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Review

Prospect of nanomaterials as antimicrobial and antiviral regimen

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Abatract: In recent years studies of nanomaterials have been explored in the field of microbiology due to the increasing evidence of antibiotic resistance. Nanomaterials could be inorganic or organic, and they may be synthesized from natural products from plant or animal origin. The therapeutic applications of nano-materials are wide, from diagnosis of disease to targeted delivery of drugs. Broad-spectrum antiviral and antimicrobial activities of nanoparticles are also well evident. The ratio of nanoparticles surface area to their volume is high and that allows them to be an advantageous vehicle of drugs in many respects. Effective uses of various materials for the synthesis of nanoparticles impart much specificity in them to meet the requirements of specific therapeutic strategies. The potential therapeutic use of nanoparticles and their mechanisms of action against infections from bacteria, fungi and viruses were the focus of this review. Further, their potential advantages, drawbacks, limitations and side effects are also included here. Researchers are characterizing the exposure pathways of nano-medicines that may cause serious toxicity to the subjects or the environment. Indeed, societal ethical issues in using nano-medicines pose a serious question to scientists beyond anything.

Keywords: nanotechnology; nanovehicles; nanoparticles; nanocomposites; nanopolymer; nanoviricide; antimicrobial; antiviral; TheraCour; SARS-CoV-2

1. Introduction

Infectious disease, in recent times, is a great concern in public health. Around the world, microbial infection causes mortality in millions of people every year [1–4]. Further, the microbes can turn resistant to antibiotics due to their high mutative capacity and morphological changes [5–7].

A nanoparticle (NP)-based treatment approach could be promising to overcome the drug-resistant effects of the microbes. Further, NPs can have innate antimicrobial activities [8,9]. NPs can generate reactive oxygen species (ROS), which can damage DNA and proteins and block the growth of bacteria, fungi and viruses. Antibiotics conjugated with nanoparticles have therefore been thought to be an efficient antimicrobial regimen [10]. The antibiotic cefaclor attached to gold nanoparticles (52–22 nm) showed significant antibacterial activity [11,12]. Biogenic selenium nanoparticles have anti-biofilm activity and effectively retard the growth of *Pseudomonas aeruginosa,* a Gram-negative bacteria [13,14]. Similarly, TiO_2 nanoparticles have been found to inhibit the formation of fungal biofilms [15].

Nanotechnology can help the world's medical community to fight against virus infection also [16,17]. For example, studies have been done successfully on the effects of nano-materials as antivirals against the virus SARS-CoV-2, inhibiting its entry into cells, its RNA replication and, finally, its release [18–20]. In addition, nano-materials provide a wide range of opportunities for diagnosis, treatment and in controlling the biofilm formation. Recent advances of applications of various nanomaterials in the diagnosis and treatments of microbial infections have been reviewed elsewhere [21–24]. However, their impact on human tissues and the environment should be assessed before implementations in large-scale industry are carried out [25].

Here, we discuss several aspects of using nanoparticles in infectious diseases, their pros and cons, challenges for nanoparticles and future prospects.

2. Nanoparticles/Nanocomposites and their antimicrobial properties

Nanoparticles (NPs) belong to a group of substances having diameters ranging from 1–100 nm [26–29], and they possess the ability to penetrate the bacterial cell wall, which is made up of peptidoglycan. NPs can dismantle the peptidoglycan layer from Gram-positive bacteria and also overcome antimicrobial resistance [5,30,31],

2.1. NPs and their antibacterial activities (Table 1)

Table 1. Antiviral nanoparticles and antibacterial activities.

Antibacterial Nanoparticles	Functions
Gentamicin coated phosphatidylcholine–chitosan hybrid nanoparticles [32]	Inhibit the growth of Gram-positive and Gram-negative bacteria [32]
Supramolecular polyelectrolyte complexes, (like NH_3^+ of the β-cyclodextrin-chitosan complexes with the negatively-charged SO_3^- groups) [33].	Silver sulfadiazine molecules complexed with β-cyclodextrin releases silver ions which damages the bacterial cell wall [33]
Vancomycin antibiotic encapsulated in polymersomes [34]	Antibacterial effects against methicillin-resistant *S. aureus* [34]
Mannose-chitosan complex nanoparticles [35]	Mannose-chitosan complex nanoparticles have antibacterial activities against gram-positive and gram-negative bacteria [35]
Teicoplanin-containing polylactic-*co*-glycolic acid (PLGA) nanoparticles [36]	Showed an antibacterial effect on *S. aureus* [36]

Continued on next page

Antibacterial Nanoparticles	Functions
Pistacia lentiscus L. var. chia essential oil can be encapsulated within PLA nanoparticles [37]	Showed an inhibitory effect on gram-positive and gram-negative bacteria [37]
Silver nanoparticles with PLA nanocoatings and with polyethylene terephthalate nanofibers [38]	Works against gram-positive and gram-negative bacteria, both [38]

2.2. NPs as an antiviral regimen (Table 2)

Viruses can infect prokaryotes as well as eukaryotes. Vaccines are effective in some of viral diseases such as smallpox, polio, etc, yet further opportunities to overcome antiviral drug resistance is possible by using NPs [39,40].

Table 2. Antiviral nanoparticles and their functions.

Antiviral Nanoparticles	Functions
Chitosan nanoparticles complex with peptides derived from HIV-1 P24 protein [41].	Showed reduced toxicity and sustained peptide drug release [41].
NPs attached with hydroxypropyl-β-cyclodextrin and loaded with Dolutegravir [42].	Results in improved permeation of the drug through nasal mucosa without damaging the mucosa [42].

2.3. Application of NPs in fungal and parasite infections (Tables 3 and 4)

Table 3. Antifungal nanoparticles and their functions.

Antifungal Nanoparticles	Functions
Administration of miconazole and farnesol together with chitosan NPs [43]	The minimum inhibitory concentration (MIC) of nanosystems against *C. albicans* is similar to the values for the miconazole free drug [43]
Chitosan nanoparticles incorporating itraconazole [44]	Potentially inhibits the growth of *C. neoformans*, *C. albicans* and *A. fumigatus* [44]
Nanocapsules containing modified polysaccharide for the delivery of amphotericin B [45]	This nanosystem showed significant antifungal activity against *C. albicans* strains, compared to the free drug [45]

Table 4. Antiparasitic nanoparticles and their functions.

Antiparasitic Nanoparticles	Functions
A poorly water-soluble compound, Triclabendazole, encapsulated within chitosan [46–49]	Found successful in treatment of fascioliasis [46]
	Showed an inhibitory effect on *Leishmania* promastigotes protozoan parasites [47]

Some industrial and biomedical applications of nano-materials as alternatives to commercially available antibiotics and anti-fungal medications are reviewed in [22,24] (Tables 5 and 6).

Table 5. Nanomaterials with antifungal activities.

Targets	Antifungal activity	Nanoparticle type	Route of administration	References
Trichophyton rubrum	AmB, CLT	SLN, SLN	Topical	[50,51]
Candida albicans	CLT, ECN, MN	SLN-based stearate, SLN, SLN	Topical	[52–54]
Candida species	MN	SLN-bearing Hydrogel, SLN	Topical, Oro mucosal	[55,56]
Aspergillus flavus	ITZ; VRZ	SLN	Ocular	[57,58]
Candida glabrata	VRZ	SLN	Ocular	[59]
Candida species	FLZ	SLN	Topical	[60]
Dermatophyte	GF	SLN	N/A	[61]
Candida tropicalis	AmB	Ag	N/A	[62]
Aspergillus niger	AmB	Ag	N/A	[63]
Fusarium culmorum	AmB	Ag	N/A	[63]
Aspergillus brasiliensis	NYS, FLZ	Ag	N/A	[64]
Malassezia furfur	KTZ	Ag	Topical	[65]
Paracoccidioides brasiliensis	AmB	PLGA	N/A	[66]
Candida parapsilosis	AmB	CS-coated PCL	Oral	[67]
Aspergillus fumigatus	AmB	L/CS	N/A	[68]

Table 6. Nanomaterials with antibacterial activities.

Biomaterials	Potential applications	Bacteria	Reference
Cotton/silk fabrics containing reduced graphene oxide (RGO) and Ag/Cu NPs	Antimicrobial protective medical textiles	*P. aeruginosa* *E. coli* *S. aureus*	[69]
Polyvinyl alcohol containing Ag/Cu NPs	Antibacterial contact lenses	*S. aureus* *P. aeruginosa*	[70]
Lysozyme-coated Au NPs in combination with β-lactam	Diabetic wound healing	*S. aureus* *Acinetobacter calcoaceticus* *P. aeruginosa* *E. coli* *Klebsiella pneumoniae* *Bacillus subtilis, B. cereus*	[71]
Keratin containing Ag NPs	Skin wound healing and tissue recovery	*E. coli* *S. aureus*	[72]
Ag NPs-loaded bacterial cellulose hydrogels	Moist wound-healing hydrogels	*S. aureus* *P. aeruginosa*	[73]

3. Nanoparticles (NPs) and their biological compatibility (Table 7)

When NPs come into contact with blood, they may initiate some biological effects, which could be good or bad. Hence, it is important to determine the blood-NPs compatibility before they can be used in humans [74,75]. A few observations are the following:

- The blood-NPs compatibility depends on the size, structure and formulation of the NPs [74,76].
- Biopolymeric NPs have been found compatible when used in the treatment of asthma, tuberculosis and lung cancer [77,78].

Table 7. Comparative biocompatibilities of several NPs.

NPs	*In vitro* and *in vivo* toxicity
Dendrimers	No toxic effects [79]
Au NPs	No toxic effects [80]
Carbon nanotubes	No toxic effects [81]
Superparamagnetic Fe_3O_4 nanoparticles (SPIONs)	No toxic effects [82]
Silica-based NPs	Si NPs cause toxicity to immune cells and tissues. The main mechanisms were pro-inflammatory responses, oxidative stress autophagy and so on. Surface and shape modifications may mitigate the toxicity effects of Si NPs, providing a new way to produce these NMs with less toxic impact [83,84].
Ag NPs	• Induce cell shrinkage, apoptosis [85,86] • Release free radicals and cause DNA damage [87] • Immunotoxicity in rats [88,89] • Ag NP-biopolymer showed anti-bacterial activity but no toxic effects on mouse fibroblasts (NIH-3T3), human osteosarcoma cells (MG63) or human hepatocarcinoma cells (HepG2) [90,91]
Fe_3O_4-Au NPs	No toxicity was observed in any cell types in culture [92]
Manganese ferrite ($MnFe_2O_4$) NPs	Showed biocompatibility at 125 μg/mL or below in 4T1 cells (a murine breast cancer cell line) [93]
Ferrite NPs (Fe_3O_4, $ZnFe_3O_4$ and $NiFe_3O_4$)	Showed toxicity against HeLa cell lines at and above 100 μg/mL dosage [94]
TiO_2 NPs	These NPs are non-toxic (at <l00 μg/mL) to humans [95]
$CaFe_2O_4$ NPs	Showed toxicity in humans at >250 μg/mL concentration [96]

4. Nanoparticles (NPs): Encapsulation and biodegradability

Since the accumulation of nanoparticles in the spleen and liver may turn out as toxic, biodegradable NPs (BNPs) should be more appropriate than non-degradable NPs [97]. Other significant factors are the following:

- Nanopolymers are biodegradable and can encapsulate other therapeutic regimens to deliver them to the action site [98].
- Polysaccharides, proteins and some synthetic polymers are the main sources of BNPs.
- Polymersomes (or polymer vesicles) can be used for drug delivery as their coronas and membranes can be modified for biomedical active different groups. Polymersomes are very suitable drug deliver agent for bacterial infection, and cancer therapy, as well.
- Antibacterial polymersomes are divided into three categories:
    1. polymersomes as antibiotic nanocarriers,
    2. intrinsically antibacterial polymersomes and
    3. antibacterial polymersomes with supplementary means, including photothermal and photodynamic therapy.
- Similarly, the anticancer polymersomes are divided into two categories:
    1. Polymersome-based delivery systems, and
    2. Anticancer polymersomes with supplementary means.

In this review, the prospective antibacterial and anticancer polymersomes are discussed.

4.1. Selection of polymers and the synthesis of BNPs

The end application is the main criterion for the selection of the polymer, but their size, biocompatibility, biodegradability and the capability of encapsulation of the drug materials are similarly important factors to be considered [99]. Some of the different biodegradable polymers and their merits for use as BNPs are listed in Table 8

Table 8. Some polymers for the synthesis of BNPs.

Poly lactic-*co*-glycolic acid (PLGA)	• Produce biodegradable products, lactic and glycolic acids [100] • Generally used in the production of nanovaccines, gene delivery and also the production of protein/peptide-based nanomedicines [100,101]
Poly lactic acid (PLA)	• PLA is biocompatible and biodegradable, breaking down to lactic acid in the body [102]
Gelatin	• Gelatin is a polyampholyte and is used in food products and also in medicine [103]
Polycyclic aromatic compounds (PACs)	• Upon biodegradation, PACs produce compounds toxic to the central nervous system [104]

5. Nanoparticles-mediated microbial targeting strategies

NPs may be considered by the human body as a foreign particle, so macrophages / phagocytic cells can remove them from blood circulation. Therefore, the surfaces of NPs should be modified to allow them to bypass the immune system of the body [105], so they can stay in the vascular system for a longer period of time and may reach their target safely [106]. PEGylation of NPs results in less interaction with phagocytes and being sustained longer in the circulation system [107]. Similarly, tocopherol PEG-1000 succinate can modify NPs, which then in turn exhibit increased adhesion towards tumor cell surfaces [108,109].

The conventional methods of drug delivery have several limitations, such as poor biodistribution, lack of selectivity and limited effectiveness [110,111]. Attachment of NPs to the therapeutic drug can make possible site-specific delivery and can reduce any undesirable side effects [112,113]. Representative clinical trials with small molecule-based targeting have been tabulated elsewhere [114,115].

5.1. Evidence for the attachment of NPs to therapeutic drugs for site-specific delivery

The use of nanotechnology in medicine is mostly for targeted drug delivery and also to reduce toxicity and side effects of the drugs. Until recently, it was not realized that these carrier systems themselves may cause risks to the patient. Therefore, a conceptual understanding of biological responses to nanomaterials is needed to develop [116–123].

6. Limitations

- The major concern is to maintain the proper size and shape of mono-dispersed NPs with stability during synthesis [124].
- NPs may accumulate in different bio-organs, which may cause problems in normal biological

function in the future [125].

- Since NPs may escape the immune challenge of the body, they may cause some sort of inflammation or toxicity [126].
- NPs can generate ROS, which are major contributors of inflammation, oxidative stress and apoptosis [127].
- Still, there are many other disadvantages in using NPs. For example, toxicity, environmental harm and organ damage may be caused by nanoparticles [128].
- Nanoparticles, after a threshold limit, may be toxic in nature and have to be degraded chemically.
- Some identified toxic mechanisms are through the production of ROS, which is cytotoxic, genotoxic, and neurotoxic, also. Those toxic effects of nanoparticles' depends on its type, size, surface area, shape, aspect ratio, surface coating, crystallinity, dissolution and agglomeration properties. Therefore, it is important to consider of any toxic effects of nanoparticles when it is being synthesized [129,130].

6.1. Limited availability and side effects

It has already been demonstrated that many nanoparticles in lab rats have resulted in lung inflammation and blood clotting, and in the human body they could trigger unwanted reactions like damage to cells and organs [131].

- Nanoparticles produce ROS and oxidative stress, which may cause neurodegenerative diseases such as Alzheimer's and Parkinson's diseases [132].
- Uptake of the nanoparticles through the olfactory epithelium can also take place, leading to epithelial cell injury, which can compromise the basic functions of the nose [133].
- Silica exposure causes oxidative stress. At high doses, silica induces membrane damage and cytotoxicity [134].
- Another limitation of using nanotechnology in medicine is its high expense. The use of nanomedicine would increase the cost of health care, which would make its access difficult for the poor [135]. Furthermore, the ethical, social and legal facets of nanomedicine need to be handled tactfully to gain civic backing. Though efforts are being made to increase the understanding of using nanomedicine in living beings, there is still ambiguity surrounding the risks that humans would be exposed to with its use. As a result, the clinical trials involving nanomedicine pose distinctive challenges. The leading ethical issues encompass assessing, managing and communicating the risk during clinical trials. To evade the possibility of public criticism, it becomes imperative to educate the people about the benefits and pitfalls of nanomedicine [136].

7. Nanoviricide (NV-387)

A new antiviral regimen could emerge as an antimicrobial. NV-387 is a self-assembling, uniform and tailorable linear homopolymer designed and designated as a TheraCour platform polymer. Here, the monomer is functionalized by attaching polyethylene glycol (PEG) connected covalently with a site-targeting ligand [137] (Figure 1).

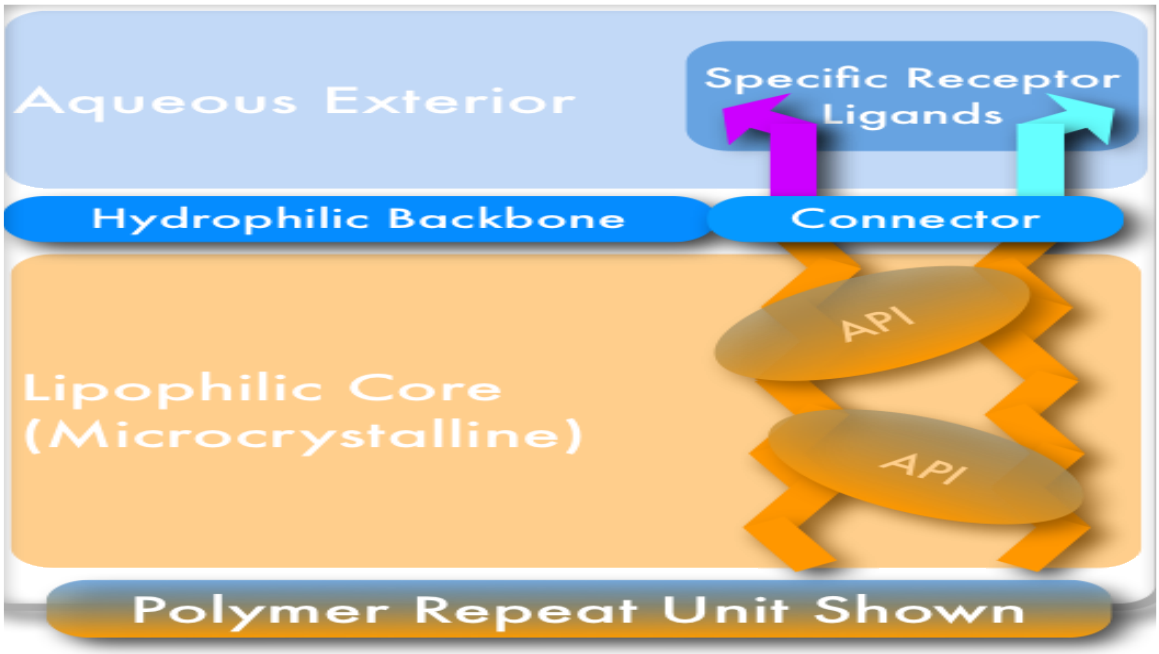

Figure 1. Schematic design of TheraCour NV-387 biopolymer.

This binding results in avidity and that force leads to passive fusion of the virus. Further, being encapsulated, the loaded drug can be released from the polymer backbone in a covalent system immediately [19,138,139], TheraCour platform polymer (NV-387) adds further advantages providing an extreme level of tailorability, also:

(A) Different ligands can be chosen for different targets.

(B) By changing the appropriate lipid length and balancing the PEG-monomer chain length, one can balance the hydrophobic/hydrophilic balance of the PEG Polymer. The longer lipid chain would be more suitable for dermal delivery of the drug as a cream or ointment. In contrast, short lipid chains would result more hydrophilic in nature and merely assist in conformational stability and adherence to the cell membrane.

(C) The rate of release of the API can be modified by tailoring the connector, like pH-sensing, or esterase or protease-specific functions, etc.

(D) The polymerization can be controlled within the limits (Flory equation), to provide a desirable clearance characteristics.

NV-387 is a non-crystalline semi-solid, off-white, waxy in texture material (at room temperature). It's theoretical molecular formula is $C_{104}H_{188}N_2O_{44}S_4$. The calculated formula weight of the polymer repeat unit (RU) is 2298.85 g/mol. The degree of polymerization, *"n"*, in P10M2DT (HDA)x (MMSA)y polymer is 8 ± 2 [19]. Pharmaceutical properties, formulations for injection, physical properties, and chemical properties are all available elsewhere [19].

7.1. Chemical charateristics of TheraCour biopolymer NV387

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Pharmaceutical properties, formulations for injection, physical properties, and chemical properties are all available elsewhere [19].

These materials have been shown to be capable of (a) site-directed (address-based) cell or virus targeting, (b) protective active pharmaceutical ingredient (API) encapsulation, (c) direct delivery of such encapsulated APIs into the address-specified cell or virus, (d) tailorable circulation lifetime and (e) sustained delivery characteristics, while at the same time being biocompatibility, non-toxic, non-immunogenic, and biodegradable [137].

7.2. Antiviral activity of TheraCour polymer, NV387:

In viral diseases, TheraCour platform based nanopolymer, NV-387, is noticeable. The therapeutic principle of NV-387 is based on its unique structure. As we know that the virus envelope carry a lipid membrane derived from the host cell membrane, the TheraCour polymer can attack viruses. Interestingly, no active API is required in this scenario if the ligand is properly chosen for making the biopolymer. Once the virus is attached by the micelle carrying ligands, lipid-lipid mixing essentially pulls the lipid membrane of the virus to the site of the attack and the virus gets dispersed, resulting a naked virus capsid that cannot infect cells (Figure 2) [139–143].

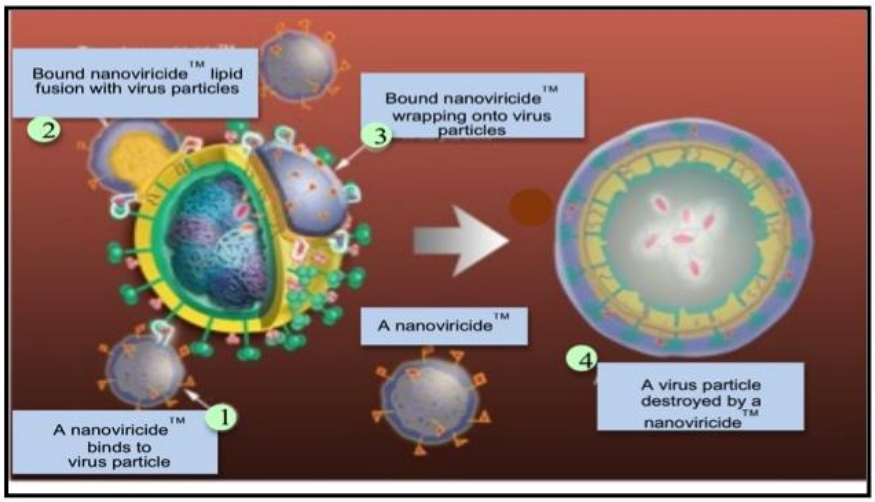

Figure 2. TheraCour Platform Technology based Nanoviricide is a Cell Mimic. A nanoviricide "looks like" a human cell to the virus. A nanoviricide micelle encapsulates the virus particle, even they mutate, and dismantle the virus structure. Step 1: A Nanoviricide™ binds to virus particle; Step 2: Lipid-Lipid fusion of Nanoviricide™ with virus particles; Step 3: Encapsulation of virus particle by Nanoviricide™; Step 4: Nanoviricide™ destroy the virus particle.

7.3. Nanoviricide polymeric micelle works against SARS-CoV-2

This model is the most advanced in the antiviral field. In particular, a drug, targeting for SARS-CoV-2 virus, NV-CoV-2 has completed preclinical studies including GLP Safety/Toxicology and is expected to enter human clinical trials soon. Another derivative, NV-CoV-2-R that encapsulates remdesivir within the core of NV-CoV-2 has shown effectiveness significantly surpassing that of the standard remdesivir formulation, which correlates with significantly improved pharmacokinetics of remdesivir *in vivo* in animal model studies. Some uses of TheraCour polymer are the entire drug use chain are shown in Tables 9 and 10.

Table 9. TheraCour drug solves problems in the drug use chain.

Vehicle	Administer	Blood Stream	Specific Targeting	Cell Membrane
TheraCour	Injection	Encapsulated	"Nano Velcro Snaking"	Take API Across
Liposomes	Infusion	Unstable	Not Much Success	Partial Effect
Cremophore	Infusion	Unstable	None	Some Effect?
Cydex	Infusion	Full Apart	None	None
PEGylation	Infusion	Stable	None	None
Polydrug	Injection	Stable	None	Depends
Polypeptides	Infusion Injection	Stable	None	None
Dendrimers	Infusion Injection	Toxic	Hard Sphere Few Points	May Take API Across

Table 10. TheraCour approach is a unique beneficiaL feature than other nanomedicine approaches.

Vehicle	TheraCour	Dendrimer	PLA/PLGA	Virus Based	Nanoshells, Metalics
Nanoscale Velcro Effect with Wrap-On	Yes	No	No	No	No
Technology Complexity	Simple	Complex	Medium	Complex	Complex
Safety	Safe	No	Medium	No	Medium
Specific Targeting	Yes: Flexible Wrap-ON	Yes: Limited by Hard Bal	No	No	May be
Detection	Yes	Yes	No	No	May be
Extended Release	Yes	May be	Yes	Yes	Accumulate
Controlled Release	Yes	May be	Yes	No	No
Efficacy Improvements	Yes, Very Large	Yes	No (Slow release only)	Yes but infectious	May be

SARS-CoV-2 belongs to a β-family of human coronavirus, which causes the severe lower tract infectious disease called COVID-19 [144]. Throughout the world this pandemic disease virus once evolved in November 2019 is continuously mutating to a new form and infecting people till date. The newer variants (Omicron BA.2) possess greater transmissibility with R0 as 12 [145].

The once effective drugs against SARS-CoV-2, like remdesivir (Gilead), molnupiravir (Merck), and Paxlovid™ (Pfizer) turnout with significant limitations in humans. Molnupiravir is reported as mutagenic and further has poor efficacy. Paxlovid is virostatic and the virus rebounds once the drug is withdrawn. Remdesivir is highly effective *in vitro* studies, however, *in vivo*, its efficacy is not satisfactory at all. This may be due to the instability of Remdesivir in the body circulation system [146,147].

NV-387 is highly effective in cell cultures against coronavirus hCoV-NL63 which like SARS-CoV-2, binds to the ACE2 cell receptor [140]. hCoV-229E that binds to a different cellular receptor, Aminopeptidase N (APN), also can be inhibited by NV-387, indicating itself as a broad-spectrum anti-coronavirus nanopolymer [20,147,148].

7.4. Encapsulation of the virus leads to its disintegration

The mechanism of *nanoviricide's* function is shown through electron photomicrographs (Figure 3). In this study, the murine cytomegalovirus (MCMV) was incubated with a *nanoviricide* containing sialic acid as a ligand. The light area at top right corner in Figure 3-II indicates that the lipid coat was deformed due to the binding of nanoviricide micelle in that area. The loss of the viral envelope results the lack of viral glycoproteins required for cellular entry and thus becomes non-infectious. Figure 3-III shows that only virion capsids remain as a result of the attack. We have demonstrated a convincing success of our drug NV-CoV-2-R which is an encapsulated remdesivir into the polymeric micelle (NV-CoV-2), in inhibiting the virus growth in animal models [139,142].

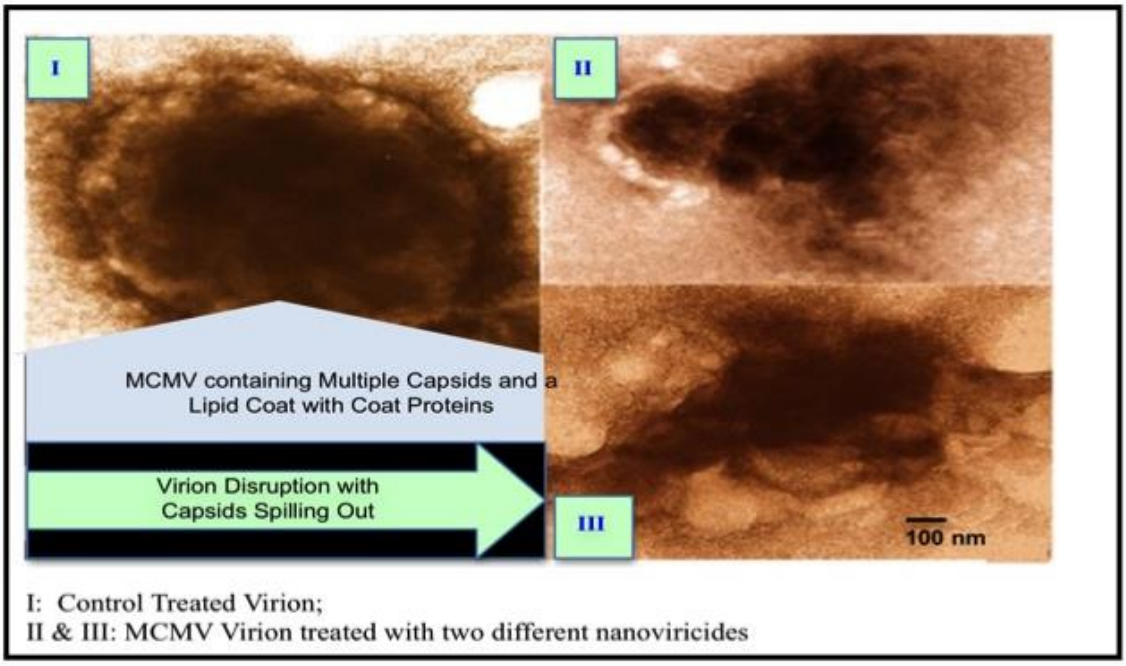

Figure 3. Effects of Two Different Nanoviricides Binding to Murine Cytomegalo virus (MCMV). I: Control virion: MCMV containing multiple capsids and a lipid coat with coat proteins; II & III: MCMV virion treated with two different nanoviricides. Virion disruption with capsids spilling out.

7.5. Safety Studies of NV-387, and NV-CoV-2

NV-387 is a TheraCour biopolymer (API) which on formulation was converted to a drug product against corona virus, and designated as NV-CoV-2. Safety studies on NV-387/NV-CoV-2 indicate that:

- No abnormal respiratory function or in neurobehavioral aspects were notices in all doses of the test compounds was observed in a rat model.
- No change in body temperature after the i.v. administration of NV-CoV-2 in rats.
- Heart rate, blood pressure, cardiac rhythm, and ECG parameters of cynomolgus monkeys were noticed normal after i.v. administration of NV-CoV-2 in them [19].
- Additionally, NV-387/NV-CoV-2, both were non-immunogenic, non-mutagenic, and non-genotoxic in a rat model.

8. Discussion and conclusions

The use of nanomaterials has been increasing, with concerns about drug-nanomaterial stability, biocompatibility and biodegradability; and there is interest in control and tailored payload release of the drug, without any side effects, and improving patient compliance [149,150]. With these concerns, recently, nucleic acid-based cross-linkers, as they are able to self-assemble into a stable 3-dimensional structures, have gained much attention [149–151]. In addition, nucleic acids can act as a targeting agent through engineered aptamer and drug payload carriers. They also have shown the ability to control the release of proteins [152–155]. Owing to these versatile characteristics, it is expected that nucleic acid-based hydrogels will be an important regimen in the future for targeted drug release.

Treatment of infectious disease with antibiotics becomes a challenge when the organisms evolve drug resistance. Therefore, discovery of methods of treatment and/or therapeutic regimen warrants great priority. Nanotechnology offers an innovative advance in NP-based bio-imaging, which can be used for early detection, diagnosis and treatment of many diseases, especially those that are caused by drug-resistant microorganisms. Nanoparticles have been shown, due to their unique size, shape, charge and surface area, to possess unique activity against different microbial infections. In addition, NPs find their other uses in drug delivery, gene delivery and targeted therapy of various diseases including cancer.

The development of nanotechnology for the synthesis of NPs/nanocomposites can be used to treat various diseases which are difficult to treat with the conventional approaches. However, the limitations and health risks that are associated with these nano-sized particles should not be ignored. Nowadays, in many cases, nanotherapy along with the conventional antibiotic therapy is used to overcome microbial resistance. NPs/nanocomposites may resolve difficulties in managing complicated diseases. However, safety and efficacy issues of NPs are now the main concern before their use in humans.

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Conflict of interest

Authors Anil Diwan and Jayant Tatake are employed by the company NanoViricides, Inc, and they declare no conflicts of interest between the companies, AllExcel, Inc, TheraCour Pharma, Inc. and NanoViricides, Inc. The research was funded by NanoViricides, Inc.

References

1. Sethi S, Murphy TF (2001) Bacterial infection in chronic obstructive pulmonary disease in 2000: a state-of-the-art review. *Clin Microbiol Rev* 14: 336–363. https://doi.org/10.1128/CMR.14.2.336-363.2001
2. Durand ML, Calderwood SB, Weber DJ, et al. (1993) Acute bacterial meningitis in adults-A review of 493 episodes. *N Engl J Med* 328: 21–28. https://doi.org/10.1056/NEJM199301073280104
3. Lara HH, Ayala-Nu~nez NV, Ixtepan-Turrent L, et al. (2010) Mode of antiviral action of silver nanoparticles against HIV-1. *J Nanobiotechno* 8: 1–10. https://doi.org/10.1186/1477-3155-8-1
4. Singh SR, Krishnamurthy NB, Mathew BB (2014) A review on recent diseases caused by microbes. *J Appl Environ Microbiol* 2: 106–115.
5. Laxminarayan R, Duse A, Wattal C, et al. (2013) Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 13: 1057–1098. https://doi.org/10.1016/S1473-3099(13)70318-9
6. Friedman H, Newton C, Klein TW (2003) Microbial infections, immunomodulation, and drugs of abuse. *Clin Microbiol Rev* 16: 209–219. https://doi.org/10.1128/CMR.16.2.209-219.2003
7. Atolani O, Baker MT, Adeyemi OS, et al. (2020) Covid-19: critical discussion on the applications and implications of chemicals in sanitizers and disinfectants. *EXCLI J* 19: 785–799.
8. Gurunathan S, Han JW, Kwon DN, et al. (2014) Enhanced antibacterial and antibiofilm activities of silver nanoparticles against Gram-negative and Gram-positive bacteria. *Nanoscale Res Lett* 9: 1–17. https://doi.org/10.1186/1556-276X-9-373
9. Yien L, Zin NM, Sarwar A, et al. (2012) Antifungal activity of chitosan nanoparticles and correlation with their physical properties. *Int J Biomater* 632698. https://doi.org/10.1155/2012/632698
10. Sobhani Z, Samani SM, Montaseri H, et al. (2017) Nanoparticles of chitosan loaded ciprofloxacin: fabrication and antimicrobial activity. *Adv Pharmaceut Bull* 7: 427. https://doi.org/10.15171/apb.2017.051
11. Rai A, Prabhune A, Perry CC (2010) Antibiotic mediated synthesis of gold nanoparticles with potent antimicrobial activity and their application in antimicrobial coatings. *J Mater Chem* 20: 6789–6798. https://doi.org/10.1039/c0jm00817f
12. Alshammari F, Alshammari B, Moin A, et al. (2021) Ceftriaxone mediated synthesized gold nanoparticles: A nano-therapeutic tool to target bacterial resistance. *Pharmaceutics* 13: 1896. https://doi.org/10.3390/pharmaceutics13111896
13. Cepas V, López Y, Gabasa Y, et al. (2019) Inhibition of bacterial and fungal biofilm formation by 675 extracts from microalgae and cyanobacteria. *Antibiotics (Basel)* 8: 77. https://doi.org/10.3390/antibiotics8020077
14. Cremonini E, Zonaro E, Donini M, et al. (2016) Biogenic selenium nanoparticles: characterization, antimicrobial activity and effects on human dendritic cells and fibroblasts. *Microb Biotechnol* 9: 758–771. https://doi.org/10.1111/1751-7915.12374
15. Haghighi F, Roudba Mohammadir S, Mohammadi P, et al. (2013) Antifungal acitivity of TiO_2 nanoparticles and EDTA on Candida abicans Biofilms. *Infect Epidemiol Med* 1: 133–138.
16. Singh P, Singh D, Sa P, et al. (2021) Insights from nanotechnology in COVID-19: prevention, detection, therapy and immunomodulation. *Nanomedicine (Lond)* 16: 1219–1235. https://doi.org/10.2217/nnm-2021-0004

17. Singh CK, Sodhi KK (2023) The emerging significance of nanomedicine-based approaches to fighting COVID-19 variants of concern: A perspective on the nanotechnology's role in COVID-19 diagnosis and treatment. *Front Nanotechnol* 4: 1084033. https://doi.org/10.3389/fnano.2022.1084033
18. Yang D (2021) Application of nanotechnology in the COVID-19 pandemic. *Int J Nanomedicine* 16: 623–649. https://doi.org/10.2147/IJN.S296383
19. Diwan A, Chakraborty A, Vijetha Chiniga V, et al. (2022) Dual effects of NV-CoV-2 biomimetic polymer: An antiviral regimen against COVID-19. *PLOS One* 17: e0278963. https://doi.org/10.1371/journal.pone.0278963. https://doi.org/10.1371/journal.pone.0278963
20. Chakraborty A, Diwan A, Arora V, et al. (2022) Mechanism of antiviral activities of nanoviricide's platform technology based biopolymer (NV-CoV-2). *AIMS Public Health* 9: 415–422. https://doi.org/10.3934/publichealth.2022028
21. Mubeen B, Ansar AN, Rasool R, et al. (2021) Nanotechnology as a novel approach in combating microbes providing an alternative to antibiotics. *Antibiotics (Basel)* 10: 1473. https://doi.org/10.3390/antibiotics10121473
22. Hung YP, Chen YF, Tsai PJ, et al. (2021) Advances in the application of nanomaterials as treatments for bacterial infectious diseases. *Pharmaceutics* 13: 1913. https://doi.org/10.3390/pharmaceutics13111913
23. Ozdal M, Gurkok S (2022) Recent advances in nanoparticles as antibacterial agent. *ADMET DMPK* 10: 115–129. https://doi.org/10.5599/admet.1172
24. Hussain FS, Abro NQ, Ahmed N, et al. (2022) Nano antivirals: A comprehensive review. *Front Nanotechnol* 4: 1064615. https://doi.org/10.3389/fnano.2022.1064615
25. Nami S, Aghebati-Maleki A, Aghebati-Maleki L (2021) Current applications and prospects of nanoparticles for antifungal drug delivery. *EXCLI J* 20: 562–584.
26. Khan I, Saeed K, Khan I (2017) Nanoparticles: properties, applications and toxicities. *Arab J Chem* 12: 908–931. https://doi.org/10.1016/j.arabjc.2017.05.011
27. Song X, Bayati P, Gupta M, et al. (2021) Fracture of magnesium matrix nanocomposites-a review. *Int J Lightweight Mater Manufact* 4: 67–98. https://doi.org/10.1016/j.ijlmm.2020.07.002
28. Vert M, Doi Y, Hellwich KH, et al. (2012) Terminology for biorelated polymers and applications (IUPAC Recommendations 2012). *Pure Appl Chem* 84: 377–410. https://doi.org/10.1515/amma-2016-0032
29. Von Nussbaum F, Brands M, Hinzen B, et al. (2006) Antibacterial natural products in medicinal chemistry—Exodus or revival? *Angew Chem Int Ed* 45: 5072–5129. https://doi.org/10.1002/anie.200600350
30. Akhtar M, Swamy MK, Umar A, et al. (2015) Biosynthesis and characterization of silver nanoparticles from methanol leaf extract of Cassia didymobotyra and assessment of their antioxidant and antibacterial activities. *J Nanosci Nanotechnol* 15: 9818–9823. https://doi.org/10.1166/jnn.2015.10966
31. Fröhlich E, Salar-Behzadi S (2014) Toxicological assessment of inhaled nanoparticles: Role of in vivo, ex vivo, in vitro, and in silico studies. *Int J Mol Sci* 15: 4795–4822. https://doi.org/10.3390/ijms15034795

32. Qiu Y, Xu D, Sui G, et al. (2020) Gentamicin decorated phosphatidylcholine-chitosan nanoparticles against biofilms and intracellular bacteria. *Int J Biol Macromol* 156: 640–647. https://doi.org/10.1016/j.ijbiomac.2020.04.090
33. Evangelista TF, Andrade GR, Nascimento KN, et al. (2020) Supramolecular polyelectrolyte complexes based on cyclodextrin-grafted chitosan and carrageenan for controlled drug release. *Carbohydr Polym* 245: 116592. https://doi.org/10.1016/j.carbpol.2020.116592
34. Walvekar P, Gannimani R, Salih M, et al. (2019) Self-assembled oleylamine grafted hyaluronic acid polymersomes for delivery of vancomycin against methicillin resistant Staphylococcus aureus (MRSA). *Colloids Surf B Biointerfaces* 182: 110388. https://doi.org/10.1016/j.colsurfb.2019.110388
35 Ejaz S, Ihsan A, Noor T, et al. (2020) Mannose functionalized chitosan nanosystems for enhanced antimicrobial activity against multidrug resistant pathogens. *Polym Test* 91:106814. https://doi.org/10.1016/j.polymertesting.2020.106814
36. Ucak S, Sudagidan M, Borsa BA, et al. (2020) Inhibitory effects of aptamer targeted teicoplanin encapsulated PLGA nanoparticles for Staphylococcus aureus strains. *World J Microbiol Biotechnol* 36: 69. https://doi.org/10.1007/s11274-020-02845-y
37. Vrouvaki I, Koutra E, Kornaros M, et al. (2020) Polymeric nanoparticles of pistacia lentiscus var. chia essential oil for cutaneous applications. *Pharmaceutics* 12: 353. https://doi.org/10.3390/pharmaceutics12040353
38. Gherasim O, Grumezescu AM, Grumezescu V, et al. (2020) Bioactive surfaces of polylactide and silver nanoparticles for the prevention of microbial contamination. *Materials* 13: 768. https://doi.org/10.3390/ma13030768
39. Grumezescu AM, Stoica AE, Dima-Balcescu MS, et al. (2019) Electrospun polyethylene terephthalate nanofibers loaded with silver nanoparticles: novel approach in anti-infective therapy. *J Clin Med* 8: 1039. https://doi.org/10.3390/jcm8071039
40. Khandelwal N, Kaur G, Kumara N, et al. (2014) Application of silver nanoparticles in viral inhibition: A new hope for antivirals. *Dig J Nanomater Biostruct* 9: 175–186. https://nanogo.co.uk/wp-content/uploads/2021/12/application-of-nanosilver.pdf
41. Alamdaran M, Movahedi B, Mohabatkar H, et al. (2018) In-vitro study of the novel nanocarrier of chitosan-based nanoparticles conjugated HIV-1 P24 protein-derived peptides. *J Mol Liq* 265: 243–250. https://doi.org/10.1016/j.molliq.2018.05.137
42. Belgamwar AV, Khan SA, Yeole PG (2019) Intranasal dolutegravir sodium loaded nanoparticles of hydroxypropyl-beta-cyclodextrin for brain delivery in Neuro-AIDS. *J Drug Deliv Sci Technol* 52: 1008–1020. https://doi.org/10.1016/j.jddst.2019.06.014
43. Costa AF, Araujo DE, Cabral MS, et al. (2018) Development, characterization, and *in vitro-in vivo* evaluation of polymeric nanoparticles containing miconazole and farnesol for treatment of vulvovaginal candidiasis. *Med Mycol* 7: 52–62. https://doi.org/10.1093/mmy/myx155
44. Reddy YC (2018) Formulation and evaluation of chitosan nanoparticles for improved efficacy of itraconazole antifungal drug. *Asian J Pharm Clin Res* 11: 147–152. https://doi.org/10.22159/ajpcr.2018.v11s4.31723
45. Sombra FM, Richter AR, De Araújo AR, et al. (2020) Development of amphotericin B-loaded propionate Sterculia striata polysaccharide nanocarrier. *Int J Biol Macromol* 146: 1133–1141. https://doi.org/10.1016/j.ijbiomac.2019.10.053

46. Real D, Hoffmann S, Leonardi D, et al. (2018) Chitosan-based nanodelivery systems applied to the development of novel triclabendazole formulations. *PLOS One* 13: e0207625. https://doi.org/10.1371/journal.pone.0207625
47. Durak S, Arasoglu T, Ates SC, et al. (2020) Enhanced antibacterial and antiparasitic activity of multifunctional polymeric nanoparticles. *Nanotechnology* 31: 175705. https://doi.org/10.1088/1361-6528/ab6ab9
48. Binder U, Aigner M, Risslegger B, et al. (2019) Minimal Inhibitory concentration (mic)-phenomena in *candida albicans* and their impact on the diagnosis of antifungal resistance. *J Fungi (Basel)* 5: 83. https://doi.org/10.3390/jof5030083
49. Kesharwani P, Fatima M, Singh V, et al. (2022) Itraconazole and difluorinated-curcumin containing chitosan nanoparticle loaded hydrogel for amelioration of onychomycosis. *Biomimetics (Basel)* 7: 206. https://doi.org/10.3390/biomimetics7040206
50. Butani D, Yewale C, Misra A (2016) Topical amphotericin B solid lipid nanoparticles: Design and development. *Colloids Surf B* 139: 17–24. https://doi.org/10.1016/j.colsurfb.2015.07.032
51. Souto E, Wissing S, Barbosa C, et al. (2004) Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. *Int J Pharm* 278: 71–7. https://doi.org/10.1016/j.ijpharm.2004.02.032
52. Cassano R, Ferrarelli T, Mauro MV, et al. (2016) Preparation, characterization and in vitro activities evaluation of solid lipid nanoparticles based on PEG-40 stearate for antifungal drugs vaginal delivery. *Drug Deliv* 23: 1037–46. https://doi.org/10.3109/10717544.2014.932862
53. Sanna V, Gavini E, Cossu M, et al. (2007) Solid lipid nanoparticles (SLN) as carriers for the topical delivery of econazole nitrate: *In-vitro* characterization, ex-vivo and in-vivo studies. *J Pharm Pharmacol* 59: 1057–64. https://doi.org/10.1211/jpp.59.8.0002
54. Bhalekar MR, Pokharkar V, Madgulkar A, et al. (2009) Preparation and evaluation of miconazole nitrate-loaded solid lipid nanoparticles for topical delivery. *AAPS PharmSciTech* 10: 289–96. https://doi.org/10.1208/s12249-009-9199-0
55. Jain S, Jain S, Khare P, et al. (2010) Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. *Drug Deliv.* 17: 443–451. https://doi.org/10.3109/10717544.2010.483252
56. Kenechukwu FC, Attama AA, Ibezim EC (2017) Novel solidified reverse micellar solution-based mucoadhesive nano lipid gels encapsulating miconazole nitrate-loaded nanoparticles for improved treatment of oropharyngeal candidiasis. *J Microencapsul* 34: 592–609. https://doi.org/10.1080/02652048.2017.1370029
57. Mahato R, Tai W, Cheng K (2011) Prodrugs for improving tumor targetability and efficiency. *Adv Drug Deliv Rev* 63: 659–70. https://doi.org/10.1016/j.addr.2011.02.002
58. Kumar R, Sinha VR (2016) Solid lipid nanoparticle: An efficient carrier for improved ocular permeation of voriconazole. *Drug Dev Ind Pharm* 42: 1956–67. https://doi.org/10.1080/03639045.2016.1185437
59. Füredi P, Pápay ZE, Kovács K, et al. (2017) Development and characterization of the voriconazole loaded lipid-based nanoparticles. *J Pharm Biomed Anal* 132: 184–9. https://doi.org/10.1016/j.jpba.2016.09.047
60. El-Housiny S, Shams Eldeen MA, El-Attar YA, et al. (2018) Fluconazole-loaded solid lipid nanoparticles topical gel for treatment of pityriasis versicolor: formulation and clinical study. *Drug Deliv* 25: 78–90. https://doi.org/10.1080/10717544.2017.1413444

61. Anurak L, Chansiri G, Peankit D, et al. (2011) Griseofulvin solid lipid nanoparticles based on microemulsion technique. *Adv Mater Res* 197–198: 47–50. https://doi.org/10.4028/www.scientific.net/AMR.197-198.47
62. Ahmad A, Wei Y, Syed F, et al. (2016) Amphotericin B-conjugated biogenic silver nanoparticles as an innovative strategy for fungal infections. *Microb Pathol* 99: 271–81. https://doi.org/10.1016/j.micpath.2016.08.031
63. Tutaj K, Szlazak R, Szalapata K, et al. (2016) Amphotericin B-silver hybrid nanoparticles: Synthesis, properties and antifungal activity. *Nanomedicine* 12: 1095–103. https://doi.org/10.1016/j.nano.2015.12.378
64. Hussain MA, Ahmed D, Anwar A, et al. (2019) Combination therapy of clinically approved antifungal drugs is enhanced by conjugation with silver nanoparticles. *Int Microbiol* 22: 239–46. https://doi.org/10.1007/s10123-018-00043-3
65. Mussin JE, Roldán MV, Rojas F, et al. (2019) Antifungal activity of silver nanoparticles in combination with ketoconazole against Malassezia furfur. *AMB Express* 9: 131. https://doi.org/10.1186/s13568-019-0857-7
66. Souza AC, Nascimento AL, de Vasconcelos NM, et al. (2015) Activity and in vivo tracking of Amphotericin B loaded PLGA nanoparticles. *Eur J Med Chem* 95: 267–276. https://doi.org/10.1016/j.ejmech.2015.03.022
67. Vásquez Marcano RGDJ, Tominaga TT, Khalil NM, et al. (2018) Chitosan functionalized poly (ε-caprolactone) nanoparticles for amphotericin B delivery. *Carbohydr Polym* 202: 345–354. https://doi.org/10.1016/j.carbpol.2018.08.142
68. Chhonker YS, Prasad YD, Chandasana H, et al. (2015) Amphotericin-B entrapped lecithin/chitosan nanoparticles for prolonged ocular application. *Int J Biol Macromol* 72: 1451–8. https://doi.org/10.1016/j.ijbiomac.2014.10.014
69. Bhattacharjee S, Joshi R, Chughtai AA, et al. (2021) Graphene-and nanoparticle-embedded antimicrobial and biocompatible cotton/silk fabrics for protective clothing. *ACS Appl Bio Mater* 4: 6175–6185. https://doi.org/10.1021/acsabm.1c00508. 10.1021/acsabm.1c00508.
70. Kharaghani D, Dutta D, Gitigard P, et al. (2019) Development of antibacterial contact lenses containing metallic nanoparticles. *Polym Test* 79: 106034. https://doi.org/10.1016/j.polymertesting.2019.106034.
71. Kalita S, Kandimalla R, Bhowal AC, et al. (2018) Functionalization of β-lactam antibiotic on lysozyme capped gold nanoclusters retrogress MRSA and its persisters following awakening. *Sci Rep* 8: 1–13. https://doi.org/10.1038/s41598-018-22736-5
72. Konop M, Czuwara J, Kłodzińska E, et al. (2020) Evaluation of keratin biomaterial containing silver nanoparticles as a potential wound dressing in full-thickness skin wound model in diabetic mice. *J Tissue Eng Regen Med* 14: 334–346. https://doi.org/10.1002/term.2998
73. Gupta A, Briffa SM, Swingler S, et al. (2020) Synthesis of silver nanoparticles using curcumin-cyclodextrins loaded into bacterial cellulose-based hydrogels for wound dressing applications. *Biomacromolecules* 21: 1802–1811. https://doi.org/10.1021/acs.biomac.9b01724
74. Urbán P, Liptrott NJ, Bremer S (2019) Overview of the blood compatibility of nanomedicines: A trend analysis of in vitro and in vivo studies. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 11: e1546. https://doi.org/10.1002/wnan.1546

75. de la Harpe KM, Kondiah PPD, Choonara YE, et al. (2019) The hemocompatibility of nanoparticles: A review of cell-nanoparticle interactions and hemostasis. *Cells* 8: 1209. https://doi.org/10.3390/cells8101209
76. Guo S, Shi Y, Liang Y, et al. (2021) Relationship and improvement strategies between drug nanocarrier characteristics and hemocompatibility: What can we learn from the literature. *Asian J Pharm Sci* 16: 551–576. https://doi.org/10.1016/j.ajps.2020.12.002
77. Mikušová V, Mikuš P (2021) Advances in chitosan-based nanoparticles for drug delivery. *Int J Mol Sci* 22: 9652. https://doi.org/10.3390/ijms22179652
78. Pathak N, Singh P, Singh PK, et al. (2022) Biopolymeric nanoparticles based effective delivery of bioactive compounds toward the sustainable development of anticancerous therapeutics. *Front Nutr* 9: 963413. https://doi.org/10.3389/fnut.2022.963413
79. Chen HT, Neerman MF, Parrish AR, et al. (2004) Cytotoxicity, hemolysis, and acute in vivo toxicity of dendrimers based on melamine, candidate vehicles for drug delivery. *J Am Chem Soc* 126: 10044–10048. https://doi.org/10.1021/ja048548j
80. Jia YP, Ma BY, Wei XW, et al. (2017) The in vitro and in vivo toxicity of gold nanoparticles, *Chin Chem Lett* 28: 691–702. https://doi.org/10.1016/j.cclet.2017.01.021.
81. Chetyrkina MR, Fedorov FS, Nasibulin AG (2022) *In vitro* toxicity of carbon nanotubes: a systematic review. *RSC Adv* 25: 16235–16256. https://doi.org/10.1039/D2RA02519A
82. Mahmoudi M, Hofmann H, Rothen-Rutishauser B, et al. (2012) Petri-Assessing the *in vitro* and *in vivo* Toxicity of Superparamagnetic Iron Oxide Nanoparticles**.** *Chem Rev* 112: 2323–2338. https://doi.org/10.1021/cr2002596
83. Chen L, Liu J, Zhang Y, et al. (2018) The toxicity of silica nanoparticles to the immune system. *Nanomedicine* 13: 1939–1962. https://doi.org/10.2217/nnm-2018-0076
84. Hadipour Moghaddam SP, Mohammadpour R, Ghandehari H (2019) *In vitro* and *in vivo* evaluation of degradation, toxicity, biodistribution, and clearance of silica nanoparticles as a function of size, porosity, density, and composition. *J Control Release* 311–312: 1–15. https://doi.org/10.1016/j.jconrel.2019.08.028
85. Zhang XF, Shen W, Gurunathan S (2016) Silver nanoparticle-mediated cellular responses in various cell lines: An *in vitro* model. *Int J Mol Sci* 17: 1603. https://doi.org/10.3390/ijms17101603
86. Yuan YG, Zhang S, Hwang JY, et al. (2018) Silver nanoparticles potentiates cytotoxicity and apoptotic potential of camptothecin in human cervical cancer cells. *Oxid Med Cell Longev* 18: 6121328. https://doi.org/10.1155/2018/6121328
87. Rim KT, Song SW, Kim HY (2013) Oxidative DNA damage from nanoparticle exposure and its application to workers' health: a literature review. *Saf Health Work* 4: 177–186. https://doi.org/10.1016/j.shaw.2013.07.006
88. Wen H, Dan M, Yang Y, et al. (2017) Acute toxicity and genotoxicity of silver nanoparticle in rats. *PLOS One* 2: e0185554. https://doi.org/10.1371/journal.pone.0185554
89. Hassanen EI, Khalaf AA, Tohamy AF, et al. (2019) Toxicopathological and immunological studies on different concentrations of chitosan-coated silver nanoparticles in rats. *Int J Nanomedicine* 14: 4723–4739. https://doi.org/10.2147/IJN.S207644
90. Panyam J, Labhasetwar V (2003) Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Adv Drug Deliv Rev* 55: 329–347. https://doi.org/10.1016/S0169-409X(02)00228-4

91. Almofti MR, Ichikawa T, Yamashita K, et al. (2003) Silver ion induces a cyclosporine a-insensitive permeability transition in rat liver mitochondria and release of apoptogenic cytochrome C. *J Biochem* 134: 43–49. https://doi.org/10.1093/jb/mvg111
92. Iancu SD, Albu C, Chiriac L, et al. (2020) Assessment of gold-coated iron oxide nanoparticles as negative T2 contrast agent in small animal MRI studies. *Int J Nanomedicine* 4811–4824. https://doi.org/10.2147/IJN.S253184
93. Akhlaghi N, Najafpour-Darzi G (2021) Manganese ferrite ($MnFe_2O_4$) Nanoparticles: From synthesis to application-A review. *J Ind Eng Chem* 103: 292–304. https://doi.org/10.1016/j.jiec.2021.07.043.
94. Ganapathe LS, Mohamed Md A, Yunus RM (2020) Magnetite (Fe_3O_4) Nanoparticles in biomedical application: from synthesis to surface functionalisation. *Magnetochemistry* 6: 68. https://doi.org/10.3390/magnetochemistry6040068
95. Liu Z, Liu Y, Liu S, et al. (2021) The effects of TiO_2 nanotubes on the biocompatibility of 3D printed Cu-bearing TC4 alloy. *Mater Des* 207: 109831. https://doi.org/10.1016/j.matdes.2021.109831.
96. Andrade RGD, Ferreira D, Veloso SRS, et al. (2022) Synthesis and cytotoxicity assessment of citrate-coated calcium and manganese ferrite nanoparticles for magnetic hyperthermia. *Pharmaceutics* 14: 2694. https://doi.org/10.3390/pharmaceutics14122694
97. Rudramurthy GR, Swamy MK, Sinniah UR, et al. (2016) Nanoparticles: alternatives against drug-resistant pathogenic microbes. *Molecules* 21: 836. https://doi.org/10.3390/molecules21070836
98. Shiri S, Abbasi N, Alizadeh K, et al. (2019) Novel and green synthesis of a nanopolymer and its use as a drug delivery system of silibinin and silymarin extracts in the olfactory ensheathing cells of rats in normal and high-glucose conditions. *RSC Adv* 9: 38912–38927. https://doi.org/10.1039/C9RA05608D
99. Sharma S, Sudhakara P, Singh J, et al. (2021) Critical review of biodegradable and bioactive polymer composites for bone tissue engineering and drug delivery applications. *Polymers (Basel)* 13: 2623. https://doi.org/10.3390/polym13162623
100. Makadia HK, Siegel SJ (2011) Poly Lactic-co-Glycolic Acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers (Basel)* 3: 1377–1397. https://doi.org/10.3390/polym3031377
101. Félix Lanao RP, Jonker AM, Wolke JG, et al. (2013) Physicochemical properties and applications of poly(lactic-co-glycolic acid) for use in bone regeneration. *Tissue Eng Part B Rev* 19: 380–390. https://doi.org/10.1089/ten.teb.2012.0443
102. da Silva D, Kaduri M, Poley M, et al. (2018) Biocompatibility, biodegradation and excretion of polylactic acid (PLA) in medical implants and theranostic systems. *Chem Eng J* 340: 9–14. https://doi.org/10.1016/j.cej.2018.01.010
103. Ramos DP, Sarjinsky S, Alizadehgiashi M, et al. (2019) Polyelectrolyte vs polyampholyte behavior of composite chitosan/ gelatin films. *ACS Omega* 4: 8795−8803. http://pubs.acs.org/journal/acsodf
104. Olasehinde TA, Olaniran AO (2022) Neurotoxicity of polycyclic aromatic hydrocarbons: a systematic mapping and review of neuropathological mechanisms. *Toxics* 10: 417. https://doi.org/10.3390/toxics10080417

105. Liu Y, Hardie J, Zhang X, et al. (2017) Effects of engineered nanoparticles on the innate immune system. *Semin Immunol* 34: 25–32. https://doi.org/10.1016/j.smim.2017.09.011
106. Corbo C, Molinaro R, Parodi A, et al. (2016) The impact of nanoparticle protein corona on cytotoxicity, immunotoxicity and target drug delivery. *Nanomedicine (Lond)* 11: 81–100. https://doi.org/10.2217/nnm.15.188
107. Suk JS, Xu Q, Kim N, et al. (2016) PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Adv Drug Deliv Rev* 99: 28–51. https://doi.org/10.1016/j.addr.2015.09.012
108. Tan X, Fang Y, Ren Y, et al. (2019) D-α-tocopherol polyethylene glycol 1000 succinate-modified liposomes with an siRNA corona confer enhanced cellular uptake and targeted delivery of doxorubicin via tumor priming. *Int J Nanomedicine* 14: 1255–1268. https://doi.org/10.2147/IJN.S191858
109. Neophytou CM, Mesaritis A, Gregoriou G, et al. (2019) d-a-Tocopheryl Polyethylene Glycol 1000 Succinate and a small-molecule Survivin suppressant synergistically induce apoptosis in SKBR3 breast cancer cells. *Sci Rep* 9: 14375. https://doi.org/10.1038/s41598-019-50884-9
110. Dang Y, Guan J (2020) Nanoparticle-based drug delivery systems for cancer therapy. *Smart Mater Med* 1: 10–19. https://doi.org/10.1016/j.smaim.2020.04.001
111. Adepu S, Ramakrishna S (2021) Controlled drug delivery systems: current status and future directions. *Molecules* 26: 5905. https://doi.org/10.3390/molecules26195905
112. Yu B, Tai HC, Xue W, et al. (2010) Receptor-targeted nanocarriers for therapeutic delivery to cancer. *Mol Membr Biol* 27: 286–298. https://doi.org/10.3109/09687688.2010.521200
113. Yu H, Yang Z, Li F, et al. (2020) Cell-mediated targeting drugs delivery systems. *Drug Deliv* 27: 1425–1437. https://doi.org/10.1080/10717544.2020.1831103
114. Zhao Z, Ukidve A, Kim J, et al. (2020) Targeting strategies for tissue-specific drug delivery. *Cell* 181: 2020. https://doi.org/10.1016/j.cell.2020.02.001
115. Manzari MT, Shamay Y, Kiguchi H, et al. (2021) Targeted drug delivery strategies for precision medicines. *Nat Rev Mater* 6: 351–370. https://doi.org/10.1038/s41578-020-00269-6
116. Mitchell MJ, Billingsley MM, Haley RM, et al. (2021) Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov* 20: 101–124. https://doi.org/10.1038/s41573-020-0090-8
117. Xie J, Lee S, Chen X (2010) Nanoparticle-based theranostic agents. *Adv Drug Deliv Rev* 62: 1064–1079. https://doi.org/10.1016/j.addr.2010.07.009
118. Chatterjee DK, Diagaradjane P, Krishnan S (2011) Nanoparticle-mediated Hyperthermia in Cancer Therapy. *Ther Deliv* 2: 1001–1014. https://doi.org/10.4155/tde.11.72
119. Jacque D, Martínez Maestro L, del Rosal B, et al. (2014) Nanoparticles for photothermal therapies. *Nanoscale* 6: 9494–9530. https://doi.org/10.1039/C4NR00708E
120. Zhou Y, Quan G, Wu Q, et al. (2018) Mesoporous silica nanoparticles for drug and gene delivery. *Acta Pharmaceutica Sinica B* 8: 165–177. https://doi.org/10.1016/j.apsb.2018.01.007.
121 Li Z, Barnes JC, Bosoy A, et al. (2012) Mesoporous silica nanoparticles in biomedical applications. *Chem Soc Rev* 41: 2590–2605. https://doi.org/10.1039/c1cs15246g
122. De Jong WH, Borm PJ (2008) Drug delivery and nanoparticles:applications and hazards. *Int J Nanomedicine.* 3: 133–149. https://doi.org/10.2147/IJN.S596
123. Patra JK, Das G, Fraceto LF, et al. (2018) Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol* 16: 71. https://doi.org/10.1186/s12951-018-0392-8

124. Masarudin MJ, Cutts SM, Evison BJ, et al. (2015) Factors determining the stability, size distribution, and cellular accumulation of small, monodisperse chitosan nanoparticles as candidate vectors for anticancer drug delivery: application to the passive encapsulation of [(14)C]-doxorubicin. *Nanotechnol Sci Appl* 8: 67–80. https://doi.org/10.2147/NSA.S91785
125. Ajdary M, Moosavi MA, Rahmati M, et al. (2018) Health concerns of various nanoparticles: a review of their *in vitro* and *in vivo* toxicity. *Nanomaterials (Basel)* 8: 634. https://doi.org/10.3390/nano8090634
126. Ray P, Haideri N, Haque I, et al. (2021) The impact of nanoparticles on the immune system: a gray zone of nanomedicine. *J Immunological Sci* 5: 19–33. https://doi.org/10.29245/2578-3009/2021/1.1206
127. Abdal Dayem A, Hossain MK, Lee SB, et al. (2017) The role of reactive oxygen species (ros) in the biological activities of metallic nanoparticles. *Int J Mol Sci* 18: 120. https://doi.org/10.3390/ijms18010120
128. Ray PC, Yu H, Fu PP (2009) Toxicity and environmental risks of nanomaterials: challenges and future needs. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 27: 1–35. https://doi.org/10.1080/10590500802708267
129. Egbuna C, Parmar VK, Jeevanandam J, et al. (2021) Toxicity of nanoparticles in biomedical application: nanotoxicology. *J Toxicol* 2021:9954443: 1–21 https://doi.org/10.1155/2021/9954443.
130. Huang YW, Cambre M, Lee HJ (2017) The toxicity of nanoparticles depends on multiple molecular and physicochemical mechanisms. *Int J Mol Sci* 18: 2702. https://doi.org/10.3390/ijms18122702
131. You DJ, Bonner JC (2020) Susceptibility factors in chronic lung inflammatory responses to engineered nanomaterials. *Int J Mol Sci* 21: 7310. https://doi.org/10.3390/ijms21197310
132. Singh A, Kukreti R, Saso L, et al. (2019) Oxidative stress: A key modulator in neurodegenerative diseases. *Molecules* 24: 1583. https://doi.org/10.3390/molecules24081583
133. Gänger S, Schindowski K (2018) Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. *Pharmaceutics* 10: 116. https://doi.org/10.3390/pharmaceutics10030116
134. Guo C, Xia Y, Niu P, et al. (2015) Silica nanoparticles induce oxidative stress, inflammation, and endothelial dysfunction in vitro via activation of the MAPK/Nrf2 pathway and nuclear factor-κB signaling. *Int J Nanomedicine* 10: 1463–1477. https://doi.org/10.2147/IJN.S76114
135. Uskoković V (2021) Nanomedicine for the poor: a lost cause or an idea whose time has yet to come? *Nanomedicine (Lond)* 16: 1203–1218. https://doi.org/10.2217/nnm-2021-0024
136. Kwatra Shubhika (2013). Nanotechnology and medicine–The upside and the downside*Int. J Drug Dev Res* 5: 1–10. http://www.ijddr.in
137. Diwan A, Tatake J, Chakraborty A (2022) Therapeutic uses of TheraCour™ polymeric nanomicelles against cancer, infectious diseases and more. In: Chaughule, R.S., Patkar, D.P., Ramanujan R.V., *Nanomaterials for Cancer Detection Using Imaging Techniques and Their Clinical Applications*. 1 Ed., *Springer Nature*, 473–506. https://doi.org/10.1007/978-3-031-09636-5_17
138. Chakraborty A, Diwan A, Barton R, et al. (2022) A new antiviral regimen against sars-cov-2 based on nanoviricide's biopolymer (NV-CoV-2). *Front Nanotechnol* 4: 891605. https://doi.org/10.3389/fnano.2022.891605

139. Barton RW, Tatake JG, Diwan AR (2011) Nanoviricides-A novel approach to antiviral therapeutics. In: Reisner, D.E., *Bionanotechnology II,* 1 Ed., CRC Press, 141–154.
140. Chakraborty A, Diwan A (2020) NL-63: A better surrogate virus for studying SARS-CoV-2. *Integr Mol Med* 7: 1–9. https://doi.org/10.15761/IMM.1000408
141. NanoViricides, Inc., Pan-coronavirus COVID-19 Drug Candidates Are Highly Effective in Pre-clinical Animal Studies in Support of FDA Pre IND Application. 2021. Available from: https://www.bloomberg.com/press-releases/2021-03-09/nanoviricides-inc-pan-coronavirus-covid-19-drug-candidates-are-highly-effective-in-pre-clinical-animal-studies-i.
142. Barton RW, Tatake JG, Diwan AR (2016) Nanoviricides: Targeted Anti-Viral Nanomaterials In: Bawa, R., Audette, G.F., Rubinstein I., *Handbook of Clinical Nanomedicine, Nanoparticles, Imaging, Therapy, and Clinical Applications,* Eds, Jenny Stanford Publishing, 1039–1046.
143. NanoViricides is Developing Drugs Against SARS-CoV-2 with an Integrated Approach to Combat COVID-19, as Reported at The LD 500 Virtual Conference, 2020, Available from: https://www.accesswire.com/604794/NanoViricides-is-Developing-Drugs-Against-SARS-CoV-2-with-an-Integrated-Approach-to-Combat-COVID-19-as-Reported-at-The-LD-500-Virtual-Conference.
144. Pal M, Berhanu G, Desalegn C, et al. (2020) Severe acute respiratory syndrome coronavirus-2 (sars-cov-2): an update. *Cureus* 12: e7423. https://doi.org/10.7759/cureus.7423
145. Chatterjee S, Bhattacharya M, Nag S, et al. (2023) A detailed overview of sars-cov-2 omicron: its sub-variants, mutations and pathophysiology, clinical characteristics, immunological landscape, immune escape, and therapies. *Viruses* 15: 167. https://doi.org/10.3390/v15010167
146. Beigel JM, Tomashek KM, Dodd LE, et al. (2020) Remdesivir for the treatment of Covid-19 final report. *N Engl J Med* 83: 1813–1826. https://doi.org/10.1056/NEJMoa2007764
147. ClinicalTrials.gov, multicenter, retrospective study of the effects of remdesivir in the treatment of severe Covid-19 infections, 2021 Available from: https://clinicaltrials.gov/ct2/show/NCT04365725
148. Chakraborty A, Diwan A, Arora V, et al. (2022) Polymer protects the drug and improves its pharmacokinetics. *EC Pharmacol Toxicol* 10.2: 108–118. https://ecronicon.org/assets/ecpt/pdf/ECPT-10-00707.pdf
149. Osorno LL, Brandley AN, Maldonado DE, et al. (2021) Review of contemporary self-assembled systems for the controlled delivery of therapeutics in medicine. *Nanomaterials (Basel).* 11: 278. https://doi.org/10.3390/nano11020278
150. Yadav S, Sharma AK, Kumar P (2020) Nanoscale self-assembly for therapeutic delivery. *Front Bioeng Biotechnol* 8: 127. https://doi.org/10.3389/fbioe.2020.00127
151. Li H, Labean TH, Leong KW (2011) Nucleic acid-based nanoengineering: novel structures for biomedical applications. *Interface Focus* 1: 702–24. https://doi.org/10.1098/rsfs.2011.0040
152. Marshall ML, Wagstaff KM (2020) Internalized functional DNA aptamers as alternative cancer therapies. *Front Pharmacol* 11: 1115. https://doi.org/10.3389/fphar.2020.01115
153. Ni X, Castanares M, Mukherjee A, et al. (2011) Nucleic acid aptamers: clinical applications and promising new horizons. *Curr Med Chem* 18: 4206–14. https://doi.org/10.2174/092986711797189600
154. Li J, Mo L, Lu CH, et al. (2016) Functional nucleic acid-based hydrogels for bioanalytical and biomedical applications. *Chem Soc Rev* 45: 1410–31. https://doi.org/10.1039/C5CS00586H

155. Abune L, Wang Y (2021) Affinity hydrogels for protein delivery. *Trends Pharmacol Sci* 42: 300–312. https://doi.org/10.1016/j.tips.2021.01.005

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