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Bioengineered Silver Nanoparticles as Peptide Inhibitors Derived from *Crateva religiosa* G. Forst. Bark for Targeting Cancer Cells

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Abstract:
This study investigates the potential of bioengineered silver nanoparticles (AgNPs) derived from Crateva religiosa G. Forst. bark as peptide inhibitors for targeting cancer cells. The synthesis of AgNPs was achieved through a green and eco-friendly approach, utilizing the aqueous extract of C. religiosa bark. The synthesized AgNPs were characterized using various analytical techniques to confirm their size, morphology, and surface properties. Peptides derived from the bark were identified and screened for their inhibitory effects on cancer cells. The anticancer activity of both AgNPs and peptide inhibitors was evaluated using cell viability assays, cellular uptake studies, and molecular docking simulations. Results demonstrate that the bioengineered AgNPs exhibit significant cytotoxic effects on cancer cells, with enhanced efficacy when conjugated with bark-derived peptides. Furthermore, molecular docking simulations reveal potential binding interactions between the peptides and key biomolecules involved in cancer progression. Overall, this study highlights the promising potential of bioengineered AgNPs derived from C. religiosa bark in cancer therapy, particularly when combined with bark-derived peptides as targeted inhibitors against cancer cells.
Keywords: Bioengineered silver nanoparticles, Crateva religiosa, peptide inhibitors, cancer cells, cytotoxicity, molecular docking, targeted therapy.

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide, posing significant challenges to healthcare systems[1]. Traditional cancer treatments, including surgery, chemotherapy, and radiation therapy, have been the cornerstone of cancer management. However, these modalities often come with severe side effects and limited efficacy, especially in advanced stages of the disease[2]. Chemotherapy, for instance, targets rapidly dividing cells, which unfortunately includes not only cancerous cells but also healthy cells such as those in the bone marrow, gastrointestinal tract, and hair follicles[3]. This non-specific targeting leads to side effects like immunosuppression, nausea, vomiting, and hair loss. Additionally, many cancer cells develop resistance to chemotherapeutic agents over time, further complicating treatment regimens. Radiation therapy, while more localized, still damages surrounding healthy tissues and can lead to secondary malignancies. Surgery, although effective in removing localized tumors, is not always feasible, especially in cases of metastasis or when tumors are located in inaccessible areas[4]. Moreover, surgical interventions can lead to complications and are often followed by adjuvant therapies to ensure complete eradication of cancer cells. The heterogeneous nature of cancer, involving genetic, epigenetic, and environmental factors, also presents a significant challenge. Each patient's cancer can have a unique molecular profile, making a one-size-fits-all treatment approach ineffective[5]. This has led to a paradigm shift towards personalized medicine, where treatments are tailored to the individual's specific

genetic makeup and the molecular characteristics of their cancer. One of the foremost challenges in cancer treatment is the development of drug resistance. Cancer cells can evolve and adapt, developing mechanisms to evade the effects of drugs designed to kill them[6]. This can occur through various pathways, such as drug efflux pumps, mutations in drug targets, and alterations in cell signaling pathways. The result is a continual arms race between the development of new drugs and the cancer cells' ability to resist them. Another major issue is the toxicity of conventional treatments[7]. Chemotherapy and radiation can cause significant damage to normal tissues, leading to debilitating side effects that impact the patient's quality of life. This toxicity often limits the dose that can be administered, reducing the overall effectiveness of the treatment. Furthermore, the diagnosis and treatment of cancer are often delayed due to the lack of early detection methods[8]. Many cancers are asymptomatic in their early stages, and by the time symptoms appear, the disease may have progressed to an advanced stage, reducing the chances of successful treatment. There is also a need for treatments that can effectively target metastases[9]. Metastasis is responsible for the majority of cancer-related deaths, and current treatments are often less effective against metastatic tumors compared to primary tumors. Developing therapies that can prevent or treat metastases is crucial for improving cancer outcomes.

Need for Novel and Effective Treatments

Given these challenges, there is a pressing need for novel and effective cancer treatments that are less toxic, more specific, and capable of overcoming drug resistance. Researchers are exploring various innovative approaches, including targeted therapies, immunotherapy, and nanomedicine. Targeted therapies involve drugs that specifically target molecular abnormalities unique to cancer cells, sparing normal cells and reducing side effects[10]. These therapies have shown promise, particularly in cancers with well-defined genetic mutations. Immunotherapy leverages the body's immune system to fight cancer. By boosting the immune response or targeting immune checkpoints, these therapies can provide durable and long-lasting responses in some patients[11]. However, not all patients respond to immunotherapy, and there is a need to identify biomarkers that can predict response. Nanomedicine, the use of nanotechnology in medicine, offers another promising avenue[12]. Nanoparticles can be engineered to deliver drugs specifically to cancer cells, enhancing efficacy and minimizing toxicity. Among various nanoparticles, silver nanoparticles (AgNPs) have garnered attention due to their unique properties and potential applications in cancer therapy[13].

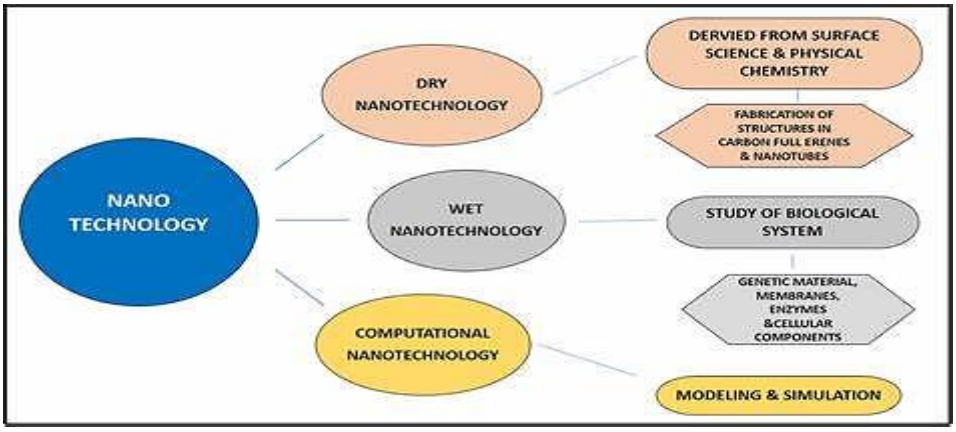

Figure 1: Nanotechnology in pharmaceutical

Silver Nanoparticles in Medicine

Silver has been used for its medicinal properties for centuries. Ancient civilizations, including the Greeks and Romans, used silver containers to store water and food to prevent spoilage. In the early 20th century, silver nitrate was used to prevent blindness in newborns caused by gonococcal infections[14]. With the advent of antibiotics, the use of silver in medicine declined, but interest has been renewed with the development of nanotechnology. Silver nanoparticles (AgNPs) have unique physical, chemical, and biological properties that make them attractive for medical applications[15]. AgNPs exhibit strong antimicrobial activity, which has been harnessed in wound dressings, coatings for medical devices, and other applications to prevent infections. Their small size and large surface area enhance their reactivity and interaction with microbial membranes, leading to cell death[16]. In addition to antimicrobial properties, AgNPs have shown promise in anti-inflammatory and anticancer applications. Their ability to generate reactive oxygen species (ROS) and induce apoptosis in cancer cells has been a focal point of research. AgNPs can be synthesized through various methods, including chemical, physical, and biological approaches[17].

Table1 Commercial products containing ionic (Ag+) or metallic silver (Ag0/AgNPs) including

Product Type	**Product Trademark**	**Company**	**Uses**	**References**
Wound dressings	Acticoat	Smith & Nephew	Antimicrobial	[18]
Wound dressings	Aquacel Ag	Convatec	Antimicrobial	[3]
Wound dressings	Silverlon	Argentum Medical	Antimicrobial	[7]
Bandages	Silverline	Hartmann	Antimicrobial	[19]
Catheters	Bardex I.C.	Bard	Antimicrobial	[2]
Catheters	Cook Spectrum	Cook Medical	Antimicrobial	[15]
Catheters	Silverhawk	Covidien	Antimicrobial	[12]
Catheters	Silzone	Bard	Antimicrobial	[2]
Surgical implants	SilvaSorb	Medline	Antimicrobial	[20]
Surgical implants	Acticoat Flex	Smith & Nephew	Antimicrobial	[21]
Surgical implants	AQUACEL Ag+	Convatec	Antimicrobial	[22]
Water purification	PurGuard	PuriCore	Bactericidal	[11]
Water purification	PURINIZE	Purinize	Water purification	[9]
Water purification	Katadyn	Katadyn	Water filtration	[5]

Advantages of AgNPs in Biomedical Applications

One of the primary advantages of AgNPs in biomedical applications is their size. Nanoparticles can penetrate biological barriers, allowing for targeted delivery of therapeutic agents. This is particularly important in cancer therapy, where the ability to deliver drugs directly to tumor cells while sparing healthy tissues can significantly improve outcomes[22]. AgNPs can be functionalized with various molecules, including drugs, peptides, and antibodies, to enhance their specificity and efficacy[23]. This functionalization allows for the development of multifunctional nanoparticles that can target cancer cells, deliver therapeutic agents, and provide imaging capabilities for diagnosis and monitoring. The high surface area-to-volume ratio of AgNPs also enhances their reactivity and interaction with biological molecules[24]. This can lead to improved therapeutic effects at lower doses, reducing the risk of toxicity. Furthermore, AgNPs have been shown to induce apoptosis in cancer cells through multiple pathways, including the generation of ROS, disruption of mitochondrial function, and activation of apoptotic signaling pathways[25]. This multifaceted mechanism of action can help overcome the issue of drug resistance in cancer therapy. This review aims to explore the potential of bioengineered silver nanoparticles as peptide inhibitors derived from Crateva religiosa G. Forst. bark for targeting cancer cells. Bioengineering of nanoparticles using plant extracts is an emerging field that combines the principles of green chemistry with nanotechnology. Plant-mediated synthesis of nanoparticles offers a sustainable and eco-friendly alternative to traditional methods[26].

Bioengineering of Silver Nanoparticles

Synthesis Methods

Silver nanoparticles (AgNPs) can be synthesized through various methods, each with its own advantages and drawbacks. The synthesis methods are broadly categorized into chemical, physical, and biological approaches[27].

Chemical Synthesis:

Chemical synthesis of AgNPs involves the reduction of silver salts (commonly silver nitrate) using reducing agents such as sodium borohydride, hydrazine, or ascorbic acid. This method is widely used due to its simplicity and ability to produce nanoparticles with controlled sizes and shapes. However, chemical synthesis often involves toxic chemicals and harsh reaction conditions, raising concerns about environmental impact and biocompatibility[3,6]. The reduction of silver ions (Ag^+) to silver atoms (Ag^0) by a reducing agent initiates the formation of silver nanoparticles. These reduced silver atoms nucleate to form small clusters that grow into nanoparticles. To stabilize the nanoparticles and prevent aggregation, capping agents such as polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), or citrate are added[8]. This chemical approach allows for precise control over nanoparticle size, shape, and dispersion, which is critical for specific applications. However, the use of hazardous chemicals and the generation of toxic by-products necessitate careful handling and disposal, limiting the method's sustainability[17].

Biological Synthesis:

Biological synthesis, also known as green synthesis, uses biological entities such as plants, bacteria, fungi, and algae as reducing and stabilizing agents. This method is environmentally friendly, cost-effective, and avoids the use of toxic chemicals, making it an attractive alternative to chemical synthesis[28]. Extracts from plants, microorganisms, or other biological sources

are prepared, containing bioactive compounds capable of reducing silver ions. When mixed with a silver salt solution, these bioactive compounds reduce the silver ions to form nanoparticles and also act as capping agents to stabilize the nanoparticles and prevent aggregation[29]. Biological synthesis is advantageous due to its eco-friendliness, biocompatibility, and the potential for functionalizing nanoparticles with bioactive molecules inherent in the biological extracts[7]. However, controlling the size and shape of nanoparticles can be more challenging compared to chemical synthesis, and the process may require optimization for each specific biological source used[30].

Green Synthesis Approaches

Green synthesis is a subset of biological synthesis that emphasizes the use of environmentally benign solvents, reducing agents, and stabilizers. This approach aims to minimize the ecological footprint of nanoparticle production while maintaining efficacy and functionality[31]. Plant-mediated synthesis utilizes plant extracts containing phytochemicals such as flavonoids, terpenoids, and phenolics to reduce silver ions, offering a simple, scalable method that uses readily available plant materials. Microbial synthesis employs bacteria, fungi, and algae, which secrete enzymes and metabolites to reduce metal ions and stabilize the formed nanoparticles[12]. Polymer-based synthesis uses natural polymers such as starch, cellulose, and chitosan as reducing and stabilizing agents, taking advantage of their biodegradability and non-toxicity[7]. Each green synthesis approach offers unique benefits and challenges plant-mediated synthesis can be performed at room temperature and pressure, reducing energy consumption microbial synthesis, while potentially more complex, leverages microbial metabolic diversity to produce nanoparticles with unique properties and polymer-based synthesis enhances nanoparticle versatility through additional functionalization and stabilization[32,3].

Role of Plant Extracts

Plant extracts play a crucial role in the green synthesis of silver nanoparticles, containing a variety of phytochemicals that act as reducing and stabilizing agents. Phytochemicals such as flavonoids, terpenoids, phenolics, and alkaloids present in the plant extract reduce Ag^+ ions to Ag^0 atoms by donating electrons to the silver ions, initiating the reduction process[33]. The reduced silver atoms then nucleate to form small clusters, a critical step that determines the initial size and shape of the nanoparticles[34]. These small clusters grow into larger nanoparticles, with the phytochemicals adsorbing onto their surface as capping agents to prevent aggregation and control the growth process, resulting in stable nanoparticles. The specific composition of the plant extract influences the size, shape, and stability of the synthesized nanoparticles[13]. For instance, different plants contain varying levels of reducing sugars, proteins, and secondary metabolites, which can lead to nanoparticles with distinct properties[3].

Advantages of Using Crateva religiosa G. Forst. Bark

Crateva religiosa G. Forst., commonly known as the sacred garlic pear or temple plant, has been used in traditional medicine for its various therapeutic properties. The bark of this plant contains a rich array of bioactive compounds, making it an excellent candidate for the green synthesis of silver nanoparticles[35]. The bark contains flavonoids, tannins, terpenoids, and phenolic compounds, which act as effective reducing and capping agents, facilitating the reduction of silver ions and stabilizing the nanoparticles to ensure uniformity and prevent

aggregation[36]. Using Crateva religiosa bark for nanoparticle synthesis is environmentally friendly and sustainable, avoiding toxic chemicals and harsh conditions and aligning with green chemistry principles. Additionally, the plant is readily available and can be harvested without causing significant ecological damage. Nanoparticles synthesized using plant extracts are often more biocompatible compared to those produced via chemical methods[37]. The natural capping agents from the plant extract enhance the biocompatibility of the nanoparticles, making them suitable for biomedical applications, including drug delivery and cancer therapy[38]. The bioactive compounds from Crateva religiosa bark not only stabilize the nanoparticles but may also confer additional therapeutic properties, such as antioxidant, anti-inflammatory, and anticancer effects, potentially enhancing the overall therapeutic efficacy of the nanoparticles[4,7]. The unique phytochemicals present in Crateva religiosa bark may interact selectively with cancer cells, providing a basis for targeted therapy. The inherent bioactivity of the plant-derived compounds can complement the anticancer effects of the silver nanoparticles, leading to synergistic effects and improved outcomes[39].

Mechanism of Action

The bioactive peptides from Crateva religiosa bark exhibit a range of interactions with cancer cells, contributing to their therapeutic effects by targeting various cellular components and pathways[22]. One primary mechanism involves the direct interaction with the cancer cell membrane, where peptides can insert into the lipid bilayer, causing membrane disruption and increased permeability, leading to cell lysis or facilitating the entry of therapeutic agents[7]. Once inside the cell, these peptides can interact with intracellular targets such as mitochondria, disrupting mitochondrial membrane potential and triggering the release of cytochrome c, which initiates the intrinsic apoptotic pathway leading to programmed cell death. Additionally, some peptides can enter the nucleus and interact with DNA or nuclear proteins, inducing DNA damage or interfering with transcription and replication processes, resulting in cell cycle arrest and apoptosis[18]. Peptides can also inhibit critical enzymes and proteins involved in cell survival and proliferation, such as proteasomes, leading to the accumulation of misfolded proteins and cell death. Furthermore, these bioactive peptides can generate reactive oxygen species (ROS) within cancer cells, causing oxidative stress that damages cellular components like lipids, proteins, and DNA, ultimately triggering apoptosis through the activation of stress-responsive signaling pathways[40].

Activation of Apoptotic Pathways:

Peptides from Crateva religiosa bark can activate both intrinsic and extrinsic apoptotic pathways. The intrinsic pathway, which is mitochondria-dependent, is triggered by the release of pro-apoptotic factors from the mitochondria[12]. Peptides can induce the release of cytochrome c, which interacts with Apaf-1 and procaspase-9 to form the apoptosome, activating caspase-9 and leading to the activation of downstream caspases (caspase-3, -6, and -7) that execute apoptosis[6,9]. The extrinsic pathway involves the activation of death receptors on the cell surface, such as Fas and TNF receptors. Peptides can enhance the binding of ligands to these receptors, triggering the formation of the death-inducing signaling complex (DISC), which activates caspase-8 and subsequently activates downstream caspases to induce apoptosis[22]. Additionally, peptides from Crateva religiosa can inhibit angiogenesis by targeting endothelial cells and disrupting the signaling pathways involved in blood vessel formation, starving the tumor of nutrients and oxygen. These peptides also modulate the

immune response by increasing the activity of immune cells such as natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), which can recognize and kill cancer cells[41]. Furthermore, peptides can reduce the immunosuppressive environment often created by tumors, allowing for a more effective immune response[12]. Functionalization of silver nanoparticles (AgNPs) with these bioactive peptides can provide targeted delivery to cancer cells by binding specifically to receptors or antigens overexpressed on the surface of cancer cells, enhancing therapeutic efficacy and reducing off-target effects[16]. Overall, the bioactive peptides from Crateva religiosa bark offer a promising avenue for cancer therapy by disrupting cancer cell membranes, inducing oxidative stress, activating apoptotic pathways, inhibiting angiogenesis, and modulating the immune response. When integrated into the synthesis of silver nanoparticles, these peptides enhance the therapeutic potential of the nanoparticles, providing a green and effective strategy for cancer treatment[42].

Anti-Cancer Mechanisms

Nanoparticle-Cell Interactions

Understanding the interaction between silver nanoparticles (AgNPs) and cancer cells is crucial for optimizing their use as therapeutic agents, as the uptake and intracellular distribution of AgNPs determine their effectiveness in targeting and killing cancer cells[43,44]. The primary mechanisms by which cancer cells internalize AgNPs include endocytosis—comprising phagocytosis, pinocytosis, and receptor-mediated endocytosis—and diffusion. In receptor-mediated endocytosis, AgNPs functionalized with targeting ligands or peptides bind to specific receptors on the cancer cell surface, enhancing selective uptake[45]. Once inside the cell, AgNPs are distributed to various organelles where they exert cytotoxic effects. They often first travel to endosomes and lysosomes, where the acidic environment releases silver ions (Ag^+), contributing to cytotoxicity. Some nanoparticles escape the endosomal pathway, distributing in the cytoplasm and interacting with cellular components to induce oxidative stress[46]. Smaller AgNPs, or those designed with nuclear localization signals, can enter the nucleus and directly interact with DNA and nuclear proteins, causing significant damage. The cytotoxic effects of AgNPs on cancer cells are primarily mediated through the induction of oxidative stress, mitochondrial dysfunction, and activation of apoptotic pathways[47]. AgNPs catalyze the production of reactive oxygen species (ROS), overwhelming cellular antioxidant defenses and causing oxidative damage that can initiate apoptosis or necrosis. In mitochondria, AgNPs disrupt membrane potential, triggering the release of pro-apoptotic factors like cytochrome c, which then activate caspase-9 and a cascade of downstream caspases that execute apoptosis[48]. In the nucleus, AgNPs can cause direct DNA damage, activating the p53 pathway and leading to cell cycle arrest or apoptosis. Additionally, AgNPs can interact with the cancer cell membrane, increasing its permeability, which can cause cell lysis or facilitate the entry of more nanoparticles and therapeutic agents[49]. By targeting key signaling pathways involved in cell survival, proliferation, and apoptosis, such as ROS-mediated pathways, the mitochondrial pathway, the p53 pathway, the PI3K/Akt pathway, and the death receptor pathway, AgNPs exert multifaceted anticancer effects[50]. Compared to conventional anticancer agents, AgNPs offer unique advantages, such as the ability to disrupt multiple cellular processes simultaneously, making them effective and promising agents in cancer therapy.

Advantages and Challenges

Bioengineered silver nanoparticles (AgNPs) synthesized using plant extracts, such as those derived from Crateva religiosa bark, offer several advantages over traditional cancer therapies and chemically synthesized nanoparticles, including enhanced specificity and efficiency in targeting cancer cells, leading to improved therapeutic outcomes[51]. Targeted delivery is achieved through the functionalization of AgNPs with biomolecules like peptides, proteins, and other phytochemicals present in the plant extract, which can recognize and bind to specific receptors or antigens overexpressed on cancer cells[52]. This ensures that the nanoparticles preferentially accumulate in tumor tissues, minimizing impact on healthy cells and reducing off-target effects. The surface chemistry of bioengineered AgNPs, influenced by plant extract capping agents, enhances their cellular uptake via efficient and specific endocytic pathways, including receptor-mediated endocytosis[53]. Additionally, the phytochemicals and bioactive peptides from Crateva religiosa provide synergistic therapeutic effects, such as anticancer, anti-inflammatory, and antioxidant properties, which can enhance the cytotoxic effects of AgNPs and more effectively inhibit cancer cell growth[54]. These nanoparticles efficiently induce apoptosis through multiple mechanisms, including ROS generation, mitochondrial disruption, and activation of intrinsic and extrinsic apoptotic pathways, targeting cancer cells through various cellular processes and reducing the likelihood of resistance development[55]. The biocompatibility of bioengineered AgNPs is enhanced by natural capping agents from Crateva religiosa bark, stabilizing the nanoparticles and reducing their cytotoxicity towards normal cells, thus minimizing side effects and improving safety for clinical use.

Challenges

The full realization of the potential of bioengineered silver nanoparticles (AgNPs) faces hurdles in stability and reproducibility of synthesis. Variability between batches arises from differences in plant extract composition influenced by factors like geographic location and extraction methods, impacting AgNP characteristics and efficacy[56]. Standardized synthesis protocols are imperative for consistent quality and scalability, necessitating optimization of parameters like extract concentration and pH. Stability challenges during storage and use call for formulation improvements to prevent aggregation and oxidation[33]. Rigorous characterization methods such as dynamic light scattering and transmission electron microscopy are vital for quality control. Despite improved biocompatibility, concerns persist regarding potential cytotoxicity to normal cells, long-term effects, and environmental impact, underscoring the need for comprehensive safety assessments and environmental management strategies[5,9].

Future Perspectives

Advancements in bioengineering techniques are pivotal for the future of bioengineered silver nanoparticles (AgNPs), particularly those synthesized using Crateva religiosa bark[4]. These innovations aim to bolster nanoparticle production efficiency, consistency, and scalability, thereby tackling existing challenges and unlocking new therapeutic potentials[57]. Green synthesis protocols must be optimized for reproducibility, possibly through the development of automated synthesis platforms ensuring precise control over reaction parameters[14]. Genetic engineering of plants could boost the production of bioactive compounds facilitating nanoparticle synthesis[3]. Nano-bioreactors, mimicking natural biological environments, may refine the synthesis process by maintaining optimal conditions and controlling nanoparticle

characteristics more precisely. Post-synthesis surface modification techniques, like ligand exchange and coating with biocompatible materials, can enhance stability and functionality. Hybrid nanoparticles, combining silver with other materials, offer improved properties for various applications[58]. Advanced characterization methods, including high-resolution imaging, spectroscopic techniques, dynamic light scattering, atomic force microscopy, mass spectrometry, in situ monitoring, and computational modeling, are indispensable for deeper insights into AgNPs' attributes[59]. These advancements pave the way for broader applications beyond cancer therapy, spanning antimicrobial agents, anti-inflammatory treatments, drug delivery systems, biosensors, environmental applications, cosmetic products, and agricultural practices[19]. Moreover, the synergistic potential of AgNPs with chemotherapy, radiation therapy, immunotherapy, photothermal therapy, gene therapy, and magnetic hyperthermia promises enhanced therapeutic outcomes with reduced side effects, shaping the future of nanomedicine[60].

Conclusion

In the realm of bioengineered silver nanoparticles (AgNPs), the future is brimming with promise, heralding significant advancements in synthesis, characterization, and broader applications extending beyond cancer therapy. Leveraging their unique properties and synergizing with other treatments, bioengineered AgNPs stand poised to revolutionize diverse fields, offering innovative solutions to complex medical and environmental challenges. Our comprehensive review has meticulously explored the potential of AgNPs derived from Crateva religiosa bark as peptide inhibitors for targeting cancer cells, spanning synthesis methods, preclinical and clinical studies, and future perspectives. These nanoparticles offer a sustainable, green approach to cancer therapy with scalability and biocompatibility advantages. Advanced bioengineering techniques and characterization methods provide profound insights into nanoparticle properties, paving the way for therapeutic optimization. AgNPs possess distinctive physical, chemical, and biological attributes, rendering them promising candidates for cancer therapy, demonstrating selective targeting of cancer cells while sparing normal cells. Mechanistically, AgNPs enact anticancer effects via multiple pathways, including ROS generation, apoptosis induction, and cellular signaling modulation, offering a multifaceted treatment approach. Preclinical studies underscore their efficacy in inhibiting tumor growth and inducing apoptosis across various cancer models, findings corroborated by promising outcomes from clinical trials regarding safety, tolerability, and therapeutic efficacy.

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