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A SYSTEMATIC REVIEW ON GREEN SYNTHESIS OF NANOPARTICLES AND ITS MEDICAL APPLICATIONS

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Abstract

In recent years the nanotechnology has vast applications in the field of medicine. Nanotechnology will cover the wide range of research field, needs pure interdisciplinary and multidisciplinary efforts. Nanotechnology has the potential to develop new sensors with the help of nano particles synthesized using the biological green synthesis of metal nanoparticles in nanometer scale. These nano sized particles have an enormous application because of its non-toxicity, non-immunogenicity and capable of getting modified to target specific applications. These metal nanoparticles can be used to overcome many problems and it can treat diseases by which it may adaptable to any environment. Various metal nanoparticles (NPs) such as copper, silver, gold, zinc, etc have been synthesized using plant extracts. This paper deals with advancement and emerging techniques in nanoparticle synthesis for the development of a nanosensor for medical applications.

Key words: Nanotechnology, green synthesis, plant extracts, sensor fabrication and medical applications.

Introduction

A device which can be able to sense changes in the physical parameter and convert it into signals which can be measured is called a sensor. Initially the physical value can be acquired by the sensor to convert it as the crave signal for processing. Nano is the measurement of one billionth of a single unit as scientifically, i.e. a billionth of a meter is nanometer. Nano science is the study of properties of material's atomic molecular and macromolecular scale, whereas in nanotechnology the scientists design, construct, make devices and systems for controlling their shape and its size on a nanometer scale. The combination of nano science and nano technology makes the advances in nano medicine. Nano medicine development of fields of analysis and treatment in biological systems at the cellular and sub- cellular levels has provided revolutionary methods for the detection and prevention of certain fatal diseases.

These are mainly achieved by the nano scale materials which have unique properties compared to larger ones and sometimes the nano scale range can increase to 1,000 nm. Since a number of biological organisms, such as proteins, antibodies, viruses and bacteria, are located within the nano range, they are often referred to as Nano-biological materials. The high tendency to design non-biological nano-materials is due to their specific functions and the properties of nano scale biological materials. At the same time, nano scale materials can be used to access or manipulate non-biological nano materials because they have the right size (Mousavi *et al*., 2018). The properties of nanoscale materials are decided by the quantum impacts of a nanoparticle (Hewakuruppu *et al*., 2013).

NPs are mainly divided into two categories known as organic and inorganic NPs. Organic NPs are nanoparticles which contains carbon NPs such as fullerenes, carbon nanotubes, etc. While inorganic NPs contains magnetic NPs, noble metal NPs such as silver (Amlan Kumar Das *et al*., 2012), gold (Hideaki Itoh *et al*., 2004), semi-channel (Tianyou Peng *et al*., 2005) and zinc oxide (Hingorani *et al*., 1993). Metallic NPs like silver (Sathishkumar *et al*., 2009), gold (Martin Moller *et al*., 1996), copper (Brindaban *et al*., 2007) are showing a good functional properties so it is used as an essential tool for the researchers to their biomedical applications.

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The most widely used metallic NPs are silver, aluminium, gold, zinc and platinum and titanium, palladium, iron and copper whereas the gold NPs are used for both therapeutic and recoloring purposes.

Synthesis of Nanoparticles

NPs can be synthesized using different methods which includes physical, chemical, biological and hybrid technologies. The two approaches for nanoparticles synthesis are commonly known as bottom up approach which uses physical process and top down approach done with the help of chemical and biological process (Bali *et al*., 2006). The top-down and bottom-up approach are shown in fig. 1.

In top-down approach a large material is breaking into smaller nano sized particles without considering the atomic level. An example for physical methods is laser ablation (Szu-Han Wu *et al*., 2004), vacuum vapor deposition (Lisiecki and Pileni, 1993), pulsed wire discharge (Zhou *et al*., 2008) and mechanical milling (Tanori and Pileni, 1997). In bottom up approach nanoparticles are synthesized either by atoms, molecules or cluster. The chemical methods used for synthesis are chemical reduction (Song *et al*., 2004), microemulsion procedures (Kapoor and Mukherjee, 2003), electrochemical (Mott *et al*., 2007), hydrothermal methods (Janafi *et al*., 2000), microwave assisted (Panigrahi, 2006) and non-chemical reduction (Huang, 1997). The biological methods used for synthesis of metal NPs utilizing the plants inactivated tissue (Shankar *et al*., 2004), plant extracts (Sajadi *et al*., 2016), enzymes (Willner *et al*., 2006) and microorganisms (Klaus *et al*., 1999).

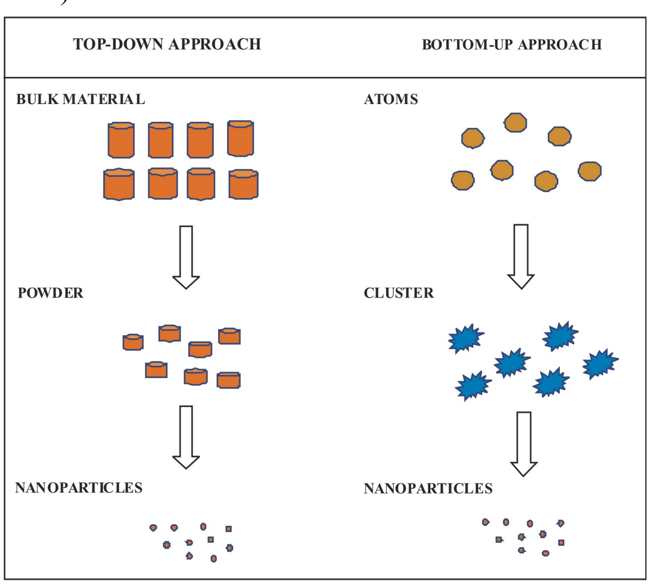

Fig. 1: Synthesis of NPs Using Top-down and Bottom-up Approach.

Is biological green synthesis may be beneficial over conventional physical and chemical methods ?

The conventional physical and chemical techniques produce toxic and harmful byproducts that may be environmentally hazardous therefore it cannot be used for medicinal field due to health issues (Prashar *et al*., 2009 and Parashar *et al*., 2009). These conventional methods can produce in bulk quantities of NPs with definite shape and size over a period of time but it is very complicated process, costlier and outdated technique. Nano particle produced via green route is the need of the hour as it is eco friendly and non toxic (Chauhan *et al*., 2012; Daniel and Astruc, 2004 and Li *et al*., 2011). This green synthesis using biotechnological tools is safe and ecological sound for nanofabrication to create eco-friendly products. Green nanobiotechnology using the plant extracts (Jain *et al*., 2009; Song *et al*., 2009 and Bar *et al*., 2009), bacteria (Saifuddin *et al*., 2009), fungi (Bhainsa and D'souza, 2006) and enzymes (Willner *et al*., 2007) or its byproduct protein (Esteban-Cubillo *et al*., 2006) are used for synthesizing the nanoparticles. Green nanobiotechnology acts as an backup of synthesizing an eco-friendly, stable and biocompatible NPs (Narayanan and Sakthivel, 2011).

Green Synthesis of Nanoparticles

Many researchers have searched an efficient method of green synthesis of metal NP over decades (Raveendran *et al*., 2003; Iravani and Zolfaghari, 2013 and Mittal *et al*., 2013) and there arises the idea of using plant and plant extracts (Thakkar *et al*., 2010) rather than microorganisms (Mandal *et al*., 2006). The plant and plant extract is an uninvestigated method which offers absolute results. The synthesis of metal NPs over plant extracts has many advantages than biological methods by eliminating the action of cell cultures. Moreover, by enhancing the use of plant extracts there it gains a loss of pathogenicity. This paper examines the synthesis of metal NPs by using plant extracts.

Green synthesis of NPs is based on the bottom-up approach with reducing and stabilizing agents. Three fundamental steps for synthesis of NPs are described as follows:

i. Proper selection of solvent medium

ii. Eco-friendly selection of reducing agent

iii. Selection of a non-toxic capping agent for settling the synthesized NPs (Shankar *et al*., 2004; Singh *et al*., 2011).

The general block diagram for the synthesis route is shown in fig. 2.

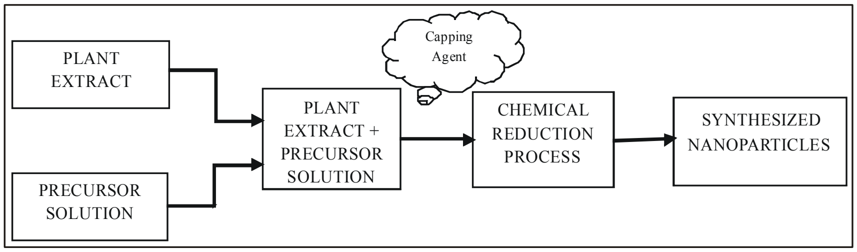

Fig. 2: Block diagram of green synthesis of metal NP's.

1. Example for Green Synthesis of NPs

• Green synthesis of Zinc Oxide NPs using plant extracts *Aloe barbadensis* leaf extract:

Zinc nitrate (99% purity) was taken as solvent medium and *Aloe barbadensis* leaf extract is taken as a reducing agent. There are two different methods for extracting the aloe vera extracted solution. At first process, aloe vera leaves are washed thoroughly, cut them finely and boiled in the deionized water in medium flame. The precipitate was settled at the bottom which indicates the resulting product was obtained. The solution was then filtered and stored in refrigerator for further process. The second process was done by extracting the inner gel of aloe vera leaves, then crushed and ground through thin paste with deionized water followed by filtering with fine mesh. The final product was stored at 10°C for further process.

The aloe leaf and aloe gel broth extracts were prepared at different concentrations such as 50%, 25%, 15%, 10% and 5% using deionized water and the volume was made up to 250 ml. Zinc nitrate was dissolved in the aloe vera extract using magnetic stirrer to attain the constant stirring. When the mixture attains the complete dissolution it was kept under vigorous stirring at 150°C for about 5-6 hours. Then the mixture was allowed to cool at room temperature to eliminate the supernatant. A pale white solid precipitate obtained was centrifuged twice for 15 minutes at 4500 rpm. Then washed thoroughly with double deionized water to remove ions and dried at 80 °C in hot air oven for about 7-8 hours. The resulting precipitate was crushed into powder and it was stored using air tight container for further process.

The characterization using SEM and TEM analysis resulted NPs morphological properties and its size ranges from 25-55 nm (S 35 nm) and it has a spherical shape (Gunalan Sangeetha *et al*., 2011). The other green synthesis of different metal NPs using different plant / plant extracts and its morphological properties are given in the table 1.

Medical Applications of NPs

Applications of Copper NPs

The need for Cu - NPs in the marketing field increases because of its chemical (Nasrollahzadeh *et al*., 2015), mechanical, catalytic and electrical properties (Salvati-Nisari *et al*., 2008). Now a days, it is used as an alternative to gold, silver and platinum in various research areas such as thermal conducting materials and microelectronics applications (Eastman *et al*., 2001 and Lu *et al*., 2001). The NPs synthesized from the plant extract showcase a good medicinal plant properties which helps medication, targeted drug delivery and cosmetic applications (Mallikarjuna and Dig, 2011), wound dressings and biocidal properties (Borkow and Gabbay, 2009 and Rubilar *et al*., 2013), potential industrial utilizations by using the sensors such as gas sensors, catalytic process (Atroad *et al*., 2015 and Nasrollahzadeh *et al*., 2015) high temperature superconductors and solar cells (Li *et al*., 2008; Carnes and Klabunde, 2003 and Yuhas and Yang, 2009). Cu-NPs has a very good physical properties so it is used as an antibiotics. It acts as an bactericide agent to coat hospital equipment, acts as heat transfer systems (Li and Peterson, 2006), effective antimicrobial materials (Wang *et al*., 2002 and Gunduru *et al*., 2007) super strong materials (Kang *et al*., 2007 and Male *et al*., 2004). Due to its small size, the bactericidal effect of NPs has been increased. Cu-NPs has high surface to volume ratio which makes them a reactive one and it helps to easily attach on the microbial membrane (Narayanan and El-Sayed, 2004). These NPs enhance their antimicrobial activity by ejecting metal ion in solution.

Applications of Au Nanoparticles

• Protein Based Recognition systems: Enhanced Immunosensing:

Protein has large number of complementary binding pairs which is based on the conjugation of nucleic acid that will be beneficial over protein based assembly (Akbarzadeh *et al*., 2014). The coupling system of these biomolecules will be very much useful in the diagnostic applications and it helps in generating the inorganic nanoparticle networks (Huang *et al*., 2009). The electrostatic interactions between the negatively charged citrate over the surface of gold NPs and positively charged protein groups is responsible for the conjugation of proteins on colloidal gold NPs (Rezaei-Sadabady *et al*., 2013). The experimental gold NP-protein conjugate does either direct binding of antigen-gold NPs that bioconjugates in the surface of an modified antibody or the exposure from the surface of derived antibody to free antigen and then to a secondary antibody-gold NPs

Table 1: Different Precursors, Plant / Plant Extract for Synthesis of Nanoparticles.

S. No	Precursor	Plant/Plant Extract	Part Used	Size Of NP's	Shape / Structure / Morphology	Reference
1	Copper Sulphate ($CuSO_4$)	*Caparris zeylanica*	Leaves	50-100 nm	Cubical structure	(Saranyaadevi *et al.*, 2014)
2	Copper II Sulphate Pentahydrate ($CuSO_4.5H_2O$)	*Citrus medica Linn.*	Fruit	20 nm	Crystalline	(Sudhir Shende *et al.*, 2015)
3	Copper Chloride ($CuCl_2$)	*Citrus lemon*	Fruit	60-100 nm	Nearly Spherical	(Jayandran *et al.*, 2015)
4	Cupric Chloride Dihydrate ($CuCl_2.2H_2O$)	*Ginkgo biloba Linn*	Leaves	15-20 nm	Spherical	(Mahmoud Nasrollahzadeh and Mohammad Sajadi, 2015)
5	Copper Acetate $Cu(CH_3COO)_2$	*Calotropis p-rocera L.*	Latex	15 ± 1.7 nm	Polydisperse Spherical	(Harne *et al.*, 2012)
6	Copper II Acetate ($Cu(CH_3COO)_2H_2O$)	*Aloe Vera F.*	Flower	40 nm	Spherical	Karimi and Mohsenzadeh, 2015
7	Tetrachloroaurate ($HAuCl_4$)	*Garcinia mangostana*	Fruit	540-550 nm	Crystalline (FCC)	Kar Xin Lee *et al.*, 2016
		Polyscias scutellaria	Leaves	5-20 nm	Crystalline (FCC)	Yoki Yulizar *et al.*, 2017
		Ocimum sanctum	Leaves	~30 nm	Hexagonal	Daizy Philip and Unni, 2011
		Gymnocladus assamicus	Pod extract	(4.5 ± 0.23) - (22.5 ±1.24) nm	Hexagonal, Pentagonal & Triangular	Chanadan Tamuly *et al.*, 2013
8	Auric Acid (Gold III Hydroxide)	*Chenopodium album*	Leaves	10-30 nm	Spherical	Amarendra Dhar Dwivedi and Krishna Gopal, 2011
9	Silver Nitrate ($AgNO_3$)	*Chenopodium album*	Leaves	10-30 nm	Spherical	Amarendra Dhar Dwivedi and Krishna Gopal, 2011
		Geranium	Leaves	16-40 nm	Polydisperse	Shiv Shankar *et al.*, 2003
		Ocimum sanctum	Leaves	10-20 nm	Spherical	Daizy Philip and Unni, 2011
10	Zinc Oxide (ZnO)	*Coptidis Rhizoma*	Dried Rhizome	2.9-25.2 nm	Spherical & Rod shaped	Nagajyothi *et al.*, 2014
		Solanum nigrum	Leaves	50 nm	Wurtzite, hexagonal & quasi spherical	Ramesh *et al.*, 2015
		Cocus nucifera	Coconut water	20-80 nm	Spherical & predominantly hexagonal	Krupa and Vimala, 2016
		Gossypium	Cellulosic fibre	13 nm	Wurtzite, spherical & nanorod	Aladpoosh and Montazer, 2015
		Moringa olifera	Leaves	16-20 nm	Spherical	Elumalai *et al.*, 2015

conjugate. Biosensors are developed for the immunoassays in human serum (Huang *et al*., 2008).

Applications of Ag Nanoparticles

- **Medical diagnosis and treatment of ailment:**

The silver NPs reveals a wide range of antibactericidal, antiviral, anti-inflammatory, anti-tumour, anti-oxidative and antiangiogenic properties over the biological and chemical sensing, imaging, drug carrier and diagnosis of cancer, HIV and AIDS (Alivisatos, 2004; Hong *et al*., 2010; Tripp *et al*., 2008; Samanta *et al*., 2011 and Kumar *et al*., 2011). The near-infrared laser light was directed over the skin of mice and over the tumours, due to the resonant absorption of energy in the embedded nanoshells which raises temperature at the cancerous tissue from 37°C to 45°C. This photothermal heating kills the cancer cells without affecting the surrounding healthy tissues. By treating the mice using nanoshells all the cancer cells were disappeared within 10 days; while in control groups the tumours were started to grow rapidly (Atwater, 2007).

In orthopaedics, the silver nanotechnology has developed rapidly because of its antimicrobial properties. Due to this silver NPs were emerged as a huge impact in the applications of orthopaedics such as tumour prostheses, trauma implants, bone cement and hydroxyapatite coatings for preventing the formation of biofilms. In orthopaedic surgery, the formation of biofilm acts as a major source of morbidity. The use of Ag NPs reduces the risk of infection due to its high tendency of biocompatibility and also achieves promising results in both *in vitro* and *in vivo* conditions (Brennan *et al*., 2015).

Conclusion

This paper deals with the green synthesis and medical applications of the NPs. The essential way to discover a method where it emerges as more authentic, eco-friendly, non-hazardous and environmentally benign when compared to other conventional methods. Green synthesis of NPs accomplishes and makes an efficient way revealing more authentically than other ones. The NPs synthesized using plant and plant extracts have enormous applications such as catalytic properties, antimicrobial activities, biomedical field, ecological areas and drug delivery system. Different morphological properties of metal NPs using green synthesis are discussed and detailed study of applications of NPs are described for their effective use in specific area of interest. This study about the green synthesis of NPs enhance thorough knowledge about green synthesis of NPs and its applications elaborate high demands in the future trends.

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