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Nanotechnology to Nanotoxicity, Showing its Injuries Concerns on Human Health

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Abstract: *Nanotechnology is widely used in medical applications and personal care products for the potential benefits of diagnosis and treatment. Nanomaterials and nanodevices s are being produced intentionally, unintentionally and manufactured or engineered by different methods and release into the environment without any safety test. Nanotoxicity has become a subject of concern in nanoscience and nanotechnology Because of increasing toxic effect of nanomaterials on living organisms The technical advances in nanotechnology must be balanced with the potential human health and environmental adverse effect. The Mechanism Underlying The Toxicity Of Nanomaterials Have Recently Been Studied Intensively. An Important Mechanism of nanotoxicity is Generation Of Reactive Oxygen species (ROS). Over production of ROS can induce oxidative stress resulting in cell failing to maintain normal physiological redox regulated functions. This in turn leads to DNA damage unregulated cell signaling, changes in cell motility, cytotoxicity, apoptosis and cancer initiation.*

Keywords: Nanoparticles, Nanotoxicity, ROS, Fullerenes, DNA damage, oxidative stress

I. INTRODUCTION

In the term nanotechnology, the prefix "nano" is termed to as a Greek prefix that means 'dwarf' or anything very small and depicts one thousand millionth of a meter. Nanoscience is the study of the molecules and structure having the size between 1 and 100 nm, the technology which use in it's practical application is called as nanotechnology. As for consideration, single human hair is 60000 nm thickness and 1 nm is the radius of the DNA double helix. (1)At California Institute of technology in the annual meeting of American physical society give a lecture on entitled "there's a plenty of room at the bottom" (1)Nanotechnology has applications in different areas of human activities like health, food, nutrition, water treatment, engineering and production and also in our daily life. In 2014 is is reported that 6214 organizations from 32 countries have been using nanomaterials in 1814 products, most of which (about 42%)are in the field of health. (14) The period in between 2011 and 2015, there was a 30-fold increase in nanomaterial products and an approximate global market of over $1 trillion in 2018 (8).With the rise of marketing in nanotechnology, the main question whether nanomaterials possess toxicity has started to appear on the agenda. (14)nanomaterials shows different physicochemical properties than the parent bulk material, that may contribute to potential source of toxicity from nanomaterials. (4)In the review, nanotechnology is discussed, because it is an important challenge and double edged sword that awaits for future technologies and medicines.

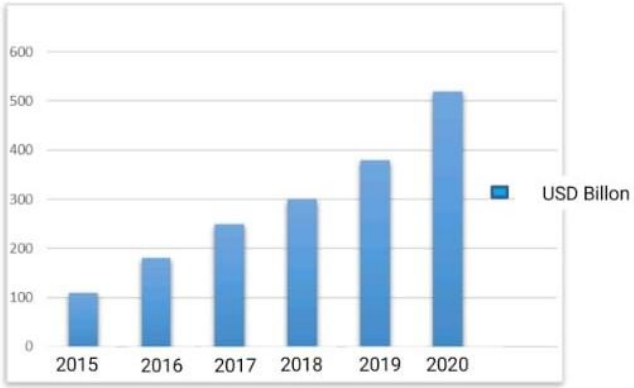

Fig. 1 Nanomaterial products and its approximate global market

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II. HISTORY OF NANOTECHNOLOGY

The concept of nanotechnology is not new, many researchers are working on it from years. Here We have mentioned some milestones in research of nano :-

1959:Richard feyman introduced the concept of manipulating matters at atomic level.

1974:-Norio taniguchi, was the first to use nanotechnology to describe semiconductor process that occurred on order of nanometer.

1980:_golden era of nanotechnology began kroto, Smalley and curl discovered fullerenes.

1980: Eric Drexler takes up Feymans' idea that "there is plenty of room at the bottom" and also taniguchi's term nanotechnology in book titled, "Engines of creation - coming era of nanotechnology."

2000 jan :President Bill Clinton advocated for funding of reasearch in this emerging nanotechnology.

2003:-President George. W. Bush sign into the law the 21st century nanotechnology research and the development act. (2)

III. NANOMATERIALS

Nanomaterials is the material which has the any external dimension in nanoscale .(3). The toxicity of nanoparticles can be determined by their complexity for predicting potential toxicity.. The Toxicity of nanomaterial depends on the primary characteristics of the particle and also on some of the secondary characteristics(4)

1. Tio2:-In this Tio2 molecule, two arrangements are founded such as Anatase and Rutile. The Rutile form has applications in the sunscreen products, cosmetics and food additives. Tio2 reported to penetrate the hair follicles on skin, they are found to trap in oil pores and hairs in skin. The Anatase form has applications in photocatalytic air purification, self cleaning surface, solar cell, paints. (4)
2. Silver :Recently the interest in study of silver nanoparticles is increased with to their behaviors,because of their unique physical, chemical and biological properties. Silver nanoparticles are known to have unique property in surface plasmon resonance, electrical resistance. A research works have been conducted to investigate potential applications and properties in the anti microbial agent for wound dressing, anticancer agents, water treatment and electronic devices. (5)
3. Gold :Gold nanoparticles are present in colloidal form and they are helpful in color stained glass, since many years. It is also used in cancer treatment, in vivo sensor, identification of bacteria, identification of enzyme.
4. Zinc : Nano specific toxicity can be investigated by the use the of nanoparticles of the zinc oxide, by comparing the changes in gene expression or cytotoxicity respective to bulk zinc oxide. Zinc oxide nanoparticles are being studied to determine if they can be used safely as a UV filter in sunscreen or any other cosmetic products. There is no detection of the Dermal penetration determined using parane in the vitro model.

Carbon nanotubes: The toxicological investigation done on the carbon nanotubes shows that, they may produce pulmanory toxicity, lung inflammation is also reported. MWCNT can also cause the mutation in epithelial cells in vitro and in vivo, inflammatory and toxicity activities are related to the defects in nanotunes structures. (4)

ENP	Applications
Carbon nanotubes	Computers, plastic, batteries, super capacitors, aircraft, sporting goods, car parts, concrete, textiles.
Titanium dioxide	Cosmetics, sunscreen lotions, skin care products, food colourant, paints, photocatalyst, packaging.
Graphene	Nanofiltration, ultrafiltration, energy storage devices, optoelectronics, photovoltaic cells.
fullerenes	Cancer treatment, removal of organo-metallic compounds, X-ray constrating agent, anti viral therapy.
Zinc oxide	Contaminant sensors, photocatalysts, gas purification, bottle coatings, skin care products.

Table.1 Engineered Nanoparticles and its Applications

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IV. NANOTOXICITY

Definition:

Nanotoxicity term is used to determine the adverse effect of nanoparticles on health of human or environment. To determine toxicity, a multidisciplinary study is requiren which include the chemistry, physics, toxicology, biology, material science, geology, medicine and pharmacokinetics. (6)

Physical and chemical factors affecting nanotoxicity

1. Size and shape :- nanoparticles cause cell damage by penetrating cell membrane and other biological barrier. Studies has reported increased toxicity of nanoparticles when correlated with their larger bulk particles. Minimum Aggregation potential for smallest silver nanoparticles (i.e,10nm VS 35 and 600 - 1600 nm) and was maximally gathered in gills and liver of fish. (7)acute and chronic toxicity effect of bulk and nano ceo2and Ag nanoparticles are studied. The motility rate of Ag and AgNP were follows :micro - Ag at 0.1mg/l was 13% and at 1mg /L was 80 %, while for AgNP at 0.1mg/l was 57%and at 1mg/l was 100%.carbon nanotubes have show to produce death of kidney cells and also retard their cell growth (9)Zno nanocrystals with hexagonal shape shows higher activity than rod shaped crystals. As the contact area increases their biocompatibility also increases. In addition external morphology may affect uptake into cell as follows :Rods /Spheres >cylinder >cubes. (10)
2. Particle surface and surface charges :- In the biomedical applications, the silica mesocompounds are mainly studied nanomaterial. Colloidal silica and mesoporous silica posses different surface area and pore structures also different pore volume, have differential nanotoxicity for the cell uptake and immune response. fullerene induced toxicity can be determine by different functional groups attached to fullerene surface .(10)
3. Surface containing groups :- various surface ligands such as 8-mercaptooctonoic acid, 12-mercaptododecanoic acid and 16-mercaptohexadecanoic acid are present on the copper nanoparticles, that tends to shows different oxidation of surface which later leads to the generation of the Reactive Oxygen species at different levels. (11)
4. Solubility :-Nanoparticle-induced cytotoxicity is influenced by intercellular solubility. Copper oxide nanoparticles are more toxic than its soluble metallic copper. (12)
5. Aggregation /mode of interaction with the cells :- Graphene nanomaterial has many biomedical applications containing bacterial inhibition, sensors, cell labeling and drug delivery. Toxicity of this two dimensional carbon based nanomaterial Graphene and Graphene oxide depends on whether or not they aggregate and how they interact with cells (13)
6. PH of system :- Nanoparticles of fe3o4 possesses intrinsic peroxidase activity in the acidic pH, and at neutral pH it shows catalyze like activity. Studies indicates that acidic pH leads to Fenton and Fenton like reactions which causes production of hydroxyl radicals. (10)

V. ENTRY ROUTES OF NANOPARTICLES IN BODY

1. Ingestion :- Gastrointestinal tract has been divided into upper which consist the esophagus, stomach, duodenum and lower consist of small intestine and large intestine.A large number of nanoparticles inhaled by any means can cross the trachea from the mucociliary cells and then enter the stomach.
2. Inhalation :- Size of nanoparticles has important role in ability to invade human respiratory tract. Larger nanoparticles (5-30micrometer) remain in nasopharangeal region, small nanoparticles (1-5 micrometer) deposit in tracheobronchial region.
3. Skin exposure :- Nanomaterials have a wide application in the field of cosmetics. It is estimated that cosmetics have Tio2 nanoparticles (70/80%),Zno nanoparticles (70%)and Ag Nanoparticles (20%).Size influences the entry of the nanoparticles in body. In human Dermal fibroblast mitochondrial damage is observed , after 4 hours of exposure to the 10,50 and 100 mg /l of 20 nm Zinc oxide nanoparticles, activates the protein P53. (14)

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VI. TOXIC EFFECT OF NANOMATERIALS ON BODY SYSTEMS

1. Cardiovascular system: Gold and polystyrene are cationic nanoparticles that exhibit hemolysis and blood coagulation, while anionic nanoparticles are less toxic. When particles from diesel exhaust are inhaled at the maximum concentration they changes hearts rate in rats with hypertension and leads to direct effect on pacemaker activity of the heart. (15)
2. Central nervous system :- Different pathologies such as hypertension and allergic encephalomyelitis is linked and related with increased permeability of the blood-brain barrier to the nanoparticles in an experimental setup.blood brain integrity is changed by the surface charges which are present on nanoparticles. Nanoparticles e causes production of Reactive Oxygen species, which leads to pathogenesis of parkinson's and Alzheimer's. (16)
3. Integumentary system :- Different nanoparticles ranging from size 50-500 nm used in cosmetic products of concentration at least 3%.The dermatological effect of nanoparticles depends on whether they penetrate through the skin or not. In vitro studies have shown that carbon nanotubes can localize and initiate an irritation response in human epidermal keratinocytes. (17).
4. Circulatory system :- In study if nickel nanoparticles in rats, toxic for the heart effect on organs such as liver, lung, spleen is observed after intravenous administration. (18)
5. Digestive system: In zebra fish after exposure to silver nanoparticles and copper nanoparticles from contaminated good disrupt endogenous microbiota. (19)
6. Immune system: An increase in number of white blood cells, liver and spleen are affected after exposure to iron oxide nanoparticles. (20)

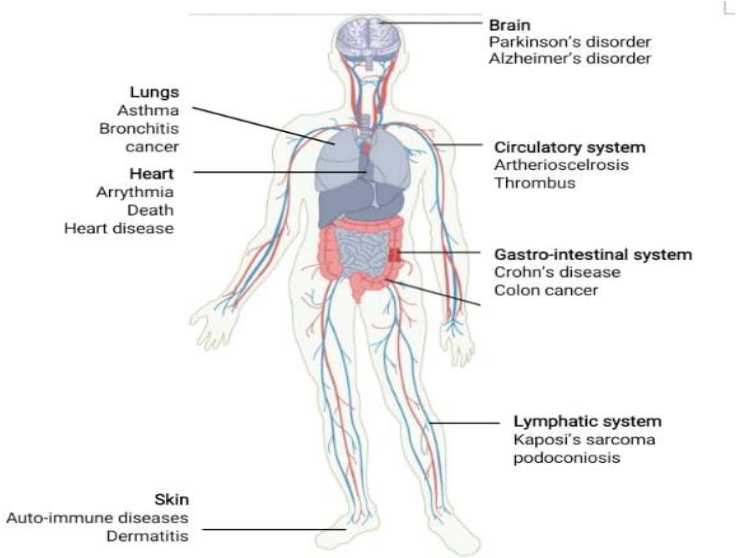

Fig. 2 Toxic effect of nanoparticles on body system

VII. MECHANISM OF TOXICITY OF NANOMATERIALS

Many studies have attempted to explain the toxicity of the nanoparticles. Nanomaterials have the differential properties from their bulk compounds which consist of surface /volume ratio, size, shape and surface coating. (7)

Overproduction of Reactive Oxygen species: Oxidative stress is produced due to the imbalance between cellular capabilities to reduce the Reactive Oxygen species and cells ability to defence decreased due to the production of ROS.(7)ATP are synthesizer by reduction of molecular oxygen to water, in mitochondria through series of coupled proton and electron transfer reactions. During these, a small amount of oxygen is not completely reduced, which tends to form anionic superoxide radicals and which then forms oxygen radicals. Biologically relevant ROS includes superoxide anion radicals, singlet oxygen, hydrogen peroxide and hydroxyl radicals. It has been studies that age related degenerative

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diseases caused by Reactive oxygen species and oxidative stress such as cardiovascular disease, arthritis, parkinson's disease, cancer and diabetes (10)

DNA damage : Tio2 is chemically inert but it can cause harmful health effects, like respiratory tract cancer in rats (21)Gold nanoparticles are administered to rats and are evaluated for their DNA damage in Cerebral cortex. Gold nanoparticles of 10 nm and 30 nm diameter are administered to rats, results in both causing DNA damage, although chronic one shows higher DNA damage. (22)ROS critically target DNA. Oxidative DNA damage involve DNA protein crosslink, base and sugar lesions, single and double strands breaks and formation of abasic sites (23)

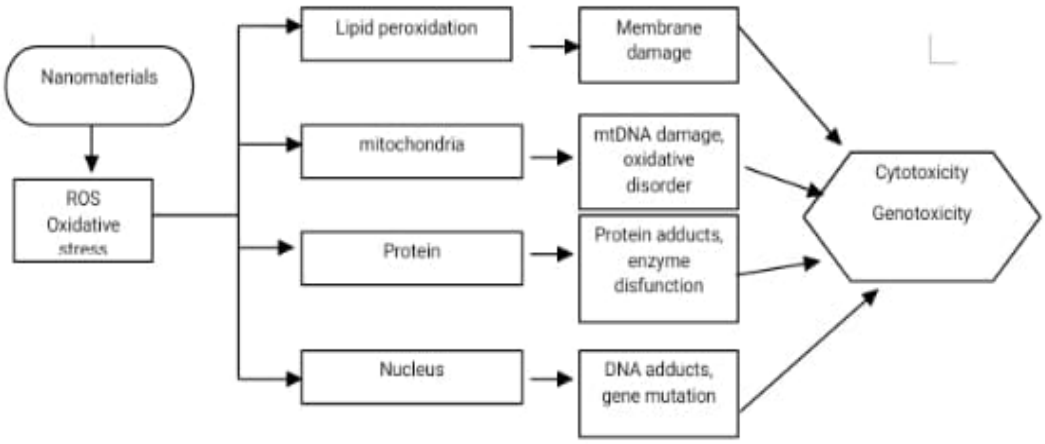

Fig. 3 Mechanism of toxicity of nanomaterials

Toxicity Testing :- In vitro studies are performed more widely than In vivo experiment. To determining toxicity dosing may be a crucial factor. To determine the toxicity of the nanoparticles in vitro models are used such as sedimentation diffusion and dosimeter . (24) Cell viability and the proliferation can be determined by In vivo studies, such studies are used to determine the toxicity. Gene expression analysis, genotoxicity detection and In vitro hemolysis also used for determination. Microscopic and spectroscopic methods are used to determine the physicochemical structure of cells such as scanning electron microscopy, x-ray spectroscopy (SEM-EDX), atomic force microscopy (AFM) and fluorescence spectroscopy are be used to determine the toxicity. When these methods used together with each other it becomes easier to detect nanotoxicity. (25).A Previously conducted studies list regarding nanomaterials, purpose of test and toxicity test is given in table below. (14)

Table No.2 Toxicity test for nanomaterials

Toxicity test	**Purpose**	**Nanomaterials**
Micronucleus test	Genotoxicity	Different types of nanoparticles
Transmission electron microscopy	Determination of intracellular localization	Tio_2,silver,fullerene
Light microscopy	Physicochemical properties	Single walled carbon nanotubes,silver
Commet assay test	DNA damage	Metal,metal oxide
Tetrazolium salts	Cell viability	Carbon nanoparticles,fullerenes
Alamar blue	Cell viability	Quantam dots
ROS production	Oxidative stress	Tio_2
Lipid peroxidation,vitamin E	Oxidative stress	Single walled carbon nanotubes

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VIII. CONCLUSION

Particular attention should be paid to nanomedicine, as these are areas where exposure would be greater. Their is a growing global debate on the ethical, social aspects of the nanotechnology, in particular the potential risk to human health and the environment caused by manufactured nanomaterials. Nanotechnology can be defined as a "double-edged sword", "the same property that proves it very useful but also the properties that can increase their harmfullness".Although current toxicity testing protocols is generally applicable to identify deleterious effects associated with nanoparticles, the mechanism of action that govern toxicity of nanomaterial are the subject of ongoing research. Research into the new analytical methods is also required to address the special properties of nanoparticles.

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