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MANISH ABHINAV PLAZA-II, ABOVE FEDERAL BANK,
PLOT NO-5, SECTOR-5, DWARKA, NEW DELHI, INDIA-110075,
PHONE: - + (91)-(11)-47026006

Editor in chief

Sevil Şenkardeş

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Marmara University, Istanbul, Turkey.

E-mail: sevil.aydin@marmara.edu.tr

Ali Zarrabi

Department of Biomedical Engineering, Faculty of Engineering and Natural Sciences, Istinye University, Istanbul, 34396, Turkey.

E-mail: alizarrabi@gmail.com

Marlus Chorilli

IDepartment of Drugs and Medicines, School of Pharmaceutical Sciences of São Paulo State University (UNESP), Rodovia Araraquara Jau, Km 01 – s/n – Campos Ville, Sao Paulo, Araraquara, 14800-903, Brazil.

E-mail: marlus.chorilli@unesp.br

Hélder A. Santos

Drug Research Program, Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland.

E-mail: helder.santos@helsinki.fi

Susi Ari Kristina

Department of Pharmaceutics, Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia.

E-mail: jacqui_mclaughlin@unc.edu

Ahmed Awaisu

Qatar University, QU Health, College of Pharmacy, Department of Clinical Pharmacy and PracticeThe institution will open in a new tab, Doha, Qatar.

E-mail: aawaisu@qu.edu.qa

Jacqueline E. McLaughlin

University of North Carolina Eshelman, School of Pharmacy, Center for Innovative Pharmacy Education and Research, Chapel Hill, NC, United States.

E-mail: jacqui_mclaughlin@unc.edu

José Carlos Tavares Carvalho

Laboratory of Drugs Research, Department of Biological and Health Sciences, Federal University of Amapá, Macapá, Brazil.

E-mail: farmacos@unifap.br

Bandana H.K. Saini

University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, NSW, Australia.

E-mail: bandana.saini@sydney.edu.au

Tarik Ainane

Superior School of Technology Khenifra (ESTK), University of Sultan Moulay Slimane, Khenifra, Morocco.

E-mail: t.ainane@usms.ma

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Contents

A Comprehensive Review of Nipah Virus Infection: Origin, Transmission, and Pathogenesis

Ramdas Bhat1*, Preeti Shanbhag1, Ramakrishna Shabaraya2
1Department of Pharmacology, Srinivas College of Pharmacy, Mangalore, Karnataka, India. 2 Srinivas College of Pharmacy, Mangalore, Karnataka, India.

ABSTRACT

This comprehensive review provides a deep exploration of Nipah virus (NiV) infection, encompassing its virology, epidemiology, pathogenesis, clinical manifestations, treatment, prognosis, and prevention strategies. NiV is an enveloped virus with crucial glycoproteins for host cell entry, and it poses an ongoing threat with unpredictable outbreaks occurring in Southeast Asia. The pathogenesis involves both respiratory and neurological manifestations, often resulting in severe outcomes, highlighting the importance of early diagnosis and supportive care. While treatment options are limited, experimental therapies such as ribavirin and monoclonal antibodies show potential efficacy. The prognosis varies widely, underscoring the importance of swift medical intervention. Prevention strategies, including stringent infection control measures in healthcare settings and public health interventions, are pivotal in curtailing NiV outbreaks. The future outlook involves intensive efforts in vaccine development and antiviral research to enhance preparedness. Epidemiological studies, robust surveillance, and community education are essential components of a comprehensive approach to NiV management. This review serves as a valuable resource, emphasizing the urgent need for ongoing research and global collaboration in our continued battle against the NiV. With a concise summary of key aspects, this review provides a comprehensive understanding of NiV, serving as a valuable reference for researchers, healthcare professionals, and policymakers, ultimately contributing to our collective efforts to combat this challenging zoonotic pathogen.

Key Words: Nipah virus (NiV), Zoonotic pathogen, Ribavirin, Monoclonal antibodies, Favipiravir

INTRODUCTION

Nipah virus (NiV) emerged on the global stage in the late 1990s, originating in the serene Malaysian village of Kampung Sungai Nipah. This formidable zoonotic pathogen is exceptionally lethal and capable of causing severe respiratory distress, encephalitis, and death in humans [1]. Its primary natural reservoir comprises fruit bats, particularly those of the Pteropus genus. However, it has demonstrated the ability to infect a diverse range of animals, including pigs, horses, and others. Transmission from animals to humans can occur through direct contact with infected bodily fluids or indirectly via contact with contaminated food or water sources [2].

The discovery of the NiV traces back to early March 1999 when virologists from the University of Malaya isolated the virus from the cerebrospinal fluid of an encephalitis patient. When Vero cells were exposed to this cerebrospinal fluid, the development of syncytia, multinucleated cells indicative of viral infection, was observed. Electron microscopic studies confirmed its classification within the Paramyxoviridae family.

The name "Nipah virus" was proposed due to the initial isolate obtained from a tragic human case in Kampung Sungai Nipah, a village in Negeri Sembilan, Malaysia [1, 3]. Further investigations revealed that NiV-infected cells strongly reacted with Hendra virus antiserum, indicating a close relationship between these two viruses. However, these cells did not exhibit reactivity with antisera against other paramyxoviruses or unrelated viruses like measles virus, respiratory syncytial virus, parainfluenza viruses, herpesvirus, enteroviruses, or Japanese encephalitis virus[4]. In-depth studies disclosed that while the NiV and the Hendra virus shared a relationship, they were not identical. Cross-neutralization studies demonstrated an 816 fold difference in neutralizing antibodies between the two viruses. Initially classified as a potential new member of the genus Morbillivirus and tentatively named equine morbillivirus (EMV), whole-genome analysis ultimately revealed significant molecular distinctions setting NiV apart from known morbilliviruses. Subsequent scrutiny of the NiV genome solidified its status as a novel paramyxovirus, necessitating the creation of the new genus Henipavirus [5]. In 2002, the International Committee for Virus Taxonomy (ICTV) approved the establishment of the new genus Henipa virus to accommodate these distinct and potent viruses. It's essential to note that the Malaysian strain of NiV (NiVMY) exhibits slight variations from the strain found in Bangladesh (NiV-BD). The outbreak in the Philippines was most likely caused by the NiV-MY strain, emphasizing the genetic diversity and complexity of this formidable viral pathogen [6].

The initial documented outbreak of NiV in humans occurred in Malaysia during 1998-1999, and since then, it has spread to other countries and regions, encompassing Bangladesh, India, Indonesia, and the Philippines [3]. Notably, the most recent NiV outbreak unfolded in India in 2022, marking it as the deadliest encounter with the virus to date. This current outbreak of NiV in India commenced in May 2022 within the state of Kerala, gradually extending its grip into other states, including Karnataka, Tamil Nadu, and Telangana [7, 8]. A chilling aspect of this outbreak is the predominant affliction of young adults, with a staggering case fatality rate exceeding 70%, serving as a dire testament to the gravity of the situation [6].

This comprehensive review article endeavors to provide an in-depth understanding of the NiV, covering its origin, transmission, pathogenesis, and the measures implemented to control and prevent its spread. It serves as an invaluable resource for researchers, healthcare professionals, and policymakers grappling with the daunting challenge posed by this infectious disease threat.

RESULTS AND DISCUSSION

Structure of NiV

The NiV, an enveloped pathogen, possesses a distinctive viral structure that plays pivotal roles in its lifecycle and pathogenicity. Encased within a lipid envelope derived from host cell membranes, the virus harbors essential glycoproteins crucial for its infectious prowess. Two major glycoproteins, Fusion (F) and Attachment (G), adorn the viral envelope. The F glycoprotein orchestrates the fusion of the viral envelope with the host cell membrane, facilitating viral entry. Meanwhile, the G glycoprotein acts as a key liaison, binding to specific cellular receptors and initiating the viral entry process. Beneath the envelope lies the Matrix (M) protein, providing structural integrity to the virion and participating in viral assembly and budding. Deep within the viral particle, the genetic material is encapsulated in ribonucleoprotein (RNP) complexes. These RNPs consist of the viral RNA genome intricately wrapped with nucleocapsid (N) proteins, serving as the core machinery for viral replication and transcription once inside the host cell. Understanding this intricate viral structure, particularly the role of glycoproteins in

attachment and fusion, is fundamental for developing antiviral therapies and vaccines, as it offers potential targets to inhibit viral entry and infection. Furthermore, the structural insights aid in comprehending the virus's interaction with host cells and immune responses, paving the way for strategies to control and treat NiV infections [9-11].
The structure of NiV is presented in **Figure 1.**

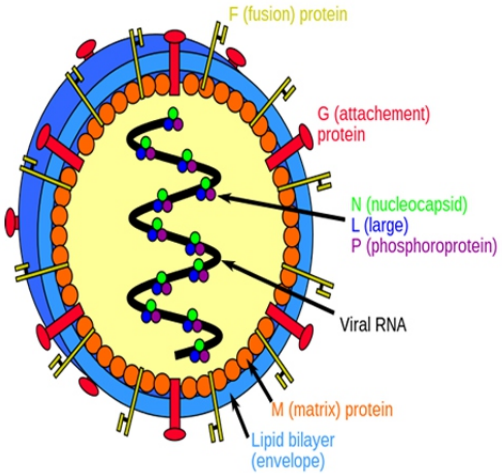

Figure 1. Structure of NiV [12].

Epıdemıology
The first known occurrence of the NiV in MalaysiaSingapore during 1998-1999 initially puzzled health authorities, as it was initially mistaken for Japanese encephalitis. However, after a thorough investigation, it was correctly identified as the NiV. Subsequent outbreaks in different regions, like the Meherpur district of Bangladesh and Siliguri city in West Bengal, India, in 2001, showed significant differences compared to the Malaysian outbreak. These Indo-Bangladesh outbreaks had unique characteristics, including a higher likelihood of human-to-human transmission and infections within healthcare settings, often through droplets or contaminated surfaces. Moreover, the disease seemed more severe and progressed rapidly in these outbreaks, possibly leading to complications like acute respiratory distress syndrome (ARDS) and respiratory failure, resulting in multiple organ dysfunction syndrome (MODS) [1, 3, 6, 13].

A common factor in these Indo-Bangladesh outbreaks, including the 2018 outbreak in Kerala, India, was the link to the consumption of raw date palm sap contaminated by fruit bats. This mode of transmission gained attention due to the virus's remarkable stability in date palm sap, remaining viable for up to seven days at 22 °C, and its resilience across a wide pH range from 3-11. Additionally, human-to-human transmission became evident in these outbreaks, highlighting the complex nature of NiV transmission dynamics. For instance, in the Siliguri outbreak in 2001, a single patient admitted to a private hospital infected 23 hospital staff and 8 visitors, largely due to inadequate adherence to standard precautions. Furthermore, variations in viral strains (BD vs. MY) contributed to differences in transmission rates, with studies indicating that the BD strain resulted in higher levels of viral RNA in the blood and increased viral shedding in oral secretions, potentially explaining the higher secondary infection rates and more severe illnesses [14, 15].

NiV research is also marked by the existence of various strains, such as s, NiV-C, and NiV-I, each having differences in their genetic makeup and disease severity. For instance, NiV-M caused the initial Malaysian outbreak, while NiV-B was associated with outbreaks in Bangladesh and India. These strains exhibit variations in how they spread, with NiV-M being considered more readily transmitted from animals to humans [3]. India has been grappling with a particularly deadly NiV outbreak, marked by a daunting case fatality rate exceeding 60%. Fruit bats are believed to be the primary source of this outbreak, which has spread across multiple states. Despite government efforts to control the outbreak, the risk of further transmission remains alarmingly high [16]. It's essential to remember that the NiV situation is continually evolving, and the most recent statistics may not be fully reflected in this response.

Mode of transmission

The mode of transmission of the NiV primarily involves direct or indirect contact with infected animals or their bodily fluids, as well as human-to-human transmission. Here are the key modes of transmission:

Direct contact with infected animals

The primary natural reservoir of the NiV is fruit bats, particularly those of the Pteropus genus. People can become infected when they come into direct contact with infected bats or their excretions, such as saliva, urine, orfeces. Handling or consuming products from these bats, like raw date palm sap contaminated with bat excreta, can lead to transmission [17].

Indirect contact with contaminated surfaces

NiV can survive on surfaces and in the environment for a certain period. Contact with surfaces, equipment, or objects contaminated with infected bat excreta or bodily fluids can result in transmission if individuals touch their eyes, nose, or mouth after such contact without proper hand hygiene [16].

Consumption of contaminated food or water

In some outbreaks, NiV transmission has occurred through the consumption of raw date palm sap that has been contaminated with the saliva or urine of infected fruit bats. The virus can remain viable in date palm sap for a certain period, making it a potential source of infection [17].

Human-to-human transmission

The NiV has the capacity for human-to-human transmission, primarily through close contact with an infected person's bodily fluids, including respiratory secretions, blood, urine, and saliva. This type of transmission is a significant concern during outbreaks, particularly in healthcare settings where there may be exposure to infected patients or their contaminated medical equipment [15].

Nosocomial transmission

NiV outbreaks in healthcare settings have occurred due to lapses in infection control measures. Healthcare workers and caregivers are at risk of infection if they do not take appropriate precautions when caring for patients with NiV infection, including the use of personal protective equipment (PPE) [3].

Airborne transmission (Rare)

Although not the primary mode of transmission, there have been rare instances of airborne transmission of the NiV in healthcare settings, particularly when aerosolgenerating procedures are performed on infected patients. This emphasizes the importance of strict infection control measures, including the use

of N95 respirators in such situations [7].

Pathogenesis

The pathogenesis of NiV infection is a multifaceted and highly intricate process, encompassing a series of interconnected stages that collectively contribute to the severity and complexity of the disease. This journey begins with NiV's primary target: the epithelial cells that line the respiratory tract, with a notable predilection for the bronchioles. Upon breaching this initial defense, NiV establishes a foothold within the bronchial and alveolar tissues, setting the stage for a robust immune response [11].

This immune response is characterized by the release of an array of cytokines and chemokines, signaling molecules that orchestrate the body's defense mechanisms. However, in the context of NiV infection, this immune activation often leads to a cascade of events akin to ARDS. Patients may experience respiratory distress, compromised lung function, and a host of respiratory symptoms as the immune system fights to contain the virus. As the infection progresses, the airway epithelium responds by releasing inflammatory mediators, including interleukins and granulocyte-colony stimulating factors. These compounds further fuel the inflammatory response, intensifying the overall pathology of the infection and exacerbating respiratory symptoms. The heightened inflammation within the respiratory tract can have a profound impact on the patient's well-being, making respiratory management a critical aspect of care [11, 18].

However, the consequences of NiV infection extend far beyond the respiratory system. The virus possesses the ability to disseminate systematically, infiltrating the endothelial cells that line blood vessels. This facilitates NiV's entry into the bloodstream, enabling it to infiltrate and affect various organ systems throughout the body. The outcome is often multi-organ failure, a dire condition where several vital organs malfunction simultaneously.

It's noteworthy that in animal models, NiV has demonstrated its capacity to infect leukocytes, a subset of white blood cells, further complicating the immune response and contributing to the lethal nature of the infection.

Moreover, NiV displays a pronounced neurotropism, a characteristic that allows it to target neural tissues effectively. This neurotropic inclination has profound implications as it enables the virus to infiltrate the Central Nervous System (CNS) through multiple routes. One such pathway involves NiV entering the CNS via blood vessels, particularly those within the cerebrum. This mode of entry can potentially disrupt the protective Blood-Brain Barrier (BBB), which typically serves as a formidable defense against pathogens gaining access to the brain. Consequently, this breach can result in severe neurological complications, further complicating the clinical picture.

Recent research has uncovered an alternative route of CNS invasion. In this scenario, NiV gains access to the CNS via the olfactory nerve, responsible for the sense of smell. Once inside the olfactory nerve, the virus can disperse throughout the ventral cortex of the brain, exacerbating neurological dysfunction and potentially leading to life-threatening outcomes [11, 18].

Clinical manifestations and symptoms

The clinical manifestation of NiV in humans is provided in **Figure 2.**

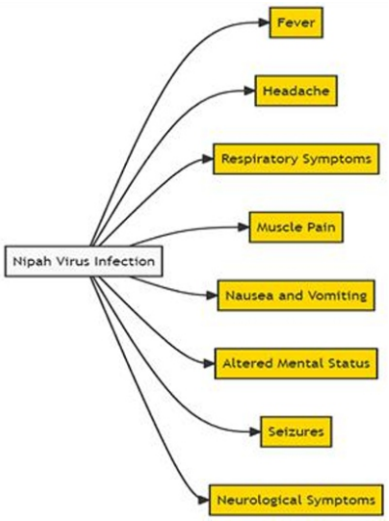

Figure 2. Clinical manifestation of NiV in humans.

Clinical manifestation in humans

NiV infection, known primarily for its impact on the nervous system, has shown that it can affect various parts of the body, including the respiratory system. In the Malaysian outbreak, reports suggested that respiratory issues were seen in about 14-29% of cases. However, it wasn't clear whether these respiratory problems were part of the initial symptoms or developed later, possibly due to aspiration or ventilator-related pneumonia. In contrast, the Singapore outbreak had a unique pattern. Two out of eleven patients primarily had respiratory symptoms without accompanying brain inflammation, while the rest had brain inflammation. On the other hand, cases in Bangladesh and India had a higher occurrence of respiratory issues, accounting for up to two-thirds of cases, and some even developed ARDS. The differences in these respiratory involvement rates could be linked to variations in the virus strains, which we'll delve into further [19, 20].

Besides the clinical symptoms, findings from brain scans have been crucial in understanding NiV infection. In the Malaysian outbreak, MRI scans showed extensive damage in specific brain regions like the cortex, temporal lobe, and pons. Notably, patients who had relapsed or developed brain inflammation later showed multiple areas with patchy and connected cortical damage. In contrast, patients in the Singapore outbreak had a different pattern on their MRI scans. They had small lesions, each less than 1 cm in size, distributed on both sides of the deep white matter and subcortical regions. Some of these lesions became more visible after contrast material was given. These affected areas included the cerebral cortex, brainstem, and corpus callosum. Interestingly, these abnormalities were mainly detected through diffusionweighted (DW) MRI, a technique commonly used to identify conditions like stroke. This pattern, characterized by tiny DW abnormalities followed by T1 hyperintensities, was distinct from what's typically seen in herpesvirus and Japanese encephalitis. Instead, it seemed more aligned with virus-related microangiopathy and resulting small-scale brain tissue damage [17, 20].

Clinical manifestation in animals

NiV infection in animals, with a particular focus on species such as pigs and certain bat species, presents a multifaceted spectrum of clinical manifestations that play a pivotal role in comprehending the intricacies of viral dynamics within both natural reservoirs and intermediate hosts. This comprehensive understanding, rooted in a scientific perspective, forms the cornerstone for the development of targeted

strategies aimed at disease control and prevention [15, 16].

In pigs, which serve as recognized intermediate hosts for NiV transmission to humans, a wide array of clinicalsigns may manifest. These encompass a range of respiratory issues, including persistent coughing and conspicuous dyspnea, reflecting the virus's propensity to target the respiratory system. Neurological symptoms also come into play, with observable tremors, muscle weakness, and impaired coordination providing further insight into the virus-host interaction. Notably, NiV infections in pigs have been linked to reproductive complications, with instances of abortion and stillbirths in pregnant sows. Most alarmingly, sudden and unanticipated deaths can occur among infected pigs, frequently in the absence of overt preceding clinical signs, underscoring the elusive nature of this virus [17, 18]. Fruit bats, notably, the species classified as flying foxes, serve as the natural reservoir hosts for the NiV. Remarkably, these bats tend to exhibit a lack of discernible clinical signs when infected, serving as asymptomatic carriers of the virus. Instead, they harbor and excrete the virus within their bodily fluids and excreta, highlighting their pivotal role as a source of transmission. This unique characteristic underscores the significance of bat-to-animal or bat-to-human transmission via contaminated excretions or saliva [21, 22].

Prognosis of NiV infection

The prognosis of NiV infection varies based on factors like illness severity, timely medical care, and individual characteristics. NiV infection varies widely, with case fatality rates ranging from 40-100%. Several poor prognostic factors have been identified, including older age, severe brain-stem involvement characterized by reduced consciousness, vomiting, abnormal Doll's-eye reflex, abnormal pupils, hypertension, and tachycardia during the illness. These factors signal the potential for severe neurological and systemic complications. However, it's important to recognize that individual outcomes can differ, and early diagnosis, prompt supportive care, and experimental treatments when available are critical in improving the chances of a better prognosis. Public health measures also play a vital role in containing NiV outbreaks and preventing further transmission. Severe cases, especially encephalitis, have higher mortality rates. Early medical intervention, maintaining hydration, and managing symptoms can improve outcomes. Case fatality rates differ between outbreaks and regions, influenced by virus strains and healthcare resources. Survivors may experience long-term neurological issues. Effective transmission control measures and ongoing research into treatments and vaccines offer hope for improved outcomes in the future [11, 22].

Diagnosis of NiV infection

Diagnosing NiV infection involves a comprehensive approach combining clinical evaluation, laboratory tests, and epidemiological investigation:

Clinical evaluation

Healthcare professionals begin by conducting a meticulous assessment of the patient's symptoms and medical history. They inquire about potential exposure to the NiV, which can cause symptoms ranging from mild respiratory illness to severe encephalitis. Neurological symptoms, including disorientation and coma, are particularly concerning.

Laboratory tests

Various laboratory methods play a critical role in confirming NiV infection:

Enzyme-linked immunosorbent assay (ELISA)

ELISA is a widely used serological test that detects viral antigens and evaluates the antibody response. Different techniques of ELISA are employed, including ELISA capture, recombinant protein-based ELISA, and indirect ELISAs for IgG and IgM. These tests are valuable for specific virus detection and assessing the immune response [23].

Virus neutralization test (VNT)

VNT measures the ability of serum to neutralize the virus and prevent its cytopathic effect. It is considered the reference serological test and can be performed using Vero cells or a pseudo-type vesicular stomatitis virus (VSV) containing viral envelope proteins. Plate-based VNT tests are also available [24].

Molecular biology methods

Polymerase chain reaction (PCR) techniques, including reverse transcription PCR (RT-PCR) and nested PCR, are highly sensitive and specific for detecting viral genetic material. These methods target specific viral sequences, such as the N, M, and P genes. Quantitative real-time PCR (qRT-PCR) allows for quantifying viral RNA accurately [25].

Viral isolation

Viral isolation involves culturing samples suspected of containing the virus in suitable cell lines, such as Vero cells. Cytopathic effects, like syncytia formation and plaques, indicate viral growth. Additional tests, including immunostaining, seroneutralization (SN), and PCR, are performed on culture supernatants [26].

Immunohistochemistry (IHC)

IHC uses specific antibodies to stain formalin-fixed tissues, helping detect viral antigens and associated lesions in various organs. This technique is valuable for understanding the virus's impact on different tissues [27].

Epidemiological ınvestigation

Public health authorities conduct epidemiological investigations to understand virus transmission and implement control measures:

- *Case ıdentification:* Confirmed cases are identified, and relevant information is collected.
- *Contact tracing:* Close contacts of confirmed cases are located and identified.
- *Case ınvestigation:* Detailed information about each confirmed case, including sources of exposure and risk factors, is gathered and analyzed.
- *Source ıdentification:* Epidemiologists work to identify potential sources of the virus, including reservoirs, intermediate hosts, and environmental factors.
- *Control measures:* Appropriate control measures, such as isolation and quarantine, are implemented based on investigation findings.
- *Communication:* Clear and timely communication is maintained throughout the investigation to inform the public and relevant stakeholders.
- *Evaluation:* The effectiveness of control measures is assessed to refine strategies for mitigating the virus's impact [2, 28].

Epidemiological investigations provide crucial insights into virus transmission dynamics and guide public health interventions to prevent further spread. This multifaceted approach is essential for diagnosing NiV infection and responding effectively to outbreaks.

Treatment of NiV infection

NiV is a zoonotic virus that can cause severe respiratory and neurological symptoms in humans. Given the absence of a specific antiviral medication approved for NiV, medical management primarily focuses on supportive care.

Isolation and infection control

Patients suspected or confirmed to have NiV infection should be isolated in dedicated healthcare facilities to prevent the spread of the virus to healthcare workers and other patients. Strict infection control measures are crucial. Healthcare personnel must wear appropriate PPE, including gloves, gowns, masks, and goggles, to minimize the risk of transmission [29].

Supportive care

Hydration is a critical aspect of care. Intravenous fluids are often administered to maintain hydration levels, as severe cases of NiV infection can lead to dehydration.

Pain relief medications may be provided to alleviate discomfort and pain experienced by the patient. Fever management is essential. Antipyretic medications, such as acetaminophen, can be administered to reduce fever. In severe cases, patients may experience respiratory distress, and mechanical ventilation may be necessary to assist with breathing [30].

Experimental treatments

Several experimental treatments have been explored for NiV infection.

Ribavirin

Ribavirin, an antiviral medication, has been under investigation for its potential to treat NiV infection. Studies conducted in a laboratory setting (in vitro) and on animals have shown mixed results regarding the effectiveness of ribavirin against NiV and the related Hendra virus. Some laboratory studies have suggested that ribavirin can effectively inhibit the replication of the virus in cell cultures. However, when tested in animal models, ribavirin treatment has yielded varying outcomes, with some studies indicating that it only delayed the progression of the disease but didn't prevent death from NiV or Hendra virus infection. During the NiV outbreak in Malaysia in 1998-1999, there was a notable human study involving patients who either received ribavirin treatment or did not due to unavailability or refusal. This study indicated a 36% reduction in mortality among the treated group. However, it's important to note that the allocation of treatment was not done through randomization, which could introduce bias into the results. The precise dosage of ribavirin for NiV treatment has not been firmly established, but it may follow guidelines similar to those recommended by the World Health Organization (WHO) for Lassa fever. This could include an initial dose of 30 mg/kg for children and 2,000 mg/kg for adults, followed by a 10-day treatment with specific dosing schedules. Ribavirin's oral bioavailability varies (between 32.6% and 52%), and it undergoes firstpass metabolism. It can partially cross the blood-brain barrier. Ribavirin is associated with significant adverse drug reactions, including neutropenia (8-40%), anemia (11-35%, with higher rates in children and adolescents), and lymphocytopenia (12-14%). There have even been reports of suicidal thoughts associated with its use, primarily observed with long-term

administration. Animal studies have shown that ribavirin can cause birth defects, but there is a lack of human studies on its teratogenic effects. Due to its long elimination half-life, it's recommended to wait at least seven months after ribavirin treatment before attempting pregnancy. In 2008, the Infectious Diseases Society of America recommended the use of ribavirin for NiV infections. However, further research is necessary to establish its effectiveness definitively, particularly through controlled trials [1, 3133].

Monoclonal antibody m102.4

parts The experimental monoclonal antibody m102.4 targets specific of the Henipavirus G envelope glycoprotein. In vitro studies have shown that m102.4 is a potent cross-reactive neutralizing antibody against NiV. In animal experiments, including studies on ferrets and African green monkeys, m102.4 has demonstrated effectiveness in preventing infection and death following NiV exposure. In a real-world case in Queensland, Australia, m102.4 was offered on compassionate grounds to individuals exposed to Hendra virus, and they did not develop Hendra virus infection. However, it remains uncertain whether the treatment was effective or if these patients were not infected [34, 35].

Favipiravir

The viral RNA-dependent RNA polymerase inhibitor favipiravir was developed by Toyama Chemical Company as an antiviral for use against influenza. In a Syrian hamster model for NiV infection, favipiravir was successfully used in lethally challenged hamsters [36].

4'azidocytidine and 4'-chloromethyl-2'-deoxy-2'fluorocytidine

These compounds, which are similar to cytidine, have demonstrated potent antiviral effects against NiV when tested in a laboratory setting (in vitro). However, the prodrug version of 4'azidocytidine, known as Balapiravir, did not yield promising outcomes in clinical trials aimed at treating infections caused by flaviviruses. Consequently, it was discontinued due to its poor performance as a prodrug and the presence of undesirable side effects. Nevertheless, modified versions of 4'azidocytidine showed more promising results when compared to the original compound [37-39].

Peptide fusion ınhibitors

Peptide fusion inhibitors have a specific purpose to hinder the fusion of the virus with the host cell's membrane. In animal studies, finely tuned lipopeptide fusion inhibitors have demonstrated their ability to shield against fatal NiV infections. Interestingly, Enfuvirtide (marketed as Fuzeon™), an FDA-approved therapeutic for HIV-1, also falls into the category of lipopeptide fusion inhibitors. This suggests that Enfuvirtide may hold promise as a treatment against NiV due to its mechanism of action [40, 41].

Defective ınterfering particles (DIPs)

DIPs harbor defective genetic material capable of modifying the behavior of a viral population, effectively impeding the replication of the NiV. Laboratory tests conducted in controlled environments have demonstrated that DIPs can significantly lower the viral concentration and mitigate damage to host cells. Although their application as a NiV treatment is in the early exploratory stages, further investigations involving animal studies are warranted. It's worth noting that DIPs have also exhibited potential in combating the influenza A virus, showcasing their broader antiviral potential [42, 43].
NiV vaccine in clinical trial [44] is presented in **Table 1.**

Table 1. NiV vaccine in clinical trial [44].

Candidate Name /Identifier	Development stage	Developers
Subunit vaccine		
HeV sG	Preclinical	Zoetis, Inc./USU
Vectored vaccines		
VSV-NiVB F and/or G	Preclinical	UTMB
VSV-NiVM G	Preclinical	CDC
VSV-NiVM G	Preclinical	RML
VSV-NiVM F and/or G	Preclinical	Yale University
VSV-HeV G	Preclinical	TJU/RML
RABV-HeV G	Preclinical	TJU/RML
ALVAC-F/G	Preclinical	CFIA-NCFAD
AAV-NiVM G	Preclinical	INSERM
rMV-Ed-G	Preclinical	UoT
V-NiVG	Preclinical	USU
rLa-NiVG and/or rLa-NiVF	Preclinical	CAAS-SKLVB
Passive antibody transfer		
Polyclonal serum NiV F or G	Preclinical	INSERM
Mouse mAbs NiV F or G	Preclinical	INSERM
Human mAb m102.4 Henipah G	Preclinical	USU

Disease prevention

Preventing NiV infection, especially among healthcare workers (HCWs), is of utmost importance due to the potential severity of this pathogen. Lessons learned from previous outbreaks like Ebola and severe acute respiratory syndrome (SARS) have led to the establishment of robust guidelines for HCW protection. The core elements of an effective infection prevention and control strategy include standard precautions, rigorous hand hygiene, and the use of PPE. These measures are critical for all patient-care activities, including procedures that generate aerosols. In the event of a NiV infection within a healthcare setting, swift implementation of additional precautions such as droplet, contact, and airborne precautions is essential. This may involve isolating infected patients in singlepatient rooms or cohorting them to minimize contact with susceptible individuals. Immediate isolation and strict adherence to infection control protocols are imperative at the first suspicion of a NiV case [11, 14, 45].

In regions at risk for NiV outbreaks, healthcare facilities should be well-prepared to handle NiV cases. This readiness includes comprehensive screening, admission procedures, and efficient triage systems. Management of visitor access and movement should also be established to minimize potential exposure risks. Adherence to standard precautions should be unwavering across all aspects of patient care, encompassing patient handling, specimen collection, cleaning, and waste disposal. Hand hygiene plays a pivotal role in preventing NiV transmission, with consistent and thorough handwashing using soap and water or alcohol-based hand rubs before and after any patient contact being paramount. The persistence of NiV on surfaces, as observed in previous outbreaks, underscores the importance of rigorous hand hygiene practices. When conducting procedures that generate aerosols or patient examinations, proper PPE usage is imperative. For NiV, the highest level of protection (Level B/A OSHA) is recommended. HCWs should receive thorough training on the correct use and, importantly, the safe removal or doffing of PPE to minimize contamination risks [3, 29, 44, 46].

Preventative measures extend to avoiding contact with infected animals, particularly fruit bats, and their secretions, as NiV is transmitted from animals to humans. Public health measures, such as contact tracing to identify potential exposures and isolating confirmed cases, are crucial to prevent further spread [11, 13, 47]. Additionally, quarantine measures may be implemented for individuals with close contact with confirmed cases, allowing for symptom monitoring and reducing transmission risks [21, 29].

Prospects

Prospects for NiV research are promising and encompass a wide range of critical areas. Currently, there is no vaccine available for NiV infection, vaccine development will continue to be a top priority, with researchers working towards safe and effective vaccines for both humans and potential intermediate hosts like pigs. Various vaccine candidates, including subunit vaccines, virus-like particles, and live attenuated vaccines, will undergo rigorous testing to assess their efficacy and safety, aiming for emergency use authorization and widespread deployment during outbreaks.

Concurrently, research into antiviral therapies will intensify, exploring both existing antiviral drugs for repurposing and the development of novel therapeutic agents. The goal is to identify treatments that can effectively inhibit NiV replication and improve patient outcomes. Additionally, diagnostics will be refined to include rapid point-of-care tests, improved molecular assays, and serological tests, enhancing early and accurate detection of the virus. Epidemiological studies will provide valuable insights into NiV transmission dynamics, reservoirs, and risk factors. Longitudinal studies in endemic regions will help uncover seasonal patterns and potential hotspots for virus spillover. The One Health approach, involving collaboration among experts in virology, epidemiology, veterinary medicine, and environmental science, will be crucial in understanding the complex interplay between human, animal, and environmental factors in NiV transmission. Enhanced surveillance systems will be established to monitor bat populations and detect potential outbreaks early, enabling rapid response and containment efforts. Research into the behavior and ecology of natural reservoir hosts, particularly fruit bats, will contribute to targeted prevention measures. International collaboration, data sharing, and the exchange of best practices will facilitate a coordinated global response to NiV threats. Community education initiatives will be vital in at-risk regions, raising awareness about the risks associated with NiV and promoting preventive behaviors. Finally, global preparedness efforts will focus on stockpiling medical supplies, establishing rapid response teams, and conducting simulation exercises to ensure effective responses to future NiV outbreaks.

CONCLUSION

The NiV remains a formidable global health concern, demanding continued research and preparedness efforts. While treatment options and prognosis vary, early diagnosis and supportive care are pivotal in improving outcomes. Prevention, through stringent infection control and future vaccine deployment, is paramount. Collaborative research, surveillance, and public awareness initiatives offer hope in our ongoing battle against this deadly pathogen.

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Phytochemical Screening and Antibacterial Potential of the Trunk Bark of Ochthocosmus africanus

Viviane Raïssa Sipowo Tala1*, Olivier Tene Tcheghebe2, Marcime Zavier Yamdjeu Happi1, Tambo Ernest1, Aristide Mfifen Munvera3, Pierre Mkounga3, Augustin Ephrem Nkengfack3, Pierre René Fotsing Kwetche1,4

1Higher Institute of Health Sciences, Université des Montagnes, Bangangté-Cameroon. 2Department of Inorganic Chemistry, Faculty of Science, University of Yaoundé I, Yaoundé-Cameroon. 3Department of Organic Chemistry, Faculty of Science, University of Yaoundé I, Yaoundé-Cameroon.

A B S T R A C T

An estimated 57 million deaths are recorded worldwide every year out of which infectious diseases are responsible for 17 million; one-third of the overall mortality rate. To face this crucial issue, the search for new anti-infective agents that could be used by needy populations appeared primordial. The present work aims at detecting a few phytochemical compounds it contains and determining the antibacterial potential of the hydroethanolic extract from the trunk bark of Ochthocosmus africanus (Ixonanthaceae). More especially, it will investigate through the minimal inhibitory and minimal bactericidal concentration (MIC and MBC, respectively) of the extract on common etiologies of bacterial diseases. The phytochemical screening of the hydroalcoholic extract from the plant trunk bark was followed by the determination of its antibacterial potential by macro-dilution in a liquid medium. The minimal inhibitory and bactericidal concentrations (MIC and MBC, respectively) were assessed on six gram-negative rods (Klebsiella pneumoniae, Enterobacter aerogenes, Moraxella spp., Escherichia coli, Serratia odorifera, and Shigella sonnei) and three gram-positive rods (Lactobacillus bulgaricus, Clostridium spp., and Bacillus spp.). The phytochemical screening revealed the presence of secondary metabolites like flavonoids, anthocyanins, tannins, saponosides, triterpenes, cardiotonic heterosides, and reducing sugars. The antibacterial tests further revealed inhibitory and bactericidal features of the extract with MIC values ranging from 25 through 100 mg/mL; while the MBCs were recorded between 50 and 200 mg/mL. Bactericidal activity was observed on Escherichia coli, Enterobacter aerogenes, Shigella sonnei, Clostridium spp., and Lactobacillus bulgaricus (CMB/CMI = 2) and bacteriostatic activity on the others. These findings could justify, at least partially, the use of this plant in infectious; but additional efforts on toxicity are needed for safer healthcare.

Key Words: Ochthocosmus africanus, Phytochemical screening, CMI, CMB, Bacteria

INTRODUCTION

In many developing countries, access to quality medicines remains limited to large cities while infectious diseases (IDs) are rampant in remote areas. In connection with the paucity of mobility facilities, the high cost of pharmaceutical drug specialties and various other socioeconomic constraints, lots of community members in these countries rely on drugs from doubtful origins and traceability to manage disease in general. The available drugs generally have poor quality in most cases of common pathologies. The high expectations that followed the Penicillin introduction in the 1940s to improve

human lifespan rapidly faded away with their abusive use that resulted in the selection and dissemination of adapted microbial strains otherwise referred to as microbial resistance [1]. Microbial resistance makes the control of microbial conditions more and more costly and is associated in these areas with low purchasing power and ancestral traditional disease control practices.

Trends of resistance to conventional drugs and reliance on non-conventional alternatives stimulated the new paradigms about effective anti-infective agents available and affordable to the majority of needy populations. This makes traditional medicine a very important component of the cultural heritage with the abundance of natural resources that could be used as raw materials. Accordingly, and based on the fact that more than 80% of African populations used resources from traditional medicine, the WHO encouraged research in that field acknowledging that scientific knowledge of traditional drugs could significantly improve their efficacy in managing human disorders. These conditions include Ids which represent one of the most common public health issues throughout the world [2]. Several related studies have been conducted in Cameroon in that vein [3-6] with extracts from several species of plants belonging to various botanical families. The present investigation focuses on Ochthocosmus africanus (O. africanus) a plant species from the Isonanthaceae family. O. africanus is widely used in traditional medicine for severe stomachaches [7], as an expectorant, in diarrheal conditions, in the management of sexual impotence, and breastfeeding stopping [8-10].

Previous investigations on O. africanus revealed the presence of ochtofridelane, stigmasterol, N-p-transcoumaroyltyramide, and taraxerol [11]. Scientific pieces of evidence related to the bioactivity of plants from the Isonanthaceae family have been reported on extracts and/or isolated compounds [12, 13]. To present knowledge, however, no studies on antimicrobial potential have yet been performed on members of the Ochthocosmus genus. The present work aims at detecting a few phytochemical compounds it contains and determining the antibacterial potential of the hydroethanolic extract from the trunk bark of O. africanus. More especially, it will investigate through the minimal inhibitory and minimal bactericidal concentration (MIC and MBC, respectively) of the extract on common etiologies of bacterial diseases. In the short run, the findings will primarily serve traditional practitioners in their daily activities. In the intermediate and long runs, standards will be produced for more effective use of this plant's resources in addition to isolation of active secondary metabolites that could be used as concentrated bioactive in the control of Ids.

MATERIALS AND METHODS

Plant material and extraction

The plant material used consisted of the trunk bark of O. africanus, harvested on November 1st, 2016 in Batouri (East Cameroon). The identity was subsequently confirmed at the National Herbarium of Cameroon under reference Voucher 45453 HNC.

The extraction was carried out with 70% ethanol. In the process, 2.2 kg of powder from the bark of the plant's trunk was macerated in 8 L 70% ethanol for 72 hours. The filtrate obtained through Whatman® No. 1 paper was concentrated by rotative evaporation (Heldolph®) at 65 °C and 200 mBars. The total extract obtained was subsequently dried in an oven at 40 °C.

Phytochemical screening

The aqueous test solution was prepared by homogenizing with a magnetic stirrer 1 g of the total extract in

20 mL of distilled water. The preparation obtained was then subjected to phytochemical screening for the detection of secondary metabolites according to Bruneton 1999 [14].

Alkaloids test

In a test tube containing 5 mg of the extract dissolved in 1 mL of methanol, 1 mL of 1% H2SO4 was added. The resulting preparation was heated to ebullition in a water bath for 5 minutes. After cooling and filtration, 5 drops of Mayer's reagent were added to the filtrate. The development of a precipitate indicated the presence of alkaloids.

Anthocyanins test

In a test tube containing 5 mg of the extract dissolved in 1 mL of methanol, five drops of concentrated hydrochloric acid were added. The development of the orange color was characteristic of the presence of anthocyanin in the extract.

Anthraquinones test

In 1 mL of ether-chloroform (1:1), 5 mg of extract was dissolved. The mixture was treated with 4 mL of 10% sodium hydroxide. The development of a red color testified to the presence of anthraquinones.

Flavonoids test

For this test, 5 mg of extract was dissolved in 1 mL of methanol. The mixture was then treated with 0.05 g of magnesium shavings and 3 drops of concentrated H2SO4. The presence of flavonoids was characterized by the development of the following colors: yellow for flavones, red for flavonols, and pink for flavanones.

In a test tube containing 5 mL of distilled water, 5 mg of extract was dissolved, then heated to ebullition in a water bath for 5 minutes. After cooling the preparation was stirred vertically for 15 seconds and then allowed to stand. The appearance of more than one centimeter’s high persistent foam reflected the presence of saponins.

Tannins test

In this test, 5 mg of extract was dissolved in 1 mL of ethanol. Then, 3 drops of 10% Iron Chloride III were added. The development of a blue-violet or greenish color was characteristic of the presence of the tannins.

Triterpenes and steroid tests

In a test tube containing 1 mL of methanol, 5 mg of the extract was dissolved. To the resulting mixture, 0.2 mL of each of the following reagents was added: chloroform, glacial acetic acid, and concentrated H_2SO_4. Development of a purple or greenish color indicated the presence of triterpenes or steroids, respectively.

Test for reducing sugars

To 2 mL of the extract in a test tube, 1 mL of an equal volume of Fehling A and B solutions was added. The mixture was heated to ebullition for 3 to 10 minutes. The development of a brick-red precipitate indicated the presence of reducing sugars.

Cardiotonic heterosides test

2 mL of the alcoholic filtrate, 1 mL of glacial acetic acid, 1-2 drops of FeCl3, and 1 mL of concentrated H2SO4 were added. Cardiotonic heterosides were characterized by the development of a brown ring at the interface. A purple ring could also appear under the brown ring.

Extract antibacterial potential

Bacteria types used

Nine bacteria types were chosen for their frequent implications in human pathologies and their ubiquitous distribution. All the isolates were provided by the Laboratory of Microbiology at the Université des Montagnes Teaching Hospital. These included six gramnegative rods (Klebsiella pneumoniae, Enterobacter aerogenes, Moraxella spp., Escherichia coli, Serratia odorifera, and Shigella sonnei) and three gram-positive rods (Lactobacillus bulgaricus, Clostridium spp., and Bacillus spp.).

Before the tests were conducted, all the isolates were grown on Mueller Hinton agar at 37 °C for 18-24 h. The colonies from this fresh bacterial population were then used for the preparation of a suspension in 5 mL of sterile physiological saline. The resulting preparation was thereafter adjusted to a turbidity standard comparable to that of 0.5 on the McFarland scale.

The dilution range of the extract and susceptibility tests

The macro-dilution in liquid medium technique was used in this investigation. The stock extract solution was prepared at 800 mg/mL. This was obtained by dissolving 6 g of the powder in 7.5 mL of Mueller Hinton broth. The mixture was homogenized by vortexing. For the dilution range, 1500 µL of Mueller Hinton broth was dispensed from the first to the last tube in the range, as well as in the 3 control tubes. Then an equal volume (1500 µL) of the mother solution above prepared was added to the first tube of the dilution range. From this arrangement, a serial dilution (order 2) followed in the other tubes of the series and resulted in a concentration range found between 4000.39 mg/mL. In each of the dilution tubes (except the negative and reagent control), 15 µL of the bacterial inoculum was added. The preparations were incubated at 37 °C for 18 to 24 hours. Upon completion of incubation, the turbidity was first assessed visually, and then the tubes were centrifuged at 5000 rpm for 5 minutes to detect the sediment in case of growth.

Antibacterial's potential parameters

• *Minimal inhibitory concentration (MIC)*

The MIC was identified from the first tube (lowest extract concentration) of the range in which no growth (absence of turbidity) was recorded and for which no bacterial sediment was observed upon centrifugation. The experiment was repeated three times in each case.

• *Minimal bactericidal concentration (MBC)*

In each of the tubes for which no bacterial growth was recorded and in the controls of the concentration range carried out for the MIC, about 5 µL of re-homogenized bacterial suspension were streaked on Mueller Hinton agar. The set was incubated overnight at 37 °C. The CMB of the extract was detected from the first dilution (lowest in the range) in which no culture was recorded. The operation was repeated three times.

• *MBC/MIC ratio*

This report confirms the bacteriostatic or bactericidal character of a substance. When the value is greater

than or equal to 4, the substance is said to be bacteriostatic.

If it is less than 4, the substance is regarded as bactericidal. If it is equal to 1 then it is said to be absolutely bactericidal.

• *Inhibition diameter: Method by diffusion in agar medium*

The inhibition diameter was assessed by the disc diffusion method carried out on extract concentrations equal to the MIC and CMB values recorded. This test was carried out on all bacterial subjects.

The culture was performed by swabbing the agar surface with the above-prepared bacterial suspension (0.5 McFarland). Sterile 6 mm diameter discs cut from sterilized Whatman No. 3 paper were firmly adjusted to the swabbed preparation. On the surface of these discs, 15 µL of the extract at the MIC and CMB values were delicately dispensed. The preparations were incubated at room temperature for 15 minutes on the bench top, then allowed to an overnight incubation at 37 °C. Upon completion of incubation, the inhibitory diameters around the discs were recorded in millimeters. The test was carried out 5 times in each case.

RESULTS AND DISCUSSION

The semi-quantitative result from the phytochemical screening of the hydroethanolic extract of the trunk bark (8.36%) is shown in **Table 1.**

Table 1. Phytochemical composition of the hydroethanolic extract

Phytochemical group	Reagent	Result obtained
Alkaloids	Valser-Mayer	-
Anthocyanin	$H_2SO_4 + NH_4OH$	+ + +
Anthraquinones	10% NaOH	+ + +
Cardiotonic heterosides	Glacial$CH_3COOH + FeCl_3 + H_2SO_4$	++
Flavonoids	1% $FeCl_3$	+ + +
Saponosides	None	+ + +
Reducing sugars	Fehling A and B solutions	+ + +
Steroids	$CHCl_3$ + Glacial$CH_3COOH + H_2SO_4$	+
Tannins	10% $FeCl_3$	+
Triterpenes	$CHCl_3$ + Glacial$CH_3COOH + H_2SO_4$	+

+++: Highly concentrated; ++: Averagely concentrated; +lowly concentrated; -: not detected

It comes out that the O. africanus raw material contains 90% of the target secondary metabolites. About 55% of these metabolites are also highly concentrated and include anthocyanin, anthraquinones, flavonoids, saponosides, and reducing sugars. Relatively low concentrations of cardiotonic heterosides, sterols, triterpenes, and tannins were observed in addition.

Susceptibility test

Antibacterial activity of the extract was observed on all the isolates subjected. Based on the extract concentrations that were necessary for the activity recorded, the minimal inhibitory concentrations (MIC), the minimal bactericidal concentrations (MBC), and the MBC/MIC ratio (R) were presented as

displayed in **Table 2.**

Table 2. MIC, MBC, MBC / MIC ratio, and inhibition diameters

Bacterial type	MIC (mg/mL)	MBC (mg/mL)	Inhibition diameter (mm)		Ratio (MBC/MIC)
			CMI	CMB	
Escherichia coli	50	100	11.66	12.66	2
Enterobacter aerogenes	50	100	11.33	12.33	2
Shigella sonneii	50	100	10.66	11.66	2
Clostridium spp.	25	50	11	13.33	2
Serratia odorifera	25	100	12	13.33	4
Bacillus spp.	25	100	11.33	12.33	4
Moraxella spp.	50	200	12	12	4
Lactobacillus bulgaricus	50	100	11	12	2
Klebsiella spp.	100	200	12.33	12.33	2

MIC: minimal inhibitory concentration; MBC: minimal bactericidal concentration; R: MBC/MIC

It reveals that the lowest MIC and MBC values were obtained on the Clostridium with 25 mg/mL for the MIC and 50 mg/mL for the CMB, while the highest MBC was recorded with Klebsiella (200 mg/mL). Five out of the 9 isolates had identical MICs (50 mg/mL). In addition, the bactericidal potential was observed in 67% of cases while in 33%, the bacteriostatic effect was recorded. Globally, the inhibition diameter values ranged from 11.66-13.33 mm.

For the present investigation, the choice of O. africanus was based on its use in traditional medicine for the caretaking of intestinal disorders in Batouri, East Cameroon. Phytochemical screening of the hydroalcoholic extract of the trunk barks revealed the presence of flavonoids, anthocyanins, saponosides, triterpenes, cardiotonic heterosides, and reducing sugars. The relative concentrations in anthocyanins, anthraquinones, flavonoids, saponosides, and reducing sugars were higher than those of tannins, triterpenes, and steroids. Previous work on the same part of this plant [11] reported the presence of ochtofridelane, stigmasterol, N-p-transcoumaroyltyramide, and taraxerol. According to certain sources, these compounds have antibacterial and antiparasitic potentials [15].

The biological activity of these metabolites is essential in research and development related to pharmaceutical industries. This is the case, for instance, of highly concentrated phenolic compounds which associate a very large set of substances that are difficult to define in time and space because of the large diversity and environmental variations regulating growth and responses to local stressors. The fundamental structural element that characterizes these metabolites is the presence of a benzene nucleus, directly linked to at least one hydroxyl group, free or engaged in other chemical groups like ethers, esters, or heterosides [16, 17]. These associations could play important and differential roles in the degree of activity.

Investigating the antimicrobial potential of the hydroalcoholic extract from the trunk bark of O. africanus, it appeared that it is active on all the isolates subjected to varied concentrations, regardless of the bacterial gram type. Though yet to be accurately demonstrated, these findings could be attributed to the inherent metabolites association discussed above. This activity could also be justified by microbial characteristics, the overall chemical composition of the extract, the stability of the antimicrobial agents,

or specific cellular organization [18]. Antimicrobial activity tests revealed MIC values for all the isolates subjected in the present survey; ranging from 25 to 100 mg/mL. The lowest one (25 mg/mL) was recorded on Clostridium spp., Serratia odorifera, Bacillus spp., and the highest (100 mg/mL) on Klebsiella. The higher value on Klebsiella could be linked to the bacterial capsule known to play an important role in cellular protection from external constraints compared to those recorded on other gram-negative and gram-positive rods. Spore-forming Bacillusis behaved differently than Klebsiella. The difference in the inhibitory concentrations between these two bacterial types may be related to the composition of their outermost coverage; the capsule for Klebsiella and the spore for Bacillus. More specifically, the role of their chemical composition might reasonably be pointed out, though the gram type might be key in a typical cell organization. The capsules and spores have chemically different compositions. The combined influence of both bacterial components should, however, not be ruled out. This development is supported by the values recorded with Bacillus spp., Lactobacillus bulgaricus, and Clostridium spp., on one hand, and Klebsiella capsule on the other. The MBCs obtained varied between 50 and 200 mg/mL. The lowest value (50 mg/mL) was recorded on the Clostridium and the highest (200 mg/mL) on Moraxella. Previous findings reported the antibacterial potential of other plant extracts on several microorganisms including Staphylococcus aureus, Escherichia coli, and Klebsiella pneumonia [19-22]; in agreement with the findings from the present one. Accordingly, it could reasonably be anticipated that the potential of the hydroalcoholic extract of the trunk bark of O. africanus observed in the present survey likely extends to other clinical and other environmental hosts; further indicating how plants from the Ixonanthaceae family could be used in disease control and prevention [12, 13].

A glance at the MBC/MIC ratio values showed bacteriostatic activity on Serratia odorifera, Bacillus spp., and Moraxella spp. (MBC/MIC ≥ 4); and bactericidal potential on Escherichia coli, Enterobacter aerogenes, Lactobacillus bulgaricus, and Klebsiella pneumoniae (MBC/MIC ≤ 4). This activity might theoretically be associated with the secondary metabolites in the extract which act either individually or in combination. Flavonoids, for instance, are known for their antibacterial potential on many bacterial types. It has also been reported that several mechanisms could be enacted simultaneously [23-25]. Some other findings highlighted sets of interactions between flavonoids and mammalian cells [26], justifying the necessity for additional research initiatives in connection with their toxicity, and their preservation the adequate dosages during caretaking. This development is true for triterpenes [27] and tannins which are largely used in traditional medicine. Triterpenes act by altering bacterial proteins through precipitation and/or making the nutritional proteins unavailable [28, 29]. In other words, as a combination of many antibacterial agents that could act individually or collectively, the activity recorded with the extract used in the present study could be defensible. Acknowledging, however, the role of combinations in the survival of plants under various natural environmental influences, it is likely that these secondary metabolites act together in a complex of interactions that are not predictable to current knowledge.

The inhibition parameters (MIC and MBC) were evidence to confirm, quantify, and compare the activities on one hand and appreciate isolate action-specific trends on the other. The results of this in vitro investigation provide an important basis for the use of the extract of O. africanus in the control of infections associated with the microorganisms subjected and their likes, provided that studies on toxicity are conducted. These developments justify future related surveys for standardization that is necessary to appropriately use the virtues of this plant. This would take into account massive experiences resulting in the production of comparable standards for the type of extract in connection with other conventional antibacterial agents.

CONCLUSION

The present study revealed that O. africanus contains phytochemicals with valuable antimicrobial potential etiologies of bacterial infections. This could serve in the development of improved traditional medicines, provided that future steps are taken in the research on other key characteristics with patients, did not suggest any significant difference.

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Pharmacogenomics Approaches in Alzheimer's Disease: A Comprehensive Review

Ramdas Bhat1*, Varshini1, Himasvi1, Ramakrishna Shabaraya1
1Department of Pharmacology, Srinivas College of Pharmacy, Mangalore, Karnataka, India.

A B S T R A C T

Alzheimer's disease (AD) stands as an intricate neurodegenerative condition impacting numerous individuals globally. The present study aimed to comprehensively review pharmacogenomics approaches in AD. In pursuit of enhancing the efficacy and safety of AD treatments, pharmacogenomic strategies have emerged. These methods encompass the identification of genetic variations influencing drug metabolism, the utilization of genetic testing to spot individuals vulnerable to AD, and the pinpointing of potential drug targets grounded in the genetic underpinnings of the ailment. As a demonstration, differences in the genetic variations present within the CYP2D6 gene can mold the processing of donepezil extensively employed cholinesterase inhibitor crucial in the treatment of AD. Identifying these genetic nuances can potentially facilitate personalized dosing or the exploration of alternative drugs. Correspondingly, genetic tests targeting the APOE gene can unmask individuals at a heightened risk of developing AD, enabling early interventions to deter or postpone the onset of the condition. Lastly, leveraging insights into the genetic origins of the disease, pharmaceuticals targeting the beta-amyloid protein, which accumulates in the brains of AD patients, are being crafted. Collectively, pharmacogenomic approaches harbor the potential to refine AD treatment by customizing therapy according to each individual's genetic blueprint.

Key Words: Alzheimer's disease, Pharmacogenomics, Genetic variations, Apolipoprotein E, Personalized medicine

INTRODUCTION

Alzheimer's disease (AD) is a substantial global health concern owing to its increasing occurrence and the constraints of available treatment alternatives [1, 2]. The intricate genetic landscape of AD has long been acknowledged as a pivotal element in its pathogenesis [3, 4]. Recent strides in the realm of pharmacogenomics have ushered in fresh avenues for delving into the unique ways individuals react to medications within the complex tapestry of this disorder [5, 6]. This section aims to provide a thorough introduction, shedding light on the multifaceted essence of AD, its genetic bedrock, and the compelling rationale for seamlessly integrating pharmacogenomic strategies into its management.

AD, a progressively degenerative affliction of the nervous system, casts a profound impact marked by the gradual erosion of cognitive faculties, dwindling memory, and perturbed behaviors, chiefly afflicting the elder populace [7]. Yet, despite intensive research, the creation of treatments that target the very roots of AD remains an elusive aspiration, with prevailing interventions merely affording temporary respite from symptoms [1].

Extensive research into the genetic aspect of AD has revealed that the Apolipoprotein E (APOE) 4 allele plays a significant role in the development of late-onset AD. This momentous revelation has fundamentally transformed our comprehension of the ailment, and subsequent investigations have unveiled additional genes of susceptibility such as triggering receptor expressed on myeloid cells 2 (TREM2), ATP-binding cassette subfamily a member 7 (ABCA7), and clusterin (CLU), further illuminating the intricate genetic architecture underpinning AD. Concurrently, the domain of pharmacogenomics has gained traction, providing a fresh lens through which to scrutinize the diversity in drug responses amongst AD patients. The convergence of genetic insights and pharmacological avenues presents a promising trajectory towards tailored treatment strategies, potentially untangling the complexities of varied drug responses and ultimately enhancing therapeutic outcomes. Decoding the impact of genetic variations on drug metabolism, efficacy, and unfavorable reactions holds the key to crafting interventions that suit the individual patient, heralding a new era of precision medicine for AD [8-12]. As we plunge deeper into the complexities of AD and its genetic substratum, pharmacogenomic approaches furnish a unique vantage point for unraveling the intricate interplay of genetics, drug targets, and the course of the ailment. This exposition seeks to scrutinize the present terrain of pharmacogenomic inquiry in AD, underscoring the latent potential of personalized medicine to revolutionize strategies of treatment, casting a ray of hope upon patients and their close ones.

RESULTS AND DISCUSSION

Mechanism underlying pathogenesis of AD

The development of AD arises from an imbalance in the generation and removal of amyloid-beta (A-beta) peptides. This disbalance triggers the buildup of A-beta clusters, setting off a sequence of repercussions affecting both glial cells and neurons [13, 14]. Specific A aggregates, known as A oligomers, engage receptors on neuron surfaces, impairing regular synaptic function. Simultaneously, the overall neuroinflammatory environment escalates due to astrocytes releasing proinflammatory agents in response to this disarray [15, 16]. Concurrently, tau, a pivotal protein in upholding neuron microtubules, undergoes abnormal chemical changes. These alterations lead to the emergence of tau oligomers and larger aggregations, disrupting synaptic communication. Additionally, brain microglia, the immune cells, internalize these anomalous tau forms. This interaction prompts microglia to produce proinflammatory cytokines, intensifying neuroinflammation [17].

The intricate interplay between Aβ and tau disruption forms the bedrock of AD's advancement. The breakdown of synaptic functionality, coupled with the accumulation of neurotoxic variants and ensuing neuroinflammation, contributes to the cognitive deterioration witnessed in individuals with AD.

Genetic variants associated with AD

AD shows dual variants: early-onset AD (EOAD) and late-onset AD (LOAD), contingent on the symptom debut age. Genetic factors play a substantial role in shaping the paths of both EOAD and LOAD [18]. EOAD arises from genetic changes in genes such as amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2), adhering to Mendelian inheritance guidelines. Conversely, LOAD vulnerability encompasses a collection of genes illuminated by genome-wide association studies (GWAS). While APP, PSEN1, and PSEN2 illuminate a substantial portion of EOAD narratives, LOAD's vulnerability dances to a distinct tune, one that doesn't solely adhere to Mendelian symphony.

The presence of a first-degree relative affected by AD amplifies LOAD's vigilance in their kin, with monozygotic twins resonating more intensely compared to dizygotic counterparts, accentuating the genetic orchestration [19, 20]. APOE ε4, a well-recognized protagonist in the realm of risk, exerts its influence across both EOAD and LOAD [21]. Yet, within the realm of genetics' enduring legacy, AD's tapestry is also woven with non-genetic accents. This mosaic encompasses occupational nuances (pesticides, electromagnetic fields), lifestyle choices (alcohol, smoking, cognitive engagement), antecedent medical histories (head trauma, hypertension), and the interplay with metals such as aluminum, zinc, and lead [22].

The genetic architecture of LOAD spans like a constellation. APOE ε4 guides the choreography of amyloid-beta, while variants of the TREM2 gene delicately influence microglial dynamics and the clearance of toxins. ABCA7 mutations alter the processing of amyloid, and CLU gene variations direct the aggregation and dissolution of amyloid. Alongside these, susceptibility genes interweave within lipid metabolism (B1N1), the tapestry of inflammation (INPP5D), and the whispers of synaptic function (PICALM), collectively composing the mosaic of AD risk [23-26]. The amalgamation of these genetic constituents, intricately entwined with their synergies and the interplay of environmental elements, fashions the grand tableau of AD risk. It is crucial to recognize that while these genetic markers elevate the likelihood of AD, they do not definitively foretell its manifestation. Beyond genetics, a symphony of factors plays a role in the multifaceted landscape of Alzheimer's. Notably, broad genetic testing for AD risk is seldom endorsed due to the intricate and multifaceted nature of the condition, as well as the limited predictive strength of genetic assessments alone.

Pharmacogenomics in drug metabolism and efficacy for AD

Pharmacogenomics is increasingly crucial in AD treatment, introducing genetic variations that impact medication metabolism and effectiveness. Patient genetics significantly influence drug metabolism, particularly through enzymes like cytochrome P450 (CYP). Genetic variants modify enzyme activity, resulting in diverse drug metabolic kinetics, affecting medication efficacy and safety. Genetic diversity in CYP enzymes categorizes individuals as extensive (EM), intermediate (IM), or poor metabolizers (PM), influencing drug journeys in the body [27, 28].

Beyond metabolism, pharmacogenomics also affects AD medication efficacy. Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine (an N-methylD-aspartate receptor antagonist) constitute standard treatments. However, these interventions lack universal efficacy and may lead to adverse reactions. Pharmacogenomic studies decode genetic factors influencing individual responses [29].

Genetic variations, like those in the butyrylcholinesterase (BCHE) and NMDA receptor gene (GRIN2B), impact responses to cholinesterase inhibitors and memantine. Pharmacogenomic insights empower clinicians to tailor treatments based on genetic information, optimizing outcomes while minimizing side effects. This precision medicine approach promises improved AD management [30, 31].

Pharmacogenomic products for the treatment of AD

AD treatment encompasses five FDA-approved drugs: acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine), memantine, and aducanumab. The latter, stirring controversy due to concerns about efficacy and safety, targets amyloid beta plaques [32]. Personalizing AD treatment

involves a genetic panel that includes APOE4, CYP2D6, and BChEK genes. APOE4 variations amplify AD risk and modulate treatment response, CYP2D6 gene variants impact drug metabolism, while BChEK gene alterations influence acetylcholine levels, thereby influencing AD symptoms [33, 34]. This genetic understanding steers gene-focused therapies (like gantenerumab), companion diagnostics (as seen in aducanumab), BAN2401, ALZ-801, and personalized medicine paradigms, fostering more efficient and individualized AD treatment [35].

Pharmacogenomic offerings, such as ApoE4 and CYP2D6 tests, provide clinicians with tools to gauge AD risk and optimize medication choices. By integrating pharmacogenomics, AD treatment attains greater precision, potentially enhancing outcomes and curtailing side effects [36]. The realm of pharmacogenomics is everevolving, carrying the potential to redefine AD treatment by tailoring medication choices to individuals' genetic profiles, thus enhancing therapeutic results and mitigating unfavorable effects. Pharmacogenomics is a swiftly progressing domain, and it's conceivable that more such tests will arise for AD treatment in the future. These evaluations possess the potential to empower physicians to select the most fitting medications for individual patients, possibly leading to an enriched quality of life and a slower AD progression [37].

In conjunction with pharmacogenomic assessments, a multitude of other individualized medicine approaches are under exploration for AD treatment. For instance, researchers are crafting fresh drugs that focus on precise genetic mutations linked to AD. They're also devising novel delivery techniques for existing medications to boost their effectiveness. Personalized medicine emerges as a promising avenue for AD treatment. By considering an individual's unique genetic blueprint, physicians can decide on treatments most likely to yield efficacy while curbing side effects [38, 39]. This could translate into an ameliorated quality of life and a more gradual AD advancement for those affected [40].

Personalized treatment approaches in AD

The approach to treating AD is shifting towards personalization, driven by enhanced comprehension of its intricate nature and individualized variations [41]. This multifaceted neurodegenerative condition, characterized by cognitive decay and memory disturbances, is being tackled through a spectrum of tailored methodologies [42]. These encompass early identification and diagnosis, where precise detection at initial stages facilitates focused interventions utilizing biomarkers, genetics, and advanced imaging modalities [43, 44].

Genetic profiling assumes a pivotal role by uncovering distinct variants such as APOE ε4, aiding in risk prognosis, and guiding therapeutic determinations [45]. Personalized dosing strategies consider an individual's genetic makeup, medical history, and stage of disease, tailoring medications such as cholinesterase inhibitors and memantine to control cognitive symptoms [46]. Precision nutrition schemes, like the Mediterranean diet, are formulated to synchronize with individual dietary inclinations and needs, potentially influencing cerebral health and ailment progression [47]. Tailored lifestyle adjustments encompass bespoke plans for physical exercise, cognitive drills, social interaction, and stress alleviation, fostering the conservation of cognitive function and general wellness [48].

Personalized cognitive stimulation programs challenge and engage an individual's cognitive strengths and weaknesses, potentially reducing the rate of cognitive decline [49]. Acknowledging the indispensable role of caregivers, personalized education, and backing mitigate their burdens. Participation in pertinent clinical trials provides access to avant-garde treatments and interventions that

align with an individual's profile. Adaptations to the home environment enhance safety and autonomy by introducing modifications that cater to individual requirements. Capitalizing on cutting-edge technologies such as wearable gadgets and digital applications enables personalized monitoring of cognitive and physical transformations, facilitating disease management and intervention evaluation. Lastly, individualized psychological support and therapy tackle the emotional ramifications of AD for patients and their families [50]. These bespoke strategies collectively epitomize the evolving panorama of Alzheimer's treatment, aiming for more potent, focused, and individualized care paradigms.

Challenges and limitations of using pharmacogenomics in AD treatment

Applying pharmacogenomics to tailor treatments for AD holds intriguing potential, but it comes with intricate hurdles and multifaceted contemplations. One primary obstacle lies in the limited empirical substantiation [51]. While various pharmacogenomic investigations have been conducted in AD, the modest scale of many studies and their potential lack of universal applicability hinder the robust evidence needed to confidently shape clinical decisions [52-54].

Furthermore, the intricate complexity of AD, shaped by an interplay of genetic and environmental elements, adds a dimension of intricacy to the realm of pharmacogenomics Though pharmacogenomics furnishes valuable insights into potential medication responses, it's unable to encompass the full scope of influences that contribute to treatment outcomes. Augmenting these intricacies are practical and ethical dimensions [55]. These encompass conceivable cost and access barriers linked to pharmacogenomic testing, with concerns about insurance coverage and availability across diverse geographical locales and healthcare settings. Also, pharmacogenomics' current scope is confined to existing drugs, rendering limited guidance for emerging therapies under development. Ethical questions also come to the fore, spanning matters of privacy, potential bias, and the risk that genetic data might fuel stigmatization [56].

Steering through these multifaceted hurdles necessitates a cautious and holistic approach to incorporating pharmacogenomic testing into AD treatment strategies. It demands further research to formulate evidence-based guidelines for pragmatic implementation, all while fostering comprehensive discourse on the wider ethical and societal implications. Ensuring that patients gain a comprehensive understanding of the potential benefits and drawbacks of undergoing pharmacogenomic testing remains central within this evolving realm of tailored medical approaches [57].

Future directions and potential impact of pharmacogenomics in AD treatment

Amidst the challenges and constraints associated with pharmacogenomics in AD treatment, there is a burgeoning interest in its prospective impact. The envisioned directions and potential implications arenoteworthy. Firstly, it can pave the way for targeted therapies by unraveling genetic variations that influence drug reactions, thus enabling the creation of precision treatments that surpass prevailing options in effectiveness and minimizing side effects. Moreover, the integration of pharmacogenomic data into clinical determinations holds the promise of tailored Alzheimer's treatment strategies, meticulously tailored to an individual's genetic composition [38, 58].

Furthermore, the realm of drug development stands to gain from pharmacogenomics, as it offers insights into the genetic facets steering the course of AD. This knowledge not only opens avenues for identifying novel drug targets but also for formulating treatments that outshine current therapies [59]. The far-reaching impact extends to healthcare economics, where individualized treatment plans derived from pharmacogenomics may optimize the allocation of resources, thus potentially curtailing costs. Most

notably, patient outcomes could undergo a paradigm shift. The optimization of drug regimens based on intricate genetic cues has the potential to substantially elevate patient well-being and overall quality of life. Realizing this transformative potential necessitates a concerted effort in two key domains. Firstly, there's an imperative for deeper research into the intricate genetic underpinnings of drug responses, to comprehensively exploit pharmacogenomics' potential. Simultaneously, the establishment and seamless integration of evidencebacked protocols for integrating genetic insights into clinical decisions is paramount [36, 40].

Through a dedicated resolve to address these challenges, pharmacogenomics stands poised to usher in a new era in AD treatment, one characterized by enhanced efficacy, individualized approaches, and improved patient outcomes.

CONCLUSION

Pharmacogenomics offers personalized Alzheimer's treatment using genetic insights on drug response. Challenges include limited evidence, complex genetics, cost, drug options, and ethics. Yet, benefits like targeted therapies and patient outcomes are substantial. Future practice needs provider education, guidelines, and patient access to testing. Research is crucial for realizing pharmacogenomics' potential in Alzheimer's treatment.

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Estimation Method for Dapagliflozin in Bulk and Marketed Dosage Form: Development and Validation by UV-Spectroscopy

Saipranavi Vadla1, Vaishnavi Putta1, Saipriya Nadipudi1, Sowmaya Bilakanti1, Neelima Kudumula1*

1Department of Pharmaceutical Analysis, Sarojini Naidu Vanita Pharmacy Mahavidyalaya, Affiliated to Osmania

ABSTRACT

The present study aimed to develop a novel and sensitive method for spectrophotometric estimation in the UV region for the determination of dapagliflozin in its tablet formulation and to validate all analysis parameters according to ICH guidelines. Dapagliflozin was found to show its λ max at 220 nm using a UV-Vis spectrophotometer with a 1 cm quartz cell and methanol: water in the ratio of 15:85 for the preparation of stock solution (1000 µg/ml) and distilled water was used for further dilutions, for the preparation of working solutions. The technique used followed Beer's Lambert's law in the concentration range of 5–30 µg/ml, with a correlation value of 0.999. The limits of detection (LOD) and quantification (LOQ) were 0.623 µg/ml and 1.889 g/ml, respectively. The estimated percentage of the drug was nearly 103%, in good agreement with the marketed dosage form label (Udapa*10). Recovery experiments were carried out at three distinct levels, and the results were determined to be good. Furthermore, the findings of the methodologies devised for robustness and roughness are within their limitations. The suggested method is inexpensive, simple to use, and appropriate for regular analysis of dapagliflozin in bulk and commercial dose forms.

Key Words: Dapagliflozin, UV-Spectrophotometer, Bulk and marketed dosage form, Validation

INTRODUCTION

Dapagliflozin is a Category III antidiabetic drug under the Biologics Classification System (BCS) of the European Medicines Agency (EMA). These inhibitors are a new class of antidiabetic drugs called flozins, which are more soluble and nearly impermeable [1]. It is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that works largely by inhibiting glucose reabsorption from the liver, resulting in higher urine glucose excretion and, as a result, decreased blood sugar levels in type 2 diabetes patients. The medication has demonstrated an enhanced mode of action that is independent of insulin and only depends on plasma glucose and renal function. Dapagliflozin is a pill that is taken orally. It is particularly effective in the treatment of type 2 diabetes mellitus (DM) patients, both as a single agent and in combination with other anti-diabetic medications. Recent studies have shown that the fast action of dapagliflozin decreased the fasting plasma glucose levels within one week of treatment [2].

This is a crystalline white powder that is readily soluble [3] in methanol, ethanol, dimethylformamide, and dimethylsulfoxide. Chemically, it is (1S)-1, 5-Anhydro1-[4-chloro-3-(4-ethoxybenzyl) phenyl]-D-glucitol with a molecular weight of 408.98 and a molecular formula of C24H33ClO8. Figure 1 depicts the chemical structure of dapagliflozin.

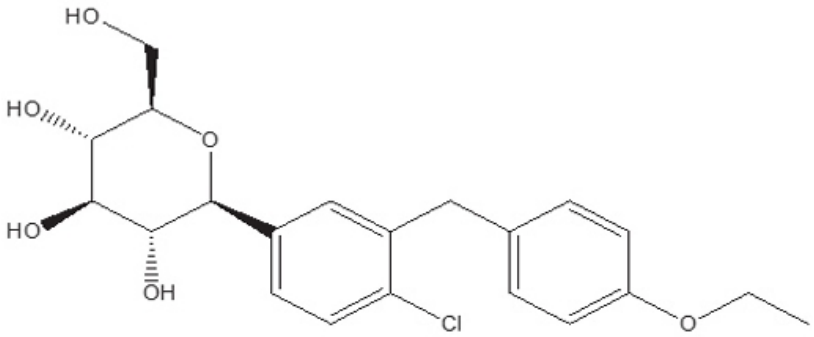

Figure 1. Chemical Structure of dapagliflozin

Literature review [4] and overview [5] deduce the drug from bulk and marketed formulations by UV spectroscopy [6-9] and RP-HPLC [10-18], UPLC [19, 20]. There have been only a couple of techniques published for UV spectrophotometric measurement of dapagliflozin alone and in combination with other drugs [21, 22], utilizing commercially available solvents and buffers. The present study aimed to develop a novel and sensitive method for spectrophotometric estimation in the UV region for the determination of dapagliflozin in its tablet formulation and to validate all analysis parameters according to ICH guidelines. This method was developed using methanol for solubilization and distilled water as the solvent for dilution. This is the most economical method of routine analysis and has not been previously reported based on a literature search performed before the work began. In addition, the newly proposed technique was validated for accuracy, precision, robustness, and linearity following ICH Q2 (R1) [23]. The results showed the reliability of the method.

MATERIALS AND METHODS

Equipment

The suggested study was conducted using a UV-1800 SHIMADZU and UV-3200 LAB INDIA UV-visible spectrophotometer with 1 cm quartz-matched cells. Weighing was done on an electronic balance (ShimadzuBL220H), sonicated with Sonica Ultrasonic Cleaner, Spincotech PVT LTD.

Chemicals and reagents

Dapagliflozin-standard was acquired as a gift sample from Dr.Reddy Laboratories, Hyderabad, dapagliflozintablets (Udapa*10) label claim 10 mg produced by MSN Laboratories was purchased from the local market, and Analytical grade solvent-methanol was obtained from Rankem, Maharashtra, India.

Standard preparation

Considering that methanol was discovered to make the medicines soluble, the standard stock solution was produced by dissolving 10 mg of dapagliflozin in 1.5 ml of methanol and then increasing the volume to 10 ml with distilled water to reach a concentration of 1000 g/mL. A suitable dilution of the standard stock solution using distilled water was used to create the working standard solution, which contained 10 g/ml.

Determination of wavelength of maximum Absorption

The drug's maximum absorbance (max) was discovered to be 220 nm, as shown in **Figure 2** when 10

g/ml of standard dapagliflozin was scanned in a UV spectrophotometer between 190 and 300 nm.

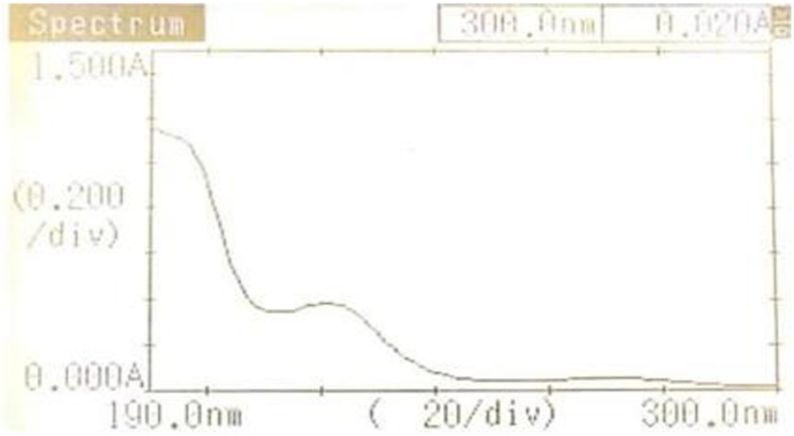

Figure 2. λmax of dapagliflozin

Assay

The quantity of tablet powder equal to 10 mg of dapagliflozin was precisely weighed, transferred to a 100-ml volumetric flask, and solubilized by dissolving in 15 mL of methanol, sonicating for 10 minutes, and then diluting with distilled water to the mark to obtain a concentration of 100 g/ml, followed by filtering through a Whatman filter paper. A 10 ml volumetric flask containing 1 ml of the filtrate was filled with the mixture, which was then diluted with distilled water to achieve the final concentration of 10 g/ml. The results of measuring the absorption using a selected wavelength are displayed in Table 1.

Weight of 10 tablets = 2830 mg
10 tablets average weight = 2830/10 = 283 mg

$$Weight\ to\ be\ taken = \frac{Weights\ to\ be\ taken \times Equivalent\ weight}{Label\ claim} = \frac{283 \times 10}{10} = 283\ mg \quad (1)$$

$$Assay = 100 \times \frac{Absorbance\ sample}{Absorbance\ standard} \times \frac{Concentration\ standard}{Concentration\ sample} = 100 \times \frac{0.455 \times 10\ \mu g/ml}{0.441 \times 10\ \mu g/ml} = 103\% \quad (2)$$

Table 1. Percentage assay of dapagliflozin

S. No	Brand name	Available form	Label claim	Standard absorbance (10 µg/ml)	Sample absorbance (10 µg/ml)	Assay (%)
1	UDAPA*10	Tablets	10 mg	0.441	0.455	103

Method validation

The process of creating a narrative proof that a system, procedure, or movement has been put into use or tested and maintained the necessary level of consistency across all phases is known as methodology validation. Approved scientific strategies are essential for improving diagnostic techniques and have

been time and again tested for specificity, linearity, accuracy, precision, range, limits of detection, and quantization cutoffs. In summary, the development and approval of a systematic strategy confirm that accurate and reliable potency estimation of medicinal products has been performed.

Validation parameters

To prove in writing that a method's performance complies with the demands of the intended analytical application, validation parameters are utilized. The purpose of the verification is to demonstrate that the analytical results obtained using a particular method are suitable for that purpose and are as specified below.

Method validation

The goal of this work was to provide a novel, simple, and affordable method for measuring dapagliflozin spectroscopically. Following the ICH recommendations, the method's linearity, accuracy, precision, and dependability were evaluated.

Linearity

The Linear relationships must be evaluated using a variety of analysis methods. For linearity to be established, at least five concentrations are advised. By diluting the standard stock solution using the suggested technique, it may be directly identified with the API. The correlation coefficient, the point of intersection with the ordinate, and the slope of the regression line should be provided.

Accuracy

Recovery tests were carried out by combining known quantities of the standard medication with formulation samples to verify the validity of the aforementioned procedure. Three distinct levels—50%, 100%, and 150%—were used for recovery tests.

Precision

The accuracy of the process is determined by the degree of agreement between the individual test results when it is employed for several samples of a homogeneous sample. The performance of feature parameters and the statisticalprocessing of analytical data for both intraday and Interday are both necessary for the validation of analytical procedures. These procedures establish the analytical data's tolerance for variance. Typically, the variance, standard deviation, or coefficient of variation of a collection of measurements is used to describe the analytical procedure's accuracy.

Reproducibility

Reproducibility is also referred to as intra-assay precision. Reproducibility is defined as short-term accuracy under identical conditions of use.

Robustness

Robustness evaluation relies on the type of approach being researched and should be taken into account throughout the design process. The reliability of the assay concerning intentional changes to method parameters should be demonstrated.

LOQ (Limit of detection) and LOQ (Limit of quantification)

Response standard deviation and determined by the linearity slope

The detection limit (DL) can be written as follows: DL = 3.3 σ/ S, where σ is the response's standard deviation and S is the calibration curve's slope. The limit of quantification (LOQ) can be written as LOQ = 10 σ/S, where σ is the response's standard deviation and S is the calibration curve's slope. The slope can be calculated using the analyte calibration curve.

RESULTS AND DISCUSSION

All validation parameters were carried out under the conditions mentioned in the ICH Q2 R (1) guidelines.

Linearity and range

The results from the linearity research were produced using five distinct aliquots of the reference solution and a chosen wavelength of 220 nm to test various concentrations (5, 10, 15, 20, and 25 g/mL). The limit of detection (LOD), limit of quantification (LOQ), and standard curve plot of the assay were also computed. The findings are presented in **Table 2.**

Table 2. Linearity of dapagliflozin in working standards.

S. No	Concentration in µg/ml	Absorbance
1	5	0.215
2	10	0.455
3	15	0.692
4	20	0.918
5	25	1.13
6	30	1.365
Standard deviation		0.4277
Correlation coefficient		0.999
Slope		0.045

Acceptance criteria: correlation coefficient (r^2) -0.999.

Dapagliflozin concentration was plotted on the X-axis, and absorbance was plotted on the Y-axis to create a calibration curve. Figures 3 and 4 of the r^2 correlation reveal that a linear association was seen in the concentration range of 5-30 g/ml (r^2-0.999).

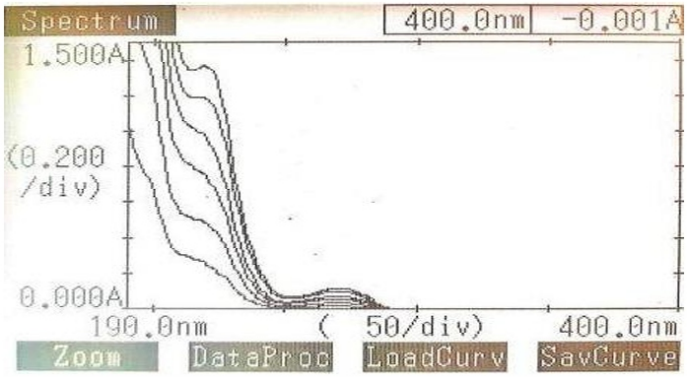

Figure 3. Overlay spectra of dapagliflozin of the concentrations used for linearity.

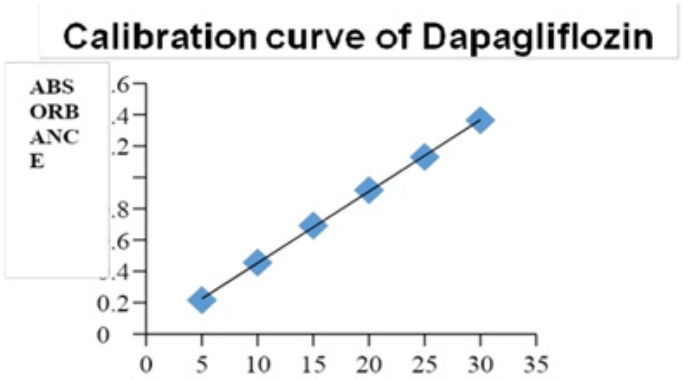

Figure 4. Linearity plot of dapagliflozin

Accuracy

Recovery studies evaluated the proposed accuracy. A known amount of the drug substance dapagliflozin (100 µg/ml) diluted from a stock solution was added to the preanalytical tablet formulation (100 µg/ml) into a 10 ml volumetric flask and volume made up to 10 ml with distilled water. Analysis of dapagliflozin was performed at 50%, 100%, and 150% concentrations. The suggested procedure's recoveries were estimated. The results are displayed in **Table 3.**

Table 3. Accuracy readings of dapagliflozin

S. No	Concentration (µg/mL)		Final concentration (µg/ml)	Absorbance	Recovery (%)	Standard deviation	RSD (%)
	Sample volume (ml Taken)	Standard volume (ml Spiked)					
50%	0.4	0.1	5	0.224	98.46153846	0.001527525	**0.67%**
	0.4	0.1	5	0.226	99.34065934		
	0.4	0.1	5	0.227	99.78021978		
100%	0.4	0.2	6	0.271	99.26739927	0.001527525	**0.56%**
	0.4	0.2	6	0.272	99.63369963		
	0.4	0.2	6	0.274	100.3663004		
150%	0.4	0.3	7	0.317	99.52904239	0.00057735	**0.18%**
	0.4	0.3	7	0.317	99.52904239		
	0.4	0.3	7	0.318	99.84301413		

Precision

The accuracy of an analytical procedure is defined as the degree of agreement between a series of measurements obtained using the same homogeneous sample many times under particular circumstances. The findings are shown in **Table 4.**

Table 4. Precision studies data of dapagliflozin

Intraday precision		**Interday precision**	
Sample No	Absorbance	Day	Absorbance
1	0.439	Day 1	0.452
2	0.446	Day 2	0.449
3	0.454	Day 3	0.44
4	0.445	Day 4	0.449

5	0.441	Day 5	0.444
6	0.441		
Mean	0.4443333	**Mean**	0.4468
SD	0.0054283	**SD**	0.004764452
RSD (%)	**1.2216776**	**RSD (%)**	**1.066349978**

Acceptance criteria: less than 2
quation-1 Standard deviation (x-x) 2/n
quation-2 S σ/x *100

Robustness

Robustness is an indicator of dependability under normal circumstances since it quantifies the capacity to be unaffected by small but intentional adjustments in procedure parameters.

By adjusting the λmax and monitoring the generated drug concentrations' absorbance, this method was carried out. Equations 1 and 2 were used to obtain the standard deviation and percent RSD. The findings are displayed in **Table 5.**

Table 5. Robustness of dapagliflozin

Concentration (10 µg/mL)	**Wavelength 220 NM**	**Wavelength 223 NM**
	Absorbance	**Absorbance**
1	0.441	0.399
2	0.439	0.397
3	0.444	0.4
4	0.445	0.398
5	0.441	0.41
6	0.446	0.399
Mean	0.442666667	0.4005
SD	0.00273252	0.004764452
RSD (%)	**0.617286191**	**1.189625893**

Ruggedness

It determined the intraday and Interday accuracy of the approach. A repeatability study (intra-day) was performed by repeatedly evaluating the dapagliflozin solution (10 µg/ml) throughout the day. Dapagliflozin solution (10 µg/ml) was frequently examined on multiple days to get inter-day precision. Results are displayed in Table 6.

Table 6. Ruggedness of dapagliflozin

Concentration (10 µg/ml)	Day-1		Day-2	
	Analyst-1	Analyst-2	Analyst-1	analyst-2
	Absorbance	Absorbance	Absorbance	Absorbance
1	0.449	0.439	0.439	0.44
2	0.455	0.441	0.441	0.439
3	0.454	0.439	0.451	0.45
4	0.445	0.447	0.442	0.44
5	0.446	0.45	0.447	0.441
6	0.435	0.448	0.439	0.436
Mean	0.4473	0.444	0.443	0.441
SD	0.0072	0.00489	0.00483	0.0047
RSD (%)	1.628	1.1033	1.09	1.073

The limit of detection and limit of quantification

The formulas were used to calculate the limits of detection and quantification that are listed in **Table 7.**

$$LOD = (3.3\ X\ \sigma)\ /S \quad (3)$$

$$LOQ = (10\ X\ \sigma)\ /S \quad (4)$$

σ = standard deviation,
S = slope of the calibration curve.

Table 7. LOD and LOQ value for dapagliflozin

Name of the Drug	LOD (ppm)	LOQ (ppm)
Dapagliflozin	0.62362	1.88976

CONCLUSION

Dapagliflozin dose composition in tablet and bulk form was both examined. It was determined that the formulation's medication content was within acceptable limits. All validation parameters were tested following ICHQ2 (R1) criteria, and it was found that every parameter was within allowable ranges. As a result, the recommended method may be used to determine dapagliflozin concentration using a UV-visible spectrophotometer in both bulk and commercial dosage forms.

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Current Trends and Future Directions in Nanomedicine: A Review

Sachin Namdeo Kothawade1*, Vishal Vijay Pande1, Sandesh Sachhidanand Bole1, Prashant Bapusaheb Patil1, Vaibhav Sudhakar Wagh2, Rajashri Balasaheb Sumbe2, Jayprakash Sitaram Suyrawanshi3, Kalyani Appasaheb Autade4

1Department of Pharmaceutics, RSM's N. N. Sattha College of Pharmacy, Ahmednagar, Maharashtra, India.

2Department of Pharmaceutical Chemistry, RSM's N. N. Sattha College of Pharmacy, Ahmednagar, Maharashtra, India.

3Department of Pharmacognosy, RSM's N. N. Sattha College of Pharmacy, Ahmednagar, Maharashtra, India.

4Department of Pharmacology, RSM's N. N. Sattha College of Pharmacy, Ahmednagar, Maharashtra, India.

A B S T R A C T

Nanomedicine is a rapidly growing field that applies the principles of nanotechnology to improve healthcare, with a focus on the diagnosis, treatment, and prevention of diseases. Nanoparticles offer unique properties that make them useful in medicine, including a high surface area-to-volume ratio and specific targeting capabilities. The article reviews the different types of nanomedicines used in the pharmaceutical industry and their potential benefits, as well as the mechanisms of targeted drug delivery. While nanomedicine has led to the development of globally marketed therapies such as Doxil and Abraxane, regulatory and ethical considerations must be addressed to ensure safety and efficacy. The limitations of nanomedicines in targeted drug delivery, such as limited drug payload capacity and lack of specificity, must also be addressed. Despite the challenges, the prospects for nanomedicine are promising, with the potential to revolutionize personalized medicine, improve disease diagnosis and treatment, and support tissue regeneration and repair. Integration with artificial intelligence can lead to more precise and efficient drug delivery and disease diagnosis. Continued investment and collaboration between researchers, healthcare providers, and industry partners can help overcome obstacles and unlock the full potential of nanomedicine. Overall, nanomedicine is an exciting and promising field that has the potential to significantly improve healthcare outcomes.

Key Words: Nanomedicine, Targeted drug delivery system, Treatment, Healthcare, FDA (food and drug administration)

INTRODUCTION

Nanomedicine is an interdisciplinary field that applies the principles of nanotechnology to the diagnosis, treatment, and prevention of diseases. It involves the use of nanoparticles, which are typically between 1 and 100 nanometres in size, to develop new and innovative therapies that can improve patient outcomes [1]. The unique properties of nanoparticles, such as their high surface area to volume ratio, unique optical and magnetic properties, and ability to target specific cells, make them useful in medicine [2].

The objective of studying nanomedicine is to develop more effective and personalized treatments for a range of diseases, from cancer to infectious diseases to neurological disorders [3]. By engineering nanoparticles to selectively accumulate in diseased tissues, release drugs in a controlled manner, and enhance the efficacy and safety of existing therapies, researchers aim to overcome many of the limitations of conventional drugs [4, 5]. Nanomedicine offers a promising approach to improve the diagnosis and treatment of diseases and has the potential to revolutionize healthcare in the coming years. However, regulatory and ethical challenges must be addressed to ensure the safety and efficacy of nanomedicine therapies [6].

This study explores the different types of nanomedicines used in the pharmaceutical industry and their potential benefits, as well as targeted drug delivery mechanisms.

RESULTS AND DISCUSSION

Types of nanomedicines used in the pharmaceutical industry

Multiple sclerosis (MS) is a multifaceted autoimmune Nanomedicines are a class of medical interventions that involve the use of nanoparticles or nanoscale materials for diagnosing, treating, or preventing diseases. They offer unique advantages due to their small size, large surface area, and potential for targeted drug delivery [7, 8]. In the pharmaceutical industry, various types of nanomedicines have been developed and studied. Some of the prominent types include:

- Nano-emulsions: Nano-emulsions are thermodynamically stable systems composed of oil, water, and surfactants. They are used to encapsulate both hydrophobic and hydrophilic drugs, offering improved solubility and bioavailability. Nanoemulsions are used for various routes of administration, including oral, topical, and parenteral [9].
- Polymeric nanoparticles: As mentioned before, polymeric nanoparticles are made from biodegradable polymers and can carry drugs within their matrix. They are versatile and can be designed for targeted drug delivery, sustained release, and improved stability [10].
- Solid-Lipid nanoparticles (SLNs): SLNs are lipidbased nanoparticles that offer enhanced drug stability, controlled release, and improved bioavailability. They consist of a solid lipid core that can encapsulate both hydrophobic and hydrophilic drugs [11].
- Quantum dots: Quantum dots are nanoscale semiconductor crystals that emit specific wavelengths of light based on their size. They have applications in imaging and diagnostics due to their tunable optical properties and high brightness [12].
- Colloidal gold: Colloidal gold nanoparticles have unique optical properties and are used in diagnostic assays, imaging, and targeted drug delivery. They can be conjugated with ligands for specific cell targeting [13].
- Dendrimers: Dendrimers are highly branched polymers with a well-defined structure. They can be used to encapsulate drugs within their interior and can be functionalized for targeted drug delivery, gene delivery, and imaging [14].
- Nanocrystals: Nanocrystals are crystalline particles with nanometer-scale dimensions. They improve drug solubility and dissolution rate, enhancing the bioavailability of poorly water-soluble drugs [15].
- Liposomes: Liposomes, as described earlier, are vesicles composed of lipid bilayers that can encapsulate drugs. They are widely used for drug delivery, particularly for improving the pharmacokinetics and targeting of drugs [16].

• Carbon nanotubes: Carbon nanotubes have been explored for drug delivery, imaging, and even as carriers for gene therapy due to their unique structural and surface properties [17].

Targeted drug delivery by nanomedicines

Targeted drug delivery using nanomedicines is a strategy that aims to deliver therapeutic agents specifically to the site of action within the body while minimizing their exposure to healthy tissues. This approach enhances the therapeutic efficacy of drugs and reduces potential side effects [18]. Here's how targeted drug delivery by nanomedicines works:

• Design and functionalization: Nanoparticles are designed and engineered to have specific properties that enable them to target certain cells, tissues, or organs. Surface modifications, such as attaching targeting ligands (antibodies, peptides, aptamers) or coatings, allow nanoparticles to interact selectively with receptors on the target cells [19].

• Active targeting: Active targeting involves nanoparticles binding to specific molecules or receptors on the surface of target cells. This binding can be facilitated by the functionalized nanoparticle ligands or antibodies, ensuring a higher concentration of the therapeutic agent at the desired site [20].

• Passive targeting (Enhanced Permeability and Retention (EPR)): Tumors and inflamed tissues often have leaky blood vessels and compromised lymphatic drainage. Nanoparticles can exploit this phenomenon by accumulating at these sites due to their size and charge. This passive accumulation is known as the EPR effect [21].

• Responsive targeting: Some nanoparticles are designed to respond to specific environmental cues at the target site, such as changes in pH, temperature, or enzymatic activity. This responsiveness can trigger drug release only when the nanoparticles are close to the target, further enhancing the selectivity of drug delivery [22].

• Internalization and drug release: Once the nanoparticles reach the target site and bind to the target cells, they are often internalized by the cells. The nanoparticles then release the therapeutic agent in a controlled manner, either due to the local environment or through an external trigger (e.g., light, magnetic field) [23].

• Avoiding the immune system: Nanoparticles can be designed to evade recognition and clearance by the immune system, allowing them to circulate in the bloodstream and reach their target more effectively [24].

• Reduced systemic toxicity: Targeted drug delivery reduces the exposure of healthy tissues to the drug, minimizing off-target effects and toxicity [25, 26].

This targeted approach is particularly advantageous in the treatment of diseases like cancer, where conventional chemotherapy can damage healthy tissues and cause severe side effects. By concentrating the therapeutic effect at the tumor site, targeted nanomedicines enhance the effectiveness of treatment while mitigating harm to healthy tissues [27]. However, it's important to note that achieving successful targeted drug delivery involves complex factors, including nanoparticle design, choice of targeting ligands, understanding the target's molecular characteristics, and ensuring safety and regulatory approval. The field of nanomedicine continues to advance, refining these techniques and pushing the boundaries of targeted drug delivery for a wide range of medical applications.

Applications of nanoparticles in medicine: targeted therapies and beyond

Nanoparticles have found diverse applications in medicine, extending beyond targeted therapies to encompass a wide range of innovative approaches. These versatile nanoscale materials are being harnessed for various purposes that have the potential to revolutionize diagnostics, treatment, and

disease management [28]. Nanoparticles revolutionize medicine with applications like targeted therapies (oncology), improved diagnostics (MRI, CT, PET), regenerative medicine (tissue repair), enhanced vaccines (antigen delivery), gene therapy (genetic disorders), antimicrobial agents (infections), personalized medicine (individualized treatment), bloodbrain barrier penetration (neurological disorders), wound healing (growth factors), organ transplantation (immunosuppression), drug combinations (synergy), theranostics (visualization and treatment), neurological disorders (Alzheimer's, Parkinson's), cardiovascular health (atherosclerosis), and organ imaging (precision surgeries) [29-43].

Globally marketed nanomedicines

Pharmaceutical nanomedicine products have achieved remarkable prominence within the global healthcare landscape. With over 70 nanomedicine products securing approval from the FDA and EMA since 1995, and an even larger number progressing through clinical trials, nanomedicine's trajectory is one of robust growth. This surge is driven by the pursuit of elevated drug effectiveness coupled with diminished toxicity, effectively showcasing nanotechnology's prowess in revolutionizing drug delivery [44].

Since 1989, the global market has welcomed 78 nanomedicines, with the FDA granting 66 approvals and the EMA endorsing 31. Among these, 20 have earned the coveted joint approval of both agencies, while others have secured the backing of either the FDA (43) or the EMA (12) individually. The dynamic focus on nanomedicine development, fortified by its transformative healthcare advantages, has precipitated a substantial upswing in market presence post-2010. This diverse array ofnanomedicines encompasses an assortment of nanocrystals, lipid-based and polymer-basednanoparticles, dendrimer-based nanoparticles, proteinbased nanoparticles, and inorganic nanoparticles [6]. Inorganic nanoparticles constitute a particularly intriguing facet, offering a dual role encompassing diagnostics and therapy. Ranging from metal and carbon nanotubes to calcium phosphate, iron oxide, silica, and quantum dot nanoparticles, these agents adeptly serve as stable and biocompatible carriers for therapeutic agents [45]. However, the journey is not without challenges, as their gradual dissolution and lack of biodegradation present obstacles to sustained, long-term utilization [46]. Conversely, organic carriers encompassing lipid-based vectors, polymer-based vectors, and dendrimers act as protective envoys for therapeutic agents, boosting drugloading capacity and fine-tuning pharmacokinetic profiles. As nanomedicine's transformative journey unfolds, it continues to redefine the boundaries of pharmaceutical methodologies [47].

In tandem with this, numerous exemplars of globally marketed nanomedicines accentuate the substantial potential of this field. Noteworthy instances include Doxil (liposomal doxorubicin), Abraxane (nanoparticle-bound paclitaxel), Onivyde (liposomal irinotecan), and other innovations spanning nanocrystal-based formulations, iron replenishment therapies, and precision-targeting antibody-drug conjugates. Collectively, these pioneering nanomedicines underscore the diversified applications of nanotechnology in amplifying therapeutic outcomes and elevating overall patient well-being [48-51].

Regulatory and ethical considerations in nanomedicine

Nanomedicine has the potential to transform healthcare, but with this potential comes a need for responsible and ethical development, as well as stringent regulation to ensure safety and efficacy [1]. The unique properties of nanoparticles raise concerns about their potential toxicity and long-term effects

on human health and the environment. Thus, it is crucial to evaluate and minimize potential risks associated with nanomedicine development and application [52]. Regulatory bodies such as the FDA have developed guidelines for the evaluation and approval of nanomedicine products. These guidelines include recommendations for testing and evaluation of the safety and efficacy of nanomedicine products. Furthermore, ethical considerations are crucial, including issues related to patient consent, privacy, and informed decisionmaking. Ensuring the safety and efficacy of nanomedicine requires collaboration between regulatory agencies, researchers, healthcare providers, and patients. Additionally, clear communication and education about nanomedicine development and its potential risks and benefits are necessary to establish public trust and facilitate responsible and ethical development [53].

Limitations of nanomedicines in targeted drug delivery

While nanomedicines hold great promise for targeted drug delivery, they are not without limitations. One significant challenge is their limited drug payload capacity, which can restrict the number of therapeutic agents that can be loaded onto nanoparticles [7]. Moreover, the lack of absolute specificity in targeting can lead to off-target effects, potentially affecting healthy tissues and diminishing the desired precision [25]. The efficiency of targeting is another concern, as successful delivery to specific cells or tissues may not always be achieved, reducing the therapeutic impact [54]. The variability in biological responses among individuals can also influence the effectiveness of nanomedicines, making it challenging to predict uniform outcomes [6]. Navigating regulatory challenges poses another hurdle, as the approval process for novel nanomedicines involves demonstrating their safety, efficacy, and manufacturing consistency [55]. Additionally, the cost considerations associated with developing and producing nanomedicines can be substantial, potentially limiting their accessibility to a wider population [6]. These limitations underscore the need for ongoing research and development efforts to overcome these challenges, optimize nanomedicine designs, and unlock their full potential for revolutionizing targeted drug delivery in healthcare.

*Future prospects of nanomedicine in targeted drug delivery*The prospects for nanomedicine are exciting, with the potential to revolutionize personalized medicine, improve disease detection and treatment, and support tissue regeneration and repair. One important direction in nanomedicine is the development of nanorobots and nanosensors that can perform complex tasks within the body, such as drug delivery, disease detection, and tissue repair. Nanoparticles can also be used to deliver multiple drugs or therapies simultaneously, leading to more effective treatments for complex diseases. Additionally, nanoparticles can be used as non-invasive diagnostic tools to detect diseases in their early stages. The integration of artificial intelligence and nanomedicine can also lead to more precise and efficient drug delivery and more accurate disease detection and diagnosis. However, there are still challenges to address, such as safety and toxicity concerns, regulatory issues, and cost-effectiveness. Continued investment and collaboration between researchers, healthcare providers, and industry partners can help to overcome these challenges and unlock the full potential of nanomedicine [56-58].

CONCLUSION

Nanomedicine is a rapidly growing field with promising applications in drug delivery, disease detection, and tissue regeneration. Targeted therapies with nanoparticles have shown the potential to improve patient outcomes and quality of life. However, there are also limitations and challenges to address, including safety and toxicity concerns, regulatory issues, and cost-effectiveness. Despite these

challenges, the future of nanomedicine is promising, and continued investment and collaboration between researchers, healthcare providers, and industry partners can help to overcome these obstacles and realize the full potential of this exciting field.

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