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REVIEW ARTICLE

A state-of-the-art review on the application of various pharmaceutical nanoparticles as a promising technology in cancer treatment

Marischa Elveny [a,*], Afrasyab Khan [b], Ali Taghvaie Nakhjiri [c], Ahmad B. Albadarin [d,]**

[a] *Data Science & Computational Intelligence Research Group, Universitas Sumatera Utara, Medan, Indonesia*
[b] *Institute of Engineering and Technology, Department of Hydraulics and Hydraulic and Pneumatic Systems, South Ural State University, Lenin Prospect 76, Chelyabinsk 454080, Russian Federation*
[c] *Department of Petroleum and Chemical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran*
[d] *Department of Chemical Sciences, Bernal Institute, University of Limerick, Limerick, Ireland*

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Abstract Recently, rapid advancement in nanomedicine has opened new horizons towards the treatment of disparate types of cancer. Nanomedicine is considered as the science of applying nanoparticles (NPs) for various diagnostic or therapeutic aims. Nanoparticles (NPs) have attracted increasing interest all over the world for the treatment of disparate types of cancer due to their noteworthy properties such as negligible toxicity and great bioactivity. The main objective of this paper is to present a comprehensive review about the potential of various NPs including silver NPs (AgNPs), gold NPs (AuNPs), selenium NPs (SeNPs), titanium oxide NPs (TiO_2NPs) and iron oxide NPs (FeONPs) to treat tumoral cells, and investigate the molecular interaction at the cellular level. Moreover, different synthesis mechanisms of NPs along with their operational roles in enhancing the efficiency of conventional chemotherapeutic agents and reducing the toxicity are discussed in detail. Finally, future challenges towards the application of NPs in the field of cancer treatment are presented, and appropriate solutions to remove the ambiguities are suggested.

* Corresponding author.
** Corresponding author.
E-mail addresses: marischaelveny@usu.ac.id (M. Elveny), ahmad.b.albadarin@ul.ie (A.B. Albadarin).
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Contents

1. Introduction

Anthropogenic application of nanoparticles (NPs) has been reported by ancient people from 4500 years ago (Martínez et al., 2021, Zhu et al., 2021). NPs are described as those particles with diameters of less than 100 nm. The existence of very small size has resulted in generating an extensive range of applications in various scientific areas (Strambeanu et al., 2015, Alsaba et al., 2020). Recently, nanotechnology has achieved significant approval in disparate industries such as pharmacology, environmental engineering, thermal engineering, medicine and agriculture (Kołątaj et al., 2020, Pishnamazi et al., 2020a, Yang et al., 2021). This increased use of NPs has resulted in the need to evaluate their effects on human health. Indeed, applications of nanoparticles and nanostructured materials in environmental and pharmaceuticals have attracted more attentions.

Fig. 1 schematically depicts the categorization of NPs and their prominent industrial-based applications.

Cancer has been a major concern worldwide for a long time. This lethal disease, which is defined as the abnormal mutation of cells with great probability of spreading to other organs of the body (Aroef et al., 2020), has more than 100 types. In recent years, cancer has caused considerable economic burden on humans due to expensive cancer treatments (Meropol and Schulman, 2007, Mariotto et al., 2011). For instance, the overall cancer expenditure in the EU was prognosticated to be €126 billion in 2009 while the overall cancer expenditure in the US was estimated to be $173 billion in 2020 (Mariotto et al., 2011, Luengo-Fernandez et al., 2013). Therefore, the development of promising and economical strategies for enhancing the efficacy of cancer treatment is of great demand. Over the last 20 years, outstanding advances in the field of nanotechnology and nanoscience have offered new prospects for overcoming the drawbacks of conventional cancer therapies (Rahman et al., 2021). Several investigations have demonstrated the suitable efficacy of NPs in various existing medical therapies. The linkage of drugs with NPs can improve the drugs accumulation in cancerous tissues and enhance their penetration capabilities through cell membranes (Youssef et al., 2017, Hassanzadeganroudsari et al., 2020). Improvements in nanotechnology have resulted in the extensive use of nanoparticles in the cancer treatment (Jiang et al., 2018, Correa et al., 2020, Taleghani et al., 2021). The enhanced permeation and retention (EPR) effect, which is defined as the selective accumulation of NPs / polymeric medicines in solid

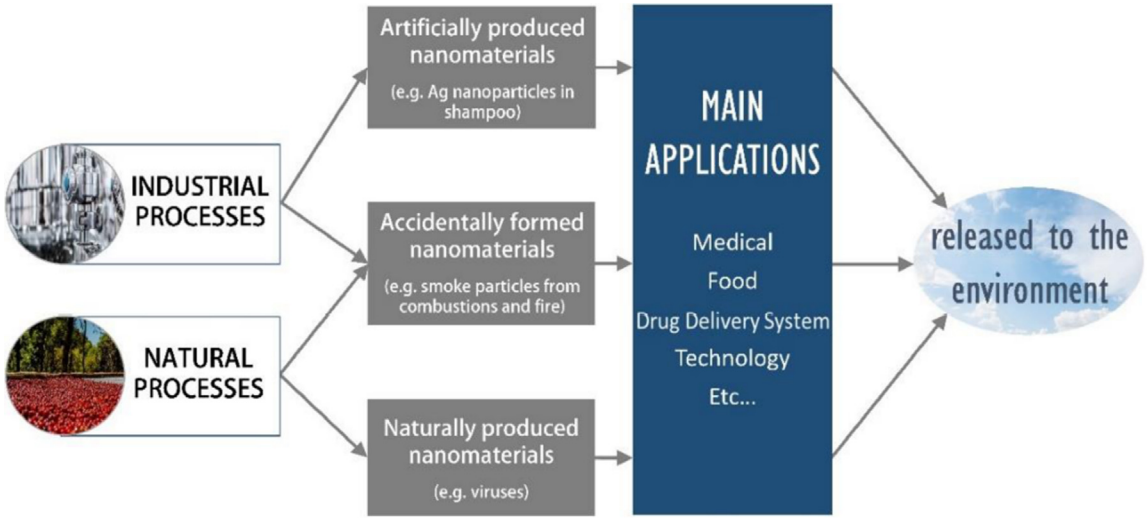

Fig. 1 Schematic illustration of NPs classification and their industrial-based applications. Reprinted with permission from (Martínez et al., 2021).

Table 1 Detailed information about the roles of various types of NPs for cancer treatment.

Nanoparticles	Treatment approach	Mechanism of action	Advantages	Ref.
AuNPs	• Antigen /adjuvant delivery • Photothermal therapy	• Enhanced Cytotoxic T lymphocytes responses • Tumor ablation released tumor antigens	• In-vivo decrement of tumor growth • Prevention of tumor growth in vivo	(Dreaden et al., 2011, Almeida et al., 2014, Evans et al., 2018)
FeONPs	• Protein delivery • Photothermal therapy • M1 macrophage polarization	• Improvement of pro-inflammatory macrophage proliferation • Thermal tumor ablation	• Prevention of tumor growth • Protective immunity due to ablation	(Shevtsov et al., 2015, Zanganeh et al., 2016)
TiO_2NPs	• Immune stimulation	• Reactive oxygen species (ROS) Significantly enhances the generation of pro-inflammatory cytokines and interleukins in the tumor	• Suppression of tumor growth in vivo	(You et al., 2016)
AgNPs	• Reduce tumor-promoting cytokines	• Decrement of IL-1b signaling through tumor microenvironment	• Prevention of fibrosarcoma tumor growth in vivo	(Chakraborty et al., 2016)
$Al_2O_3NP_S$	• Adjuvant therapy	• Increment of anti-cancer influences of tumor cell vaccines	• Shrinkage of tumor sizes and better specific Cytotoxic T lymphocytes by co-administration with a tumor cell vaccine	(Sun et al., 2010)
ZnONPs	• Antigen delivery	• Modification of antigen-specific Cytotoxic T lymphocytes responses	• Delayed tumor growth in vivo	(Cho et al., 2011)

tumors, has been observed in the 80 s decade (Wu et al., 2019). Hence, due to the EPRE, nanotechnology has been offered as a suitable platform to synthesize anti-tumor drug delivery (Dai et al., 2017, Zhang et al., 2021).

Cancer nanomedicine has recently focused on nanotechnology methodology in order to design various nanodrugs for cancer treatment due to its brilliant physicochemical properties of materials at the nanoscale (Boomi et al., 2019). For instance, Metallic nanoparticles (MNPs) have gained popularity due to their obvious optical, physical, electrical and chemical properties as well as their great surface-to-volume ratio, which have made them promising for cancer therapeutic / imaging purposes (Barabadi, 2017, Ovais et al., 2018, Barabadi et al., 2020). MNPs possess the ability to emit fluorescent emission when exposed to X-rays. The fact that the locations of MNPs inside the body can be detected via fluorescent emission out of the body makes them ideal for diagnostic purposes (Barabadi et al., 2017). In terms of cancer treatment, it has been reported that the cytotoxicity of MNPs in cancer cells is 9 times greater than in normal cells, which is an acceptable evidence of MNPs ability to poison cancer cells and destroy them (Barabadi et al., 2020).

The biosynthesis process of NPs takes place by absorbing the target ions by microorganisms and changing the metal ions to the element metal through fabricated enzymes by the cell activities. Based on the location of NPs formation, the biosynthesis process of NPs can be categorized into intracellular and extracellular synthesis (Mann, 2001, Simkiss and Wilbur, 2012, Cao et al., 2021, Zhu et al., 2021). The intracellular synthesis procedure includes the transporting process ions into the microbial cell to form NPs in the existence of enzymes. The extracellular process consists of trapping the metal ions on the surface of the cells and decreasing the amounts of ions in the presence of enzymes. The biosynthesized NPs have brilliant potential of application in various pharmaceutical-based approaches such as cancer treatment, targeted drug delivery, DNA analysis, antibacterial agents, separation science and magnetic resonance imaging (MRI) (Zhang et al., 2011, Pishnamazi et al., 2020e, Marjani et al., 2021, Zhang and Zhang, 2021). Table 1 presents comprehensive information about the roles of various types of NPs for cancer treatment.

This paper aims to systematically review the potential of different NPs including AgNPs, AuNPs, SeNPs, TiO_2NPs and FeONPs to treat to treat / shrink cancerous cells. Moreover, different synthesis mechanisms towards NPs production along with their roles in improving the efficiency of conventional chemotherapeutic agents while reducing the toxicity are discussed. At the end, future challenges towards the application of NPs in the field of cancer treatment are presented and appropriate solutions to remove the ambiguities are suggested.

2. Investigation on the efficacy of silver nanoparticles (AgNPs) in cancer treatment

In recent decades, silver nanoparticles (AgNPs) have found numerous applications in the medical / pharmaceutical areas due to their obvious therapeutic properties. Current investigations have corroborated the anti-viral / anti-cancer character-

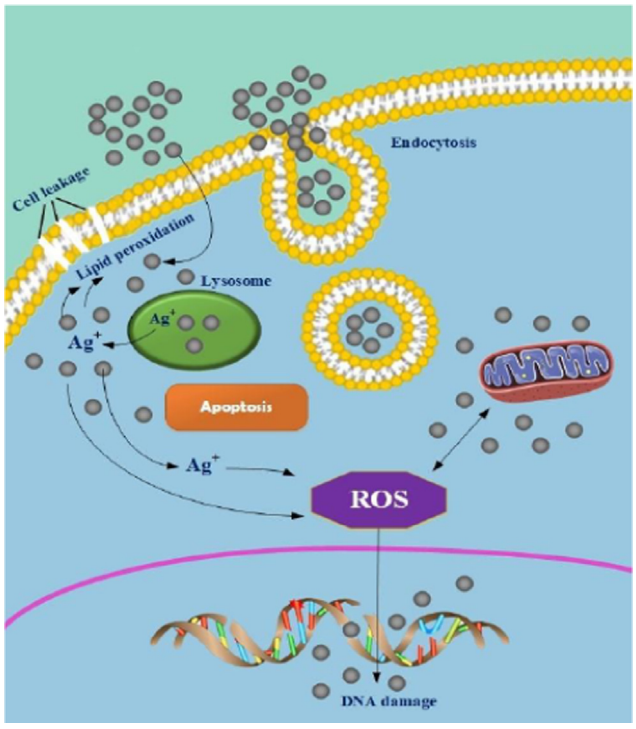

Fig. 2 Demonstration of the mechanism of AgNPs in cancer treatment. Reprinted with permission from (Yesilot and Aydin, 2019).

istics of AgNPs. Suitable knowledge about these characteristics is of great importance to increase their potential applications in various fields while reducing their feasible detriments for human health and the environment (Abdel-Fattah and Ali, 2018, Chugh et al., 2018, Beik et al., 2019, Pishnamazi et al., 2020b). Significant breakthroughs in the emergence of novel therapeutic approaches have caused the rise of use of NPs in medicine. Silver is known as a rare element widely applied in the jewelry industry. This precious metal is resistant to bacteria and therefore, can be used as an anti-bacterial agent with minimal toxicity (Loo et al., 2016, Guan et al., 2020, Nguyen et al., 2020b).

In order to increase the potential of application in nanotechnology-based industries, silver ions are processed into very fine particles in nanometers (nm) scale (Silver et al., 2006, Ong et al., 2013). Changing the silver ions to AgNPs will provide great physicochemical / biological capabilities for use in a broad range of applications as an anti-bacterial, anti-angiogenic or anti-tumor therapeutic agent. It has been reported in recent scientific investigations that AgNPs do not have any detrimental effects on humans and only kill viruses, bacteria and other eukaryotic microorganisms (Wei et al., 2015, Hosseini et al., 2018). Various researches have proved the efficiency of AgNPs in treating various cancers as an anti-tumor agent (Raghunandan et al., 2011, Abdel-Fattah and Ali, 2018).

Disparate in vitro investigations have shown that AgNPs possess the ability to enter cells by endocytosis (Greulich et al., 2011, Pradheesh et al., 2020). Additionally, AgNPs may be potent enough to move into the mitochondria and provide reactive oxygen species (ROS) by influencing the cells' respiration. In essence, AgNPs as cytotoxic agent damage the DNA of cancerous cells and their apoptosis, which results in the shrinkage of tumoral cells (Sukirtha et al., 2012, Vlăsceanu et al., 2016, Yousefi Rad et al., 2019). The mechanism of AgNPs in cancer treatment is schematized in Fig. 2. The abovementioned characteristics of AgNPs have made these nanoparticles promising and noteworthy for cancer treatment. A detailed summarization about the application of AgNPs for treating different types of cancers and their biosynthesis procedures is presented in Table 2.

3. Advancements in the applications of gold nanoparticles (AuNPs) in cancer treatment

Recently, attention towards the noble MNPs (particularly gold nanoparticles (AuNPs)) has increased due to their versatile features and fusible applications in clinical chemistry, targeted

Table 2 Comprehensive data about the application of AgNPs for treating different types of cancers and their biosynthesis techniques.

Cancer type	Plant	NPs size/ shape	Cell line	Ref.
Cervical cancer	Azadirachta indica	2–18 nm/triangular, hexagonal	Siha	(Mishra et al., 2012)
	Acorous calamus	31.86 nm/spherical	HeLa	(Nakkala et al., 2014)
	Calotropis gigantea	5–30 nm/spherical	HeLa	(Rajkuberan et al., 2015)
	Cymodocea serrulata	17–29 nm/spherical	HeLa	(Chanthini et al., 2015)
	Sargassum vulgare (algae)	10 nm/spherical	HeLa	(Govindaraju et al., 2015)
	Podophyllum hexandrum	14 nm/spherical	HeLa	(Jeyaraj et al., 2013)
Colon Cancer	Rosa indica	23.52–60.83 nm/spherical	HCT 15	(Manikandan et al., 2015)
	Commelina nudiflora L.	24–80 nm/spherical, triangular	HCT-116	(Kuppusamy et al., 2016)
	Gymnema sylvestre	N.A/spherical	HT29	(Arunachalam et al., 2015)
Gastric Cancer	Artemisia marschalliana	5–50 nm/spherical	AGS	(Salehi et al., 2016)
Liver (Hepatic) cancer	Allium sativum	100–1200 nm/spherical	HEP-G2	(Pandian et al., 2015)
	Citrullus colocynthis	7.39 nm/spherical	HEP-G2	(Patra et al., 2015)
	Rubus glaucus Benth	12–50 nm/Quasi-spherical	HEP-G2	(Kumar et al., 2016)
Intestinal Cancer	Taxus yunnanensis	6.4–27.2 nm/spherical	SMMC-7721	(Xia et al., 2016)
	Citrullus colocynthis	13.37 nm/spherical	Caco-2	(Patra et al., 2015)
Leukemia	Dimocarpus longan	8–22 nm/spherical	H1299	(He et al., 2016)
Epidermoid Cancer	Cucurbita maxima	76 nm /cuboidal, spherical	A431	(Nayak et al., 2015)
Laryngeal Cancer	Suaeda monoica	31 nm/spherical	Hep-2	(Satyavani et al., 2012)

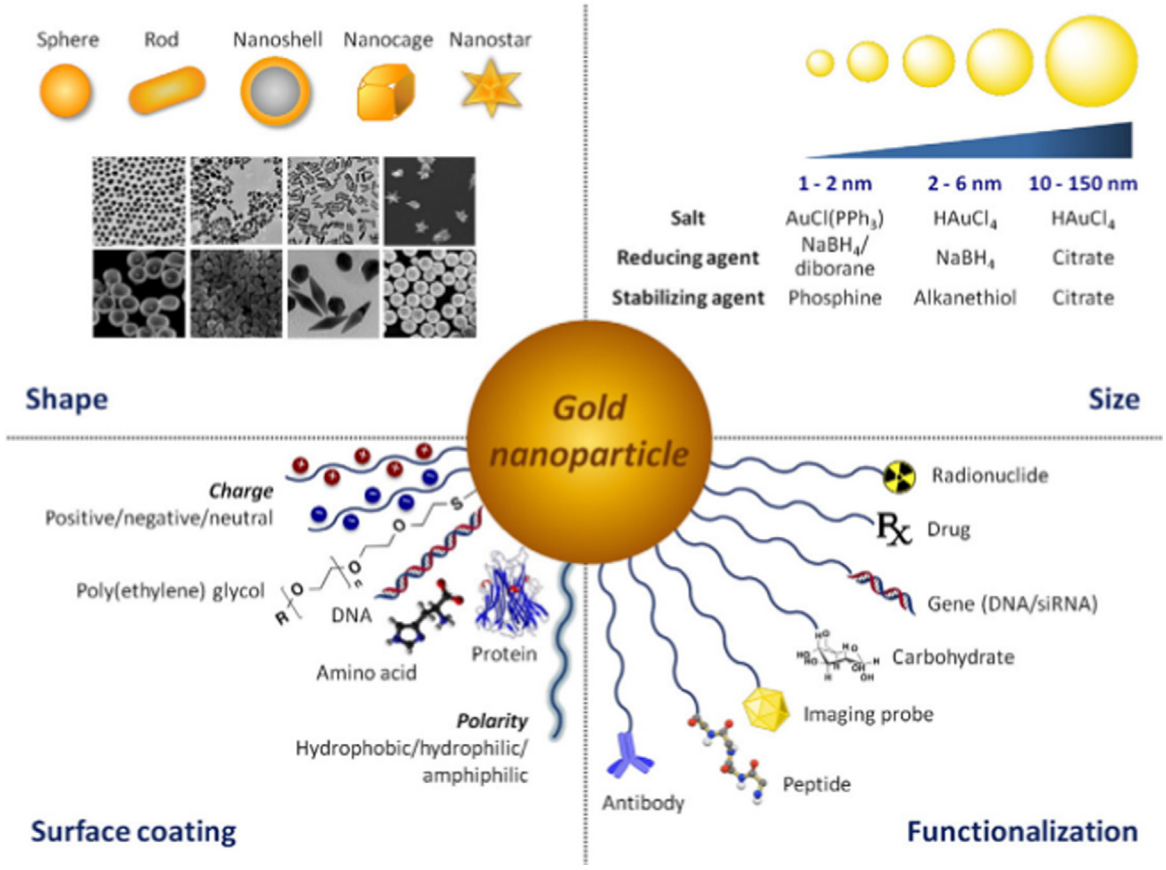

Fig. 3 Schematic demonstration of different applied shape, size, surface coating and functionalization of AuNPs. Reprinted with permission from (Her et al., 2017).

drug delivery (TDD) and cancer treatment (Keshavarz et al., 2018, Fan et al., 2020, Zhang et al., 2020, Zhu et al., 2021). The use of AuNPs for such purposes originated many hundreds of years ago. The first report on the use of colloidal suspension of AuNPs is found in ancient Chinese, Arabian and Indian papers, which offered the nanoparticles of this precious metal as a cure for a number of diseases. In medieval time, European pharmacology laboratories investigated and, consequently, applied the colloidal suspension of AuNPs in the treatment of an extensive range of diseases (such as syphilis, diarrhea) (Dykman and Khlebtsov, 2011, Zhu et al., 2021).

Fig. 3 renders a schematic depiction of different applied shape, size, surface coating and functionalization of AuNPs. In the field of treating cancerous tumors, AuNPs can possess different capabilities in radiotherapy and tomography as a contrast agent and dose modifier, respectively (Martelli and Chow, 2020, Mututantri-Bastiyange and Chow, 2020). Current improvement in the synthesis and fabrication procedures of NPs has facilitated the control of their important variables like size and morphology (Chow, 2018, Chen et al., 2021). In recent years, AuNPs have been of much technological interest due to their indisputable optical characteristics, simplicity of synthesis and chemical resistance against unfavorable conditions. These NPs possess undeniable potential for application in numerous medical approaches such as chemotherapeutic tumor shrinkage, imaging and TDD (Beik et al., 2018, Abdulle and Chow, 2019, Kang et al., 2020, Siddique and Chow, 2020). However, the existence of significant toxicity and side effects on the human well-being has convinced the researchers to investigate further before using them in clinical trials (Alkilany and Murphy, 2010, Fan et al., 2020).

Recent researches have presented a novel viewpoint towards the development of TDD and systemic cancer treatments (Indoria et al., 2020, Lavacchi et al., 2020, Pedziwiatr-Werbicka et al., 2020). Despite the existence of numerous available procedures for the synthesis of AuNPs, they are usually synthesized using a colloidal method (Khademi et al., 2018, Slepička et al., 2020). Those Au particles, which are able to be synthesized applying this technique, are spherical, nanorods, and nano-cages (Austin et al., 2014, Khademi et al., 2018, Tang et al., 2021). Galvanic replacement is considered as another less prevalent method that can be applied for the synthesis of the hollow AuNPs (Adams and Zhang, 2016, Guarino-Hotz and Zhang, 2021). The bottom-up is a noteworthy technique for preparing AuNPs in biomedical applications (Zhao and Friedrich, 2017, Slepička et al., 2020). Detailed information about disparate synthesis procedures for AuNPs is presented in Table 3.

Application of AuNPs is a noteworthy approach for cancer treatment by showing cytotoxic characteristics against various sorts of cancer cell lines. However, due to the fact that the cytotoxicity mechanisms of AuNPs are not completely understood, their application as an anticancer agent needs more investigation (Peng and Liang, 2019, Guan et al., 2020).

Table 3 Comprehensive data of disparate synthesis procedures for AuNPs.

Synthesis procedure	NP Size [nm]	Ref.
PVD in liquid substrate	2–10	(Slepička et al., 2015)
Sol–gel micro reactors	5–50	(Mikhlin et al., 2011)
Reduction process	2–40	(Doyen et al., 2013, Liu et al., 2013b)
γ-Irradiation	3–30	(Hori et al., 2014)
Biosynthesis	9–25	(Bankar et al., 2010, Ren et al., 2012)

Prevention of the tumoral angiogenesis is known as a promising strategy for using AuNPs in treating various cancers (Bergers and Benjamin, 2003, Pretze et al., 2021).

4. Development of selenium nanoparticles (SeNPs) in cancer treatment

Up until now, various therapeutic medicines have been proposed for treating cancerous cells at different stages. However, these therapeutic agents suffer from low selectivity against tumoral cells and result in significant toxicity for healthy cells (Sinha et al., 2006). The emergence of nanomedicine has opened a novel horizon in the field of cancer treatment. Selenium (with atomic number 34) is an important chemical element in the 16th group of periodic table, which plays an important role in improving the immune system of the human body, and preventing tumoral growth due to having antioxidant/antitumor effects (Khurana et al., 2019, Vahidi et al., 2020).

SeNPs have recently created great interest among various researchers all over the world because of their brilliant catalytic / photoelectrical features. They possess great potential for synthesis by means of various physical (e.g. UV radiation), chemical (e.g. acid decomposition) and biological (e.g. microbial synthesis) procedures (Wadhwani et al., 2016). Some physical and/or chemical procedures are costly or toxic, while biological techniques are regarded economical and environmentally-friendly for SeNPs preparation (Srivastava et al., 2014, Cittrarasu et al., 2021). Fig. 4 provides a schematic demonstration about the application of SeNPs in various therapeutic purposes.

It has been reported that despite the inherent antioxidant capability of the selenium compounds (e.g. selenite), they have higher liver toxicity than SeNPs (Cruz et al., 2019). Therefore, negligible toxicity of SeNPs along with remarkable physicochemical characteristics provides an opportunity to investigate the therapeutic potential of these NPs. SeNPs have recently gained considerable popularity for their therapeutic potentials.

The advantages of SeNPs in the treatment of various illnesses such as hepatic damage, Corona virus, diabetes, drug-induced nephrotoxicity and inflammatory disorders have been reported in numerous papers (El-Ghazaly et al., 2017, Cengiz et al., 2021, He et al., 2021, Ikram et al., 2021, Selvam, 2021). Moreover, SeNPs (e.g. polyamidoamine dendrimer-modified SeNPs) have excellent potential of application as drug carriers in drug delivery systems (Zheng et al., 2015, Zhao et al., 2017, Ikram et al., 2021, Nayak et al., 2021). The combination of SeNPs with different therapeutic medicines is regarded as the future perspective for developing next generation of anticancer treatments (Kumari et al., 2017).

In recent decades, SeNPs have illustrated great potential of applications in medical-associated diagnosis (Liao et al., 2020, Gao et al., 2021). Particularly, the significant antitumor characteristics of SeNPs against disparate types of cancers such as glioma, lung cancer and breast cancer have been reported by investigators (Winkler et al., 2016, Tugarova et al., 2018, Nguyen et al., 2020a). The enhancement of apoptosis process through cancer cells using SeNPs is principally believed to be a noteworthy mechanism towards the growth of malignant tumors (Nakhjiri and Roudsari, 2016, Tugarova et al., 2018, Zhang et al., 2019). SeNPs possess the capability to regulate key apoptotic proteins (i.e., caspase family, p53, and ROS) (Cruz et al., 2019, Ghadiri et al., 2020). Table 4 represents the detailed information about the activity of biosynthesized SeNPs in cancer treatment.

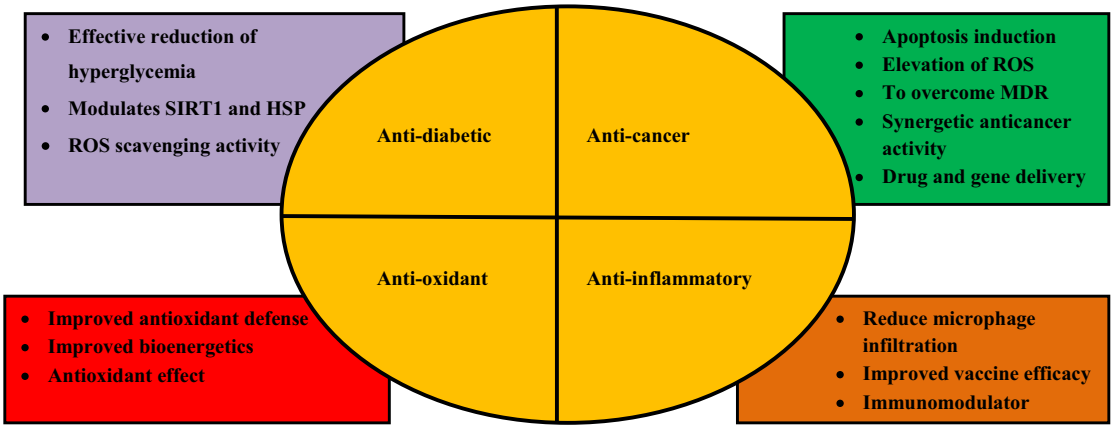

Fig. 4 Schematic demonstration of SeNPs application in various therapeutic purposes. Reproduced with permission from (Khurana et al., 2019).

Table 4 Comprehensive data about the efficacy of biosynthesized SeNPs in cancer treatment.

Biological source (Scientific name)	NPs size/ shape	Cancer cell line	Characterization technique	Ref.
Bacterium (Escherichia coli)	Spherical / 60 nm	A549	UV–vis, XRD, TEM	(Cruz et al., 2019)
Bacterium (Lactobacillus casei ATCC 393)	Spherical / 50–80 nm	HepG2	TEM, SEM, EDX, XPS, FT-IR	(Xu et al., 2018)
Bacterium (Streptomyces griseoruber)	Spherical / 100–250 nm	HT-29	UV–vis, TEM, XRD, FT-IR, DLS, zeta potential	(Ranjitha and Ravishankar, 2018)
Bacterium (Acinetobacter sp. sW30)	Polygonal/average: 79 nm	4 T1, MCF-7	TEM, SEM, XRD, EDX, FT-IR	(Wadhwani et al., 2017)
Plant (Castanea mollissima Blume)	Spherical / 53.7 ± 4.0 nm	HeLa	TEM, DLS, FT-IR	(Li et al., 2019)
Bacterium (Idiomarina sp. PR58-8)	Spherical / 150–350 nm	HeLa	TEM, XRD	(Srivastava and Kowshik, 2016)
Bacterium (Streptomyces Minutiscleroticus M10A62)	Spherical / 10–250 nm	HeLa, HepG2	UV–vis, TEM, XRD, EDX, FTIR	(Ramya et al., 2015)

5. Emergence of titanium oxide nanoparticles (TiO_2NPs) in cancer treatment

In this section, the authors aim to review TiO_2NPs as one of the prominent classifications of MNPs. Titanium oxide (TiO_2) has shown great potential for use in disparate industrial-based activities such as pharmaceutics and cosmetics due to its affordability and non-toxic feature (Pokharna and Shrivastava, 2013, Ziental et al., 2020). Scientific investigations on the feasibility of using TiO_2NPs in the medical industry go back to 1985 (Matsunaga et al., 1985). Since then, the application of these nanoparticles in the photodynamic therapy (PDT) treatment of cancer (as photosensitizing agent) has been constantly enhanced. TiO_2NPs have recently gained great attention in the bioconjugates synthesis process with cell-specific monoclonal antibodies for eradicating various types of cancerous tumors or the provision of black TiO_2NPs for antimicrobial treatment of those bacteria that are resistant to different class of antibiotics (Matsunaga et al., 1985, Rao et al., 2019, Khalid et al., 2021).

The pharmacokinetics of MNPs rely on numerous parameters such as NPs type, surface charge / coating and NPs size (Carlander et al., 2016, Xiao et al., 2021). As demonstrated in Fig. 5, TiO_2NPs have great ability to enter the body following oral, transdermal and injection delivery. Investigations into the bioaccessibility of TiO_2NPs from the gastrointestinal tract are being conducted (Janer et al., 2014, Morita et al., 2021). The non-toxic characteristic of TiO_2NPs is the main reason for their extensive applications in various pharmaceutical industries such as cancer treatment. Numerous researches have evaluated various sizes of TiO_2NPs along with their crystalline forms to evaluate their impacts on skin, respiratory and immune systems (Hajirezaee et al., 2020, Nho, 2020, Pishnamazi et al., 2020c, Song et al., 2021). Although TiO_2NPs is widely used in disparate cosmetic formulations (e.g. sunscreens and eyeshadows), it is believed that their size and crystalline forms affect their industrial-based applications (Grande and Tucci, 2016, Baranowska-Wójcik et al., 2020). In an animal study, Wu et al. evaluated the toxicity of TiO_2NPs in hairless mice and porcine skin after their dermal exposure subchronically. They corroborated that TiO_2NPs can have potential health-related detriments to humans after their dermal exposure over a relatively long period. This potential health-related harm can be attributed to the deeper tissue distribution of TiO_2NPs following their long-term exposure to skin (Wu et al., 2009).

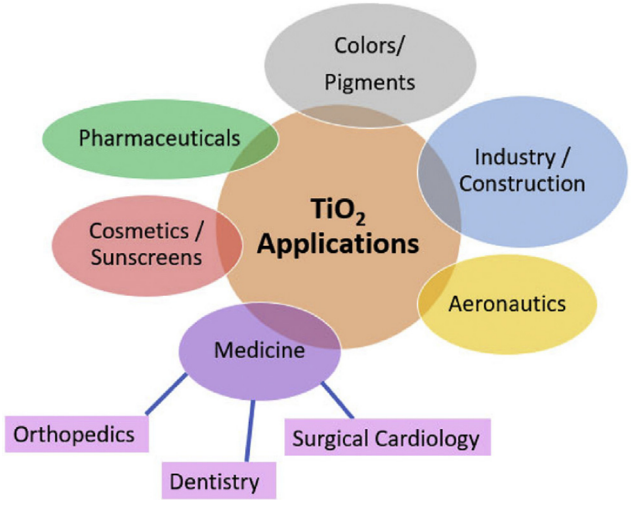

Fig. 5 The main applications of TiO_2NPs. Reprinted with permission from (Lagopati et al., 2020).

The potential harm of TiO_2 particles on the respiratory system is currently the subject of numerous researches. Evaluation of the toxicity demonstrated some unfavorable impacts related to TiO_2NPs (Liu et al., 2013a, Mohammadipour and Abudayyak, 2021, Zhu et al., 2021). These NPs can enter the body by crossing the pulmonary blood barrier and deposit in lung and liver tissues and other organs to induce poisonous impacts (Muller et al., 2005, Moller et al., 2008). Moreover, persistent exposure of the body to TiO_2NPs may result in an immune response leading to chronic inflammation (CI). CI is a detrimental human-based condition, which is responsible for the failure of bodily organs and the emergence of other ailments (Moller et al., 2008, Pishnamazi et al., 2020d). Fig. 6

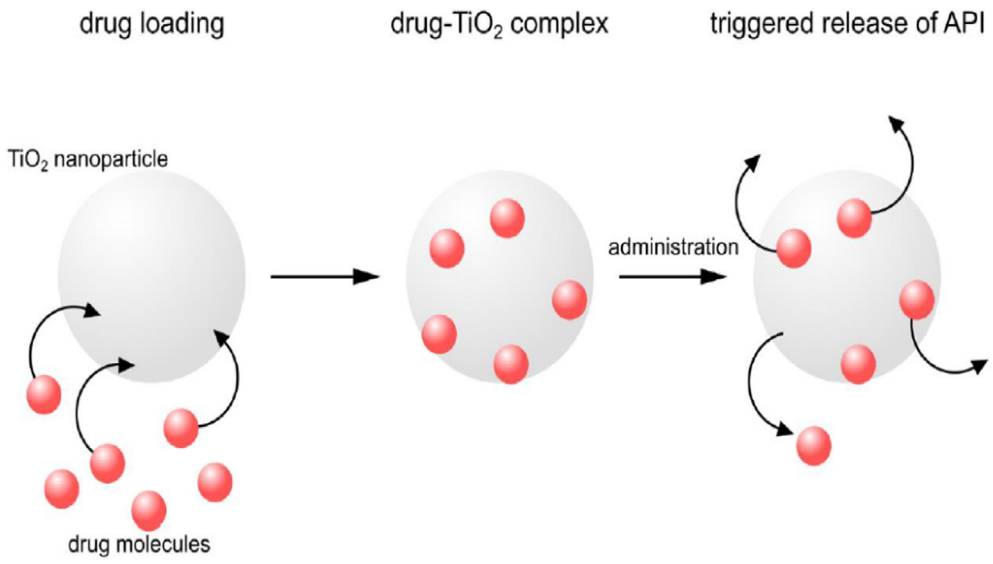

Fig. 6 Schematic demonstration of drug delivery applying TiO_2NPs for cancer treatment. Reprinted with permission from (Ziental et al., 2020).

schematically illustrates the simplified mechanism of drug delivery applying TiO_2NPs for cancer treatment. As mentioned before, MNPs have demonstrated brilliant photodynamic activity in several in vitro / in vivo biological investigations (Avgustinovich et al., 2020, Babanezhad et al., 2020a, Barani et al., 2021, D'Acunto et al., 2021). NPs have shown great potential as carriers for TDD. The application of appropriate TDD systems as photosensitizers permits PDT in specific tissues (Jia and Jia, 2012).

Table 5 represents detailed information about the synthesis procedure, physicochemical properties and medical utilizations of TiO_2NPs.

6. Application of iron oxide nanoparticles (FeONPs) in cancer treatment

FeONPs relate to the class of magnetic / metallic NPs. FeONPs are known as the only magnetic NPs approved by the US Food and Drug Administration (FDA) for clinical application due to significant toxicity of other magnetic / metallic NPs such as nickel and cobalt (Wang et al., 2010, Kong et al., 2014, Chattopadhyay et al., 2015). In contrast, FeONPs have shown negligible toxicity and very good biocompatibility / biodegradability (Yigit et al., 2012, Gobbo et al., 2015, Martinkova et al., 2018). In recent decades, FeONPs have been commercialized as a promising nanomedicine to treat cancerous cells and iron-deficiency anemia. These NPs have shown great potential due to their remarkable therapeutic efficiency derives from their capability to target a tissue and activate various biological drugs / materials (Alphandéry, 2020). The main procedures for the synthesis of FeONPs are presented as follows (Ge et al., 2009, dos Santos Monteiro and da Guarda Souza, 2016, Karimzadeh et al., 2017, Groult et al., 2018, Sharafi et al., 2018, LaGrow et al., 2019):

1) Co-precipitation between Fe^{2+} and Fe^{3+} in fundamental situation
2) Thermal-based dissociation of organo-iron in organic solvents in the presence of surfacting agents
3) Hydrothermal synthesis

Table 5 Comprehensive data about the synthesis procedure, physicochemical properties and medical utilizations of TiO_2NPs.

Morphology/size	Synthesis procedure	Medical purpose	Ref.
TiO_2 nanowhiskers / less than 100 nm	Undefined deposition in water	Photodynamic therapy and bioimaging	(Zhao et al., 2015)
P25 TiO_2 / 25 nm	Commercial distribution	Antimicrobial photodynamic therapy	(Sułek et al., 2019)
Spherical / 23 nm	• Macro-cycle deposition in tetrahydrofuran • From $TiCl_4$ and benzyl alcohol	Photodynamic therapy in breast and cervical cancers	(Yurt et al., 2018)
Anatase / 25 nm	Commercial distribution	toxicity decrement of teeth whitening gels	(Kurzmann et al., 2019)
Anatase / 25 nm	Deposition in pyridine / ethanol mixture	Antimicrobial photodynamic therapy	(Mantareva et al., 2015)
N-TiO_2-NH_2 / 20–30 nm	N-doping using the calcination process of accessible anatase TiO_2NPs in ammonia atmosphere	Photodynamic therapy in cancer treatment	(Pan et al., 2017)

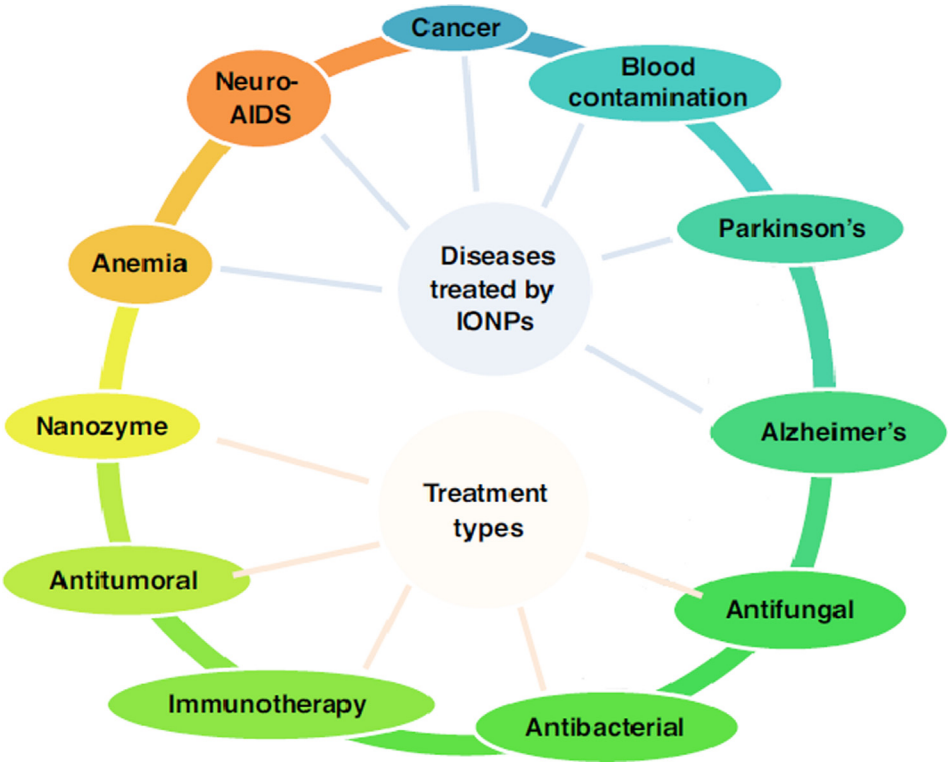

Fig. 7 Schematic demonstration of FeONPs application for various therapeutic purposes. Reprinted with permission from (Alphandéry, 2020).

4) Formation of NPs in the micelles
5) Sol-gel techniques
6) Cathodic electrochemical deposition

These procedures produce FeONPs with different sizes ranging from 1 to 120 nm (Mosayebi et al., 2017, Hu et al., 2018, Babanezhad et al., 2020b). Fig. 7 renders various sorts of diseases, which can be cured by the application of IONPs. Generation of reactive oxygen species (ROS) or localized heat using IONPs-based chemotherapeutic agents (e.g. FeONPs-based paclitaxel) may significantly enhance the effect of chemotherapeutic drugs and reduce their unfavorable side effects in cancer treatment (El-Zahaby et al., 2019).

The conjugation process of FeONPs with disparate chemotherapeutic drugs (e.g. docetaxel, cisplatin and carboplatin) produces a drop in their toxicity by improving the performance of TDD to tumoral cells and, consequently, by decreasing the necessary dose to reach therapeutic efficiency (Chowdhury et al., 2017). Apart from the abovementioned mechanisms, it has been observed that FeONPs have great potential to modify the tumor microenvironment by blocking the artery that feeds the tumor (Wang et al., 2018).

Although FeONPs exist in three formations (hematite, magnetite and maghemite), only magnetite and maghemite possess a biocompatibility characteristic and thus may be used in biomedicine (Li et al., 2011). Outstanding characteristics of FeONPs have made these NPs promising for application in cancer treatment by hyperthermia. Hyperthermia is a novel cancer treatment strategy based on enhancing body temperature through an exterior medical device. This method is attracting interest as it has been shown that the higher temperature damages tumoral cells and tumor sensitivity to radiotherapy and chemotherapeutic agents [157,158,159]. Schematic illustration of TDD for an anticancer agent applying FeONPs in presented in Fig. 8.

7. Conclusions and future outlook

In recent decades, NPs have illustrated superior performance compared to conventional cancer therapeutic agents due to their outstanding characteristics such as designability in different size, bioactivity, tendency of accumulation in tumoral cells and negligible toxicity to the human body. The main objective of this paper is to present a systematic review about the performance of prominent NPs including AgNPs, AuNPs, SeNPs, TiO_2NPs and FeONPs to treat various cancerous cells. Additionally, study on how NPs can reduce the toxicity and enhance the efficiency of conventional chemotherapeutic agents is regarded as the second target of this paper. AgNPs have shown excellent antibacterial characteristics and, hence, are commonly applied in medical / biomedical, food and cosmetic industries. Novel properties along with the rapid transfer of application fields have caused the popularity of AgNPs in disparate industrial-based activities. Especially, recent advancements in various synthesis procedures of AgNPs result in an increase in the application fields in nanomedicine. Green biosynthesis, whereby plant extracts or microorganisms are applied, is known as one of the promising methods of AgNPs production, and is believed to be more appropriate for clinical approaches than the physical / chemical techniques due to its affordability, safety and simplicity of application. AuNPs are

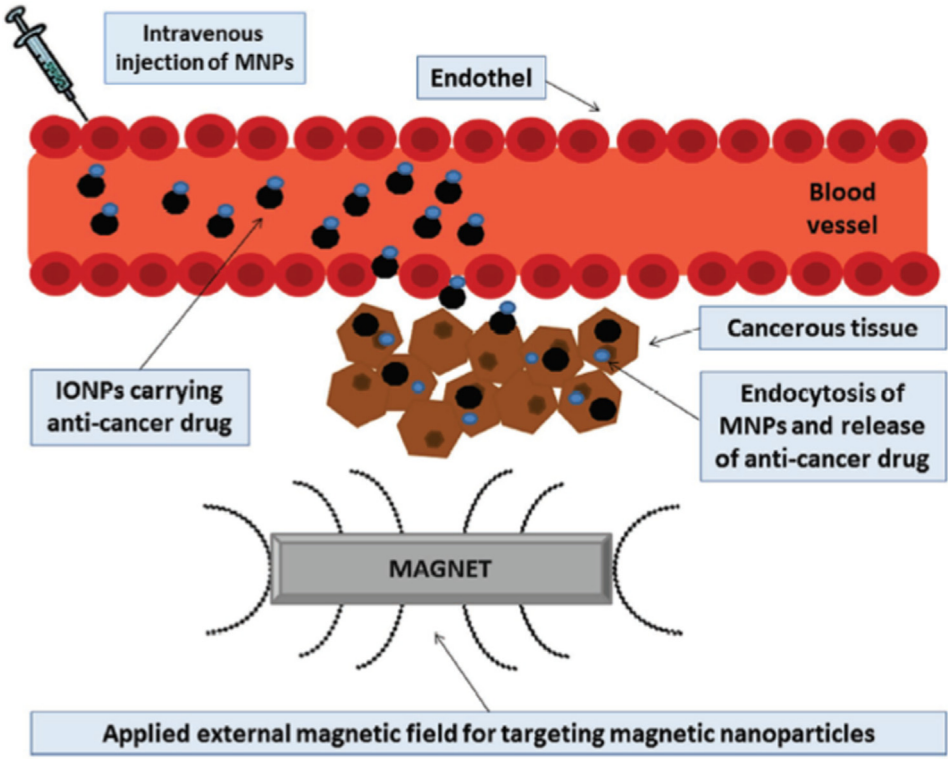

Fig. 8 Presentation of TDD for an anticancer agent applying FeONPs. Reprinted with permission from (Martinkova et al., 2018).

other NPs, which have been of great interest in therapeutic applications, particularly for cancer treatment. An extensive range of feasible synthesis procedures permits the achievement of AuNPs with specific size, structure and characteristics, depending on the intended use. As outlined in the review, various physicochemical properties of AuNPs have given new hope for their application as a TDD device and angiogenesis modulators for tumor shrinkage. As the future perspective, many questions and ambiguities still exist as highlighted in available scientific articles in terms of the biological effect of AuNPs due to differences in synthesis technique, applied doses and conducted experimental methods. Therefore, more investigations must be undertaken to remove the ambiguities and obstacles towards the use of AuNPs as a promising nanomedical cancer treatment. SeNPs are noteworthy and novel options for curing disparate sorts of cancer either alone or in combination with other chemotherapeutic agents (antitumoral drugs). As described, numerous investigations have confirmed the capability of SeNPs as a drug carrier and TDD agent. Therefore, biogenic SeNPs are believed to possess great potential of conjugation with special ligands or theranostic agents for efficacious TDD. For future studies, it is highly recommended that the researchers / scientists evaluate the efficiency of SeNPs in combination with disparate FDA approved anticancer medicines for shrinking cancerous tumors. Also, more studies must strive to address the challenges and solve the ambiguities of SeNPs application such as toxicity and in vivo pharmacokinetics / pharmacodynamics as well ways of administrating the drug.

TiO_2NPs are other well-known and commercially accessible MNPs, which have attracted the attention of many scientists due to their potential for applications in advanced technology. These promising NPs can be applied in medicine / pharmacology due to their outstanding photocatalytic properties, and acceptable biocompatibility. It has been discussed in this paper that photoactivated TiO_2NPs encourage the induction process of reactive oxygen species (ROS) and, hence, result in the breakdown of cancerous cells. TiO_2NPs are novel NPs, which have been commercially accessible to treat iron-deficient anemia and for cancer treatment. To accelerate the commercialization of FeONPs for different industrial-based applications, novel advances in their synthesis procedures and better bioactivity must be conducted to make them more promising for use in hospital environments while at the same time, examining affordability. In doing so, great endeavors are required to optimize the size, shape, and other characteristics and evaluate the potential risks of NPs before their applications in clinical practice. Depending on more awareness about nanomedicine, NPs possess great potential to revolutionize cancer treatment in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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