Green Synthesized Nano Particles Based Inspection of Ethano-Medicinal Flora of Cholistan Desert, Pakistan

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Abstract: Besides the availability of herbal drugs in accordance with their native areas, mankind appreciates the benefits of green gold for curing the diseases from prehistoric times. The advancement to overcome the basic problem of delayed action of these herbal drugs is effectively tackled by the introduction of Nanotechnology specifically in this field. Some of the admiring aspects of this technique are the improvement of the drug delivery system which improves its effectiveness against diseases and worldwide spread of the drug is possible. Deserted land of the Cholistan region, Punjab; Pakistan, provides an excellent source for the supply of many medicinally important plants, attracting researchers for the exploration of Nanomedicines against several diseases. This review emphasizes the importance of Cholistan desert flora and discusses the prospects of the medicinal corridor through the gateway of the Cholistan desert not only in the advanced field of Nanomedicines but also for providing the better living standards.

Keywords: Green chemistry, Nano particles, Flora

1. Introduction

Plant source-based herbal drugs are the natural compounds isolated to formulate the traditional medicines known to the human race from prehistoric times[1]. A large number of medicines almost 90-95% were obtained from natural sources in early age. Herbal drugs are preferred over the others because of their effective therapeutical nature with the less toxic effects on living beings, thus improves the quality of life in all ages of mankind. In the present era of science and technology advancements, the complications of the drug delivery system enhance the focus of many scientists and pharmacologists on the establishment of novel pathways for the efficient performance of herbal drugs. For the sake of maximum performance of herbal drug, it is necessary to deliver the remedial quantity of the drug to the appropriate location in the body[2,3]. For the
sake of achieving these goals, a number of advancements including liposomes, phytosomes, pharma
cosomes, niospheres, microspheres, ethosomes and nanotechnology had been reported
recently. Nanotechnology among other establishments, about 90-95% is responsible for the
production of herbal drugs from the plant extracts of medicinally sustainable flora throughout
the world, during a range of diseases of diverse toxic levels. According to one of the reports,
nanotechnology was responsible for the manufacturing of almost 50% of drugs in the era of 1981-
2007 specifically from the green sources[4]. The shape and compactness of the nanoparticles of
herbal drugs that range from 1-100nm in size are achieved by optimizing various experimental
conditions. Nano size of these herbal drugs is responsible for the availability at a particular site in
the living being with the increased effective surface area against the attacking species that reduce
the chances of possible side effects. Time and again desert plant proved its effectiveness against
a number of diseases by not only in extract form but can also be applied directly in many cases
for the curing purpose. Widening this aspect of desert flora, Cholistan desert spread over an area
of about 26,000 Km², located along the south of Punjab of Pakistan[5], exhibiting about 154 plant
species belongs to 106 genera and 38 families can provide the traditionally and pharmacologically
important green gold, as desert plants being rich in metabolites can work wonders against diseases.
On addition of nanotechnology to this flora of desert plants can progressively increase the
effectiveness of their drug material. Compounds like terpenes, steroids, phenolics, flavonoids,
quinones, anthocyanidins, saponins, antioxidants form the majority of the phytochemical
composition of Cholistan desert plants. Thus, their extracts are employed by native people to cure
a wide range of human ailments[6]. To enhance the medicinal importance of flora of the Cholistan
desert, researchers are now utilizing nanotechnology to make their drug material more available
to the mankind effectively and efficiently. In this specific perspective, not much study has been
done on the medicinal exploration of flora of the Cholistan desert. Very few species have been
reported for synthesizing nanoparticles of metals like Ag, Au, CuO, and ZnO etc. as in Table I.

Anti-microbial, anti-diabetic, anti-analgesic, anti-plague are some of the worth mention biological
activities possessed by green gold of Cholistan desert[7]. This review presented the encyclopedic
approach to explore the already investigated and utilized flora of Cholistan Desert green gold, so
far been neglected, provides the treasure for the betterment of suffering humanity as well as an
uplift country’s economy exhibiting the diverse range of prospects too.

2. Importance of Nanoparticles

Synthetic and semi-synthetic polymer-based NPs, ranges from 1-100 nm in size, primarily
preferred for its drug delivery action at a specific targeted place. NPs are applied in the
encapsulated format of NPs delivery enables them to easily interact with the blood and thus on
dissolving promotes the optimum amount of medicinal drug to the targeted[8]. Compactness and
resilient drug-delivering capacity to the diseased site of this technology makes them accountable
over other medicines. Barriers in the living beings like acidic pH of the stomach, liver metabolism
hindered the drugs to perform with optimization but the small size of NPs facilitates its passage
through these barriers with ease resulting in an increased amount of circulation in the blood.
Besides this, NPs reduce side effects including toxicity of liver and risk of tumor etc[9]. Another
significant feature of NPs is their tendency to perform various functions such as metal-based NPs
(Au, Ag, Cd) used to treat cancer, lipid-based NPs (liposomes, neosomes) are easily
biodegradable, polymer-based NPs (dendrimers, micelle) are the carriers of DNA in protein, peptides and gene therapy, biological NPs (Bovine-albumin serum) are also observed performing important actions in the living beings. The most admiring feature of NPs is that it can perform its therapeutic action on the targeted area without influencing the surrounding environment[10]. Keeping in mind the all above mentioned characteristics, NPs provides the set of exclusive standards that ideal drug should exhibit are more willingly captivated than synthetic drugs.

3. Why green synthesized nanoparticles are preferred over plant extract?

An essential drawback that makes herbal drug less efficient is the prolonged time of action to combat a specific disease at a particular position in the living being. Lack of research in the specific field governed by the herbalist makes this problem even more unbearable. On the other hand, herbal medicines are reported to interact with other medications e.g. antidepressants causing the problem in its therapeutic action, causing side effects on the biological system. While NPs being small in size can show spectacular drug action rate as the available activity area being increased as well as fairly easy to prepare and use. NPs based drugs are encapsulated which is a step forward for the inert nature of drug action making it more effective for disease curing. Time of action taken by herbal medicines is too prolonged resulting in a very slow process while NPs are taken up by the cell because of their nanometer size by capillary action resulting in efficient drug action at a specific target. Thus, NPs increased the therapeutic efficiency as well as the bioavailability of herbal extracts. Some plant chemicals can be toxic to the body or somewhat allergic while carrying drugs via NPs source have no biotoxicity of the carrier thus safe to use with less side effects. Herbal medicines can cause long term negative side effects, preparation of NPs with the help of biodegradable materials results in sustained drug release within the target site over a specific period of time.

4. Methods of synthesis of nanoparticles

There had been observed a lot of diversity in the methodology of NPs both by chemical and physical methods but these to some extent proved hazardous to the environment. An eco-friendly approach involving plant-mediated synthesis of NPs is being used extensively nowadays to promote less toxic cure for living being[11].
Figure 1. General method of green synthesis of nanoparticles

In the case of chemical methods use of toxic chemicals limits their synthesis in the clinical field while the physical methods employ costly techniques like laser lights, UV rays extra hence not considered economical [12]. Effectiveness of plant-mediated synthesis of NPs preferred over the other techniques because of the fact that it produces less residual waste, involves low energy usage, renewable materials that ensure the cost-effectiveness, low risk of hazards and are environment-friendly work that produces less pollution even on the large-scale production. Many microorganisms including fungi, actinobacteria, algae, fungi, yeast, and viruses have been used as source for green synthesis of NPs as reported by [13-15], plant extract-based NPs that have significant importance in medicines have also been cited [16].
By plant extract several nano-particles are synthesized such as; Ag, Au, Mg, Fe, Ca, Cu, Cr, Zn, Pt, Pd, etc. All these NPs are used in herbal drug delivery system. The plants are taken from the Cholistan desert some plants are; Echinopsechinatus, Alhagia urorum, Acacia nilotica etc[69] and many more. The data presented in the table 1 gives insight about the diversity in the application of different herbal plants utilizing the nanotechnology, thus provides the basis for the future aspects.
Table 1. Reported Green synthesized metallic nanoparticles by different researcher using different plant extracts available in Cholistan desert

| Sr. No. | Family      | Scientific name of Plant | Common name of Plant | NPs | Size (nm) | Shape      | Activities of NPs                      | Ref.          |
|---------|-------------|--------------------------|----------------------|-----|-----------|-----------|----------------------------------------|---------------|
| 1       | Mimosaceae  | Acacia nilotica          | Babul or Kikar       | Ag  | 10-40     | Spherical | Reduction of 4-nitrophenol            | [17]          |
|         |             |                          |                      | Au  | 6-12      | Spherical | Catalytic reduction of p-nitrophenol to p-aminophenol | [18]          |
|         |             |                          |                      | Ag  | 10-15     | Roughly circular, Irregular           | Detection of p-nitrophenol | [19]          |
|         |             |                          |                      | Ag  | 20-30     | Spherical | Reduction of benzyl chloride          | [20]          |
|         |             |                          |                      | Au  | 20-50     | Quasi-spherical                       | Detection of nitrobenzene | [21]          |
| 2       | Acanthaceae | Barleria prionitis       | Porcupine flower     | Pt, Pd | 1-2, 5-10 | Spherical | Anti-cancer                           | [22]          |
|         |             |                          |                      | Au  | 10-20     | Spherical (irregular)                 | Reduction of o-nitrophenol | [23]          |
| 3       | Asclepiadaceae | Calotropis procera   | Aak                  | Ag  | 4-25      | Spherical | Antimicrobial                          | [24]          |
|         |             |                          |                      | Cu  | 40-46     | Cylindrical | Anti-cancerous activities          | [25]          |
|         |             |                          |                      | ZnO | 15-25     | Spherical | Photodegradation of methyl orange     | [26]          |
|         |             |                          |                      | Ag  | 19-45     | Cubic     | Anti-microbial                         | [27]          |
|         |             |                          |                      | Ag  | 35        | Cubic     | Anti-oxidant                          | [28]          |
| 4       | Capparidaceae | Capparis decidua    | Karir                | Ag  | 1-19      | Spherical | Anti-oxidant                          | [30, 31]      |
|         |             |                          |                      | Cu  | 1.7-1.15  | Spherical | Anti-cancer                           |               |
| Family          | Genus/Species                  | Form | Material | Shape/Structure     | Activities                                                                 |
|-----------------|--------------------------------|------|----------|---------------------|---------------------------------------------------------------------------|
| 5 Capparidaceae | Capparis spinosa               |      | Ag       | Spherical           | Antibacterial activities                                                  |
| 6 Cucurbitaceae | Citrullus colocynthis          |      | Ag       | Spherical           | Anticancer                                                               |
|                 |                                |      | ZnO      | Flower like, hexagonal, block shaped | Antimicrobial, antioxidant activities                                      |
| 7 Tiliaceae     | Corchorus depressus            |      | Ag       | Spherical           | Antibacterial activities                                                  |
| 8 Convolvulaceae| Cressa cretica                 |      | Ag       | Rod, Spherical, Pentagonal. | Catalytic activities                                                      |
| 9 Verbenaceae   | Vitex negundo Chinese chaste tree |      | Ag       | Spherical           | Antimicrobial activities                                                  |
| 10 Cyperaceae   | Cyper rotundus                 |      | Ag       | Spherical           | Antimicrobial activities                                                  |
| 11 Euphorbiaceae| Euphorbia prostrata            |      | TiO₂     | Spherical           | Antileishmanial activity                                                  |
|                 |                                |      | Ag       | Rod                 | anti - parasitic activity                                                |
| 12 Convolvulaceae| Cuscuta reflexa               |      | Cu       | Rod                 | Reduction of nitroarenes and organic dyes                                |
| 13 Molluginaceae| Mollugo nudicaulis             |      | Ag       | -                   | Antibacterial activities                                                  |
| 14 Cucurbitaceae| Mukia maderaspatana            |      | Ag       | Irregular           | Antimicrobial activities                                                  |
|                 |                                |      | Au, Ag   | Spherical           | Antimicrobial activities                                                  |
|                 |                                |      | Cf       | -                   | Antibacterial activities                                                  |
|                 |                                |      | Ag       | Spherical           | Larvicidal activities                                                     |
| 15 Zygophyllaceae| Peganum harmala               |      | Ag       | Spherical           | Antibacterial activities                                                  |
| No. | Family           | Genus                        | Species                        | Metal | Form          | Property                        | Ref. |
|-----|-----------------|------------------------------|--------------------------------|-------|---------------|---------------------------------|------|
| 16  | Asclepiadaceae  | Pergularia                  | daemia                         | Ag    | Spherical     | Larvicidal activity             | [52] |
| 17  | Mimosaceae      | Prosopis                    | cineraria                       | Ag    | Hexagonal     | Anti-bacterial, anti-cancer     | [53] |
|     |                 |                              |                                |       | Spherical     | Anti-bacterial, anti-cancer     | [53] |
|     |                 | Cu                           | 18. 9-32.09                    |       | Spherical     | Anti-bacterial, anti-cancer     | [54] |
| 18  | Zygophyllaceae  | Tribulus                    | longipetalus                    | Ag    | Spherical     | Anti-oxidant                    | [55] |
| 19  | Solanaceae      | Withania                    | coagulens                       | Pd/   | Spherical     | Catalytic reduction of 4-nitrophenol | [56] |
|     |                 |                              |                                | RG O/F|              |                                 |      |
|     |                 |                              |                                | e:O4  |              |                                 |      |
| 20  | Solanaceae      | Withania                    | somnifera                       | Ag    | Spherical     | Anti-bacterial, Anti-fungal     | [57] |
|     |                 |                              |                                |       | Spherical     | Anti-bacterial, Anti-fungal     | [57] |
|     |                 | Au                           | 200                            |       | Pseudo-spherical | -                              | [58] |
| 21  | Rhamnaceae      | Ziziphus                     | nummularia                      | Ag    | Spherical     | Anti-bacterial, Anti-fungal, Anti-oxidant | [59] |
|     |                 |                              |                                |       | Spherical     |                                 |      |
|     |                 | ZnO                          | 12.47-26.97                    |       | Spherical and irregular | Cytotoxic effect, Anti-fungal | [60] |
| 22  | Salvadoraceae   | Salvadora                    | persica L.                      | Ag    | Spherical     | Anti-bacterial                  | [61] |
|     |                 |                              |                                |       | Spherical     | Photo catalytic activity, Water purification | [62] |
| 23  | Euphorbiaceae   | Securinega                   | leucopyrus                      | Ag    | Oval to spherical | Anti-bacterial                  | [63] |
| No. | Family       | Species               | Plant Name          | Ag Kind | Size (nm) | Shape     | Property                                | Reference |
|-----|--------------|-----------------------|---------------------|---------|-----------|-----------|-----------------------------------------|-----------|
| 24  | Zygophyllaceae | Tribulus terrestris   | Bindii              | Ag      | 15-40     | Spherical | Photo catalytic activity, water purification | [64]      |
|     |              |                       |                     |         |           |           |                                        |           |
|     |              |                       |                     | ZnO     | 6-10      | Spherical | Gas sensor                              | [65]      |
|     |              |                       |                     | Ag      | 16-28     | Spherical | Anti-bacterial                          | [66]      |
| 25  | Simaroubaceae | Ailanthus excels      | Mahanimba           | Ag      | 22-30     | Spherical | Anti-bacterial                          | [67]      |
|     |              |                       |                     |         |           |           | Anti-cancer                             |           |
| 26  | Amaranthaceae | Aerva javanica        | Desert Cotton       | Ag      | 10-21     | Spherical | Burn wound Healer                      | [68]      |

**Table 2.** TEM images of few metallic NPs of plant extract available in Cholistan desert
5. Application of Nanoparticles

5.1 Antimicrobial activities
Bacteria being responsible for a large number of diseases is the main point of concern by many researchers, mostly proved to be sensitive to metallic nanoparticles i.e. Ag. The Ag nanoparticles of *Calotropis procera* showed anti-microbial properties to a larger extent as the experimentation proved that the growth of bacteria and fungi was inhibited by the Ag nanoparticles of *Calotropis procera* [24]. ZnO nanoparticles of *Citrullus colocynthis* shows antibiological activity for *E. coli*, *P. aeruginosa* and *B. subtilis* and results establish the procedure of drug action by penetrating into the cell membrane of the bacteria and kill them [50]. *Pergularia daemia* provided the exclusive drug action in the form of Ag NPs on two mosquitoes species, *A. aegypti*, *A. stephensi*, which limits larvicidal activities and is established as an excellent anti-larvicidal drug as well as these NPs even responsible for killing the larva of these mosquitoes [52]. While Ag nanoparticles of *Ziziphus nummularia* showed antifungal property as well as anti-bacterial properties against *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [59].

![Antibacterial activity of metallic NPs (Stop protein synthesis, DNA replication and cause cell death)](image)

Figure 3. Antibacterial activity of metallic NPs (Stop protein synthesis, DNA replication and cause cell death)

5.2 Anti-cancer activities
Cancer is the most exclusive and adverse problem throughout the world attracts most of the attention specifically in the field of green source-based Nanochemistry and many establishments have been made to tackle the problem utilizing herbal drug based NPs. Cu NPs of *Calotropis procera* have been studied on HeLa, A549, and BHK21 cell lines [29] show appreciable results on this particular cell line. The anti-cancerous activity of green synthesized Ag and Cu NPs *Prosopis cineraria* have been studies for human breast cell line [53]. While Ag NPs of *Ailanthus excels* showed excellent anti-cancer properties against MCF-7 cell line [67].
5.3 Anti-oxidant activities
Living being, considered to be the most complex creation, responsible for many chemical processes within the body, one of which is oxidation which is mainly caused by the involvement of free radicals free. These oxidative changes caused by the free radicals may cause a number of damages to the living beings e.g. protein and DNA damage, oxidative stress, and cancer which can easily be stabilized by the Metal NPs formation of these free radicals [70,71] and thus these effects can easily be suppressed. One of the most devastating features of these free radicals is Parkinson’s disease, based on the oxidative changes in the body. Ag NPs of Tribulus longipetalus and ZnO nanoparticles of Citrullus colocynthis have been studied as potential anti-oxidant [50,55], exhibiting greater chances of future prospects in the concerned application of anti-oxidative properties.

5.4 Water purification
One of the biggest problems of the progressively growing world is the availability of pure water for drinking purposes and for other water-related applications. Green chemistry in this scenario provides extensive applications from water purification to the detection of pollutants and many more. Desert plant-based metallic nanoparticles also shows multi-dimensional applications towards this particular problem as Ag NPs of Cucumis melo studied for the removal of Nickel (II) from water. So, these NPs can serve as potential pollution-reducing agents and detector in water and thus ensures its purification or detection of Nickel (II) respectively[51]. ZnO NPs of Peganum harmala and Ag NPs of Salvadora persica L. and Tribulus terrestris have been studied for detection and removal of Cr(IV) from aqueous solution and its purification respectively[62,64,72-74]. These applications of heavy metal detection and purification of water makes the herbal plant-based nanoparticle to serve as the basic cell for the establishment of large scale detectors and purifiers that can be used for industrial purpose for future advancements.
5.5 Catalytic activities

Catalytic activities are one of the important changes both in the biological and physical systems that can easily be controlled by using suitable NPs of green resources. During reduction of 4-nitrophenol to 4-aminophenol, Au NPs of *Acacia nilotica* was used as catalyst[18] that shows optimum activity in the conversion of the product. Ag NPs of *Acacia nilotica* were found with reducing power for the electrocatalytic reduction of benzyl chloride[20]. ZnO NPs of *Calotropis procera* were found as a reducing agent during photo-degradation of methyl orange[26]. Pd/RGO/Fe3O4 nanocomposite of *Withania coagulens* used were used as a catalyst for the reduction of 4-nitrophenol[56]. Ag NPs of *Salvadora persica L.* and *Tribulus terrestris* have been studied for the reduction of methylene blue[62,64].

![Figure 5. Mechanism of green synthesis of metallic NPs (Active compounds of Cholistan plants extract act as reducing, stabilizing and capping agents)](image)

6. Conclusion

The undeniable importance of Cholistan desert plants is being explored in this review in concern of its applications as well as the exploration of so far neglected flora of limitless medicinal and industrial applications. Desert green gold, is extremely useful as trivial medicines, are contributing a major part in developing herbal drug system for curing a diverse range of fatal diseases. The present study aims to glorify its influence relating it to most advanced drug delivery techniques for more competent action as metal-based nanoparticle formation, utilizing Cholistan desert flora. As a number of biologically active compounds are indicated in the phytochemical studies of these desert flora species, can pave new pathways to advance the already reported applications to a step forward i.e. industrialization for water purification by utilizing these green resources which will create less pollution and also renewable and entire new collection of nanoparticles employed in drugs for the sake of curing fatal ailments are some highlighted ones. The numerous new fields that can be explored utilizing this green gold involves optical sensors and probes, electronics and disease diagnosis, etc. Above all main concern on the specific location of Pakistan, Cholistan desert, is driven based on the fact that every year these valuable gems of nature are being wasted because of ignorance and non-exploration, that needs to be conserved for the sake of humanity and its betterment.
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