Bacterially-Synthesized Green Nanoparticles: A Promising Approach for the Targeted Therapy of Breast Cancer

Yasin SarveAhrabi[1,*] - Fatemehsadaat Kia[2] – Behin Omidi
[1,*] Department of Biology, CT.C., Islamic Azad University, Tehran, Iran. E.mail: Yasin.ahrabi2016@gmail.com.
[2] Department of Biology, CT.C., Islamic Azad University, Tehran, Iran.
[3] Department of Biology, CT.C., Islamic Azad University, Tehran, Iran.

ABSTRACT

Breast cancer remains a formidable global health challenge, with current therapeutic regimens often plagued by systemic toxicity, drug resistance, and non-specific biodistribution. The emergence of nanotechnology has revolutionized oncology, offering novel avenues for targeted drug delivery. Among these, "green" nanoparticles (NPs) synthesized using biological entities, particularly bacteria, present a sustainable, eco-friendly, and biocompatible alternative to conventional chemical and physical methods. This review meticulously examines the paradigm of bacterially-synthesized nanoparticles (BSNPs) as a next-generation platform for breast cancer therapy. We delve into the mechanisms of bacterial biosynthesis of metallic and non-metallic NPs, highlighting their unique physicochemical properties. The core of the review focuses on the multifunctional applications of BSNPs, including their intrinsic anticancer activity, role as targeted drug delivery vehicles, and utility in combination therapies and theranostics. We further explore the mechanisms underlying their selective cytotoxicity towards breast cancer cells. Despite the promising outlook, challenges pertaining to standardization, pharmacokinetics, and large-scale production are critically discussed. Finally, we provide insights into future perspectives, concluding that bacterially-synthesized green nanoparticles hold immense potential to enhance the specificity, efficacy, and safety of breast cancer treatment.

Keywords: *Green Synthesis, Nanoparticles, Breast Cancer, Targeted Therapy, Drug Delivery.*

1. *INTRODUCTION*

Breast cancer is the most commonly diagnosed cancer in women worldwide, characterized by heterogeneous subtypes with distinct molecular profiles and clinical outcomes [1]. While advancements in surgery, chemotherapy, radiotherapy, and hormone therapy have improved survival rates, the quest for more selective and less toxic treatments continues. Conventional chemotherapeutic agents suffer from a low therapeutic index, indiscriminately affecting rapidly dividing cells and causing severe side effects like myelosuppression, cardiotoxicity, and neurotoxicity [2]. Nanotechnology has emerged as a beacon of hope, enabling the design of particles in the 1-100 nm range that can be engineered for targeted drug delivery [3]. However, the synthesis of these nanoparticles often involves toxic chemicals, high energy consumption, and generates hazardous by-products, raising concerns about their environmental impact and biocompatibility [4]. This has spurred the development of "green nanotechnology," which utilizes biological resources—plants, fungi, algae, and bacteria—for the eco-friendly synthesis of NPs [5]. Bacteria, in particular, are exceptional bio-factories for NP synthesis [6]. Their rapid growth, genetic manipulability, and ability to reduce metal ions through various enzymatic and non-enzymatic pathways make them ideal candidates [7]. This review synthesizes current knowledge on the application of bacterially-synthesized green nanoparticles for the targeted therapy of breast cancer, outlining their synthesis, mechanisms of action, and future trajectory.

2. *Bacterial Biosynthesis of Nanoparticles: Mechanisms and Types*

The microbial synthesis of NPs is a bottom-up approach where bacterial cells or their metabolites (enzymes, proteins, polysaccharides) act as reducing and stabilizing agents [8].

2.1 Mechanisms of Synthesis:

Intracellular Synthesis: Metal ions from the precursor salt diffuse into the bacterial cell and are reduced by intracellular enzymes (e.g., nitrate reductases, hydrogenases) or electron shuttle compounds, leading to NP formation within the cytoplasm or periplasmic space [9]. Extracellular Synthesis: Bacterial cells secrete reducing enzymes and stabilizing proteins into the culture medium. The metal ions are reduced extracellularly, simplifying the downstream purification process of the NPs [10].

2.2 Common Types of Bacterially-Synthesized NPs for Cancer Therapy:

Table 1 summarizes the key types of bacterially-synthesized nanoparticles, their common microbial sources, and their primary applications in breast cancer therapy.

Table 1. Overview of Key Bacterially-Synthesized Nanoparticles for Breast Cancer Therapy

Nanoparticle Type	**Example Bacterial Sources**	**Key Properties & Applications in Breast Cancer Therapy**	**Ref**
Silver (AgNPs)	*Bacillus sp., Pseudomonas stutzeri, Escherichia coli*	Potent intrinsic cytotoxicity; induces ROS and apoptosis; antimicrobial coating for medical devices.	[11, 12]
Gold (AuNPs)	*Rhodopseudomonas capsulata, Bacillus subtilis*	Excellent biocompatibility; easy surface functionalization; used for photothermal therapy (PTT) and drug delivery.	[13, 14]
Selenium (SeNPs)	*Streptomyces bikiniensis, Lactobacillus acidophilus*	High biocompatibility and selective cytotoxicity; antioxidant properties at low doses; chemopreventive agent.	[15, 16]
Iron Oxide (Fe_3O_4 NPs)	*Magnetospirillum gryphiswaldense*	Superparamagnetic; enables magnetic hyperthermia and MRI contrast; targeted drug delivery via external magnets.	[17, 18]
Zinc Oxide (ZnO NPs)	*Aeromonas hydrophila, Lactobacillus sporogens*	ROS generation under UV light; selective toxicity to cancer cells; drug delivery vehicle.	[19]

3. Applications of BSNPs in Breast Cancer Therapy

3.1 Intrinsic Anticancer Activity:

Many BSNPs exhibit inherent cytotoxicity against breast cancer cell lines (e.g., MCF-7, MDA-MB-231). The primary mechanisms include:

- ROS Generation: NPs, especially AgNPs and SeNPs, induce oxidative stress by generating reactive oxygen species, leading to lipid peroxidation, protein denaturation, and DNA damage [20]. For instance, AgNPs synthesized by Escherichia coli demonstrated significant ROS-mediated cytotoxicity in MDA-MB-231 cells [12].
- Induction of Apoptosis: BSNPs can trigger both the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways. This is characterized by the upregulation of pro-apoptotic proteins (Bax, caspase-3/9) and downregulation of anti-apoptotic proteins (Bcl-2) [21].
- Cell Cycle Arrest: NPs can arrest the cell cycle at specific checkpoints (e.g., G1/S or G2/M), preventing uncontrolled proliferation [22].

3.2 Targeted Drug Delivery Systems:

The true potential of BSNPs lies in their functionalization as "magic bullets."

- Surface Functionalization: The natural bio-organic capping on BSNPs provides an excellent platform for attaching targeting ligands [23].
- Active Targeting: By conjugating BSNPs with breast cancer-specific ligands such as folic acid (targeting folate receptors), HER2 antibodies (for HER2+ breast cancer), or transferrin (targeting transferrin receptors), the NPs can be directed specifically to tumor cells, enhancing cellular uptake and minimizing off-target effects [24].

- Drug Loading and Controlled Release: Chemotherapeutic drugs like Doxorubicin, Paclitaxel, and Curcumin can be loaded onto BSNPs. The tumor's unique microenvironment (e.g., acidic pH, specific enzymes) can then be exploited to trigger the controlled release of the drug at the site of action [25].

3.3 Combination Therapy and Theranostics:

BSNPs serve as multifunctional platforms for combination therapy. For instance, AuNPs synthesized by bacteria can be loaded with a chemotherapeutic drug and also used for Photothermal Therapy (PTT) [26]. Upon irradiation with near-infrared light, the AuNPs generate heat, ablating the tumor cells while simultaneously releasing the drug. This synergistic approach can overcome drug resistance and improve therapeutic outcomes [27]. Similarly, bacterially-synthesized magnetic nanoparticles can be used for both magnetic hyperthermia (therapy) and as contrast agents in Magnetic Resonance Imaging (MRI), enabling therapy and diagnosis—a theranostic approach [28].

4. Advantages and Challenges

The development of bacterially-synthesized nanoparticles (BSNPs) for breast cancer therapy is not without its complexities. A balanced consideration of their significant advantages against the existing challenges is crucial for guiding future research and translation.

4.1. Advantages

The appeal of BSNPs is rooted in their alignment with the principles of green chemistry and their inherent biological compatibility. Unlike conventional chemical synthesis, which often employs toxic reducing agents like sodium borohydride and stabilizing agents like citrate, bacterial synthesis utilizes biological pathways, resulting in a process that is inherently more eco-friendly and sustainable [5]. This method typically occurs under ambient temperature and pressure, significantly reducing energy consumption and the generation of hazardous waste. From an economic standpoint, the cost-effectiveness of this approach is a major advantage [29]. Bacterial biomass is readily available, inexpensive to culture using simple growth media, and can be easily scaled up in bioreactors, making the production process potentially more economical than traditional nanofabrication techniques. Furthermore, the nanoparticles produced are often superior in their biomedical applicability. The biocompatibility and stability of BSNPs are enhanced by the natural biological capping layer—comprising proteins, peptides, and polysaccharides—that forms around them during synthesis [30]. This "bio-corona" not only prevents aggregation, ensuring colloidal stability in physiological solutions, but also reduces the intrinsic cytotoxicity often associated with bare, chemically synthesized NPs. Perhaps most importantly, BSNPs frequently exhibit inherent bioactivity [31]. For instance, bacterially-synthesized silver nanoparticles (AgNPs) possess intrinsic antimicrobial and anticancer properties, primarily through the generation of reactive oxygen species (ROS). This intrinsic activity can work in synergy with chemotherapeutic drugs loaded onto the NPs, enabling lower dosages of toxic drugs and reducing the likelihood of inducing resistance, thereby creating a powerful combinatorial therapeutic effect.

4.2. Challenges and Future Considerations

Despite the promising advantages, the path to clinical adoption of BSNPs is paved with significant challenges that must be addressed. A primary hurdle is the standardization and control of NP synthesis [32]. Bacterial synthesis is a biologically complex process, leading to batch-to-batch variations in critical parameters such as size, shape, and crystal structure. Achieving the monodispersity required for reproducible therapeutic outcomes and regulatory approval is considerably more challenging than with precisely controlled chemical precipitation methods. Closely related to this is the incomplete understanding of the mechanisms involved [33]. The precise enzymatic pathways (e.g., the role of specific nitrate reductases or electron-shuttling molecules) responsible for metal ion reduction and stabilization are not fully elucidated for many bacterial species. Similarly, the detailed molecular mechanisms by which BSNPs induce cancer cell death, beyond general ROS generation, require deeper investigation to optimize their efficacy and safety. Moreover, the translational gap is wide. A critical lack of comprehensive data on the pharmacokinetics and toxicology of BSNPs exists [34]. While in vitro studies show promise, rigorous in vivo studies are essential to understand the absorption, distribution, metabolism, excretion, and long-term toxicity of these novel entities. Questions regarding their potential for accumulation in off-target organs, immunogenicity, and chronic effects remain largely unanswered. Finally, the issue of scalability presents a significant logistical challenge [35]. Transitioning from small-scale laboratory flasks to industrially viable, large-volume bioreactor production while maintaining

consistent NP quality and yield is a non-trivial engineering and biological problem that must be solved for clinical and commercial viability.

5. Conclusion and Future Perspectives

In conclusion, bacterially-synthesized green nanoparticles represent a paradigm shift in the nanomedicine approach to breast cancer. They successfully merge the principles of sustainable green chemistry with the cutting-edge demands of advanced oncology, offering a potent, targeted, and potentially safer alternative to conventional chemotherapeutic regimens. Their versatility, functioning as intrinsic therapeutic agents, targeted drug carriers, and multimodal theranostic tools, underscores their immense potential to redefine cancer treatment by enhancing specificity, overcoming drug resistance, and minimizing systemic side effects. To fully realize this potential and bridge the gap between laboratory promise and clinical reality, future research must be strategically directed. First, Genetic Engineering approaches should be employed to metabolically engineer bacterial hosts to overexpress specific metal-reductase enzymes or export systems, thereby exerting greater control over the synthesis process to improve the yield, uniformity, and functional properties of the NPs [7]. Concurrently, High-Throughput Screening of diverse microbial libraries, including extremophiles from unique environments, can identify novel bacterial strains with superior NP-synthesizing capabilities or the ability to produce NPs with unique compositions and morphologies [6]. On the application front, the development of Advanced Functionalization strategies is crucial. This involves conjugating BSNPs with more sophisticated targeting moieties, such as nanobodies or aptamers specific to various breast cancer subtypes (e.g., triple-negative or HER2-positive), to achieve unparalleled cellular specificity [24]. Ultimately, the most critical step will be the initiation of Robust Pre-clinical and Clinical Trials. Comprehensive in vivo studies using immunocompetent animal models are urgently needed to validate the therapeutic efficacy, biosafety, and pharmacokinetic profiles of lead BSNP formulations, paving the way for eventual clinical translation [34]. In conclusion, the integration of bacterially-synthesized green nanoparticles into the oncologist's arsenal holds the promise of a new era in breast cancer therapy—one that is more precise, effective, and aligned with the principles of sustainable science. By addressing the existing challenges through interdisciplinary collaboration, this innovative bio-nano platform can be transformed from a compelling research concept into a life-saving clinical reality.

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