Bio-Inspired Smart Nanoparticles in Oncology

Subjects: Nanoscience & Nanotechnology

Contributor: Khushabu Gulia, Abija James, Sadanand Pandey, Kamal Dev, Deepak Kumar, Anuradha Sourirajan

Compared with traditional treatment, nanotechnology offers new therapeutic options for cancer due to its ability to selectively target and control drug release. Among the various routes of nanoparticle synthesis, plants have gained significant recognition. The tremendous potential of medicinal plants in anticancer treatments calls for a comprehensive research of existing studies on plant-based nanoparticles. The research examined various metallic nanoparticles obtained by green synthesis using medicinal plants. Plants contain biomolecules, secondary metabolites, and coenzymes that facilitate the reduction of metal ions into nanoparticles. These nanoparticles are believed to be potential antioxidants and cancer-fighting agents.

Keywords: nanotechnology ; cancer theranostics ; biosynthesis ; therapeutics ; anticancer

1. Introduction

In terms of mortality, cancer is one of the major causes. Despite significant advances in diagnostics and treatments, effective and safe anticancer drug delivery remains a more critical barrier in related therapies. Cancer that spreads to other body parts requires a more comprehensive and rigorous treatment regime as a first line approach, including chemotherapy either separate or combined with radiotherapy, surgeries, etc., [1]. The inability of current chemotherapies to differentiate between healthy and cancerous cells after being regularly administered is a major source of concern [2]. Standard cancer therapies sometimes fail to deliver chemotherapeutic drugs to tumor cells in an effective manner, paving the way toward new adaptations in the field of research.

Plant-based synthesis of nanoparticles is a way to improve the disadvantages of current procedures, thus avoiding the drawbacks of the current procedures. The combination of medicinal plants, nanoparticles, and oncology, termed “Phytonanoncology”, is providing new opportunities in cancer therapeutics. In addition to being a valuable source with anticancer potential, medicinal plants can be used to make metallic nanoparticles in an eco-friendly and green way [3]. Plant-based synthesis of nanoparticles contains biologically active components derived from natural extracts and has anticancer efficacy in cancer cells [4]. Recent studies have demonstrated that green synthesis has gained a lot of popularity since it can produce NPs with superior morphological, photochemical, photocatalytical, and electrochemical properties compared to physiochemical synthesis. This method has become one of the preferred methods for synthesizing ZnO nanoparticles [5]. Similarly, BSA (bovine serum albumin)-silver nanoparticles are potentially promising candidates for treating skin cancer in a multimodal manner [6].

2. Phytogenic Nanoparticles in Oncology—“Phyto-Nano-Oncology”

Plants, as a natural resource with a vast diversity of phytocomponents and medicinal properties, play a crucial role in the treatment of various diseases, including cancer [7]. Certain medicinal plants produce anticancerous and tumor-fighting secondary metabolites, which further inhibit or activate various signal transduction pathways in body cells. Several phytocompounds like protein, carbohydrates, alkaloids, and organic acids act as good reducing, stabilizing, and capping agents for chloride and nitrate precursors during phytogenic synthesis of metallic nanoparticles [8]. The biogenic method allows for better control of particle size and shape compared to physical and chemical methods of nanoparticle synthesis, which are crucial for many biomedical applications. Various plant, algae, fungi, or microorganism metabolites are utilized as capping agents, reductants, and stabilizing agents for the respective NPs. Biological resources may also be used. However, they raise the issue of biosafety. In addition, maintaining cell cultures with microorganisms involves extensive and multiple steps. Thus, medicinal plants are preferable to microbes for nanoparticle synthesis [9].

Green nanoparticle synthesis provides many additional advantages, including cultivability, cost effectiveness, stability, and rapid synthesis. Moreover, using plant compounds, different shapes and sizes of nanoparticles can be produced [10]. Metallic nanoparticles can deliver hydrophilic and hydrophobic compounds, plant-derived drugs, siRNA, peptides, antibiotics, chemotherapeutic agents, and small molecules to the targeted tumor location without causing toxicity to the healthy or surrounding tissues of the tumoral site [11]. The drug enclosed in the nanoparticles is shielded from enzyme degradation in the bloodstream. Natural extracts, essential oils, and their bioactive constituents have been shown to have multiple targeted modes of action with minimum side effects, which would be beneficial in the treatment of cancer [12]. The synthesis of plant-based nanoparticles has been shown in **Figure 1**.

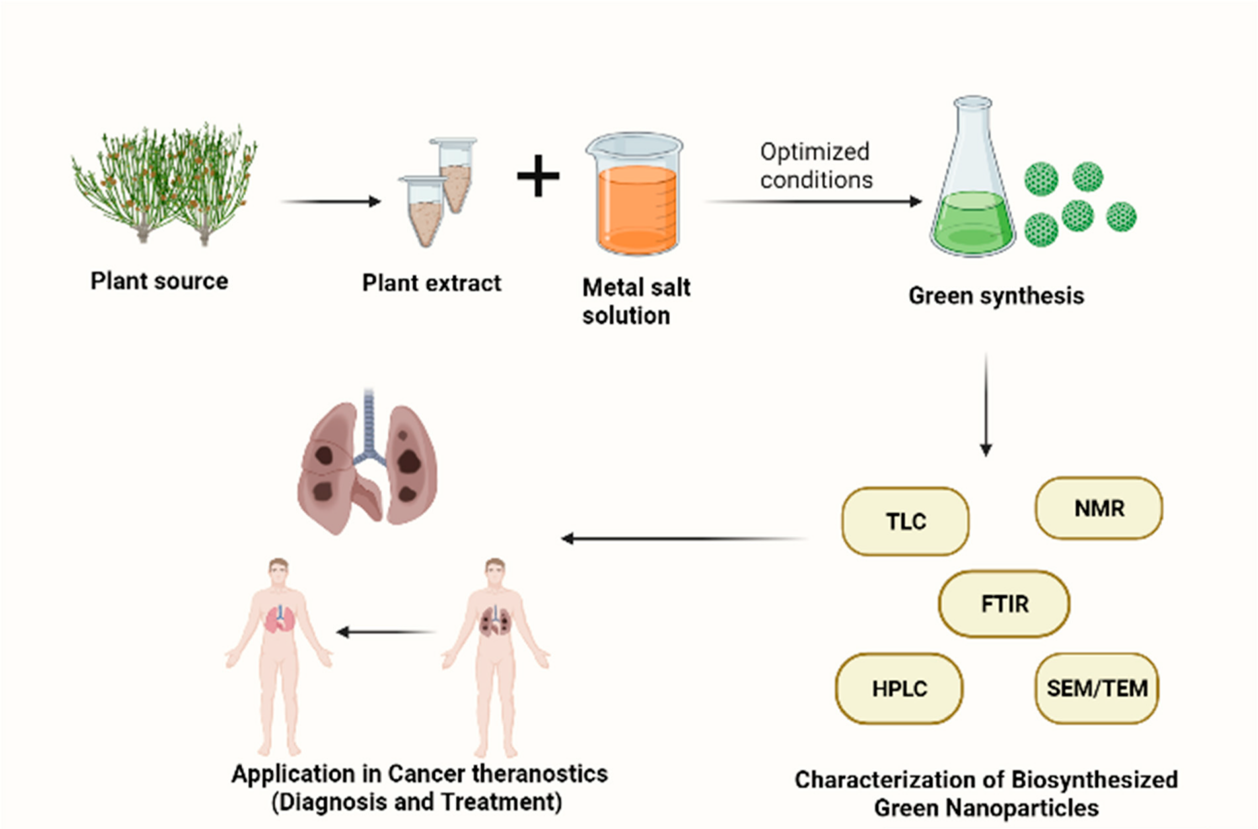

Figure 1. Plant-mediated process for biosynthesis of nanoparticles: optimization, characterization, and potential application in cancer theranostics. (Created with BioRender.com).

3. Synthesis of Plant-Based Nanoparticles

A considerable interest has arisen in phytogenic formulation of metallic nanoparticles because the method itself is environmentally benign, simple to follow, and relies on phytochemicals like flavonoids, alkaloids, and phenol. Nanoparticle synthesis can be accomplished in two ways: top-down and bottom-up. Top-down methods seek to assemble nanoscale objects by using large microchips that are extremely controlled, while bottom-up approaches incorporate molecular-based components that are built up into more complex assemblies. Microfabrication techniques, which use externally controlled tools, are often used to cut, mill, and shape materials into the desired shape and size using the top-down approach [13][14]. Several studies have been reported in the past few years describing the relevance of MNPs such as gold (Au), silver (Ag), copper (Cu), and zinc (Zn) nanoparticles etc., because of their tiny size (nm), surface plasmon nature, and their physicochemical characteristics [15]. Nanoparticles are used across a range of industries, from cancer theranostics to drug delivery to treating wastewater. They are also used as biosensors, DNA analyzers, antibiotics, and catalysts.

Currently, plants are being used to synthesize metal nanoparticles. As an alternative to chemical and physical methods, plants (inactivated plant tissue, plant extracts, and live plants) are increasingly being used to synthesize metal nanoparticles. Plant extracts can be used to synthesize metallic nanoparticles economically and on a large scale, so they can be used as a valuable alternative for large scale production. Nanoparticles can be synthesized using phytocompounds as both reduction and capping agents [16]. Bioreduction of metallic nanoparticles by combining different biomolecules found in plant extracts (e.g., amino acids, enzymes, vitamins, polysaccharides, proteins, and organic acids such as citrates) is chemically complex but environmentally friendly. Plants have shown great promise in accumulating and detoxifying heavy metals. Several studies have reported that plants, such as *Arabidopsis halleri* and *Thlaspi caerulescens*, detoxify and accumulate harmful metals [17].

4. Drug Encapsulation in Plant-Based Nanoparticles

Encapsulation is the process of entrapping bioactive substances with a covering material in order to deliver the core at the appropriate time and location. The sizes of particles can be divided into macro (>5000 µm), micro (1–5000 µm), and nano

(<1 µm) [18]. It is challenging for phytocompounds to traverse the blood-brain barrier (BBB), mucosa, gastrointestinal tract, and endothelium lining of blood vessels due to their polar nature and huge size. Additionally, they are enzymatically broken down in the digestive system. Therefore, by modifying their gastrointestinal stability, rate of dispersion, and absorption, encapsulation, or conjugation of these drugs with nanocarriers may be a different strategy to improve their bio effectiveness [19].

Generally, there are different methods used for developing micro and nanocarriers used in the encapsulation of bioactive compounds. The first category of carriers requires the use of sophisticated machinery, such as electrospinning/spraying [20], freeze-drying [21], and spray-drying [22]. Ionic gelation, an encapsulation technique carried out via electrostatic spray processes, dripping (extrusion, coextrusion) or atomization, produces nano/microcarriers [23]. Furthermore, lipid-based carriers made of fats and oils, such as liposomes and emulsions, have been successfully used to encapsulate various bio-compounds. With applications in nanomedicine, phytochemical-based nanoparticles can thus be demonstrated to be particularly effective in terms of their improved drug transport characteristics, stability, and biocompatibility [24].

5. Plant-Based Nanoparticles in Enhanced Cancer Imaging and Diagnosis

Detecting cancer at a late stage can make it more difficult to cure. Timely detection and diagnosis are necessary for treating cancer and preventing its complications [25]. Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Ultrasound and Positron Emission Tomography (PET) are some of the most common medical imaging procedures [26]. The lack of preciseness, effectiveness, and higher expense of the existing diagnostic methods suggest the need for novel strategies [27]. The decreased pharmacological effectiveness, expeditious removal, indefinite dissemination, and unfavorable outcomes of conventional imaging techniques suggest the necessity for a unique imaging system [28]. Biosensors are instruments used to sense signals that can be received by a detector element. The biosensors made using different nanoscale substances enhance their imaging properties to a great extent [29]. Nanoparticles such as iron, gold, titanium, silver, and copper, which are synthesized in a green manner, disperse light a million times more prominently than molecules due to their plasmon excitation, and have a pronounced ability to induce optical imaging [30].

Because of their unique characteristics, biologically synthesized silver nanoparticles would be an alternative that is more economical and straightforward, and they have proven to be highly effective with cancer theranostics [31]. Silver nanoparticles are extensively used for cancer treatment [32][33][34]. The green chemistry approach is advantageous over conventional chemical methods in the synthesis of silver nanoparticles due to the following advantages: (i) simple, one-step, fast, affordable, and most reliable method; (ii) environmentally friendly due to minimal use of toxic chemicals; (iii) convenience of using bio-resources such as plants, fungi, algae, and microorganisms that act as reduction agents and stabilizing bases; and (iv) water as a universal solvent. Successful bioimaging has been demonstrated in the non-invasive in vivo imaging of silver nanoparticles using *Zinnia elegans* leaf extract in C57BL6/J mice. This can be used as a potential biosynthesized nanoparticle for future cancer imaging [35]. The intense fluorescence activity of *Olax scandens* leaf extract using methanol is already established. It was found that the silver nanoparticles made from *Olax scandens* extract incubated with A549 and B16 cells exhibited red fluorescence, and this could be used for cancer diagnosis in the future.

6. Targeted Drug Delivery Using Phytogenic Nanoparticles

Over 60% of anti-cancer drugs available today are derived from plants; plants have traditionally been used to treat diseases such as cancer. The discovery of anti-cancer drugs is fueled by the discovery of plants, animals, aquatic organisms, and microbes in nature [36]. Many potentially therapeutic drugs found in nature are anticancer agents, such as vinca alkaloids, taxanes and their analogs, podophyllotoxin, camptothecin (CPT) and its derivatives, anthracyclines, etc. Approximately half of the anticancer drugs approved worldwide are either natural compounds or their derivatives [37]. There are several significant disadvantages associated with most clinically used anticancer drugs, including low water solubility, incapacity for oral administration, short half-lives, and poor specificity.

The nanotech-based combinations of drugs formulated from nature-derived molecules have enormous potential for targeting tumor microenvironments in order to combat multidrug resistance (multidrug resistant) as these nanotech-based delivery systems have several advantages similar to water solubility, lower toxicity, biocompatibility, and the ability to modify their surface for further applications [38]. Drug delivery systems that are engineered at the nanoscale have been extensively studied and are by far the most advanced technology in the field of nanoparticle applications due to their potential advantages, such as the ability to modify physical properties such as solubility, release profiles, diffusion, bioavailability, and immunogenicity [39][40]. The delivery of engineering drug systems either targets a specific site or injects therapeutic agents into the site in a controlled manner [41]. **Figure 2** shows the efficacy of a chemotherapeutic drug when it is encapsulated in green nanoparticles.

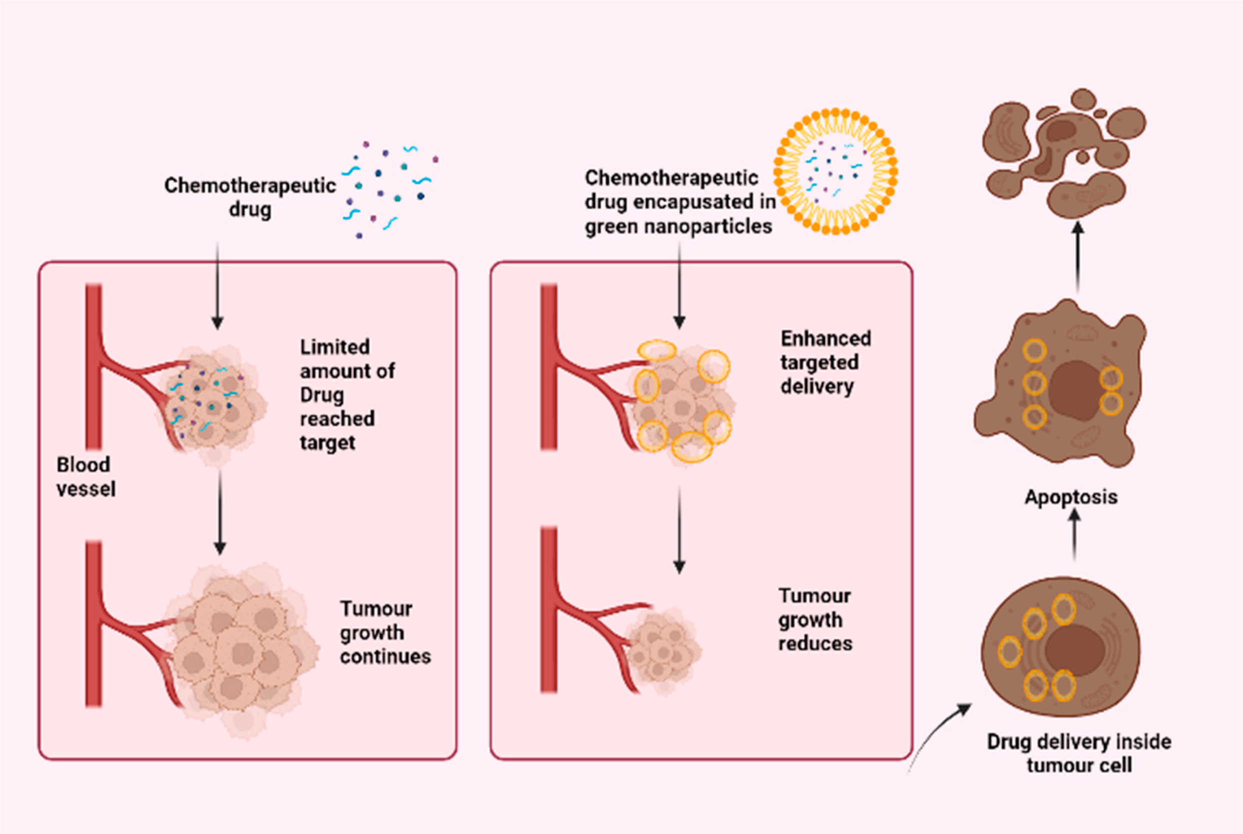

Figure 2. Comparison of the efficacy of chemotherapeutic drugs when incorporated into nanoparticles. (Created with BioRender.com).

In the drug delivery of natural phytochemicals, nanoparticles, and nanocarriers can target specific tissues or organs. This feature offers several benefits. Various targeting strategies of natural compounds can be achieved with nanoparticles. The first type of targeting involves attaching a therapeutic ligand to the surface of a nanoparticle, enhancing drug bioavailability by increasing doses that reach target tissues. Active targeting usually involves conjugating nanoparticles with proteins, peptides, antibodies, or small molecules. This enables specific tissues and organs to internalize and localize the particles. Passive targeting, on the other hand, is the delivery of drugs to a specific area of the body without the use of certain chemical interactions, but rather by relying on the intrinsic properties of the particles, such as size, shape, and surface charge. Because the drug is only being released to that specific area, the aftereffects of the drug are also reduced [42][43]. **Figure 3** shows active and passive targeting of tumor cells using nanoparticles.

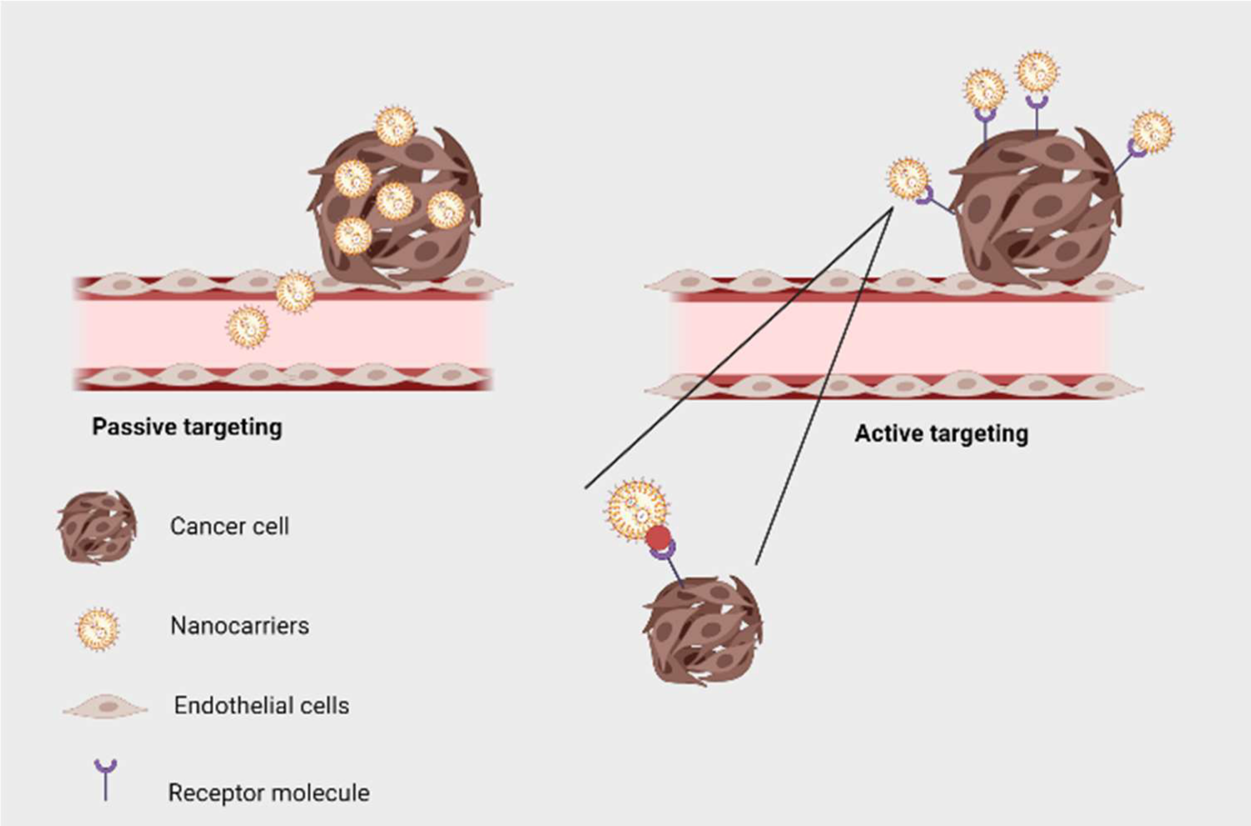

Figure 3. Active and passive targeting for drug delivery using nanoparticles (Created with BioRender.com).

Additionally, as a new way, combining natural products with radiotherapy, chemotherapy, and immunotherapy can enhance the synergistic effect of natural products, restricting the doses for patients and reducing toxicity [44].

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