressful conditions, extensive autophagy will result in irreversible cellular damage and ultimate cell death (Bhutia *et al.*2013). Autophagy is regulated in cancer cells by mTOR by means of anabolic biosynthesis stimulation and through AMPK by activation of catabolism via lysosomal degradation of macromolecules pathways in response to tumour metabolic contexts. There are several studies that show that inhibition of autophagy by means of deletion of autophagy-related gene Beclin-1 or through accumulation of autophagy adaptor protein p62/SQSTM1 or via mutant p53 protein associated with tumorigenesis and also poor prognosis of cancer patients (Shen *et al.*2008, Moscat *et al.*2009, Liu *et al.*2011). Different NPs were known to induce autophagy these include the metals, metal oxides, SiNPs, CNPs such as graphene oxide (GO) fullerene and certain heavy earth metal NPs (Yu *et al.*2009, Bhutia *et al.*2013). Exopolysaccharides (EPS) coated Ag-NPs were found to exhibit cytotoxicity towards difference cancer cell lines via the elevation of ROS and subsequently the induction of apoptosis, autophagy, and cell death (Buttacavoli *et al.*2018).

6. Plant Based Nanoparticles in Gene Therapy: The recently emerged technology alternative to conventional treatment of disease is gene therapy that operates through the introduction of genetic material. Building on the central dogma that genetic information flows from DNA to RNA to proteins, researchers have attempted to induce therapeutic effects by replacing defective proteins through introduction of DNA or mRNA that can express normal proteins. Among the various strategies to combat diseases through gene therapy, RNA interference by small inhibitory RNA (siRNA) or microRNA (miRNA) has also become a major tool that has shown a great potential in various disease that were once considered hard to treat with drugs (Kin *et al.* 2020). The ideal of genome surgery, in which the harmful genes are replaced by normal genes is a more advanced form of gene therapy in that it leads to changes in the genome either by DNA cleavage at a desired gene locus and restoration through non homologous end joining (NHEJ) or suppression of the prevailing genes (Ran *et al.* 2013, Lim *et al.* 2020, Xia *et al.* 2020).

In the concept of gene therapy, the treatment strategy required the delivery of short fragment of DNA/RNA into cells. The oligonucleotide consists of 8-50 nucleotides of DNA or RNA that could be an anti-sense oligonucleotide, a complementary chain of target mRNA to block a specific protein. It can also act as an aptamer that has a strong affinity towards certain molecules. In addition, the delivered short segments of DNA could act as splice-switching oligonucleotide, anti-gene oligonucleotide, small interference RNA (siRNA), ribozymes, etc. To treat diseases through gene therapy, tremendous efforts are being devoted for as oligonucleotides are believed to demonstrate higher specificity, lower side effect, less cytotoxicity and lower possibility to cause drug resistance than small molecule drugs (Zang and Ge 2020)

With the successful inhibition of virus replication of peripheral cytomegalovirus retinitis in patients with AIDS demonstrated initially by Zamecnik and Stephenson in 1978 and later approved by FDA in 1998, several oligonucleotide therapies have been approved in the past 20 years (Bonn 1996, Stein and Castanotto 2017, The Vitravene Study Group 2002). However, there are several challenges that exists to hasten the development of oligonucleotide therapy which include 1) Single stranded DNA fragment instability due to nuclease degradation, 2) precise delivery of the genes to the target tissue, 3) Poor internalization of the oligonucleotides of the target cells due to their negative charge, 4) dose dependencies as lower doses result in insufficient therapies (Zang and Ge 2020). To overcome these difficulties, different strategies have been proposed which include the 1) Replacement of the skeleton of the DNA fragment used in gene therapy, 2) Conjugate oligonucleotides with functional ligands or polymers that could avoid uptake and clearance by cells of the reticuloendothelial system, 3) encapsulate DNA into nanocarriers. Although each of these strategies have their own advantages and disadvantages, one of the major drawbacks of using nanocarriers is their long-term toxicity and poor biodistribution which may hinder the gene therapy (Geary *et al.* 2002, Liu *et al.* 2012, Juliano 2016). Considering these facts, green/plant-based nanoparticles take the advantage in using oligonucleotide for curing diseases through gene therapy.

7. Plant Polyphenols as Green Nanoparticles for Gene Delivery: The delivery of siRNA-based therapeutics into cytosol has become a major challenge that limits the clinical translation. Even though there are several polymers that were developed for siRNA

delivery into cells, the toxicity exerted by these polymers have limited their efficiency and success. Shen *et al.*(2018)reported the formulation of nanoparticle prepared by entropy-driven complexation of siRNA with a green tea catechin ((-)-epigallocatechin gallate (EGCG)) to yield a negatively charged core, followed by coating low-molecular-weight polymers to form the shell. This supramolecular strategy was found to facilitate the polymers condensing siRNA into uniform nanoparticles which specifically down-regulates the target genes both *in vitro* and *in vivo*, and effectively diminishes chronic intestinal inflammation in an inflammatory bowel disease model. Remarkably, these nanoparticles were applied to several other topologies and chemical combination that provided a versatile drop down of the toxicity correlation of cationic polymers. This study has further facilitated in a series of efficient polyphenolic siRNA cargoes (Shen *et al.*2020).

The use of EGCG was further expanded the scope of nanocarriers for RNA delivery where this natural polyphenol from the green tea as “glutinous” can bind and protect the RNA molecules. Due to their innocuous nature, these nanoparticles are termed as “green nanoparticles” (GNPs) (Cheng *et al.*2014). Cheng and co-workers reported the low cytotoxicity of ECGC compared to the commercially available Trans Excellent-siRNA (TE) polymer and Lipofectamine 2000 (LPF) made from lipid, especially when delivering the much fragile single-strand ASO or anti-miRNA. They also showed that the ECGC could also be used to deliver the RNA molecules including siRNA and DNAzymes. These reports demonstrate the remarkable ability of polyphenols from plants and the facile way of preparation the the low cost facilitating the scale-up production of GNPs for gene therapy.

- 8. Plant Based Lipid Nanoparticles for Gene Delivery:** Lipids are important constituents along with proteins and carbohydrate in animals or plant cells. The most significant component of either plant derived nanoparticles (PDNPs), mammalian exosomes and liposomes are lipids. The uniqueness of PDNPs from mammalian cell derived exosomes and artificial liposomes is their decreased levels of phosphatidylcholine and percentage of cholesterol. Analytic results of active-ginger derived NPs revealed a cholesterol free lipid and comprised of 42% phosphatidic acid (PA), 27% digalactosyldiacylglycerol (DGDG), and 19% monogalactosyldiacylglycerol (MGDG). Although the cholesterol profile of NPs derived from grapefruit are different from active ginger, it is commonly considered that the plant derived lipids are cholesterol free as most of the dibble plants and vegetables lack cholesterol (Reviewed by Yang *et al.*2019).

A prerequisite to use PDNPs as drug delivery vehicles is to generate uniform sized nanoparticles. Zang *et al.*(2017)used the Blight and Dyer method to generate uniform sized siRNA-CD98/ginger-derived lipid vesicles with approximate size of 189.5 nm while Wang *et al.*(2013) could generate multiplayer flower-like NPs of 200 nm size from grapefruit using the same method. From the generated PDNPs, therapeutic agents such as siRNAs, DNA expression vectors and protein could be loaded to target different disease tissues (Zhang *et al.*2016). In addition, PDNPs were found to carry a considerable number of miRNAs where deep sequencing of ginger-derived NPs was found to harbour 125 different miRNAs of each containing 15- 27 nucleotides and *in silico* analysis predicted that 124 of these miRNAs could potentially target and regulate the expression of human genes (Zang *et al.*2016).

9. Plant Based Nanoparticles in Cell Science (Cell Labelling and Photoimaging): In the field of disease diagnosis and therapy, bioimaging techniques have provided a substantial platform. Since most of the diseases involve mechanisms at molecular level, understanding/ studying these illnesses in real time have become a major challenge to researchers. Although solutions to these tasks were shown by nanotechnology with the creation of fluorescent nanomaterials, they have downsides in biomedical applications as they are synthesized by high energy ion beam radiation, laser ablation and electrooxidation methods and are thus toxic in nature (Jha *et al.* 2014). Restrictions to currently accessible fluorescent probes like organic dyes, fluorescent inorganic/organic nanoparticles, and fluorescent proteins bioimaging using inorganic fluorescent nanoparticles are also imposed due to reduced membrane permeability and susceptibility to photo-bleaching and accumulation in the reticuloendothelial system. These situations demand for an urgent requirement for novel fluorescent materials with good biocompatibility, high fluorescence, and low toxicity (Zhang *et al.* 2012, Zhang *et al.* 2014).

Plant extracts assisted synthesis of inorganic nanoparticles has become a chosen way of synthesizing biocompatible nanoparticles for bioimaging and cell labelling. Using simple reduction technique, Sankar *et al.* (2016) have used *Curcuma longa* tuber powder in synthesizing fluorescent nanoparticles of silver, copper, and iron. The physicochemical properties of the synthesized metal nanoparticles showed that the silver nanoparticles had high fluorescence intensity. In addition, these synthesized NPs when used *in vitro* cell imaging using A549 cell lines showed that they can enter the cell without any further modification displaying their beneficial abilities in fluorescence-based cell imaging applications. An interesting work reported recently by Kotcherlakota *et al.* (2020) have shown the use of extracts of *Zinnia elegans* used in the synthesis of biocompatible gold (AuZE) NPs that found an application in non-invasive bioimaging in near infrared fluorescence imaging. The verification of the source of fluorescence showed that it originates from the fluorescence molecule present in the plant extract. These reports show that biosynthesized inorganic NPs open new directions for future research to explore these latest observations in the field of disease diagnosis and therapy.

Among the plant-based molecules for synthesis of biocompatible NPs, silica derived from natural silica sources such as corn cob, coffee husk, rice husk, sugarcane bagasse and wheat husk wastes have found applications as in designing NPs useful as biosensors, bioimaging, drug delivery and supercapacitors (Reviewed by Prabha *et al.* 2020). Meso-silica nanoparticles derived from rice husk were composited with green, fluorescent carbon dots that showed high drug loading efficiency and stronger fluorescence compared to carbon dots alone. In addition, rice husk-derived silica composite with rare earth elements, europium/gadolinium ions are found to be a good alternative for developing cost-effective bioimaging contrast agents (Araichimani *et al.* 2020).

10. Use of Plant Nanoparticles in Treating/Detecting Neurological Disorders: Disruption in function and structure of central nervous system or neurons is defined as the neurodegenerative disorders (NDs). This dysfunction leads to disabilities in thinking, movement, cognition and memory. The most prevalent NDs include Alzheimer's disease (AD) and other types of dementias; Parkinson's disease (PD) and PD related disorders;

Multiple sclerosis (MS); Huntington's disease (HD); and Amyotrophic lateral sclerosis (ALS). While genetic susceptibility, aging, lifestyle, nutrition, chemicals, specific viruses, and exposure to some environmental toxins are found to be the risk factors for NDs (Moradi et al., 2020). Since the current strategies for the treatment of NDs have adverse effects, the use of natural products sounds propitious. However, the major obstacle for the use of these products as therapeutic agents is exerted by blood brain barrier (BBB) of the brain. Thus, nanotechnology/ nanomedicine proves to be a superior drug delivery strategy for the management of NDs (Dwivedi et al. 2019). Nano formulations of these natural products is a better effective way to overcome such challenges and can enhance their biocompatibility (Moradi et al. 2020).

11. Plant Based Nanoparticles for Treating NDs: Plant extracted metal salts is the most common extracted strategy of preparing green NPs particularly for Ag and Au NP synthesis that are more secure in comparison to inorganic NPs. To treat AD with plant extracted Ag NPs, Youssif et al. (2019) evaluated the aqueous extracts of aerial parts of *Lampranthuscoccineus* and *Malephora lutea* F for reducing AgNPs and evaluated the neuroprotective potential of the NPs by assessing the antioxidant and cholinesterase inhibitory activity in rats. The study found that the nanosilver aqueous extracts of *L. coccineus* and *M. lutea* showed the highest anti acetylcholinesterase and antioxidant activity compared to the aqueous extracts of *L. coccineus* and *M. lutea*. The study also showed that these green AgNPs had the ability to cross the BBB and increase the level of acetylcholinesterase and decrease the level of oxidative stress. Using *in vivo* experiments to treat AD using nano formulations.

Ginkgo biloba is an ancient Chinese tree rich in flavanol glycosides, bilobalide, terpene trilactones, and varied forms of ginkgolides, and ginkgolic acid and is used that is used for medicinal purposes and is broadly used to improve the conditions of dementia in patients (Maurer et al. 1997, Luo 2001). *G. biloba* extracted with ethanol and finely grounded by wet and dry process was evaluated by Shinji et al. (2011) and the work showed that the rats with nanosized *G. biloba* extract administered showed a trend of acetylcholine release from cerebral cortical synapses and a greater amplitude of population spike at hippocampal CA1 pyramidal cell layer than the control rats.

Nanodroplet formulation of pomegranate seed oil (PSO) rich large concentrations of a unique polyunsaturated fatty acid, Punicic acid, among the strongest natural antioxidants was evaluated to improve Creutzfeldt Jacob disease (CJD) in TgMHu2ME199K mice. The study found that Nano-PSO treatment did not decrease PrP^{Sc} prions accumulation, but rather reduced lipid oxidation and neuronal loss, indicating a strong neuroprotective effect. In addition, Binyamin et al. (2015) who also used Nano droplet formulation of PSO also showed it could treat multiple sclerosis (MS) in mice. Similar work was carried out by Ismail et al. (2017a) who used nano emulsion of thymoquinone (TQ), a major active component of *Nigella Sativa* (Ranunculaceae) seed. The authors studied the antioxidant effect of TQ rich fraction in high-fat cholesterol diet rats and showed that administration of TQ nano emulsion decreased Ab40 and Ab42 levels by modulating APP processing, up-regulating IDE and LRP1, and down-regulating BACE1 and RAGE which otherwise has decreased activity without the nano formulations (Alam et al. 2012; Ishmael et al. 2017a). Similarly, it also improved memory deficits and

enhanced the total antioxidant status and significantly decreased the Ab expression (Ismail *et al.*2017b)

12. Plant Natural Products Nano Formulations for Treating NDs: Apart from using plant extracted NPs in treating NDs, the natural products derived from various plants have shown curative effect against NDs. However, due to certain drawbacks such as inappropriate pharmacokinetics due to limited absorption, negligible bioavailability and fast elimination has limited their effectiveness. Thus, to improve their pharmacokinetic abilities and biocompatibilities of these potential natural products, various studies have prepared NPs formulations through and evaluated their probable outcomes through *in vitro* and *in vivo* studies.

13. Curcumin: Curcumin is one of the most popular natural products derived from *Curcuma longa* L and was known to have pharmacological targets which include transcriptional factors, growth factors, genes and cytokines (Moradi *et al.*2020). Despite its natural therapeutic properties, certain disabilities of curcumin have been increased with its modification with NP preparations. While curcumin loaded lactoferrin NPs were found to protect SKN-SH dopaminergic cells from rotenone-induced neurotoxicity (Bollimpelli *et al.*2016), several *in vitro* studies showed that the NP preparation of curcumin such as lipid- polyethyleneglycolpolylactide (PEG)-Cur, Cur-derivative liposomes and anti-transferrin antibody liposomes were able to control or decrease the Ab oligomers or the fibril formation (Taylor *et al.*2011, Mathew *et al.*2012, Mourtaset *et al.*2014). Next to *in vitro* studies, *in vivo* studies conducted with curcumin-based NPs have been shown therapeutic effects over several NDs (Reviewed by Moradi *et al.*2020).

VI. PLANT BASED NANOPARTICLES IN AGRICULTURE.

The introduction of nanotechnology in agriculture has been proposed to enhance the crop protection from the previous way of redemption of harmful pesticides. It is also to formulate new pesticides that are nanotechnology based for ease application with controlled delivery on plants and grains. Thus, there is an increase in interest among scientists and extension agents to formulate nano-pesticides that consist of nano-sized particles of organic/inorganic constituents or other nano scale structures that have pesticide properties (Bergeson 2010). With agriculture being the most important source of human food, genome editing technology in plants has been used to produce plant with improved yields, with improved nutritional qualities and with higher resistance to pests and microbial diseases. However, the current genome editing practices that use DNA delivery in plants and tissue culture have certain limitations which include the time-consuming and complicated protocols, potential tissue damage, DNA incorporation in the host genome, and low transformation efficiency. To overcome these issues, the conventional DNA delivery systems were bypassed through the introduction of nanotechnology by means of nanoparticle-mediated gene delivery which enhances the transformation efficiency for both temporal (transient) and permanent (stable) genetic modifications in various plant species (Ahmar *et al.*2021)

Crop Development towards Pathogen Resistance

Insect pests, diseases and weeds cause substantial damage to the crops or agricultural produce causing huge amount of loss to the food quality. In this context, conventional

synthetic pesticides have been used widely beyond geographically and saved agriculture with their potential toxicity against pests and other diseases. However, with the accumulation of chemicals in the ground water, pest outbreak, insect resistance against pesticides, pest resurgence, health hazards to human beings, as well as domestic and wild animals have impeded the use of pesticides. The World health organization (WHO) has estimated the death of 20,000 people annually in the third world (Casida and Quistad 2000).

With the conventional pesticides showing disadvantages at various levels, the plant extracts were used as pesticides with an advantage of non-toxic to animals and humans. Plant derived metabolites such as alkaloids, terpenoids, flavonoids, phenol, glycosides and tannins show toxicity against pests at various levels. Some of the common examples of insect pests that could be controlled using plant extracts and powders include *Anopheles subpictus*, *Bacillus thuringiensis*, *Bacillus thuringiensis serovar kurstaki*, *Beauveria bassiana* and *Culex quinquefasciatus*, Mosquito and *Helicoverpa armigera*. Extracts from curative plants such as neem extract, *Acorus calamus*, *Annona squamosa*, *Vitex negundo*, *Gnidia glauca*, *Toddalia asiatica* and *Argemone mexicana*, *Calotropis procer* were found to have larvicidal and pesticidal activity. Several such examples of plant extracts from various plants used for infestation control were the upper choice from the ecological point of view (Reviewed by Lade *et al.* 2017). However, indiscriminate use of these plant derived formulations as pesticides would lead to the development of resistance that led to an emergence of novel products to tackle the pest situation. Thus, there is a requirement of another alternative to explore for minimizing the pest effects on crop plants.

With nanotechnology being applied in numerous fields, it has also been proposed to a considerable extent in the agriculture such as fertilizers, pesticides, plant protection biomass, bio composites and agrochemical industries. Thus, nano-based pesticides such as Ag, Cu, SiO₂, ZnO and nano formulations show better broad-spectrum pest protection efficiency, reducing water, soils, and environmental pollution in comparison with conventional pesticides (Ladet *et al.* 2017). Among the inorganic NPs that are reduced with plant extracts are used as biopesticides in agriculture. Among these several varieties of plant extracts generating AuNPs and AgNPs were reported to have greater antimicrobial activity against both fungi and bacteria (Ali *et al.* 2019, Nishanthi *et al.* 2019).

The control of plant diseases caused by phytopathogens such as fungus and bacteria have been achieved by spraying green synthesis AgNPs derived from *Fusarium solani* (El. Aziz *et al.* 2015) evaluated their effect on fungi and found that 4% NP formulation caused complete elimination of the fungus compared to 1% solution that had no effect on any fungus. Similarly, the AgNPs synthesized from leaf extracts of *Rhizophora mucronate* showed potential larvicidal activity against *Aedes aegypti* and *Culex quinquefasciatus*, two vectors that affect workers in agricultural fields, causing dengue and filariasis (Gnanadesigan *et al.* 2011). In another study, AgNPs synthesized from *Aristolochia indica* L. leaf extract showed antifeeding activity against instar larvae of cotton bollworm/gram caterpillar, *Helicoverpa armigera* using various formulations. NP preparation of TiCl₄ derived from neem bark gum extract evaluated on two important polyphagous insect pests, *H. armigera* and *Spodoptera litura* (Fb.) showed 100% antifeeding activity in the larvae when used at 100 ppm (Kamaraj *et al.* 2018). Zahir *et al.* (2012) while studying the green synthesized AgNPs, found that nano formulations derived from *Euphorbia prostrata* Aiton leaves was the most effective with 100% mortality of the rice weevil, *Sitophilus oryzae* (L.). Similarly,

Sankar and Abideen (2015) who synthesized Ag and lead NPs from mangrove plant *Avicennia marina* (Forssk.) Vierh extract and reported 100% mortality in *S. oryzae* adults within 4 days of treatment.

VII. FUTURE PERSPECTIVES

In the wake of green chemistry technology, the alternative for the conventional chemical NPs have been proposed. The green nanotechnology warrants that the plant derived NPs are benign, hazardous free, free from toxicity and are inexpensive. In addition, the biological route of producing NPs has advantages; among the biological materials, the plants are abundant, easy to access, and are better source of numerous active compounds and has simplified processes.

Despite with all these well-known facts and advantages, there is still a lag, technical challenges and/or key issues to be addressed for the successful use of green NPs in different sectors. Given below are the key aspects for the successful development of green NPs.

- Increasing the awareness and importance for the use and developing plant-based NPs
- As plant-based NPs producing protocols results in NPs of various sizes and shape, protocols need to be standardized to ensure uniformity.
- Protocols need to be standardized to ensure maximum conversion of the salts to ions when preparing plant derived NPs from metals
- Active research needs to be conducted in terms of understanding various plant derived biologically active groups that attach to the NP with higher efficiency
- Knowledge needs to be increased towards the mechanism of synthesis, action, and stabilization of the biological NPs
- The final yield of NPs corresponding to the metal salt concentration, biological resources, parameters to overcome polydispersity need to be elucidated
- *In vivo* or clinical trials are still required to address the issues related to the use of plant-based NPs in biomedical applications or in food sectors including the distribution, clearance/excretion.

VIII. CONCLUSION

Herein we have provided a comprehensive data on the applications of plant-based nanoparticles in three important sectors such as agriculture, food and medicine that have intimate connection with human health. The use of NPs in food sector from food processing to preservation and in agriculture from manure to gene delivery in commercial plants as well as from diagnosis to gene therapy in human diseases shows the growing intimate association of NPs with human life. As the conventional methods of producing metallic NPs are toxic to the environment as well as the human and animal life, we highlight the studies that have supported the use of plant derived NPs. However, most of efforts are still at the root levels of investigation and had not been brought to the industrial or application stages. In this we highlight the future perspectives of NPs with strong suggestions and impose changes for developing NPs that are safe and biocompatible. Considering the advantage and disadvantages of NPs, researchers developing NPs need to underscore the existing and novel mechanisms of reduction of metallic NPs by each plant component. Developing such

biocompatible NPs may thus find their way in agriculture, food and medicine for a better human and environmental welfare.

ACKNOWLEDGEMENTS

DD is grateful to Mount Carmel College, Autonomous. This research has not received any other funds, grants, or other financial support.

Declaration of Interest Statement: The authors declare no conflict of interest.

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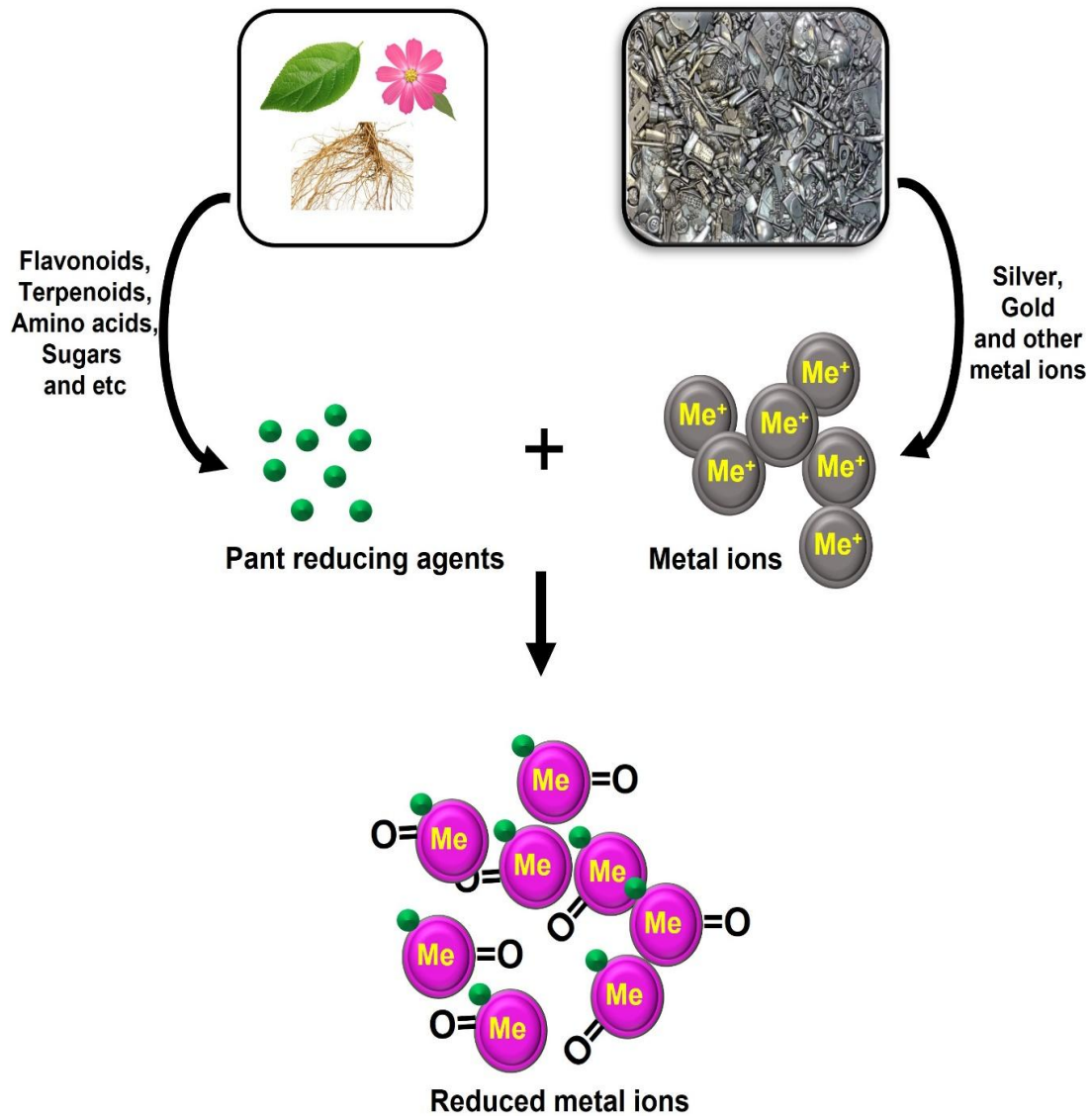


Figure 1: Mechanism of reduction of metal ions by plant metabolites

ADVANCED APPLICATIONS OF PHYTONANOTECHNOLOGY IN FOOD, AGRICULTURE, AND
MEDICINE AND ASSOCIATED CHALLENGES TO OVERCOME

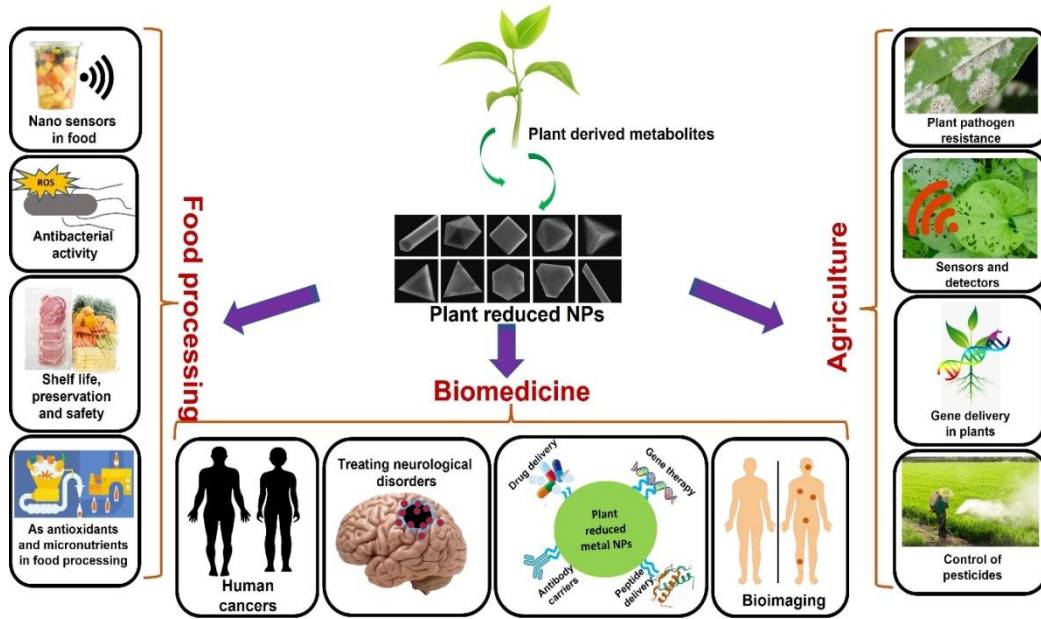


Figure 2: Applications of plant derived NPs in food sector, agriculture, and biomedicine.