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Antiviral Flavonoids: Exploring Their Potential as Natural Medicines

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KEYWORDS

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ABSTRACT:

Flavonoids, a diverse group of natural compounds found abundantly in plants, have garnered attention for their potential antiviral properties. This review summarizes key findings from various studies elucidating the antiviral activity of flavonoids, including their ability to inhibit viral entry, replication, and induce apoptosis in infected cells. Moreover, it emphasizes the importance of exploring flavonoids as alternative therapies against viral infections, especially considering emerging drug-resistant viral strains and the limited efficacy of current antiviral medications. Understanding the mechanisms by which flavonoids exert their antiviral effects holds promise for the development of novel therapeutic interventions. Hence, further research into the antiviral potential of flavonoids is warranted, including elucidation of structure-activity relationships, investigation of synergistic effects with conventional antiviral drugs, and evaluation of their safety and efficacy in clinical settings. Such endeavors could ultimately lead to the development of effective and safe flavonoid-based antiviral medicines, offering new strategies for the management and prevention of viral diseases.

Introduction:

Flavonoids represent a diverse group of polyphenolic compounds found abundantly in nature, particularly in fruits, vegetables, grains, herbs, and beverages such as tea and wine. Their structural diversity and ubiquitous presence in the plant kingdom have long attracted scientific interest, leading to extensive research into their various biological activities and potential health benefits[1]. In recent years, flavonoids have emerged as promising candidates for the development of natural medicines, particularly in the context of antiviral therapy.

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Flavonoids are classified into several subclasses based on their chemical structure, including flavones, flavonols, flavanones, flavan-3-ols (catechins), anthocyanidins, and isoflavones[2]. Each subclass possesses distinct molecular features, which contribute to their specific biological activities and pharmacological properties[3]. For instance, flavonols such as quercetin and kaempferol are known for their antioxidant and anti-inflammatory effects, while flavanones like hesperidin and naringenin exhibit potential cardioprotective properties. These bioactive compounds are primarily obtained from plant-based sources, where they serve various physiological functions including UV protection, pigmentation, and defense against pathogens. Common dietary sources of flavonoids include citrus fruits, berries, onions, parsley, and cocoa, among others[4]. The widespread consumption of flavonoid-rich foods in traditional diets has been associated with numerous health benefits, including reduced risk of chronic diseases such as cardiovascular disease, cancer, and neurodegenerative disorders. Moreover, flavonoids have a long history of use in traditional medicine systems, where they are employed for their purported therapeutic properties[5]. Traditional herbal remedies containing flavonoid-rich botanicals have been utilized for centuries in different cultures around the world to treat various ailments, ranging from digestive disorders to infectious diseases. The empirical knowledge of these traditional healing practices has provided valuable insights into the potential pharmacological activities of flavonoids, paving the way for scientific investigation and validation. In addition to their well-documented antioxidant, anti-inflammatory, and cytoprotective effects, flavonoids have also been recognized for their antiviral properties[6]. Numerous in vitro and in vivo studies have demonstrated the ability of certain flavonoids to inhibit viral replication and modulate host immune responses against viral infections. The mechanisms underlying the antiviral activity of flavonoids are multifaceted and include interference with viral entry and fusion, inhibition of viral RNA or DNA synthesis, modulation of viral protein expression, and enhancement of host antiviral defenses[7]. The antiviral potential of flavonoids extends across a wide spectrum of viral pathogens, including RNA viruses such as influenza virus, respiratory syncytial virus (RSV), hepatitis C virus (HCV), and dengue virus, as well as DNA viruses such as herpes simplex virus (HSV) and human papillomavirus (HPV). This broad-spectrum activity makes flavonoids particularly attractive as candidates for the development of novel antiviral therapies, especially in the context of emerging viral threats and the increasing incidence of drug-resistant viral strains[8]. In this review, we aim to provide a comprehensive overview of the antiviral properties of flavonoids and explore their potential as natural medicines for the prevention and treatment of viral infections. We will discuss the underlying mechanisms of action of flavonoids against viral pathogens, highlight specific flavonoid subclasses and compounds with promising antiviral activity, evaluate the pharmacokinetic properties and safety profile of flavonoids, and discuss future directions and challenges in the development of flavonoid-based antiviral therapies. By elucidating the therapeutic potential of flavonoids in combating viral infections, this review aims to contribute to the growing body of evidence supporting the use of natural compounds as alternative strategies for antiviral intervention.

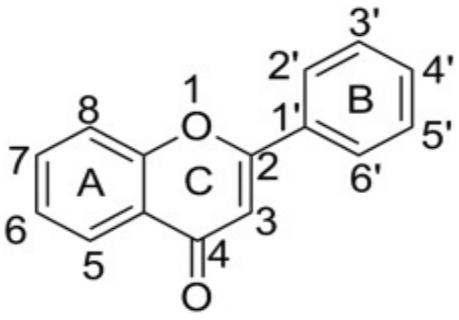

Figure 1: Basic structure of flavonoid

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Antiviral Activity of Flavonoids:

Flavonoids, a diverse group of polyphenolic compounds found abundantly in plants, have garnered considerable attention for their potential antiviral properties[9]. The mechanisms underlying their antiviral activity are multifaceted and involve inhibition of viral entry and fusion, interference with viral replication processes, modulation of host immune responses, and induction of apoptosis in virus-infected cells. Here, we delve into each of these mechanisms and explore the specific flavonoids that exhibit potent antiviral activity[10].

1. Inhibition of Viral Entry and Fusion:

Flavonoids have been shown to interfere with the initial stages of viral infection by inhibiting viral entry and fusion with host cells. This activity is often attributed to their ability to disrupt viral envelope glycoproteins or cellular receptors necessary for viral attachment and entry[11]. For instance, flavonoids such as quercetin and epigallocatechin gallate (EGCG) have been demonstrated to block the entry of influenza virus by binding to viral hemagglutinin and preventing its interaction with host cell receptors. Similarly, flavonoids like baicalein and hesperidin have been reported to inhibit the fusion of viral membranes with cellular membranes, thereby preventing viral entry into target cells[12].

2. Interference with Viral Replication Processes:

Flavonoids exert inhibitory effects on viral replication by targeting various stages of the viral life cycle, including viral RNA or DNA synthesis, protein translation, and assembly of viral particles. Several flavonoids have been shown to disrupt viral replication complexes or interfere with viral enzymes essential for genome replication and transcription[13]. For example, flavonoids such as catechins and flavones have been found to inhibit the activity of viral RNA polymerases, thereby suppressing viral replication. Additionally, flavonoids like apigenin and luteolin have been shown to downregulate the expression of viral proteins involved in viral replication and assembly[14].

3. Modulation of Host Immune Response Against Viral Infections:

Flavonoids possess immunomodulatory properties that can enhance the host immune response against viral infections. They are known to regulate various aspects of innate and adaptive immunity, including cytokine production, antigen presentation, and T cell activation. Certain flavonoids have been shown to stimulate the production of antiviral cytokines such as interferons and interleukins, which play crucial roles in orchestrating the immune response to viral pathogens[15]. Moreover, flavonoids can enhance the activity of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), thereby promoting the clearance of virus-infected cells. Flavonoids such as quercetin and resveratrol have been reported to modulate immune signaling pathways involved in antiviral defense, including the NF-κB and JAK-STAT pathways[16].

4. Induction of Apoptosis in Virus-Infected Cells:

Apoptosis, or programmed cell death, is a natural mechanism employed by the host to eliminate virus-infected cells and limit viral spread. Flavonoids have been shown to induce apoptosis in virus-infected cells through various signaling pathways, including the intrinsic and extrinsic apoptotic pathways. By promoting apoptosis, flavonoids can effectively eliminate virus-infected cells without causing excessive inflammation or tissue damage[17]. Several flavonoids, including flavones, flavonols, and flavanones, have been demonstrated to induce apoptosis in virus-infected cells by activating pro-apoptotic proteins and inhibiting anti-apoptotic factors. For example, flavonoids such as fisetin and quercetin have been shown to activate caspases and induce mitochondrial membrane permeabilization, leading to apoptotic cell death in virus-infected cells[18].

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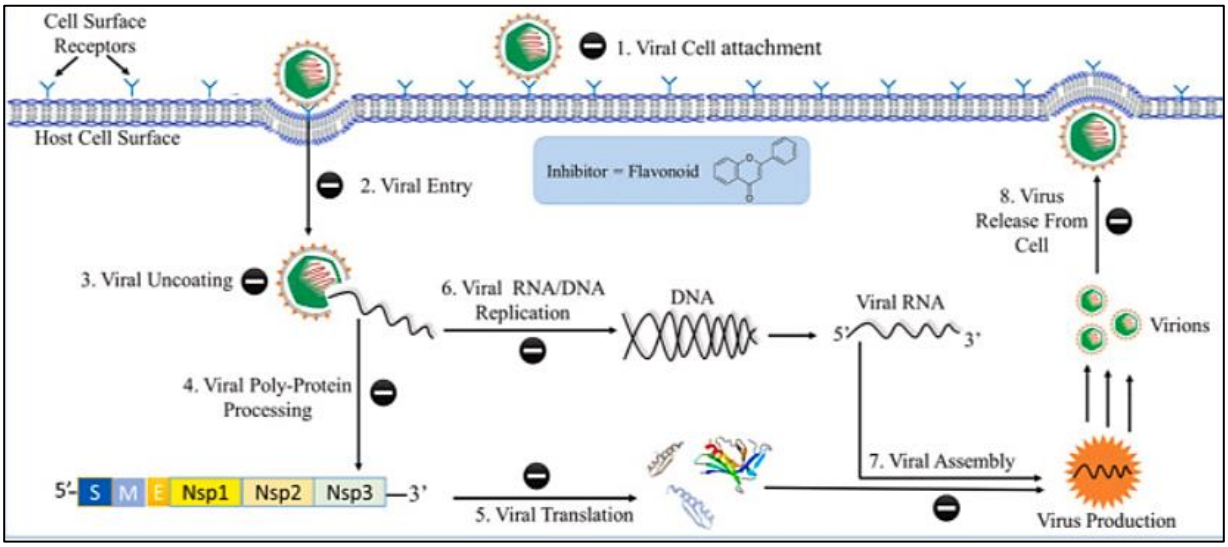

Figure 2: Antiviral mechanism of Flavonoids

Antiviral Activity of Specific Flavonoids:

Numerous studies have identified specific flavonoids with potent antiviral activity against a wide range of viral pathogens. These flavonoids vary in their chemical structure, bioavailability, and mode of action, but collectively contribute to the overall antiviral potential of flavonoid-rich botanical extracts. Some notable examples include:

Quercetin: A flavonol found in onions, apples, and tea, quercetin exhibits broad-spectrum antiviral activity against influenza virus, herpes simplex virus, and respiratory syncytial virus. It inhibits viral entry, replication, and gene expression, while also modulating host immune responses[19].

Epigallocatechin gallate (EGCG): The major catechin in green tea, EGCG has been shown to inhibit the replication of influenza virus, hepatitis C virus, and human immunodeficiency virus (HIV) by targeting viral polymerases and proteases. It also enhances host antiviral defenses and reduces viral-induced inflammation[20].

Hesperidin: A flavanone abundant in citrus fruits, hesperidin possesses antiviral activity against herpes simplex virus, dengue virus, and hepatitis B virus. It inhibits viral entry and replication, suppresses viral gene expression, and modulates immune responses against viral infections[21].

Baicalein: A flavone isolated from the roots of Scutellaria baicalensis, baicalein exhibits potent antiviral activity against influenza virus, HIV, and enterovirus. It interferes with viral entry and fusion, inhibits viral RNA synthesis, and induces apoptosis in virus-infected cells[22].

Flavonoid Subclasses and Their Antiviral Mechanisms:

Flavonoids encompass a diverse group of compounds classified into several subclasses based on their chemical structure. Each subclass exhibits unique antiviral properties, often targeting different stages of the viral life cycle. For example, flavones such as baicalein and apigenin have been shown to inhibit viral replication by interfering with viral RNA synthesis or viral protein expression[23]. Flavonols like quercetin and kaempferol possess broad-spectrum antiviral activity by blocking viral entry and fusion, as well as modulating host immune responses. Flavanones such as hesperidin and naringenin exhibit potent antiviral effects against various viruses, including influenza virus and dengue virus, through mechanisms involving inhibition of viral replication and induction of apoptosis in infected cells[24].

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Table 1: Antiviral Activities of Flavonoids

Phytochemical Name	Plant Source	Model	Dose/Concentration	Mechanisms/Outcomes	References
Quercetin	Various plants (e.g., onions, apples)	HCV (Hepatitis C Virus)	Not specified	Inhibition of NS3 protease activity (Bachmetov et al., 2012); Inhibition of viral entry (Haid et al., 2012)	[25]
Epigallocatechin gallate (EGCG)	Green tea (Camellia sinensis)	HBV (Hepatitis B Virus)	Not specified	Inhibition of HBV DNA synthesis (He et al., 2011)	[26]
Baicalin	Scutellaria baicalensis	HIV-1 (Human Immunodeficiency Virus type 1)	Not specified	Inhibition of viral entry (Li et al., 2000)	[27]
Apigenin	Various plants (e.g., parsley, chamomile)	EV71 (Enterovirus 71)	Not specified	Disruption of viral RNA association with trans-acting factors (Zhang et al., 2014)	[28]
Kaempferol	Various plants (e.g., kale, broccoli)	CoV (Coronavirus)	Not specified	Inhibition of the 3a channel protein of coronavirus (Schwarz et al., 2014)	[29]
Genistein	Soybeans (Glycine max)	HIV	Not specified	Antiviral activity against HIV ion channel (Sauter et al., 2014)	[30]
Rutin	Various plants (e.g., buckwheat, citrus fruits)	HSV (Herpes Simplex Virus), HIV	Not specified	Anti-HIV and -HSV activity (Tao et al., 2007); Microbicide candidate (Tao et al., 2007)	[31]
Isoquercitrin	Various plants (e.g., apples,	Zika Virus	Not specified	Prevention of Zika virus infection in human cells (Gaudry et al., 2018)	[32]

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	onions)				
Naringenin	Citrus fruits (e.g., grapefruit, oranges)	Zika Virus	Not specified	Impairment of Zika virus infection in human cells (Cataneo et al., 2019)	[33]

Efficacy of Flavonoids Against Specific Viruses:

Several flavonoids have demonstrated remarkable efficacy against specific viral pathogens, making them promising candidates for antiviral therapy. For instance, quercetin, a flavonol found in fruits and vegetables, has been shown to inhibit the replication of influenza virus by blocking viral RNA polymerase activity and suppressing viral gene expression[4,8]. Similarly, epigallocatechin gallate (EGCG), a catechin abundant in green tea, exhibits potent antiviral activity against hepatitis C virus (HCV) by inhibiting viral entry and replication. Moreover, flavonoids such as hesperidin and baicalein have demonstrated efficacy against herpes simplex virus (HSV) by interfering with viral attachment and entry, as well as inhibiting viral DNA synthesis and viral protein expression[34].

Synergistic Effects and Combination Therapies:

Flavonoids have been investigated for their potential synergistic effects when used in combination with conventional antiviral drugs or other natural compounds. Studies have shown that combining flavonoids with antiviral agents can enhance their efficacy and reduce the risk of drug resistance[7]. For example, the combination of quercetin with oseltamivir, a neuraminidase inhibitor used to treat influenza virus infection, has been shown to exert synergistic antiviral effects against drug-resistant strains of influenza virus. Similarly, the combination of EGCG with interferon-alpha, a cytokine with antiviral activity, has been found to enhance the antiviral response against hepatitis C virus[35].

Synergistic Effects of Flavonoids with Conventional Antiviral Drugs:

Combining flavonoids with conventional antiviral drugs has been explored to enhance therapeutic efficacy and overcome drug resistance. Studies have demonstrated synergistic interactions between flavonoids and antiviral drugs, leading to improved antiviral activity against a variety of viral pathogens[21,3]. For example, the combination of flavonoids such as quercetin or epigallocatechin gallate (EGCG) with oseltamivir, a neuraminidase inhibitor used to treat influenza virus infection, has shown synergistic effects in inhibiting viral replication and reducing the risk of drug-resistant strains of influenza virus. Similarly, flavonoids like baicalein or luteolin have been found to enhance the antiviral activity of nucleoside analogs such as acyclovir against herpes simplex virus (HSV) by promoting viral DNA chain termination and inhibiting viral DNA synthesis[36].

Investigation of Combination Therapies with Flavonoids and Other Natural Compounds:

In addition to conventional antiviral drugs, combination therapies involving flavonoids and other natural compounds have also been investigated for their potential synergistic effects against viral infections. Natural compounds such as curcumin, resveratrol, and berberine have been shown to possess antiviral activity through different mechanisms of action, including inhibition of viral replication, modulation of host immune responses, and induction of apoptosis in infected cells[18]. Combining flavonoids with these natural compounds may offer complementary or additive effects, leading to enhanced antiviral efficacy. For instance, the combination of quercetin with curcumin has been reported to exhibit synergistic antiviral activity against hepatitis B virus (HBV) by inhibiting viral entry and replication, as well as promoting the clearance of virus-infected cells[37].

Potential of Flavonoid-Based Combination Therapies to Combat Viral Resistance:

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One of the key advantages of flavonoid-based combination therapies is their potential to overcome viral resistance, which is a major challenge in antiviral treatment. By targeting multiple viral and host factors involved in viral replication and pathogenesis, flavonoid-based combination therapies can reduce the likelihood of viral resistance development and improve treatment outcomes[24]. Moreover, flavonoids possess immunomodulatory properties that can enhance the host immune response against viral infections, further reducing the risk of viral escape. However, more research is needed to optimize the selection and dosing of flavonoids in combination therapies, as well as to evaluate their long-term efficacy and safety in clinical settings[15].

Pharmacokinetics and Bioavailability of Flavonoids:

Understanding the pharmacokinetics and bioavailability of flavonoids is essential for optimizing their use in combination therapies and ensuring therapeutic efficacy. Flavonoids exhibit poor oral bioavailability due to their low aqueous solubility, rapid metabolism, and extensive first-pass metabolism in the liver[37]. Strategies to improve the bioavailability of flavonoids include formulation approaches such as nanotechnology, lipid-based delivery systems, and prodrug design. Moreover, co-administration of flavonoids with food components or inhibitors of drug-metabolizing enzymes can enhance their absorption and systemic exposure[5]. However, variability in individual pharmacokinetic profiles and potential drug interactions with other medications must be considered when designing flavonoid-based combination therapies. Overall, optimizing the pharmacokinetic properties and bioavailability of flavonoids is essential for maximizing their therapeutic potential in combating viral infections[38].

Overview of Factors Influencing the Pharmacokinetics of Flavonoids:

The pharmacokinetics of flavonoids, including their absorption, distribution, metabolism, and excretion, are influenced by various factors that impact their bioavailability and therapeutic efficacy. These factors include:

1. Chemical Structure: The chemical structure of flavonoids, including their molecular weight, lipophilicity, and degree of glycosylation, affects their absorption and metabolism in the body. For instance, flavonoids with higher lipophilicity tend to have better absorption across biological membranes, while glycosylated flavonoids may undergo hydrolysis by intestinal enzymes before absorption[39].

2. Food Matrix: The presence of food components, such as dietary fats and proteins, can influence the absorption of flavonoids by affecting their solubility and stability in the gastrointestinal tract. Co-administration of flavonoids with food can enhance their absorption and bioavailability, particularly for poorly soluble compounds[40].

3. Intestinal Transporters: Flavonoids are substrates for various intestinal transporters, such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRPs), which regulate their absorption and efflux from enterocytes. Interactions with these transporters can influence the oral bioavailability of flavonoids and contribute to their pharmacokinetic variability[14].

4. First-Pass Metabolism: Flavonoids undergo extensive first-pass metabolism in the liver, where they are metabolized by phase I and phase II enzymes, including cytochrome P450 enzymes (CYPs) and uridine diphosphate glucuronosyltransferases (UGTs). Metabolic reactions such as hydroxylation, methylation, and glucuronidation can modify the chemical structure of flavonoids and influence their pharmacological properties[4].

5. Tissue Distribution: Following absorption, flavonoids are distributed throughout the body via the systemic circulation and may accumulate in specific tissues or organs, depending on their lipophilicity and protein binding properties. Flavonoids have been detected in various tissues, including the liver, kidneys, lungs, and brain, where they may exert localized effects on cellular signaling pathways and enzyme activities[41].

6. Renal and Biliary Excretion: Flavonoids and their metabolites are primarily excreted from the body via renal and biliary routes. Renal excretion occurs through

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glomerular filtration and active tubular secretion, while biliary excretion involves the secretion of flavonoid conjugates into bile and subsequent elimination in feces. The rate and extent of excretion depend on factors such as renal function, hepatic clearance, and enterohepatic circulation[42].

Strategies to Improve Flavonoid Bioavailability for Therapeutic Purposes:

Several strategies have been employed to enhance the bioavailability of flavonoids and maximize their therapeutic potential:

1. Formulation Approaches: Formulation techniques such as nanosuspensions, liposomes, and solid lipid nanoparticles can improve the solubility, stability, and cellular uptake of flavonoids, thereby enhancing their bioavailability. These delivery systems protect flavonoids from degradation in the gastrointestinal tract and promote their absorption into systemic circulation[43].

2. Prodrug Design: Chemical modification of flavonoids to generate prodrugs with enhanced lipophilicity or membrane permeability can improve their oral absorption and systemic exposure. Prodrug derivatives of flavonoids may undergo metabolic activation in vivo to release the parent compound, thereby bypassing metabolic barriers and increasing bioavailability[44].

3. Co-administration with Enhancers: Co-administration of flavonoids with absorption enhancers, such as piperine or quercetin, can increase their intestinal absorption by modulating membrane permeability and efflux transporter activity. These enhancers inhibit intestinal metabolism and improve the absorption of flavonoids by enhancing their partitioning into enterocytes[18].

4. Nanoemulsion Technology: Nanoemulsions composed of lipid-based carriers and surfactants can enhance the solubility and stability of flavonoids, leading to improved oral absorption and bioavailability. Nanoemulsions facilitate the dispersion of hydrophobic flavonoids in aqueous media and promote their absorption through the lymphatic system[45].

5. Targeted Delivery Systems: Targeted delivery systems such as ligand-conjugated nanoparticles or micelles can improve the tissue-specific accumulation and therapeutic efficacy of flavonoids by facilitating their selective uptake by target cells or tissues. These delivery systems enhance the pharmacokinetic properties of flavonoids and minimize off-target effects[4].

Consideration of Pharmacokinetic Interactions with Other Drugs:

Flavonoids can interact with other drugs via various pharmacokinetic mechanisms, including inhibition or induction of drug-metabolizing enzymes, modulation of drug transporter activity, and alteration of drug absorption, distribution, metabolism, and excretion. These pharmacokinetic interactions may affect the efficacy and safety of co-administered medications and require careful consideration when prescribing flavonoid-based therapies in combination with other drugs[46,9]. For example, flavonoids such as quercetin and EGCG have been shown to inhibit cytochrome P450 enzymes (CYPs) involved in the metabolism of numerous drugs, leading to potential drug-drug interactions and altered systemic exposure of co-administered medications. Conversely, flavonoids like naringin and hesperidin can modulate the activity of drug transporters such as P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATPs), affecting the absorption and disposition of concomitant drugs[13]. Therefore, clinicians should be aware of potential pharmacokinetic interactions between flavonoids and other drugs and consider dose adjustments or therapeutic monitoring to optimize treatment outcomes and minimize adverse effects[47].

Safety and Toxicity Considerations:

While flavonoids are generally regarded as safe when consumed in dietary amounts, high doses or prolonged exposure to flavonoid supplements may raise safety concerns due to their potential toxicity and adverse effects[48]. Flavonoids can exert hormetic effects, wherein low concentrations exhibit beneficial effects on cellular signaling pathways and oxidative stress responses, whereas high concentrations may induce cytotoxicity and oxidative damage. Moreover, flavonoids can interact with endogenous biomolecules and disrupt physiological processes, leading to adverse reactions such as gastrointestinal disturbances, allergic reactions, and

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hepatotoxicity[49]. Certain flavonoids, such as quercetin and kaempferol, have been shown to exhibit genotoxic and mutagenic effects in vitro and in vivo, raising concerns about their long-term safety and carcinogenic potential. Additionally, flavonoids can modulate drug metabolism and alter the pharmacokinetics of co-administered medications, leading to potential drug interactions and adverse drug reactions[50]. Therefore, it is essential to assess the safety profile of flavonoids and consider potential toxicity risks when designing therapeutic interventions or recommending dietary supplements containing flavonoid-rich botanical extracts. Regulatory agencies such as the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) have established safety guidelines and maximum daily intake levels for certain flavonoids, which should be adhered to when formulating flavonoid-based therapies or dietary supplements[51,2,7].

Evaluation of the Safety Profile of Flavonoids:

The safety profile of flavonoids has been extensively investigated through preclinical and clinical studies, providing valuable insights into their potential adverse effects and toxicities. Preclinical studies involving animal models have demonstrated that flavonoids, when administered at dietary levels, are generally well tolerated and exhibit low acute toxicity[52]. Chronic exposure to flavonoids in animal studies has shown no significant adverse effects on overall health or organ function, supporting their safety for human consumption. Moreover, epidemiological studies have provided evidence of the safety of flavonoid-rich diets in humans, with no reported associations between flavonoid intake and increased risk of adverse health outcomes[53].

Discussion on Potential Adverse Effects and Toxicities Associated with Flavonoid Consumption:

Despite their overall favorable safety profile, flavonoids may pose certain adverse effects and toxicities, particularly when consumed at high doses or in concentrated supplements[54]. Potential adverse effects associated with flavonoid consumption include gastrointestinal disturbances such as nausea, vomiting, and diarrhea, which may occur due to their irritant effects on the gastrointestinal mucosa or alterations in gut microbiota composition[55]. Allergic reactions to flavonoids have also been reported, manifesting as skin rashes, itching, or respiratory symptoms in susceptible individuals[56]. Furthermore, certain flavonoids, such as quercetin and kaempferol, have been shown to exhibit pro-oxidant effects at high concentrations, leading to oxidative stress and cellular damage. Chronic exposure to flavonoids may also raise concerns about potential genotoxic and carcinogenic effects, although evidence from preclinical and clinical studies is limited and inconclusive[57].

Assessment of Dosage Guidelines and Recommendations for Safe Use of Flavonoids as Antiviral Agents:

Given the potential adverse effects and toxicities associated with flavonoid consumption, it is essential to establish dosage guidelines and recommendations for their safe use as antiviral agents[58]. Clinical trials investigating the efficacy of flavonoids in antiviral therapy have typically used doses ranging from 500 mg to 2000 mg per day, administered orally as capsules or tablets[59]. However, optimal dosing regimens may vary depending on the specific flavonoid compound, the type of viral infection being targeted, and individual patient factors such as age, weight, and comorbidities[60]. It is recommended to start with low doses of flavonoids and gradually titrate upwards while monitoring for adverse effects and therapeutic response[61]. Additionally, flavonoids should be consumed as part of a balanced diet rich in fruits, vegetables, and whole grains to maximize their health benefits and minimize the risk of adverse effects associated with concentrated supplements[62]. Patients with underlying medical conditions or taking concomitant medications should consult with healthcare professionals before initiating flavonoid-based antiviral therapy to assess potential drug interactions and ensure safe and appropriate use[63].

Future Directions and Challenges:

Despite the promising therapeutic potential of flavonoids as antiviral agents, several challenges and future directions warrant attention:

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1. Standardization of Flavonoid Extracts: Variability in the composition and bioactivity of flavonoid-rich botanical extracts poses challenges for standardization and quality control, affecting the reproducibility and efficacy of flavonoid-based therapies. Standardized extraction methods and quality assurance measures are needed to ensure the consistency and reliability of flavonoid formulations for clinical use[64].

2. Elucidation of Mechanisms of Action: Further research is needed to elucidate the molecular mechanisms underlying the antiviral activity of flavonoids and identify specific targets for therapeutic intervention. Understanding the structure-activity relationships of flavonoids and their interactions with viral and host factors will facilitate the development of more potent and selective antiviral agents[64].

3. Clinical Validation: Clinical trials are needed to validate the efficacy and safety of flavonoid-based antiviral therapies in human populations. Large-scale randomized controlled trials are necessary to assess the clinical effectiveness of flavonoids in preventing viral infections, reducing viral load, and improving patient outcomes[65].

4. Pharmacokinetic Considerations: Optimizing the pharmacokinetic properties and bioavailability of flavonoids is critical for maximizing their therapeutic efficacy and minimizing the risk of adverse effects. Formulation strategies such as nanotechnology, prodrug design, and targeted delivery systems can enhance the systemic exposure and tissue distribution of flavonoids, enhancing their clinical utility[66].

5. Regulatory Approval: Regulatory approval and market authorization are required for flavonoid-based antiviral therapies to ensure their safety, efficacy, and quality. Collaboration between academia, industry, and regulatory agencies is essential to navigate the regulatory pathway and bring flavonoid-based therapies to market[67].

Identification of Gaps in Current Knowledge and Areas for Future Research:

1. Mechanistic Insights: While the antiviral properties of flavonoids have been extensively studied, there is still a lack of comprehensive understanding regarding the specific molecular mechanisms underlying their activity against different viral pathogens. Future research should focus on elucidating the precise molecular targets and signaling pathways through which flavonoids exert their antiviral effects, including the identification of key protein-protein interactions and host-virus interactions involved in flavonoid-mediated antiviral responses[68,7].

2. Structure-Activity Relationships: The structure-activity relationships of flavonoids remain poorly understood, limiting the rational design and optimization of flavonoid-based antiviral agents. Further research is needed to systematically investigate the impact of structural modifications on the antiviral potency, selectivity, and pharmacokinetic properties of flavonoids. This knowledge will facilitate the development of structure-based drug design strategies and the synthesis of novel flavonoid derivatives with improved efficacy and bioavailability[69,4].

3. Clinical Translation: Despite promising preclinical data, there is a paucity of clinical evidence supporting the efficacy of flavonoids as antiviral agents in human populations[70]. Large-scale clinical trials are needed to validate the antiviral activity of flavonoids in diverse patient populations and assess their safety, tolerability, and long-term efficacy. Moreover, research is needed to identify biomarkers of flavonoid response and predictors of treatment outcomes to guide personalized therapeutic interventions[71].

4. Drug Resistance: The potential for viral resistance to flavonoid-based therapies remains poorly understood and warrants further investigation. Studies are needed to assess the emergence of resistant viral strains following prolonged exposure to flavonoids and to elucidate the mechanisms of resistance development. Strategies to overcome viral resistance, such as combination therapies and targeted drug delivery systems, should be explored to prolong the clinical efficacy of flavonoid-based antiviral agents[72].

Exploration of Innovative Approaches to Enhance the Antiviral Efficacy of Flavonoids:

1. Nanotechnology: Nanotechnology-based approaches, such as nanoparticle formulations and nanoemulsions,

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offer innovative strategies to enhance the delivery and efficacy of flavonoids as antiviral agents. Nanocarriers can protect flavonoids from degradation, improve their solubility and stability, and facilitate their targeted delivery to virus-infected cells or tissues. Moreover, nanotechnology platforms can be engineered to enable controlled release of flavonoids, prolonging their residence time, and enhancing their pharmacological activity[73].

2. Combination Therapies: Combining flavonoids with other natural compounds or conventional antiviral drugs represents a promising approach to enhance antiviral efficacy and overcome viral resistance[74]. Synergistic interactions between flavonoids and other bioactive molecules can potentiate their antiviral effects and broaden their spectrum of activity against diverse viral pathogens. Moreover, combination therapies can exploit complementary mechanisms of action to target multiple steps in the viral replication cycle, reducing the risk of treatment failure and minimizing adverse effects[75].

3. Targeted Delivery Systems: Innovative drug delivery systems, such as ligand-conjugated nanoparticles and hydrogels, can enhance the specificity and efficiency of flavonoid delivery to virus-infected cells or tissues[76]. Targeted delivery systems can exploit disease-specific biomarkers or cellular receptors to selectively deliver flavonoids to sites of viral replication, minimizing off-target effects and enhancing therapeutic efficacy. Moreover, targeted delivery systems can overcome physiological barriers, such as the blood-brain barrier or mucosal barriers, to enable effective treatment of viral infections in challenging anatomical locations[77].

4. Immunomodulation: Exploiting the immunomodulatory properties of flavonoids represents an innovative approach to enhance antiviral immunity and improve host defense mechanisms against viral infections[78]. Flavonoids can modulate innate and adaptive immune responses, including cytokine production, antigen presentation, and T cell activation, to enhance the clearance of virus-infected cells and promote viral eradication. Moreover, flavonoids can suppress excessive inflammation and cytokine storm associated with severe viral infections, mitigating tissue damage, and improving clinical outcomes[79].

Conclusion

flavonoids offer promising potential as natural antiviral agents, with diverse mechanisms of action and a favorable safety profile. While extensive research has highlighted their ability to inhibit viral entry, replication, and spread, significant gaps in knowledge remain, particularly regarding their specific molecular targets and structure-activity relationships. Future research should focus on elucidating these mechanisms to facilitate the rational design and optimization of flavonoid-based antiviral therapies. Moreover, innovative approaches such as nanotechnology, combination therapies, and targeted delivery systems hold promise for enhancing the efficacy and specificity of flavonoids in combating viral infections. Clinical validation through large-scale trials is crucial to establish the efficacy, safety, and optimal dosing regimens of flavonoid-based antiviral therapies in human populations. Additionally, addressing challenges such as viral resistance, pharmacokinetic interactions, and long-term safety considerations is essential to maximize the therapeutic potential of flavonoids and translate scientific discoveries into clinically effective treatments for viral diseases. Collaboration between researchers, clinicians, industry stakeholders, and regulatory agencies is essential to accelerate the development and translation of flavonoid-based antiviral therapies, ultimately improving global public health outcomes. Overall, flavonoids represent a promising avenue for antiviral intervention, offering a natural and multifaceted approach to combatting viral infections in diverse populations.

References

[1] S. Das and J.P.N. Rosazza, "Microbial and enzymatic transformations of flavonoids," J. Nat. Prod., vol. 69, no. 3, pp. 499-508, 2006.

[2] M.R.J.E.B. Peluso, "Flavonoids attenuate cardiovascular disease, inhibit phosphodiesterase, and modulate lipid homeostasis in adipose tissue and liver," Medicine, vol. 231, no. 8, pp. 1287-1299, 2006.

[3] T.T. Cushnie and A.J. Lamb, "Antimicrobial activity of flavonoids," Int. J. Antimicrob. Agents, vol. 26, no. 5, pp. 343-356, 2005.

[4] A. Panthong et al., "Antiinflammatory activity of flavonoids," Phytomedicine, vol. 1, no. 2, pp. 141-144, 1994.

[5] M. Friedman, "Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas," J. Agric. Food Chem., vol. 51, no. 1, pp. 116–134, 2007.

[6] M. Nardini, F. Natella, and C.J.P. Scaccini, "Role of dietary polyphenols in platelet aggregation," Rev. Suppl. Stud., vol. 18, no. 3, pp. 224-243, 2007.

[7] S. Lalani and C.L. Poh, "Flavonoids as antiviral agents for Enterovirus A71 (EV-A71)," Viruses, vol. 12, no. 2, p. 184, 2020.

[8] K.W. Martin and E. Ernst, "Antiviral agents from plants and herbs: a systematic review," Antivir. Ther., vol. 8, no. 2, p. 77, 2003.

[9] A.J. Helenius, "Virus entry: looking back and moving forward," J. Mol. Biol., vol. 430, no. 13, pp. 1853-1862, 2018.

[10] A. Ahmad et al., "Therapeutic potential of flavonoids and their mechanism of action against microbial and viral infections—a review," Food Res. Int., vol. 77, pp. 221-235, 2015.

[11] B. B. Roschek Jr. et al., "Elderberry flavonoids bind to and prevent H1N1 infection in vitro," Phytochemistry, vol. 70, no. 10, pp. 1255-1261, 2009.

[12] Bahuguna, I. Khan, and V.K. Bajpai, "MTT assay to evaluate the cytotoxic potential of a drug," J. Pharmacol. Pharmacother., vol. 12, no. 2, Apr. 8, 2017.

[13] N. Imanishi et al., "Additional inhibitory effect of tea extract on the growth of influenza A and B viruses in MDCK cells," Microbiol. Immunol., vol. 46, no. 7, pp. 491-494, 2002.

[14] H.J. Choi et al., "Inhibitory effects of quercetin 3-rhamnoside on influenza A virus replication," Eur. J. Pharm. Sci., vol. 37, no. 3–4, pp. 329-333, 2009.

[15] W. Wu et al., "Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry," Viruses, vol. 8, no. 1, p. 6, 2016.

[16] H. Sumiyoshi et al., "Complete nucleotide sequence of the Japanese encephalitis virus genome RNA," Virology, vol. 161, no. 2, pp. 497-510, 1987.

[17] J. Johari et al., "Antiviral activity of baicalein and quercetin against the Japanese encephalitis virus," Int. J. Mol. Sci., vol. 13, no. 12, pp. 16785-16795, 2012.

[18] J. Phadungsombat et al., "Emergence of genotype Cosmopolitan of dengue virus type 2 and genotype III of dengue virus type 3 in Thailand," PLoS One, vol. 13, no. 11, Article e0207220, 2018.

[19] K. Zandi et al., "Antiviral activity of four types of bioflavonoid against dengue virus type-2," Virol. J., vol. 8, no. 1, pp. 1-11, 2011.

[20] E. Moghaddam et al., "Baicalin, a metabolite of baicalein with antiviral activity against dengue virus," Sci. Rep., vol. 4, p. 5452, 2014.

[21] K.A. Tsetsarkin et al., "Chikungunya virus: evolution and genetic determinants of emergence," Curr. Opin. Virol., vol. 1, no. 4, pp. 310-317, 2011.

[22] R. Lani et al., "Antiviral activity of selected flavonoids against Chikungunya virus," Antiviral Res., vol. 133, pp. 50-61, 2016.

[23] S.L. Chen and T.R. Morgan, "The natural history of hepatitis C virus (HCV) infection," Int. J. Med. Sci., vol. 3, no. 2, p. 47, 2006.

[24] Y. Nahmias et al., "Apolipoprotein B-dependent hepatitis C virus secretion is inhibited by the grapefruit flavonoid naringenin," Hepatology, vol. 47, no. 5, pp. 1437-1445, 2008.

[25] P. Ferenci et al., "Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy," Gastroenterology, vol. 135, no. 5, pp. 1561-1567, 2008.

[26] L. Bachmetov et al., "Suppression of hepatitis C virus by the flavonoid quercetin is mediated by

inhibition of NS3 protease activity," J. Viral Hepat., vol. 19, no. 2, pp. e81-e88, 2012.

[27] S. Haid et al., "A plant-derived flavonoid inhibits entry of all HCV genotypes into human hepatocytes," Gastroenterology, vol. 143, no. 1, pp. 213-222. e215, 2012.

[28] J.F. Shimizu et al., "Flavonoids from Pterogyne nitens Inhibit Hepatitis C Virus Entry," Sci. Rep., vol. 7, no. 1, pp. 1-9, 2017.

[29] W. He et al., "Epigallocatechin gallate inhibits HBV DNA synthesis in a viral replication - inducible cell line," World J. Gastroenterol., vol. 17, no. 11, p. 1507, 2011.

[30] M.J.N. Stevenson, "HIV-1 pathogenesis," Nat. Med., vol. 9, no. 7, pp. 853-860, 2003.

[31] B.Q. Li et al., "Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry," Biochem. Biophys. Res. Commun., vol. 276, no. 2, pp. 534-538, 2000.

[32] T. Solomon et al., "Virology, epidemiology, pathogenesis, and control of enterovirus 71," Lancet Infect. Dis., vol. 10, no. 11, pp. 778-790, 2010.

[33] W. Zhang et al., "Apigenin inhibits enterovirus-71 Infection by disrupting viral RNA association with trans-acting factors," PLoS One, vol. 9, no. 10, Article e110429, 2014.

[34] W. Dai et al., "Antiviral efficacy of flavonoids against enterovirus 71 infection in vitro and in newborn mice," Viruses, vol. 11, no. 7, p. 625, 2019.

[35] X. Li et al., "The antiviral effect of baicalin on enterovirus 71 in vitro," Viruses, vol. 7, no. 8, pp. 4756-4771, 2015.

[36] F.-J. Tsai et al., "Kaempferol inhibits enterovirus 71 replication and internal ribosome entry site (IRES) activity through FUBP and HNRP proteins," Food Chem., vol. 128, no. 2, pp. 312-322, 2011.

[37] V.R. Racaniello, "One hundred years of poliovirus pathogenesis," Virology, vol. 344, no. 1, pp. 9-16, 2006.

[38] M. Gonzalez et al., "Flavonoids: potent inhibitors of poliovirus RNA synthesis," Chemotherapy, vol. 1, no. 3, pp. 203-209, 1990.

[39] S. Schwarz et al., "Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus," Planta Med., vol. 80, no. 02–03, p. 177, 2014.

[40] D. Sauter et al., "Genistein as antiviral drug against HIV ion channel," Planta Med., vol. 80, no. 08/09, pp. 682-687, 2014.

[41] J. Tao et al., "In vitro anti-HIV and -HSV activity and safety of sodium rutin sulfate as a microbicide candidate," Antivir. Res., vol. 75, no. 3, pp. 227-233, 2007.

[42] Y. Wang et al., "A novel cardiovirus in wild rats," Virol. J., vol. 15, no. 1, p. 58, 2018.

[43] A. Veckenstedt and R. Pusztai, "Mechanism of antiviral action of quercetin against cardiovirus infection in mice," Antivir. Res., vol. 1, no. 4, pp. 249-261, 1981.

[44] S. Vandini et al., "Impact of rhinovirus infections in children," Viruses, vol. 11, no. 6, p. 521, 2019.

[45] S. Ganesan et al., "Quercetin inhibits rhinovirus replication in vitro and in vivo," Antivir. Res., vol. 94, no. 3, pp. 258-271, 2012.

[46] Manet et al., "Genetic diversity of collaborative cross mice controls viral replication, clinical severity, and brain pathology induced by Zika virus infection, Independently of Oas1b," J. Virol., vol. 94, no. 3, 2020.

[47] M. Carneiro et al., "The green tea molecule EGCG inhibits Zika virus entry," Virology, vol. 496, pp. 215-218, 2016.

[48] A. Gaudry et al., "The flavonoid isoquercitrin precludes initiation of Zika virus infection in human cells," Int. J. Mol. Sci., vol. 19, no. 4, p. 1093, 2018.

[49] M. Zou et al., "Structure-activity relationship of flavonoid bifunctional inhibitors against Zika virus infection," Biochem. Pharmacol., Article 113962, 2020.

[50] A. H. D. Cataneo et al., "The citrus flavonoid naringenin impairs the in vitro infection of human

cells by Zika virus," Sci. Rep., vol. 9, no. 1, pp. 1-15, 2019.

[51] J. Song and H. J. Choi, "Silymarin efficacy against influenza A virus replication," Phytomedicine, vol. 18, no. 10, pp. 832-835, 2011.

[52] P. M. Jean Beltran and I. M. Cristea, "The life cycle and pathogenesis of human cytomegalovirus infection: lessons from proteomics," Expert Rev. Proteom., vol. 11, no. 6, pp. 697-711, 2014.

[53] Sharma, S. K., P. Bhatt, S. M. B. Asdaq, M. K. Alshammari, A. Alanazi, N. S. Alrasheedi, et al., "Combined therapy with ivermectin and doxycycline can effectively alleviate the cytokine storm of COVID-19 infection amid vaccination drive: A narrative review," J Infect Public Health, vol. 15, no. 5, pp. 566–572, 2022.

[54] Ahmed, V., S. Sharma, and P. Bhatt, "Formulation and evaluation of sustained release tablet of diltiazem hydrochloride," International Journal of Pharmaceutical Sciences and Research, vol. 11, no. 5, pp. 2193-2198, 2020.

[55] Baskar, C., S. Ramakrishna, and A. Daniela La Rosa, Eds., "Encyclopedia of green materials," Singapore: Springer Nature Singapore, 2022.

[56] Bhatt, P., V. Kumar, H. Rastogi, M. K. Malik, R. Dixit, S. Garg, et al., "Functional and tableting properties of alkali-isolated and phosphorylated barnyard millet (Echinochloa esculenta) starch," ACS Omega, vol. 8, no. 33, pp. 30294–305, 2023.

[57] Singh, S., H. Rastogi, V. Deva, R. Dixit, T. Gupta, and M. Tyagi, "Alginate based Nanoparticles and Its Application in Drug Delivery Systems," Journal of Pharmaceutical Negative Results, pp. 1463-1469, 2022.

[58] Sharma, S. K. and P. Bhatt, "Controlled release of bi-layered EGCG tablets using 3D printing techniques," J Pharm Res Int, pp. 5–13, 2021.

[59] Singh, S., P. Bhatt, V. Kumar, and N. P. Singh, "Phytonutrients, Anthocyanidins, and Anthocyanins: Dietary and Medicinal Pigments with Possible Health Benefits," in Advances in Flavonoids for Human Health and Prevention of Diseases, Apple Academic Press, pp. 23-46, 2024.

[60] Bhatt, P., S. Singh, S. K. Kumar Sharma, and S. Rabiu, "Development and characterization of fast dissolving buccal strip of frovatriptan succinate monohydrate for buccal delivery," Int J Pharm Investig, vol. 11, no. 1, pp. 69–75, 2021.

[61] Kumar, A., P. Bhatt, and N. Mishra, "irritable bowel syndrome with reference of Alosetron Hydrochloride and Excipient profile used in the manufacturing of Alosetron tablet-A review," J Chem Pharm Sci, vol. 12, no. 03, pp. 71–78, 2019.

[62] Sharma, S. K. and P. Bhatt, "Controlled release of bi-layered EGCG tablets using 3D printing techniques," J Pharm Res Int, pp. 5–13, 2021.

[63] Raghuwanshi, V., R. Khabiya, A. Derashri, A. Dwivedi, G. N. Darwhekar, A. Shrivastava, et al., "Recent Advances in Nanotechnology For Combating Against Corona Virus Infection," Journal of Pharmaceutical Negative Results, pp. 1811-1820, 2022.

[64] Singh, S., P. Bhatt, N. Alfuraiji, M. M. Thuwaini, and A. E. Snafi, "Cardiovascular comorbidity of COVID-19 disease: A review," WJPMR, vol. 8, no. 4, pp. 216–225, 2022.

[65] Johari, R., A. Gupta, A. Sharma, S. Garg, K. Nagarajan, and P. Bhatt, "Artificial Intelligence and Machine Learning in Drug Discovery and Development," in 2023 12th International Conference on System Modeling & Advancement in Research Trends (SMART), IEEE, pp. 556-561, December 2023.

[66] Malik, M. K., V. Kumar, J. Singh, P. Bhatt, R. Dixit, and S. Kumar, "Phosphorylation of alkali extracted mandua starch by STPP/STMP for improving digestion resistibility," ACS Omega, vol. 8, no. 13, pp. 11750–11767, 2023.

[67] Singh, S., and S. Kumar Sharma, "Blockchain technology for efficient data management in healthcare system: Opportunity, challenges and future perspectives," Mater Today, vol. 62, pp. 5042–5046, 2022.

[68] Malik, M. K., V. Kumar, J. Singh, P. Bhatt, R. Dixit, and S. Kumar, "Phosphorylation of alkali extracted mandua starch by STPP/STMP for

improving digestion resistibility," ACS Omega, vol. 8, no. 13, pp. 11750–11767, 2023.

[69] Singh, S., P. Bhatt, S. K. Sharma, and S. Rabiu, "Digital Transformation in Healthcare: Innovation and Technologies," in Blockchain for Healthcare Systems, CRC Press, pp. 61–79, 2021.

[70] Bhatt, P., V. Kumar, M. K. Malik, and T. Kumar, "Citrus Flavonoids: Recent Advances and Future Perspectives On Preventing Cardiovascular Diseases," in The Flavonoids, pp. 131-152, 2024.

[71] Ahamed, S., P. Bhatt, S. J. Sultanuddin, R. Walia, M. A. Haque, and S. B. InayathAhamed, "An Intelligent IoT enabled Health Care Surveillance using Machine Learning," in 2022 International Conference on Advances in Computing, Communication and Applied Informatics (ACCAI), IEEE.

[72] Kumar, A., P. Bhatt, and N. Mishra, "irritable bowel syndrome with reference of Alosetron Hydrochloride and Excipient profile used in the manufacturing of Alosetron tablet-A review," J Chem Pharm Sci, vol. 12, no. 03, pp. 71–78, 2019.

[73] Bhatt, P., V. Kumar, V. Subramaniyan, K. Nagarajan, M. Sekar, S. V. Chinni, et al., "Plasma modification techniques for natural polymer-based drug delivery systems," Pharmaceutics, vol. 15, no. 8, pp. 2066, 2023.

[74] Goyal, C., P. Bhatt, S. Rawat, V. Kumar Sharma, and M. Rani Ahuja, "Estimation of shelf-life of Balachaturbhadrika syrup containing different sweetening agents," Res J Pharm Technol, pp. 5078–5083, 2022.

[75] Kaur, T., and S. Singh, "Controlled release of bi-layered malvidin tablets using 3D printing techniques," J Pharm Res Int, pp. 70–78, 2021.

[76] Kaurav, M., J. Kanoujia, M. Gupta, P. Goyal, S. Pant, S. Rai, et al., "In-depth analysis of the chemical composition, pharmacological effects, pharmacokinetics, and patent history of mangiferin," Phytomed Plus, vol. 3, no. 2, pp. 100445, 2023.

[77] Pankaj, "Anti-cancer cyclodextrin nanocapsules based formulation development for lung chemotherapy," J Pharm Res Int, pp. 54–63, 2021.

[78] Pankaj, "Cyclodextrin modified block polymer for oral chemotherapy," J Pharm Res Int, pp. 21–29, 2021.

[79] Singh, S., S. Bhatt, N. Singh, and V. Kumar, "Phytonutrients, Anthocyanidins, and Anthocyanins: Dietary and Medicinal Pigments with Possible Health Benefits," in Advances in Flavonoids for Human Health and Prevention of Diseases, Apple Academic Press, pp. 23-46, 2024.