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Selenium Nanostructures: Microbial Synthesis and Applications

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Due to considerable impact on day-to-day life through superior functioning of energy, medicine, electronics, sensors and space industries young researchers are being attracted towards nanotechnology/biotechnology field. Selenium (Se) is acting as an essential element in most of the organism and beneficial nutrient in higher plants. Se nanostructures (NSs) i.e. nanospheres or particles (NPs) and nanowires (NWs) have unusual properties compared to their bulk counterparts. It has seven-fold lower toxicity than its other biologically utilizable materials. Several physical & chemical methods are being applied for the synthesis of Se NSs, but development of eco-friendly routes is of considerable importance towards biological applications. Recently microorganisms are being reported for the synthesis of Se NSs by reduction of oxyions in anaerobic and aerobic environments. This review briefly proposes the recent developments in the microbial synthesis, characterization, synthesis mechanism of Se NSs along with non-biological (solar, sensor, photocatalysis etc.) and biological (anticancer, antioxidant, antiprotozoal etc.) applications. Advantages of Se NSs synthesized using green approaches, over commonly used, are explored.

1. Introduction

Nanotechnology, an interdisciplinary field, includes the understanding of biological, material, physical and chemical sciences for the development of variety of technologies. Nanostructures (NSs) including nanoparticles or nanospheres (NPs) and nanowires (NWs) are found to be structural and functional part of nanotechnology. These are materials of one or more dimensions in the order of 100 nm or less.[1] Nanostructured materials are being attracted considerable attention in recent years as they exhibit useful and unusual properties as compared to their polycrystalline counterparts. The physical and chemical properties like colour, melting temperature, conductivity, reactivity of metal NPs are mainly depend upon their sizes, shapes, compositions, crystallinities and structures.[2] NPs display high surface/volume ratio and are being used to build long lasting, cleaner and safer products for variety of applications in medicine, transportation and agriculture. Nanotechnology not only offers quality products but also improves the manufacturing processes.[3] Based on chemical composition, NPs are of two types i.e. carbon-based (fullerenes, carbon nanotubes, etc.) and inorganic. Inorganic NPs can further be categorized as metal oxides (zinc oxide, iron oxide, titanium dioxide, etc.), metals (gold, silver, iron, etc) and quantum dots (cadmium sulphide, cadmium selenide etc.).[4] NPs can also be categorized as engineered NPs (ENPs) and non-engineered NPs (NENPs). ENPs are, usually, produced intentionally by considering specific application. Their origin can be biological, like lipids, phospholipids, and lactic acid etc., or chemical, such as carbon molecules, silica and various metals etc. On the other hand, NENPs are obtained in undesired ways such as particles emitted as a byproduct; for example, during the combustion of fuels.[5] There are four types of NSs based on their dimensions that are 0D-nanoclusters, 1D-multilayers, 2D-nanograin layers, and 3D- bulk solids etc.[6] Se is one of the chalcogenides naturally occurs as selenate (SeO_4^{2-}) and selenite oxyions (SeO_3^{2-}, Se^{2-}) which can be reduced to elemental form Se^0 in the presence of an appropriate reducing agent. The reduction of soluble Se^{4+} and Se^{6+} by microbes to insoluble non-toxic elemental Se is an effective way to remove it from an environment.[7]

Variety of physical, chemical, biological, and hybrid methods are being used for synthesizing different types of NPs.[8, 9] Although physical and chemical methods are popular in the synthesis of NPs but in both methods toxic chemicals are required which greatly reduces their biomedical applications. Physical and chemical methods produce large quantities of NPs with finite sizes and shapes in a short time. These methods are complicated, costly, and resulting in hazardous toxic waste as byproducts; which are harmful not only to ecosystem but also human health too. Therefore, development of safer and eco-friendly methods for synthesis of Se NPs is of utmost importance to expand their biomedical applications. One of the choices in achieving this goal is to use microbial methods. NPs produced by biogenic enzymatic processes are far superior, in several ways, to those produced by chemical methods. With an enzymatic process which is also known as green synthesis, the use of expensive chemicals and high temperature can be eliminated. The "biogenic" approach is further supported by the fact that the majority of the bacteria inhabit ambient conditions of temperature, pH and pressure etc. The NPs generated through green processes revealed higher catalytic reactivity and greater specific surface area.[10] Biogenic synthesis of Se NPs is frequently achieved through the reduction of selenate/selenite in presence of bacterial proteins or plant extracts containing phenolic, flavonoids, alcohols, proteins and aldehydes etc. However, simple and reproducible bio-inspired

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method for preparation of stable Se NPs on large scale with potential applications is still missing. This review provides a brief overview of the current research activities that center on the microbial synthesis, characterization of Se NPs followed discussion on available mechanisms and plausible applications.

1.1Role of Se in mammals

Dietary Se metabolites are taken up into the cell where, together with the existing intracellular pool they become metabolized by different pathways. As a result of metabolic pathway, there is formation of selenide, which serves as the Se source for selenocysteine (Secys) biosynthesis. Fig.1a gives simplified view of Se metabolism in mammals. Most of the metals interact with proteins in the form of cofactor likewise Se can be incorporated into the polypeptide chain as SeCys amino acid. Proteins contain SeCys as an integral part of their polypeptide chain is known as selenoprotein. Selenoproteins are present in all the living entities, thirty different types of selenoproteins have been, so far, characterized.[11] Seventeen selenoprotein families together form a selenoproteome of human. It consist of glutathione peroxidases (GPx), thioredoxin reductases (TrxR), iodothyronine deiodinases, selenophosphate synthetases 2(SPS2), Sep15, SelH, SelI, SelK, SelM, SelN, SelO, SelP/SepP, SelR, SelS, SelT, SelV, and SelW etc. These selenoproteins have antioxidant properties and they, in addition, help in cellular processes like biosynthesis of dNTPs, in removing signalling peroxides, reducing oxidized proteins and membranes, regulating redox signalling, thyroid hormone metabolism, protein folding and selenium transportation. Summary of the human selenoproteins and their functions is presented in Fig. 1b.[11] The deficiency of Se is known to be associated with over forty diseases in human.[12]

1.2 Role of Se in plants

Se acts as beneficial nutrient in higher plants which is not as an essential element. Plant homolog of selenoproteins like glutathione peroxidase (GPX) does not contain SeCys, but contains Cys in their active sites.[13] Under low dosages it can stimulate the growth of the plant while at high dosages it can cause harm to plants.[14] Members of the genus *Brassica,* e.g. mustards and cabbages, normally known as accumulators, accumulate 0.1 % Se of their total dry weights. Plants belong to families *Fabaceae,* and *Asteraceae,* are only found on seleniferous soils and typically accumulate Se to level hundred-fold higher than the nearby vegetation in the field and are called as hyperaccumulators.[15] Higher plants take up inorganic Se from the surrounding environment and convert it into organic compound using sulphur assimilating enzymes. Firstly, it forms SeCys amino acid which non-specifically incorporates into proteins which results to the toxicity development. An alternative SeCys changed to selenomethionine (SeMet), which is also going incorporate into proteins, but showing less harmful effects. SeMet is the major selenocompound in cereal grains, legumes, and soybeans, which can be transformed to volatile dimethylselenide (DMSe) so that plant can release excess Se. SeCys can also be transformed in plants as elemental Se and alanine.[16] Fig.1c represents possible Se metabolism pathways in higher plants.

2. Existing methods

Methods employed for the synthesis of NPs are broadly classified under two processes; “Top-down” process and “Bottom-up”. In top-down approach, bulk material is broken down into NPs at nanoscale level with various lithographic techniques like grinding and milling. While in bottom-up approach, atoms self-assemble to new nuclei grow into a particle of nanoscale.[9] Currently, a number of chemical and physical methods are being used for synthesis of Se NPs.

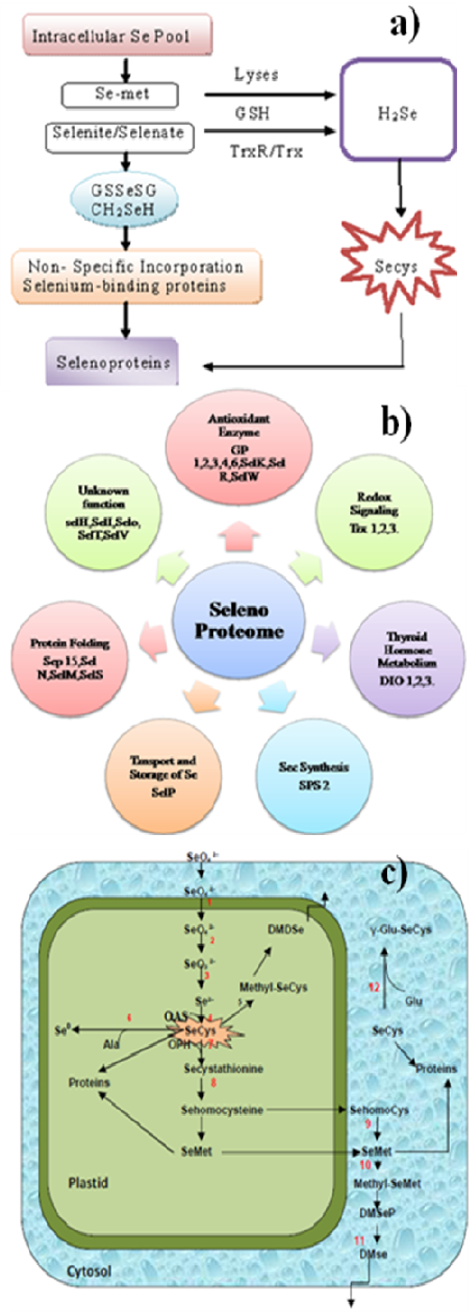

Fig. 1: a) Selenium metabolism in mammalian organisms (Se-selenium, GSSeSG- selenodiglutathione, CH_3SeH –methylselenol, H_2Se –selenide, SeMet-selenomethionine, Secys- selenocysteine, GSH-glutathione, TrxR-thioredoxin reductase, and Trx-thioredoxin). b) Human selenoproteome and its functions, and c) Schematic overview of Se metabolism in plants. APSe- adenosine phospho selenate, SAT-serine acetyl transferase, OAS-O-acetylserine, OPH-O-phosphohomoserine, SeCys-selenocysteine, SeMet-selenomethionine, DMSeP-dimethylselenoproprionate, DMSe-dimethylselenide, DMDSe-dimethyldiselenide. Numbers denote known enzymes. (1) ATP sulfurylase, (2) adenosine phosphosulfate reductase, (3) sulfite reductase (or glutathione), (4) OAS thiol lyase, (5) SeCys methyltransferase, (6) SeCys lyase, (7) cysthathionine-g-synthase, (8) cysthathionine-b-lyase, (9) methionine synthase, (10) methionine methyltransferase, (11) DMSP lyase, (12) g-glutamylcysteine synthetase (*Reprinted with permission of ref. 13*).

The summary (with 17-31 references) in Table 1 encompasses the existing physical and chemical methods used in synthesis of Se NPs with their respective importance.

3. Biosynthesis

Biological entities and inorganic materials are in constant contact with each other ever since start of life on the earth. Because constant interaction of cells to metal, living cells have well-organized deposit of minerals and these metals play an important functions in these cells. Recently scientists are paying attention in finding the interaction between inorganic molecules and biological species.[32] A variety of microorganisms, enzymes and fungi, plant extracts have been used to synthesize Se NPs of different sizes and morphologies. The summary in Table 2 presents ways preferred so far for developing various NPs from different micro-organisms.[33-60] Micro-organisms reduce the toxic, selenate and selenite oxyions into non-toxic elemental Se which is insoluble in water. It is a simple process of detoxification of selenites/selenates to Se NPs as the reverse reaction is too slow to produce Se compounds.[61] There are two modes of oxyions reduction as presented below;

3.1 Anaerobic reduction of oxyions by microorganism

Thauera selenatis,[61] *Enterobacter cloacae,*[62] *Shewanella sp.HN-41,*[63] *Sulfurospirillum barnesii, Bacillus selenitireducens*, *Selenihalanaerobacter shriftii,*[64] *Clostridrium pasteurianum*[65] etc, strains are found and studied to reduce selenium oxyions from selenate/selenite oxyions. These strains grow microaerophilically but reduce selenium oxyions to elemental selenium only in anaerobic condition with the formation of stable, uniform NPs of Se.[64] Se nanowires (NWs) and stellated polyhedral structures have been successfully synthesized by *Shewanella putrefaciens*. The mercury (Hg) was directly reacted with Se NWs or stellated polyhedral structures in water and coated the Se nanostructures to form the core–shell structure of Hg–Se after 12 h incubation at ambient temperature.[66] It has been reported that the membrane associated proteins plays an important role in reduction of Se oxyions. The reduction occurs at cell surface and the precipitate is rapidly expelled through membrane-associated efflux pumps.[67] But exact biochemistry and enzymology behind the reduction of Se oxyions are still unprecedented.[68]

3.2 Aerobic reduction of oxyions by microorganism

Large scale biomanufacturing process for the synthesis of Se NPs through anaerobic mode is very tedious and challenging. Researchers are actively engaged in finding aerobic microorganism which tolerate the high concentration of Se oxyions and reduce them to elemental Se within NPs range. Different types of the Se NPs were synthesized using proteins, small peptides and other reducing agents.[69] It has been reported that the particle size is decreased in the presence of O_2 because oxygen promotes oxidation of Se (backward reaction) as a consequence of which the redox step becomes slower by producing smaller Se NPs.[70] Smaller particle size can be obtained through aerobic respiration in contrast to anaerobic reduction mode of Se NP synthesis. Microbes like *Aspergillus terreus,*[70] *Klebsiella pneumonia,*[71] *Pseudomonas Sp.,*[72, 73, 74] *Bacillus Sp.,* [69,75] *Duganella sp.,* [76] *Agrobacterium sp.,*[76] *Bacillus selenireducens strain MLS10,*[77] *Rhodospirillum rubrum,*[78] *Stenotrophomonas maltophilia,*[79] and *Wollinella succinogenes*[80] etc., have been majorly reported to reduce selenium oxyions in aerobic condition with the formation of NPs of Se with different sizes. *Bacillus Subtilis* reduce the Se oxyions initially so as to form spherical Se NPs. Once these unstable Se NPs dissolved into the solution develop Se atoms. Se atoms were precipitated out as nanocrystalline (trigonal) t-Se by self-aggregation process and grow into the t-Se nanorods.

4. Characterization of Se NPs

4.1 Structure

Bacterial cells when incubated with selenite/selenate oxyions gradual colour change with time is observed from colorless to red followed intense red. The distinguishing red colour of Se NPs is due to the excitation of the surface plasmon vibration of the monoclinic Se. The UV-Visible absorption spectrum of selenium NPs recovered from the culture broth give characteristic peak at 590 nm (Fig. 2a). Se NPs produced by anaerobic bacteria *Sulfurospirillum barnesii*, *Bacillus selenitireducens* and *Selenihalanaerobacter shriftii* present large variations in UV-visible and Raman shift measurements. Se-reducing bacteria produce Se NPs with different atomic structures because of the diversity of enzymes that catalyze the reduction of Se oxyanions.[69]

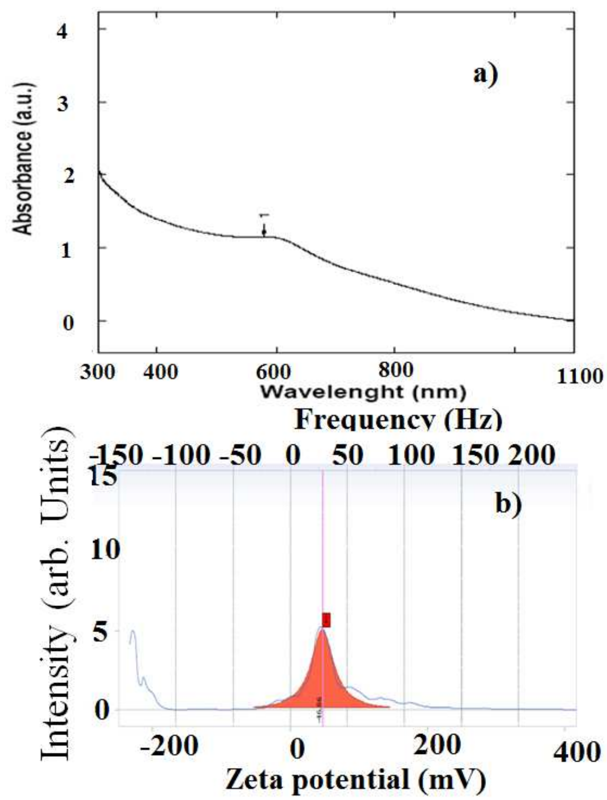

Fig.2: a) Absorption spectra and b) Zeta potential measurements of the selenium NPs isolated from Bacillus cereus strain CM100B and b) (*Taken from an open access, ref. 69*).

4.2 Stability

Se NSs stored for prolong period confirm agglomeration property by changing their appearance as black. Zeta potential measured Se NPs produced by different microorganisms demonstrated relatively higher negative charge (Fig 2b). If all the particles in suspension have a large negative or positive zeta potential then they have little tendency of agglomeration and greater stability. Fourier transport infrared analysis spectra of Se NPs produced by *P. alcaliphila* with and without Se NPs confirm that the intensity of the spectral peaks containing Se NPs is drastically diminished, suggesting a strong interaction between Se atoms and the protein molecules present in the *P. alcaliphila*. Se NPs and protein links *via* electrostatic interaction because the intensity of sample containing Se atoms was decreased with an increase of wave number from 3421 to 3435 cm^{-1}. Se NPs produced by microorganisms can tightly bound with proteins produced by cells and protect Se NPs from further transformation to black form, indicating the greater stability and prolonged shelf life.[81]

4.3 Size and shape

Size and shape of NPs produce changes in properties such as conductivity, color, mechanical strength, magnetic behaviour and melting point etc. Se NPs produced by all the reported microorganisms were spherical and in some cases transformed from spherical particles to nanowires. The size of Se NPs depends on the production time and the type of micro-organism reducing Se oxyanions. All microorganisms studied, so far, have produced polydisperse NPs with sizes ranging from 50 nm to 500 nm. The average size is above 100 nm.[64, 69] Temperature, oxygen concentration and production time have strong influence on the size and the shape of Se NP. The average size of the NPs was higher at elevated (4, 15 and 30 ^{o}C) temperatures.[82] When the O_2 concentration in the medium was increased, the average size of the Se NPs decreased and the shape of the particles became more irregular (Fig. 3). In *Shewanella sp HN-41* the production time was increased from 2h to 12 h, Se NP size also was increased from 35-40 nm to 120 nm.[63] The spherical (50-400 nm) monoclinic Se NPs generated by *Bacillus subtilis* was changed into an anisotropic, one dimensional (1D) trigonal structure in 24 h when kept at ambient temperature in aqueous solution.[82] The color of the solution was changed from red to black, recognizing the formation of trigonal Se NWs (Fig.4).

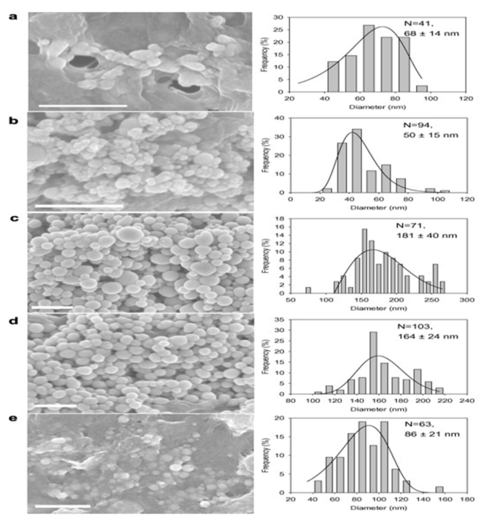

Fig.3: The SEM images and the size distributions of Se (0) NPs produced from N_2-purged incubations at 4^0C (a), 15^0C (b), and 3^0C (c), from N_2–O_2-purged (d), and from O_2-purged incubations (e). The number of particles counted, and the average and standard deviation of diameters of Se(0) nanoparticles are shown in side-diagrams. The scale bars given represent 500 nm. Solid lines depict the estimation by log normal function *(reprinted with permission of ref. 82*).

5. Probable mechanism

Microbial transformations of Se oxyions (selenite/selenate) to insoluble forms such as elemental Se^0 may not be the only end product in transformation process.[68, 69] It also can generate assimiable organic volatile forms like dimethyl selenide (DMSe, CH_3SeCH_3), and dimethyl diselenide (DMDSe, $CH_3SeSeCH_3$), dimethyl selenenyl sulfide (DMSeS, CH_3SeSCH_3) in the headspace of culture.[83] Majority of metal transformations in anaerobic and aerobic environments is the result of the direct enzymatic activity of bacteria.[77]

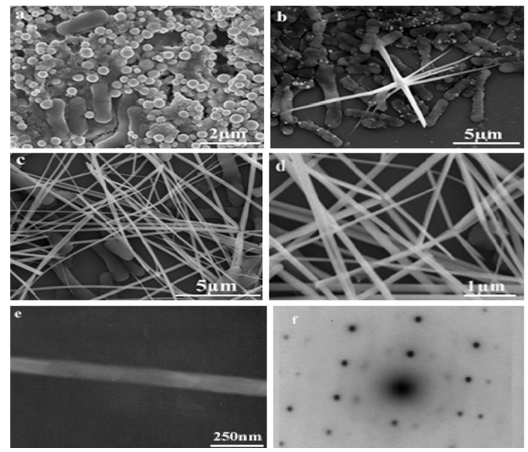

Fig.4: Spherical Se NPs change their crystal structure from monoclinic to trigonal selenium over time. This transformation was observed on Se NPs produced by Bacillus *subtilis*. Field emission scanning electron microscope and transmission electron microscopy TEM images of selenium nanoparticles a) 0 h, b) 12 h, c) 24 h and d) the high magnification of (c). TEM image (e) and electron diffraction pattern (f) of an individual Se NW (*Reprinted with permission of ref. 85*).

In some of the bacterial species, selenite reduction may serve functions of detoxification and upholding of redox component of the electron transport system by cytoplasmic reductase enzymes.[73] Selenite/selenate reduction activity is observed mainly in membrane fraction when it is incubated in the presence of selenite/selenate as a substrate.[69] In few bacterial strains growth took place in the presence of selenite, suggesting that these reductases are probably respiratory enzymes.[67] Studies have indicated that NADPH/ NADH dependent selenate reductase enzymes are responsible for reduction of Se (selenite/selenate) oxyions.[74, 75] The reduction seems to be initiated by electron transfer from the NADPH/NADH by NADPH/ NADH-dependent reductase as electron carrier (Fig.5).[69] Recently it has been reported that *E. coli* can also produce specific types of proteins (AdhP, Idh, OmpC and AceA) which are associated with synthesis of Se NPs. These proteins play an important role in generating uniform sized Se NPs. It is found that AdhP proteins have had a strong affinity with Se NPs.[84]

6. Applications

6.1 Non-biological

Se has low melting point (~217^0C), a high photoconductivity (~0.8 10^5 S cm±1), catalytic activity toward hydration and corrosion reactions, and high piezoelectric, thermoelectric, and nonlinear optical responses. Se can react with wealth of chemicals that can be used to convert Se into other functional materials such as Bi_2Se_3, ZnSe, and CdSe etc.[31] Due to these properties Se find non-biological applications.

i) Photocatalysis

Polluting substances such as antibiotics, personal care products, plasticizers, surfactants, herbicides, and other persistent organic compounds generate significant environmental problems around the world. Nanotechnology is providing novel and cost-effective ways for removal of these contaminants through catalytic destruction and adsorption.

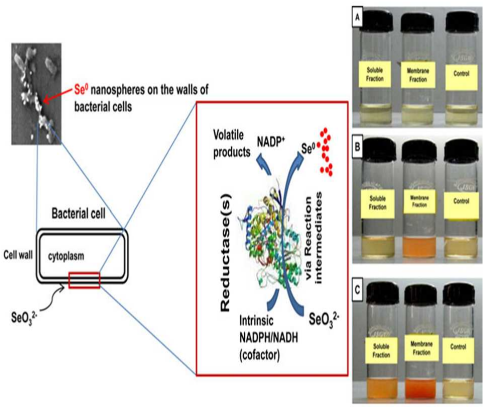

Fig.5: Schematic representation of proposed mechanism of biogenesis of Selenium (Se^0) nanospheres (*Taken from open access, ref. 69*).

A number of studies were carried out on the use of semiconductor photocatalysts for environmental remediation. Se is one of the most important semiconductors photocatalysist as it shows a photomemory effect. When Se is illuminated with light, some activity is maintained in the dark. Se NPs synthesized by tungstosilicate acid (TSA) ion shows very good catalytic activity in degradation of congo red. TSA ion acts as reducing agent while synthesis of Se NPs, it also prevents aggregation of the Se particles and offers stability. For photodegradation process, aqueous solutions of cango red were employed along with Se-TSA solution for UV irradiation. The progress of the dye decolorization was observed through a decrease of absorbance of cango red at 488 nm. The UV light leads to the degradation of the dye structure and overall reaction follows first-order kinetics. Se NPs without TSA ion degrade congo red but, a fast degradation was occurred with Se-TSA. The decolorization of the dye increases with the increase in concentration of the catalyst particles used. The rate of decolorization of congo red was increased with decrease in size of Se NPs.[21] Photodegradation of methyl orange can be achieved with metal selenides such as ultrathin ZnSe nanorods upon illumination with UV light.[31]

ii) Rectifier

It is an electrical device that converts alternating current, which periodically reverses direction, to direct current, which flows in only one direction. Currently various semiconductor materials like Zn and Hg are used for the fabrication of rectifier. Se NPs are used in this rectification process. The rectification in a junction between NPs and an organic molecule is due to the parity between free carriers in the former component and the type of carrier-accepting nature in the latter one. Rectifiers fabricated from Se NPs are cheaper and simpler to specify and install than other rectifiers. These rectifiers are used in detection of amplitude modulated radio signals, welding etc.[85]

iii) Sensor

Hydrogen peroxide (H_2O_2) is harmful to biological systems and it is the cause of neuropathology of central nervous system diseases. Se NPs synthesized from *B. Subtilis* is utilized for detection of H_2O_2. With Se sensor, one can detect very low concentration of H_2O_2 in food pharmaceutical, clinical, industrial and environmental sample.[85] Melamine is criminally added in milk, baby food, animal feed to increase nitrogen content, it has serious health hazards. Se NPs conjugated with melamine antibody strips are developed which is the simplest method used for the detection of melamine even at very low concentration.[86] Dinitrobutylphenol is very detrimental to human and aquatic animals as it has carcinogenicity. Dinitrobutylphenol is released in to waste water causing environmental pollution, SeNPs based chemiluminescence system is, so far, best for its detection.[87]

iv) Solar cell

Several research groups, including ours, are searching for efficient materials that can be used in solar cells which efficiently convert solar energy into electrical energy.[88-90] Due to the unusual properties Se can be used in solar cells. Selenium generates electric current proportional to the amount of light falling on its surface due to this inexpensive solar cell can be produced by Se NPs. Se NPs synthesized *via* microwave method using $SeCl_4$ as precursor have been used to fabricate inexpensive solar cell by considering FTO/TiO_2/Se/Pt-FTO and FTO/Se/CdS/Pt-FTO (where abbreviations have their usual meanings) configurations with remarkable solar-to-power conversion efficiencyvalues.[91]

v) Waste water treatment

Higher doses of Se oxyanions (selenate and selenite) are toxic to humans, animals and aquatic organisms, so they need to be removed from waste-waters prior to release into environment. Aerobic reduction of Se oxyanions to either volatilized Se compounds followed by gas trapping or Se NPs entrapment in microbial biomass would be a one-step process for the treatment of selenite containing waste-water. Activated sludge is more suitable for treating Se rich waste-water compared to pure cultures as it can easily handle and cheap. The presence of Se NPs in the activated sludge flocs improves their settleability. Solid–liquid separation on the basis of gravity settling is a cost-effective method for industry. Se NPs activated sludge were used as a fertilizer for selenium deficient soils and decontamination of heavy metal as Se NPs absorb heavy metal specially mercury polluted soils.[92]

6.2 Biological

Nanomedicine is a burgeoning field of research with tremendous prospects for the improvement of the diagnosis and treatment of human diseases. NPs are being used for various medical applications due to their smaller sizes and higher surface-to-volume ratios that allow more active sites for interacting with biological molecules such as microorganisms and other bioactive entities.[93] There is a fine line between optimum limit/or deficiency and excess of Se in living system causes toxicity. Se NPs have seven-fold lower acute toxicity than sodium selenite and subchronic toxicity was lower than that of the selenite.[94] Also Se NPs demonstrated higher efficiency than that of other organic Se forms in upregulating selenoenzymes.[95] When Se is reduced to NP range its biological activity remains the same as that found to previously used form.[96] Due to this unique property of Se NPs they are enormously considered in the various fields of medicine and pharmacy.

i) Anticancer

Most of the times Se deficiency is found to be associated with cancer. As Se compounds have low therapeutic index Se compounds have fewer applications in cancer treatment. Se NPs-functionalized folic acid (FA) are treated with breast cancer cell line (MCF-7), apoptosis can be induced in cell lines. FA-Se NPs entered into mitochondria have increased the reactive oxygen species (ROS) production capacity, finally caused the damage to mitochondria and induced MCF-7 cell cycle arrest.[97] Researchers are also found that prostate cancer cell line (PC3) when treated with Se NPs, the viability of cells can be decreased in comparison with selenomethionine major dietary supplement form of Se. After the treatment of Se NPs, PC3 cells lost their typical morphology, became shrunken. Cells were detached from plate surface and adhesion property is also decreased with increase with the increase in Se NP concentration. They were able to induce cytotoxicity in PC3 cell through caspase independent necrotic pathway without affecting non-cancerous hPBMC cell line after ApoTox-Glo triplex assay.[98]

ii) Antioxidant

Free radical molecules can lost one or more electrons, responsible for biological oxidation. Free radicals steal electrons from the proteins, DNA and other cell structures. UVB radiation generates oxidative stress indirectly through ROS. ROS induce DNA single-strand breaks where DNA-protein cross-linking takes place with the formation of oxidized base derivatives, such as 7, 8 dihydro- 8-oxoguanine (8-oxoG). This genotoxic effect of UV radiation can be reduced by bio-functionalized Se NPs. When lymphocyte cells expose to UVB radiation DNA damage is seen in comet assay but upon addition of Se NPs DNA damage can be prevented.[99] Human umbilical vein endothelial cells were exposed to higher level of D-glucose where increased fluorescence of fluorescent probe 2`7`-diclorodihidrofluroresceına diacetate acetyl ester was confirmed.[100] Higher level of D-glucose and stress situation resulted in the formation of ROS. When cells were pre-incubated with cysteine functionalized Se NPs then fluorescence level was decreased to a value still lower than in the untreated cells.

iii) Antiprotozoal

Leishmaniasis is one of the most important public health issues in tropical and sub-tropical countries. It is endemic in ninety-eight countries and territories, affected on twelve million people and approximately threatens three hundred fifty million, worldwide. Antileishmanial activity of biogenic Se NPs alone and in grouping with Meglumine antimoniate have tested against sensitive and glucantime-resistant *L. tropica* on *in vitro*. Cell viability MTT assay shows that Se NPs toxic to promastigotes stage of *L. tropica.*[101]

iv) Antibacterial

With the prevalence and increase of microorganisms resistant to multiple antibiotics it is necessary to find new drugs with greater activity. When antimicrobial activity of Se NPs are evaluated it is was found that Se NPs inhibit the growth of *S. aureus* within 3–4 h with a very low concentration, indicating Se NPs are influential against bacterial infection in normal tissues.[102] Se NPs also show antimicrobial activity against *C. albicans*[103] and pathogenic *Escherichia coli.*[104]

v) Immune-regulation

Prolong viral infections and alcohol abuse cause hepatocellular carcinoma through chronic hepatitis, fibrosis, and cirrhosis. Melatonin-Se NPs (MT-Se NPs) treated to mice having immunological liver injury caused by bacillus Calmette-Guérin.[105] After treatment it was observed that MT-Se NPs had an immunoregulatory effect on inhibiting proinflammatory cytokines and activated lymphocytes. Radiotherapy and chemotherapy cause considerable depression of the immune system, by paralyzing the Bone Marrow. This leads to a decrease of white blood cells, red blood cells, and platelets cell in patients undergoing chemotherapy or radiotherapy. Decrease in host immunity and ultimately increase in the risk of infectious diseases is caused by opportunistic microorganisms. Oral supplementation of Se NPs for 30 days to X-ray irradiated mice for recovering of BM suppression has provided information that many types of important white cells, specially lymphocytes and neutrophils counts are significantly increased.[106]

vi) Dietary supplement

The capita consumption of broiler chicken meat has been increased from 0.8 to 2.8 kg during the period from 2000 to 2012. To meet the growing demand broiler chickens has to gain market weight at 40th day of their growth. Rapid weight gain can be achieved with high metabolic activity, low disease susceptibility, less physical stress and inadequate micronutrients and trace minerals. During rearing of broiler chicken, stressors are responsible for causing immunosuppression. Incompetency of the immune system increases susceptibility to various infectious, malignant auto-immune and inflammatory disorders consequential decreased productive performance and dietary supplementation of Se NPs improved the growth performance, feed conversion efficiency and antioxidant enzyme activity of the broiler chickens.[107]

vii) Inhibitor of protein glycation

Reduction of sugar molecules reacted with amino acid of the protein stimulates a series of chemical changes that leads to the formation of advanced glycation end products (AGEs). AGEs cause tricky situation in diabetic such as nephropathy, neuropathy, and retinopathy, Alzheimer's disease and aging. Bovin serum albumin (BSA) and glucose incubated with and without Se NPs at 55 °C for 40 h were employed to evaluate the antiglycation effect of Se NPs. After incubation amount of glucose covalently bound onto BSA, the formation of fructosamine and fluorescent products were measured. It was found that addition of Se NPs together with glucose to a BSA solution significantly decreased the development of protein glycation.[108] As Se NPs have large surface to volume ratio BSA has already bond upon the surfaces of Se NPs, thus, deceases the reactivity of glucose molecule towards the amino acids of BSA and consequently inhibiting protein glycation. Se NPs inhibit the protein glycation in a dose-dependent but time-independent manner under the selected reaction conditions. Se NPs show the greatest inhibitory effect in the early stage, than in the advanced stage.[108]

6. Conclusion

The biosynthesis of nanoparticles by microbial methods is clean, safe, and environmentally acceptable as "Green Chemistry" measures. Microorganisms are a prospective source for the synthesis of Se NSs which have applications in non-biological fields like photocatalysis, rectifier, sensor and solar cell and biological fields like anticancer, antimicrobial, antiprotozoal, dietary supplementation etc. Though the microbial synthesis is the best approach for the Se NPs synthesis but considerable research is needed to improve the quality of products. Microbiologically synthesised Se NSs follow the principle of Ostwald ripening and thus the size of formed Se NPs is a function of time. Se NPs produced from reported microorganisms are generally polydisperse form with an average diameter greater than 100 nm. Effort should be made to control the size and polydispersivity. Also method should monitor to have high yield of Se NPs. Extracellular producers are best for synthesis of Se NPs where purification process from cells is considered. Recent progress and the ongoing efforts in improving particle synthesis efficiency and exploring their non-biological and biological applications would definitely benefit the society. There is no doubt that implementation of these approaches on commercial scale find usefulness in medicine and health care in the coming years.

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Table 1. Physical and chemical methods for synthesis of selenium nanoparticles.

Method of Synthesis	Nanostructure material synthesized	Disadvantages	References
Wet chemical Reduction	Amorphous Se NPs	Capital intensive, low production rate, difficult to scale up.	17- 22
Hydrothermal Routes	Amorphous Se NPs, Se NWs , t-Se NWs and nanotubes	Difficult to control process reproducibility	23-26
Solvothermal and Aging Routes	Se NPs	High cost	22
Sonochemical Approaches	Se NPs	Inability to Control particle size	27-29
Photothermal Assisted synthesis methods	Se NPs	Low rate of production,high energy consumption,highly eneconomical	22
Photocatalytic Reduction	Se NPs	High energy consumption	30, 31

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Table 2. Biosynthesis of metal NPs by different microorganisms.

Microorganisms	Nanoparticle Synthesized	Size (nm)	Shape	Site of Synthesis	References
Rhodococcus sp.	Au	5–15	spherical	Intracellular	33
Plectonemaboryanum	Au	<10–25	cubic	Intracellular	34
Plectonema boryanum UTEX 485	Au	10 nm–6 μm	octahedral	Extracellular	34
Escherichia coli	Au	20–30	Triangles, hexagons	Extracellular	35
Yarrowia lipolytica	Au	15	Triangles	Extracellular	33
Pseudomonas aeruginosa	Au	15–30	Not available	Extracellular	36
Rhodopseudomonas capsulate	Au	10–20	Spherical	Extracellular	37
Shewanella algae	Au	10–20	Not available	Intracellular	38
Brevibacterium casei	Au, Ag	10–50	Spherical	Intracellular	39
Trichoderma viride	Ag	5–40	Spherical	Extracellular	40
Phaenerochaete chrysosporium	Ag	50–200	Pyramidal	Extracellular	41
Corynebacterium glutamicum	Ag	5–50	Irregular	Extracellular	42
Bacillus cereus	Ag	4-5	Spherical	Intracellular	43
Aspergillus flavus	Ag	8.92 ± 1.61	Spherical	Extracellular	41
Aspergillus fumigatus	Ag	5–25	Spherical	Extracellular	44
Verticillium sp.	Ag	25 ±8	Spherical	Extracellular	45
Fusarium oxysporum	Ag	5–50	Spherical	Extracellular	45
Neurospora crassa	Au, Au/Ag	32, 20–50	Spherical	Intracellular, extracellular	46
Shewanella algae	Pt	5	Not available	Intracellular	47
Enterobacter sp	Hg	2–5	Spherical	Intracellular	48
Escherichia coli	CdTe	2.0–3.2	Spherical	Extracellular	49

yeast	Au/Ag	9–25	Irregular polygonal	Extracellular	50
Desulfovibrio desulfuricans	Pd	50	Spherical	Extracellular	51
Shewanella oneidensis	Fe3O4	40–50	Rectangular, rhombic, hexagonal	Extracellular	52
Saccharomyces cerevisiae	Sb2O3	2–10	Spherical	Intracellular	53
Lactobacillus sp.	BaTiO3	20–80	Tetragonal	Extracellular	54
Fusarium oxysporum	TiO2	6–13	Spherical	Extracellular	55
Fusarium oxysporum	BaTiO3	4-5	Spherical	Extracellular	56
Fusarium oxysporum	ZrO2	3–11	Spherical	Extracellular	57
Rhodopseudomonas palustris	CdS	8	Cubic	Intracellular	58
Rhodobacter sphaeroides	ZnS	10.5 ± 0.15	Spherical	Extracellular	59
Sulfate-reducing bacteria	FeS	2	Spherical	Extracellular	60