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Green nanotechnology: The path to new generation nanomedicine

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Abstract
Nanotechnology has revolutionized several scientific disciplines with its ability to engineer and modify materials at the nanoscale. Due to its environmental friendliness and prospective uses across many industries, green nanoparticle synthesis has attracted much attention. Green nanoparticle synthesis produces nanoparticles by using natural resources instead of toxic chemicals and energy-intensive processes, such as plants, microorganisms, and biomolecules. Recent trends include utilizing microbes, biomolecules including enzymes and proteins, and plant extracts as reducing and stabilizing agents. This process gives nanoparticles unique features that increase their potential applications across medicine, catalysis, and agriculture**.** The key pathways for synthesizing nanoparticles are physical and chemical, usually expensive and possibly hazardous to the environment. In the recent past, the evaluation of green chemistry or biological techniques for synthesizing metal nanoparticles from plant extracts has drawn the attention of many researchers. Algal/cyanobacterial secondary metabolites have emerged as one of the the most promising natural compounds in the field of biotechnology and biomedical research. Formation of nano-conjugates from such compounds is still an unexplored and interesting field of research.

Keywords: Green nanotechnology, microbes, nanoparticles, nano-conjugates, secondary metabolites

Introduction
Nanotechnology is a fast-expanding and multidisciplinary field with many applications in science and technology. This field combines key concepts from a variety of disciplines, including chemistry, engineering, physics, and biology, in order to provide novel methods for controlling and generating nanoparticles (NPs). These NPs are particles with at least one dimension ranging from 1-100 nm. Nanotechnology deals with the synthesis, characterization, and applications of a variety of NPs. Noble metals, such as gold, silver, or platinum, are commonly used to synthesize NPs by a variety of chemical and physical techniques; however, these processes are not ecologically friendly. There is a pressing need to develop a non-toxic, environmentally friendly NPs production technology. Several safe, easy, cost-effective, reproducible, and scalable green synthesis approaches for NPs have been developed in recent years, inspired by the safety-by-design concept. As a result, several biological systems, such as yeast, fungus, bacteria, and plant extracts, are currently extensively employed in green synthesis approaches for the generation of NPs (Pathak *et al*. 2021; 2024) [154].

Cyanobacteria are among the most primitive group of photoautotrophic prokaryotes, which appeared on Earth during Precambrian era when there was absence of ozone-shield around the Earth's surface (Tomitani *et al*., 2006) [234] and Earth faced highly intense solar radiation along with lethal incidence of ultraviolet radiation (UVR). Anthropogenically released atmospheric pollutants such as chlorocarbons, chlorofluorocarbons and organobromides have depleted the stratospheric ozone layer which protects the Earth from the deleterious short-wavelength solar UVR (Crutzen, 1992; Stolarski *et al*., 1992; Lubin and Jensen, 1995) [32, 224, 112]. This has resulted in an increased UVR reaching onto the Earth's surface in the past few decades arousing the scientific concern about it. Reactive nitrogen species such as nitrous oxide, nitric oxide and peroxynitrite which are naturally produced from unpolluted aquatic and terrestrial ecosystems and from anthropogenic sources as well which also contribute to the ozone depletion (Kramlich and Linak, 1994) [91]. In the Antarctic region, ozone depletion is more pronounced in comparison to mid-latitudes (Smith *et al*., 1992) [212]. Highly energetic

UV-C (100-280 nm) radiation is absorbed by atmospheric ozone and O_2 and does not reach the Earth's surface. Hence, the incoming solar radiation on Earth consists of primarily highly energetic UV-B (280-315 nm), which is lethal for most sun-exposed organisms ranging from prokaryotic to eukaryotic organisms including humans (Sinha *et al*., 2008; Hansson and Hylander, 2009; Häder *et al*., 2015; Richa and Sinha, 2015a; Pathak *et al*. 2018a, 2019a) [210, 66, 65, 178, 181] as it is easily absorbed by the biomolecules such as proteins and nucleic acids (Richa and Sinha, 2015b; Rajneesh *et al*. 2018a; 2019) [178, 156] and indirectly through the production of reactive oxygen species (ROS) (Rajneesh *et al*., 2017a, 2019) [216]. Contrastingly, UV-A (315-400 nm) radiation effects the organisms indirectly *via* energy transfer to the DNA target from UV-A-stimulated chromophores or *via* photosensitized (phycobilins and chlorophylls can act as photosensitizers) production of ROS (Singh *et al*., 2010a; Pathak *et al*., 2019a) [119, 155].

Cyanobacteria constitute the largest group of oxygenic, Gram-negative, photoautotrophic prokaryotes which have cosmopolitan distribution ranging from Antarctic to Arctic regions and are important biomass producers of aquatic and terrestrial ecosystems (Stanier and Cohen-Bazire, 1977; Häder *et al*., 2015; Rajneesh *et al*., 2017b; Pathak *et al*., 2018b) [221, 65, 216, 181]. They serve as important source of numerous valuable natural products of commercial and medicinal importance (Rastogi and Sinha, 2009; Richa and Sinha 2013; Rajneesh *et al*., 2017b; Pathak *et al*., 2018b; Richa *et al*., 2018) [172, 181]. Also, these photosynthesizers which are ecologically very important, form the dominant microflora of the wetland soils such as in paddy fields where cyanobacteria enhance the fertility of soil by acting as biofertilizer by fixing the inert atmospheric N_2 in the presence of enzyme "nitrogenase" (Vaishampayan *et al*., 2001; Pathak *et al*., 2018b) [238, 181]. Harvesting of solar energy for performing carbon fixation (photosynthesis) and nitrogen fixation, exposes cyanobacteria to harmful doses of damaging UVR (Fig. 1) in their natural brightly lit habitats (Sinha *et al*., 1998; Pathak *et al*., 2015a, 2015b, 2017a, 2017b, 2017c) [206, 181].

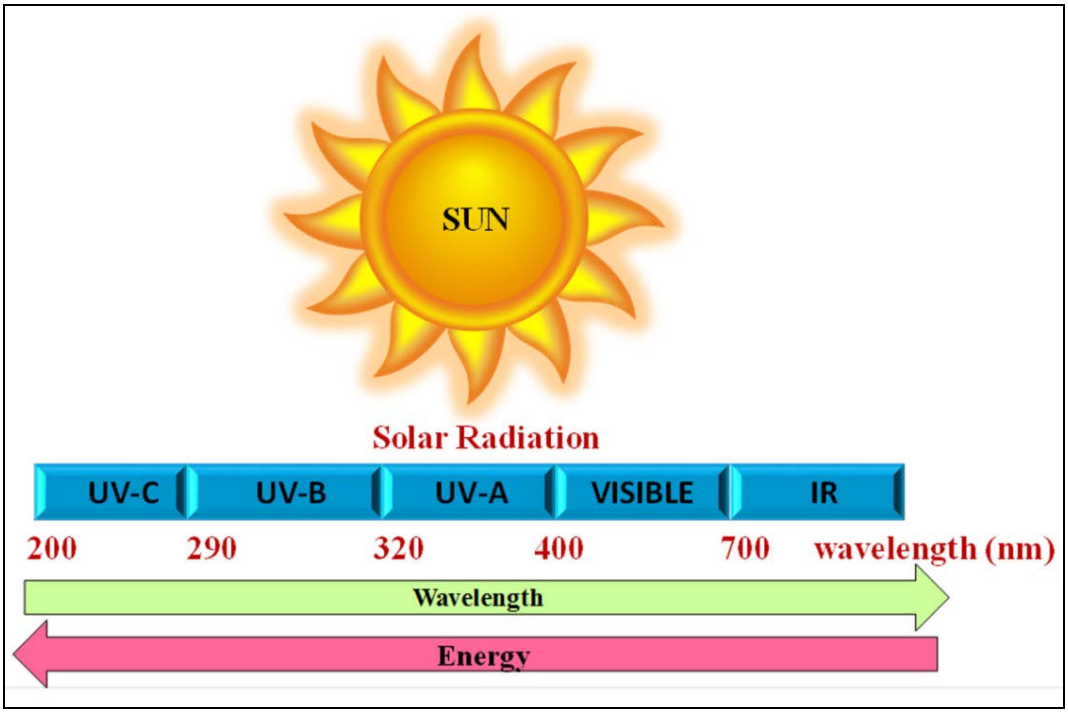

Fig 1: Solar spectrum depicting the ranges of photosynthetically active radiation (PAR), ultraviolet radiation (UVR), and infrared radiation (IR)

In aquatic ecosystems UVR affects the cyanobacteria indirectly and directly as it penetrates deeper into the water column up to the depth of 20 m and to a few centimeters in rivers and lakes owing to its high energy (Richa *et al*., 2016; Pathak *et al*., 2018c) [179, 181]. As cyanobacteria inhibit wide range of habitats in different extreme environments they synthesize an elaborate array of secondary metabolites having unusual structures and significant bioactivity (Rastogi and Sinha, 2009; Rajneesh *et al*., 2017b; Pathak *et al*., 2018b) [172, 216, 181]. These secondary metabolites include numerous compounds having antifungal, antibacterial, cytotoxic, antitumor, antimalarial, antiinflammatory, antituberculosis, antiprotozoal, anticoagulant, antiviral activities and animal toxicity (Rajneesh *et al*., 2017b; Pathak *et al*., 2018b) [216, 181]. UVR adversely affects various life processes of organisms including cyanobacteria such as survival, growth, pigmentation, motility, $^{14}CO_2$ uptake, photosynthetic oxygen production, nitrogen metabolism and phycobiliprotein composition (Sinha *et al*., 1996, 2005; Xue *et al*., 2005; Gao *et al*., 2007; Lesser, 2008; Richa and Sinha, 2015a, 2015b; Rajneesh *et al*., 2019) [205, 148, 135, 107, 178]. Several genetic, physiological, metabolic and biochemical processes have been developed by cyanobacteria to overcome the damage caused by harmful ultraviolet radiation which are termed as "different lines of defense mechanisms in cyanobacteria". These mechanisms include various non-enzymatic/enzymatic defense systems along with some very efficient repair mechanisms to counteract the harmful effects of UVR (Sinha *et al*., 2008; Singh *et al*. 2013; Carreto and Carignan, 2011; Gao and Garcia-Pichel, 2011; Rastogi and Madamwar, 2015; Pathak *et al*., 2018a, 2019a, 2019b) [210, 202, 54, 169, 181]. Such

protective mechanisms include avoidance (migration), synthesis of UV-absorbing/screening compounds, scavenging of ROS by antioxidants, resynthesis and repair, and programmed cell death (PCD) (Richa and Sinha, 2015b; Pathak *et al*., 2017a, 2017b, 2017c, 2018; Richa *et al*., 2018; Pathak *et al*., 2019a, 2019b; Rajneesh *et al*., 2019) [178, 183, 181].

Cyanobacteria produce their own sun-screening compounds/pigments such as mycosporine-like amino acids (MAAs) (Garcia-Pichel *et al*., 1993, Rastogi *et al*., 2010; Richa and Sinha, 2015a; Richa *et al*., 2018) [58, 170, 181] and scytonemin (Scy) (Rastogi *et al*., 2013; Pathak *et al*., 2017a, 2017b, 2019a, 2019b) [173, 178] to screen the UVR. UV-protecting/screening compounds namely Scy and MAAs plays significant role in protecting microorganisms from lethal UVR (Richa and Sinha, 2015b; Pathak *et al*., 2017a, 2017b, 2018a, 2018b, Richa *et al*., 2018; Pathak *et al*., 2019a, 2019b) [181, 178]. Other than UV protection these compounds have pharmaceutical and biotechnological utility alongwith numerous applications in biology and allied disciplines. Nanotechnology has affected almost every sphere of our day to day life and is a rapidly growing field having several applications in science and technology (Richa *et al*., 2017; Sonker *et al*., 2017a; Pathak *et al*., 2018c) [183, 216, 178]. Bionanotechnology serves as connective link between nanotechnology and biotechnology for developing environmental-friendly biosynthetic technology for the production of nanomaterials.

MAAs lipophilic a water soluble, colorless compounds which have molecular mass of <400 Da and forms a diversified groups of UV-absorbing compounds. These are conjugated products of a cyclohexenone or cyclohexenimine chromophore having the nitrogen substituent of an amino acid or its imino alcohol as depicted from structural studies (Singh *et al*., 2008a) [197]. They dissipate excess amount of energy in the form of heat after absorbing highly energetic UVR to their surroundings and hence protect the cells from UV (Conde *et al*., 2000) [30]. Biosynthesis of MAAs have been studied in bacteria, cyanobacteria, phytoplankton and macroalgae. In organisms (animals) which lack shikimate pathway (the predicted pathway for MAAs biosynthesis), no MAAs biosynthesis was found but in them it was found to be accumulated either through their biosynthesis in symbiotic algal partner or through food chain (Shick and Dunlap, 2002; Sinha *et al*., 2007; Singh *et al*., 2010b) [195, 211, 119]. UVR and PAR were found to be effective in induction of MAAs biosynthesis in cyanobacteria (Singh *et al*., 2008b). However, in MAAs biosynthesis most significant effect was of UV-B as it was most effective in comparison to radiation of other wavelength ranges (Singh *et al*., 2008a) [210]. Other environmental factors also effects MAAs biosynthesis in cyanobacteria such as temperature, osmotic stress and salt stress (Portwich and Garcia-Pichel, 2000; Singh *et al*., 2010a) [157, 210]. Scy was first of all reported as sheath pigment in extracellular sheath of some terrestrial cyanobacteria by Nägeli (1849) [126] which was later formally named as “scytonemin” (Nägeli and Schwenderer, 1877) [126]. Vaious different forms of Scy have been reported so far. Initially oxidized (green) and reduced (red) forms of Scy were reported which were named as fuscochlorin and fuscorhodin respectively (Kylim, 1927, 1937; Garcia-Pichel and Castenholz, 1991) [100, 55]. Scy biosynthesis is usually initiated by high photon fluence rate and metabolites of aromatic amino acid acts as precursors of its biosynthesis (Garcia-Pichel and Castenholz, 1991) [55]. Out of UV-A, UV-B and PAR, UV-A radiation was found to be most efficient in scy biosynthesis induction in comparison to red, green and blue light of the same fluence rates (Garcia-Pichel and Castenholz, 1991) [55].

Nanotechnology has emerged as an interdisciplinary stream of science. The application of nanoscale structures and materials of size usually varying between 1-100 nm, is an rapidly growing field of science and technology. Property of nanoparticles (NPs) of having higher surface area per weight compared to larger particles makes them more reactive to other molecules and makes them very useful to be used or being evaluated for use in various fields (Kathiresan *et al*., 2009) [84]. In science and engineering, “nano” is a metric system, which has its origin from Greek word for “dward” (Kawadkar *et al*., 2011) [85], it uses the prefix (10^{-9}). This prefix helps in determination of the range of NPs to be produced in nanomaterials and hence is very important. In engineering nanotechnology has emerged as an attractive field, which bridges with medicine and lifesciences. Furthermore, in 21st century nanotechnology has come up as one of the most promising engineering fields with tremendous applications, especially in molecular biology and related fields (Kawadkar *et al*., 2011; Khan *et al*., 2015) [85, 86].

Rapid advances in the field of nanotechnology have revolutinized the field of medicine and biotechnology. Properties of NPs such as small size, their structural variation, differences in their reactivity i.e. some are noble whereas others are highly reactive, makes these NPs of great use for several diagnostic/biomedical purposes in the research laboratory as well as treatments/medicine as these NPs can be inhaled, injected or digested for different treatments. NPs can be designed/biosynthesized in different shapes such as wires, spheres, core-shells or rods tubes for attaching functional molecules outside, inside or as desired to aid drug delivery or molecular recognition and here comes the part of novel bioconjugates of these NPs which could be of great significance.

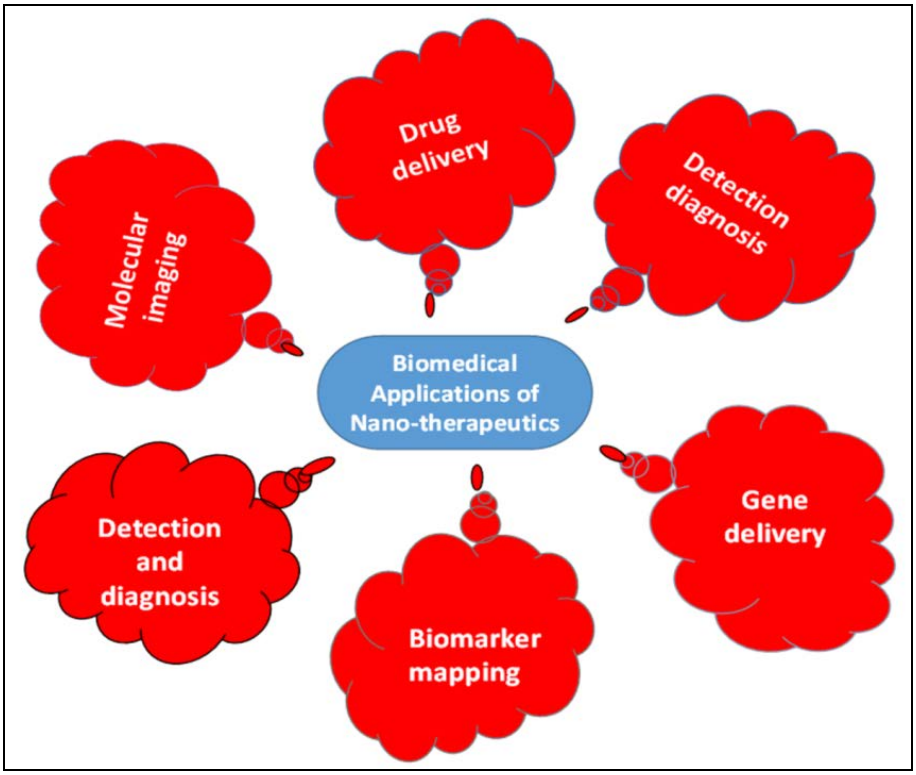

Fig 2: Biomedical application of nano based therapeutics (Modified from Gelperina *et al*., 2005) [59]

Cyanobacterial secondary metabolites

Here we will emphasize primarily on cyanobacterial UV-Screening compounds: MAAs and Scy. Both MAAs and scy are well studied UV-absorbing/screening compounds and their pivotal role in photoprotection of cyanobacterial cells against harmful UVR and high intensity solar radiation is well established (Rastogi *et al*., 2010) [170]. Some of these compounds such as MAA shinorine and porphyra-334 have been already used as commercial sunscreen products such as M-Rose, Helioguard 365, and Helionori to screen harmful UVR (Rastogi *et al*., 2014) [174]. In phytoplankton it is very well evident that the presence of MAAs help in protecting vital functions from deleterious short wavelength UVR (Klisch *et al*., 2001, Singh and Sinha, 2011) [90, 120]. Although most of the MAAs were found to be stable, mycosporine-glutamine and mycosporine-glycine can undergo photosensitized hydrolysis (Bernillon *et al*., 1990) [9]. These compouds also showed significant radical scavenging capacities as extracted MAAs and scy showed antioxidative potentials as measured using a DPPH (2, 2-diphenyl-1-picrylhydrazyl) free radical scavenging assay described by Kulisic *et al*. (2004) [95]. In the cyanobacterium *Nostoc commune*, presence of the glycosylated MAAs having radical scavenging potentials was reported (Matsui *et al*., 2011) [119]. Daniel *et al*. (2004) [35] formulated a cream having 0.005% MAAs (porphyra-334+shinorine) which neutralized UV-A effects with the same efficiency as a suntan cream having 1% synthetic UV-A filters and 4% UV-B filters, showing potentials of MAAs have in commercial cosmetics products.

Upto 90% of the incident solar UVR can be prevented by Scy from entering the cell, hence, it helps in maintaining the normal cellular biochemistry and physiology (Garcia-Pichel and Castenholz, 1991) [55]. Cyanobacteria such as *Chroococcidiopsis* sp. (Dillon *et al*., 2002) [38] and *Scytonema* sp. R77DM (Rastogi *et al*., 2014) [174] showed induction of Scy biosynthesis in response to environmental factors such as enhanced temperature and oxidative stress in combination with UV-A. UVR induced biosynthesis as well as accumulation of Scy strongly support its phooprotective and UV-screening functions (Rastogi and Incharoensakdi, 2014; Rastogi *et al*., 2014) [168, 174]. The UV-screening/absorbing potentilas of Scy is v ery well established in several cyanobacteria (Mushir and Fatma, 2012; Garcia-Pichel *et al*., 1992) [125, 57]. Apart from UV protection, Scy also shopwed significant pharmacological potentials with promising anti-proliferative and anti-inflammatory activities (Stevenson *et al*., 2002) [223]. Upto certain concentration (up to 10 µM) it is non-cytotoxic to non-proliferating cells. It displayed a inhibition (concentration-dependent) of phosphorylation of cdc25C mediated by a polo-like kinase 1 (PLK1) and hence was found to play a significant role in controlling the G2/M transition during the process of cell cycle (Stevenson *et al*., 2002) [223]. MAAs was found to be very effective in blocking the UVR-induced formation of thymine dimers *in vitro* (Misonou *et al*., 2003) [121]. These photoprotective compounds have been reported to be present mainly in the cytoplasm of cyanobacterial cells and prevent the photons (three out of every ten) from reaching sensitive cellular targets such as nucleic acids and proteins (García-Pichel and Castenholz, 1993; Gracia-Pichel *et al*., 1993; Lechowski Z and Białczyk, 2003) [56, 101].

High stability of Scy and its ability of performing screening/absorbing activity without any metabolic investment under the prolonged physiological inactivity conditions also when other protective mechanisms make Scy very effective photoprotective pigment (Brenowitz and Castenholz, 1997; Ehling-Schulz *et al*., 1997; Sinha *et al*., 1999) [14, 43, 207]. So far, seven different forms of Scy have been identified (Fig. 3a and b). Scy is a multipurpose photoprotective pigment having several applications not only as a photoprotective compound but also as a pharmacophore. Scy serves as an antiproliferative agent by

inhibiting cell cycle kinases (Stevenson *et al*., 2002) [223]. Killing of Human T-lymphoid cell line Jurkat cells through induction of autophagic cell death in the cells was performrd by reduced Scy purified from *Nostoc commune* (Itoh *et al*., 2013) [72].

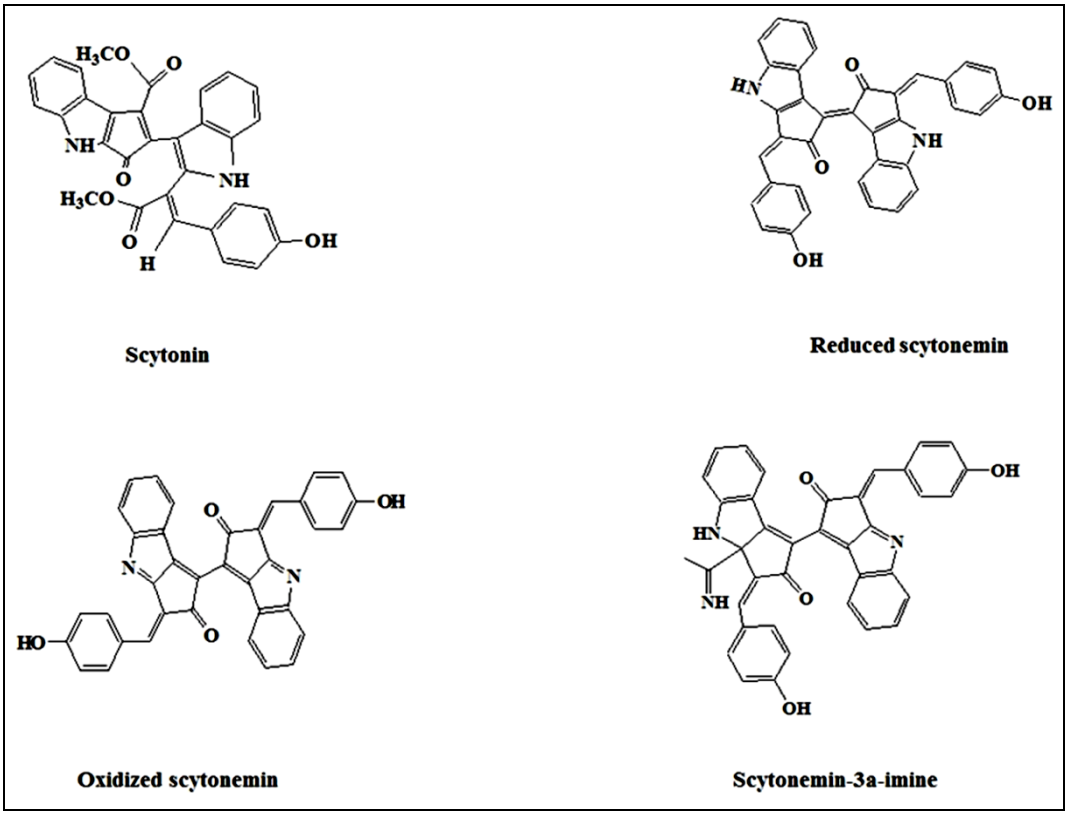

Fig 3a: Molecular structures of various forms of scytonemin commonly present in cyanobacteria

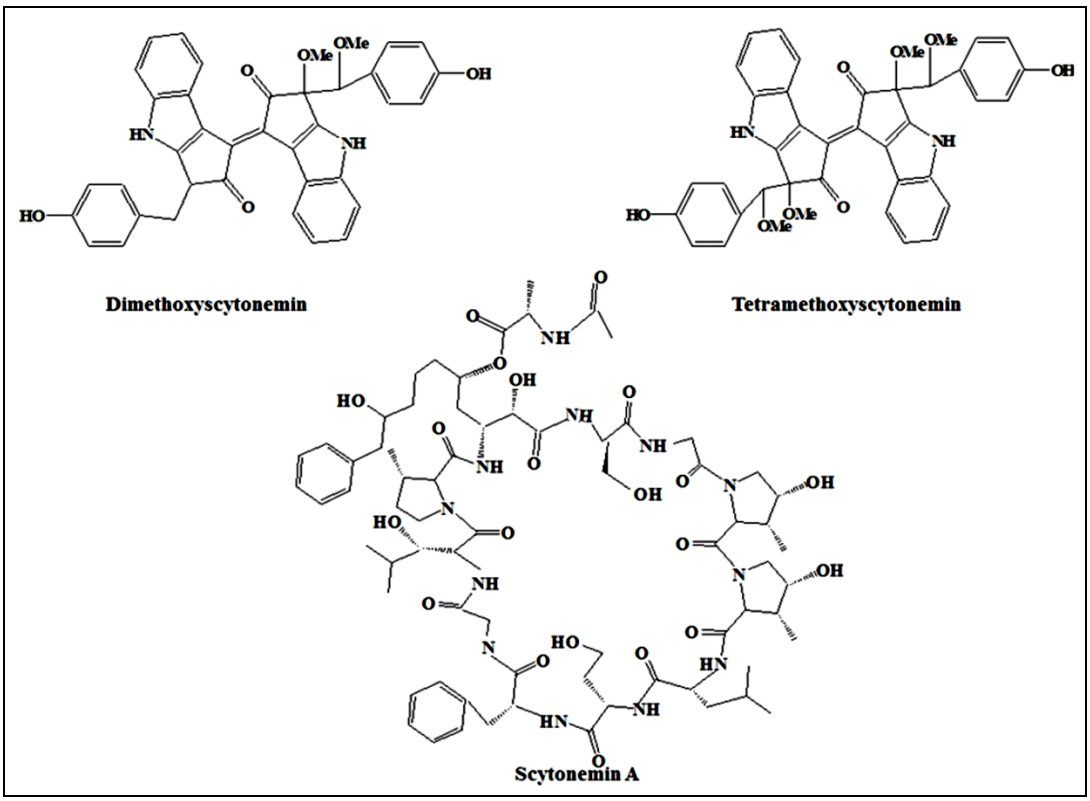

Fig 3b: Molecular structures of various forms of scytonemin commonly present in cyanobacteria

Absorption maxima ranged between 309-362 nm for MAAs and Scy shows *in vivo* absorption maximum at 370 nm and purified Scy has absorption maximum at 386 nm. It also absorbs significantly at 252, 278 and 300 nm (Fig. 4). MAAs find potential applications in tolieteries and cosmetics as activators of cell proliferation and UV

protectors due to their high absorption in the UV region (Shick and Dunlap, 2002; Whitehead and Hedges, 2005; Torres *et al*., 2006) [195, 245, 235].

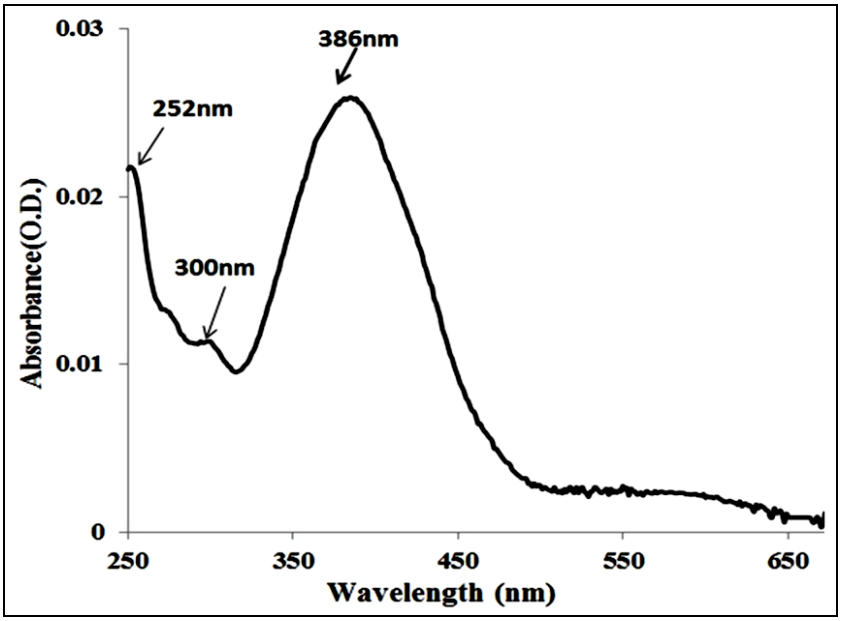

Fig 4: Absorption spectrum of scytonemin showing peaks at 252, 300 and 386 nm

These compounds show significant antioxidant, anti-inflammatory activities and inhibit lipid peroxidation (Coba *et al*., 2007a, b; Rastogi and Sinha, 2009) [26, 172] occuring due to the UV-induced production of reactive oxygen species (ROS) (Suh *et al*., 2003; Oren and Gunde-Cimerman, 2007) [227, 132]. Different types of MAAs (>30) have been identified so far from different natural sources (Bandaranayake, 1998; Richa and Sinha, 2013; Pathak *et al*., 2018) [8, 181, 178]. MAAs porphyra-334 (P-334) and shinorine contributes in the expression of Hsp70 and in maintainence of the antioxidant defense systems of the skin (Coba *et al*., 2009a) [27]. MAAs (Mycosporine-glycine, P-334 and Shinorine) were also found to protect the fibroblast cells from cell death induced due to UVR (Oyamada *et al*., 2008) [134].

Applications of photoprotective compounds Scy and MAAs

Antioxidative Potentials

MAAs and Scy show significant antioxidative potentials and anti-inflammatory and antioxidant properties of MAAs and Scy have been well reviewed by workers (Rastogi and Sinha, 2009; Pathak *et al*., 2017c; Richa *et al*., 2018) [172, 178, 181]. MAAs have shown significant antioxidant activity by scavenging superoxide anions and inhibition of lipid peroxidation resulting from ROS generated through UVR (Suh *et al*., 2003; Coba *et al*., 2009a; Oren and Gunde-Cimerman, 2007) [227, 27, 132].

Presence of cetonic group in the molecular structure of MAAs render them potent antioxidative properties, while its second group having nitrogen in the structure i.e. imino-MAAs, have been not much studied as they were presented as strong antioxidants in lipid medium (phosphatidylcholine peroxidation inhibition assay) (Dunlap and Yamamoto, 1995) [40]. As mentioned previously the role of MAAs P-334 and shinorine in maintaining the antioxidant defense mechanism of the skin has been worked out by Coba *et al*. (Coba *et al*., 2009a) [27]. The *in vitro* antioxidative potentials of formulation of P-334 and shinorine extracted from *Porphyra* and other MAAs extracted from different red algae and marine lichen was also studied. Coba *et al*. (2009b) [27] confirmed the high antioxidant activity of MAAs by demonstrating inhibition of lipid peroxidation and scavenging of superoxide anions by MAAs. Ability to inhibit lipid peroxidation by the MAAs usujilene and glycine was also reported in aqueous extract of marine organisms and these compouds showed ability of single oxygen scavenging which is generated by certain endogenous photosensitizers (Nakayama *et al*., 1999; Shick and Dunlap, 2002; Suh *et al*., 2003) [127, 195, 227]. Dose dependent antioxidative activities of MAAs such as shnorine, P-334, palythine and asterina-330 in terms of scavenging of hydrosoluble radicals was reported which increased with increasing alkalinity of the medium (pH 6-8.5) (Coba *et al*., 2009b) [27]. Antioxidative role of mycosporine-glycine (MG) was illustrated by Yakovleva *et al*. (2004) [229] in the thermal stress susceptibility of corals, *Stylophora pistillata* and *Phatygyra ryukyuensis*. These findings indicated antioxidative potentials of MG as antioxidant in corals and zooxanthellae and revealing importance of MAAs in the growth/survival of reef-building corals under temperature/heat stress. Similarly, Scy also displayed the photoprotective potentials in terms of its radical scavenging ability (Rastogi and Incharoensakdi, 2013) [173]. The antioxidant activity (dose-dependent) of Scy at concentrations of 0.5, 1.0 and 2.0 mg mL^{-1} was found to be 12 %, 33 % and 57 % respectively. Scy purified from *Nostoc commune* quenched an organic radical *in vitro* and accounted for up to 10% of the total activity of an ethanol extract of *N. commune* (Matsui *et al*., 2012) [118].

Role in minimizing DNA damage

DNA lesions (thymine dimers) are formed in organisms on exposure to solar UVR. Chemiluminescence and immuno dot blot methods were employed for detection of UV-B radiation induced thymine dimer formation in *Rivularia* sp. strain HKAR-4 and *A. varabilis* PCC 7937 (Rastogi, 2010; Rastogi *et al*., 2011) [170, 171]. With increasing exposure of

UVR increased frequency of thymine dimer was observed in *A.variabilis* PCC 7937 (Rastogi *et al*., 2011) [171]. Role of MAAs in elimation of DNA lesions was also studied by Rastogi, (2010) [170] and a steady decrease in thymine dimer formation was observed in the cells of *Rivularia* sp. strain HKAR-4 and *A.varabilis* PCC 7937 which were treated with MAAs.

Role as osmoregulator

Oren (1997) [131] reported accumulation of high concentrations of MAAs in cyanobacterial community (unicellular) inhabiting gypsum crust of a hypersaline saltern pond. This observation indicated role of MAAs in osmotic stabilization of cyanobacterial cells. MAAs is highly soluble, uncharged, polar, zwitterionic amino acid derivative and hence fulfill some of the criterias for osmotic solutes (Carreto *et al*., 1990; Galinski, 1993) [18, 53].

Role in tracing evolution

For tracing the expansion and evolution of cyanobacterial populations, Scy can be used as biomarker, especially in association with elevated UV stress. As this pigment is exclusive to cyanobacteria, it can act as a diagnostic biomarker, particularly for growth conditions of high UV-exposure (Fulton *et al*., 2012) [52]. Workers have tried for reconstruction of the historical UV-B and ozone levels for periods prior to the modern instrumental records as well as prior to human impacts, by analysis of this UV-screening pigment in herbarium specimens over a period of upto ~100 years (Huttunen *et al*., 2005) [70], such attempts are still in its developmental stage, but show considerable potentials for the future.

Role in space research and geo sciences

In the planets such as Mars, Scy can be used as indicator/biosignature of life. Raman spectroscopic characterization of the samples (mineral phases) of the Rio Tinto system which is "Terrestrial Mars analogue", was carried out (Edwards *et al*., 2007) [42]. Scy, carotenoids, and MAAs served as the key biosignatures i.e. indicators of the biological colonization of mineral substrates. Scy and its reduced counterparts have been isolated experimentally from these habitats and their characterization through Raman spectroscopy was carried out for both the samples i.e. in extracts as well as in living extremophilic colonies of cyanobacteria (Varnali and Edwards, 2013) [238]. In stressed environments, presence of Scy can be treated as an important biomarker for presence or absence of terrestrial organisms. The detailed structural analysis/study of Raman spectrum of the parent Scy molecule helped in the analysis of its methoxy derivatives which were extracted from cyanobacteria inhabiting various stressed habitats (Varnali and Edwards, 2013) [238]. Such information would help in future search for scientific evidence for an iron-Scy complexes, which can serve as a novel biosignature for the search of life in extremophilic terrestrial iron-rich habitats.

Nanotechnology

As mentioned above nanotechnology is an exciting and promising interdisciplinary subject of present time and in modern era application of nanoscale structures and materials (1-100 nm) is the most endeavoured area of science and technology. Higher surface area per weight compared to larger particles makes them more reactive than other molecules hence these materials are used/being evaluated for applications in different fields (Kathiresan *et al*., 2009) [84]. In medicine nano sized materials find several applications due to their properties (Bhatia, 2016) [11] such as decreased patient-to-patient variability, decreased fed/fasted variability, enhanced solubility, increased rate of dissolution, increased oral bioavailability, less dose requirement, increased surface area and rapid therapeutic action.

NPs can be classified in to three categories:

One dimensional NPs: One dimensional NPs in the form of thin film/manufactured surfaces have been used for long time. Thin films of NPs of size ranging from 1-100 nm or in the form of monolayer is commonly used in the field of solar cells and it offers various technological applications, such as biological/chemical sensors, magneto-optic and optical device information storage systems and fiber-optic systems.

Two dimensional NPs: It constitutes structures such as "Carbon nanotubes"

Three dimensional NPs: It constitutes quantum dots, dendrimers and Fullerenes (Carbon 60).

Different forms of NPs

Liposomes

Liposomes are bilayered vesicles which are concentric having an aqueous volume which is enclosed entirely by a lipid bilayer membrane composed of synthetic/natural phospholipids. These liposomes are characterized in terms of their size, number of bilayers and surface charge. Pharmacokinetic profile of the drugs loaded on liposomes gets altered to significant extent mainly in case of peptides and proteins. These properties get modified by surface attachment of polyethylene glycol-units (PEG) which makes it as stealth liposomes and therby increasing its circulation half-life (Redhead, 1997) [175].

Polymeric nanoparticles (PNPs)

There are several advantages of PNPs in drug delivery process but their most significant property is their tendency to increase the stability of volatile pharmaceuticals and also that they can be cheaply and easily constructed/produced in large quantities by a number of processes. PNPs may also have engineered specificity which allow the delivery of pharmaceutical agent of higher concentration to the desired site (Jain and Jain, 2002; Khopde and Jain, 2001; Baba, 2007) [75, 88, 5].

Dendrimers

The unique class of polymers, "Dendrimers" are macromolecules with high branching and their shape and size can be controlled precisely. Dendrimers are being studied for their potential role in gene and drug delivery, in anticancer therapy and as carriers for penicillin (Hussain *et al*., 1997; Venkatesan *et al*., 2009; Sathia sundar *et al*., 2010; Venkatesan *et al*., 2011; Arunkumar *et al*., 2016a, 2016b) [69, 228, 243, 242, 1].

In areas such as chemistry, engineering, physics, biology and medicine the versatility of metal nanoparticles (MNPs) is well established (Jan and Pal, 2007; Marambio-Jones and Hoek, 2010; Dos santos *et al*., 2014; Singh *et al*., 2014a,

2014b) [76, 117, 39, 203]. Some important biomedical applications of MNPs are in drug delivery systems, the photodynamic therapy (PDT) of cancer, and as antifungal and antibacterial (Cho *et al*., 2005; Sanvicens and Marco, 2008; Sonker *et al*., 2017b; Richa *et al*., 2017; Pathak *et al*., 2019c) [23, 186, 216, 183, 155]. MNPs can attach themselves to the cell wall of the microorganisms such as fungi/bacteria due to their small size through self-assembly which causes death of cell (Managa *et al*., 2014) [116]. Additionally, antibacterial activity is present in metals such as zinc, silver and gold (Fateixa *et al*., 2009; Pinto *et al*., 2013; Sousa *et al*., 2014; Sonker *et al*., 2017a, 2017b) [148, 156, 218, 183]. In order to prevent aggregation/agglomeration phenomena, the MNPs should have appropriate dimension, otherwise significant reduction in the antimicrobial effect of these MNPs is observed. Still, the mechanism of action of these MNPs has not been fully disciphered. Several theories have been proposed regarding functioning of MNPs based on the damage of the microbial enzymes by the release of metal ions, membrane integrity modifications with their penetration in the bacterial cytoplasm, accumulation of MNPs in the periplasmic space, or damage due to the action of ROS generated by MNPs (Seil and Webster, 2012; Sonker *et al*., 2017b; Pathak *et al*., 2019c) [191, 183, 154].

Important types of MNPs

Zinc NPs (ZnNPs) find significant utility in the field of water purification specially in removal of metals such as As, Cd (II), organic dyes, brown CGG dye, methylene blue, phenol, formaldehyde and malachite green (Kruefu *et al*., 2012; Srivastava *et al*., 2013; Jain *et al*., 2014; Darvishi Cheshmeh *et al*., 2015; Islam *et al*., 2015; Khezami *et al*., 2016; Sanna *et al*., 2016) [94, 220, 36, 71, 87, 184]. Gold NPs (AuNPs) are biocompatible NPs and therefore can be utilized in the diagnosis and therapy of diseases. AuNPs also have utility in remediation of methyl orange, methylene blue and dichloromethane (Huang *et al*., 2012; Suvith and Philip, 2014; Soomro and Nafady, 2015) [68, 229, 217]. Iron NPs (FeNPs) were the first NPs which were used in cleaning of environmental (Tratnyek and Johnson, 2006) [236]. These FeNPs can be synthesized, coated or modified easily and has super paramagnetic characteristics (McHenry and Laughlin, 2000) [102]. Hence, on application of external magnetic field, these super magnetic particles can be separated from complicated matrices and aqueous solution. Several workers have attempted synthesis of silver NPs (AgNPs) using cell extracts of cyanobacteria such as *Spirulina platensis*, *Oscillatoria willel*, *Plectonema boryanum* and *Nostoc* sp. strain HKAR-2 (MubarakAli *et al*., 2011; Mahdieh *et al*., 2012; Aishwarye Sharma *et al*., 2016; Sonker *et al*., 2017b) [123, 124, 196, 216]. For the biosynthesis of Au, Ag and Au core-Ag shell NPs, interaction of aqueous chloroauric acid ($HAuCl_4$) and silver nitrate ($AgNO_3$) with single cell protein of *Spirulina platensis* was investigated (Govindaraju *et al*., 2008) [61]. showed the formation of AgNPs (extracellular) by cyanobacterium *Plectonema boryanum*. X-ray photoelectron spectroscopy (XPS) and transmission electron microscopy (TEM) were utilized for analysis of the reaction products. MubarakAli *et al*. (2011) [123] reported the biosynthesis of AgNPs (extracellular) from *Oscillatoria willei* NTDM01 and it was found that a secreted protein played role in reduction of silver ions also stabilized the AgNPs. The $AgNO_3$ solution incubated with marine cyanobacteria, changed its color to yellow after 72h of incubation due to the formation of AgNPs.The extracts of cyanobacterium *Spirulina platensis* were tested for their potentials as antimicrobial agents against some human pathogenic bacteria namely, *Proteus vulgaris* (NCIM 2027), *Klebsiella pneumoniae* (NCIM 2063), *Pseudomonas aeruginosa* (NCIM 2076) and *Salmonella typhi* (NCIM 2080), *Escherichia coli* (NCIM 2065).

Silver nanoparticles (AgNPs)

Green synthesis of NPs using various microorganisms including cyanobacteria is an open field to endaveour (Sonker *et al*., 2017b; Pathak *et al*., 2019c). Several properties of AgNPs such as unique chemical, optical and electrical properties have attracted much attention towards its synthesis. AgNPs find applications as catalysts in chemical reactions, biolabeling agents, as bactericide on burn wounds, as fillers of dental cavities for preventing infection, in water/air purification systems, thin coats of AgNPs on medical devices prevent formation of bacterial biofilms, in wastewater treatment plants and in controlling microbial contamination during food processing (Jain and Pradeep, 2005; Kumar *et al*., 2008; Parashar *et al*., 2011) [74, 209, 134]. The AgNPs, unlike other MNPs, at their lower concentrations are non-toxic to the human, hence are widely used at lower concentrations (Oberdorster *et al*., 2005; Lengke *et al*., 2007; Sharma *et al*., 2009; Gurunathan *et al*., 2009; Sonker *et al*., 2017a, 2017b) [129, 104, 196, 63, 183].

Lengke *et al*. (2007) [129] biosynthesized extracellular and intracellular AgNPs of octahedral and spherical shapes utilizing cyanobacterium, *Plectonema boryanum* UTEX 485, by incubation of algal extract in a temperature range of 25 to 100 °C for 28 days. The size of the intracellular and extracellular AgNPs was 10 nm and 1-200 nm respectively. For intracellular bioreduction of $AgNO_3$, the possible mechanism could be the metabolic processes of cyanobacteria in which utilization of NO_3 occurs by reduction of NO_3^- to NO_2^- and NH_4^+ which is incorporated in glutamine whereas extracellular bioreduction may be occurring by organic compounds such as proteins released from dead cyanobacteria in the higher temperatures. MubarakAli *et al*. (2011) [123] showed that *Oscillatoria willei* NTDM01 reduced silver ions to spherical AgNPs having size variation of 100-200 nm on the cell surface i.e. extracellularly. The study indicated the role of protein molecules as a capping agent during the process of biosynthesis of NPs. Extracellular synthesis of AgNPs was carried out by Tsibakhashvili *et al*. (2011) [237], from *Arthrospira (Spirulina) platensis* and results showed that the number, size and shape of the biosynthesized NPs were dependent on the time period of exposure and concentrations of silver ions. Biosynthesis of AgNPs having an average size of 11.6 nm was carried out in another study, and the synthesis occurred within 24 h at 25 °C from same cyanobacterium (*A. platensis*) (Mahdieh *et al*., 2012) [114]. Extracts of cyanobacteria isolated from mangroves region such as *Aphanothece*, *Arthrospira (Spirulina)*, *Phormidium*, *Oscillatoria*, *Lyngbya*, *Microcoleus*, *Gloeocapsa*, *Aphanocapsa* and *Synechococcus* were tested for biosynthesis of AgNPs (Sudha *et al*., 2013) [225]. Out of the above mentioned cyanobacterial extracts, only *Microcoleus* sp. showed potential for biosynthesis of AgNPs which were spherical in shape having size range of 44-79 nm after 72 h of incubation of the algal extract with $AgNO_3$ solution in the

dark. Recently, Tomar *et al*. reported the ammonia-sensing potential of the AgNPs synthesized from cyanobacteria. Biosynthesis of highly monodispersed AgNPs having size range of 5-6.5 nm were reported from *Phormidium fragile*, a marine cyanobacterium (Satapathy and Shukla, 2017) [188]. Biosynthesis of AgNPs from the hot spring isolate *Nostoc* sp. strain HKAR-2 was carried out and they showed significant cytotoxic activity against MCF-7 anti-cancer cell lines, as well as significant antimicrobial potentials (Sonker *et al*., 2017a) [183].

Recently, a simple, cheap and easy method for "green" synthesis of AgNPs was demonstrated utilizing the cellular extracts of the cyanobacterium *Anabaena doliolum* (Singh *et al*., 2014a) [203]. These AgNPs were tested for their antibacterial potentials against three different multidrug-resistant bacteria and results indicated its potent efficacy as antibacterial agent. Its effect on Dalton lymphoma cells as well as on human carcinoma colo205 was studied and these AgNPs strongly affected survival of these cells at a very low concentration. The cell extract of *A. doliolum* contains a wide variety of metabolites including pigments such as carotenoids, phycobiliproteins, UV-absorbing compounds such as MAAs and these compounds might be involved in reduction of Ag^+ and synthesis of AgNPs. As mentioned above the biosynthesized AgNPs showed significant antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Klebsiella pneumonia* at a very low concentration of 5 µg/disc. Such antibacterial activity of AgNPs is promising as the antibiotics such as amikacin, ampicillin and several others were not effective against some of these bacteria such as *K. pneumoniae* and *E. coli* even at a very high concentration of 500 µg/disc.

As discussed previously the exact mechanism of AgNPs action as an antibacterial agent is not completely understood. It was found that AgNPs change the permeability of membrane because of formation of perforations in the cell wall of bacterial which leads to the release of lipopolysaccharides and membrane proteins (Fig. 5) (Sondi and Salopek-Sondi, 2004; Sharma *et al*., 2009) [214, 196]. Other studies reflect that the cellular damages may be the result of the interaction of biomolecules such as proteins and DNA with AgNPs (Sharma *et al*., 2009; Sriram *et al*., 2010) [296, 119].

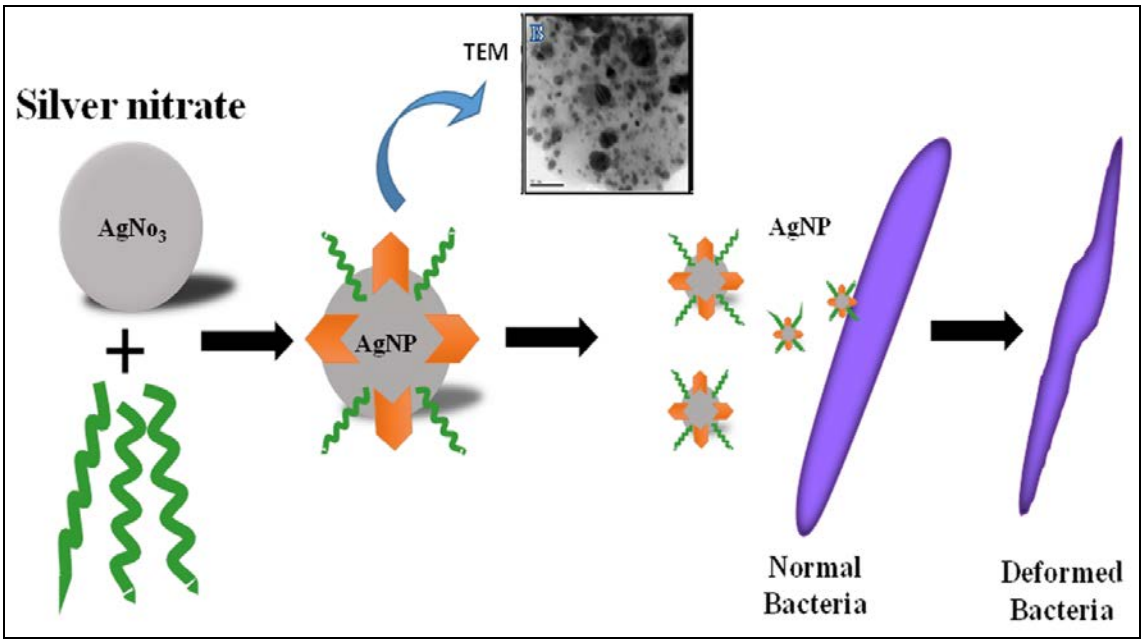

Fig 5: AgNPs synthesis from *spirulina platensis* and its antibacterial activity

Hence, it was concluded that the AgNPs-mediated killing of bacteria may be due to the formation of pores in the bacterial cell wall or its interaction with vital biomolecules such as DNA and protein resulting in the arrest of metabolic activities of the cell. Additionally, significant anticancerous activity have been reported from these biologically synthesized green AgNPs from different sources (Saraniya and Valentin Bhimba, 2012; Jeyaraj *et al*., 2013; Prabhu *et al*., 2013; Sonker *et al*., 2017b) [187, 80, 57, 216]. Sriram *et al*. (2010) [119] reported antitumor activity of AgNPs in Dalton's lymphoma ascites (DLA) tumor. Dose-dependent cytotoxic effects were elicited by AgNPs in DLA cells *via* activation of the capsase-3 enzyme and apoptosis induction. Apart from the antibacterial activity of the biosynthesized AgNPs, these NPs also showed inhibitory effects on the growth and survival of DL (tumor cells) and human colo205 cancer cells (Singh *et al*., 2014a) [203]. Treatment of these cells with AgNPs showed a drastic decrement in the survival of DL (tumor) cells. Loss of viability of ~75% was observed in MTT assay at AgNPs concentration of 20 µg/mL *in vitro* condition. Similarly, a reduction of ~ 50% was observed in the survival of human colo205 cells with treatment of AgNPs (30µg/mL). On the basis of these observations it could be concluded that that AgNPs in lower concentrations can be safely utilized for arresting growth of human colo205 and DL. Another interesting point which needs to be emphasized is that the inhibitory effect of AgNPs on the viability of cancer cells appeared to be specific, as there was least affect on growth and survival of normal thymocytes cells with the concentrations of AgNPs employed for evaluating the viability of cancer cells. These biosynthesized AgNPs showed significant potentials as a biocidal agent which was evident by the higher survival of colo205 cells and DL cells with the treatment of cisplatin, a standard antitumor drug at similar AgNPs concentrations used in the assay. AgNPs treatment (10 and 30 µg/mL)

resulted in significant increase in generation of ROS, in particular hydrogen peroxide, peroxyl and hydroxyl radicals was observed in DL and human colo205 cells respectively in comparison to normal cells (thymocytes) (Singh *et al*., 2014a) [203]. Thse findings indicate that AgNPs results in induction of cell death possibly *via* ROS mediated apoptotic pathway as enhanced ROS results in extreme oxidative stress in cells. Enhanced toxicity of AgNPs was reported in the cancer cells in comparison to normal human lung fibroblast cells (IMR-90) (AshaRani *et al*., 2009) [3]. It was found that mitochondrial respiratory chain disruption by AgNPs resulted in the production of ROS and interruption of ATP biosynthesis, which finally culminated in DNA damage (Asha Rani *et al*., 2009) [3]. The biosynthesized AgNPs possessed significant biological activity against several bacteria including human pathogens such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Corynebacterium*, *Vibrio cholerae* and *Salmonella typhi*.

Nanoscale AgNPs (<100 nm) having high surface-area-to-volume ratio are of much interest because of their antimicrobial actions against both Gram negative and Gram-positive bacteria, fungi, viruses as well as other microorganisms in comparison to other MNPs (Sonker *et al*., 2017a; 2017b) [216]. It is also effective against multidrug resistant and susceptible strains such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pyogenes*, *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (VRSA).

Biosynthesis of AgNPs have also been carried out by phycoerythrin extracted from the cyanobacterium *Nostoc carneum*, which reduced $AgNO_3$ to AgNPs. *Oscillatoria willei* NTDM01 was used by MubarakAli *et al*. (2011) [123] for green synthesis of AgNPs. Phycocyanin and polysaccharides present in the cyanobacterial extracts have been used for production of AgNPs (Patel *et al*., 2015) [141]. *In vitro* cytotoxic effect of these AgNPs against human breast cancer (MCF-7) cell lines and normal cells and against Ehrlich Ascites Carcinoma (EAC) cells have been investigated. Further, analysis of degree of dispersion of AgNPs and their stability was also carried out. AgNPs showed anti-hemolytic activity with 96.4% inhibition (3.6% reduction in erythrocyte hemolysis) and this activity was comparable to vitamin C which exhibited anti-hemolytic activity of 96% inhibition. The possible mechanism for this anti-hemolytic potential of AgNPs may be due to the capping agents which surrounded AgNPs such as amino compounds (-NH_2) having anti-hemolytic properties and Ar-OH phenols having anti-oxidative properties against free radicals depending on the ressemblence of their redox characters (Visioli *et al*., 1998; Mallesha *et al*., 2016) [224, 115].

Application of AgNPs for treating breast cancer could be better than using the fluorouracil (5-FU) as toxic effects of AgNPs on normal cells is much lower than 5-FU. AgNPs exhibit cytomorphological changes on MCF-7 cells as cell shrinkage, oxidative stress, involution and other biochemical reactions finally causes apoptosis (Jannathul *et al*., 2015) [78]. Oxidative degradation of lipids can be enhanced by AgNPs which may result in DNA deterioration apoptosis and necrosis (Oberley *et al*., 2006; Xia *et al*., 2006). AgNPs can induce hyperthermia within the breast cancer cells and hence is considered as an effective photothermal agent in cancer therapy (Thompson *et al*., 2014) [230]. Dysfunctioning of mitochondria may cause apoptosis resulting in inhibition of proliferation of MCF-7 cells (Jeyaraj *et al*., 2015) [81]. The anticancerous activity of biosynthesized AgNPs from the cell free extract of *Nostoc* sp. HKAR-2 against breast cancer cell lines, MCF-7 was investigated (Sonker *et al*., 2017a) [216]. The extract of the hot-spring cyanobacterium *Nostoc* sp. strain HKAR-2 efficiently reacted with $AgNO_3$ to form AgNPs.

Cytotoxicity of AgNPs in the dose-dependent manner was observed in treated MCF-7 cells. However, the possible mechanism of such cytotoxicity of AgNPs is still not yet clear, but some investigations indicated that the biosynthesized AgNPs causes disruption of the genes which are involved in the regulation of cell cycle and also causes induction of DNA damage as well as apoptosis in cancer cells (Sanpui *et al*., 2011) [185]. The AgNPs treatment suppressed the angiogenesis process and caused decrement in the EAC (Ehrlich ascites carcinoma) nourishment and caused decrease in nutritional fluid volume thereby arresting the tumor growth (El-Sonbaty, 2013). It has been found that in mice, AgNPs possess anti-cancer efficiency against EAC due to their potential oxidative damage effect which was evident from elevated malondialdehyde (MDA) and H_2O_2 content in the solid tumor tissue which served as indicator for free radicals production and lipid peroxidation in tumor tissues and thereby, induction of apoptosis in the cells *via* caspase 3 activation (El Bialy *et al*., 2017) [44].

Gold nanoparticles (AuNPs)

AuNPs have wide range of applications/utility in the field of medicine, catalysis, diagnostics, and as sensors because of their significant properties. Au is precious and less toxic metal, and has been employed in the treatment of various diseases. AuNPs find several uses in biomedicine and nanobiotechnology because of their plasmon resonance optical properties and convenient surface bioconjugation with biomolecular investigation (Kreibig and Vlloner, 1995; Daniel and Astruc, 2004; Wu and Chen, 2010) [92, 35, 246]. These biosynthesized green AuNPs have aroused interest for the migration of proteins, nucleic acids, gene therapy, drug targeting and delivery (Tiwari *et al*., 2011) [231]. Biomolecules such as polysaccharides and proteins present in the algal/cyanobacterial cell extract can be utilized for reduction of Au ions and production of AuNPs. The intracellular and extracellular synthesis of AuNPs having size range of 10-25 nm by addition of gold(III) chloride $(AuCl_4)^-$ and gold(I) thiosulphate $(Au(S_2O_3)_2^{3-})$ solutions to the extract of *P. boryanum* UTEX 485 was reported by Lengke *et al*. (2006a) [106]. Govindaraju *et al*. (2008) carried out biosynthesis of AgNPs and AuNPs and bimetallic nanoalloy (Au core-Ag shell NPs) from the cyanobacterium *A. platensis*. On addition of cyanobacterial biomass to $AgNO_3$ and 10^{-3} M solution of $HAuCl_4$ for 120 h, change in the colour of the reaction mixture was observed to brown and ruby red in the case of $AgNO_3$ and $HAuCl_4$ respectively, whereas in bimetallic NPs, reaction mixture's colour changed from purple to brown. The size of these biosynthesized NPs varied from 6-10 nm for AuNPs, 7-16 nm for AgNPs and 17-25 nm for bimetallic (50:50) Au-AgNPs, respectively. *A. platensis* was also utilized for the biosynthesis of AgNPs and AuNPs (Kalabegishvili *et al*., 2011) and uniform and stable AuNPs of size ~5 nm of ruby red colour were synthesized after 48 h of incubation from *A.*

platensis (Uma Suganya *et al*., 2015) [226]. *Spirulina subsalsa* and *Lyngbya majuscula* were investigated for biosynthesis of AuNPs (Chakraborty *et al*., 2009) [220]. Both the cyanobacterial species were exposed to Au solution, and their tendency for gold uptake was observed. Different percentages of gold uptake were observed with *S. subsalsa* (20-35%) and *L. majuscula* (35-60 %). Further, a change in color was recorded i.e. from colourless to purple which confirmed the reduction of Au (III) to Au(0). In peripheral regions of the cytoplasm of the cells, formation of AuNPs (spherical) having size <20 nm was observed. *Synechocystis* sp. PCC 6803 was used by Focsan *et al*. (2011) [50] for biosynthesis of AuNPs. Addition of the $HAuCl_4$ solution resulted in a brown-coloured formation, reflecting the reduction of Au ions. Formation of AuNPs (intracellular) having size of 13±2 nm was observed in the form of dark spots in the cytoplasm, cell wall, thylakoid and plasma membrane (Focsan *et al*., 2011) [50]. AuNPs of different sizes and shapes were biosynthesized intracellularly by incubating the biomass of, *Phormidium tenue*, *Phormidium valderianum* and *Microcoleus chthonoplastes* at 20 °C with 75 ppm solution of $HAuCl_4$ for 72h (Parial *et al*., 2012a) [139].

Conjugated Au nanorods with photosensitizers showed potentials to kill MRSA by *near-infrared* (NIR) photothermal radiation and photodynamic antimicrobial chemotherapy. Conjugated Au nanorods with a photosensitizer (hydrophilic) namely toluidine blue O serve as dual-function agents in the process of photodynamic hyperthermia and inactivation against *Staphylococcus aureus* (methicillin-resistant). For photothermal killing of *Staphylococcus aureus* utilizing laser, conjugated light absorbing AuNPs with specific antibodies have been used. Addition of antibiotics increases the efficacy of the AuNPs as antibacterial agents as antimicrobial potential of the vancomycin increased on coating with AuNPs when tested against vancomycin resistant *Enterococci* (VRE). The AuNPs coated aminoglycosidic antibiotics displayed antibacterial effects on several Gram negative and Gram-positive bacteria. AuNPs reduced by cefaclor (β- lactam antibiotic of second generation) showed enhanced antimicrobial activity on Gram-negative (*E. coli*) and Gram positive (*S. aureus*) bacteria compared to AuNPs and cefaclor alone.

The intracellular biosynthesis of AuNPs was shown by using *Lyngbya majuscule* isolated from the Arabian Gulf. The workers (Bakir *et al*., 2018) [7] demonstrated the role of AuNPs in combination with *Lyngbya majuscule* as an anti-myocardial infraction agent. Blue-green algae such as *Spirulina subsalsa* was utilized for biosynthesis of AuNPs have. AuNPs were also synthesized from cyanobacteria *Spirulina platensis* and were examined for their antibacterial activity. The algal-mediated biosynthesis of AuNPs exhibited electrostatic interactions between algal functional groups and Au anions. The interaction occurs between the amino groups, bound to the surface of algae and $AuCl_4^-$ anion. During the course of reaction, the cellular extracts reduced the Au (III) to AuNPs. These AuNPs also showed antibacterial efficacy against bacteria such as *S. aureus* and *Bacillus subtilis*. *Anabaena flos-aquae* also promoted the intracellular biosynthesis of akageneite (-FeOOH) nanorods (Dahoumane *et al*., 2010; Brayner *et al*., 2012) [33, 13].

Coper oxide nanoparticles (CuONPs)

Cell-free extract of cyanobacterium *Spirulina platensis* was utilized for the biosynthesis of CuONPs having size range of 30-40 nm. These green CuONPs exhibited high antibacterial potentials against some pathogenic Gram-negative bacteria such as *Proteus vulgaris*-MTCC-7299, *Escherichia coli*-MTCC-9721, *Klebsiella pneumonia* -MTCC-9751 and Gram positive bacteria such as *Staphylococcus epidermidid*-MTCC- 2639, *S.aureus*-MTCC-9542 and *Bacillus cereus* - MTCC-9017. These CuONPs formed maximum zone of inhibition in *P. vulgaris i.e.* 28.0±0.41 mm. Few studies have reported the antibacterial activity of CuONPs which have significant efficacy as bactericidal agent (Cioffi *et al*., 2005). Yoon *et al*. (2007) [24, 250] demonstrated the antibacterial property of CuONPs against bacterial strains of *E. coli* and *Bacillus subtilis*. CuONPs supported on different suitable materials/structures, such as polyurethane foam, carbon, sepiolite and polymers have shown significant potentials in bactericidal applications (Jain and Pradeep, 2005; Esteban-Cubillo *et al*., 2006; Chatterjee *et al*., 2014) [74, 46, 21].

Greater abundance of functional groups such as amines and carboxyl groups on the surface of bacterial cell and higher affinity of released Cu ions from these biosynthesized CuONPs toward these groups attributes to their significant antibacterial activity against both the Gram-negative and Gram-positive bacteria (Beveridge and Murray, 1980) [10]. Enormously large surface area of these biosynthesized CuONPs enables them with competent antibacterial property, which provides better contact of these with CuONPs microorganisms leading to their death. The released Cu ions consequently may interact/bind with nuclic acids (DNA molecules) which lead to degradation of their helical structure through initiating the process of cross-linking between and within the nucleic acid strands. CuONPs/CuNPs were found to cause toxicity/multiple toxic effects such as generation of ROS, lipid peroxidation and protein oxidation as well as disrupting several cellular biochemical processes (Kim *et al*., 2000; Chatterjee *et al*., 2014) [89, 21].

Zinc oxide nanoparticles (ZnONPs)

Synthesis of ZnONPs from the bacterium *Aeromonas hydrophila* was carried out by Jayaseelan *et al*. (2012) [79]. The antibacterial potentials of ZnONPs biosynthesized from *Anabaena variabilis* NTSS17, were investigated against bacterial strains such as *Rhodococcus rhodochrous, P. aeruginosa* and *E. coli* following the method of Kirby Beyer method and Muller- Hinton agar (Ramasamy *et al*., 2015) [164]. The maximum zones of inhibition formed by ZnONPs against *R. rhodochrous* MTCC 265, *E. coli* MTCC B948, and *P. aeruginosa* MTCC 2453 were 13, 16 and 12 mm, respectively with a concentration of 5 mg/1000 mL. The cell free extract of the cyanobacterium *Anabaena* isolate L31 was used for green synthesis of ZnONPs and it was found that the cyanobacterial extract efficiently reacted with $ZnNO_3$ and formed ZnONPs (Singh *et al*., 2014b) [204]. The antibiogram study of biosynthesized ZnONPs has been previously reported by different workers/researchers against various pathogenic microorganisms (Oberdörster *et al*., 2005) [128]. Antibacterial nature of of ZnONPs was found to be due to chemical reactions/interactions between membrane proteins and hydrogen peroxide or between the outer lipid bilayer of bacteria and other chemical

species/molcules produced in the presence of ZnONPs (Zhang *et al*., 2010) [253]. Entry of the produced hydrogen peroxide inside the cell membrane of bacteria kills the cells. ZnONPs were found to be responsible for inhibiting bacterial growth as shown in different studies. Thus, the utility of such green, eco-friendly ZnNPs in anticancer, bactericidal and other electronic and medical applications, make the method of green synthesis potentially exciting and interesting for the commercial/large scale synthesis of other inorganic nano material/NPs (Singh *et al*., 2014b) [203]. Further works/researches are needed for proper understanding of the different molecular mechanisms involved in the ZnONPs activity, its immunity, toxicity, and mode of action, which is very much needed for effective and safe utilization of ZnNPs in bionanotechnology based industries/sectors.

Applications of NPs in medical/healthcare sectors

Several workers have reported applications of NPs in various fields of medical and healthcare sectors (Fig. 6) (Jani *et al*., 1989; Lehr *et al*., 1990; Hedley *et al*., 1998; Russell-Jones *et al*., 1999; Schipper *et al*., 1999; Gurunathan *et al*., 2000; Florence and Hussain, 2001; Panyam *et al*., 2002; Pardridge *et al*., 2002; Chen *et al*., 2004; Kreuter, 2004; Scherrmann and Temsamani, 2005; Ji *et al*., 2006; Venkatesan *et al*., 2011) [77, 103, 67, 182, 190, 64, 49, 136, 138, 22, 93, 189, 82, 243]. Some of them are listed below:

- Targeted drug delivery
- Cancer treatments
- Alternative vaccine and drug delivery mechanisms such as inhalation or oral in place of injection
- Bone growth promoters
- Sunscreens and cosmetics utilizing ZnO and TiO_2
- Biocompatible coatings for implants
- Detection and bio-labeling (using Au)
- Fungicides (using ZnO)
- Carriers for drugs with low water solubility
- New dental composites
- MRI contrast agents (using superparamagnetic FeO)
- Antibacterial, antiviral (Ag), anti-spore non-chemical creams
- Powders (to destroy biological particles utilizing surface tension energy on the nanoscale)
- Biological binding agents (for high phosphate levels)

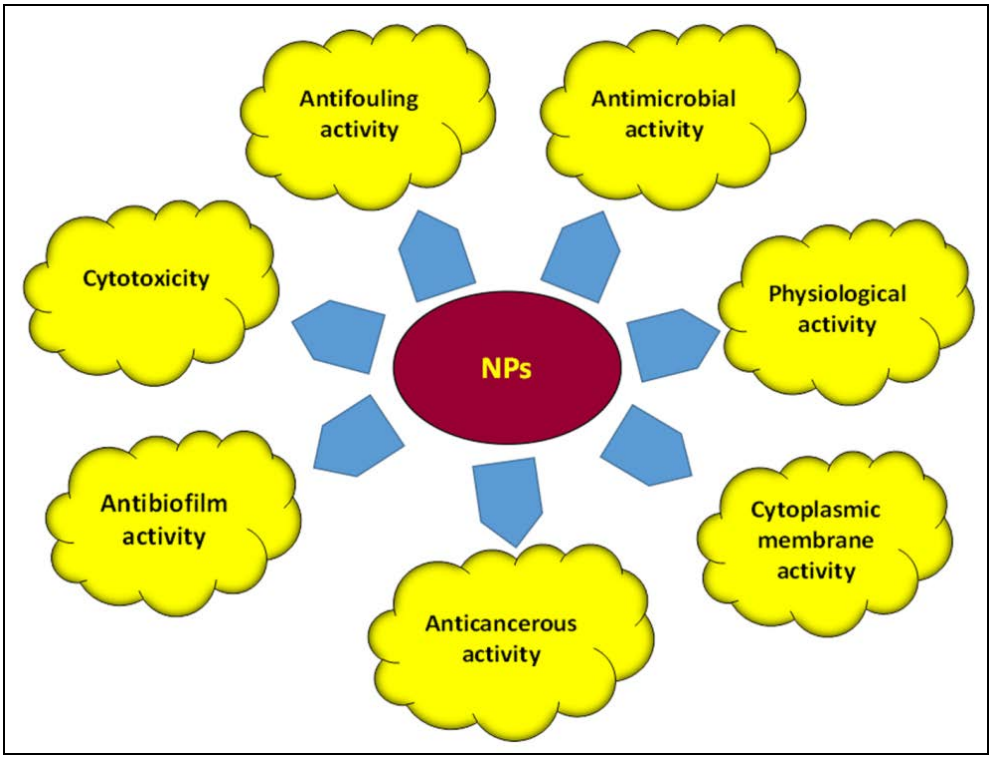

Fig 6: Various biological activities of metal nanoparticals

In cancer therapy, the primary objective of nanotechnology, suitable targeting delivery systems have been developed, which has been taking the lead in overcoming the problem of "Multi-Drug Resistance (MDR)". Such targeted delivery systems which are based 'Nanosizing' of drugs show following properties (Lobenberg *et al*., 1998; Lee *et al*., 2006; Dutta and Jain, 2007; Liu *et al*., 2009; Samori *et al*., 2010; Mahajan *et al*., 2010; Brewer *et al*., 2011; Goldberg *et al*., 2011) [111, 108, 41, 110, 183, 113, 15, 60]:

- Decreased toxicity
- Decreased drug resistance
- Enhanced rate of dissolution
- Enhanced oral bioavailability
- Enhanced solubility
- Increased drug targeting ability
- Increased stability of formulation and drug
- Increased patient compliance
- Enhanced surface area
- Reduced need of dose

Additionally the drug delivery site could be made visible to us by integration of imaging contrast agents within NPs which can allows the examination of *in vivo* efficacy of the therapeutic agents (Cai and Chen, 2007) [16]. The US Food and Drug Administration (FDA) have approved various nanotechnology products so far for clinical use, and several

products are under preclinic and clinic development (Davis and Chen, 2008) [252]. Some of the important products have been given below:

- **In Drug and gene delivery**
  Dendrimers have been investigated for gene and drug delivery, penicillin carriers, and in anticancer therapy.

- **In Treatment of cancer**
  Conjugating NPs with anti-cancer drugs like cisplatin, methotrexate or Adriamycin have been employed for treatment of cancer (Tomalia *et al*., 2007) [232]. PAMAM dendrimers have also been utilized in treatment of cancer.

- **In Gene therapy**
  Dendrimers have been used for gene therapy where conventional viral vectors can be replaced by them. Their entry inside the cells is made through endocytosis and the DNA gets transported into the cell's nucleus for transcription of the desired gene.

- **In Chemotherapy**
- Tectodendrimers are the nano structures which have shown potential applications in chemotherapy for cancer treatment as a mode of targeted drug therapy (Baker *et al*., 2001) [6].

- **In Gene transfer**
  Nanotechnology provides an effective alternative to viral vectors of gene transfer for treatment of various cancers/tumors (Pan *et al*., 2007) [135]

- **In Transfection**
  These nano structures have claimed low toxicity to cells and improved transfection efficacy.

- **In clearing the blood circulation**
  It has been reported that microbivores can clear the blood stream in septicaemia at a much faster rate than the natural defense mechanism with antibiotics (Freitas, 2005) [51].

- **In Antiretroviral therapy**
  For antiretroviral therapy, dendrimer based drugs have been investigated. Successful prevention of simian HIV infection was reported by some of the dendrimer based drugs.

Numerous techniques are available for synthesis of various types of MNPs in the form of colloids, thin films, powders, tubes, clusters, rods, wires and so on. Scientists have tried various methods for synthesis of inorganic materials utilizing biomaterials such as DNA, enzymes and cellular/orgenell membranes. Attempts have been made for synthesis of biocompatible biopassive or bioactive materials, especially for various biomedical applications such as drug delivery, body implants and cancer therapy. Nanotechnology has paved way for fabricating NPs of desired size and shape having utility in a number of products.
Several of the materials/structures biosynthesized by several microorganisms (bacteria, algae, cyanobacteria, fungi and viruses), plants and animals naturally can indeed be synthesized in laboratories using them even on commercial scale (Pathak *et al*., 2019c) [181]. This can lead to the development of a very attractive probability of having ecofriendly or commonly called as "green synthesis". Therefore, for synthesis of nanomaterials, various chemical, physical, biological and hybrid techniques are available. Out of various techniques, for synthesis of desired nanomaterial the choice of technique to be used for synthesis depend on the material of interest, their sizes, type of nanomaterials, and quantity. Anyone of the following approaches can be employed for synthesis of nanomaterials utilizing biological ingredients, which are listed as follows (Richa *et al*., 2017) [183]:

- Employing intact /whole cells of bacteria, fungi, yeasts, algae, actinomycets, cyanobacteria and other microorganisms.
- Using cellular enzymes or extracts of algae/fungi/ plant or its parts.
- Using templates such as membranes, diatoms, DNA and viruses.

Synthesis of Nanoparticles Utilizing Biomolecules Such as Slime Layers, DNA and UV-Screening Compounds
Tendency to integrate with inorganic materials makes biological systems unique. This property is of great use for synthesis of NPs and for obtaining superlattices, hierarchical structures or organized arrays of inorganic materials utilizing biological systems (Richa *et al*., 2017) [183]. In biological systems of different microorganisms components such as S-layers (slime layer), DNA or various membranes are present which have periodic order of long-range in terms of some of their constituent molecular groups. Hence, some of such periodic active serve as anchorage sites for preformed NPs. Some protocols have been devised which synthesizes NPs utilizing biological templates such as membranes and DNA (Richa *et al*., 2017; Rajneesh *et al*., 2018b) [183, 156]. Microorganisms have capacity to interact with metals which come in their contact and on further reactions lead to the formation of NPs. Because of the complex nature of biological cells, it becomes difficult to understand the interactions between metals and cells. Polymeric materials such as exopolysaccharides secreted by several microorganisms contain functional groups such as carboxyl, hydroxyl and phosphate anionic groups, which form complexation with metal ions by binding extracellularly. The chemical processes such as methylation, demethylation, reduction and oxidation are responsible for reaction of cells with ions or metals. The most primitive and ancestral groups of photoautotrophic organism on Earth "cyanobacteria", serves as a potent source of natural compounds of great pharmacological and commercial potentials. They have fairly large amounts of phycobiliproteins, the water-soluble fluorescent light harvesting pigment and novel UV-screening compounds such as scytonemin and MAAs, which are biosynthesized under the stress conditions of damaging UVRs (MubarakAli *et al*., 2012; Pathak *et al*., 2017a; 2019b) [124, 154]. Hence, cyanobacteria may be a suitable/potent candidate for green synthesis of MNPs (Pathak *et al*., 2019c) [154]. MAAs are a class of compounds which are colorless, water-soluble and photostable which absorb UVR, similarly as inorganic compounds such as ZnONPs and ZnO (Bandaranayake, 1998; Singh *et al*., 2014b) [8, 203]. Through oxidation of

ZnONPs, surface-coated MAAs significantly reduce the risk of generation of free radicals (Pinnell, 2003). Hence, it can be expected that conjugation of ZnONPs with MAAs may result in considerable sunscreening activity. Synthesis of such conjugated nanoproducts/NPs from biological entities can be achieved through one of the following mechanisms/methods (Cederquist and Keating, 2009) [19]:

1. Biofunctional linkers aided covalent binding
2. Electrostatic adsorption
3. Specific affinity interactions
4. Chemisorption of thiol derivatives directly

Electrostatic adsorption is employed for physical fixation of biomolecules on the surface of NPs. The NPs and biomolecules have opposite charges which result in the biosynthesis of the NPs-biomolecule complex. In comparison to other NPs, synthesis of ZnONPs utilizing cyanobacteria is comparatively less endeavoured. Singh *et al*. (2014b) [203] attempted for biosynthesis of ZnONPs from the cellular extracts of cyanobacterium *Anabaena* strain L31 and these biosynthesized ZnONPs were conjugated with MAA shinorine. Treatment of these novel ZnONPs-shinorine bionanoconjugate to *Anabaena* strain L31 showed decrement in generation of ROS *in vivo* by ~75% as compared to ZnONPs alone. These ZnONPs-shinorine bionanoconjugate possessed desired properties for their potential use in development of environmental-friendly natural sunscreen filters/agents. Similarly novel bionanoconjugate of vaious MNPs with scytonemin and other MAAs can be made and their potentials as photoprotectants and antioxidants can be studied.

Bionanoconjugates of Cyanobacterial MAA with ZnONPs

Biosynthesis of MNPs have been attempted by several researchers/workers employing biological routes (Sharma *et al*., 2009; Zhang *et al*., 2011; Otari *et al*., 2014; Liu *et al*., 2014) [193, 253, 133, 252]. However, less or very scarce studies are available depicting the use of cellular extracts of cyanobacteria in synthesis of MNPs (Sharma *et al*., 2009) [196]. As mentioned in earlier sections Singh *et al*. (2014b) [203] demonstrated novel biosynthesis of bionanoconjugate of ZnONPs and shinorine. The cell free extract of *Anabaena* strain L31 reacted efficiently with $ZnNO_3$ for biosynthesis of ZnONPs. The biosynthesis of ZnONPs was indicated from the absorption peak at 370 nm, characteristic for ZnONPs, of the reaction mixture (Zhang *et al*., 2002) [251]. Sharp peak at 374 nm of was also reported for ZnONPs biosynthesized by utilizing the biomass of *A. hydrophila* (Jayaseelan *et al*., 2012) [79] but the exact mechanisms/reactions involved in biosynthesis of ZnONPs still could not be disciphered. From previous studies it was found that cysteine residues or free amine groups of proteins or negatively charged carboxylate groups of enzymes aids in binding of these biomolecules to NPs (Sharma *et al*., 2009; Jayaseelan *et al*., 2012; MubarakAli *et al*., 2012; Singh *et al*., 2014b) [79, 124, 203]. Size of NPs varies depending upon the routes and conditions of their synthesis (Jayaseelan *et al*., 2012) [79]. It is believed that conjugation of MNPs with biomolecules such as UV-screening compound shinorine, allows the overall stabilization of the conjugate system and further it also induces novel biocompatible functionalities onto the NPs which provide them significant potentials for their wide applications (Crespilho *et al*., 2009; Molina *et al*., 2011; Richa *et al*., 2017) [31, 122, 144]. Change in the pH of the system causes change in the agglomerate size and zeta potential and this could be utilized as a predictive tool of nanotoxicity (Sharma *et al*., 2009; Brar *et al*., 2010) [196, 12]. Under neutral conditions (pH=7), shinorine exists in protonated form, and it is well established that out of different functional groups, carboxylic group shows high tendency for complexation (Güngör *et al*., 2010; Zhang *et al*., 2008; Richa *et al*., 2017) [62, 252, 144]. Ashift in zeta potential was observed from +30.25 mV to -3.75 mV in the samples which reflected the interaction of functional groups of shinorine which were negatively charged (Singh *et al*., 2014b) [203]. Effecient dissipation of absorbed radiation as heat (less toxic form of energy) without producing ROS makes MAAs unique UV-screening compounds (Conde *et al*., 2000; Richa and Sinha, 2015a; Richa *et al*., 2017) [30, 143, 144]. Most probably, the electrostatic attractive forces play crucial role in interaction between UV-screening compound shinorine and ZnONPs. For fixing biomolecules such as shinorine on the surface NPs, electrostatic adsorption is the major approach (physical) employed wherein biomolecules such as MAAs, enzymes and proteins having opposite charges are expected to form NPs-biomolecules bionanoconjugates (Aubin-Tam and Hamad-Schifferli, 2008) [4].

Conclusions

Biosynthesis of novel bionanoconjugates is a new and interesting field of research. For such biosynthesis background of biomolecule concerned and NPs to be used is mandatory. Knowledge of structure, chemical nature and mode of biosynthesis of both the interacting units of any bionanoconjugate is needed for their successful conjugation and synthesis. This field is still in its infancy stage and very few reports are available related to such bioconjugates especially with UV-screening compounds such as MAAs and Scy. These compounds in addition to their photoprotective properties play significant roles as antioxidant, as intracellular nitrogen reservoir, as compatible solutes and also significantly contribute to defense against desiccation, thermal, salinity and oxidative stress conditions. Their chemical properties such as high-UV absorption coefficients, effective capacity of UV-filtering and capability of preventing UV-induced skin damage make them of great use in the field of cosmetics. In the last decade significant advancements in the knowledge have been made in the field of Scy and MAAs regarding their genetics and biosynthesis. Also, tremendous progress has been achieved in the field of green synthesis of MNPs and for biosynthesis of nanoconjugates of such value added biomolecules, further studies are needed. Such information can be utilized for the commercial production of Scy and MAAs based nanoconjugates and their applications in various spheres of life.

Conflict of Interests

Authors declare no conflict of interest

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