

Review Article

# The efficiency of metal, metal oxide, and metalloid nanoparticles against cancer cells and bacterial pathogens: different mechanisms of action



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## ABSTRACT

The applications of nanoparticles in various practical fields, owing to their unique properties compared with bulk materials, have been occupying the minds of scientists for several decades. In this regard, a combination of pharmacology and nanotechnology has contributed to producing newer effective anticancer and antimicrobial agents to inactivate resistant cancer cells and microorganisms, specifically multidrug-resistant ones. The physicochemical properties of nanoparticles based on metalloid, metal, and metal oxides such as selenium, silver, gold, titanium dioxide, zinc oxide, copper oxide, platinum, and magnesium oxide, have been well known and referred to as anticancer and antimicrobial agents or carriers. The inactivation and eradication of Gram-positive and Gram-negative bacteria may be mainly resulted from the oxidative damages in the bacterial medium. Overall, metalloid, metal and metal oxide NPs can be functionalized by other antibacterial or anticancer agents and biocompatible stabilizers to increase their efficiency in physiological conditions. However, the undesirable cytotoxicity of these nanoparticles in physiological conditions is the major hindrance to their application in the pharmaceutical industry and therapeutics. Nevertheless, it is expected that these problems will be solved in the near future. Therefore, the main objective of this review is to report an overview of the recent signs of progress in increasing anticancer and antibacterial mechanisms of metal and metal-based nanoparticles.

## 1. Introduction

Drug resistance to various antibiotics and chemotherapeutic agents is the major hindrance to treating microbial and viral

infections as well as cancers [1-5]. Recent advances in nanotechnology have made it possible to produce nanomaterials of different sizes, shapes, and charges that can interact

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with cancer and bacterial cells, developing new effective antimicrobial agents [6-8]. As it is well-known, researchers use various physical and chemical methods to synthesize nanoparticles (NPs) [9-11]. In recent years, the biological synthesis of green metal-based NPs is a new eco-friendly strategy without the physical and chemical methods [9, 12]. In this way, bacteria, fungi, lichens, and plants may be exploited to fabricate NPs without using toxic and/or expensive reactants [13-17].

Primary and secondary metabolites of plants can donate both therapeutic and biocompatible properties to NPs. For instance, Ag-Cu-turmeric nanocomposites and turmeric bulk powder exhibited 45% and 2.5% growth reduction in the case of *E. coli* after 24 hours of incubation, respectively [18]. NPs have unique properties such as a large surface area to volume ratio that increase the antibacterial activity against various bacteria [19-21]. Moreover, various micro- and nanoformulations may inhibit and eradicate cancer cells [22, 23]. Thus, there are several antibacterial and anticancer mechanisms for metalloids, metal oxides, and metal NPs [24, 25], which are presented here based on the related unique properties of NPs.

## 2. Anticancer mechanisms

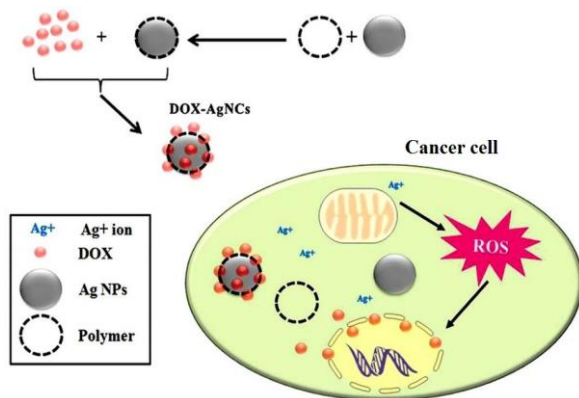
Multidrug-resistance in cancer cells is a major hindrance for their eradication which may be the result of several mechanisms involving drug efflux pumps (the ATP-binding cassette family including P-glycoprotein (P-gp), multidrug-resistance-associated protein 1 (MRP-1), and ATP-binding cassette transporter G2 (ABCG2)), drug inactivation by specific enzymes such as glutathione S-transferases (GST), changing of drug targets (down-regulating the expression of topoisomerase II for resistance to adriamycin), inactivation of DNA damage repairing system, dysfunction of apoptosis pathways, change of extracellular matrix, and the over-expression of HIF-1 $\alpha$  (vital factor in anoxia) for resistance to radiation and chemotherapy [26, 27]. For these reasons, the co-delivery of anticancer agents with organic and inorganic nanomaterials has been exploited in many studies [25, 28].

Formulation of metal or metal oxide-based NPs with chemotherapeutic drugs may bypass these mechanisms. For instance, camptothecin nanocrystals were decorated by silver NPs (AgNPs) through self-polymerized dopamine to obtain a nanoformulation with the size range of 50-150 nm. This study showed the uptake ratios between the camptothecin/Ag nanocrystals and pure camptothecin nanocrystal which were 1.19, 2.03, 1.88, 2.57, and 3.54 SKBR3 cells, MDAMB231, Hela, MCF7, and A549 cancer cell lines, respectively. Probable anticancer mechanisms for these nanoformulations were escaping from the drug efflux pumps as well as the synergistic effect as induction of apoptosis pathways and DNA damage from the co-delivered camptothecin and AgNPs [29]. Another example of synergistic anticancer activity was reported for nano-combination of AgNPs, some polymers (polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and polyethylene glycol (PEG)), and doxorubicin (DOX) (Figure 1).

More anticancer activity was found in the case of DOX-Ag/PVP nanocomposites with 1ppm against MCF-7 cells. Interestingly, the cell line of human fibroblast (1BR hTERT) displayed a lower sensitivity as cell viability of ~80 to these nanocomposites at a concentration of 1ppm after 48h exposure [30]. Changing tumor-associated macrophages (TAMs) from the M2 to M1 phenotype and reduction in the expression of HIF-1 $\alpha$  and hypoxia in TAMs were reported as main anticancer mechanisms for Ag and gold NPs (AuNPs) [31]. In addition, the anti-angiogenesis activity of AgNPs can reduce new blood vessel formation and extension of cancer cells via hindering vascular endothelial growth factors [32].

The cancer cell cycle arrest and apoptotic pathways have been induced for selenium NPs (SeNPs) as metalloids NPs upon reactive oxygen species (ROS) production. Moreover, surface modification and combination of SeNPs with anticancer agents enhance antitumor activity. On the other hand, various investigations confirm the anticancer activity of secondary metabolites of medicinal plants. In this regard, ascorbic acid and curcumin were applied as reducing and stabilizing

agents to biosynthesize SeNPs followed by combination with irinotecan (a medication exploited for treating small cell lung cancer and colon cancer). By entering through the lysosomal pathway, these nano-compounds displayed a reduced size of HCT-8 tumors and DNA breakage of cancer cells [33].



**Fig. 1.** nanoformulation of AgNPs, PVP, and doxorubicin and their anticancer mechanisms (Permission upon <http://creativecommons.org/licenses/by/4.0/>) [30].

### 3. Antibacterial mechanisms

Metal-based NPs can interact with bacterial envelopes and penetrate bacterial cell walls and membranes, leading to bacteriostatic and bactericidal effects [34]. These NPs provide a new effective way to overcome common mechanisms of antibiotic resistance such as permeability regulation, multidrug efflux pumps, antibiotic degradation, antibiotic modification, etc. It is worth noting that a critical mechanism to overcoming bacterial resistance is the production of antibacterial drugs with the ability of penetration and inactivation of the biofilm-forming multidrug-resistant bacterial strains [35]. In addition, the application of metal-based NPs may be an alternative option to minimize microbial resistance and toxicity to human cells. The prolonged half-life and hydrophilic properties of common antibiotics such as beta-lactams and aminoglycosides make blood clearance and bacterial penetration difficult [36]. NPs are attractive agents to overcome the hydrophilic problem because most NPs can penetrate bacterial envelopes, which may be used to carry antibiotics and increase their intracellular activity [37]. For instance,

spherical kanamycin-AuNPs with 20 nm size exhibited the lowest inhibitory concentration on the bacterial strains of *S. epidermidis*, *P. aeruginosa* PAQ1, and *P. aeruginosa* UNC-D, with values of 3.3, 6.3, and 6.3  $\mu\text{g}/\text{mL}$ , respectively [38].

In another study, ampicillin, penicillin, neomycin, kanamycin, enoxacin, and tetracycline were combined with AgNPs. In all nanocomposites, growth inhibition of *Salmonella typhimurium* DT104 was higher at concentrations of 0.5, 2, 8, and 16  $\mu\text{M}$  compared to AgNO<sub>3</sub>, AgNPs, and antibiotics [39]. In another study, phosphatidylcholine-AuNPs were functionalized with gentamicin antibiotic, which displayed a prominent decrease in biofilm mass of *S. aureus* (~0.2) and *P. aeruginosa* (~0.5) relative to phosphatidylcholine-decorated AuNPs (~1.5 and ~0.8) and gentamicin antibiotic (~1 and ~0.6) [40]. Metal-based NPs have specific antibacterial toxicity mechanisms that can overcome the mechanisms of antibiotic resistance by the formation of pits and disrupting the membrane or preventing the formation of biofilms [41]. However, agglomeration of NPs can be a severe problem because if the NPs clump together, they will be prevented from interacting with the bacterial cell wall, and their activity will be disrupted [42].

NPs aggregation can be reduced by controlling the zeta potential, which indicates the stability of NPs in colloidal suspensions. Commonly, highly positive or negative zeta potential values means that the colloidal suspension is very stable (implying very low aggregation) [43]. The zeta potential can be good to excellent in a range of  $\pm 40$  to  $\pm 60$  mV and  $>61$  mV [44]. Even at optimal zeta potential, NPs can still aggregate as a result of the function of serum components and the reticuloendothelial system [45, 46].

High stable metal-based NPs in physiological medium including silver (Ag), gold (Au), zinc oxide (ZnO), copper oxide (CuO), and magnesium nanoparticles (MgO) NPs can be employed for inactivation of bacteria with toxicity to eukaryotic cells. However, the addition of common non-toxic surface stabilizers such as polymers of

polyethylene glycol, chitosan, cellulose and proteins and enzymes from bacteria yeast, plants, and fungi can increase the biocompatibility and stability of these NPs [47]. It has been reported that functionalization of the silica-coated zinc oxide nanoparticles (ZnONPs) with thiol and amine can prevent the aggregation of these NPs in a colloidal dispersion [48] or the nanosheets prepared with NPs of Bi<sub>2</sub>WO<sub>6</sub> that present an antibacterial and antibiotic-modulation in the association of visible light irradiation (LEDs) [49].

Some NPs such as gold and iron oxide NPs have shown an appropriate level of biocompatibility [50]. Metal-based NPs release metal ions when they dissolve in the environment, which can react with the bacterial membrane as a main antibacterial mechanism [51]. However, poor ability to target cells results in weak antibacterial activity of these NPs in physiological conditions. To solve this hindrance, NPs can be functionalized by biological components to bind to selected target cells. Cytotoxic effects of NPs may be attributed to various factors (Figure 2) [52].

In physiological conditions, the interaction of NPs with major biological macromolecules should be considered to evaluate the side effects of NPs. For example, deformation of the secondary structure of human hemoglobin protein as  $\beta$ -sheet increasing of 8.42% and  $\alpha$ -helix decreasing of 63.8% were found under the effect of AgNPs [53]. However, in another study, stabilization of secondary structure of hemoglobin was observed after interaction with AuNPs, wherein hydrogen bonds were the main primary force in nano-compound of hemoglobin-AuNPs [54].

The production of reactive oxygen species (ROS) is a major determinant of in vitro and in vivo cytotoxicity of metal-based NPs [55]. It should be noted that ROS are physiologically essential because lower levels of ROS control several cellular processes, but when they increase beyond a certain range, they could cause severe oxidative stress, leading to cell death through lipid peroxidation and alteration of DNA and protein structures [56]. The toxic effects produced by ROS are not

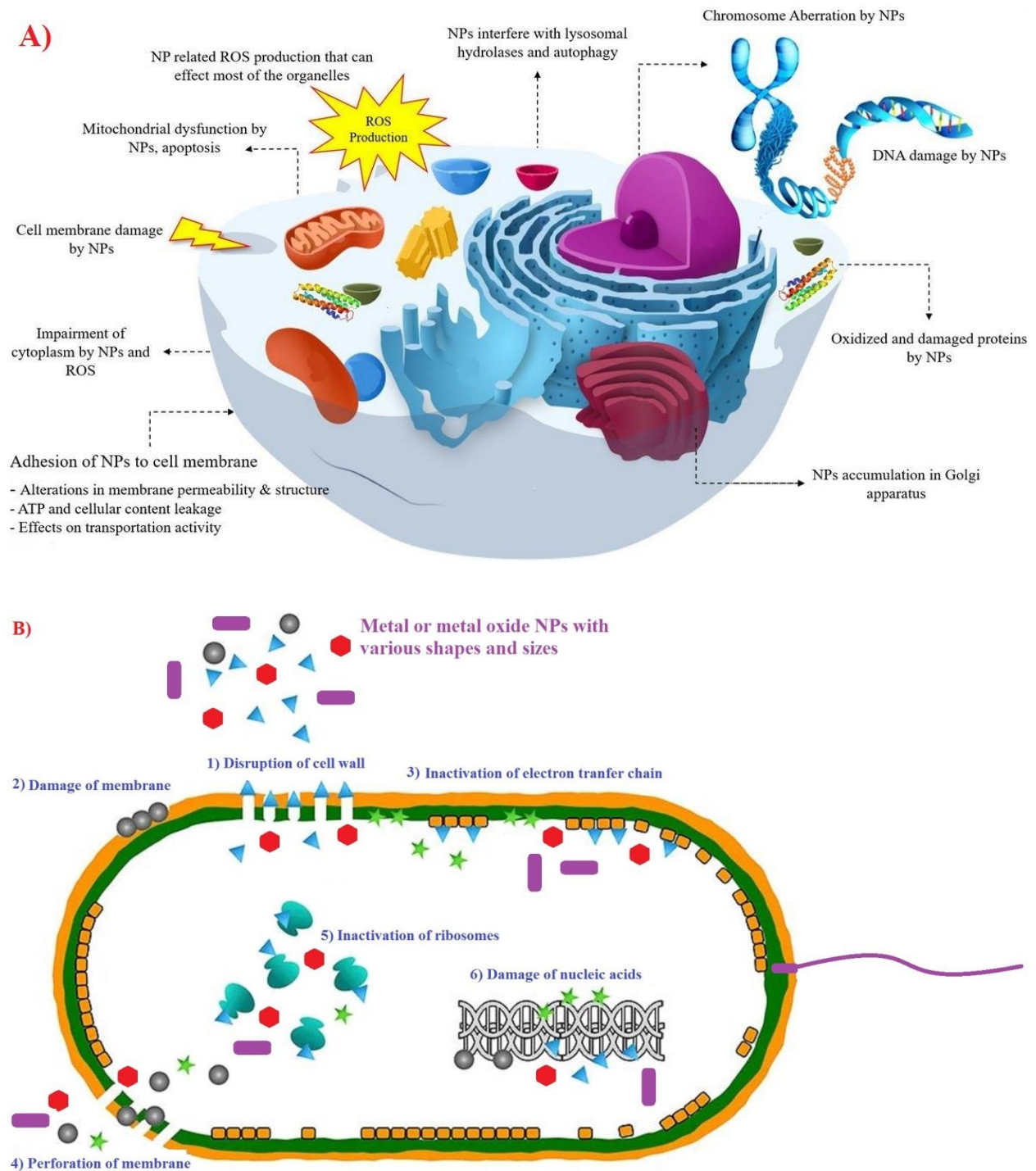
limited to specific cells or organs but also affect various systems and functions of the body, including the central nervous system, respiratory system, and cardiovascular system, by related mechanisms such as regulation of microRNA expression, which may also be suitable for hindrance of cancer cells (Figure 3) [57-59]. CuO and Ag-CuO NPs in spherical shape were synthesized by *Malus domestica* leaf extract with a diameter of 18 and 20 nm, respectively. Inhibition zones of CuO and Ag-CuO NPs at 100  $\mu$ g/ml concentration on *S. aureus* were 19 and 15 mm, respectively. Moreover, cleavage of pBR 322 DNA was observed in high levels for CuONPs relative to Ag-CuO NPs [60].

The shape and size of NPs can determine the intensity of their antibacterial activity. For instance, rod-shaped AgNPs-doped hydrogels showed lower antibacterial activity than spherical and triangular AgNPs-doped hydrogels [61]. This difference is attributed to the facets number of the NPs and the interaction with the bacterial components. As a comparative study, there was more inhibition zone for cubical-shaped Cerium Oxide NPs (CeO<sub>2</sub>NPs) than spherical-shaped CeO<sub>2</sub>NPs against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus* [62].

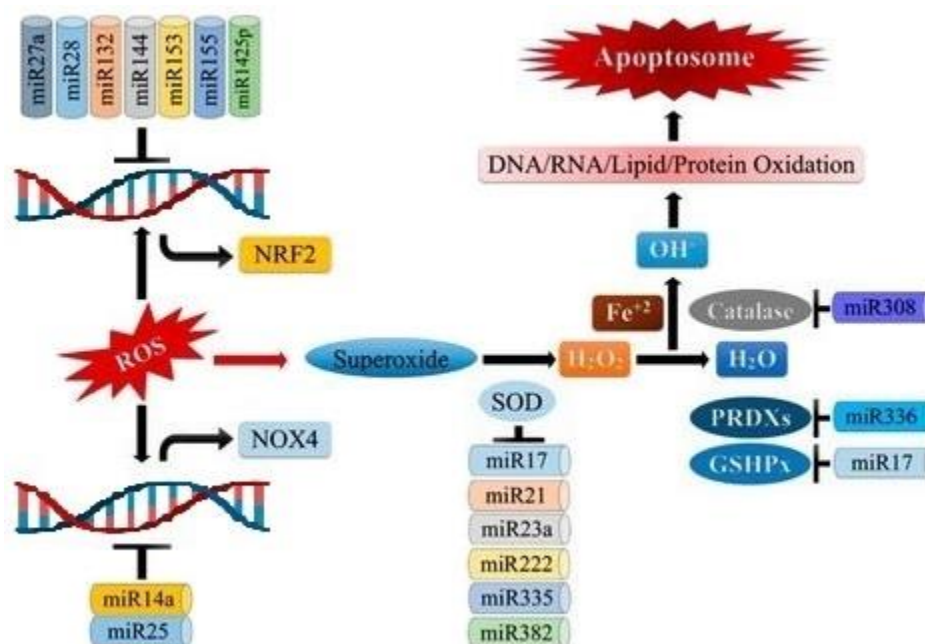
The concentration of NPs can also determine the capacity of antibacterial activity. Low, medium, and high concentrations of rod-shaped and spherical NPs displayed weak, strong, and weak antibacterial effects on *Klebsiella pneumoniae*, respectively [63]. In addition, NPs have surface charge-dependent toxicity. Accordingly, the more positive charge of the NPs surface can lead to higher antiplanktonic and antibiofilm activities. The surface charge of NPs improves their electrostatic interaction with the negative charge of the bacterial envelope. In this way, during NPs preparation, a coating agent is added to increase the stability, positive charge, and facilitate the dispersion of the NPs in the colloidal medium. Moreover, the surface properties of NPs can also impact bacterial activity. The different molecular mechanisms were found for *E. coli* on nano-rough and flat gold substrate, as the expression of type-1 fimbriae was active on a



flat surface. At the same time, it was inactive on the rough surface [34].



**Fig. 2.** A) Cytotoxicity mechanisms of metal-based NP (Permitted by the terms of the Creative Commons Attribution License (CC BY)) [52]; B) antibacterial mechanisms of metal or metal oxide NPs in various shapes [64].



**Fig. 3.** Regulation of microRNA biogenesis via ROS production in eukaryotic cells. The Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>) [59].

It should be considered that long-term application of AgNPs can result in a low sensitivity of *P. aeruginosa* biofilm by the resistance mechanism to penetration of silver ions into biofilm structure [65]. Metal NPs can block the quorum sensing of bacteria. For example, based on molecular docking investigation, AgNPs strongly locked the active sites of RhlR, RhlI, LasR, and LasI [66]. Inhibition of the bacterial growth led to bacterial destruction by ROS production, without cytotoxicity for the surrounding tissues, has been reported to SeNPs. For example, *P. aeruginosa* and *E. coli* showed more sensitivity under the stress of SeNPs (biosynthesized by *Providencia* sp. DCX) with a spherical shape, a mean size of 120 nm, and 500 mg/L concentration relative to *S. aureus*. For this study, the oxidative damages resulting from ROS have been indicated for inactivation and eradication of both Gram-negative and Gram-positive bacteria [67].

#### 4. Conclusion

After reviewing the literature it was found that metal, metal oxide and metalloid NPs may be regarded as desirable alternatives for fighting against bacterial pathogens and cancer tumors, particularly multidrug-resistant bacteria and cancer cells. Reprogramming pro-inflammatory cytokine

cascades, redox pathways, and immunosuppressive actions, have been indicated as the main anticancer mechanisms of Ag and Au NPs. Also, metal NPs, specifically AgNPs, can reduce new blood vessel formation and extension of cancer tissue via inhibiting the vascular endothelial growth factor. In the case of functionalized noble metal NPs, escaping from the drug efflux pumps, as well as, the synergistic effect as induction of apoptosis pathways and DNA damage were indicated for co-delivery of AgNPs with anticancer drugs such as doxorubicin and camptothecin.

For antibacterial ability, using a suitable dose during an effective incubation time should be precisely controlled to reduce cytotoxicity effects on eukaryotic cells and inhibit the emergence of new resistant strains. In addition, the inactivation and eradication of Gram-negative and Gram-positive bacteria may be mainly caused by the oxidative damages resulting from ROS in the bacterial medium. Overall, metalloid, metal and metal oxide NPs can be functionalized by other antibacterial agents and biocompatible stabilizers to increase their efficiency in physiological conditions.

## Abbreviation

AgNPs: silver NPs

DOX: doxorubicin

GST: glutathione S-transferases

PEG: polyethylene glycol

PVA: polyvinyl alcohol

PVP: polyvinylpyrrolidone

ROS: reactive oxygen species

TAMs: tumor-associated macrophages

ZnONPs: zinc oxide nanoparticles

## Conflict of Interests

All authors declare no conflict of interest.

## Ethics approval and consent to participate

No human or animals were used in the present research.

## Consent for publications

All authors read and approved the final manuscript for publication.

## Availability of data and material

All the data are embedded in the manuscript.

## Authors' contributions

Main draft of the manuscript was written by Dr. Alavi and revised by other authors.

## Informed Consent

The authors declare not used any patients in this research.

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