



Original Article

Synthesis of Gadolinium Complexes Using Medicinal Plant Extracts

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Article history:

Received: 25 Aug. 2021

Accepted: 28 Aug. 2021

ePublished: 30 Dec. 2021

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Abstract

Background: Gadolinium compounds are used as contrast enhancers in MRI imaging. Generally, free metal ions are not used in MRI imaging due to their toxicity. To reduce the toxicity of the free form of the metal, complexing agents are employed for making nanoparticles. Due to their low toxicity and natural abundance, plant extracts having potential to function as chelating agents are good alternatives for the formation of gadolinium nanoparticles.

Methods: Aqueous extracts of five plant species, including *Thymus daenensis* Celak, *Nepeta sessilifolia* Bung, *Crocus sativus* L., *Salvia hydrangea* DC. ex Benth, and *Hymenocrater incanus* Bunge were prepared. Five complexes were produced as the result of each extract's reaction with gadolinium nitrate solution in the presence of 1 mM solution of NaOH. The obtained complexes were analyzed adopting the Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and Energy dispersive x-ray analysis (EDAX) techniques.

Results: EDAX analysis of the obtained complexes confirmed the presence of gadolinium in all complexes. Among the five complexes, the highest percentage of gadolinium (21.07) was recorded for the complex derived from the extract of *H. incanus* Bunge, while the lowest one (9.33) was detected for the complex derived from the *T. daenensis* Celak. Despite adopting various methods to disperse the complex particles in deionized water in order for determining the particle size, the high adhesion of the particles prevented the determination of the desired particle size in nanoscale.

Conclusion: Although synthesizing the complexes was successful and EDAX confirmed the presence of gadolinium metal in them, SEM analysis failed to prove their nanoparticle structure. The high tendency of solid particles to adhere was found to prevent the formation of independent nanoparticles in solution.

Keywords: Gadolinium complexes, Medicinal plants, Extract, MRI imaging



Please cite this article as follows: Ghavam M, Dastan D, Fadaei E, Chehardoli G. Synthesis of gadolinium complexes using medicinal plant extracts. Avicenna J Pharm Res. 2021; 2(2):44-48. doi:10.34172/ajpr.2021.09

Introduction

One of the most important and advanced imaging techniques is magnetic resonance imaging (MRI). In modern diagnostic medicine, MRI provides high spatial and anatomical resolution images of soft tissue without causing dangerous radiation. MRI is improved to the cellular and molecular level when contrast enhancing agents are used (1). Contrast agent (CA) can enhance the MRI contrast by inducing the relaxation rate of nearby water protons spins in a CA concentration-dependent method.

As a paramagnetic metal ion, gadolinium (Gd^{3+}) is an ideal CA candidate and the most commonly used ion for such purposes. Free Gd^{3+} is very toxic to mammalian

cells and tissues, and must be controlled in its stable form to prevent the release of metal ion into the body (2). Gadolinium is usually used in the chelated form in order to reduce its toxicity because the chelated form is much less toxic than the free form (3).

Several studies have recently investigated the synthesis and applications of metal nanoparticles using plant extracts. The synthesis of metal nanoparticles using plant extracts is of great interest to researchers because medicinal plant extracts are inexpensive, available, and compatible with the human body and the environment (4). Consider, for example, the following subjects having been studied recently: application of silver plant nanoparticles (from *Spondias mombin* extract) to deal



with multidrug resistance bacteria (5); antioxidant effects, DNA interaction, and anti-cancer effects of silver and gold plant nanoparticles (from *Aristolochia indica* and *Indigofera tinctoria* extract) (6); antioxidant, antibacterial, anti-diabetic, anti-inflammatory properties of magnesium oxide plant nanoparticles (from *Pterocarpus marsupium* extract) (7); and anticancer properties of plant nanoparticles of copper oxide (II) (from *Scoparia dulcis* extract) (8).

Synthesizing gadolinium plant nanoparticles based on plant extracts has attracted considerable research attention in the field due to the importance of gadolinium metal in MRI imaging and its toxicity.

Materials and Methods

Preparation of Extracts

Five plant species including *Thymus daenensis* Celak, *Nepeta sessilifolia* Bung, *Crocus sativus* L., *Salvia hydrangea* DC. ex Benth and *Hymenocrater incanus* Bunge were prepared. To prepare the extracts, the plants were first thoroughly washed with deionized water to remove dust and insects and dried in a room without light. The ground pulverized plant (10 g) was dissolved in deionized water (100 mL) and extracted at 80°C. After cooling, the resulting extract was centrifuged at 4000 rpm and then filtered by the Whatman's No. 1 filter paper.

Preparation of Complexes

Ten milliliters of the extract was mixed with 90 mL of 5 mM gadolinium nitrate solution and 10 mL of 1 mM NaOH. Then the solution was stirred for one hour with a stirrer. The reaction mixture was centrifuged at 4000 rpm for 15 minutes and then was filtered. The resulting solid was dried in an oven at 80°C for 24 hours.

Characterization of Complexes

Infrared (IR), scanning electron microscopy (SEM) and Energy Dispersive X-Ray Analysis (EDAX) analyses were used to identify the products. IR spectra were recorded by Bruker-Alpha Fourier transform infrared spectroscopy (FTIR). The SEM imaging was performed by TESCAN MIRA III FESEM. EDAX analysis was performed using TESCAN SAMX FESEM/EDAX.

Results and Discussion

Five complexes were generated as a result of the reactions of plants' extracts with gadolinium solution, which are listed as follows:

- Complex No. 1: obtained from *T. daenensis* Celak extract
- Complex No. 2: obtained from *N. sessilifolia* Bung extract
- Complex No. 3: obtained from *C. sativus* L. extract
- Complex No. 4: obtained from *S. hydrangea* DC. ex Benth extract

- Complex No. 3: obtained from *H. incanus* Bunge extract.

All products were solid and their colors was burnt brown.

Considering the fact that hydroxyl (OH) group can form the complex with metals (9), the focus of attention in our study was on the selection of medicinal plants with high phenolic content. To this end, five plant species including *T. daenensis* Celak, *N. sessilifolia* Bung, *C. sativus* L., *S. hydrangea* DC. ex Benth. and *H. incanus* Bunge were selected to prepare the extract. The extraction process of the plants was simply performed according to the usual extraction instructions. In addition, the complexes were synthesized easily, and the solid product was separated using a simple centrifuge.

Results of EDAX, SEM, and IR Analyses of Products

EDAX Analysis

EDAX analysis was used to confirm the presence of gadolinium metal in the complexes. Table 1 shows the weight percentages of gadolinium, carbon, oxygen, and sulfur elements in products.

Figure 1 shows the EDAX graphs of the complexes:

SEM Analysis

SEM analysis was performed to determine morphology and particle size. Figure 2 shows the SEM images of the complexes.

IR Analysis

IR spectrophotometric analysis was performed to determine the presence of some factor groups in the complexes. Figure 3 shows the IR spectra of complex.

Various techniques such as FT-IR, SEM, EDAX, X-ray diffractometry (XRD), etc are used to determine the structure of plant complexes. The importance of the FT-IR spectrum lies in the fact that it is capable of showing the chelating groups in the complexes. SEM analysis determines the morphology of the particles and their particle size. EDAX evaluates the percentage of metal in the complexes, and XRD technique is employed to identify the crystalline properties of the complexes (10).

The results from EDAX analysis confirmed the presence of gadolinium metal in all complexes. Among five complexes, the product obtained from the extract of *H. incanus* Bunge showed the highest percentage

Table 1. Weight Percentage of Gadolinium, Carbon, Oxygen and Sulfur Elements in 5 Complexes

Elements	1 (W%)	2 (W%)	3 (W%)	4 (W%)	5 (W%)
C	41.04	29.51	34.94	19.93	25.79
O	49.16	56.46	50.75	58.83	52.82
S	0.48	0.45	0.56	0.56	0.32
Gd	9.33	13.57	13.74	20.68	21.07
	100.00	100.00	100.00	100.00	100.00

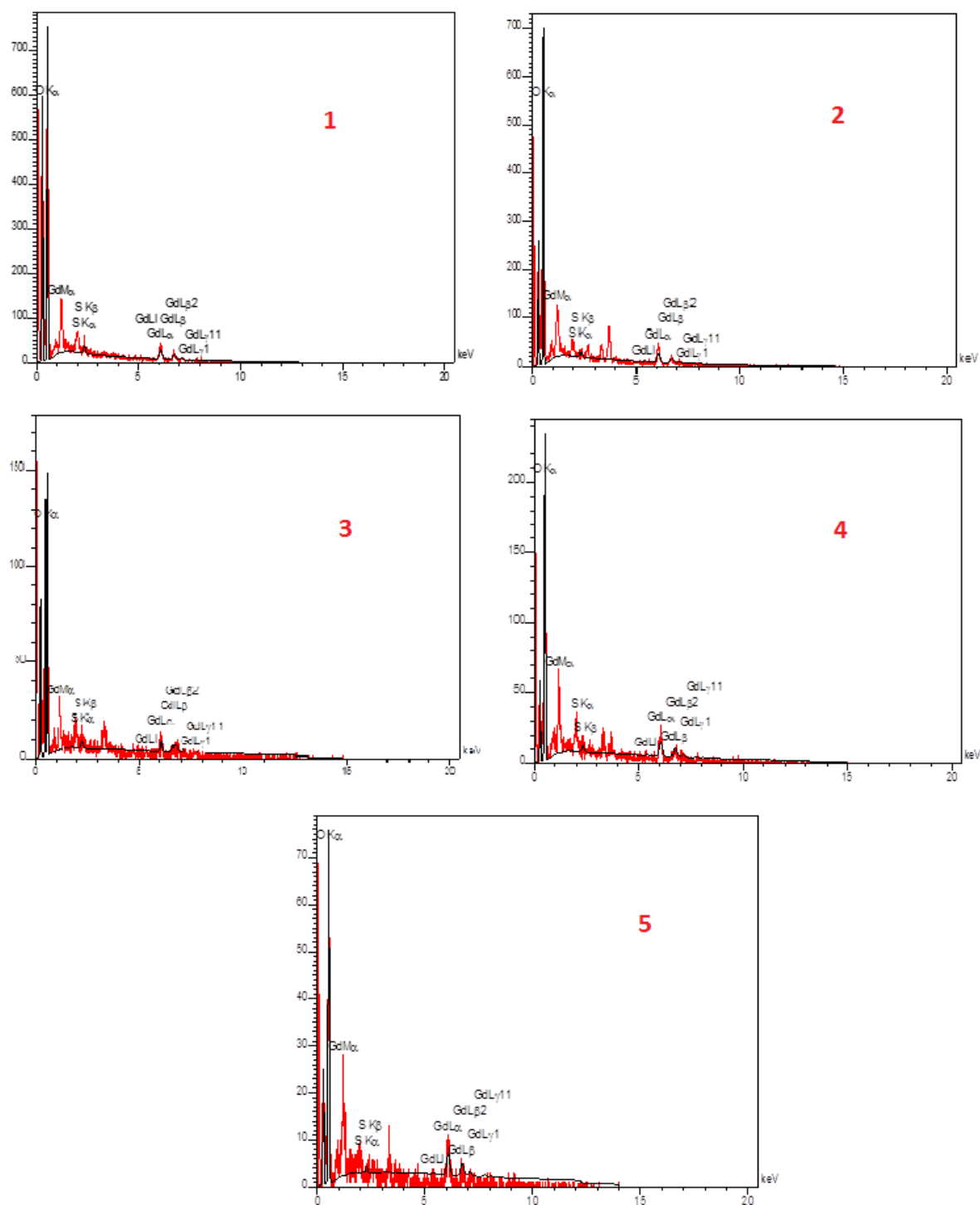


Figure 1. The EDAX Graphs of the 5 Complexes.

of gadolinium (21.07), while the product from that of *T. daenensis* Celak exhibited the lowest percentage of gadolinium (9.33).

As for the IR spectra, the presence of a strong peak at $3400\text{--}3300\text{ cm}^{-1}$ in all five spectra of the complexes was indicative of the presence of alcoholic or phenolic OH groups in the structure of complexes. Moreover, the peaks observed in $1600\text{--}1600\text{ cm}^{-1}$ probably was suggestive of the presence of carbonyl groups.

SEM images do not show granular and spherical morphology for the complexes. In addition, it is not possible to determine the particle size using such images.

This study mainly aimed to synthesize the gadolinium plant nanoparticles for MRI imaging application. However, it was not possible to fulfill the whole desired objectives of the study due to the inadequacy of the particle morphology and the lack of nanoparticle structure.

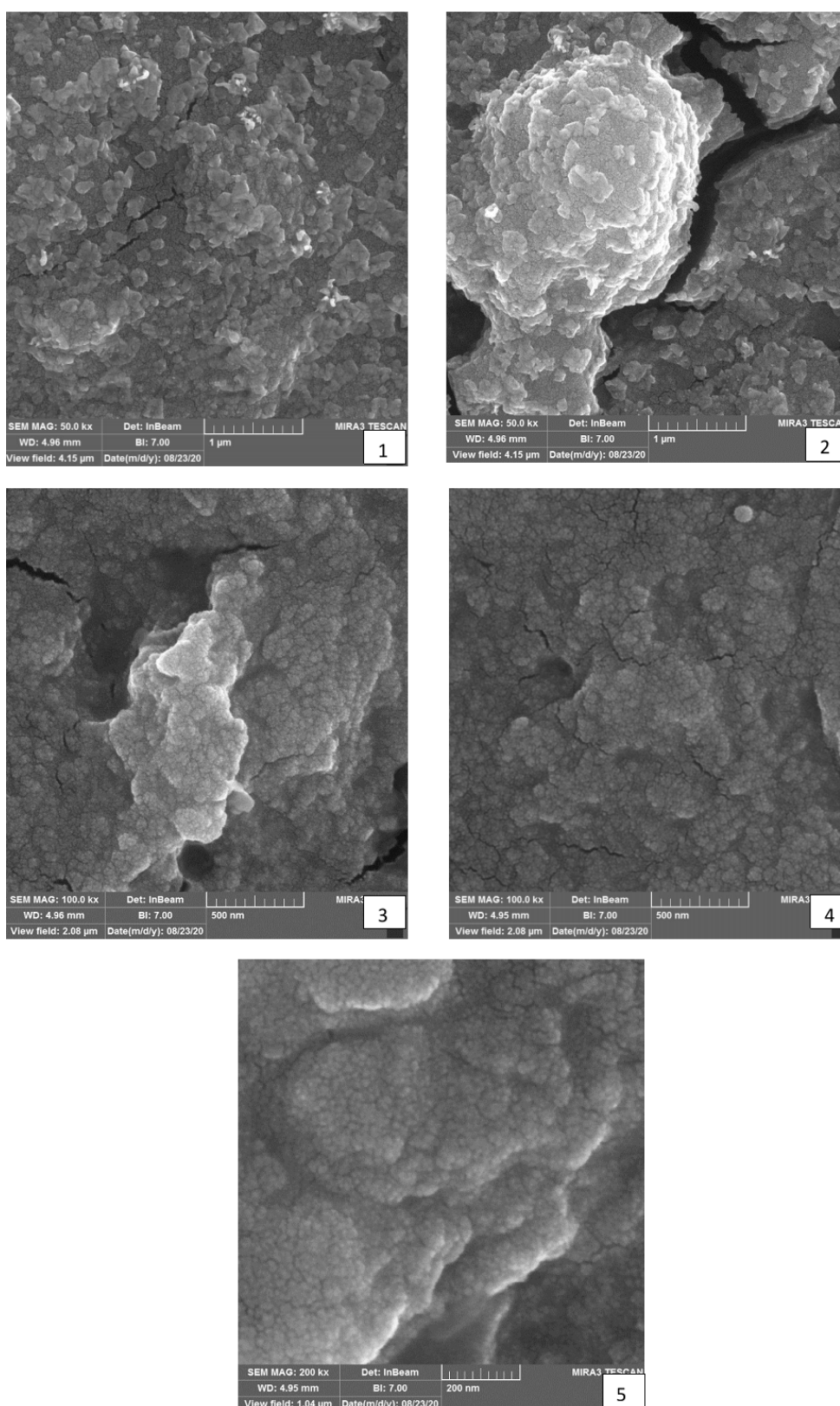


Figure 2. The SEM Images of the Complexes.

Conclusion

In sum, synthesizing the complexes was successfully performed and the results from EDAX analysis confirmed the presence of gadolinium metal in these structures; however, SEM analysis failed to prove their nanoparticle

structure. The high adhesion tendency of solid particles was found to prevent the formation of independent nanoparticles in solution and, therefore, further research and application of these materials in MRI imaging were ruled out.

Acknowledgements

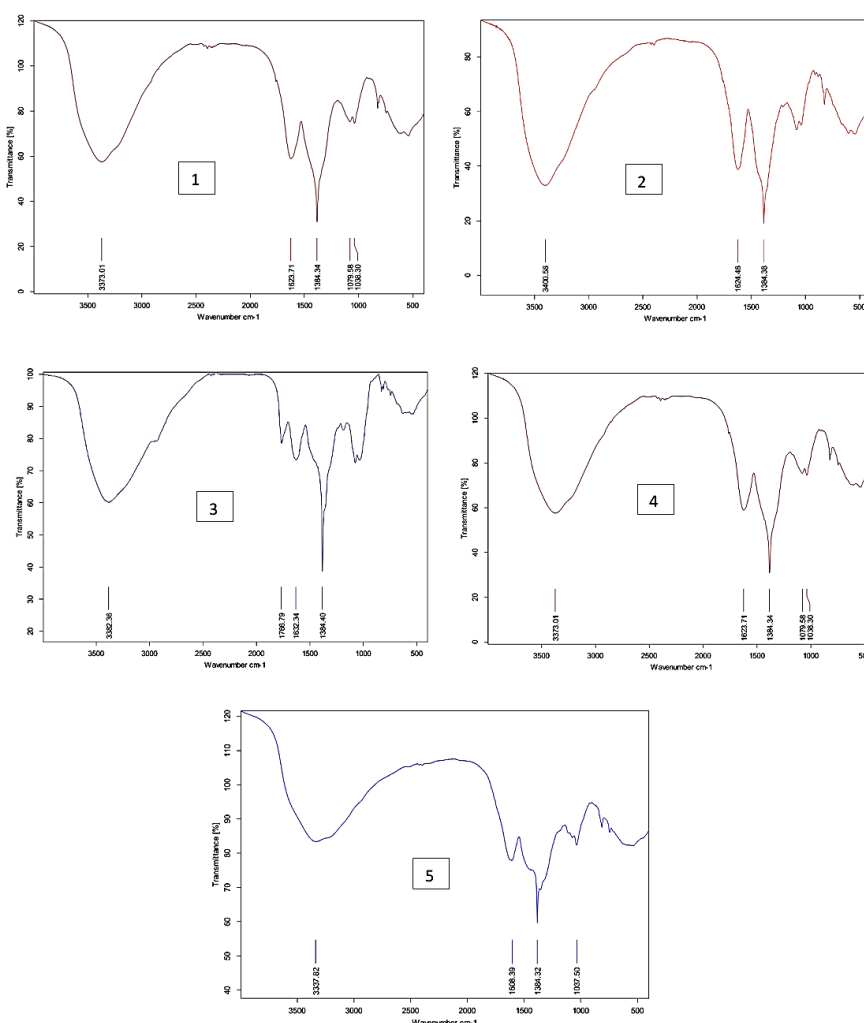


Figure 3. The IR Spectra of the 5 Complexes.

The present study is the result of a research project No. 9605103112 in Hamadan University of Medical Sciences. The authors sincerely thank the Vice Chancellor of Research and Technology for financially supporting this research.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

- Huang J, Zhong X, Wang L, Yang L, Mao H. Improving the magnetic resonance imaging contrast and detection methods with engineered magnetic nanoparticles. *Theranostics*. 2012;2(1):86-102. doi: [10.7150/thno.4006](#).
- Kim HK, Lee GH, Chang Y. Gadolinium as an MRI contrast agent. *Future Med Chem*. 2018;10(6):639-61. doi: [10.4155/fmc-2017-0215](#).
- Ranga A, Agarwal Y, Garg KJ. Gadolinium based contrast agents in current practice: risks of accumulation and toxicity in patients with normal renal function. *Indian J Radiol Imaging*. 2017;27(2):141-7. doi: [10.4103/0971-3026.209212](#).
- Soni V, Raizada P, Singh P, Cuong HN, S R, Saini A, et al. Sustainable and green trends in using plant extracts for the synthesis of biogenic metal nanoparticles toward environmental and pharmaceutical advances: a review. *Environ Res*. 2021;202:111622. doi: [10.1016/j.envres.2021.111622](#).
- Samuggam S, Chinni SV, Mutusamy P, Gopinath SCB, Anbu P, Venugopal V, et al. Green synthesis and characterization of silver nanoparticles using *Spondias mombin* extract and their antimicrobial activity against biofilm-producing bacteria. *Molecules*. 2021;26(9):2681. doi: [10.3390/molecules26092681](#).
- Subramanian PV, AlSalhi MS, Devanesan S, Thomas PA. Evaluation of antioxidant, anticancer and DNA binding potentials of noble metal nanoparticles synthesized using *Aristolochia indica* and *Indigofera tinctoria*. *J Clust Sci*. 2021;32(4):917-27. doi: [10.1007/s10876-020-01858-9](#).
- Ammulu MA, Vinay Viswanath K, Giduturi AK, Vemuri PK, Mangamuri U, Poda S. Phytoassisted synthesis of magnesium oxide nanoparticles from *Pterocarpus marsupium* Roxb heartwood extract and its biomedical applications. *J Genet Eng Biotechnol*. 2021;19(1):21. doi: [10.1186/s43141-021-00119-0](#).
- Navada KM, Nagaraja GK, D'Souza JN, Kouser S, Ranjitha R, Manasa DJ. Phyto assisted synthesis and characterization of *Scoparia dulcis* L. leaf extract mediated porous nano CuO photocatalysts and its anticancer behavior. *Appl Nanosci*. 2020;10(11):4221-40. doi: [10.1007/s13204-020-01536-2](#).
- Al-Sogair FM, Operschall BP, Sigel A, Sigel H, Schnabl J, Sigel RK. Probing the metal-ion-binding strength of the hydroxyl group. *Chem Rev*. 2011;111(8):4964-5003. doi: [10.1021/cr100415s](#).
- Jadoun S, Arif R, Jangid NK, Meena RK. Green synthesis of nanoparticles using plant extracts: a review. *Environ Chem Lett*. 2021;19(1):355-74. doi: [10.1007/s10311-020-01074-x](#).