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Advancing influenza prevention through a one health approach: A comprehensive analysis

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ABSTRACT

Background: Influenza represents a global One Health concern, and the utilization of nanoparticle-based vaccines or drugs emerges as a promising solution for its prevention and treatment. Nanoparticles, with their precision in drug distribution, heightened efficacy, and minimized adverse effects, have garnered attention as viable candidates in the fight against influenza. This meta-analysis assesses the effectiveness, safety, and potential applications of nanoparticles, particularly those incorporating natural compounds like curcumin, in influenza prevention and treatment.

Methods: A systematic literature search was conducted to gather and examine studies focusing on nanoparticle-based strategies for influenza prevention and treatment, with a specific emphasis on natural compounds such as curcumin. The results obtained were meticulously evaluated.

Findings: The results indicate that nanoparticles significantly enhance the effectiveness of influenza prevention. In animal models, nanoparticle interventions exhibit heightened antiviral activity, leading to a substantial reduction in viral load and improved survival rates. The precision of drug administration enabled by nanoparticles facilitates higher drug concentrations at the infection site, maximizing therapeutic benefits. Notably, nanoparticle-based therapies exhibit superior safety profiles compared to traditional antiviral medications, with minimal cytotoxicity and fewer side effects. The combination of phytochemicals with nanoparticles offers a promising avenue for influenza treatment, providing durable therapeutic alternatives with inherent natural qualities that enhance antiviral activity. The synergistic effect of phytochemicals and nanoparticles opens new avenues for the development of antiviral agents.

Conclusion: In conclusion, nanoparticles demonstrate both efficacy and safety in the treatment of influenza, acting as potent therapeutic agents due to their targeted drug delivery and enhanced antiviral activities. The inclusion of phytochemicals further amplifies their potential. Future research endeavours should focus on refining nanoparticle formulations, elucidating their mechanisms of action, and exploring innovative combinatorial strategies. The revolutionary impact of nanoparticles in influenza treatment holds the promise of advancing antiviral medicines and ultimately improving patient outcomes.

Introduction

The viruses that cause influenza outbreaks are immune to human defenses. For more than 500 years, influenza A viruses (IAV) have been spread through avian and mammalian species, including people (Kanekiyo et al., 2019). Spanish flu, for instance, which is brought on by influenza in 1918, the H1N1 virus burst out, infecting 500 million individuals and killing roughly 100 million of them (Sengupta and Sasisekharan, 2007). Between 1918 and 2009, IAV caused four pandemics in addition to yearly outbreaks. These are significant human respiratory tract pathogens that cause sporadic pandemics and seasonal epidemics worldwide (Organization, 2018). Influenza Virus (IFV) is a

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Table 1
Summary of all the drugs used against influenza. (RCT: Randomized Controlled Trials; EU: European Union).

Anti- virals for influenza	Target	Administration route	Resistant To	Approval organization & year	Standard adult treatment regimen	Efficacy from RCT	Ref.
Zanamivir	NA inhibitor	Inhalation or Intravenous	2009/H7N9	Worldwide (including the EU and U.S.)/ 1999	Twice daily for 5 days (inhalation) or twice-daily infusion for 5–10 days (intravenous)	Healthy, prophylaxis, and children≥5 yrs	(Hayden et al., 1997; Hedrick et al., 2000; Monto et al., 2002)
Amantadine	M2 ion channel blocker	Oral	2009/H3N2	Worldwide (including the EU and U.S.); note that it is no longer used due to widespread resistance / 1966	Once daily for ≥10 days (U.S.)	Healthy, Prophylaxis	(Hayden et al., 1980)
Oseltamivir	NA inhibitor	Oral	2009/H1N1, 2007–2009/ Seasonal flu, 2013/H5N1, 2013/H7N9	Worldwide (including the EU and U.S.) / 1999	Twice daily for 5 days	Healthy, High risk of complications, children ≥1 yr of age, prophylaxis	(Nicholson et al., 2000; Ison et al., 2020; Whitley et al., 2001; Welliver et al., 2001)
Peramivir	NA inhibitor	Intravenous	2009/H1N1	Worldwide (including the EU and U.S.) / 2014	Single infusion over 15 min (minimum)	Healthy	(Kohno et al., 2010)
Baloxavir	Endonuclease inhibitor	Oral	–	Worldwide (including the EU and U.S.) / 2018	Single dose	Healthy, High risk of complications, children ≥1 yr of age, prophylaxis	(Holmes et al., 2021)
Favipiravir	RNA-dependent RNA polymerase inhibitor	Oral	–	Japan and China (approved for novel pandemic or multiresistant strains only) / 2014	Twice daily for 5 days	Healthy	(Toyama Chemical Co 2017)

single-stranded RNA virus with an envelope, and segmented genome that belongs to the Orthomyxoviridae family (Hopken et al., 2020), it is one of the common respiratory tract infectious agents that spreads annually throughout the world and is a major concern in the medical community (Gasparini et al., 2014; Nazari et al., 2022). Based on the presence of two surface glycoproteins, hemagglutinin (HA) and neuraminidase (N), it is divided into a number of subtypes. Evidence reveals that, when compared to other genera and strains of different influenza virus species, the influenza A virus, particularly the strain H3N2, has the highest risk of morbidity and mortality. Based on the antigenicity of their hemagglutinin (16 subtypes, H1-H16) and neuraminidase (9 subtypes, N1-N9) molecules, they are divided into distinct serotypes, but H1, H2, and H3, as well as N1 and N2, are frequently seen in humans (Nazari et al., 2022; Neumann et al., 2009; Lynch and Walsh, 2007). Antigenic drift, which can happen when various IFV strains recombine generally, occurs when minor alterations in the hemagglutinin or neuraminidase antigens appear. Novel pathogenic IFV strains with the potential to start new epidemics or global pandemics can arise from either antigenic mutation or assortment (Yoo et al., 2012). Nanotechnology, gene delivery, and improvements in IFV structural biology present new potential for the development of better vaccines that can provide more broadly protective protection against a variety of influenza viruses. Currently, injectable vaccinations and antiviral medications are the two main methods used to reduce the frequency of influenza (Xiang et al., 2013). M2 channel blockers (adamantane derivatives) and neuraminidase inhibitors (oseltamivir and zanamivir) are the two classes of antiviral drugs used widely against influenza. However, their long-term effectiveness against IFV is disputed and constrained by the rising emergence of drug resistance and side effects (Xiang et al., 2013). There is a consistent need for novel strategies to stop virus replication and transmission, notably for the development of anti-IFV medicines providing broad-range protection, given the limitations of currently existing treatments to combat an influenza pandemic (Xiang et al., 2013). Surface protein inhibitors (M2 ion channel, HA, NA), RNA polymerase inhibitors (PB2, PB1, PA), and influenza vaccination are the three main classes of anti-influenza medications. Matrix 2 inhibitors successfully stop the virus' ribonucleoprotein from releasing and migrating into the host cell's nucleus. Amantadine and rimantadine are M2 ion channel inhibitors that only work against type A viruses (McKimm-Breschkin, 2013). As with other H5N1 viruses, influenza A H3N2, and pandemic A (H1N1 pdm09) viruses are currently reported to be resistant to M2 inhibitors. Oseltamivir and zanamivir are examples of neuraminidase inhibitors (NAI), which are used for the treatment and prevention of simple acute influenza caused by influenza A and B (Table 1). An essential element of effective prevention is the delivery of vaccines at the proper dosage. Vaccines have had a significant impact on medicine (Gansukh et al., 2018). Due to the frequent mutations in the HA of influenza, the development of particular treatment options is challenging, and is continuously rising (Gansukh et al., 2018). Scientists acknowledged that a potential strategy for preventing the influenza virus is to stop influenza RNA polymerase. Among recent innovations, several natural compounds have shown the ability to inhibit the influenza virus by blocking RNA polymerase. Unfortunately, the ability of present vaccine-related technology and production methods to address growing disease epidemics is constrained.

Nanoparticle-based strategies have emerged as a promising approach to the prevention and management of influenza. Nano-formulations have an advantage due to their distinctive characteristics, including their small diameters, high surface-to-volume ratios, and customizable surfaces. Nano carriers can transport small molecules, proteins, and nucleic acids, offering nanomaterials a wide range of potential therapeutic applications and the capacity to deliver medications to specific locations (Lembo and Cavalli, 2010). Green synthesis of nanomaterials is becoming more popular because it has shown to be incredibly challenging to produce these important materials without affecting the environment. Nanotechnology results in better bioavailability, controlled release, medication resistance reduction, drug protection, and targeted antiviral therapy. Over 1500 cases and 600 fatalities have been associated with human infections with the avian influenza A (H5N1) and A(H7N9) viruses in the previous three decades (Saha and Davis, 2022). Influenza virology presents numerous challenges due to the dynamic nature of the virus and its ability to undergo genetic reassortment, leading to the emergence of novel strains with pandemic potential. To address these challenges, innovative strategies such as

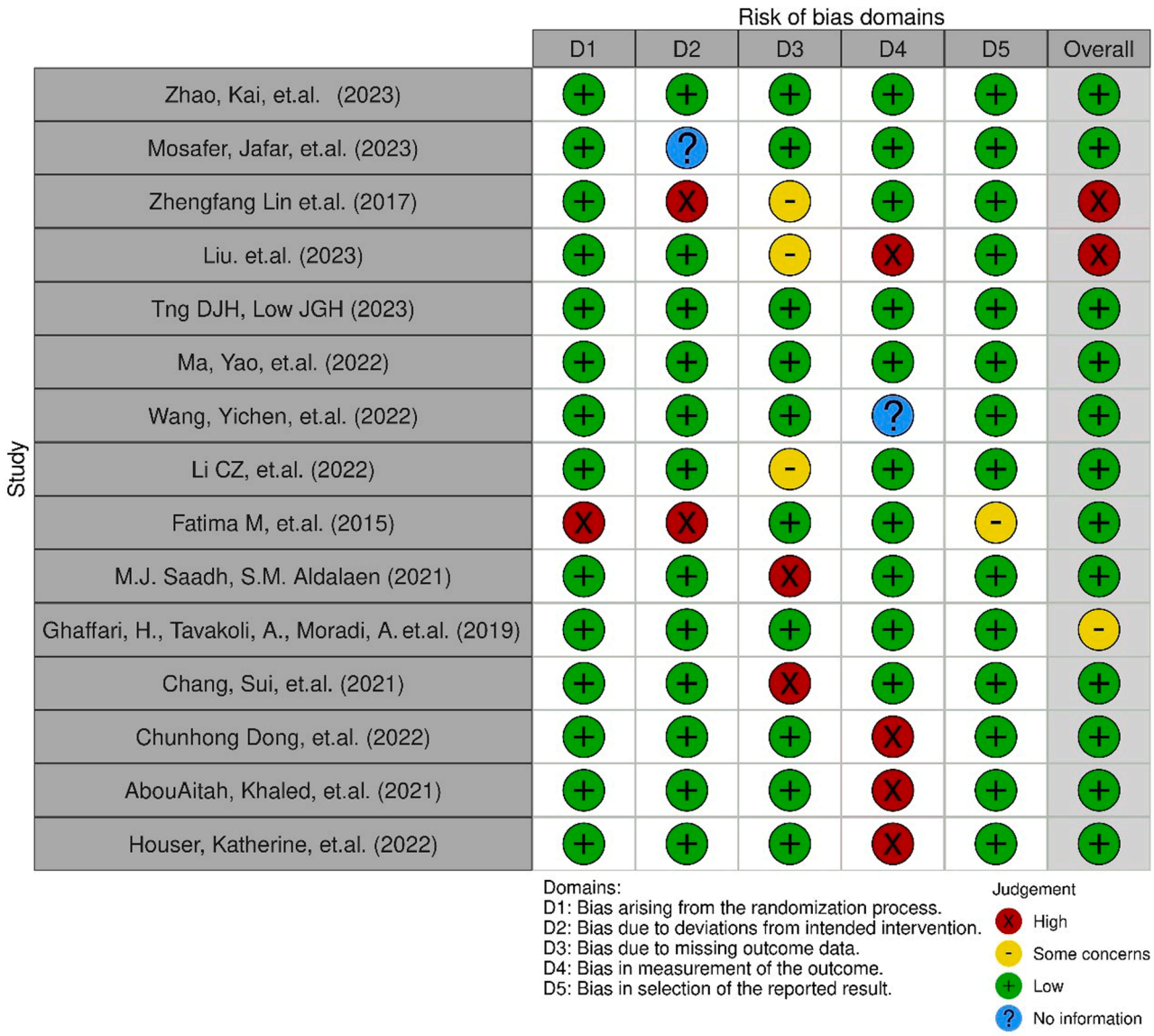

Fig. 1. Quality Assessment of the studies.

nanoparticle-based interventions have garnered attention in recent years. The rationale behind exploring nanotechnology lies in its potential for targeted delivery and enhanced efficacy, offering a promising avenue for more effective prevention and treatment approaches against influenza. With growing human and poultry populations and travels, as well as subpar biosafety and biosecurity procedures in backyard poultry farms and marketplaces, the potential of such a zoonotic illness is rising in many south Asian countries. The human and animal health sectors must work more closely together and regularly coordinate to address this issue. Surveillance data must be shared, and outbreaks must be investigated jointly, utilizing the knowledge of both sectors. However, such cross-sectoral cooperation may need organizational adjustments, resource availability, and enabling legislation. The idea of "One Health" asks for an integrated strategy that considers the health of animals, the environment, and people (Franklin, 2023).

This meta-analysis aims to provide a comprehensive overview of the current landscape of nanoparticle-based interventions for influenza prevention, considering the One Health perspective that encompasses human, animal, and environmental health. By synthesizing the available evidence, this analysis aims to shed light on the potential of nanoparticle-based strategies in combating influenza across diverse species and ecosystems. This comprehensive evaluation will contribute to our understanding of the efficacy and potential of nanotechnology in the field of influenza prevention and treatment.

Methods

Literature search

In this study, we followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Searches were conducted in Web of Science (WOS), PubMed, Science Direct, and Google Scholar to identify potentially eligible literature from the year 2015 to 2023. The search strategy used the following search terms in combination: “nano-formulations” and “nanoparticles” or “influenza”, “preventive measures” or “One Health”.

Inclusion and exclusion criteria

Following the initial search, duplicate articles were eliminated based on the title review using EndNote 20 (Clarivate Analytics, USA). After reviewing the paper’s abstracts, some unrelated studies were also eliminated. The inclusion criteria were established to choose studies that satisfy the meta-analysis’s particular goals. It is believed that studies

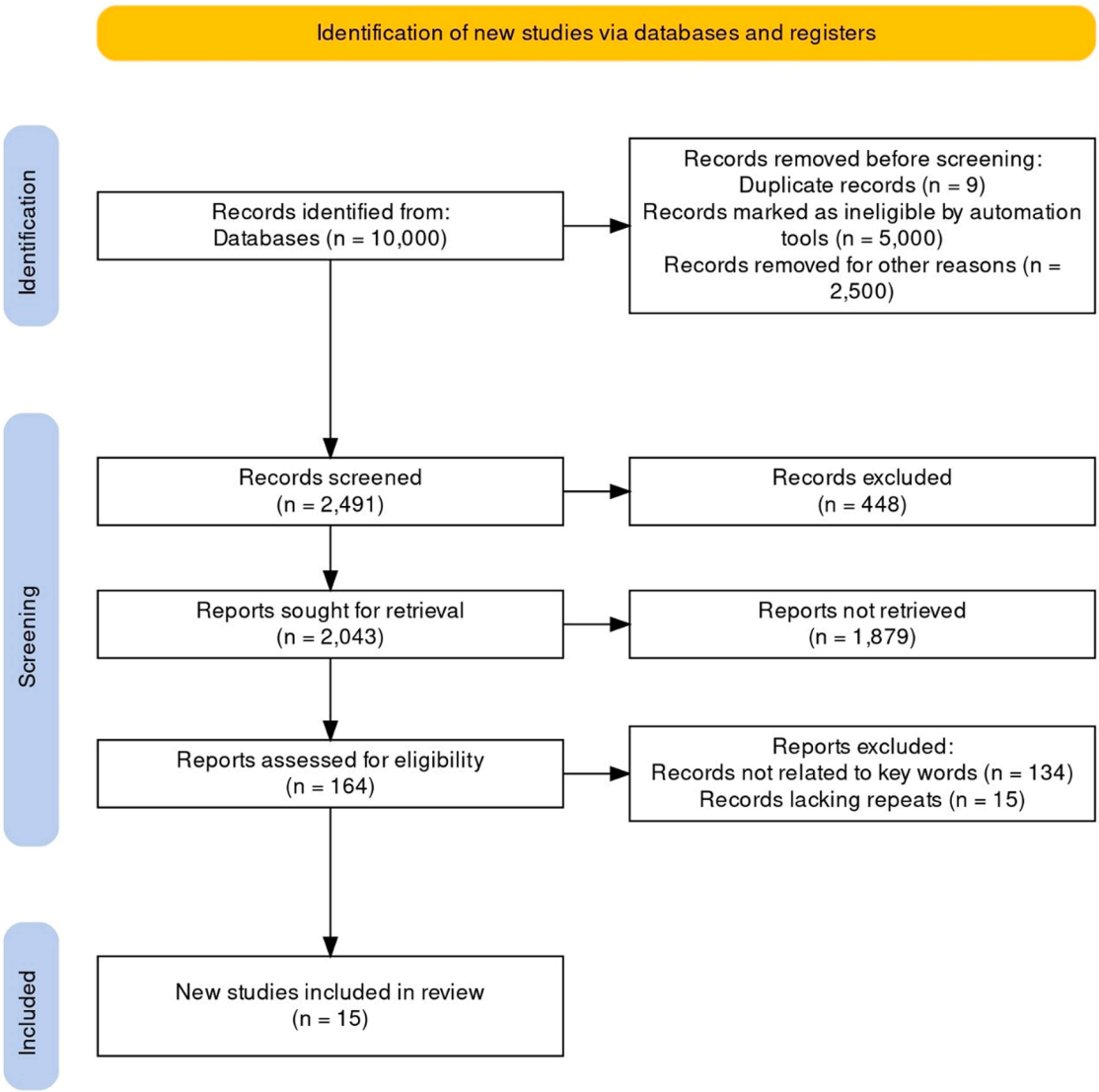

Fig. 2. Schematic workflow for the literature studies and data extraction using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

focusing on oral nano formulations will have higher effects in treating influenza. The remaining publications' entire texts were then retrieved and scrutinized using the predetermined inclusion criteria. For this investigation, the following criteria were used: (a) Recent work done on using nano formulations as a treatment process against influenza. (b) Research articles showing the effects of nano formulations against influenza. (c) The specific and most efficient routes of delivering the nano formulations against treating influenza. (d) Articles published in English language only. Furthermore, the norms used for exclusion criteria were given as (a) book chapters, only abstracts, presentations, thesis, letters to editors, conference articles, and patents were omitted (b) unrelated research articles, articles in predatory journals, low-quality articles, raw manuscripts with an absence of data, inconsistent data were also removed.

Data extraction and quality assessment

The extraction of essential data from identified studies involves proper documentation of key parameters, including authorship, publication year, study design encompassing characteristics of nanoparticles and attributes of cell lines employed for toxicity analysis, as well as details regarding the intervention (nano formulation composition, dosage, method of administration), and outcome measurements spanning effectiveness, safety, and immunogenicity. Additionally, pertinent statistical information is systematically gathered.

Within the pool of selected studies, a subset underwent rigorous quality assessments to ascertain methodological rigor and identify potential biases. The evaluation of internal study validity is facilitated through the utilization of specialized quality assessment instruments tailored to specific research designs. An exemplar tool in this regard is the Cochrane Risk of Bias Tool, chosen for its ability to comprehensively appraise methodological quality and pinpoint potential sources of bias in Fig. 1. This meticulous approach ensures a robust and systematic extraction of data, with a concurrent focus on maintaining the methodological integrity of the studies under consideration.

Results

Literature studies and data extraction

To initiate, a total of 26,267 articles were obtained through primary research, which included examining literature in digital databases. 26,200 records were obtained using Google Scholar, 53 records were obtained from ScienceDirect, 9 records were obtained from PubMed and 5 records were obtained from WOS. Through data mining, a total of 2491 records were obtained using all the databases. A few of these were

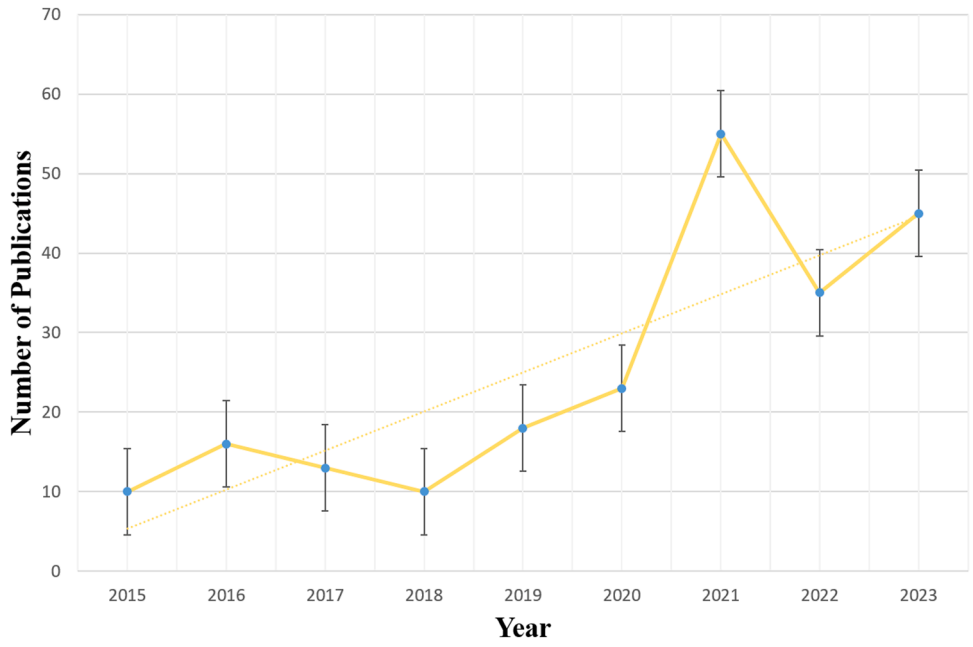

Fig. 3. Graphical representation of the number of publications from the year 2015–2023 related to nano formulations and their efficiency towards influenza strains.

excluded because of duplicates and articles in languages other than English. The abstracts and titles among the 2491 articles were scanned to eliminate the records which were of no interest. Keeping the inclusion and exclusion criteria, in mind around 164 records were identified for analysis. However, articles lacking essential quantitative data were subsequently eliminated. After reading and analyzing the complete publications around 30 records were selected for the meta-analysis (Fig. 2).

Literature screening for information extraction

A plethora of scholarly works has been disseminated between 2015 and 2023, as visually depicted in Fig. 3. The literature inquiry involved meticulous data mining aimed at elucidating nano formulations and discerning attributes emblematic of the physicochemical properties inherent to nanoparticles. This comprehensive analysis entailed a meticulous examination of diverse nanoparticle physicochemical properties, the specific cytotoxicity assays employed, the nature of cells utilized, and the delineated experimental conditions within the corpus of publications. The amalgamated summary of these attributes is systematically derived from the entirety of the dataset. The escalating volume of publications within this scientific domain serves as a tangible indicator of the heightened research activity and scholarly engagement devoted to unravelling the intricate facets of nanoparticle characteristics and their implications.

Observational studies on nanoparticles and their significance

The published papers from the years 2015 to 2023 presented observational research on the role of nanoparticles in the treatment or prevention of influenza virus, according to the methodology used for the meta-analysis (Table. 2). In 2023, it was predicted that a nanoparticle-encapsulated DNA technique might boost the effectiveness of DNA vaccinations, and it was also asserted that the research could be applied to combat the influenza virus (Lembo and Cavalli, 2010), Chitosan has demonstrated tremendous promise in the fight against the influenza virus (Lembo and Cavalli, 2010). Chitosan and trimethylchitosan are effective immunoadjuvants for immunizing against the PR8 entire influenza virus, according to the investigations (Mosafer et al., 2019). Selenium nanoparticles showed profound significance in restraining the proliferation of H1N1 virus in MDCK cell types (Lin et al., 2017; Liu et al., 2023). Silica-Based nanoparticles have shown great potential as therapies against viruses (Tng and Low, 2023).

Observational studies have provided a substantial amount of data on phytochemicals, showcasing a diverse range of potential applications. This suggests that utilizing encapsulated nanoparticles or incorporating phytochemicals into nanoparticle-based delivery systems could offer a promising novel therapeutic strategy for combating the widespread influenza virus (Table 2).

Observational studies on the characteristic of nanoparticles and their efficiency

The properties of the nanoparticles that are being taken into consideration after learning from research were discovered by the in-depth second round of observational investigations. The primary aspects considered in this study include the properties of nanoparticles, cell types on which they affect, and the strains against which they produce outcomes. Analyzed extensively are the nanoparticles in use, their features, whether functionalized or not, the influenza strains utilized, the cell types on which they affect, and their observable effects (Table 3).

Discussion

Our comprehensive meta-analysis underscores the considerable depth of research dedicated to advancing influenza prevention and treatment on a global scale. A notable focal point within this extensive body of work is the pivotal role played by nanoparticles in both prophylaxis and therapeutic interventions. The exploration of nanoparticle functionality reveals their enhanced antiviral activity and precision in drug delivery, marking a significant advancement in influenza mitigation strategies. Nanoparticles exhibit a heightened antiviral efficacy, leading to a reduction in viral load and an augmented survival rate in animal models. This empirical evidence strongly supports the assertion that nanoparticles substantially elevate the overall effectiveness of influenza prevention. Moreover, the application of tailored drug administration further amplifies therapeutic benefits, allowing for increased drug concentrations precisely at the infection site. An innovative avenue in the realm of influenza prevention and treatment is

Table 2
Observational studies conducted against HPAI strains and their importance.

Authors	Title	Publication Year	Significance	Ref.
Zhao, Kai, et al.	Preparation and Immunological Effectiveness of a Swine Influenza DNA Vaccine Encapsulated in Chitosan Nanoparticles.	2023	A DNA vaccine technique using nanoparticle-encapsulated particles may be more effective. Is clinically effective against the influenza virus and merits more research.	(Lembo and Cavalli, 2010)
Mosafer, Jafar, et al.	Preparation, Characterization and in Vivo Evaluation of Alginate-Coated Chitosan and Trimethylchitosan Nanoparticles Loaded with PR8 Influenza Virus for Nasal Immunization.	2023	For the immunization against the PR8 entire influenza virus, chitosan (CHT) and (Trimethylchitosan) TMC NPs are effective immunoadjuvants.	(Mosafer et al., 2019)
Zhengfang Lin et al.	Inhibition of H1N1 influenza virus by selenium nanoparticles loaded with Zanamivir through p38 and JNK signalling pathways	2017	The study created a brand-new substance by selenium Nps loading the antiviral medication zanamvir. This demonstrated effective biological action to stop the H1N1 virus from multiplying in MDCK cells.	(Lin et al., 2017)
Liu, et al.	Adjuvanted Quaternized Chitosan Composite Aluminum Nanoparticles-Based Vaccine Formulation Promotes Immune Responses in Chickens	2023	The N-2-HACC-Al NPs have a wide range of possible applications and can be utilized as an effective nano adjuvant to boost the efficacy of vaccines.	(Liu et al., 2023)
Tng DJH, Low JGH	Current Status of Silica-Based Nanoparticles as Therapeutics and Its Potential as Therapies against Viruses.	2023	For uses in antiviral treatments and vaccines, silica has a number of advantageous attributes, including its antiviral capabilities, efficient carrier, and release efficiency. Silica nanoparticles will continue to spark a lot of interest in biological breakthroughs against pathogens of interest, not just viruses.	(Tng and Low, 2023)
Ma, Yao, et al.	Influenza NP Core and HA or M2e Shell Double-Layered Protein Nanoparticles Induce Broad Protection against Divergent Influenza A Viruses.	2022	Desolvated NP served as the core antigen and HAs and M2e served as the shell antigens in the construction of double-layered protein nanoparticles. The M2e-specific serum antibody levels that contributed to protection via ADCC were markedly raised by the nanoparticles. The nanoparticle mixture under investigation here demonstrated extensive immune defense against various influenza A viruses and serves as an example of a superior vaccination than the present seasonal flu shot.	(Ma et al., 2022)
Wang, Yichen, et al.	Cell-Free Protein Synthesis of Influenza Virus Hemagglutinin HA2-Integrated Virosomes for SiRNA Delivery.	2022	Chitosan as a rigid core adsorbed siRNA and improved the encapsulation efficiency of siRNA. HA2 virosomes were created using cell-free protein synthesis, which opens the door to creating a novel nano vector with high siRNA delivery efficiency and biosafety.	(Wang et al., 2022)
Li CZ, *et al*	Curcumin-Loaded Oil-Free Self-Assembled Micelles Inhibit the Influenza A Virus Activity and the Solidification of Curcumin-Loaded Micelles for Pharmaceutical Applications.	2022	The Cur-SM might be used in pharmaceutical applications as a novel anti-influenza drug with improved bioactivity.	(Li et al., 2022)
Fatima M, et al.	In Vitro Antiviral Activity of Cinnamomum cassia and Its Nanoparticles Against H7N3 Influenza A Virus.	2015	When delivered to cells after infection and incubated with the virus before infection, the silver nanoparticles made from cinnamon extract were found to be successful in both treatments.	(Fatima et al., 2016)
M.J. Saadh, S.M. Aldalaen	Inhibitory effects of epigallocatechin gallate (EGCG) combined with zinc sulfate and silver nanoparticles on avian influenza A virus subtype H5N1	2021	The enhanced antiviral activity of EGCG when combined with zinc II and AgNPs suggests potential as a novel multi-activity topical treatment for H5N1 influenza.	(Saadh and Aldalaen, 2021)
Ghaffari, H., Tavakoli, A., Moradi, A. et al.	Inhibition of H1N1 influenza virus infection by zinc oxide nanoparticles: another emerging application of nanomedicine.	2019	The initial study that looked into ZnO—NPs' ability to prevent H1N1 influenza virus growth. The findings suggested that surface PEGylation of nanoparticles can be effective in enhancing antiviral activity against H1N1 influenza virus and reducing cell cytotoxicity on MDCK-SIAT1 cells. PEGylated ZnO—NPs have a higher anti-influenza activity along with lower cytotoxicity compared to bare ZnO—NPs.	(Ghaffari et al., 2019)
Chang, Sui, et al.	Nanoparticle Composite TPNT1 Is Effective against SARS-CoV-2 and Influenza Viruses.	2021	The oseltamivir-resistant H274Y strains of SARS-CoV-2, as well as human H1N1 and avian H5N1 influenza viruses, could all be successfully inhibited by TPNT1.	(Chang et al., 2021)
Chunhong Dong, et al.	Polycationic HA/CpG Nanoparticles induce cross protective influenza immunity in mice.	2022	Potential cross-protective influenza vaccine candidate PEI-H3/CpG nanoparticles.	(Dong et al., 2022)
AbouAitah, Khaled, et al.	Virucidal Action Against Avian Influenza H5N1 Virus and Immunomodulatory Effects of Nanoformulations Consisting of Mesoporous Silica Nanoparticles Loaded with Natural Prodrugs.	2020	The prodrugs shikimic acid (SH) or quercetin (QR) are loaded into mesoporous silica nanospheres (MSN), which have been functionalized with amine groups (NH2) and used in the nanoformulation. The nanoformulations have an anti-inflammatory and antiviral impact.	(AbouAitah et al., 2020)
Houser, Katherine, et al.	Safety and Immunogenicity of a Ferritin Nanoparticle H2 Influenza Vaccine in Healthy Adults: a Phase 1 Trial.	2022	An innovative, secure, and immunogenic platform with potential use in pandemic preparedness and the creation of a universal influenza vaccine is the ferritin nanoparticle vaccine technology.	(Houser et al., 2022)

Table 3
Observational studies conducted for efficacy of nanoparticles against influenza strains in vitro and in vivo.

Nanoparticle (NPs)	Characteristics of Nanoparticle (NPs)	Functionalized/ Non-Functionalized	Influenza Strains	Cell Line Types	Visible Effects	Ref.
Chitosan Nanoparticles (Chitosan-plasmid DNA nanoparticles, pDNA-CS-NPs)	Spherical Size 153.0 ± 6.2 nm zeta potential of +22.5 mV	NA	Swine Influenza, SIV Strains A (H3N2)	BHK and 293 T cells	Enhancement of humoral and cell-mediated immunity; low and high levels of cytotoxicity for pDNA-CS-NPs. Results show that intramuscular injection of pDNA-CS-NPs considerably improved induction of cellular immunity compared to DNA vaccines in aqueous solution.	(Lembo and Cavalli, 2010)
Sodium Alginate (ALG)-coated chitosan (CHT) &trimethylchitosan (TMC) nanoparticles (NPs)	PR8-CHT-ALG (Size: 239.5, Zeta potential: 32.8 mV) PR8-TMC-ALG (Size: 268.9, Zeta potential: −29.6 mV)	Sodium Alginate (ALG)-coated	PR8 Whole influenza virus	Applied in mouse model (BALB/c mice)	Effective immunoadjuvants for PR8 whole influenza vaccination include CHT and TMC NPs. Following In injection, the PR8-TMC NPs caused fewer immunological responses than the PR8-CHT NPs.	(Mosafer et al., 2019)
Selenium Nanoparticles (SeNPs)	Monodisperse & spherical structure Average sizes of Se@ZNV and SeNPs were 82 nm and 142 nm Zeta potential of SeNPs alone was −24.5 mV and increased to −34.8 mV after loading zanamivir	Surface decoration of SeNPs using Zanamivir (ZNV) Se@ZNV	Influenza A/Hubei/ 74/2009 (H1N1)	MDCK Cell lines	Good biological activity to stop the spread of the H1N1 virus was discovered by Se@ZNV. Se@ZNV inhibited caspase-3 activation and PARP cleavage during H1N1 virus infection. Se@ZNV was used to prevent the spread of the H1N1 virus using p38 and JNK signaling pathways. According to the study, Se@ZNV can successfully shield MDCK cells from H1N1 influenza virus infection.	(Lin et al., 2017)
Water-soluble N-2-Hydroxypropyl trimethyl ammonium chloride chitosan nanoparticles (N-2-HACC NPs), Nano adjuvant N-2-HACC-Al NPs	The particle size and zeta potential of the N-2-HACC-Al NPs were 300.70 ± 24.90 nm and 32.28 ± 0.52 mV	N-2-HACC-Al NPs N-2-HACC-Al NPs	H9N2 avian influenza virus (AIV) HZ strain	Mouse fibroblast cells (L929)	By altering Al with the biosafe N-2-HACC, the Al NPs with N-2-HACC were less hazardous to L929 cells. The N-2-HACC-Al NPs have a wide range of possible applications and can be employed as an effective nano adjuvant to boost the efficacy of vaccines.	(Liu et al., 2023)
Silica-based Lipid Nanoparticles (LNP)	Mesoporous Silica (MSN)				The crystalline and highly organized structure of silica-based nanoparticles allows for precise tuning to produce the required characteristics for clinical applications. Few recorded adverse effects.	(Tng and Low, 2023)
Novel double-layered protein nanoparticles. influenza nucleoprotein (NP) cores and hemagglutinin (HA) or matrix 2 protein ectodomain (M2e) shells.	The diameters of nanoparticles were approximately 200–300 nm	–	Trimeric HA (HA1 from A/Puerto Rico/ 8/1934 (PR8, H1N1) and HA3 from A/Aichi/2/ 1968 (Aichi, H3N2))	HEK-293T cells	Double-layered protein nanoparticles produced broad protection against several influenza A viruses and markedly increased the levels of M2e-specific serum antibodies, which helped to provide protection via ADCC.	(Ma et al., 2022)
Curcumin loaded oil free self-assembled micelles (Cur-M)	The micelles without curcumin and with curcumin showed small average diameters of 10.27 ± 0.109 nm and 13.55 ± 0.208 nm.	–	IAV strain PR8 (A/ Puerto Rico/8/ 1934, H1N1)	MDCK, human embryonic kidney 293T, human adenocarcinoma lung A549 cells.	Cur-M dramatically boosted the bioactivity and stability of curcumin while successfully thwarting influenza Viral entry and virus multiplication show altered curcumin-based RH 40/Tween 80 micelle formulation-based inhibitory	(Li et al., 2022)

(*continued on next page*)

Table 3 (*continued*)

Nanoparticle (NPs)	Characteristics of Nanoparticle (NPs)	Functionalized/ Non-Functionalized	Influenza Strains	Cell Line Types	Visible Effects	Ref.
					strategies against viral infection.	
Silver Nanoparticles (AgNPs)	Mean diameters of AgNP gradually increased to 8 ± 3.6, 10.6 ± 3.7, 11.2 ± 3.0, 15.4 ± 7.6, and 25.3 ± 9.4 nm The zeta potential of AgNP and AgNP/H5 was + 78 ± 0.6 and + 48 ± 0.1 mV, respectively	–	avian influenza virus, A/Ck/ Malaysia/5858/04 (H5N1) (pcDNA3.1/ H5)	MCF-7 breast cancer cells	Green synthesis AgNP is a unique and appealing alternative delivery system for oral DNA immunization since it is stable, simple to make and administer, relatively inexpensive to make in large quantities, and capable of inducing strong immune responses.	(Jazayeri et al., 2012)
Cinnamon-Based Silver Nanoparticles (AgNPs)	Spherical in shape. The average size of Cinnamon-reduced NPs was approx. 42 nm, with size ranged from 25 to 55 nm.	–	Highly Pathogenic Avian Influenza Virus Subtype H7N3	Vero cells	Cinnamon and its equivalent nanoparticles were shown to be harmless to Vero cells, while cinnamon-reduced silver nanoparticles showed an improvement in antiviral efficacy against the H7N3 influenza virus.	(Fatima et al., 2016)
Silver nanoparticles (AgNPs)	The monodispersed AgNPs had a mean diameter of around 9.5 nm.	–	A/Human/Hubei/ 3/2005 (H3N2) influenza virus	MDCK Cells	AgNPs damaged the morphologic structures of viral particles in a time-dependent way by interacting with them. AgNPs have promising antiviral activity against H3N2 IFV through multiple mechanisms, and intranasal administration of AgNPs significantly improved survival in mice, inhibited the development of pathologic lung lesions, and had a marked survival benefit on secondary passage.	(D Xiang et al., 2013)
Zinc Sulfate and Silver Nanoparticles	–	Epigallocatechin gallate (EGCG)	Avian Flu Subtype H5N1	Vero cells	Because EGCG prevents the H5N1 influenza virus from entering the host cell in vitro, it may be a good candidate for use in the treatment and prevention of infections. A novel multi-activity topical therapeutic treatment against the H5N1 avian flu virus may be developed using the potentiated antiviral activity of EGCG in combination with zinc II and AgNPs.	(Saadh and Aldalaen, 2021)
Zinc Oxide Nanoparticles (ZnO—NPs) and PEGylated zinc oxide nanoparticles (ZnO-PEG-NPs)	The average diameters of ZnO—NPs ranged between 20 and 50 nm, whereas the ZnO-PEG-NPs were ranged from 16 to 20 nm.	–	Influenza A/Puerto Rico/8/34 (H1N1; PR8)	MDCK-SIAT1 cells	A novel, powerful, and promising antiviral drug against H1N1 influenza virus infection may be PEGylated ZnO—NPs. Compared to ZnO—NPs, ZnO-PEG-NPs exhibit a higher antiviral activity and less cytotoxicity.	(Ghaffari et al., 2019)
Metal Nanoparticle composite (TPNT1) contains Au-NP (1 ppm), Ag-NP (5 ppm), ZnO—NP (60 ppm) and ClO_2 (42.5 ppm)	Formulated a metal nanoparticle composite, TPNT1 as the stock solution, which contains Au-NP (1 ppm), Ag-NP (5 ppm), ZnO—NP (60 ppm) and ClO_2 (42.5 ppm) in aqueous solution with a positive zeta potential of + 32.81 mV. Au-NP, Ag-NP and ZnO—NP are in spherical shape with 20–40, 10–40 and 25–35 nm diameters.	–	Influenza A/WSN/ 33 (H1N1), Influenza A/WSN/ 33 (H1N1) (NA H274Y), Influenza NIBRG14 (H5N1), Influenza NIBRG14 (H5N1) (NA H274Y)	HEK293T, Vero E6, and MDCK cells	The oseltamivir-resistant H274Y strains of the human H1N1 and avian H5N1 influenza viruses could be efficiently inhibited by TPNT1.	(Chang et al., 2021)

(*continued on next page*)

Table 3 (*continued*)

Nanoparticle (NPs)	Characteristics of Nanoparticle (NPs)	Functionalized/ Non-Functionalized	Influenza Strains	Cell Line Types	Visible Effects	Ref.
	The average sizes of colloidal Au-NP, Ag-NP and ZnO—NP are 78.1, 50.4 and 619.1 nm.					

illuminated through the considerable efficacy of phytochemicals when encapsulated as nanoparticles. The synergistic coupling of phytochemicals with nanoparticles holds promise for conferring enduring therapeutic options, endowed with inherent organic properties that increase the antiviral activity. This study elucidates the potential of encapsulated nanoparticles, the utilization of phyto-nanoparticles as carriers, and nanoparticles functioning as therapeutic agents, thereby proposing novel approaches to combat the influenza virus. Our findings underscore nanoparticles as a compelling avenue for the development of more efficacious antiviral drugs against influenza. The delineation of nanoparticle formulations and exploration of combinatorial approaches emerge as imperative areas for future research endeavours. Looking forward, the trajectory of research and development in the field of nanoparticle utilization for influenza prevention and treatment appears promising. The imperative for cross-sectoral collaboration is underscored, particularly within the framework of the One Health strategy, essential for addressing zoonotic diseases like influenza. The prospect of formulating influenza vaccinations or medications grounded in nanoparticle technology represents a significant stride towards more efficacious prevention and treatment modalities for this pervasive ailment.

Conclusion

In conclusion, our exhaustive meta-analysis highlights the remarkable potential of nanoparticles in revolutionizing the treatment landscape for influenza. The significant effectiveness against the influenza virus not only underscores a pivotal breakthrough but also propels us toward a paradigm shift in therapeutic strategies. The adaptability of nanoparticles opens up captivating prospects for tailoring antiviral approaches, ushering in an era of precision medicine characterized by targeted administration, heightened medication efficacy, and mitigated adverse effects. The integration of phytochemicals into nanoparticle formulations emerges as a particularly advantageous strategy, harnessing the diverse therapeutic benefits inherent in these naturally occurring bioactive substances. Beyond their well-established antiviral activity, phytochemicals contribute immunomodulation and anti-inflammatory effects, presenting a multifaceted arsenal against influenza. This synergistic alliance between phytochemicals and nanotechnology not only enhances antiviral effectiveness but also establishes a sustainable and enduring alternative for influenza therapy. Furthermore, the encapsulation of phytochemicals within nanoparticles enables regulated release, amplifying bioavailability and allowing precise targeting of specific cell types or tissues. The exploration of formulations for phytochemical-based nanoparticles holds immense promise, offering a prospect to broaden the antiviral spectrum, overcome medication resistance, and curtail potential side effects by leveraging the rich diversity of plant-derived chemicals. Looking ahead, future research must centre on refining nanoparticle formulations, their intricate mechanisms, and exploring innovative combinatorial approaches. Cross-sectoral collaboration, integral to successful prevention and treatment strategies, is imperative, with the One Health strategy serving as an essential way for managing zoonotic illnesses like influenza.

These findings not only contribute robust evidence supporting the adoption of nanoparticles in influenza treatment but also pave the way for a transformative future in antiviral therapeutics. The revolutionary impact of nanoparticles holds the promise of significantly improving patient outcomes and reshaping the landscape of influenza treatment through continued research and inventive advancements. As we stand on the edge of a new era in influenza treatment, the potential of nanoparticles emerges as a beacon of hope in our ongoing battle against this enduring viral threat.

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Availability of data and material

Not Applicable.

CRediT authorship contribution statement

Riya Mukherjee: Writing – original draft, Visualization, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Gunjan K:** Writing – review & editing, Validation, Methodology, Data curation. **Himanshu K:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Jasmina Vidic:** Writing – review & editing, Visualization, Validation, Conceptualization. **Ramendra Pati Pandey:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Chung-Ming Chang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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