







# In vitro antifungal activity of biosynthesized selenium nanoparticles using plant extracts and six comparators against clinical *Fusarium* strains

Mohsen Nosratabadi<sup>1,2,3</sup>, Mohammad Ali Ebrahimzadeh<sup>4</sup>, Seyedeh Roya Alizadeh<sup>4</sup>, Iman Haghani<sup>2,3</sup>, Leila Faeli<sup>1,2,3</sup>, Robab Ebrahimi Barogh<sup>1,2,3</sup>, Abdullah M.S. Al Hatmi<sup>5</sup>, Mahdi Abastabar<sup>2,3\*</sup>

<sup>1</sup> Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

<sup>2</sup> Department of Medical Mycology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

<sup>3</sup> Invasive Fungi Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

<sup>4</sup> Department of Medicinal Chemistry, School of Pharmacy and Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran

<sup>5</sup> Natural and Medical Sciences Research Center, University of Nizwa, Nizwa, Oman

## Article Info

### Article Type:

Original Article

### Article History:

Received: 27 January 2024

Revised: 05 March 2024

Accepted: 11 March 2024

### \* Corresponding Author:

**Mahdi Abastabar**

Department of Medical Mycology,  
School of Medicine, Mazandaran  
University of Medical Sciences, Sari,  
Iran.

Email: mabastabar@gmail.com

## ABSTRACT

**Background and Purpose:** *Fusarium* species are commonly resistant to many antifungal drugs. The limited therapeutic options available have led to a surge of research efforts aimed at discovering novel antifungal compounds in recent decades. This study aimed to assess the *in vitro* antifungal activity of plant-based biosynthesized selenium nanoparticles (Se NPs) and six comparators against a set of clinical *Fusarium* strains.

**Materials and Methods:** *In vitro* antifungal activity of Se NPs synthesized using plant extracts of *Allium paradoxum*, *Crocus caspius*, *Pistacia vera* L. hull, *Vicia faba* L. hull and *Heracleum persicum*, as well as six common antifungal drugs, namely voriconazole, itraconazole, amphotericin B, posaconazole, natamycin, and caspofungin were evaluated against 94 clinical *Fusarium* strains using broth microdilution according to Clinical and Laboratory Standards Institute guideline.

**Results:** The obtained results were intriguing since all five types of biosynthesized Se NPs demonstrated significantly higher antifungal activity, compared to antifungal drugs. It was found that Se NPs synthesized by *V. faba* L. hull extract (0.03 µg/ml) had the lowest geometric mean minimum inhibitory concentration value followed by Se NPs synthesized by *P. vera* L. hull extract (0.25 µg/ml), *A. paradoxum* extract (0.39 µg/ml), *C. caspius* extract (0.55 µg/ml), and *H. persicum* extract (0.9 µg/ml).

**Conclusion:** Plant-based Se NPs demonstrated supreme antifungal activity and could be considered promising antifungal agents for *Fusarium* infections. However, tests, such as toxicity and *in vivo* tests are needed before the product can be used in clinical settings.

**Keywords:** Antifungal activity, *Fusarium* species, Se NPs, Plant extract

### ➤ How to cite this paper

Nosratabadi M, Ebrahimzadeh MA, Alizadeh SR, Haghani I, Faeli L, Ebrahimi Barogh R, Al Hatmi AMS, Abastabar M. *In vitro* antifungal activity of biosynthesized selenium nanoparticles using plant extracts and six comparators against clinical *Fusarium* strains. *Curr Med Mycol.* 2023; 9(4): 17-23. DOI: [10.22034/CMM.2024.345189.1504](https://doi.org/10.22034/CMM.2024.345189.1504)

## Introduction

Fungal pathogens pose a serious threat to public health, affecting at least 1.5 million people worldwide each year [1,2]. Resistance to conventional antifungal drugs has emerged as a global public health concern, severely limiting available treatment options [3-6]. Furthermore, since fungal and human cells are so similar, it is difficult to discover and develop new and effective antifungal drugs [7,8].

*Fusarium* is a large and remarkably diverse genus of saprophytic fungi found throughout nature [9]. *Fusarium* species are important phytopathogenic and mycotoxin-producing fungi [10,11]. They are also opportunistic fungi that cause a wide range of infections, from superficial and localized infections,

such as onychomycosis and keratitis in healthy people to fatal systemic infections in severely ill people [12-14].

In the United States and Europe, *Fusarium* is the second most common mold-causing human infection [15-17]. This fungal genus has high levels of intrinsic resistance to commonly available antifungal agents, posing a serious challenge to healthcare systems all over the world [15,17]. Since *Fusarium* species are frequently resistant to many antifungal drugs, and since there is a limited therapeutic repository for these fungal infections, research focused on finding novel and potent antifungal compounds as well as alternatives are urgently needed [12, 18-20].

Development of nanotechnology-based therapies in recent years has opened up new avenues for the treatment of drug-resistant fungal infections. Due to their nanometer size and large surface areas, nanoparticles have unique physicochemical properties that increase interactions with microbial cells and significantly influence their antimicrobial effects [21,22].

Selenium is a trace element that is essential for human and animal health, and it is involved in antioxidant defense, metabolism, and detoxification. Due to their low toxicity, high biodegradability, and bioavailability as well as anticancer, antidiabetic, antioxidant, antibacterial, antiprotozoal, antiviral, antifungal, and antibiofilm properties, selenium nanoparticles (Se NPs) are among the most appealing nanomaterials in biomedicine [23,24].

According to some studies, the antimicrobial activity of Se NPs is often attributed to the generation of reactive oxygen species, which can damage the DNA and cell membrane. However, the precise antimicrobial mechanisms of Se NPs have not been fully elucidated, and more research is needed. According to previous research, Se NPs can be synthesized through chemical, physical, or biological processes [25-28]. However, green synthesis or biologically synthesized Se NPs using microorganisms or plant extracts as natural reducing agents provides novel, simple, low-cost, non-toxic, and environment-friendly methods for the production of Se NPs [29-32].

Some plants contain a high concentration of phytochemical compounds with important biological and medicinal properties. The efficiency and capability of these compounds as nanoparticle reductants in green synthesis have previously been demonstrated [31-33]. The current study aimed to assess the *in vitro* antifungal activity of Se NPs made from extracts of *Allium paradoxum*, *Crocus caspius*, *Pistacia vera* L. hull, *Vicia faba* L. hull, and *Heracleum persicum*, as well as six antifungal drugs, namely, voriconazole, itraconazole, amphotericin B, posaconazole, natamycin, and caspofungin against a collection of clinical *Fusarium* strains.

## Materials and Methods

### Strains

In this study, 94 clinical isolates of *Fusarium* were examined. Isolates were collected from different medical mycology centers in Iran between 2019 and 2022 [34]. The most isolates were recovered from nail samples (58.51%, 55/94), followed by cornea (40.43%, 38/94) and Sinus (1.06%, 1/94). Partial sequencing of the translation elongation factor 1- $\alpha$  (*TEF-1  $\alpha$* ) identified all *Fusarium* isolates at the species level.

### Synthesis of plant-based selenium nanoparticles

The plant-based Se NPs used in this study were synthesized by the Department of Medicinal Chemistry at the School of Pharmacy and Pharmaceutical Sciences

Research Centre of Mazandaran University of Medical Sciences, Sari, Iran [31,32]. The plants *A. paradoxum*, *C. caspius*, *P. vera* L. hull, *V. faba* L. hull, and *H. persicum* were dried in daylight, cut into small pieces (2-3 mm), and stored at room temperature. Each plant (10 g) was combined with 80 mL of deionized water and heated at 50 °C for 1 h. The mixture was then sonicated for 30 min and filtered through the Whatman filter paper. In the process of Se NPs biosynthesis using plant extracts, 17.3 mg of Na<sub>2</sub>SeO<sub>3</sub> was dissolved in 10 mL of deionized water and stirred at 45-50 °C and 500 rpm. Subsequently, 5 mL of the aqueous extract was added to the reaction mixture drop by drop. After two days, the color of the reaction changed from colorless to reddish, indicating the reduction of Se ions.

### Antifungal susceptibility testing

The *in vitro* antifungal activities of biosynthesized Se NPs using plant extracts of *A. paradoxum* (A-Se NPs), *C. caspius* (C-Se NPs), *P. vera* L. hull (P-Se NPs), *V. faba* L. hull (V-Se NPs), and *H. persicum* (H-Se NPs) as well as six routine antifungal drugs, including itraconazole (Janssen, Beerse, Belgium), posaconazole (Pfizer, Sandwich, United Kingdom), voriconazole (Pfizer, Sandwich, United Kingdom), natamycin (Sigma-Aldrich, Steinheim, Germany), amphotericin B (Bristol-Myers-Squib, Woerden, The Netherlands), and caspofungin (Merck Sharp & Dohme BV) were determined against 94 clinical *Fusarium* isolates. It was performed by using broth microdilution according to the Clinical and Laboratory Standards Institute M38-A3 [35].

The final concentrations of agents in the wells ranged from 0.016 to 16  $\mu$ g/ml for V-Se NPs, A-Se NPs, P-Se NPs, C-Se NPs, H-Se NPs, amphotericin B, voriconazole, natamycin, posaconazole, itraconazole, and 0.008 to 8  $\mu$ g/ml for caspofungin.

The *Fusarium* isolates were cultured on Sabouraud dextrose agar (Difco Laboratories, Detroit, MI, USA) and incubated at 35 °C for 5 to 7 days for adequate sporulation. Suspensions were diluted at 1:50 in RPMI 1640 medium to obtain final inoculum between  $0.4 \times 10^4$  to  $5 \times 10^4$  CFU/ml. Plates were incubated at 35 °C, and minimum inhibitory concentrations (MICs) and minimum effective concentrations (MECs) were read after 48 h.

The MIC was determined visually as the lowest concentration of agent that resulted in 100% inhibition of fungal growth while for caspofungin MEC was microscopically determined as the lowest concentration of drug that resulted in the growth of compact hyphal forms compared with growth control. *Candida krusei* (ATCC 6258), *Candida parapsilosis* (ATCC 22019), and *Aspergillus flavus* (ATCC 2004304) served as quality control strains.

## Results

All *Fusarium* strains were previously identified using *TEF1* partial gene analysis [34].

**Table 1.** Sources and the number of the *Fusarium* isolates based on the species complexes

<i>Fusarium</i> complexes	Species	Source	No.	
<i>F. fujikuroi</i> species complex (n=33)	<i>F. proliferatum</i>	Nail	15	
		Cornea	6	
		Sinus	1	
	<i>F. fujikuroi</i>	Nail	3	
		<i>F. acutatum</i>	Nail	1
		<i>F. verticillioides</i>	Nail	5
<i>F. solani</i> species complex (n=52)	<i>F. thapsinum</i>	Cornea	2	
		Nail	2	
	<i>F. falciforme</i>	Cornea	3	
		Nail	6	
	<i>F. solani sensu stricto</i>	Cornea	22	
Nail	19			
<i>F. sambucinum</i> species complex (n=1)	<i>F. brachygibbosum</i>	Cornea	1	
<i>F. incarnatum equiseti</i> species complex (n=1)	<i>F. equiseti</i>	Nail	1	
<i>F. oxysporum</i> species complex (n=7)	<i>F. oxysporum</i>	Cornea	4	
		Nail	3	

The species used in the study belonged to the *Fusarium solani* species complex (n=52), *F. fujikuroi* species complex (n=33), *F. oxysporum* species complex (n=7), *F. incarnatum equiseti* species complex (n=1), and *F. sambucinum* species complex (n=1) (Table 1). The geometric mean (GM) MICs/MECs, MIC/MEC ranges, MIC<sub>50</sub>/MEC<sub>50</sub>, and MIC<sub>90</sub>/MEC<sub>90</sub> distributions of the tested compounds are shown in Table 2 and Table 3.

The obtained results were extremely intriguing

since all five types of biosynthesized Se NPs demonstrated significantly higher antifungal activity, compared to routine antifungal drugs in the clinical settings.

According to GM MICs/MECs values, V-Se NPs (0.03 µg/ml) showed the lowest GM MICs/MECs values, followed by P-Se NPs (0.25 µg/ml), A-Se NPs (0.39 µg/ml), C-Se NPs (0.55 µg/ml), H-Se NPs (0.9

**Table 2.** In vitro susceptibilities of plant-based selenium nanoparticles in comparison with six antifungal drugs against 94 clinical *Fusarium* isolates

<i>Fusarium</i> species	Evaluated compounds	MIC <sub>50</sub> (µg/ml)	MIC <sub>90</sub> (µg/ml)	MIC range (µg/ml)	GM (µg/ml)	Mode (µg/ml)	
Total <i>Fusarium</i> isolates (n=94)	A-Se NPs	0.5	2	0.016-8	0.39	1	
	C-Se NPs	0.5	4	0.016-8	0.55	0.5	
	P-Se NPs	0.25	4	0.016-16	0.25	0.5	
	V-Se NPs	0.032	0.125	0.016-0.25	0.03	0.016	
	H-Se NPs	1	4	0.016-8	0.9	1	
	VRC	4	8	0.25-16	3.25	4	
	ITC	16	16	0.032-16	13.01	16	
	AMB	1	4	0.125-16	1.05	1	
	NAT	4	8	0.125-16	3.91	8	
	CAS	8	8	0.064-8	7	8	
	POS	8	16	0.25-16	5.29	8	
	<i>F. solani</i> complex (n=52)	A-Se NPs	1	4	0.016-8	0.56	1
		C-Se NPs	1	4	0.016-8	0.64	2
P-Se NPs		0.5	8	0.016-16	0.46	0.5	
V-Se NPs		0.032	0.125	0.016-0.25	0.03	0.016	
H-Se NPs		1	8	0.064-8	1.32	1	
VRC		4	8	0.25-16	3.74	8	
ITC		16	16	0.032-16	11.93	16	
AMB		0.5	2	0.125-16	0.67	0.5	
NAT		8	8	0.5-16	5.15	8	
CAS		8	8	0.064-8	6.46	8	
POS		8	16	0.5-16	6.55	16	
<i>F. fujikuroi</i> complex (n=33)		A-Se NPs	0.25	1	0.016-4	0.23	0.5
		C-Se NPs	0.5	2	0.016-4	0.48	0.5
	P-Se NPs	0.064	1	0.016-4	0.1	0.016	
	V-Se NPs	0.032	0.125	2-16	0.03	0.016	
	H-Se NPs	0.5	4	0.064-8	0.56	0.25	
	VRC	4	8	1-8	2.74	4	
	ITC	16	16	8-16	14.1	16	
	AMB	2	8	0.125-16	1.72	1	
	NAT	4	8	0.125-8	2.41	4	
	CAS	8	8	4-8	7.67	8	
	POS	4	16	0.25-16	4.17	16	
	<i>F. oxysporum</i> complex (n=7)	A- Se NPs	-	-	0.125-2	0.37	0.125
		C- Se NPs	-	-	0.5-1	0.61	0.5
P- Se NPs		-	-	0.125-0.5	0.18	0.125	
V- Se NPs		-	-	0.016-0.064	0.03	0.064	
H- Se NPs		-	-	0.5-2	0.6	0.5	
VRC		-	-	1-8	2.43	2	
ITC		-	-	16	16	16	

	AMB	-	-	0.5-16	2.69	2
	NAT	-	-	2-8	4	8
	CAS	-	-	8	8	8
	POS	-	-	0.5-16	4.41	8
<i>F. incarnatum equiseti</i> species complex (n=1)	A-Se NPs	-	-	0.25	-	-
	C-Se NPs	-	-	0.5	-	-
	P-Se NPs	-	-	1	-	-
	V-Se NPs	-	-	0.016	-	-
	H-Se NPs	-	-	2	-	-
	VRC	-	-	4	-	-
	ITC	-	-	16	-	-
	AMB	-	-	1	-	-
	NAT	-	-	8	-	-
	CAS	-	-	8	-	-
	POS	-	-	8	-	-
<i>F. sambucinum</i> species complex (n=1)	A-Se NPs	-	-	0.125	-	-
	C-Se NPs	-	-	0.016	-	-
	P-Se NPs	-	-	0.125	-	-
	V-Se NPs	-	-	0.016	-	-
	H-Se NPs	-	-	0.016	-	-
	VRC	-	-	4	-	-
	ITC	-	-	16	-	-
	AMB	-	-	1	-	-
	NAT	-	-	8	-	-
	CAS	-	-	8	-	-
	POS	-	-	2	-	-

MIC: minimum inhibitory concentration, GM: geometric mean, A-Se NPs: *A. paradoxum*-selenium nanoparticles, C-Se NPs: *C. caspius*-selenium nanoparticles, P-Se NPs: *P. vera* L. hull-selenium nanoparticles, V-Se NPs: *V. faba* L. hull-selenium nanoparticles, H-Se NPs: *H. persicum*-selenium nanoparticles, VRC: voriconazole, ITC: itraconazole, AMB: amphotericin B, NAT: natamycin, CAS: caspofungin, POS: posaconazole

µg/ml), amphotericin B (1.05 µg/ml), voriconazole (3.25 µg/ml), natamycin (3.91 µg/ml), posaconazole (5.29 µg/ml), caspofungin (7 µg/ml), and itraconazole (13.01 µg/ml). Moreover, the comparison of the susceptibility results revealed that the *Fusarium* strains had the lowest MIC90/MEC90 values for V- Se NPs

(0.125 µg/ml), followed by A-Se NPs (2 µg/ml), P-Se NPs (4 µg/ml), C-Se NPs (4 µg/ml), H-Se NPs (4 µg/ml), amphotericin B (4µg/ml), voriconazole (8 µg/ml), natamycin (8 µg/ml), caspofungin (8 µg/ml), posaconazole (16 µg/ml), and itraconazole (16 µg/ml).

**Table 3.** Minimum inhibitory concentrations of five Se NPs and six antifungal drugs on 94 clinical *Fusarium* isolates

Fusarium species	Evaluated compounds	MIC distribution (µg/ml)										
		0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16
Total <i>Fusarium</i> isolates (n=94)	A-Se NPs	6	2	3	16	15	17	21	6	4	4	
	C-Se NPs	6	3	2	10	10	20	12	16	12	3	
	P-Se NPs	15	5	7	18	7	18	6	2	9	5	2
	V-Se NPs	43	19	20	11	1						
	H-Se NPs	1		2	6	12	18	21	15	12	7	
	VRC					2	3	13	14	34	27	1
	ITC		1			1			1	11	80	
	AMB				6	5	23	30	14	9	2	5
	NAT				1	1	5	8	11	22	44	2
	CAS			1					1	9	83	
	POS					2	6	2	14	15	28	27
<i>F. solani</i> complex (n=52)	A-Se NPs	3	1	1	5	9	6	15	5	3	4	
	C-Se NPs	4	2	1	6	5	5	6	11	9	3	
	P-Se NPs	6	3	1	8	2	13	4	1	7	5	2
	V-Se NPs	22	11	11	7	1						
	H-Se NPs			1	1	4	10	11	10	9	6	
	VRC					2	3	2	7	16	21	1
	ITC		1			1			1	5	44	
	AMB				5	4	19	17	4	1	1	1
	NAT						4	1	2	12	31	2
	CAS			1					1	7	43	
	POS						2		8	8	17	17
<i>F. fujikuroi</i> complex (n=33)	A-Se NPs	3	1	2	7	5	9	5		1		
	C-Se NPs	1	1	1	4	5	9	4	5	3		
	P-Se NPs	9	2	6	4	5	3	1	1	2		
	V-Se NPs	16	7	6	4							
	H-Se NPs			1	5	8	4	8	3	3	1	
	VRC							10	3	15	5	
	ITC										6	27
	AMB				1	1	3	11	7	6	1	3
	NAT				1	1	1	7	6	9	8	
	CAS								2	31		
	POS					2	2	2	4	7	8	8



<i>F. oxysporum</i> complex (n=7)	A-Se NPs				3		2	1	1		
	C-Se NPs						5	2			
	P-Se NPs				5		2				
	V-Se NPs	3	1	3							
	H-Se NPs						4	2	1		
	VRC							1	4	1	1
	ITC										7
	AMB						1		3	2	1
	NAT								3	1	3
	CAS										7
	POS						2			3	2
<i>F. incarnatum equiseti</i> species complex (n=1)	A-Se NPs					1					
	C-Se NPs						1				
	P-Se NPs							1			
	V-Se NPs	1									
	H-Se NPs								1		
	VRC									1	
	ITC										1
	AMB							1			
	NAT										1
	CAS										1
	POS								1		
<i>F. sambucinum</i> species complex (n=1)	A-Se NPs				1						
	C-Se NPs	1									
	P-Se NPs				1						
	V-Se NPs	1									
	H-Se NPs	1									
	VRC									1	
	ITC										1
	AMB							1			
	NAT										1
	CAS										1
	POS								1		

MIC: minimum inhibitory concentration, MEC: minimum effective concentration, A-Se NPs: *A. paradoxum*-selenium nanoparticles, C-Se NPs: *C. caspius*-selenium nanoparticles, P-Se NPs: *P. vera* L. hull-selenium nanoparticles, V-Se NPs: *V. faba* L. hull-selenium nanoparticles, H-Se NPs: *H. persicum*-selenium nanoparticles, VRC: voriconazole, ITC: itraconazole, AMB: amphotericin B, NAT: natamycin, CAS: caspofungin, POS: posaconazole

## Discussion

*Fusarium* is a globally distributed multidrug-resistant genus that has the potential to cause a wide range of infections in humans [19]. In the present study, the inhibitory activity of five plant-based biosynthesized Se NPs and six common antifungal drugs were tested against 98 clinical *Fusarium* strains. Remarkably, it was discovered that the antifungal activity of plant-based Se NPs was superior to that of voriconazole, itraconazole, amphotericin B, posaconazole, natamycin, and caspofungin *in vitro*.

The lowest GM MICs and the highest antifungal activity among the biosynthesized selenium nanoparticles belonged to V-S eNPs (0.03 µg/ml), followed by P-Se NPs (0.25 µg/ml), A-Se NPs (0.39 µg/ml), C-Se NPs (0.55 µg/ml), and H-Se NPs (0.9 µg/ml). Additionally, the MIC<sub>50</sub> values of all five types of biosynthesized Se NPs against *Fusarium* isolates were significantly lower than those of the drugs of choice for the treatment of invasive fusariosis, which were amphotericin B (MIC<sub>50</sub>, 1 µg/ml) and voriconazole (MIC<sub>50</sub>, 4 µg/ml).

Selenium has antimicrobial properties and has been shown to inhibit the growth of fungi and bacteria. Selenium derivatives, such as selenium sulphide, are commonly used in the treatment of pityriasis versicolor [36-40]. Nanotechnology advancements in recent years have provided a safe strategy for the reduction of selenium toxicity. When compared to inorganic and

organic forms, Se NPs have lower toxicity and higher bioavailability [24,41-43].

Several studies have shown that biogenic selenium nanoparticles have antifungal activity [29,44,45]. Shakibaie et al. investigated the antifungal activity of *Bacillus* species synthesized selenium nanoparticles against *A. fumigatus* and *Candida albicans*, and the measured MICs for *C. albicans* (70 µg/ml) and *A. fumigatus* (100 µg/ml) showed that the biogenic Se NPs had good antifungal activity [44]. Shahverdi et al. also investigated the antifungal activity of *Klebsiella pneumoniae*-produced selenium nanoparticles against clinical isolates of the *Malassezia* and *Aspergillus* genus. The MICs for all fungal strains were within the range of 10-260 g/ml, with *M. sympodialis*, *M. furfur*, and *A. terreus* showing the highest antifungal activity [45].

Another study assessed the antifungal activity of Se NPs synthesized by *Lactobacillus acidophilus* in controlling wheat crown and root rot diseases caused by *Fusarium* species, and biogenic Se NPs successfully inhibited fungal growth at concentrations ranging from 20 to 40 µg/ml [46]. Furthermore, several studies on the synthesis of nanoparticles using plant extracts have been published [47-49].

There have been few studies on the antifungal activity of biosynthesized Se NPs derived from plant extracts. Gunti et al. demonstrated that biosynthesized



Se NPs derived from *Emblica officinalis* fruit extract had strong antifungal activity. The MIC values were found to be between  $07.50 \pm 1.32$  and  $25.50 \pm 2.78$   $\mu\text{g/ml}$ . The lowest and highest found MIC values were  $07.50 \pm 1.32$   $\mu\text{g/ml}$  against *Rhizopus stolonifer* and  $25.50 \pm 2.78$   $\mu\text{g/ml}$  against *A. oryzae*, respectively [50].

In another study, Kokila et al. biosynthesized Se NPs from *Diospyros montana* extract and reported antimicrobial activity in the form of zone of inhibition values of 08, 07, and 08 mm against *Staphylococcus aureus*, *Escherichia coli*, and *A. niger*, respectively [51]. Ali et al. also investigated the antifungal activity of Se NPs extracted from *Capparis decidua* fruit against *C. albicans* and discovered that biosynthesized Se NPs have a high antifungal activity [52].

In the present study, all five biosynthesized Se NPs derived from plant extracts outperformed the commonly used antifungal drugs. Biosynthesized Se NPs, particularly nanoparticles made from *V. faba* L. hull, *P. vera* L. hull, and *A. paradoxum* plant extracts demonstrated potent antifungal activity against clinical *Fusarium* isolates *in vitro*. In addition to the antifungal properties of metal ions and the size of the nanoparticles, the antifungal activity of Se NPs *in vitro* may be attributed to the phytochemical composition of the plant extracts used for green synthesis, as these factors may affect their bioavailability and antimicrobial activity [30,32].

## Conclusion

Plant-based Se NPs demonstrated supreme antifungal activity and could be considered promising antifungal agents for *Fusarium* infections. However, tests, such as toxicity and *in vivo* tests, are needed before the product can be used in clinical settings.

## Acknowledgments

This study was performed with the financial support of Mazandaran University of Medical Sciences, Sari, Iran [grant number: 10319].

## Author's contribution

M. A., I. H., M. A. E, A. M. S. A. H. conceived, designed, and supervised the study. M. N., M. A., S. R. A., R. E. B., L. F. performed the experiments and wrote the draft. M. A., A. M. S. A. H., M. A. E., and I. H. designed the study, analyzed the data, and edited the manuscript draft. All authors read and approved the final version of the manuscript.

## Conflicts of interest

The authors report no conflicts of interest.

## Financial disclosure

None.

## Ethical Approval

The current study was approved by the Ethics Committee of the Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1400.423).

## References

- Loh JT, Lam KP. Fungal infections: Immune defense, immunotherapies and vaccines. *Adv Drug Deliv Rev.* 2023; 196:114775.
- Palmieri F, Koutsokera A, Bernasconi E, Junier P, von Garnier C, Ubags N. Recent Advances in Fungal Infections: From Lung Ecology to Therapeutic Strategies with a Focus on *Aspergillus spp.* *Front Med.* 2022; 9:832510.
- Vitiello A, Ferrara F, Boccellino M, Ponzio A, Cimmino C, Comberiat E, Zovi A, Clemente S, Sabbatucci M. Antifungal Drug Resistance: An Emergent Health Threat. *Biomedicines.* 2023;11(4):1063.
- Fisher MC, Alastruey-Izquierdo A, Berman J, Bicanic T, Bignell EM, Bowyer P, Bromley M, Brüggemann R, Garber G, Cornely OA, Gurr SJ. Tackling the emerging threat of antifungal resistance to human health. *Nat Rev Microbiol.* 2022;20(9):557-71.
- Abastabar M, Haghani I, Shokohi T, Hedayati MT, Aghili SR, Jedi A, Dadashi S, Shabanzadeh S, Hosseini T, Aslani N, Meis JF. Low *in vitro* antifungal activity of tavaborole against yeasts and molds from onychomycosis. *Antimicrob Agents Chemother.* 2018;62(12):10-128.
- Abastabar M, Jedi A, Guillot J, Ilkit M, Eidi S, Hedayati MT, Shokohi T, Daie Ghazvini R, Rezaei-Matehkolaei A, Katirae F, Javidnia J. *In vitro* activities of 15 antifungal drugs against a large collection of clinical isolates of *Microsporum canis*. *Mycoses.* 2019;62(11):1069-78.
- Vanreppelen G, Wuyts J, Van Dijck P, Vandecruys P. Sources of antifungal drugs. *J Fungi.* 2023;9(2):171.
- Roy M, Karhana S, Shamsuzzaman M, Khan MA. Recent drug development and treatments for fungal infections. *Braz J Microbiol.* 2023;23:1-22.
- Al-Hatmi AM, Meis JF, de Hoog GS. *Fusarium*: molecular diversity and intrinsic drug resistance. *PLoS Pathog.* 2016;12(4): e1005464.
- Rampersad SN. Pathogenomics and management of *Fusarium* diseases in plants. *Pathogens.* 2020;9(5):340.
- Ekwomadu TI, Akinola SA, Mwanza M. *Fusarium* mycotoxins, their metabolites (free, emerging, and masked), food safety concerns, and health impacts. *Int J Environ Res Public Health.* 2021;18(22):11741.
- Al-Hatmi AM, de Hoog GS, Meis JF. Multiresistant *Fusarium* pathogens on plants and humans: solutions in (from) the antifungal pipeline?. *Infect Drug Resist.* 2019;28:3727-37.
- Hof H. The medical relevance of *Fusarium* spp. *J Fungi.* 2020;6(3):117.
- Abastabar M, Al-Hatmi AM, Vafaei Moghaddam M, De Hoog GS, Haghani I, Aghili SR, Shokohi T, Hedayati MT, Daie Ghazvini R, Kachuei R, Rezaei-Matehkolaei A. Potent activities of luliconazole, lanconazole, and eight comparators against molecularly characterized *Fusarium* species. *Antimicrob Agents Chemother.* 2018;62(5): e00009-18.
- Park BJ, Pappas PG, Wannemuehler KA, Alexander BD, Anaissie EJ, Andes DR, Baddley JW, Brown JM, Brumble LM, Freifeld AG, Hadley S. Invasive non-*Aspergillus* mold infections in transplant recipients, United States, 2001–2006. *Emerg Infect Dis.* 2011;17(10):1855.
- Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, Ito J, Andes DR, Baddley JW, Brown JM, Brumble LM. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis.* 2010;50(8):1091-100.
- Salah H, Houbraken J, Boekhout T, Almaslamani M, Taj-Aldeen SJ. Molecular epidemiology of clinical filamentous fungi in Qatar beyond *Aspergillus* and *Fusarium* with notes on the rare species. *Med Mycol.* 2023;61(1):myac098.
- Tupaki-Sreepurna A, Al-Hatmi AM, Kindo AJ, Sundaram M, de Hoog GS. Multidrug-resistant *Fusarium* in keratitis: a clinico-mycological study of keratitis infections in Chennai, India. *Mycoses.* 2017;60(4):230-3.
- Al-Hatmi AM, Bonifaz A, Ranque S, De Hoog GS, Verweij PE, Meis JF. Current antifungal treatment of fusariosis. *Int J Antimicrob Agents.* 2018;51(3):326-32.



20. Najafzadeh MJ, Dolatabadi S, de Hoog S, Esfahani MK, Haghani I, Aghili SR, Ghazvini RD, Rezaei-Matehkolaei A, Abastabar M, Al-Hatmi AM. Phylogenetic analysis of clinically relevant *Fusarium* species in Iran. *Mycopathologia*. 2020; 185:515-25.
21. León-Buitimea A, Garza-Cervantes JA, Gallegos-Alvarado DY, Osorio-Concepción M, Morones-Ramírez JR. Nanomaterial-based antifungal therapies to combat fungal diseases aspergillosis, Coccidioidomycosis, Mucormycosis, and candidiasis. *Pathogens*. 2021;10(10):1303.
22. Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *J Nanobiotechnology*. 2022 ;20(1):262.
23. Genchi G, Lauria G, Catalano A, Sinicropi MS, Carocci A. Biological activity of selenium and its impact on human health. *Int J Mol Sci*. 2023;24(3):2633.
24. Hosnedlova B, Kepinska M, Skalickova S, Fernandez C, Ruttkay-Nedecky B, Peng Q, Baron M, Melcova M, Opatrilova R, Zidkova J, Sochor J. Nano-selenium and its nanomedicine applications: a critical review. *Int J Nanomed*. 2018;13.
25. Filipović N, Ušjak D, Milenković MT, Zheng K, Liverani L, Boccaccini AR, Stevanović MM. Comparative study of the antimicrobial activity of selenium nanoparticles with different surface chemistry and structure. *Front Bioeng Biotechnol*. 2021; 8:624621.
26. Martínez-Esquívias F, Guzmán-Flores JM, Pérez-Larios A, González Silva N, Becerra-Ruiz JS. A review of the antimicrobial activity of selenium nanoparticles. *J Nanosci Nanotechnol*. 2021;21(11):5383-98.
27. Zhang H, Li Z, Dai C, Wang P, Fan S, Yu B, Qu Y. Antibacterial properties and mechanism of selenium nanoparticles synthesized by *Providencia* sp. DCX. *Environ Res*. 2021;194:110630.
28. Bisht N, Phalswal P, Khanna PK. Selenium nanoparticles: A review on synthesis and biomedical applications. *Mater Adv*. 2022;3(3):1415-31.
29. Pescuma M, Aparicio F, Zysler RD, Lima E, Zapata C, Marfetán JA, Vélez ML, Ordoñez OF. Biogenic selenium nanoparticles with antifungal activity against the wood-rotting fungus *Oligoporus pelliculosus*. *Biotechnology Reports*. 2023;37: e00787.
30. Lazcano-Ramírez HG, Garza-García JJ, Hernández-Díaz JA, León-Morales JM, Macías-Sandoval AS, García-Morales S. Antifungal Activity of Selenium Nanoparticles Obtained by Plant-Mediated Synthesis. *Antibiotics*. 2023;12(1):115.
31. Alizadeh SR, Abastabar M, Nosratabadi M, Ebrahimzadeh MA. High antimicrobial, cytotoxicity, and catalytic activities of biosynthesized selenium nanoparticles using *Crocus caspius* extract. *Arab. J. Chem*. 2023;16(6):104705.
32. Alizadeh, S.R., Seyedabadi, M., Montazeri, M., Khan, B.A. and Ebrahimzadeh, M.A., 2023. Allium paradoxum extract mediated green synthesis of SeNPs: Assessment of their anticancer, antioxidant, iron chelating activities, and antimicrobial activities against fungi, ATCC bacterial strains, *Leishmania* parasite, and catalytic reduction of methylene blue. *Mater Chem Phys*. 2023;296:127240.
33. Salih AM, Al-Qurainy F, Khan S, Nadeem M, Tarrour M, Shaikhaldain HO. Biogenic silver nanoparticles improve bioactive compounds in medicinal plant *Juniperus procera* in vitro. *Front Plant Sci*. 2022;13.
34. Nosratabadi M, Faeli L, Haghani I, Mohammadi R, Khodavaisy S, Kachuei R, Katiraei F, Aghili SR, Shokohi T, Hedayati MT, Nazeri M. In vitro antifungal susceptibility profile of Iranian *Fusarium* isolates: Emphasising on the potent inhibitory effect of efinaconazole compared to other drugs. *Mycoses*. 2023;66(3):258-75.
35. CLSI, ed. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi. CLSI standard M38. 3rd ed. Clinical and Laboratory Standards Institute. 2019.
36. Robinson HM, Yaffe SN. Selenium sulfide in treatment of pityriasis versicolor. *J Am Med. Assoc*. 1956;162(2):113-4.
37. Cohen PR, Anderson CA. Topical selenium sulfide for the treatment of Hyperkeratosis. *Dermatology and therapy*. 2018; 8:639-46.
38. Tiekink ER. Therapeutic potential of selenium and tellurium compounds: opportunities yet unrealised. *Dalton Transactions*. 2012;41(21):6390-5.
39. Savin R. Diagnosis and treatment of tinea versicolor. *Journal of family practice*. 1996; 43(2):127-39.
40. Faergemann J. Management of seborrheic dermatitis and pityriasis versicolor. *Am J Clin Dermatol*. 2000;1: 75-80.
41. Lin W, Zhang J, Xu JF, Pi J. The advancing of selenium nanoparticles against infectious diseases. *Front Pharmacol*. 2021;12:682284.
42. Zhang T, Qi M, Wu Q, Xiang P, Tang D, Li Q. Recent research progress on the synthesis and biological effects of selenium nanoparticles. *Front Nutr*. 2023;10:1183487.
43. Au A, Mojadadi A, Shao JY, Ahmad G, Witting PK. Physiological Benefits of Novel Selenium Delivery via Nanoparticles. *Int J Mol Sci*. 2023;24(7):6068.
44. Shakibaie M, Mohazab NS, Mousavi SA. Antifungal activity of selenium nanoparticles synthesized by *Bacillus* species Msh-1 against *Aspergillus fumigatus* and *Candida albicans*. *Jundishapur J Microbiol*. 2015;8(9).
45. Shahverdi AR, Fakhimi A, Mosavat G, Jafari-Fesharaki P, Rezaei S, Rezayat SM. Antifungal activity of biogenic selenium nanoparticles. *World Appl Sci J*. 2010;10(8):918-22.
46. El-Saadony MT, Saad AM, Najjar AA, Alzahran SO, Alkhatib FM, Shafi ME, Selem E, Desoky ES, Fouda SE, El-Tahan AM, Hassan MA. The use of biological selenium nanoparticles to suppress *Triticum aestivum* L. crown and root rot diseases induced by *Fusarium* species and improve yield under drought and heat stress. *Saudi J Biol Sci*. 2021;28(8):4461-71.
47. Hano C, Abbasi BH. Plant-based green synthesis of nanoparticles: Production, characterization and applications. *Biomolecules*. 2021;12(1):31.
48. Adeyemi JO, Oriola AO, Onwudiwe DC, Oyedeji AO. Plant extracts mediated metal-based nanoparticles: Synthesis and biological applications. *Biomolecules*. 2022;12(5):627.
49. Amini SM, Getso MI, Farahyar S, Khodavaisy S, Roudbary M, Mahabadi VP, Mahmoudi S. Antifungal activity of green-synthesized curcumin-coated silver nanoparticles alone and in combination with fluconazole and itraconazole against *Candida* and *Aspergillus* species. *Curr Med Mycol*. 2023;9(3):38.
50. Gunti L, Dass RS, Kalagatur NK. Phytofabrication of selenium nanoparticles from *Embllica officinalis* fruit extract and exploring its biopotential applications: antioxidant, antimicrobial, and biocompatibility. *Front microbiol*. 2019; 10:931.
51. Kokila K, Elavarasan N, Sujatha V. Diospyros montana leaf extract-mediated synthesis of selenium nanoparticles and their biological applications. *New J Chem*. 2017;41(15):7481-90.
52. Ali SJ, Preetha S, Jeevitha M, Prathap L, Rajeshkumar S. Antifungal Activity of Selenium Nanoparticles Extracted from *Capparis decidua* Fruit against *Candida albicans*. *J Evol Med Dent Sci*. 2020;9(34):2452-6.