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REVIEW PAPER

Nanotherapeutic Anti-influenza Solutions: Current Knowledge and Future Challenges

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Abstract

Nanotechnology has impacted every aspect of human life and the environment. The raising concern against influenza outbreaks is an ongoing issue. With the current drugs and natural remedies, some amount of resolution has been reached. Yet, nothing conclusive has been achieved. With every resource tapped, it is now time to combine strategies. This review highlights the low enthusiasm in this area, where not much has been probed into employing nanomaterials into influenza research. The achievements made through the intervention of nanotechnology into anti influenza research, has been surveyed in this review. Except for a few, not much progress was evidenced. Although significant progress has been achieved with nano inputs, yet nothing much has been done in this direction. This review emphasizes the need to combine strategies and find new remedies against influenza virus using nano platforms. New directions and future perspectives for accessing the nano inputs for combating the influenza issues have been discussed.

Keywords Influenza · Antiviral activity · Nanotechnology · Influenza · Resistance · Inhibition

Introduction

Nanotechnologies have impacted various branches of modern science. One of the most important nanotechnological domains comprises of bio-medical applications. With deliverables in the form of a new class of therapeutic nanomaterials, also called nanopharmaceuticals, newer prospects have been enabled. Their advantage lies in their unique properties arising from their small sizes, high surface-to-volume ratios and their modifiable surfaces. Nanoparticulate carriers can hold small molecules, as well as proteins and nucleic acids, thus bestowing nanomaterials with broad spectrum prospective therapeutic applications and the potential to target specific sites through drug delivery [1]. Synthesizing these versatile materials without affecting the environment has been a huge challenge and it is in this direction that green synthesis of nanomaterials is gaining ground [2–10].

In 2010, the prospects of nanotechnology leading to improved bioavaibility, controlled release, protection from drugs, decreased drug resistance, overcoming anatomical/cellular barriers and specific targeting during antiviral treatment have been probed [1]. The twentieth century has indeed seen an increase in influenza outbreaks leaving thousands either infected or dead [11, 12]. For example, 105,000–395,000 deaths were recorded owing to H1N1 influenza pandemic during 2009–2010 [13]. However, because of the influenza virus genetic shift and drift, there is a limitation in controlling this influenza pandemic [13]. The highly pathogenic avian influenza A virus (H5N1) causes acute respiratory distress syndrome and multi-organ failure with approximately 60% lethality with the first case of the disease being found in China and now prevalent all over the world too [14–16]. With this being the current

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scenario, the reasserted IAV (H7N9) has been found to further extrapulmonary complications, registering a fatality rate of more than 34%.

Vaccines are the means of primary prophylaxis against influenza virus. However, vaccine discovery is time-consuming and it has huge limitations and applicable to developed countries owing to the cost factor involved. Neuraminidase inhibitors such as oseltamivir and zanamivir are commonly used for inhibiting influenza virus infections. Unfortunately, the 2007–2008 seasonal influenza crisis revealed that some isolates of H1N1 were resistant towards commercial oseltamivir [17].

Thus, in this raging battle against influenza, there have been some current victories achieved. Yet, still many wars ahead. In this review, we survey the state-of-art drugs available against influenza virus and overview the side effects and limitations of these drugs. We further project the prospects of using nano-based therapeutics against influenza. This review highlights that though nanotechnology has much to offer, yet nothing much has been incorporated into influenza drugs. The reason for this standoff is presented and discussed in this review.

Current Drugs Against Influenza

Three major categories of anti-influenza drugs are as follows

Surface Protein Inhibitors (M2 Ion Channel, HA, NA)

The M2 ion channel inhibitor drugs such as amantadine (trade name: Symmetrel) and rimantadine (trade name: Flumadine) are solely effective against type A virus. Matrix 2 inhibitors effectively block the release and migration of the virus ribonucleoprotein into the nucleus of the host cells [17, 18]. Currently, influenza A H3N2 and pandemic A (H1N1 pdm09) viruses are reported to be resistant to M2 inhibitors similar to other H5N1 viruses [18]. However, these drugs also carry the vindication that they are the primary causatives of neurological side effects and widespread drug resistance [13, 19, 20]. Neuraminidase inhibitors (NAI), such as oseltamivir (trade name: Tamiflu) and zanamivir (trade name: Relenza), are those that are in use for treatment and prevention of uncomplicated acute flu caused by influenza A and B [21]. The drug peramivir (trade name: Rapivab) is the only available intravenous formulation amidst anti-influenza NAIs [22, 23]. Further research in the current decade is aiming at the use of hemagglutinin inhibitor (HAI). However, there are about 16 different hemagglutinin and 9 different neuraminidase subtypes known [24]. This estimation is perpetually growing owing to the frequent mutations on HA of influenza, rendering arrival at specific treatment strategies difficult.

RNA Polymerase Blocker (PB2, PB1, PA)

Recently, researchers have discovered that blocking influenza RNA polymerase is a novel approach for inhibiting influenza virus [12, 13, 17, 25, 26]. It is now established that natural compounds and some specifically synthesized compounds, hold promising potentials towards inhibiting influenza virus through blocking RNA polymerase [13, 25, 26]. Moreover, the advantage through this approach is that RNA polymerase is quite stable across a wide range of influenza virus strains including influenza A, B and seasonal flu [12].

Vaccination for the Influenza Virus

Appropriate vaccine administration is a crucial key to ensure successful prevention. Vaccines have had a broad medical impact. Unfortunately current vaccine-related technologies and production methods are limited in their activity to respond to emerging pathogen outbreaks. Typically, most vaccines are administered via subcutaneous or intramuscular routes and although most vaccines administered through hypodermic injection are effective. More so, there remains issues involving pain, needle-related diseases or injuries, requirement for trained personnel, appropriate needle disposal and suitable storage or transport of vaccines. Most vaccines require to be maintained within specific temperatures to retain their potency and therefore the associated expense of maintaining the “cold chain” is estimated to cost vaccine programs $200–300 million annually globally [27–29]. Moreover, influenza viruses easily mutate and thus for all the pain taken and the costs involved, it is possible that there may be mismatch of vaccines [30, 31].

Resistance and Side Effects of Current Drugs

The two classes of antiviral drugs used against influenza are neuraminidase inhibitors (oseltamivir and zanamivir) and M2 protein inhibitors (adamantane derivatives) (Table 1.) [17]. Neuraminidase belongs to the surface glycoproteins of influenza virus, these are responsible for releasing new virions from host cells to infect other cells [32, 33]. As of now, Oseltamivir is the main anti-influenza drug against influenza outbreaks. However, it is now established that neuraminidase inhibitors do not prove beneficial in those with miscellaneous health problems [34, 35]. Increasingly prevalent resistance to

Table 1 Approved antiviral drugs for influenza infections

Drug/Trade name	Routes of administration	Target	Resistance to
Amantadine/Symmetrel	Oral	M2 ion channel blocker	2009/H3N2
Oseltamivir/Tamiflu	Oral	NA inhibitor	2009/H1N1, 2007–2009/Seasonal flu, 2013/H5N1, 2013/H7N9
Rimantadine/ Flumadine	Oral	M2 ion channel blocker	2009/H3N2
Peramivir/Rapivab	Intravenous	NA inhibitor	2009/H1N1
Zanamivir/Relenza	Inhalation	NA inhibitor	2009/H7N9

neuraminidase inhibitors has led researchers to seek alternative antiviral drugs with different mode of action [36, 37]. With this being the background, the continual emergence and worldwide spread of oseltamivir-resistant seasonal A(H1N1) viruses during the 2007–2009 seasons emphasize the need for continuous monitoring of antiviral drug susceptibilities [38].

The antiviral drugs amantadine and rimantadine inhibit the viral ion channel M2 protein, thus inhibiting replication of the influenza A virus [39, 40]. These drugs are sometimes effective against influenza A, if given at the onset of infection but are absolutely ineffective against influenza B, which lack the M2 drug target [41]. Measured resistance to amantadine and rimantadine in American isolates of H3N2 increased to 91% in 2005 [42]. This high level of resistance may be due to the easy availability of amantadines as part of over-the-counter cold remedies in countries such as China and Russia, and their extensive use in farmed poultry to prevent outbreaks of influenza [43–45].

Influenza viruses possess the unique ability to switch to a new host and to escape antiviral measures [46, 47]. They have proved to exhibit high resistance against the available alternatives: neuraminidase inhibitor and M2 ion channel blockers (Table 1) [48–51]. Several discussions and research directions amidst viral researchers for inhibiting influenza virus outbreaks have still not arrived at any conclusive remedy [52]. With the available anti-influenza drugs and with the current knowledge on fighting influenza virus, no prominent breakthroughs have been achieved so far. It is now high time to improvise.

Milestones Achieved Via Nanotechnology for Anti-influenza Drug Development

Nanotechnology has been enabled via active control of matter and processes at nanoscale regimes (1–100 nm) in one or more dimensions [53]. The material and devices operated at the nanoscale regimes usually have different physical properties compared to their bulk counterparts. Nanomedicine-based approaches hold unprecedented potentials to steer biological processes through improved detection, therapy and prevention of multiple diseases. In biomedical applications, nanomaterials are mostly used either for diagnosis/detection or treatment. Nanomaterials have been used in diagnosis mostly as contrast agents for imaging. Their properties such as small sizes, higher surface to volume ratios, ability to be functionalized with therapeutic molecules, imaging agents, targeting ligands and nucleic acids prove crucial during diagnosis [53]. On the other hand, nanomaterials have been applied for treatment of multiple diseases, where they have been employed as drug delivery systems or as nano drugs [54–58]. Besides drug delivery [59], nanomaterials have proved promising in tumor therapies too, for photothermal therapy [60]. Their ability to concentrate in the diseased region, absorb light and convert it into heat to destroy the malignant cells, comes handy here.

Thus, with a long-standing reputation in biomedical research and with an accomplished career in antimicrobial applications [1–20, 61–68], influenza-related applications cannot be exceptions to nanotechnology. Inputs from nano-related solutions against the anti-influenza combat, as gathered from the few and scattered reports available online are presented below and summarized in Table 2.

Via Nanotechnology: Increased Influenza Drug Solubility

Many of the anti-influenza drugs and drug candidate compounds face solubility issues leading to decreased bioavailability [69]. For example, Saliphenylhalamide is well studied as an anti-influenza drug candidate as it inhibits acidification of endosomes, but the limitation is that the solubility of Saliphenylhalamide is very less. However, nano inputs resolved this problem and increased Saliphenylhalamide solubility using thermally hydrocarbonized porous silicon (THCPSi) nanoparticles [70].

Table 2 Nano based medicine development for antiviral drugs against influenza viruses

No.	Name	Nanotechnology/size	Target mechanism	Target influenza viruses	In vivo study	References
1.	Nanostructured glycanarchitecture	Nanoparticles (Virus like nanoparticles)/ 80–120 nm	Multiclonal antibody against NA and HA	A virus (H1N1)	Yes	Kwon et al.
2.	PLGA nanoparticles (poly-D,L-lactide-co-glycolide)	Nanoparticles	Monoclonal antibody against HA	A virus (H3N2 and H1N1) B virus (B/Brisbane/60/ 2008)	Yes	Galloway et al.
3.	Thermally hydrocarbonized porous silicon (THCPSi) nanoparticles	Nanoparticles and nanocarrier	Vacuolar-ATPase and inhibits acidification of endosomes	A virus (H1N1)	No	Bimbo et al.
4.	Biomimetic antigenic virus likenanoparticles	Nanoparticles/ 28.7 nm	CD8+ cytotoxic T cell protection	A virus (H1N1)	Yes	Patterson et al.
5.	MultivalentSialic-Acid-Functionalized Gold Nanoparticles	Nanoparticle/14 nm	HA inhibitor	A virus	No	Papp et al.
6.	KAgnanovaccine (polyanhydride nanoparticle-encapsulated KAg)	Nanoparticle/200 nm	CD4+ CD8αα+ T helper and CD8+ cytotoxic T cells, increased IFN-γ	A virus (H1N1)	Yes	Dhakal et al.
7.	Nano Copper (Nano Cu surface and powder)	Nanoparticle and nanosurface/ 60–80 nm	Ion diffusion	A virus (H3N2)	No	Sundberg et al.
8.	Self-assembling protein nanoparticles (SAPNs)	Nanoparticles/ 15–20 nm	Blocking influenza Matrix protein 2	A virus (H1N1, H5N2, H5N3, H5N9, H6N8, H7N2 and H10N7)	Yes	Karch et al.
9.	Hemagglutinin-stem nanoparticles	Nanoparticles	Monoclonal antibody against HA	A virus (H5N1)	Yes	Yassine et al.
10.	Dendrimer-RNA nanoparticles	Nanoparticles/ 30–50 nm	Stimuli CD8+ Tcell	A virus (H1N1)	Yes	Chahal et al.
11.	Matrix 2 protein (M2e) gold nanoparticles	Nanoparticles/12 nm	M2e-specific immunoglobulin (IgG)	A virus (H1N1)	Yes	Tao et al.
12.	Green synthesized Cinnamomum cassia silver nanoparticles	Nanoparticles/42 nm	Unknown	A virus (H7N3)	No	Fatima et al.

Via Nanotechnology: Increased drug interaction

Nanoparticles have similar nano-sized dimensions as viruses. This feature led several researchers to investigate the physical interaction of nanoparticles with viruses and to explore whether this interaction could be exploited as a potent antiviral strategy. Indeed, silver nanoparticles with mean particle diameters ranging from 10 to 50 nm have been shown to inhibit HIV, HBV, respiratory syncytial virus and monkey pox viruses [71, 72]. Additionally, influenza virus infection showed substantial decrease owing to the preferential interaction between virus particles and nanoparticles [73].

Via Nanotechnology: Stimulate Immune System Similar to Vaccine

Vaccines are means of primary prophylaxis against influenza virus. The host cellular immunity occupies a major role in influenza virus infection and cellular mechanisms that further virus infections [74–76]. Moreover, downstream signaling of these sensors induces distinct sets of effector mechanisms that block virus replication and promote clearance of viruses by inducing innate and adaptive immune responses [75, 76]. Through nanotechnology, researchers have introduced virus-like nanomaterials to trigger innate immune response against various influenza virus strains [77, 78]. These simulated nanoparticles consist of proteins and portions of influenza virus or are shaped mimicking influenza virus particles. For instance, it is

reported that nanoparticles have been designed for successful control of immune responses through encapsulation and sequestration of the conserved nucleoprotein from influenza to direct CD8+ cytotoxic T cell protection [77]. The expression of influenza nucleoprotein-specific CD8+ T cells was observed to be significantly higher than normal mice and the mortality of the mice was increased up to 80% [77]. Additionally, some virus-like nanoparticles conjugated with viral RNA, Matrix 2 protein and neuraminidase showed increased immunity through significantly higher IFN-γ, immunoglobulin and CD8+ T cell expression in vitro and in vivo [73, 76–80]. Such results confirm that such nano-virus-modifications can influence influenza virus infections through innate immune systems [77, 78].

Via Nanotechnology: Inhibiting Transmission of Infection (Antiviral Surface)

Recently, nanoscience has filled every aspect of our daily life [81–87]. Well established nano-based antimicrobial properties have been published, where significant antibacterial, antifungal and antiviral activities of nanoparticles have been recorded [67, 83, 88–90]. Transmission of the virus is a leading risk for spread of influenza virus related infections [83, 91, 92]. For example, tables and chairs and equipment in hospitals are modes of such transmission. Nanomaterials have been applied to surfaces to render them antimicrobial, to have a self-sterilizing effect on material surfaces; copper cold sprayed surfaces are one such example [83]. Reports show that the contact-killing rate between influenza virus and the nano-copper surface and normally grafted copper surface was significantly very high. More than 90% of influenza viral infectivity was reduced within 2 h of exposure on the nano-copper surfaces because of ion diffusion [83]. Moreover, the effectiveness of metals and metal oxides (copper oxide (CuO), iron oxide (Fe3O4), silver (Ag), titanium oxide (TiO_2), zinc oxide (ZnO)) has been widely studied for their antimicrobial activities [93, 94]. But nano-metals and their antiviral activity on influenza virus and anti-influenza mechanisms are poorly studied and not yet disclosed [83]. However, it does not mean that there is no future in this direction, the nano-copper results prove that nano inputs could lead to successful control of influenza virus transmission. More research in this direction with inclusion from promising nanomaterials will no doubt yield significant progress.

Via Nanotechnology: Reduced Toxicity

All drugs have toxicity depending on their concentrations. More antiviral activity, more drugs, leads to more toxicity. It limits the drug's effectiveness [95]. In this aspect, nanotechnology has ways to improve bioavailability and reduce toxicity [96, 97]. This has been widely studied on anticancer drug development, where increased bioavailability through improved permeability and drug delivery to tumors has been reported [97]. Significant blood clearance and reduction of normal cell death rates were recorded in animal models [97]. This idea is highly applicable to antiviral drug development and especially against influenza virus infection. For instance, quercetin is known as a traditional phytochemical possessing significant antimicrobial, anticancer and antioxidant activities [98]. Somehow its use has been limited owing to its cytotoxic effects [95]. Nanomedicine inputs have shown that quercetin nanocomposites exhibited improved anticancer efficiency and reduced toxicity [95]. It is no doubt that such inputs will have significant impacts in case of influenza virus infections too.

Via Nanotechnology: Enabling Eco-friendly (Green Synthesis)

Green synthesis of silver nanoparticles using plants provides advantages over other methods as it is easy, efficient, and eco-friendly. Nanoparticles have been extensively studied as potential antimicrobials to target pathogenic and multidrug-resistant microorganisms [47]. Plant-based silver nanoparticles are a likely source of new antiviral agents because of their multitargeting mechanism of action. Plants are readily available, have low cost, are easy to handle and nontoxic, and have a variety of metabolites that can assist the reduction of metal ions [99]. The green synthesized silver nanoparticles using Cinnamomum cassia showed enhanced anti-influenza activity against H7N3 strain than bark extracts [47]. Nature's providences are rather the choicest remedies for human health and welfare [11, 17, 30]. These have been used back in historical times and are still popular in this modern era too [11]. There are thousands of natural plant-based phytochemicals that have impacted anti-influenza drug developments [17]. Till date, scientists have always tried to develop this technology for medicinal aspects. For presenting these as mixtures [100], chemically synthesized new derivatives [101–103], biocatalysts [104–106] are clubbed with nanotechnology [96, 107]. For example, newly synthesized berberine derivatives have shown more than 10 times stronger NA inhibition activity on influenza A (H1N1). Moreover, those derivatives based on their natural structure were detected with 10 times higher influenza activity over many different strains [101]. But some of these phytochemicals are confronted with low-bioavailability and poor water solubility [107]. Gold-quercetin into poly (DL-lactide-co-glycolide) nanoparticles showed up-regulated apoptosis on liver

cancer cells markedly [96]. Similar phytochemicals related enhanced biological activities have been shown in influenza too [13, 17]. It is also reported that nanoparticles via green synthesis using plant extracts were almost twice active against influenza A virus (H7N3) [47]. Figure 1 gives a brief overview of various nanomaterial based improvisation in antiviral combat.

Impact of Integrated Nano-antiviral Technologies

The inclusion of nanotechnology into any technology or combat strategy has proved highly beneficial. The fight against influenza is still on and the battle is yet to be won. With evasive strains and mutants and resistant types evolving, the battle is likely to heat up rather than slow down. Antiviral drugs have achieved what they can achieve, progress has been made indeed. But, integrated approaches are required for the furtherance of this crucial battle, ahead towards elimination of influenza. In this direction integrating nanomaterials with anti-inflenza drugs gains paramount importance. Nano-based nanotherapeutics have been developed with respect to certain epidemic viruses. STP702 (FluquitTM) from Sirnaomics is a polymer-based nanotherapeutic that incorporates siRNA targeting the conserved regions of influenza for effective antiviral activity against H5N1 (avian flu), H1N1 (swine flu) and newly emerging H7N9.161. Such specific nanotherapeutics combining antiviral targets and nanomaterials will lead to positive enhancement of antiviral activity. 'Nanotrap' particles are thermoresponsive hydrogels that captureg live infectious virus, viral RNA, and viral proteins [108, 109]. This novel technology was demonstrated by Hendricks et al. [110], who used liposomes for the delivery of glycan sialylneolacto-N-tetraose c (LSTc)-sialoside (a synthetic decoy receptor) for influenza binding. These liposomes competitively bind and capture influenza A viruses, and can inhibit infection of target cells in a dose-dependent manner.

Hemagglutinin (HA) and neuraminidase (NA) are influenza glycoproteins, which function in viral attachment (to sialic-acid containing receptors on the cell surface) and release [111]. Oseltamivir, a NA inhibitor inhibits cell–cell spread and ongoing influenza transmission [112]. In another study [36] oseltamivir-modified silver nanoparticles were shown to efficiently decrease H1N1 infection by inhibiting HA and NA activities [36].

Titanium dioxide (TiO_2) nanoparticles functionalized with DNA fragments targeting the 3′ non-coding region of influenza A virus were synthesized using a polylysine linker. These nanocomposites were able to enter cells without transfection agents and were demonstrated against influenza A virus [113, 114]. These are the limited projections available as of now as to what integration of nano with antiviral systems can offer.

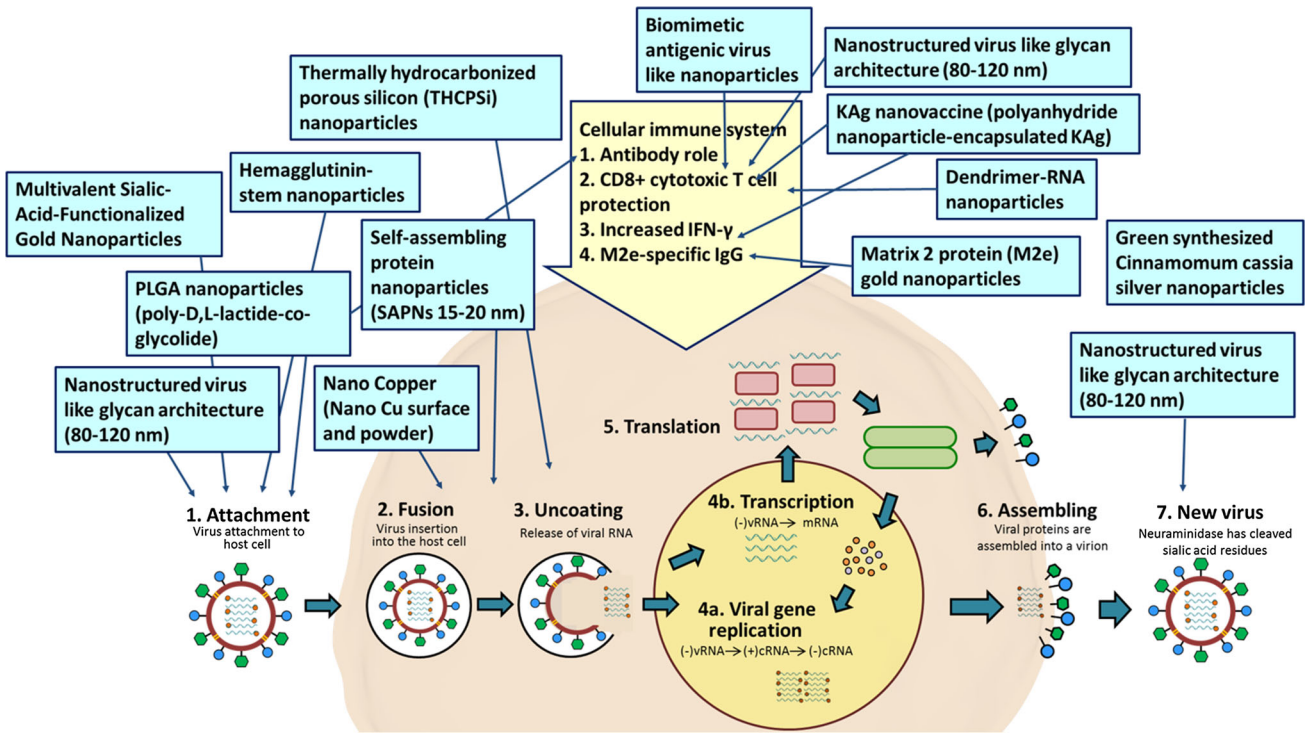

Fig. 1 Antiviral interactions inflicted by nanomaterials

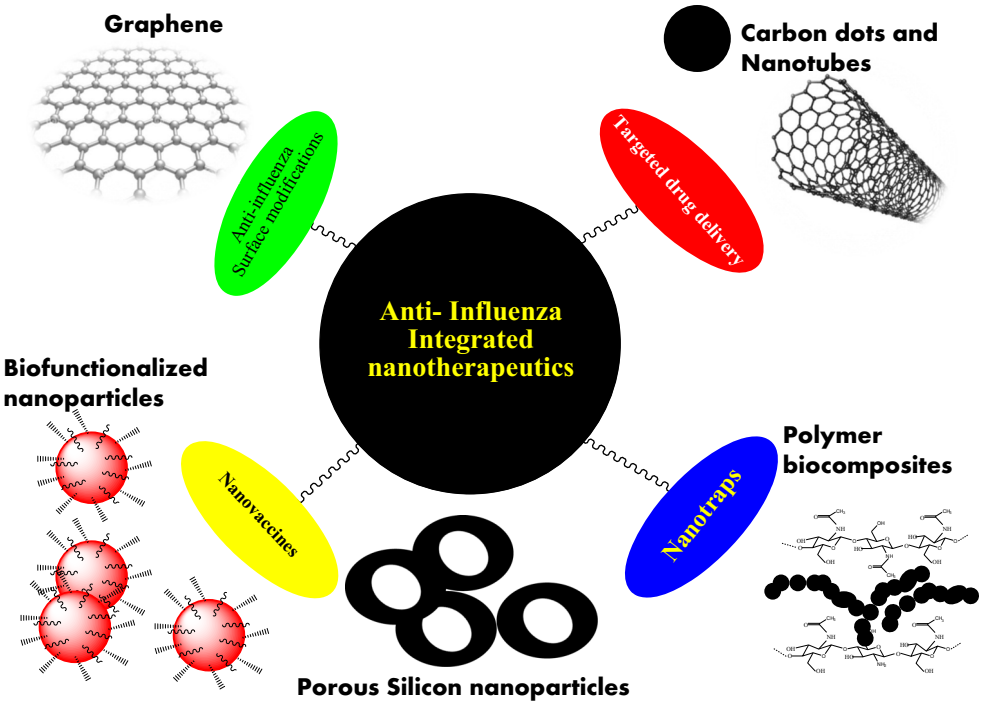

Fig. 2 The future perspective of new age nanomaterials for nanotherapeutics against influenza

Conclusion

What is intriguing is that with all the well accomplished outstanding deliverables from nanotechnology and through nano inputs in virus-related research, still there is not much enthusiasm in this area. This is what prompted this review. Integrating nanosystems into the influenza drugs would no doubt enhance the drug effect. Further, formulation of bio composites with anti-influenza phytochemicals will be a promising direction. Targeted drug delivery through novel well-established nano systems is another direction. Use of new age graphene, carbon nanotubes and other reputed antibacterial materials for surface modification of hospital equipment could help curb transmission. Figure 2 presents the areas in with nanotherapeutics can provide enhanced anti-influenza solutions. Rather than a standalone approach using either nanomaterials or anti-influenza drugs by themselves, an integrated approach is what this review projects, to come handy for progress in the anti-influenza combat. The integrated nano-anti-influenza drug approach could positively affect: (i) targeted drug delivery, (ii) nanotraps, (iii) nanovaccines and (iv) anti-influenza surface modifications. With nanotechnology having a lot to offer, and influenza research and the drugs available hitting saturation point, it is not to integrate these entities to achieve higher visions and accomplish eradication of influenza virus.

Compliance with Ethical Standards

Conflict of interest The authors declares that there are no conflict of interests.

References

1. D. Lembo and R. Cavalli (2010). *Antivir. Chem. Chemother.* **21**, 53.
2. A. Saxena, R. M. Tripathi, and R. P. Singh (2010). *Dig. J. Nanomater. Biostruct.* **5**, 427.
3. G. Benelli and C. M. Lukehart (2017). *J. Clust. Sci.* **28**, 1.
4. G. Benelli (2016). *Enzyme Microb. Technol.* **95**, 58.
5. R. Rajan, K. Chandran, S. L. Harper, S. I. Yun, and P. T. Kalaichelvan (2015). *Ind. Crops Prod.* **70**, 356.
6. G. Benelli (2017). *Acta Trop.* **178**, 73.
7. G. Benelli, R. Pavela, F. Maggi, R. Petrelli, and M. Nicoletti (2017). *J. Clust. Sci.* **28**, 3.
8. G. Benelli, F. Maggi, D. Romano, C. Stefanini, B. Vaseeharan, S. Kumar, A. Higuchi, A. A. Alarfaj, H. Mehlhorn, and A. Canale (2017). *Ticks Tick Borne Dis.* **8**, 821.
9. M. Govindarajan and G. Benelli (2017). *J. Clust. Sci.* **28**, 15. https://doi.org/10.1007/s10876-016-1035-6.
10. G. Benelli and M. Govindarajan (2017). *J. Clust. Sci.* **28**, 287. https://doi.org/10.1007/s10876-016-1088-6.
11. G. Enkhtaivan, K. M. Maria John, M. Pandurangan, J. H. Hur, A. S. Leutou, and D. H. Kim (2016). *Saudi J. Biol. Sci.* **24**, 1646.
12. G. Enkhtaivan, P. Muthuraman, and D. H. Kim (2017). *J. Mol. Recognit.* **30**, e2616.
13. E. Gansukh, Z. Kazibwe, M. Pandurangan, G. Judy, and D. H. Kim (2016). *Phytomedicine* **23**, 958.
14. N. Nakajima, N. V. Tin, Y. Sato, H. N. Thach, H. Katano, and P. H. Diep (2013). *Mod. Pathol.* **26**, 357.
15. Q. Li, L. Zhou, M. H. Zhou, Z. P. Chen, F. R. Li, and H. Y. Wu (2014). *N. Engl. J. Med.* **370**, 520.

16. T. M. Uyeki (2008). *Respirology* **13**, S2.
17. E. Gansukh, M. Muthu, D. Paul, G. Ethiraj, S. Chun, and J. Gopal (2017). *Rev. Med. Virol.* **27**, e1930.
18. J. L. McKimm-Breschkin (2013). *Influenza Other Respir. Viruses* **1**, 25.
19. H. Leonov, P. Astrahan, M. Krugliak, and I. T. Arkin (2011). *J. Am. Chem. Soc.* **133**, 9903.
20. T. G. Sheu, A. M. Fry, R. J. Garten, V. M. Deyde, T. Shwe, and L. Bullion (2008). *J. Infect. Dis.* **203**, 13.
21. N. Spanakis, V. Pitiriga, V. Gennimata, and A. Tsakris (2014). *Expert Rev. Anti Infect.* **12**, 1325.
22. T. Komeda, S. Ishii, Y. Itoh, Y. Ariyasu, M. Sanekata, and T. Yoshikawa (2015). *J. Infect. Chemother.* **21**, 194.
23. T. Komeda, S. Ishii, Y. Itoh, Y. Ariyasu, M. Sanekata, and T. Yoshikawa. *J. Infect. Chemother*. **20**, 689.
24. J. Lynch and E. Walsh (2007). *Semin. Respir. Crit. Care Med.* **28**, 144.
25. M. P. Clark, M. W. Ledeboer, I. Davies, R. A. Byrn, S. M. Jones, and E. Perola (2014). *J. Med. Chem.* **57**, 6668.
26. M. P. Clark (2014). *Abstr. Pap. Am. Chem.* **2014**, 248.
27. N. R. Hegde, S. V. Kaveri, and J. Bayry (2011). *Drug Discov. Today* **16**, 1061.
28. D. G. Koutsonanos, M. del Pilar Martin, V. G. Zarnitsyn, S. P. Sullivan, R. W. Compans, and M. R. Prausnitz (2009). *PloS One* **4**, e4773.
29. M. A. Miller and E. Pisani (1999). *Bull. World Health Organ.* **77**, 808.
30. G. Enkhtaivan, K. M. Maria John, M. Ayyanar, T. Sekar, K. J. Jin, and D. H. Kim (2015). *Saudi J. Biol. Sci.* **22**, 532.
31. J. Treanor (2004). *N. Engl. J. Med.* **350**, 218.
32. J. Yang, S. Liu, L. Du, and S. Jiang (2016). *Rev. Med. Virol.* **26**, 242.
33. J. M. Luczo, J. Stambas, P. A. Durr, W. P. Michalski, and J. Bingham (2015). *Rev. Med. Virol.* **25**, 406.
34. B. Michiels, K. Van Puyenbroeck, V. Verhoeven, E. Vermeire, and S. Coenen. *PLoS One*. **8**, e60348.
35. A. J. Wailoo, A. J. Sutton, N. J. Cooper, D. A. Turner, K. R. Abrams, and A. Brennan (2008). *Value Health* **11**, 160.
36. A. Moscona (2009). *N. Engl. J. Med.* **360**, 953.
37. K. M. Maria John, G. Enkhtaivan, M. Ayyanar, K. Jin, J. B. Yeon, and D. H. Kim (2015). *Saudi J. Biol. Sci.* **22**, 191.
38. D. B. Mendel and R. W. Sidwell (1998). *Drug Resist. Updates* **1**, 184.
39. S. D. Cady, K. Schmidt-Rohr, J. Wang, C. S. Soto, W. F. Degrado, and M. Hong (2010). *Nature* **463**, 689.
40. L. H. Pinto and R. A. Lamb (2006). *J. Biol. Chem.* **281**, 8997.
41. I. Stephenson and K. G. Nicholson (1999). *J. Antimicrob. Chemother.* **44**, 6.
42. Centers for Disease C, Prevention (2006). *MMWR Morb. Mortal. Wkly. Rep.* **55**, 44.
43. R. A. Bright, M. J. Medina, X. Xu, G. Perez-Oronoz, T. R. Wallis, and X. M. Davis (2005). *Lancet* **366**, 1175.
44. N. A. Ilyushina, E. A. Govorkova, and R. G. Webster (2005). *Virology* **341**, 102.
45. J. Parry (2005). *BMJ* **331**, 10.
46. L. M. Farigliano, S. A. Paz, E. P. M. Leiva, and M. A. Villarreal (2017). *J. Chem. Theory Comput.* **13**, 3874.
47. M. Fatima, N. U. Zaidi, D. Amraiz, and F. Afzal (2016). *J. Microbiol. Biotechnol.* **26**, 151.
48. H. L. Yen, J. L. McKimm-Breschkin, K. T. Choy, D. D. Wong, P. P. Cheung, and J. Zhou (2013). *MBio* **2013**, 4.
49. A. Jacob, R. Sood, Kh V Chanu, S. Bhatia, R. Khandia, and A. K. Pateriya (2016). *Microb. Pathog.* **91**, 35.
50. T. Ziegler, M. L. Hemphill, M. L. Ziegler, G. Perez-Oronoz, A. I. Klimov, and A. W. Hampson (1999). *J. Infect. Dis.* **180**, 935.
51. M. Nykvist, A. Gillman, H. Soderstrom Lindstrom, C. Tang, G. Fedorova, and A. Lundkvist (2017). *J. Gen. Virol.* **98**, 2937.
52. N. Khandelwal, G. Kaur, N. Kumar, and A. Tiwari (2014). *Dig. J. Nanomater. Biostruct.* **9**, 175.
53. H. Xiao and Y. Zhang (2012). *Sci. China Life Sci.* **55**, 841.
54. S. Tong, T. J. Cradick, Y. Ma, Z. Dai, and G. Bao (2012). *Sci. China Life Sci.* **55**, 843.
55. X. Nie and C. Chen (2012). *Sci. China Life Sci.* **55**, 872.
56. Z. Zhang, L. Wang, J. Wang, Z. Jiang, X. Li, and Z. Hu (2012). *Adv. Mater.* **24**, 1418.
57. A. H. Chi, K. Clayton, T. J. Burrow, R. Lewis, D. Luciano, and F. Alexis (2013). *Ther. Deliv.* **4**, 77.
58. E. Meng and T. Hoang. *Ther. Deliv.* **3**, 1457.
59. K. Gulati, M. S. Aw, D. Findlay, and D. Losic (2012). *Ther. Deliv.* **3**, 857.
60. L. C. Kennedy, L. R. Bickford, N. A. Lewinski, A. J. Coughlin, Y. Hu, and E. S. Day (2011). *Small* **7**, 169.
61. M. J. Hajipour, K. M. Fromm, A. A. Ashkarran, D. Jimenez de Aberasturi, I. R. de Larramendi, and T. Rojo (2012). *Trends Biotechnol.* **30**, 499.
62. P. L. Kashyap, S. Kumar, A. K. Srivastava, and A. K. Sharma (2013). *World J. Microbiol. Biotechnol.* **29**, 191.
63. S. Galdiero, A. Falanga, M. Vitiello, M. Cantisani, V. Marra, and M. Galdiero (2011). *Molecules* **16**, 8894.
64. P. Swain, S. K. Nayak, A. Sasmal, T. Behera, S. K. Barik, and S. K. Swain (2014). *World J. Microbiol. Biotechnol.* **30**, 2491.
65. V. Patel, D. Berthold, P. Puranik, and M. Gantar (2015). *Biotechnol. Rep. (Amst)* **5**, 112.
66. T. T. Duong, T. S. Le, T. T. H. Tran, T. K. Nguyen, C. T. Ho, and T. H. Dao (2016). *Adv. Nat. Sci. Nanosci.* **7**, 035018.
67. S. Chun, M. Muthu, E. Gansukh, P. Thalappil, and J. Gopal (2016). *Sci. Rep.* **6**, 35586.
68. J. Gopal, M. Muthu and S. C. Chun. *RSC. Adv.* **5**, 48391.
69. A. S. Gambaryan, A. B. Tuzikov, A. A. Chinarev, L. R. Juneja, N. V. Bovin, and M. N. Matrosovich (2002). *Antiviral Res.* **55**, 201.
70. L. M. Bimbo, O. V. Denisova, E. Makila, M. Kaasalainen, J. K. De Brabander, and J. Hirvonen (2013). *ACS. Nano.* **7**, 6884.
71. H. H. Lara, N. V. Ayala-Nunez, L. Ixtepan-Turrent, and C. Rodriguez-Padilla (2010). *J. Nanobiotechnol.* **8**, 1.
72. J. L. Elechiguerra, J. L. Burt, J. R. Morones, A. Camacho-Bragado, X. Gao, and H. H. Lara (2005). *J. Nanobiotechnol.* **3**, 6.
73. S. J. Kwon, D. H. Na, J. H. Kwak, M. Douaisi, F. Zhang, and E. J. Park (2017). *Nat. Nanotechnol.* **12**, 48.
74. B. M. Coates, K. L. Staricha, K. M. Wiese, and K. M. Ridge (2015). *JAMA Pediatr.* **169**, 956.
75. A. Iwasaki and P. S. Pillai (2014). *Nat. Rev. Immunol.* **14**, 315.
76. K. Zhang, W. W. Xu, Z. Zhang, J. Liu, J. Li, and L. Sun (2017). *Oncotarget* **8**, 30422.
77. D. P. Patterson, A. Rynda-Apple, A. L. Harmsen, A. G. Harmsen, and T. Douglas (2013). *ACS Nano.* **7**, 3036.
78. S. Dhakal, J. Goodman, K. Bondra, Y. S. Lakshmanappa, J. Hiremath, and D. L. Shyu (2017). *Vaccine.* **35**, 1124.
79. Correction for Chahal (2016). *Proce. Natl. Acad. Sci.* **113**, E5250-E.
80. W. Tao, K. S. Ziemer, and H. S. Gill (2014). *Nanomedicine* **9**, 237.
81. M. A. Babizhayev (2013). *Recent Pat. Drug Deliv. Formul.* **7**, 39.
82. A. M. Fan and G. Alexeeff (2010). *J. Nanosci. Nanotechnol.* **10**, 8646.
83. K. Sundberg, V. Champagne, B. McNally, D. Helfritch, and R. Sisson (2015). *J. Biotechnol. Biomater.* **5**, 205.
84. A. Mohamed and M. M. Xing (2012). *Int. J. Burns Trauma* **2**, 29.

85. B. Peretz (2005). *Refuat. Hapeh. Vehashinayim.* **22**, 88.
86. C. Schmidt and J. Storsberg (2015). *Biomedicine* **3**, 203.
87. R. F. Service (2005). *Science* **310**, 1609.
88. N. Beyth, Y. Houri-Haddad, A. Domb, W. Khan, and R. Hazan (2015). *Evid. Based Complement Altern. Med.* **2015**, 246012.
89. A. S. Brady-Estevez, S. Kang, and M. Elimelech (2008). *Small.* **4**, 481.
90. S. Brady-Estevez, T. H. Nguyen, L. Gutierrez, and M. Elimelech. *Water Res.* **44**, 3773.
91. D. H. Cheung, T. K. Tsang, V. J. Fang, J. Xu, K. H. Chan, and D. K. Ip (2015). *J. Infect. Dis.* **212**, 391.
92. G. Neumann and Y. Kawaoka (2015). *Virology* **479–480**, 234.
93. L. Loomba and T. Scarabelli (2013). *Ther. Deliv.* **4**, 859.
94. L. Loomba and T. Scarabelli (2013). *Ther. Deliv.* **4**, 1179.
95. G. Cirillo, O. Vittorio, S. Hampel, F. Iemma, P. Parchi, and M. Cecchini (2013). *Eur. J. Pharm. Sci.* **49**, 359.
96. K. W. Ren, Y. H. Li, G. Wu, J. Z. Ren, H. B. Lu, and Z. M. Li (2017). *Int. J. Oncol.* **50**, 1299.
97. L. Liu, Q. Ye, M. Lu, Y. C. Lo, Y. H. Hsu, and M. C. Wei (2015). *Sci. Rep.* **5**, 10881.
98. A. V. Anand David, R. Arulmoli, and S. Parasuraman (2016). *Pharmacogn. Rev.* **10**, 84.
99. S. W. Yoon, R. J. Webby, and R. G. Webster (2014). *Curr. Top. Microbiol. Immunol.* **385**, 359.
100. H. Satoh (2014). *J. Intercult. Ethnopharmacol.* **3**, 196.
101. G. Enkhtaivan, P. Muthuraman, D. H. Kim, and B. Mistry (2017). *Bioorg. Med. Chem.* **25**, 5185.
102. M. Veverka, J. Gallovič, E. Švajdlenka, E. Veverková, N. Prónayová, and I. Miláčková (2013). *Chem. Pap.* **67**, 76.
103. M. Thapa, Y. Kim, J. Desper, K. O. Chang, and D. H. Hua (2012). *Bioorg. Med. Chem. Lett.* **22**, 353.
104. E. K. Lim, D. A. Ashford, B. Hou, R. G. Jackson, and D. J. Bowles (2004). *Biotechnol. Bioeng.* **87**, 623.
105. J. Roepke and G. G. Bozzo (2013). *ChemBioChem* **14**, 2418.
106. S. Das and J. P. N. Rosazza (2006). *J. Natl. Prod.* **69**, 499.
107. K. Men, X. Duan, X. W. Wei, M. L. Gou, M. J. Huang, and L. J. Chen (2014). *Anticancer Agents Med. Chem.* **14**, 826.
108. L. Singh, et al. (2017). *Ther. Adv. Infect. Dis.* **4**, 105.
109. S. Barik (2012). *BMC Med.* **10**, 104. [PMC free article].
110. N. Shafagati, A. Patanarut, A. Luchini, et al. (2014). *Pathog. Dis.* **71**, 164.
111. G. L. Hendricks, K. L. Weirich, K. Viswanathan, et al. (2013). *J. Biol. Chem.* **288**, 8061.
112. R. Wagner, M. Matrosovich, and H.-D. Klenk (2002). *Rev. Med. Virol.* **12**, 159.
113. Y. Li, Z. Lin, M. Zhao, et al. (2016). *ACS Appl. Mater. Interfaces* **8**, 24385.
114. A. S. Levina, M. N. Repkova, N. A. Mazurkova, et al. (2016). *IEEE Trans. Nanotechnol.* **15**, 248.