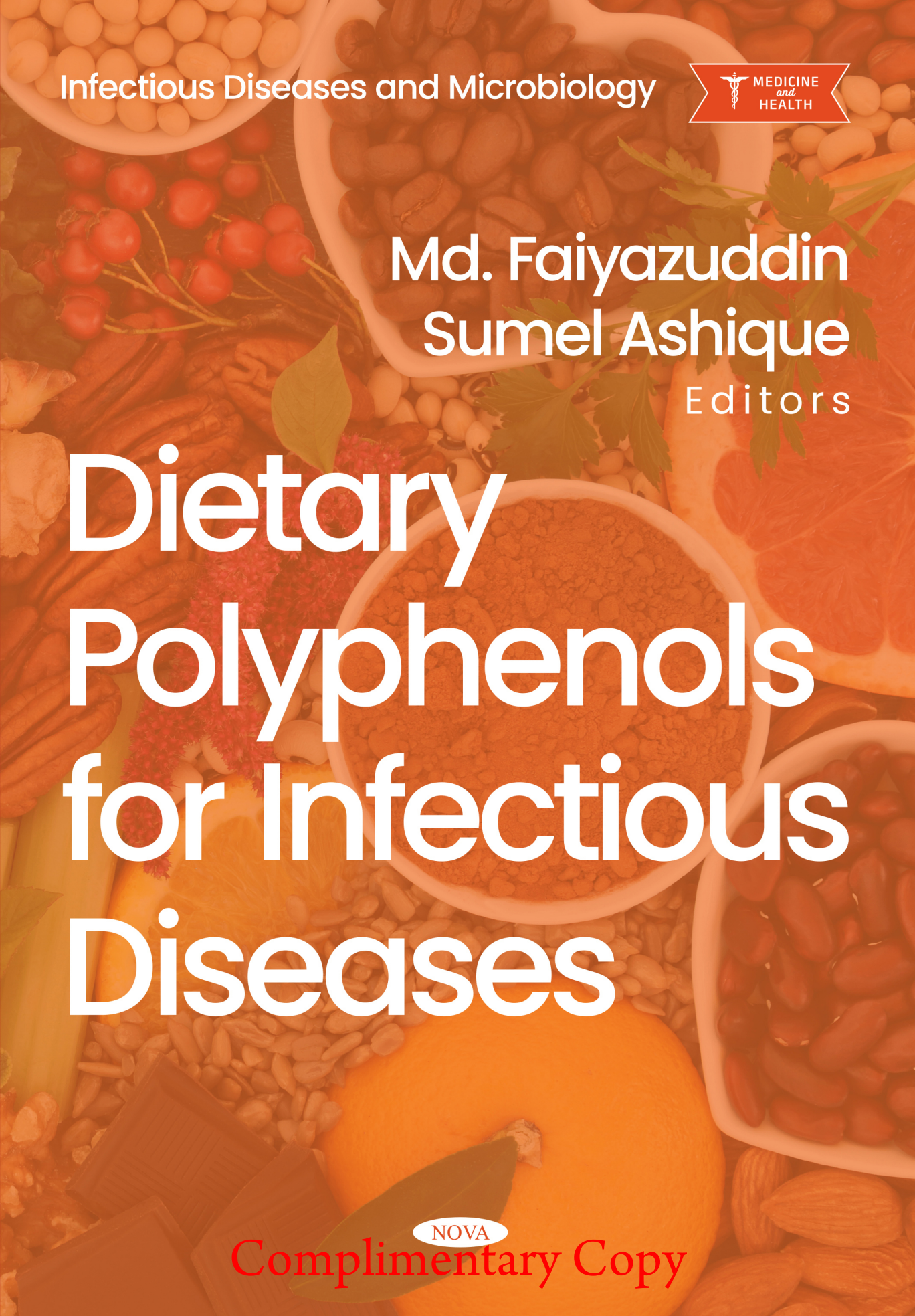
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Contents

Chapter 9

The Controlled Release of Polyphenols from Nanoformulations for the Treatment of Infectious Diseases

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Abstract

The incidence of infectious diseases has significantly increased, notably in the twenty-first century. Recent pandemics and outbreaks such as Covid-19, swine flu, MERS, Ebola, and Zika, have had far-reaching consequences on the social, psychological, and economic well-being of individuals and communities globally. Although vaccine production and medical science have seen significant advancements over the years that have drastically decreased mortality and morbidity due to infectious diseases such as tuberculosis, smallpox, diphtheria, and polio, the development of multiple drug resistance continues to be a global concern. Recent advances in formulation and drug delivery technologies have opened up research opportunities to improve the efficacy of existing pharmacological substances by targeting some *in vivo* locations with higher precision. Nanotechnology is beneficial for drug delivery systems because it improves stability, solubility, and bioavailability, leading to better therapeutic outcomes. Additionally, this allows for the design of tailor-made controlled- and sustained-release profile dosage forms. Much attention has also been focused on polyphenols, which are known to possess powerful antioxidant properties. They play the role of very useful natural molecules in defense against external stimuli and

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scavenging of reactive oxygen species (ROS), which can cause many disorders. In this chapter, we present the potential of nanotechnology-based drug delivery systems for the delivery of polyphenolic compounds for the management of infectious disorders.

Keywords: antioxidants, controlled release, drug delivery, nanotechnology, polyphenols

1. Introduction

Infectious diseases have historically been an intimidating challenge to human health, and are caused by pathogenic microorganisms such as bacteria, viruses, parasites, and fungi. These diseases have a far-reaching effect that intrudes into the social, economic, and psychological components of global community entities. Infectious diseases, for all the advances in medical science and public health that humanity has made, are still a critical global concern, particularly drug-resistant pathogens and the modern ability to spread disease almost anywhere around the globe overnight. Infectious diseases such as tuberculosis (TB), smallpox, diphtheria, and polio have caused a large number of deaths. Thanks to vaccines and antibiotics, the prevalence of these diseases has been greatly reduced, which has led to a global transformation regarding health. Nonetheless, the 21st century has seen the re-emergence of infectious diseases due to globalization, urbanization, climate change, and the emergence of antibiotic-resistant strains. Emerging from recent pandemics such COVID19, H1N1 influenza (swine flu), Middle East Respiratory Syndrome, Ebola, and Zika viruses have occurred as a constant threat to humanity, becoming a potential agent capable of destroying global society.

According to reports, COVID-19, as expressed in the emerging coronavirus SARS-CoV-2, is one of the biggest worldwide health emergencies. Since its first report in late 2019, COVID-19 has devastated economies and healthcare systems, resulting in an unthinkable death toll. The epidemic has shown how flimsy health systems are everywhere and how careful planning and reaction measures are required. Moreover, the need for vaccine development has increased, as one of the biggest successes in the history of pandemic control, resulting from the creation and use of COVID-19 vaccines at an unparalleled pace (Polack et al., 2020). Antimicrobial resistance (AMR) is one of the main obstacles to the treatment of infectious illnesses. AMR (Antimicrobial Resistance) occurs when microbes evolve in ways that render the drugs used to treat infections ineffective. “This resistance has been accelerating due to the unrestricted use and abuse of antibiotics in humans and animals” (WHO, 2020) said the World Health Organisation. AMR is among the top ten worldwide public health concerns. Treatment and management of infections such as Mycobacterium TB are made much more difficult due to the rapid development of multi-drug resistant (MDR) and extended drug-resistant (XDR) strains (Dheda et al., 2017).

Profound socioeconomic effects have also been associated with infectious illnesses. Pandemics and epidemics may tax medical systems, stymie commerce and travel, and lead to recessions. Beyond short-term medical expenses, infectious illnesses have long-term effects, including decreased productivity, higher poverty rates, and wider disparities. For example, the 2014–2016 West African Ebola epidemic had a profound negative impact on commerce, agriculture, and public services (Evans et al., 2015). Comparably, the COVID-19 pandemic brought about notable economic downturns that had a significant effect on employment, mental health, and education (ILO, 2021). Infectious disorders have strong psychological effects. The

widespread dread, worry, and stigmatization brought on by outbreaks may have an impact on social cohesiveness and mental health. For instance, lockdowns, social isolation, and uncertainty about the future are among the factors linked to higher levels of stress, anxiety, depression, and other mental health issues during the COVID-19 pandemic (Pfefferbaum et al., 2020). Stigmatizing individuals and communities affected by certain conditions can lead to their social exclusion, further deepening the disparities that already exist. When people are marginalized because of their afflictions, they are often denied access to essential resources and opportunities, making it even harder for them to improve their circumstances. This kind of social exclusion exacerbates inequality by reinforcing negative stereotypes, limiting social mobility, and perpetuating cycles of disadvantage. As a result, those who are already vulnerable may find themselves facing heightened challenges, not only due to their condition but also because of the societal barriers that compound their struggles (Xiong et al., 2020). Improving disease monitoring, increasing lab capabilities, guaranteeing prompt information exchange, and promoting international collaboration are all parts of strengthening global health security. The Global Health Security Agenda (GHSA) and other programs seek to strengthen the ability to identify, stop, and handle infectious disease threats. The COVID-19 epidemic has brought attention to the need for international cooperation and strong health systems to handle future pandemics (GHSA, 2021; Bloom et al., 2021).

1.1. Challenges Posed by Drug-Resistant Pathogens

The emergence of drug-resistant bacteria poses a serious threat to the global public health. Standard treatments become less effective when bacteria become resistant to antimicrobial medications, which prolongs diseases, raises medical expenditures, and increases death rates. The reasons, ramifications, and current initiatives to prevent antimicrobial resistance (AMR) are examined in this chapter.

1.1.1. Emergence and Spread of Drug-Resistant Pathogens

Microbes, including bacteria, viruses, fungi, and parasites, develop defense mechanisms against the effects of antibacterial medications and drug resistance. Inherent or acquired via horizontal gene transfer or genetic changes, this resistance may exist. AMR is accelerated in large part by the overuse and abuse of antibiotics in agriculture and human health (WHO, 2020). For example, selection pressure favoring resistant strains is created when antibiotics are overused in cattle to promote growth or improperly administered for viral infections (Ventola, 2015).

1.1.2. Global Impact of Antimicrobial Resistance

The impact of AMR is profound and multifaceted. The possibility of incurable infections raises the hazards of regular procedures, cancer treatment, and the care of chronic disorders, thereby undermining the progress accomplished in contemporary medicine. AMR has been named by the World Health Organization (WHO) as one of the top ten public health concerns worldwide (WHO, 2020).

Extensive drug-resistant (XDR) and multidrug-resistant (MDR) pathogenic strains make matters worse. For instance, TB control efforts are complicated by the development of MDR

and XDR strains of Mycobacterium tuberculosis, the etiological agents of tuberculosis (TB), which are resistant to first-line and second-line therapies, respectively (Dheda et al., 2017). Similar difficulties arise in hospital settings from drug-resistant forms of bacteria, such as Carbapenem-resistant Enterobacteriaceae (CRE) and Methicillin-resistant Staphylococcus aureus (MRSA) (CDC, 2019).

1.1.3. Socioeconomic Consequences

AMR is often associated with considerable socioeconomic burden. Higher healthcare costs are associated with longer stays in the hospital, expensive medications, and increased testing and number of procedures. AMR could lead to a global economic loss of 100 trillion dollars by 2050 and force an additional 24 million people into severe poverty, based on World Bank research. In addition, particularly in low- and middle-income countries, which already face the heavy burden of infectious diseases, productivity loss due to illness and premature death can stifle economic progress.

1.1.4. Public Health and Healthcare System Challenges

AMR presents massive problems for healthcare systems and public health worldwide. For chronic illnesses caused by drug-resistant bacteria, more difficult therapies have increased the incidence and death rates of such infections. The treatment of these illnesses often requires the use of last-resort antibiotics, which may be more expensive, hazardous, and less effective (Naylor et al., 2018).

Failure to administer antibiotics also jeopardizes the effectiveness of surgical operations and chronic illness therapies that require the preventive use of antibiotics. Healthcare institutions must invest more in tighter infection control measures to prevent the spread of resistant bacteria. These will involve a range of tactics that add to operating expenses, including more surveillance, isolation procedures, and personal protection equipment (Tacconelli et al., 2018).

1.1.5. Strategies to Combat Antimicrobial Resistance

Addressing AMR requires a coordinated, multi-faceted approach. Key strategies include:

- Stewardship Programs: Implementing antimicrobial stewardship programs in healthcare settings to optimize the use of antibiotics. This involves guidelines for appropriate prescription, dose optimization, and therapy duration to minimize the development of resistance.
- Surveillance and Monitoring: Enhancing global surveillance systems to monitor the spread of AMR and track the effectiveness of interventions. Organizations, such as the WHO and the Centers for Disease Control and Prevention (CDC), play a crucial role in collecting and disseminating data on AMR trends (CDC, 2020).
- Research and Development: Investing in research and development of new antibiotics, alternative therapies, and diagnostic tools. Innovations such as bacteriophage therapy, antimicrobial peptides, and rapid diagnostic tests hold promise for addressing the challenge of AMR (Conly, 2010).
- Public Awareness and Education: Raising awareness about the responsible use of antibiotics among healthcare professionals and the public. Educational campaigns can

help reduce the misuse of antibiotics and promote behaviors that prevent infections, such as vaccination and good hygiene practices (Fletcher-Miles et al., 2020).

- Regulation and Policy: Implementing and enforcing regulations to control the use of antibiotics in agriculture and healthcare. Policies that restrict the use of medically important antibiotics in animal husbandry and promote best practices in antibiotic prescription are essential (Van Boeckel et al., 2017).

1.2. Introduction to Polyphenols

Among the vast range of natural products, polyphenols are predominant in fruits, vegetables, tea, coffee, red wine, and some cereals. Strong antioxidants and polyphenols are required to protect the body from infectivity and oxidation. Both conditions are known triggers for many chronic infections and illnesses. Polyphenols are secondary metabolites of plants that contain more than one phenol unit. The important classes of polyphenolics, based mainly on their chemical structure, include flavonoids, phenolic acids, polyphenolic amides, and other polyphenolic compounds; the most diverse class is, in fact, the flavonoids, which are further categorized into six sub-classes all different in their way and having distinctive beneficial value in the maintenance of good health: flavonols, flavones, flavanones, flavanols, anthocyanins, and isoflavones (Manach et al., 2004; Tsao, 2010).

Comprising substances, such as gallic acid, ferulic acid, caffeic acid, and phenolic acids, are another important class. These acids are abundant in many foods and help them act as antioxidants. Noteworthy biological actions are also shown by polyphenolic amides, such as capsaicinoids found in chili peppers, and other polyphenolic substances, including resveratrol in grapes (Scalbert et al., 2005). All foods made from plants contain polyphenols. Rich in polyphenols include apples, grapes, berries, vegetables such as onions and broccoli, tea and coffee, and goods such as chocolate and wine (Pandey et al., 2009). However, the way polyphenols are metabolized, the dietary matrix, and the person affect how bioavailable they are. The degree of polymerization, solubility, and interactions with other food components are among the factors affecting bioavailability. Generally, polyphenols are absorbed more easily in their aglycone form than in their glycosylated form (D Archivio et al., 2007).

Polyphenols work therapeutically in several ways. Chelation of metal ions, upregulation of endogenous antioxidant defenses, and scavenging of free radicals are among their well-documented antioxidant activities (Fraga and colleagues, 2019). Polyphenols are useful in the prevention and treatment of infectious illnesses because they are antioxidants with anti-inflammatory, antibacterial, and immunomodulatory effects. The anti-inflammatory properties of polyphenols are mediated via the regulation of inflammatory cytokines, inhibition of pro-inflammatory enzymes such as lipoxygenase (LOX) and cyclooxygenase (COX), and inhibition of nuclear factor kappa B (NF-κB) signaling (Santangelo et al., 2007). Polyphenols break microbial cell membranes, block virulence factors, and alter host immune responses; they also show antibacterial efficacy against a broad spectrum of pathogens, including bacteria, viruses, and fungi (Daglia et al., 2012).

The therapeutic value of polyphenols in infectious disorders has drawn considerable interest. Their many biological actions strengthen resistance to infections and improve the effectiveness of traditional therapies. The antimicrobial effects of polyphenols, such as quercetin from apples, resveratrol from grapes, and epigallocatechin gallate (EGCG) from

green tea have been well investigated. For example, EGCG has been proven effective against Helicobacter pylori, Staphylococcus aureus, and influenza viruses among other infections. Disruption of viral envelopes, reduction of bacterial adherence, and improvement of host immunological function are among these mechanisms (Chacko et al., 2010). Because quercetin blocks viral entry and replication and alters the host immune system, it has broad-spectrum antiviral efficacy, especially against respiratory viruses such as coronaviruses and influenza (Colunga et al., 2020). Resveratrol has been shown to directly suppress viral replication and modulate cell signaling pathways, thereby inhibiting the replication of certain viruses such as respiratory syncytial virus and herpes simplex virus (Wei et al., 2023). The combined therapeutic effects of polyphenols and traditional antibiotics have further increased. For instance, drug-resistant bacteria may be responsive to antibiotics by polyphenols, thereby bypassing resistance mechanisms (Mun et al., 2013).

Polyphenols have many unanswered questions despite their significant medicinal potential. However, the clinical usefulness of polyphenols is limited by their poor absorption. Novel drug delivery vehicles such as nanoformulations have been developed to improve the stability, solubility, and bioavailability of polyphenols (Mohany et al., 2021).

1.3. Importance of Controlled Release in Drug Delivery

In drug delivery, controlled release is the process by which a medication is delivered gradually and in a predefined manner. This process may include constant or variable release rates. In contrast, traditional methods of drug delivery release medications immediately after administration. The basic goal of controlled-release systems is to keep bloodstream medication concentrations as high as possible, thereby improving therapeutic effectiveness and reducing adverse effects.

1.3.1. Advantages of Controlled Release Systems

- Improved Therapeutic Efficacy: Controlled-release formulations prolong medication concentrations inside the therapeutic window, thereby improving therapeutic effectiveness. This guarantees the presence of the medication at effective levels free from the peaks and troughs linked to traditional dosage, which may result in less effective treatment or a higher chance of adverse effects (Siepmann & Siepmann, 2008).
- Reduced Frequency of Administration: The decrease in medication administration frequency is one of the main benefits of controlled release systems. As it helps patients follow their prescription schedules better, this is especially helpful for chronic illnesses that require long-term therapy. Treatment regimens may be simplified and compliance may be increased by using once-daily dosing formulations instead of the many doses needed with immediate-release formulations (Deshpande et al., 1996).
- Minimization of Side Effects: These systems may reduce the occurrence of side effects by regulating the pace of medication release. The high peak plasma concentrations of immediate-release formulations may have unfavorable consequences. By offering a

more constant drug release, controlled-release devices reduce this danger and maintain plasma concentrations within a safe and useful range (Dash and Cudworth, 1998).

- Targeted Drug Delivery: Systemic exposure may be decreased, and therapeutic benefits may be increased by targeting certain body locations using controlled-release devices. Treatments for localized infections or malignancies that require localized action benefit from this focused approach. Drugs may be directly delivered to tumor areas using liposomes and nanoparticles to increase effectiveness and reduce damage to healthy tissues (Allen and Cullis, 2013).

1.3.2. Mechanisms of Controlled Release

- Diffusion-Controlled Systems: The Medication in diffusion-controlled systems is released gradually across a barrier. This can be accomplished using drug diffusion-regulating polymeric matrices or membranes. Drug solubility, diffusivity, and polymer characteristics control the rate of drug release (Siegel and Rathbone, 2011).
- Erosion-Controlled Systems: Drug release in erosion-controlled systems depends on the carrier matrix degradation. Medication is progressively released from these systems by eroding biodegradable polymers in the physiological environment. Modifying the structure and content of the polymer may control its release (Lu and Park, 2013).
- Osmotically Controlled Systems: Osmotic pressure drives drug release in osmotically regulated systems. In these systems, a semi-permeable membrane usually encircles an osmotically active core. The drug is pushed out via a delivery hole at a regulated pace by the pressure created by the water inflow through the membrane. Santus and Baker (1995) reported that this approach offers constant and predictable medication release, irrespective of external variables such as pH and gastrointestinal motility.
- Responsive Systems: Known by another name, stimuli-responsive or smart systems, responsive systems release the medication in reaction to certain physiological cues, such as pH, temperature, or enzymes. For applications requiring on-demand drug administration, such as the treatment of inflammation or infections, these systems provide precise control over drug release (Langer and Peppas, 2003).

Numerous controlled-release formulations have shown important therapeutic advantages. For instance, compared with immediate-release formulations, controlled-release formulations of antihypertensive medications, including nifedipine, have shown better management of blood pressure and fewer adverse effects. Comparably, controlled-release pain management systems, such as transdermal patches that release fentanyl, offer steady pain relief with shorter dose intervals (Martin et al., 2016). Controlled release systems have been used to increase the effectiveness of antibacterial medications in the treatment of infectious illnesses. Antibiotics, including amoxicillin, have been developed into controlled-release formulations, for example, to improve their therapeutic benefits and lower dosage frequency (Ning et al., 2018).

2. Polyphenols and Their Therapeutic Potential

2.1. Sources of Polyphenols

Several plant-based meals and drinks contain polyphenols. They have well-established health benefits, but various kinds of polyphenols have somewhat varying bioavailability, that is, the degree and speed at which they are absorbed and used by the body. Many foods are rich in polyphenols, including fruits, vegetables, tea, coffee, wine, and chocolate. The major dietary sources of polyphenols are as follows.

- Fruits: Apples, berries, cherries, grapes, and citrus fruits are rich in various polyphenols, such as flavonoids and phenolic acids (Bravo, 1998).
- Vegetables: Onions, spinach, and broccoli are notable sources of flavonoids such as quercetin and kaempferol.
- Beverages: Green tea, red wine, and coffee are particularly high in catechins, resveratrol, and chlorogenic acid, respectively (Manach et al., 2004).
- Nuts and Seeds: Almonds, walnuts, and flaxseeds contain large amounts of lignans and flavonoids.
- Legumes and Whole Grains: Beans and lentils, and whole grains such as oats and barley are good sources of various polyphenolic compounds.

2.2. Bioavailability of Polyphenols

Although abundant in the diet, the bioavailability of polyphenols is often poor and varies greatly based on a number of variables such as their chemical makeup, food matrix, and interactions with other dietary components (Manach et al., 2005).

- Chemical Structure: Polyphenols exist in different forms, including aglycones, glycosides, and polymers. Aglycones are more readily absorbed than glycosides, which require enzymatic hydrolysis prior to absorption (Di Lorenzo et al., 2021).
- Food Matrix: The matrix in which polyphenols are present affects their release and absorption. For instance, polyphenols in solid foods may be less bioavailable than those in liquid form, such as juices or extracts.
- Interactions with Other Dietary Components: Dietary fibers, fats, and proteins, can influence the absorption of polyphenols. For example, fats can enhance the absorption of lipophilic polyphenols, whereas fibers may bind polyphenols, thereby reducing their bioavailability (Bohn, 2014).

2.3. Metabolism and Excretion

Once ingested, polyphenols are metabolized extensively in the liver and gut. Many times, they undergo methylation, glucuronidation, and sulfation to convert into other metabolites. These

metabolites may function biologically differently than their parent chemicals (Scalbert and Williamson, 2000).

- Intestinal Metabolism: Polyphenols are partially degraded by intestinal enzymes and gut microbiota, which can produce bioactive metabolites that contribute to health effects.
- Hepatic Metabolism: In liver, polyphenols are further metabolized and circulated in the bloodstream or excreted in the bile and urine.

2.3.1. Enhancing Bioavailability

Various strategies have been explored to enhance the bioavailability of polyphenols:

- Nanoformulations: Encapsulation of polyphenols in nanoparticles or liposomes can protect them from degradation and improve their absorption (Mignet et al., 2013).
- Combination with Other Nutrients: Combining polyphenols with other nutrients such as fats or piperine can enhance their absorption and bioefficacy.
- Fermentation: Food fermentation can increase the bioavailability of polyphenols by breaking down complex compounds into more absorbable forms (Arfaoui, 2021).

2.4. Mechanisms of Action: Antioxidant, Anti-Inflammatory, and Antimicrobial Properties

One class of naturally occurring substances in plants that displays a broad spectrum of biological functions is polyphenols. Their antioxidant, anti-inflammatory, and antibacterial properties are primarily responsible for their health advantages. Polyphenols are strong agents for the prevention and therapy of many illnesses because of their methods of action.

2.4.1. Antioxidant Properties

The antioxidant properties of polyphenols are well recognized and include lowering oxidative stress and neutralizing free radicals. When reactive oxygen species (ROS) are produced in excess and the body's capacity to eliminate these dangerous wastes is imbalanced, oxidative stress develops. Polyphenols can mitigate oxidative damage via several mechanisms.

- Direct Scavenging of Free Radicals: Polyphenols can directly neutralize ROS such as superoxide anions, hydroxyl radicals, and hydrogen peroxide. This activity is attributed to their phenolic hydroxyl groups, which donate hydrogen atoms to free radicals, thereby stabilizing them (Bucciantini et al., 2021).
- Metal Chelation: Polyphenols can chelate transition metals, such as iron and copper, which catalyze the formation of ROS. Polyphenols prevent the catalytic cycle by binding to these metals, leading to oxidative damage (Singh et al., 2020).
- Upregulation of Antioxidant Enzymes: Polyphenols enhance the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. This upregulation helps to maintain redox homeostasis and protects cells from oxidative stress (Yahfoufi et al., 2018).

2.4.2. Anti-Inflammatory Properties

Polyphenols exert significant anti-inflammatory effects by modulating various signaling pathways and reducing the production of pro-inflammatory mediators. Key mechanisms include:

- Inhibition of NF-κB Pathway: Nuclear factor kappa B (NF-κB) is a transcription factor that regulates the expression of genes involved in inflammation. Polyphenols inhibit NF-κB activation, thereby reducing the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Hussain et al., 2016).
- Modulation of MAPK Pathways: Mitogen-activated protein kinases (MAPKs) are involved in inflammatory responses. Polyphenols modulate MAPK pathways, leading to decreased production of inflammatory mediators and enzymes, such as cyclooxygenase-2 (COX-2) (Crascí et al., 2018).
- Suppression of Pro-inflammatory Enzymes: Polyphenols inhibit enzymes, such as phospholipase A2 (PLA2), COX, and lipoxygenase (LOX), which are involved in the production of pro-inflammatory eicosanoids. This inhibition reduces the synthesis of prostaglandins and leukotrienes, key mediators of inflammation (Yahfoufi et al., 2018).
- Reduction of Advanced Glycation End Products (AGEs): Polyphenols prevent the formation and accumulation of AGEs, which are implicated in chronic inflammation and oxidative stress. They achieve this by trapping reactive dicarbonyl compounds and attenuating receptor for AGEs (RAGE) expression (Crascí et al., 2018).

2.4.3. Antimicrobial Properties

Polyphenols exhibit broad-spectrum antimicrobial activities against bacteria, viruses, and fungi. Their antimicrobial mechanisms include the following.

- Disruption of Microbial Cell Membranes: Polyphenols can alter the permeability of microbial cell membranes, leading to cell lysis and death. It is particularly effective against Gram-positive and Gram-negative bacteria (Daglia, 2012).
- Inhibition of Enzymatic Activity: Polyphenols inhibit key microbial enzymes involved in replication and metabolism. For example, they can inhibit bacterial DNA gyrase and viral proteases, thereby hindering the growth and proliferation of pathogens (Yuan-xi, 2012).
- Synergistic Effects with Antibiotics: Polyphenols can enhance the efficacy of conventional antibiotics through synergistic interactions. This combination can reduce the dosage required for effective treatment and to combat antibiotic resistance (Daglia, 2012).
- Interference with Microbial Adhesion: Polyphenols prevent the adhesion of pathogens to host cells, thereby inhibiting the initial step of infection. This property is particularly useful for preventing biofilm formation by bacteria and fungi (Cruciani et al., 2019).

2.5. Role of Polyphenols in Treating Infectious Diseases

Their multifaceted biological activities, including their antioxidant, anti-inflammatory, and antimicrobial properties, contribute to their effectiveness against infections.

2.5.1. Antiviral Properties

The strong antiviral effects of polyphenols have been demonstrated in many viruses. For example, certain polyphenols may stop the multiplication and spread of viruses, such as rotavirus, herpes simplex, dengue fever, coronaviruses, and influenza. These substances modulate the host immunological response and directly block viral enzymes among other ways. For instance, Citrus sinensis hesperidin may attach itself to the SARS-CoV-2 spike protein and hence prevent the virus from infecting host cells (Montenegro-Landívar et al., 2021).

2.5.2. Antibacterial Effects

The broad-spectrum antibacterial properties of polyphenols are particularly significant in view of the emergence of multi-drug resistant (MDR) bacterial pathogens. These substances may stop biofilm development, block bacterial enzymes, and damage the bacterial cell walls. For instance, polyphenols have been shown to be effective against gram-positive bacteria, including Methicillin-resistant Staphylococcus aureus (MRSA), a frequent source of hospital-acquired infections (Álvarez-Martínez et al., 2020). Moreover, synergistic benefits have been demonstrated by the combination of polyphenols with traditional antibiotics, which increases the total antibacterial efficiency and lowers the necessary antibiotic dose (Daglia, 2012).

2.5.3. Antifungal Activities

Polyphenols have antifungal properties and are helpful in the fight against fungal infections. These substances can interfere with fungal enzyme activity and damage the cell walls and membranes of fungi, thereby inhibiting their growth. For instance, polyphenols from red wine and green tea have been shown to be effective against Candida species, which cause a range of fungal diseases (Besednova et al., 2021).

2.5.4. Mechanisms of Action

- Modulation of Immune Response: Polyphenols enhance the immune system's ability to fight infections by modulating the activity of immune cells and cytokine production. They can promote the differentiation and activation of T-helper cells, which are crucial for orchestrating the immune response against pathogens (Benvenuto et al., 2021).
- Antioxidant Activity: By neutralizing reactive oxygen species (ROS), polyphenols reduce oxidative stress, which can exacerbate infections and weaken the immune response. This antioxidant activity helps maintain cellular integrity and function during infection (Rudrapal et al., 2022).
- Inhibition of Viral Enzymes: Polyphenols can inhibit viral enzymes that are essential for viral replication. For example, certain polyphenols inhibit the proteases of SARS-CoV-2, thereby blocking its ability to replicate and spread (Mehany et al., 2021).

- Antimicrobial Synergy: When used in combination with antibiotics, polyphenols enhance the effectiveness of these drugs. This synergy can help overcome antibiotic resistance and improve treatment outcomes (Daglia, 2012).

2.5.5. Applications in Treating Specific Diseases

- COVID-19: Polyphenols have shown potential for managing COVID-19 by enhancing the immune response and inhibiting viral replication. Clinical trials to evaluate the efficacy of polyphenol-rich supplements in preventing and treating COVID-19 (Khalil & Tazeddinova, 2020).
- HIV/AIDS: Polyphenols exhibit anti-HIV activity by inhibiting the ability of the virus to infect host cells and replicate. They target multiple steps in the viral life cycle, making them promising candidates for combination therapies (Andrae-Marobela et al., 2013).
- Bacterial Infections: Polyphenols are effective against various bacterial infections, including those caused by MDR strains. Their ability to disrupt biofilms and enhance antibiotic efficacy is particularly valuable for treating chronic and recalcitrant infections (Slobodníková et al., 2016).

3. Challenges in Polyphenol Delivery

3.1. Bioavailability and Stability Issues of Polyphenols

Numerous health advantages of polyphenols are well known, including their antioxidant, anti-inflammatory, and antibacterial effects. The limited bioavailability and stability of polyphenols seriously limit their clinical utilization, even with their medicinal potential. They present difficulties because of their complicated chemical makeup, interactions with other food elements, and vulnerability to physiological degradation.

3.1.1. Bioavailability Issues

Bioavailability of polyphenols refers to the proportion of compounds that are absorbed and available for use or storage in the body. Several factors contribute to low bioavailability of polyphenols.

- Chemical Structure and Solubility: The many chemical configurations that polyphenols have affect their solubility and, in turn, their absorption. Because they are poorly soluble in water, lipophilic polyphenols, such as quercetin, resveratrol, and curcumin, are not well absorbed in the gastrointestinal system (Di Lorenzo et al., 201). For instance, the partitioning of lipophilic polyphenols between the oil and water phases in emulsions affects their bioaccessibility and solubility, and thus, their gastrointestinal stability (Zhou et al., 2021).
- Metabolism and Biotransformation: Bioactivity of polyphenols may be altered by substantial digestion of the liver and intestines. Polyphenols are transformed into a range of compounds with potentially distinct biological activities via phase I and II

metabolic processes and biotransformation, mediated by the gut microbiota (Teng & Chen, 2019). These metabolites may make a major contribution to the health benefits of polyphenols even when their initial bioavailability is modest (Luca et al., 2020).

- Interaction with Food Matrix: Polyphenol release, solubility, and absorption may be profoundly influenced by the dietary matrix. Polyphenol bioavailability may be increased or decreased through interactions with dietary proteins, lipids, and fibers. Dietary lipids, for instance, might help lipophilic polyphenols to be absorbed more readily, whereas fibers may bind to them and lower their bioavailability (Hanuka Katz et al., 2020).

3.1.2. Stability Issues

Polyphenols are prone to degradation under various environmental conditions that can affect their bioactivity and therapeutic efficacy. Several factors contribute to polyphenol instability.

- Environmental Factors: Bioactivity of polyphenols may be lost via degradation by light, heat, oxygen, and pH. For example, heat and light may alter the structures of polyphenols such as catechins and anthocyanins and lessen their antioxidant effects (Yang et al., 2020).
- Food Processing: Polyphenol stability and bioavailability may be greatly affected by food processing techniques. Polyphenolic substances may degrade or have their chemical structures changed by procedures such as heating, drying, and fermentation, which would reduce their health advantages (Debelo et al., 2020).
- Interactions with Other Compounds: Polyphenols can interact with other dietary components, such as proteins and carbohydrates, which can protect them from degradation or enhance their stability. For example, protein-polyphenol interactions can form complexes that protect polyphenols from oxidative degradation during gastrointestinal digestion (Li et al., 2021).

3.2. Conventional Delivery Methods and Their Limitations

Owing to their low bioavailability and stability, polyphenols present serious obstacles for therapeutic administration. Although they are widely used, conventional distribution techniques have certain drawbacks that reduce their efficacy. In this section, we address the conventional approaches to polyphenol delivery and their disadvantages.

3.2.1. Oral Administration

Oral administration is the most common and convenient method for polyphenol delivery. It involves the consumption of polyphenol-rich foods, supplements, or extracts. However, this method is limited by the following factors.

- Low Bioavailability: Because polyphenols dissolve poorly in water, undergo substantial metabolism in the liver and gastrointestinal system, and are excreted quickly, they are often poorly bioavailable. For example, flavonoids such as catechins

and quercetin undergo a great deal of biotransformation, which lowers their bloodstream active forms (Di Lorenzo et al., 2021).

- Instability in the Gastrointestinal Tract: Many polyphenols are unstable under acidic conditions in the stomach and alkaline conditions in the intestine, leading to degradation before absorption can occur. This instability is a major limitation to maintaining therapeutic efficacy (Hoda et al., 2019).
- Interaction with Food Matrix: Polyphenols can interact with other dietary components, such as proteins and fibers, which can inhibit their absorption. For example, dietary fibers can bind polyphenols, thereby reducing their bioavailability (Hanuka Katz et al., 2020).

3.2.2. Topical Application

Topical applications involve the use of polyphenol-enriched creams, gels, or ointments for localized treatment, particularly for skin conditions. Despite its targeted approach, this method has limitations.

- Limited Penetration: Polyphenols often have poor skin penetration owing to their hydrophilic nature, which limits their effectiveness in reaching deeper layers of the skin (Yang et al., 2020).
- Stability Issues: Polyphenols are prone to degradation upon exposure to light, heat, and oxygen, which can reduce their efficacy in topical formulations. Ensuring the stability of these compounds in such formulations is challenging (Pimentel-Moral et al., 2018).

3.2.3. Intravenous Administration

Intravenous (IV) administration provides the direct delivery of polyphenols into the bloodstream, ensuring maximum bioavailability. However, this method has some drawbacks.

- Invasiveness: IV administration is invasive and typically requires medical supervision, which makes it less convenient for regular use.
- Rapid Metabolism and Clearance: Even with IV administration, polyphenols can be rapidly metabolized and cleared from the body, necessitating frequent dosing to maintain therapeutic levels (Teng & Chen, 2019).
- Cost and Accessibility: The cost and logistical challenges associated with IV administration limit its use primarily in clinical settings, making it less accessible for widespread use.

3.2.4. Conventional Extraction Methods

Extracting polyphenols from natural sources using traditional methods, such as solvent extraction, maceration, and Soxhlet extraction, has been standard practice. However, these methods also have several limitations.

- Low Efficiency and Yield: Traditional extraction methods often result in low polyphenol yields and are inefficient, requiring large amounts of solvents and long extraction times (Sridhar et al., 2021).

- Environmental Concerns: The use of organic solvents in conventional extractions poses environmental hazards and potential health risks. Disposal of these solvents contributes to environmental pollution (Pagano et al., 2021).
- Heat Sensitivity: Many polyphenols are heat-sensitive, and traditional extraction methods involving high temperatures can degrade these compounds, reducing their therapeutic efficacy (Chaves et al., 2020).

3.3. Need for Advanced Delivery Systems

Advanced delivery systems, including nanoformulations, microencapsulation, and biopolymer-based systems, offer several advantages over the conventional methods.

- Enhanced Bioavailability: Nanotechnology-based delivery systems, such as nanoparticles, liposomes, and micelles, significantly enhance the solubility and absorption of polyphenols in the gastrointestinal tract. These systems protect polyphenols from degradation and improve their bioavailability by facilitating better absorption and prolonging circulation time (Jia et al., 2023).
- Targeted Delivery: Advanced delivery systems can be engineered to target specific tissues or cells, enhancing the therapeutic effects of polyphenols while minimizing their side effects. For instance, pectin-coated nanoliposomes have been developed for the targeted delivery of polyphenols to specific sites in the body, thereby improving their efficacy (Haghighi et al., 2018).
- Controlled Release: Advanced delivery systems can provide a controlled and sustained release of polyphenols, maintaining therapeutic levels in the body over extended periods. This helps to reduce the frequency of dosing and improves patient compliance (Feng et al., 2023).
- Improved Stability: Encapsulation of polyphenols within protective matrices, such as biopolymers and nanoparticles, shields them from environmental factors, enhancing their stability and prolonging their shelf life (Zhang et al., 2021).

Examples of Advanced Delivery Systems

- Nanoformulations Polyphenol-loaded nanoparticles, liposomes, and nanoemulsions have shown significant improvements in bioavailability and therapeutic efficacy. These systems facilitate better absorption and protect polyphenols from degradation (Yang et al., 2020).
- Biopolymer-Based Systems: Polysaccharides and protein-based nanoparticles have been used to effectively deliver polyphenols. These biopolymer-based systems enhance the stability and bioavailability of polyphenols, making them suitable for use in functional food and pharmaceutical applications (Chen et al., 2021).
- Controlled Release Systems, such as hydrogels and microspheres, have been developed to provide controlled release of polyphenols, ensuring a sustained therapeutic effect over time (Khazei et al., 2021).

4. Nanotechnology in Drug Delivery

Drug administration has been transformed by nanotechnology, providing creative ways to improve the safety and therapeutic effectiveness of medications. Drug delivery systems based on nanotechnology (NDDS) use nanoscale materials to increase drug bioavailability, regulate release rates, target certain tissues or cells, and reduce adverse effects. The main ideas, categories, and benefits of NDDS are briefly reviewed in this section.

4.1. Key Concepts in Nanotechnology-Based Drug Delivery

The special qualities of nanomaterials are used by NDDS to overcome the drawbacks of traditional drug delivery systems. Drugs can be made more soluble by these technologies, which can also provide a focused and regulated distribution. The main components of the NDDS are as follows.

- Nanocarriers are nanoparticles that encapsulate or conjugate drugs, protecting them from the biological environment and improving their stability and bioavailability. Common nanocarriers include liposomes, polymeric nanoparticles, dendrimers, and carbon-based nanomaterials (Patra et al., 2018).
- Surface Functionalization: The surface of nanocarriers can be modified with targeting ligands, such as antibodies, peptides, or small molecules, to enhance specificity for certain cell types or tissues. This targeting capability reduces off-target effects and increases the therapeutic efficacy (Jhaveri et al., 2021).
- Stimuli-Responsive Systems: Some NDDS are designed to release their drug payload in response to specific stimuli, such as pH, temperature, or enzymatic activity. These systems provide precise control over drug release and enhance therapeutic outcomes (Ruttala et al., 2018).

4.2. Types of Nanotechnology-Based Drug Delivery Systems

- Liposomes: Spherical vesicles composed of lipid bilayers encapsulating hydrophilic and lipophilic drugs. They enhance drug stability and bioavailability, and can be functionalized for targeted delivery (Simonazzi et al., 2018).
- Polymeric Nanoparticles: Made from biodegradable polymers and offer controlled drug release and reduced toxicity. They can be engineered to target specific tissues, thereby improving the therapeutic index of drugs (Jacob et al., 2018).
- Dendrimers: Highly branched, tree-like structures that provide high drug-loading capacity and precise control over drug release. Their surfaces can be easily modified for targeted delivery and improved interactions with biological systems (Hoda et al., 2019).
- Carbon-Based Nanomaterials: These include carbon nanotubes and graphene oxide, which are known for their high surface area and ability to carry a variety of drugs.

They are particularly useful in cancer therapy and imaging applications (Chatterjee & Dhibar, 2023).

4.3. Advantages of Nanotechnology-Based Drug Delivery Systems

- Enhanced Bioavailability: Nanocarriers improve the solubility and stability of drugs, enhancing their absorption and bioavailability. This leads to more effective treatment at lower doses (Yang et al., 2020).
- Targeted Delivery: Surface modifications allow NDDS to target specific cells or tissues, reducing systemic side effects and increasing the drug concentration at the site of action (Nguyen et al., 2021).
- Controlled Release: NDDS can be designed to release drugs in a controlled manner, ensuring sustained therapeutic effects and improving patient compliance (Zahin et al., 2019).
- Reduced Toxicity: By enhancing drug targeting and controlling drug release, NDDS minimizes the exposure of healthy tissues to drugs, thereby reducing toxicity and side effects (Rana & Sharma, 2019).

5. Controlled Release Mechanisms

5.1. Principles of Controlled Release in Drug Delivery

Systems for controlled-release drug administration are made to provide medications locally or systemically at predefined rates for predefined lengths of time. Maintaining medication levels within the therapeutic window is the primary objective for maximizing effectiveness and reducing adverse effects. Drug delivery systems require an understanding of controlled-release principles. By using many methods, controlled-release systems control the release of therapeutic substances, thereby guaranteeing a consistent and long-lasting medication profile. The primary mechanisms include the following.

5.1.1. Diffusion-Controlled Systems

In systems, the drug diffuses through a polymer matrix or a membrane. The release rate depends on the diffusion coefficient of the drug in the polymer and thickness of the matrix or membrane. These systems can be further classified as reservoir and matrix systems.

- Reservoir Systems: These consists of a core containing a drug surrounded by a polymer membrane. The drug diffuses through the membrane at a controlled rate (Adepu & Ramakrishna, 2021).
- Matrix Systems: The drug is dispersed throughout the polymer matrix and released as the drug diffuses out of the matrix (Patel et al., 2022).

5.1.2. Dissolution-Controlled Systems

These systems rely on dissolution of the drug or matrix material to control the release rate. There are two types:

- Encapsulation Dissolution Systems: The drug is encapsulated in a dissolvable polymer. The release rate was controlled by the dissolution rate of the polymer (Heng, 2018).
- Matrix Dissolution Systems: The drug is dispersed in a matrix that dissolves gradually, controlling the release of the drug.

5.1.3. Osmotic-Controlled Systems

These systems use osmotic pressure to drive the drug release. Water enters the device through a semipermeable membrane, creating a pressure that pushes the drug out through an orifice. Osmotic systems provide zero-order release profiles, making them highly predictable (Kohrs et al., 2019).

5.1.4. Erosion-Controlled Systems

In systems, the polymer matrix erodes over time, thereby releasing the drug. This erosion can be controlled by the chemical composition of the polymer and environmental conditions such as pH and enzymatic activity (Mäder et al., 2018).

5.1.5. Stimuli-Responsive Systems

These advanced systems release drugs in response to specific physiological triggers such as pH, temperature, or enzymes. Stimuli-responsive systems can provide on-demand drug release and enhance the precision and adaptability of therapies (Yang et al., 2020).

5.2. Design Considerations for Controlled Release Systems

- Drug Properties: The physicochemical properties of the drug, such as solubility, stability, and molecular weight, significantly influence the choice and design of the delivery system and its design (Indurkhya et al., 2018).
- Polymer Selection: The choice of polymer affects the release mechanism and rate. Biodegradable polymers, such as polylactic acid (PLA) and polyglycolic acid (PGA), are commonly used because of their biocompatibility and ability to degrade into non-toxic byproducts (Paolini et al., 2019).
- Device Geometry: The size and shape of the delivery system can influence the drug-release profile. For example, thin films may provide a faster release than thicker implants because of the larger surface area-to-volume ratio (Ephraim Neumann et al., 2018).
- Target Site: The intended site of drug delivery, whether systemic or localized, impacts the design. For instance, localized delivery systems, such as implants or in situ gels, are designed for site-specific release to minimize systemic side effects (Heng, 2018).

5.3. Mechanisms of Controlled Release in Nanocarriers

Leading the way in advanced drug delivery systems, nanocarriers provide precise control over the release of medicinal chemicals. These systems improve the effectiveness and safety of medication therapies using a variety of techniques to achieve controlled release. The main processes by which nanocarriers accomplish regulated release —diffusion, degradation, swelling, and systems responding to external stimuli— are examined in this section.

5.3.1. Diffusion-Controlled Release

In diffusion-controlled release systems, the drug diffuses from the nanocarrier matrix into the surrounding environment. This mechanism is influenced by the properties of both the drug and nanocarrier material. There are two main types of diffusion-controlled system.

- Reservoir Systems: In systems, the drug is encapsulated within a core that is surrounded by a polymeric membrane. The drug diffused through the membrane at a controlled rate. The release rate is determined by the diffusion coefficient of the drug through the membrane and thickness of the membrane (Tan et al., 2018).
- Matrix Systems: The drug was uniformly distributed throughout the polymer matrix. Release occurs as the drug diffuses out of the matrix. The release rate is influenced by the diffusion coefficient of the drug within the matrix and degradation rate (Xiang et al., 2018).

5.3.2. Degradation-Controlled Release

Degradation-controlled release relies on the breakdown of nanocarrier material to release the encapsulated drug. This can occur via hydrolytic or enzymatic degradation.

- Hydrolytic Degradation: Polymers such as polylactic acid (PLA) and polyglycolic acid (PGA) degrade in the presence of water, leading to gradual release of the drug (Chen et al., 2020).
- Enzymatic Degradation: Certain polymers are degraded in the presence of specific enzymes found in the body. For example, chitosan-based nanocarriers degrade in the presence of lysozyme, an enzyme found in bodily fluids (Echeverri-Cuartas et al., 2020).

5.3.3. Swelling-Controlled Release

Systems that regulate swelling use hydrophilic polymers, which expand when they come into contact with water or bodily fluids. The gel-like structure produced by swelling enables the medicine to spread gradually. Hydrophilic medicines benefit from this process, which can be optimized by changing the polymer composition (Chen et al., 2020).

5.3.4. Stimuli-Responsive Release

Stimuli-responsive nanocarriers release their payloads in response to specific external or internal triggers. These triggers can be physical, chemical, or biological in nature.

- pH-Responsive Systems: These systems exploit the pH differences between healthy and diseased tissues, or between different compartments within the body. For example, nanocarriers designed to release drugs into the acidic environment of tumor tissues can enhance the targeted delivery of anticancer drugs (Singh et al., 2018).
- Temperature-Responsive Systems: These nanocarriers release drugs in response to temperature change. For instance, certain polymers undergo phase transitions at specific temperatures, releasing the drug as temperature changes (Yang et al., 2018).
- Light-Responsive Systems: Light-sensitive nanocarriers release their payloads upon exposure to specific wavelengths of light. This allows for precise spatial and temporal control of drug release, making it ideal for applications such as cancer therapy (Xiong et al., 2019).
- Magnetic-Responsive Systems: Magnetic nanocarriers can be manipulated using external magnetic fields to release drugs at the targeted sites. This method provides a noninvasive means of controlling drug delivery (Kwak et al., 2018).
- Enzyme-Responsive Systems: Drugs are released by these systems in response to overexpressed enzymes in certain conditions. Enzyme-responsive nanocarriers, for instance, may release anticancer medications in the presence of matrix metalloproteinases, which are often increased in tumor settings (Vázquez-González & Willner, 2021).

5.4. Benefits of Controlled Release for Therapeutic Efficacy and Patient Compliance

Drugs are released at a preset pace over a long period of time in controlled-release drug delivery systems, which guarantees constant therapeutic doses and reduces adverse effects. Effective illness treatment depends critically on both patient compliance and medication effectiveness, both of which greatly improve.

5.4.1. Enhanced Therapeutic Efficacy

- Maintaining Therapeutic Drug Levels: Long-term medication concentrations within the therapeutic window are maintained via controlled release systems, which also reduce the variations that are typical of traditional dosing forms. This guarantees a more constant therapeutic action and avoids sub-therapeutic dosage times (Kohrs et al., 2019).
- Reduced Side Effects: Controlled release systems minimize side effects and toxicity by providing a constant release of the medication, thereby reducing peak-trough variations linked to conventional dosage. This is especially crucial for medications with limited therapeutic indices (Jeganath et al., 2018).
- Improved Drug Stability: Drugs may be preserved in controlled release formulations by encapsulation from environmental variables such as pH, light, and enzymatic activity, thereby maintaining their bioactivity until they travel to the target location (Mansour et al., 2023).
- Targeted Drug Delivery: To increase the effectiveness of the medication while lowering systemic exposure, advanced controlled-release devices may be made to

target certain tissues or cells. Drugs with limited absorption windows may be better absorbed; for instance, when gastroretentive systems extend the drug's retention duration in the stomach (Vrettos et al., 2021).

5.4.2. Improved Patient Compliance

- Reduced Dosing Frequency: Controlled-release formulations allow for less frequent dosing schedules (e.g., once-daily or even less frequent), which simplifies treatment regimens and reduces the burden on patients. This is particularly beneficial for managing chronic conditions in which lifelong medication is necessary.
- Increased Convenience and Adherence: Simplified dosing regimens lead to better adherence to the prescribed therapies. Studies have shown that patients are more likely to adhere to treatment plans that require fewer daily doses, which results in better clinical outcomes (Jung et al., 2021).
- Minimized Treatment Burden: For conditions requiring frequent dosing or injections Controlled release systems can significantly reduce the treatment burden for conditions requiring frequent dosing or injections. For example, extended-release formulations for ocular diseases can reduce the need for frequent intravitreal injections, which is invasive and uncomfortable for patients (Kim et al., 2021).
- Enhanced Quality of Life: By Controlled-release systems improve the overall quality of life of patients by reducing the frequency and complexity of medication schedules. This is particularly important in pediatric and geriatric populations, where compliance can be challenging owing to difficulties in managing complex regimens (Nie et al., 2021).

6. Nanotechnology-Based Polyphenol Delivery Systems

6.1. Design and Formulation of Polyphenol-Loaded Nanocarriers

The improved therapeutic effectiveness and bioavailability of polyphenols critically depend on the design and synthesis of polyphenol-loaded nanocarriers. Although polyphenols have long been recognized for their antioxidant, anti-inflammatory, and anticancer effects, their low bioavailability and stability have restricted their therapeutic use. These problems have hopeful answers in nanotechnology, which enhances the delivery and regulated release of polyphenols.

6.1.1. Key Components in the Design of Nanocarriers

- Nanocarrier Materials: Effectiveness of nanocarriers depends critically on the materials used. Lipids, polymers, and inorganic substances are commonly used materials. Biocompatibility and encapsulation of hydrophobic polyphenols include lipid-based nanocarriers such as liposomes and solid lipid nanoparticles. Biodegradability and regulated release are features of polymer-based nanocarriers, such as poly (lactic-co-glycolic acid) (Pimentel-Moral et al., 2018).

- Encapsulation Techniques: Encapsulation methods affect polyphenol-loaded nanocarrier stability and release profile. The typical methods include emulsification, nanoprecipitation, and solvent evaporation. High-efficiency encapsulation and environmental degradation protection of polyphenols are guaranteed using these techniques (Markwalter et al., 2020).
- Surface Modification: Surface modification of nanocarriers with targeting ligands, such as antibodies, peptides, or folic acid, enhances their specificity to target tissues or cells. This targeting capability is essential for reducing off-target effects and increasing the therapeutic efficacy (Zhang et al., 2019).

6.1.2. Types of Polyphenol-Loaded Nanocarriers

- Lipid-Based Nanocarriers: These include liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). Liposomes encapsulate polyphenols within a phospholipid bilayer, thereby protecting them from degradation and enhancing their bioavailability. SLNs and NLCs offer improved stability and controlled release properties (Pimentel-Moral et al., 2018).
- Polymeric Nanocarriers: These carriers use biodegradable polymers such as PLGA, chitosan, and polycaprolactone (PCL) to encapsulate polyphenols. Polymeric nanocarriers provide sustained release and protect polyphenols from enzymatic degradation in the gastrointestinal tract (Chen et al., 2020).
- Inorganic Nanocarriers include silica nanoparticles, gold nanoparticles, and carbon-based nanomaterials, such as graphene oxide. These carriers offer high surface area and functionalization potential, which can be used for targeted delivery and imaging applications (Singh et al., 2020).

6.1.3. Formulation Strategies

- Drug Loading Efficiency: High drug-loading efficiency is essential for effective therapy. Techniques such as solvent evaporation and nanoprecipitation have been optimized to achieve the maximum loading of polyphenols without compromising the stability of the nanocarrier (Rarokar et al., 2019).
- Controlled Release Profiles: Controlled release is achieved by selecting appropriate materials and encapsulation techniques. For instance, the use of pH-responsive polymers ensures that polyphenols are released into the acidic environment of the stomach or tumor tissues, enhancing their therapeutic efficacy (Wu et al., 2021).
- Stability and Shelf-Life: Stability of polyphenol-loaded nanocarriers is enhanced through the use of stabilizers and appropriate storage conditions. Lyophilization (freeze-drying) is a common technique used to extend the shelf life of nanocarriers by removing water and stabilizing their structure (Jadhav & Cheriyan, 2021).

6.2. Techniques for Achieving Controlled and Sustained Release

Therapeutic medication levels, patient compliance, and side effect minimization depend on controlled- and sustained-release drug delivery systems. To accomplish these goals, several methods have been devised that use chemical and physical processes to regulate the release rate of active pharmacological components.

6.2.1. Diffusion-Controlled Systems

- Reservoir Systems: The medicine in these systems is contained in a core encircled by a polymeric membrane. Diffusion across the membrane causes drug release. The drug release rate is determined by membrane characteristics such as permeability and thickness. Because of their somewhat consistent release rates, these systems are appropriate for use where continuous drug levels are needed (Stevenson et al., 2012).
- Matrix Systems: When drug diffuses through a polymer matrix, it is released. The drug diffusion coefficient inside the polymer and degradation rate of the matrix affect the release rate (Prajapat et al., 2022).

6.2.2. Degradation-Controlled Systems

- Biodegradable Polymers: Drugs can be encapsulated in biodegradable polymers, such as polylactic acid (PLA) or polyglycolic acid (PGA), which degrade over time. The drug release rate is controlled by the polymer degradation rate, which can be adjusted by altering the polymer composition and molecular weight (Chen et al., 2020).
- Erosion-Based Systems: These systems rely on the erosion of the polymer matrix to release the drug. Erosion can be surface-based or bulk-based, depending on the polymer properties. Surface erosion provides a more predictable release profile, because the drug release rate is proportional to the surface area (Wakui & Aizawa, 2018).

6.2.3. Osmotic-Controlled Systems

Osmotic pressure drives drug release in osmotically controlled devices. Usually, a semipermeable membrane surrounds a core that holds the medication and the osmotic agent. across an aperture, the medication is forced out by the osmotic pressure produced by water input across the membrane. These systems are independent of external circumstances with zero-order release rates (Pophalkar & Karole, 2023).

6.2.4. Swelling-Controlled Systems

Swelling-controlled systems use hydrophilic polymers that swell upon contact with water or biological fluid. This swelling creates a gel-like matrix through which the drug diffuses. The release rate can be adjusted by modifying the polymer composition and crosslinking density (Deshmukh, 2022).

6.2.5. Stimuli-Responsive Systems

- pH-Responsive Systems: These systems release drugs in response to changes in pH. They are particularly useful for targeting specific areas of the gastrointestinal tract or tumor environments, which have distinct pH levels compared with normal tissues (Singh et al., 2018).
- Temperature-Responsive Systems: These systems release drugs in response to temperature change. Polymers that undergo phase transitions at specific temperatures can be used to control drug release in response to body temperature or externally applied heat (Yang et al., 2018).
- Light-Responsive Systems: These systems use light to trigger drug release. Light-sensitive polymers or photosensitive compounds can be incorporated into delivery systems to provide precise spatial and temporal control over drug release (Xiong et al., 2019).

6.2.6. Smart and Intelligent Systems

Recent advancements in drug delivery include the development of smart systems that can respond to multiple stimuli and provide feedback-controlled release. These systems can combine different mechanisms, such as pH and temperature responsiveness, to achieve more precise and adaptable drug delivery (Shaikh et al., 2022).

6.3. Targeted Delivery to Infected Sites

Therapeutic agents are especially directed to the site of infection in targeted medication delivery, which maximizes therapeutic effectiveness while reducing systemic adverse effects. Polyphenols especially benefit from this strategy because they increase their local concentration at the diseased location, which improves their interaction with infected tissues and harmful bacteria. By lowering the necessary dose and frequency of administration, targeted delivery also enhances patient compliance and the overall results of the therapy as a whole (Sharma, 2014). Polyphenols may be encapsulated by nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles, which can also help regulate their release in the target region and prevent degradation (Zhang et al., 2021).

Lipids loaded with polyphenols have improved stability and bioavailability; they may also be functionalized for targeted distribution using ligands or antibodies. Compared to free curcumin, liposomal preparations of curcumin have shown improved antibacterial action (Obeid et al., 2023). Biocompatible and biodegradable polymers used to prepare polymeric nanoparticles provide flexible platforms for targeted drug delivery. Polyphenols may be produced in them released in response to certain stimuli, including pH, temperature, and enzymatic activity, at the infection site. Because polymeric nanoparticles loaded with resveratrol target the infection site and provide prolonged release, they have shown better therapeutic results in treating bacterial infections (Saouti et al., 2014). Drug conjugation is possible with dendrimers and extremely branched tree-like structures with many surface functional groups. These nanocarriers improved the bioavailability, stability, and solubility of polyphenols. The development of dendrimer-based quercetin delivery systems has improved

antiviral activity and decreased cytotoxicity in the treatment of viral infections (Mukherjee et al., 202). Solid lipids can encapsulate polyphenols to prevent their degradation and allow for the regulated release of SLNs. Polyphenols such as epigallocatechin gallate (EGCG) have been delivered via SLNs for the treatment of infections. These SLNs exhibit better stability and bioavailability than free EGCG (Alsaad et al., 2020).

Targeting based on ligands involves changing the surface of nanocarriers with particular ligands that attach to overexpressed receptors on the surface of pathogens or infected cells. Through this approach, the targeted distribution of polyphenols at the infection site is improved, thereby enhancing the therapeutic effectiveness (Prabhu et al., 202). Specific physiological cues, including pH, temperature, or the presence of particular enzymes, at the infection site cause stimuli-responsive delivery systems to release their payloads. These mechanisms guarantee that polyphenols are released only when required. Quercetin has been released in the acidic milieu of sick tissues via pH-responsive nanoparticles, which increases its antibacterial activity (Karimi et al., 2016). Targeted polyphenol administration in therapeutic settings has been shown to be promising by a number of research. A recent study on liposomal resveratrol showed a significant improvement in the treatment of bacterial infections, which also decreased inflammation and improved bacterial clearance (Aiello et al., 2021). Better results in viral infection models were reported in another study on polymeric nanoparticles encapsulating EGCG, highlighting the potential of nanocarrier systems to increase the therapeutic efficiency of polyphenols (Natarajan et al., 2019).

7. Polyphenol-Nanocarrier Formulations for Infectious Diseases

One study presented a new nanoformulation that may be crucial in the battle against COVID-19 and other infectious disorders, including DNA and RNA viruses. The formulation comprised natural polyphenol ellagic acid (ELG) impregnated with zinc oxide nanoparticles (ZnO NPs) functionalized with triptycene (TRP). The virucidal mechanism in this hybrid nanoformulation directly inactivates viruses with high therapeutic indices, such as H1N1 and HCoV-229E. Using the antiviral characteristics of ELG and the special structural benefits of TRP-functionalized ZnO NPs, this novel method provides a potential low-cost and safe treatment approach. These findings highlight the potential of polyphenol-nanocarrier formulations to improve antiviral treatment and may signal the start of a new era in the treatment of infectious illnesses (AbouAitah et al., 2021). The utilization of polyphenols, especially resveratrol (RES) and epigallocatechin gallate (EGCG), in combination with gold nanoparticles (AuNPs), as antiviral agents against enteroviruses. These preparations use the inherent antiviral qualities of polyphenols and the stabilizing actions of AuNPs to group viruses, thereby inhibiting their entry into cells and decreasing their infectiousness. According to this study, these polyphenol-nanocarrier combinations have the potential to behave as widely acting antivirals, providing a viable strategy to fight infectious illnesses, particularly in cases where vaccine development and use may be postponed (Reshamwala et al., 2021).

Additional work addresses the creation of aqueous EC16 nanoformulations to fight human coronaviruses. Originating from polyphenols in green tea, EC16 exerts antioxidant, antiviral, anti-inflammatory, and neuroprotective effects. This study emphasizes the intranasal use of EC16 to reduce protracted neurological symptoms associated with COVID-19. *In vitro*,

nanoformulations demonstrated, after a 30-minute interaction, over 99.99% suppression of coronavirus infection. This raises the prospect of EC16 as a nasally administered treatment for COVID-19 and related neurological disorders (Frank et al., 2023). Innovative approaches to improve the treatment of infectious illnesses using polyphenol-nanocarrier compositions are discussed in this paper. These preparations increase the recognized antibacterial characteristics, bioavailability, and therapeutic effectiveness of polyphenols. Polyphenols can be successfully transported to infection sites by encapsulating them in nanocarriers, which presents a promising strategy to fight different infections and may lessen the need for conventional antibiotics. This work emphasizes the possibility of using nanotechnology for the treatment of infectious diseases (Santonocito et al., 2020).

The encapsulation of polyphenol-rich essential oils of peppermint and green tea in chitosan nanoparticles has been investigated. The compositions noticeably boosted the antibacterial and antioxidant properties, as well as heat stability and release control. In particular, green tea oil-loaded nanoparticles demonstrated strong antibacterial properties, indicating their potential for the treatment of infectious disorders (Shetta et al., 2019). An additional study addressed a Gel-PDA@Cur composite hydrogel intended for antibacterial wound healing. This emphasizes how the hydrogel releases the polyphenol curcumin (Cur) when it comes into contact with near-infrared (NIR) light. This on-demand release mechanism is important for treating non-healing infected wounds because it provides a multifunctional strategy that combines improved biocompatibility with quick hemostasis. PEGDA, Chi-LA, and PDA@Cur nanoparticles are among the hydrogel (Tao et al., 2021).

Conclusion

This chapter emphasizes the great promise of nanotechnology in improving the therapeutic effectiveness of polyphenols in the treatment of infectious illnesses. Infectious infections are becoming a global health concern, and drug-resistant bacteria are emerging, as in the case of COVID-19. With their reputation as antioxidant, anti-inflammatory, and antibacterial agents, polyphenols show promise for medical use. However, their low bioavailability and stability restrict their clinical use. Through the enhancement of polyphenol stability, solubility, and bioavailability, nanotechnology-based drug delivery solutions can overcome these drawbacks. Many nanocarrier technologies that improve the targeted and regulated release of polyphenols are discussed in this chapter, including liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles. In addition to preventing degradation, these cutting-edge delivery technologies enable steady and site-specific release of polyphenols, thereby optimizing therapeutic effects. The novel methods covered in this chapter, such as the functionalization of nanoparticles and the creation of stimuli-responsive systems, highlight how nanoformulations may completely transform the treatment of infectious illnesses. Overcoming the present obstacles and fully realizing the promise of polyphenol-based nanotherapies to address global health concerns will require further research and development in this area.

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