Green Silver Nanoparticles: Novel Therapeutic Potential for Cancer and Microbial Infections

Abstract

The nanomedicine is opening borders by designing and testing both novel devices for clinical diagnosis and new therapies based on chemical nanostructures that exert their direct biological action or acting as pharmacological carriers. The development of new eco-friendly chemical synthesis methods opened a field of opportunity for nanomedicine and in the last years a great number of metallic nanoparticles have been synthesized through green chemical synthesis using natural plant extracts (leaf, stem, peel, bark, fruits). This review it shows an overview of the current status with silver nanoparticles synthesized by green chemical methods regarding their therapeutic potential for use in the treatment of microbial infections and cancer. The analysis carried out in recent publications shows that green silver nanoparticles have high antimicrobial activity (antibacterial, antifungal and antiviral) which can be enhanced with the addition of functional groups contained in the natural extracts used during the synthesis. In addition, there are many studies in different types of cancer that show the anticancer activity of green silver nanoparticles. This study shows that green synthesis has improved the selectivity of biological action and the biocompatibility of silver nanoparticles, these results are encouraging for treatment of cancer and microbial infections in humans.

Keywords: Green silver nanoparticles; Cancer; Antimicrobial; Natural extract; Nanomedicine

Mini Review

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Introduction

As a result of the development of nanotechnology in the last decade, silver nanoparticles emerged as an interesting alterative for the treatment of antimicrobial diseases and cancer, but its toxicological effects and its low biocompatibility were limiting its potential for clinical application [1-3]. The development of biosynthetic methods to obtain silver nanoparticles based on silver ions and natural plant extracts (Rich in reducing, capping, and stabilizing agents) radically changes the perspective on its adverse effects, since this green synthesis method allows obtaining silver nanoparticles with more biocompatibility [4-7]. The present review aims to show an overview of the therapeutic potential of silver nanoparticles synthesized with natural plant extracts for the treatment of microbial infections and cancer, this analysis is based on recent publications.

Discussion

Antimicrobial activity

A large number of green silver nanoparticles have been synthesized using plant extracts as a reaction medium which provides reducing and stabilizing agents; most studies have been carried out with natural plants that have ethnomedical use in humans. As shown in Table 1 [8-27], the antimicrobial effect of the green silver nanoparticles, mainly their antibacterial [8-25] and antifungal action [10,12-14,17,18,23-25], has been widely reported. It is important to mention that despite a wide variety of studies existing in the literature, antimicrobial activity has generally been evaluated in the same microorganisms even though there is a large amount of bacteria, fungi and viruses of clinical importance that could be studied. Also, when existing studies are analyzed (Table 1), most suggest that biosynthesized silver nanoparticles are biocompatible and may have therapeutic use potential in humans; however, if we review the studies summarized in Table 1 very few carry out biocompatibility tests in normal cells [8,10,14,15,18,26,27]. These tests provide crucial information on the ranges of safety and cytotoxicity of the biosynthetized nanoparticles, information that result fundamental to can be designed future experiments with biomedical applications in preclinical and clinical models. Another important fact is about the physical nature of the nanoparticles with respect to their size, most of the studies obtained nanoparticles with sizes greater than 10 nm in diameter [8,10-17,19-27]; it would be interesting to know their effects with sizes smaller than 10 nm since there is evidence that their biological effects also dependent on size [28]. Furthermore, for a better comparative analysis of the therapeutic potential of green silver nanoparticles, it is important to include in future experiments reference drugs that are currently the most used and effective in antimicrobial therapy in humans (cephalosporins, quinolones, and macrolides) [29], since most studies existing do not include used-commercial drugs as control [8-9,11,13-16,18,20-21] or it is included drugs used in the past. Finally, the plant extracts used in the green synthesis of nanoparticles contain a large variety of functional groups that can be added to the chemical structure of the silver nanoparticle, in this sense the existing studies have not fully evaluated the role that can have the chemical functionalization in the biological activity of the nanoparticles, the studies included in the present review discuss very little to the regard, being a critical factor that can explain the variability in the antimicrobial effect of the different types of silver nanoparticles that are biosynthesized. Another relevant aspect is that green silver nanoparticles could be an innovative alternative to reduce resistance to antibiotics a serious problem responsible for the increase in deaths worldwide [29].

Table 1: Antimicrobial action of green silver nanoparticles and biocompatibility.

Reference	Shape/Size	Plant Used for the Synthesis	Microorganism	Biocompatibility in Normal Cell
[8]	Spherical 71 nm	Aloe Vera leaf	*S. epidermidis, P. aeruginosa*	Yes IC_{50} > 2.5 mg/mL
[9]	Spherical 7.4 nm	Hydrocotyle rotundifolia leaf	*E. coli*	n.e
[10]	Spherical 15-30nm	Thalictrum foliolosum root	*E. coli, K. pneumonia, P. diminuta, B. subtilis, S. aureus, M. smegmatis, C. albicans, T. rubrum, A. versicolor, A. niger*	Yes IC_{50} > 62.5 mg/mL
[11]	Spherical 16 nm	Ficus benghalensis leaf	*E.coli*	n.e
[12]	Spherical 9-32 nm	Longan peel	*S. aureus, B. subtilis, E. coli, P. aeruginosa, C. albicans*	n.e
[13]	Spherical 30-40 nm	O. heracleoticum L leaf	*S. aureus, E. coli, P. aeruginosa, K. pneumonia, S. pneumonia, C. albicans*	n.e
[14]	Spherical 13 nm	Alpinia katsumadai seeds	*S. aureus, B. subtilis, E. coli, P. aeruginosa C. albicans*	Yes 7.5-15 mg/mL
[15]	Spherical	Protium serratum leaf	*P. aeruginosa, E. coli, B. subtilis*	Yes IC_{50}, 600 mg/mL
[16]	Spherical 20 nm	Eriobotrya japonica leaf	*E. coli, S. aureus*	n.e
[17]	Spherical 7-44 nm	Syzygium alternifolium leaf	*B. subtilis, S. aureus, E. coli, K. pneumonia, P. vulgaris, P. aeruginosa, S. typhimurium, A. solani, A. flavus, A. niger, P. chrysogenum, T. harzianum.*	n.e
[18]	Spherical 7 nm	Rumex hymenosepalus root	*E. coli, S. aureus, S. serovar typhi, P. aeruginosa, L. monocytogenes, C. albicans*	Yes IC_{50}>> 500 mg/mL
[19]	Spherical 16-30 nm	Phyllanthus amarus, whole plant	*P. aeruginosa*	n.e
[20]	Spherical 22-32 nm	Ricinus Communis, Catha Edulis, Helianthus Annuus leaf	*E.coli, S. aureus*	n.e
[21]	Spherical 22-30 nm	Ailanthus excelsa leaf	*E. coli, K. pneumonia, S. aureus, P. aeruginosa*	n.e
[22]	Spherical 16 nm	Pongamia pinnata seeds	*E. coli*	n.e
[23]	Cubic-hexagonal 30 nm	Argemone maxicana leaf	*E. coli, P. aeruginosa, A. flavus*	n.e
[24]	Spherical 516 nm	Acalypha indica, whole plant	*B. subtilis, S.aureus, P.aeruginosa, E. coli C.albicans, A. niger*	n.e
[25]	Spherical 0-50 nm	Ocimum sanctum leaf	*E. coli , P. vulgaris, S. aureus, S. saprophyticus C. albicans, C. tropicalis, C. krusei, C. Kefyr, A. niger A. flavus, A. fumigatus*	n.e
[26]	Spherical 42 nm	Cinnamomum cassia	*Avian influenza* virus subtype H7N3	Yes IC_{50}>> 500 mg/mL
[27]	Spherical 27 nm	Garcinia imberti	*E. faecium, S. sciuri, E. faecalis.*	Yes IC_{50}>> 75 mg/mL

n.e= It was not evaluated.

Anticancer activity

Green synthesis of silver nanoparticles using plant extracts offers a simple, fast and economical method to generate new molecules with anticancer potential as has been reported in recent years as is shows in Table 2. Recent studies with biosynthesized silver nanoparticles provide encouraging information focused on finding novel therapies for different types of cancer, but there are challenges for these molecules to become clinically useful. A key point in anticancer therapy is to have drugs or molecules that are highly selective to kill cancer cells. In the literature there are green silver nanoparticles with anticancer activity but their cytotoxic effects have not been evaluated in normal cells [21,30,33,37,39,42], others show that there is little selectivity for cancer cells [14,34] and other studies show encouraging anticancer activity due to a better degree of selectivity [32,35,36,40,41,43,45]. An advantage of the use of medicinal plant extracts is the opportunity to be able to functionalize silver nanoparticles to enhance their anticancer effect and improve their specificity of action on cancer cells without affecting non-tumor cells; this represents a challenge for scientists. To date, most studies have evaluated the anticancer activity of green silver nanoparticles using in vitro assays and cell lines. Other challenge is carry out future experiments on in vivo cancer models with immunocompetent and immunosuppressed animals to evaluate anticancer activity of green silver nanoparticles and its toxicology. Current reports show that green silver nanoparticles have great potential as future therapies against cancer, but knowledge about their side effects in non-target cells and organs is very poor and requires more research. Another opportunity that results from the analysis of this minireview is to study the anticancer activity of green silver nanoparticles on other types of cancer such as leukemia, lymphoma, myeloma, ovary, pancreas, thyroid, brain, kidney, skin. Moreover, the differences in anticancer activity and biocompatibility in the studies analyzed in the present work may be due to the size of silver nanoparticle and the functional groups since the plants used for the synthesis have differences in their chemical composition.

Table 2: Anticancer action of green silver nanoparticles and biocompatibility.

References	Shape/Size	Plant Used for the Synthesis	Type of Cancer	IC_{50}	Biocompatibility in Normal Cell IC_{50}
[30]	Spherical 5-47 nm	*Vitex negundo* Linn leaf	Colon	20 mg/mL	n.e
[31]	Spherical 91 nm	*Taxus baccata* needles	Breast	0.25-5 mg/mL	n.e
[32]	Spherical 15-18 nm	*Curculigo orchioides rhizome*	Breast	19 mg/mL	42 mg/mL
[33]	Spherical 20-40 nm	*Piper nigrum*	Breast Pharinx	52 µg/mL 43 mg/mL	n.e
[12]	Spherical 9-32 nm	*Dimocarpus longan* peel	Prostate	5-10 mg/mL	n.e
[13]	Spherical 30-40 nm	*O. heracleoticum* L leaf	Breast	50-100 mg/mL	n.e
[14]	Spherical 13 nm	*Alpinia katsumadai* seeds	Gastric	7.5-15 mg/mL	7.5-15 mg/mL
[21]	Spherical 22-30 nm	*Ailanthus excelsa* leaf	Breast	265 mg/mL	n.e
[34]	Spherical 20-50 nm 8-20 nm	Green tea Coffee	Cervical	14 mg/mL 655 mg/mL	5 mg/mL 272 mg/mL
[35]	Spherical 15 nm	*Lonicera hypoglauca* flower	Breast	<<500€…γ/µΛ	500 mg/mL<<
[36]	Spherical 5-15 nm	*Panax ginseng* fresh leaf	Lung	> 20 …γ/µΛ	>> 20 …γ/µΛ
			Breast	10 mg/mL	
			Liver	> 10 …γ/µΛ	
[37]	Spherical 54–89 nm	Ficus carica fruit	Breast	12 mg/mL	n.e
[36]	Spherical 5- 50 nm	*Syzygium aromaticum*	Breast	60 mg/mL	n.e
			Lung	50 mg/mL	
[39]	Spherical 5- 21 nm	*Ficus religiosa* leaf	Lung	0.9 mg/mL	n.e
			Cervical	1 mg/mL	
			Liver	1.1 mg/mL	
			Colon	1.7 mg/mL	
			Neuroblastoma	3.8 mg/mL	
[40]	Spherical 94 nm	*Azadirachta indica* leaf	Lung	120 ppm	>> 240 ππµ
[41]	Spherical 3-10 nm	*Mentha arvensis* leaf	Breast	6.25 mg/mL	12.5 mg/mL
[42]	Spherical, hexagonal 30-80 nm	*Borago officinalis*	Lung	5 mg/mL	n.e
			Cervical	2 mg/mL	
[43]	Polygonal 100-150 nm	*Dendropanax morbifera* leaf	Lung	10-100 mg/mL	~100 …γ/µΛ
[44]	Spherical 37 nm	*Coriandrum sativum* leaf	Breast	30 mg/mL	n.e
[45]	Spherical 6-27 nm	*Taxus yunnanensis* leaf	Liver	28 mg/mL	81 mg/mL

n.e = It was not evaluated.

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Conclusion

Currently, a large number of silver nanoparticles have be synthesized through green chemical synthesis using mainly medicinal plant extracts, these nanoparticles are generally spherical in shape, chemically stable and their method of production is simple, fast, low cost and ecofriendly. These green nanoparticles have antimicrobial and anticancer activity with high therapeutic potential for biomedical applications, but future experiments are needed to improve its selectivity on cancer cells, biocompatibility in normal cells and toxicological tests in preclinical models that validate its potential clinical application. The green silver nanoparticles open a novel pathway for treatment of the cancer and microbial infections in humans.

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Conflict of Interest

The authors declare that they have no conflict of interests. A.V.O designed and wrote manuscript; A.A.I. participated in design and wrote manuscript.

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