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Naringin Nanoparticles: Nanocarriers as Novel Therapeutic Strategies for Cancer

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ABSTRACT:

Naringin, a flavonoid glycoside, mainly found in citrus fruits, has attracted considerable attention for its wide range of pharmacological activities, especially its anti-cancer properties. Its therapeutic potential is attributed to the ability to induce apoptosis, suppress cell proliferation and suppress metastases in various cancer cell lines. However, clinical application of naringin is hampered by its low bioavailability and fast metabolism. Nanotechnology offers a promising solution to these limitations by facilitating the development of nanoparticles loaded with naringin to improve their bioavailability, stability and targeted delivery to tumor locations. This review investigates the synthesis, characterization and therapeutic effectiveness of naringin nanoparticles in cancer treatment. The incorporation of Narnidin into nanocarriers such as liposomes, polymer nanoparticles, and dendrimers significantly improves its drugkinetic profile and therapeutic index. These nanocarriers allow the controlled and continuous release of naringin, leading to an increase in tumor tissue accumulation while minimizing systemic toxicity. Furthermore, naringin nanoparticles exhibit superior cell absorption and biodistribution, leading to an increased anticancer activity compared to free naringin. Key findings from preclinical studies show that nanoparticles of naringin induce apoptosis effectively, stop cell cycles, inhibit angiogenesis and reduce tumor growth in different cancer models. Furthermore, the review highlights the potential to combine naringin nanoparticles with conventional chemotherapy to achieve synergistic cancer treatments and overcome drug resistance. Despite these promising results, the translation of naringin nanoparticles from the table to the bed faces several challenges, including large-scale production, regulatory barriers and a comprehensive evaluation of long-term safety and efficacy. Future research should focus on optimizing the formulation of nanoparticles, exploring advanced targeting strategies, and conducting rigorous clinical trials.

Keywords: Naringin, Nanoparticles, Cancer Therapy, Nanocarriers, Drug Delivery

1. Introduction

Cancer remains one of the leading causes of mortality worldwide, characterized by uncontrolled cell proliferation and the potential to invade or spread to other parts of the body. Despite significant advances in cancer research and therapy, treating cancer effectively remains a substantial challenge[1]. Conventional treatment modalities include surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapy. While these treatments can be effective, they often come with severe side effects, limited specificity, and potential for resistance development[2]. Chemotherapy, for instance, lacks selectivity, targeting both cancerous and healthy cells, leading to significant toxicity and adverse effects. Similarly, radiation therapy can damage surrounding healthy tissues, and immunotherapy, though promising, is not universally effective and can cause immune-related side effects. These challenges underscore the need for novel therapeutic strategies that can improve efficacy and reduce side effects[3].

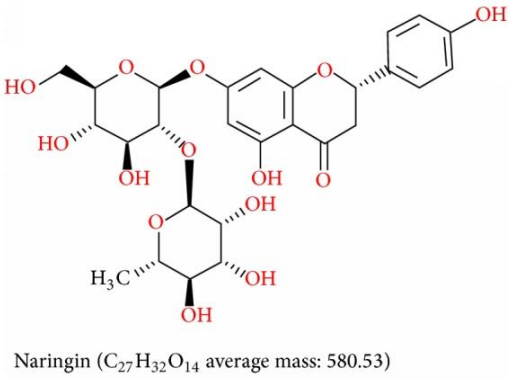
Naringin is a flavonoid glycoside predominantly found in citrus fruits such as grapefruits, oranges, and lemons. It is known for its diverse pharmacological properties, including antioxidant, anti-inflammatory, and anticancer activities[4]. Naringin exerts its anticancer effects through various mechanisms, such as inducing apoptosis, inhibiting cell proliferation, and suppressing metastasis[5]. Studies have shown that naringin can modulate multiple signaling pathways involved in cancer progression, making it a promising candidate for cancer therapy. However, the clinical application of naringin is limited by its poor solubility, low bioavailability, and rapid metabolic degradation in the body[6]. These limitations hinder its therapeutic potential and necessitate the development of novel delivery systems to enhance its efficacy. Nanotechnology offers a promising solution to overcome the limitations of conventional cancer therapies and enhance the therapeutic potential of bioactive compounds like naringin[7]. Nanoparticles, ranging from 1 to 100 nanometers in size, can be engineered to carry therapeutic agents and deliver them specifically to target sites[8]. The use of nanoparticles in cancer therapy provides several advantages, including enhanced bioavailability by improving the solubility and stability of poorly soluble drugs, targeted delivery to specific cancer cells which reduces off-target effects and minimizes toxicity to healthy tissues through passive targeting (exploiting the enhanced permeability and retention effect in tumors) or active targeting (using ligands that bind to specific receptors on cancer cells)[9]. Additionally, nanoparticles offer controlled and sustained release of drugs, maintaining therapeutic concentrations for extended periods and reducing the frequency of administration. Moreover, nanoparticles can be multifunctional, carrying not only drugs but also imaging agents for diagnosis and monitoring, as well as targeting moieties for enhanced specificity[10].

2. Naringin: Chemical Structure and Biological Activities

Chemical Structure of Naringin

Naringin is a flavonoid glycoside primarily found in citrus fruits, particularly grapefruits and oranges[11]. Chemically, it is composed of the aglyconenaringenin linked to a disaccharide, neohesperidose, through a glycosidic bond. Its molecular formula is $C_{27}H_{32}O_{14}$, and it has a molecular weight of 580.53 g/mol[12]. The aglycone part, naringenin, is responsible for the compound's pharmacological activities, while the sugar moiety influences its solubility and bioavailability[13]. The structure features phenolic hydroxyl groups that contribute to its

antioxidant properties, and the glycoside form affects its absorption and metabolism in the human body[14].



Naringin ($C_{27}H_{32}O_{14}$ average mass: 580.53)

Figure 1: structure of Naringin

Sources and Extraction Methods

Naringin is predominantly found in citrus fruits such as grapefruits, oranges, lemons, and pomelos, with especially high concentrations in the peels and pulp of these fruits[15]. The extraction of naringin typically involves several steps: collection and preparation where citrus fruits are collected, and the peels and pulp are separated from the juice; extraction using solvents like ethanol, methanol, or water, chosen[9] based on the desired purity and specific application; filtration and concentration where the extract is filtered to remove solid residues and then concentrated using techniques like rotary evaporation; purification involving additional steps such as column chromatography to isolate naringin in its pure form; and finally, drying the purified naringin to obtain it in powdered form for further research or therapeutic purposes[16,17].

Pharmacological Properties of Naringin

Naringin exhibits a broad spectrum of pharmacological activities, making it a compound of significant interest for therapeutic applications.

Antioxidant Activity Naringin is a potent antioxidant, capable of scavenging free radicals and reducing oxidative stress. The phenolic hydroxyl groups in its structure donate hydrogen atoms to neutralize reactive oxygen species (ROS)[18]. This activity helps protect cells from oxidative damage, which is a contributing factor in aging and various chronic diseases, including cancer. Naringin also enhances the activity of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, further bolstering the body's defense against oxidative stress[19].

Anti-inflammatory Activity Naringin exhibits significant anti-inflammatory properties by modulating key signaling pathways involved in inflammation. It inhibits the production of pro-inflammatory cytokines such as interleukins (IL-1β, IL-6) and tumor necrosis factor-alpha (TNF-α)[20]. Naringin also suppresses the activation of nuclear factor-kappa B (NF-κB), a transcription factor that regulates the expression of inflammatory genes[21]. Additionally, it reduces the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), enzymes that play critical roles in the inflammatory response. These anti-inflammatory effects make naringin a promising agent for treating inflammatory diseases such as arthritis, asthma, and inflammatory bowel disease[22].

Anticancer Activities Naringin has demonstrated significant anticancer activity against various types of cancer, including breast, lung, liver, colon, and prostate cancers. Naringin exerts multiple anticancer effects through various mechanisms[23]. It promotes programmed cell death in cancer cells by activating both intrinsic and extrinsic apoptotic pathways, increasing the expression of pro-apoptotic proteins like Bax and decreasing anti-apoptotic

proteins such as Bcl-2[24]. Additionally, naringin inhibits cancer cell growth by arresting the cell cycle at various phases, primarily the G1 and G2/M phases, by modulating key regulators of the cell cycle, including cyclins and cyclin-dependent kinases (CDKs)[25]. Furthermore, it reduces the metastatic potential of cancer cells by inhibiting cell migration and invasion, downregulating matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix and facilitate tumormetastasis[26]. Naringin also impedes the formation of new blood vessels required for tumor growth and metastasis by inhibiting angiogenic factors such as vascular endothelial growth factor (VEGF)[27].

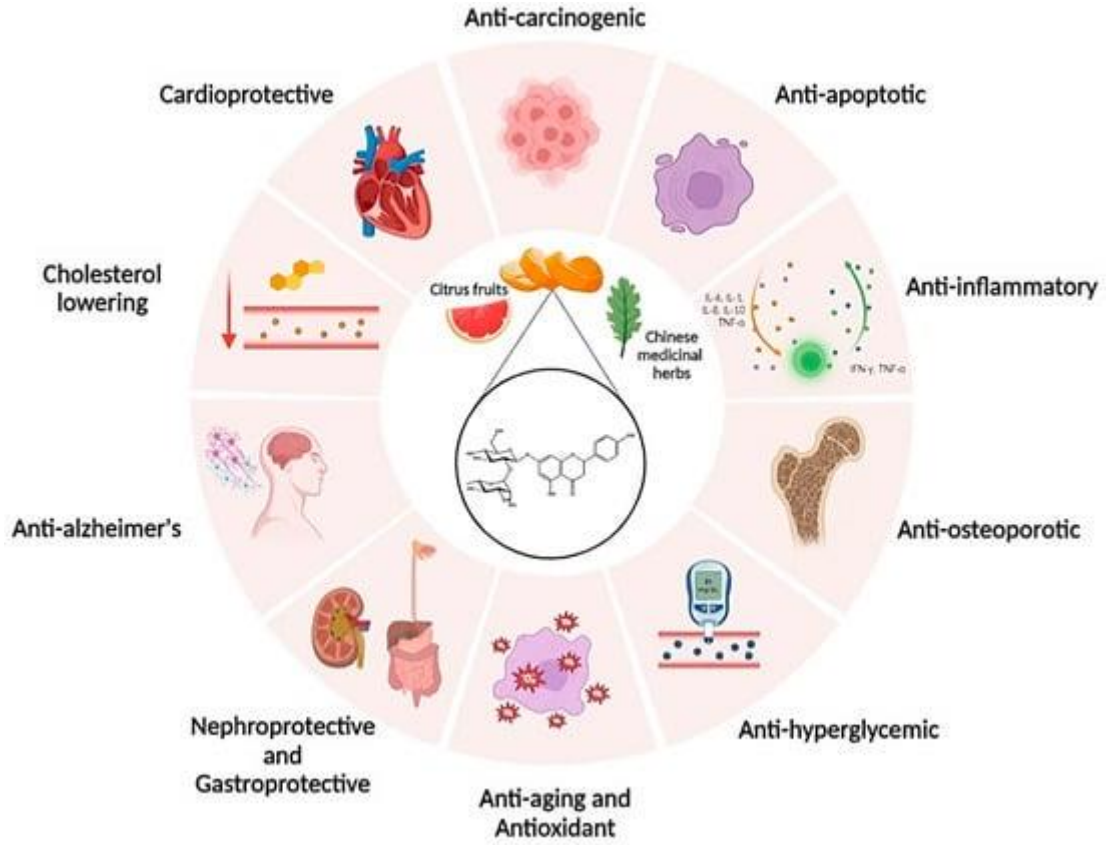


Figure 2: Health effects of naringin on different biological systems.

3. Nanotechnology in Cancer Therapy

Nanotechnology involves manipulating matter on an atomic, molecular, and supramolecular scale, typically at dimensions between 1 and 100 nanometers. In medicine, nanotechnology has revolutionized diagnostics, therapeutics, and drug delivery systems[28]. By engineering nanoparticles, scientists can create materials with unique properties and functions that are not possible at larger scales. These nanoparticles can interact with biological systems at the cellular and molecular levels, offering innovative solutions to various medical challenges[29].In diagnostics, nanoparticles enhance the sensitivity and specificity of imaging techniques, allowing for early and accurate disease detection. For example, quantum dots and gold nanoparticles are used in imaging modalities like MRI, CT, and PET scans to improve the visualization of tumors and other pathological conditions[30].In therapeutics, nanotechnology enables the development of advanced drug delivery systems that can enhance the efficacy and safety of therapeutic agents[31]. Nanoparticles can encapsulate drugs, protecting them from degradation and improving their solubility and stability. Additionally, they can be functionalized with targeting ligands, such as antibodies or peptides, to direct them specifically to diseased cells or tissues, thus minimizing off-target

effects[32].Nanotechnology also plays a crucial role in regenerative medicine, where nanoparticles are used to deliver growth factors and other bioactive molecules to promote tissue repair and regeneration[3]. Moreover, in gene therapy, nanoparticles can serve as vectors for delivering genetic material into cells to correct genetic defects or modulate gene expression[33,21,4].

Advantages of Using Nanoparticles in Cancer Treatment

Enhanced Bioavailability One of the significant challenges in cancer therapy is the poor bioavailability of many anticancer drugs[4]. Many therapeutic agents, including natural compounds like naringin, have limited solubility and stability, leading to low absorption and rapid metabolism in the body. Nanoparticles can enhance the bioavailability of these drugs by improving their solubility and protecting them from degradation[34,9]. Nanoparticles can encapsulate hydrophobic drugs, increasing their solubility in aqueous environments and facilitating their absorption[12]. Additionally, nanoparticles can shield drugs from enzymatic degradation and reduce their clearance from the body, prolonging their circulation time and enhancing their therapeutic efficacy[35,7].

Targeted Delivery Targeted delivery is a critical advantage of using nanoparticles in cancer therapy. Traditional chemotherapy lacks specificity, affecting both cancerous and healthy cells, leading to significant side effects[36]. Nanoparticles can be engineered to specifically target cancer cells, sparing healthy tissues and reducing systemic toxicity. This targeted delivery can be achieved through passive and active targeting mechanisms[37,8].Passive targeting exploits the enhanced permeability and retention (EPR) effect, a phenomenon where nanoparticles preferentially accumulate in tumor tissues due to their leaky vasculature and poor lymphatic drainage[38]. This allows nanoparticles to concentrate in the tumor microenvironment, increasing the local concentration of the therapeutic agent.Active targeting involves functionalizing nanoparticles with targeting ligands, such as antibodies, peptides, or small molecules, that can recognize and bind to specific receptors overexpressed on cancer cells. This ligand-receptor interaction facilitates the selective uptake of nanoparticles by cancer cells, enhancing the specificity and efficacy of the treatment[39,3].

Reduced Side Effects The use of nanoparticles in cancer therapy can significantly reduce the side effects associated with conventional treatments. By improving the targeted delivery of drugs, nanoparticles can minimize the exposure of healthy tissues to toxic agents, reducing adverse effects[40]. This selective targeting also allows for the use of lower doses of drugs, further decreasing toxicity.Additionally, nanoparticles can provide controlled and sustained release of therapeutic agents, maintaining therapeutic concentrations for extended periods and reducing the frequency of administration[41]. This controlled release can improve patient compliance and reduce the occurrence of dose-related side effects.Furthermore, the multifunctionality of nanoparticles allows for the co-delivery of multiple therapeutic agents, enabling combination therapy with synergistic effects[12]. This approach can enhance the overall therapeutic outcome while reducing the doses of individual drugs, minimizing their side effects[42,5].

4. Naringin Nanoparticles

Methods of Nanoparticle Synthesis

Physical Methods Physical methods of nanoparticle synthesis primarily involve mechanical processes to reduce the size of bulk materials into nanoparticles. These methods include:

1. **Ball Milling:** This technique uses mechanical force to grind bulk materials into fine particles[43]. A ball mill, consisting of a rotating cylinder filled with grinding media (e.g., steel or ceramic balls), applies mechanical energy to break down the particles[18]. Ball milling can produce nanoparticles of various sizes, but it may not be ideal for maintaining

the integrity of sensitive compounds like naringin due to potential thermal degradation[44].

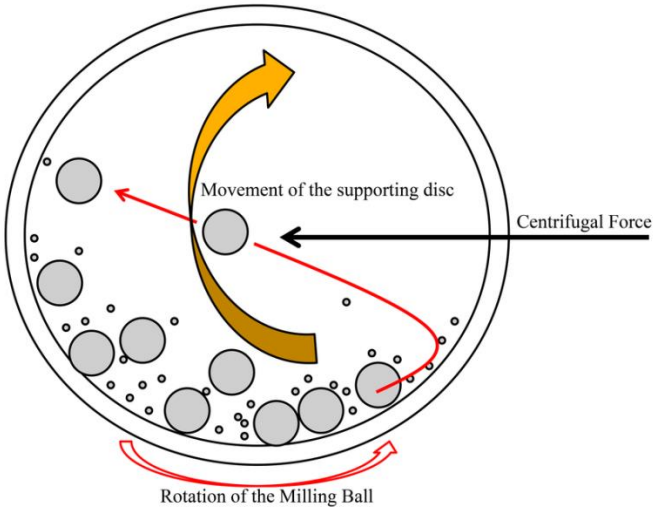


Figure 3: ball milling process of synthesis of nanoparticles

2. **Ultrasonication:** Ultrasonic waves generate high-energy acoustic cavitation, which produces microbubbles that collapse and create shock waves. This process can break down particles into nanoscale sizes. Ultrasonication is suitable for producing naringin nanoparticles as it operates at lower temperatures, preserving the compound's stability[45].
3. **High-Pressure Homogenization:** This method involves forcing a liquid through a narrow space at high pressure, causing shear forces that break down particles. High-pressure homogenization is effective for creating uniform nanoparticles and is widely used in pharmaceutical applications for its scalability[46].

2. Chemical Methods Chemical methods involve the use of chemical reactions to form nanoparticles. These methods offer precise control over the size, shape, and composition of nanoparticles. Common chemical methods include:

Sol-Gel Process: In the Sol-Gel process, metal alkoxides such as tetraethyl orthosilicate are dissolved in a solvent like ethanol, followed by the addition of water to initiate hydrolysis, with continuous stirring. An acidic or basic catalyst is added to control the rate of hydrolysis and condensation[47]. During hydrolysis, the metal alkoxide reacts with water to form a hydroxylated intermediate:

$M(OR)_n + H2O \rightarrow M(OH)(OR)_{n-1} + ROH$

During condensation, hydroxylated intermediates react to form metal-oxygen-metal bonds, creating a three-dimensional network:

$M(OH)(OR)_{n-1} + M(OH)(OR)_{n-1} \rightarrow M\text{-}O\text{-}M + H_2O$

The sol gradually evolves into a gel due to the growth of this network structure, and naringin can be incorporated into the sol before gelation to ensure it is entrapped in the matrix. The gel is then dried to remove the solvent, either at ambient temperature or under mild heating to prevent naringin degradation, resulting in a xerogel (dried gel). Finally, the xerogel is calcined at high temperatures (300-600°C) to remove any remaining organic material and densify the nanoparticles, producing naringin-incorporated nanoparticles[47].

Emulsion Polymerization: In Emulsion Polymerization, monomers such as styrene or methyl methacrylate are dissolved in an aqueous phase containing surfactants to stabilize the emulsion. Naringin is dispersed in the monomer phase if it is hydrophobic, or in the aqueous phase if it is hydrophilic[48]. Polymerization is initiated by adding an initiator like potassium persulfate to the emulsion, which decomposes to form free radicals that start the

polymerization of monomers. The monomers polymerize within the micelles formed by surfactants, creating polymer nanoparticles with naringin encapsulated during the process[49]. The nanoparticles are then separated from the emulsion by centrifugation or filtration and washed to remove any unreacted monomers and surfactants[3]. Finally, the purified nanoparticles are dried using methods such as lyophilization (freeze-drying) to obtain a stable powder form, resulting in naringin-encapsulated polymeric nanoparticles[50].

Co-Precipitation: Co-precipitation involves several steps to create naringin-loaded nanoparticles with controlled properties. First, naringin and a suitable carrier material precursor, such as metal salts like iron chloride, are dissolved in a solvent. The pH of the solution is adjusted to the desired level using acids or bases[51,52]. Next, a precipitating agent like sodium hydroxide or ammonium hydroxide is added to the solution, inducing the simultaneous precipitation of naringin and the carrier material to form nanoparticles[53]. The reaction conditions, including pH, temperature, and reactant concentration, are carefully controlled to fine-tune the size and properties of the nanoparticles, and the mixture is stirred continuously to ensure uniform particle formation[54]. The nanoparticles are then separated from the solution by centrifugation or filtration and washed to remove any residual reactants and by-products. Finally, the purified nanoparticles are dried using methods such as lyophilization or oven drying at low temperatures, resulting in naringin-loaded nanoparticles[55].

3.Biological methods for nanoparticle synthesis utilize biological molecules or systems, offering a sustainable approach. These methods include microbial synthesis and plant-mediated synthesis:

1. Microbial Synthesis:

Certain microorganisms, such as bacteria, fungi, and algae, have the capability to biologically reduce metal ions in their environment[56]. This reduction process leads to the formation of nanoparticles, where the biological molecules act as reducing and capping agents[57]. Microbially synthesized nanoparticles often exhibit unique properties such as size, shape, and surface characteristics due to the enzymatic machinery of the microorganisms involved[58]. These nanoparticles are typically biocompatible and can be tailored for various medical applications[33]. For instance, in the case of naringin, microbial synthesis can incorporate this bioactive compound into nanoparticles, potentially enhancing its therapeutic efficacy through sustained release and targeted delivery[59].

2. Plant-Mediated Synthesis:

Plant extracts contain a variety of phytochemicals, including flavonoids and polyphenols, which possess reducing properties capable of converting metal ions into nanoparticles[60]. This method is environmentally friendly as it eliminates the need for harsh chemicals and high energy inputs. Plant-mediated synthesis also results in biocompatible nanoparticles that often exhibit antioxidant properties and enhanced stability[61]. In the context of naringin, plant-mediated synthesis can utilize extracts rich in natural antioxidants to incorporate naringin into nanoparticles. This approach not only enhances the bioavailability and therapeutic potential of naringin but also provides a sustainable route for nanoparticle synthesis suitable for biomedical and pharmaceutical applications[17,3].

5. Mechanisms of Anticancer Action of Naringin Nanoparticles

Cellular Uptake and Biodistribution

The efficacy of naringin nanoparticles in cancer treatment is significantly influenced by their cellular uptake and biodistribution. Naringin nanoparticles are designed to enhance the bioavailability and targeted delivery of naringin to cancer cells. This is achieved through various mechanisms:

1. **Enhanced Permeability and Retention (EPR) Effect:**Tumors have leaky vasculature and impaired lymphatic drainage, which allows nanoparticles to accumulate preferentially in tumor tissues. This passive targeting increases the concentration of naringin in the tumormicroenvironment[62].
2. **Active Targeting:** Nanoparticles can be functionalized with ligands such as antibodies, peptides, or small molecules that specifically bind to receptors overexpressed on cancer cells. This targeted approach ensures that naringin is delivered directly to the cancer cells, enhancing its therapeutic efficacy while minimizing off-target effects[12,4].
3. **Endocytosis:**Naringin nanoparticles are taken up by cancer cells through endocytosis. This process involves the engulfing of nanoparticles by the cell membrane, forming endosomes that transport the nanoparticles into the cytoplasm. Once inside the cells, the nanoparticles can release naringin, which then exerts its anticancer effects[33].
4. **Biodistribution:** Effective biodistribution is crucial for maximizing the therapeutic impact of naringin nanoparticles. They are designed to circulate in the bloodstream for extended periods, allowing for enhanced accumulation in tumors. Nanoparticle size, surface charge, and hydrophilicity/hydrophobicity balance are key factors influencing their biodistribution[4,22].

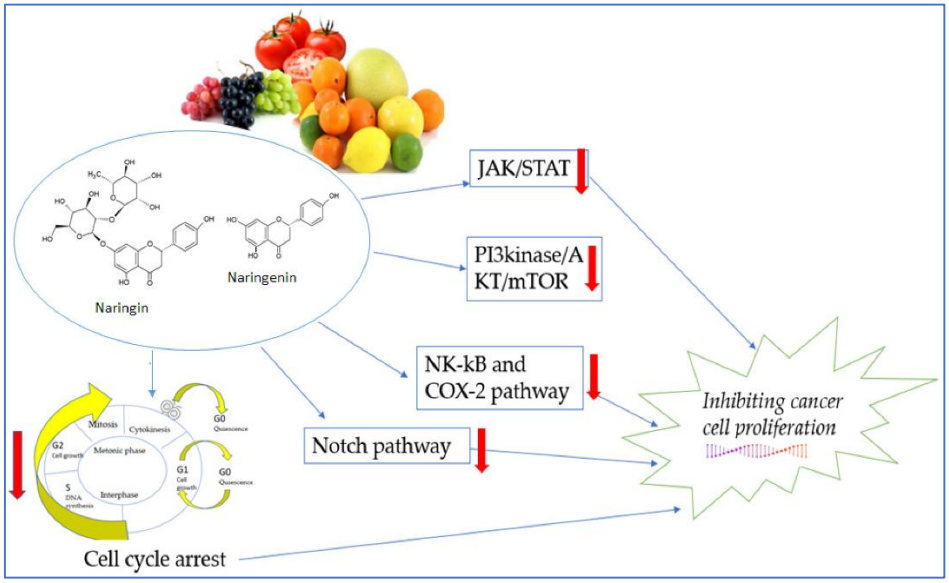


Figure 3: Inhibition of cancer cell proliferation

Induction of Apoptosis and Cell Cycle Arrest

Naringin nanoparticles exhibit potent anticancer activity by inducing apoptosis and causing cell cycle arrest in cancer cells:

1. **Apoptosis:**Naringin induces apoptosis, or programmed cell death, through intrinsic and extrinsic pathways[12,3]. Intrinsically, it disrupts mitochondrial membrane potential, leading to the release of cytochrome c and activation of caspases, which orchestrate cell death. Extrinsically, naringin can activate death receptors on the cell surface, triggering a cascade that results in apoptosis[7]. Naringin nanoparticles enhance this process by ensuring higher intracellular concentrations of naringin in cancer cells[63].
2. **Cell Cycle Arrest:**Naringin nanoparticles can halt the proliferation of cancer cells by arresting the cell cycle at various phases, primarily the G1 and G2/M phases. Naringin downregulates cyclins and cyclin-dependent kinases (CDKs) essential for cell cycle progression, leading to cell cycle arrest and inhibition of cell division[64].

Inhibition of Angiogenesis and Metastasis

Naringin nanoparticles also inhibit angiogenesis (formation of new blood vessels) and metastasis (spread of cancer):

1. **Angiogenesis Inhibition:**Tumors require a blood supply for growth and metastasis. Naringin nanoparticles inhibit angiogenesis by downregulating angiogenic factors such as vascular endothelial growth factor (VEGF) and its receptors. They also reduce the activity of matrix metalloproteinases (MMPs), which degrade the extracellular matrix and facilitate new blood vessel formation[6,9].
2. **Metastasis Inhibition:**Naringin nanoparticles impede metastasis by interfering with various steps of the metastatic cascade, including detachment of cancer cells from the primary tumor, invasion into surrounding tissues, intravasation into the bloodstream, and colonization at distant sites. Naringin reduces the expression of molecules involved in cell adhesion and motility, such as E-cadherin and integrins, thereby inhibiting the metastatic potential of cancer cells[55].

Synergistic Effects with Other Anticancer Agents

Combining naringin nanoparticles with other anticancer agents can result in synergistic effects, enhancing overall therapeutic outcomes:

1. **Chemotherapy:**Naringin nanoparticles can be co-administered with conventional chemotherapeutic drugs to improve their efficacy. Naringin enhances the sensitivity of cancer cells to chemotherapy, potentially allowing for lower doses of chemotherapeutic agents, thereby reducing their side effects[65].
2. **Radiotherapy:**Naringin nanoparticles can sensitize cancer cells to radiation, enhancing the effectiveness of radiotherapy. Naringin's antioxidant properties help protect normal tissues from radiation-induced damage, while its pro-apoptotic effects increase the susceptibility of cancer cells to radiation[20,1].
3. **Immunotherapy:**Naringin nanoparticles can modulate the immune response, enhancing the efficacy of immunotherapeutic agents. Naringin has been shown to influence the tumor microenvironment, reducing inflammation and immunosuppression, thereby improving the response to immunotherapy[66].
4. **Targeted Therapy:**Naringin nanoparticles can be combined with targeted therapies that inhibit specific molecular pathways involved in cancer progression. This combination can provide a multi-pronged approach to cancer treatment, addressing multiple aspects of tumor growth and survival[33].

6. Challenges and Future Perspectives

Challenges in the Development and Clinical Translation of Naringin Nanoparticles

Stability and Scalability One of the primary challenges in developing naringin nanoparticles is ensuring their stability and scalability for clinical use[30]. Naringin, like many natural compounds, can be unstable under certain conditions, leading to degradation and loss of efficacy. Encapsulation in nanoparticles can enhance its stability, but the formulation must be optimized to prevent premature release and degradation[2,7,19].

1. **Physicochemical Stability:** Ensuring the stability of naringin nanoparticles involves maintaining their size, shape, and surface properties over time. Factors such as pH, temperature, and ionic strength of the surrounding environment can affect nanoparticle stability. Developing formulations that can withstand these variations is crucial for their practical application[67].
2. **Scalability:** Producing naringin nanoparticles on a large scale while maintaining consistency and quality is a significant challenge. Techniques used for laboratory-scale synthesis may not be directly translatable to industrial-scale production. Ensuring batch-to-batch consistency, reproducibility, and cost-effectiveness are essential for commercial viability[44].

Regulatory and Safety Considerations Regulatory and safety considerations are critical for the clinical translation of naringin nanoparticles. Any new therapeutic formulation must undergo rigorous evaluation to ensure its safety and efficacy.

1. **Toxicity and Biocompatibility:** Nanoparticles must be non-toxic and biocompatible, meaning they should not induce adverse immune responses or toxicity in the body. Comprehensive in vitro and in vivo studies are required to evaluate the potential toxicity of naringin nanoparticles, including their long-term effects and interactions with biological systems[55,6].
2. **Regulatory Approval:** The path to regulatory approval involves extensive testing and documentation to demonstrate safety, efficacy, and quality[5,9]. Regulatory agencies such as the FDA (Food and Drug Administration) and EMA (European Medicines Agency) have stringent guidelines for approving new drug formulations, including nanoparticles. Meeting these requirements involves conducting preclinical studies, clinical trials, and submitting detailed documentation[18,30].

Future Directions and Potential Improvements

Advanced Targeting Strategies To enhance the efficacy of naringin nanoparticles, advanced targeting strategies can be employed to improve selective delivery to cancer cells while sparing healthy tissues.

1. **Ligand-Based Targeting:** Functionalizing nanoparticles with ligands such as antibodies, peptides, or small molecules that specifically bind to receptors overexpressed on cancer cells can enhance targeted delivery. This approach increases the accumulation of naringin nanoparticles at the tumor site, improving therapeutic outcomes[68].
2. **Stimuli-Responsive Nanoparticles:** Developing nanoparticles that respond to specific stimuli in the tumor microenvironment, such as pH, temperature, or enzymatic activity, can improve targeted drug release. These stimuli-responsive nanoparticles release their payload selectively in the tumor, minimizing off-target effects and enhancing efficacy[33].

Combination Therapies Combining naringin nanoparticles with other therapeutic agents can provide synergistic effects and improve treatment outcomes.

1. **Chemotherapy:** Combining naringin nanoparticles with conventional chemotherapeutic drugs can enhance the efficacy of both agents. Naringin's ability to sensitize cancer cells to chemotherapy allows for lower doses of chemotherapeutic drugs, reducing their side effects[19].
2. **Radiotherapy:**Naringin nanoparticles can enhance the sensitivity of cancer cells to radiation, improving the effectiveness of radiotherapy. This combination approach can provide a more comprehensive treatment strategy, addressing different aspects of cancer progression[69].
3. **Immunotherapy:** Combining naringin nanoparticles with immunotherapeutic agents can enhance the immune response against cancer. Naringin's immunomodulatory effects can improve the effectiveness of immunotherapy by reducing immunosuppression in the tumormicroenvironment[2,70].

Personalized Medicine Approaches Personalized medicine involves tailoring treatments to individual patients based on their genetic, molecular, and clinical profiles. Naringin nanoparticles can be integrated into personalized medicine approaches to improve therapeutic outcomes[19].

1. **Patient-Specific Formulations:** Developing nanoparticle formulations tailored to individual patients' needs can enhance efficacy and reduce side effects[71]. This approach involves understanding the patient's tumor characteristics and designing nanoparticles that target specific molecular pathways involved in their cancer[18].

2. **Biomarker-Guided Therapy:** Using biomarkers to guide the selection and dosing of naringin nanoparticles can optimize treatment. Biomarkers can indicate the likelihood of response to naringin-based therapy, allowing for more precise and effective treatment strategies[45].
3. **Adaptive Therapy:** Adaptive therapy involves continuously monitoring the patient's response to treatment and adjusting the therapy accordingly[72]. Naringin nanoparticles can be part of an adaptive treatment regimen, where the dosage and delivery method are modified based on the patient's response, maximizing therapeutic benefits[33].

While the development and clinical translation of naringin nanoparticles face challenges related to stability, scalability, regulatory approval, and safety, there are promising future directions[73]. Advanced targeting strategies, combination therapies, and personalized medicine approaches hold great potential for improving the efficacy and safety of naringin nanoparticles in cancer treatment[12]. Overcoming these challenges and leveraging these strategies can pave the way for more effective and personalized cancer therapies, ultimately enhancing patient outcomes[74,5].

2. Conclusion

Naringin nanoparticles have emerged as a promising therapeutic strategy in cancer treatment, offering significant advantages over conventional therapies. This review has highlighted the multifaceted potential of naringin, a flavonoid glycoside derived from citrus fruits, known for its antioxidant, anti-inflammatory, and anticancer properties. The encapsulation of naringin in nanoparticles enhances its bioavailability, stability, and targeted delivery, addressing some of the primary limitations of natural compounds in clinical applications.The chemical structure and biological activities of naringin underpin its therapeutic potential. Naringin's ability to induce apoptosis, arrest the cell cycle, inhibit angiogenesis, and prevent metastasis forms the basis of its anticancer action. These mechanisms are further amplified when naringin is delivered via nanoparticles, which ensure higher intracellular concentrations and prolonged circulation time. Nanoparticles also provide a controlled release profile, maintaining therapeutic levels of naringin over extended periods.Despite these challenges, the future of naringin nanoparticles in cancer therapy looks promising. Advanced targeting strategies, such as stimuli-responsive nanoparticles and patient-specific formulations, can enhance the specificity and efficacy of treatments. Combining naringin nanoparticles with other therapeutic agents, including chemotherapy, radiotherapy, and immunotherapy, can provide synergistic effects, improving overall treatment outcomes. Personalized medicine approaches, guided by biomarkers and adaptive therapy principles, can tailor treatments to individual patients' needs, maximizing therapeutic benefits while minimizing side effects.Looking ahead, further research is needed to optimize the synthesis and characterization of naringin nanoparticles, ensuring their stability, scalability, and safety. Clinical trials are essential to validate their efficacy and safety in humans, paving the way for regulatory approval and widespread clinical use. The integration of naringin nanoparticles into personalized medicine frameworks represents a significant advancement in oncology, offering tailored treatment regimens that can adapt to the dynamic nature of cancer.

3. References

1. S. Ilangumaran and D.C. Hoessli, "Effects of cholesterol depletion by cyclodextrin on the sphingolipid microdomains of the plasma membrane," *Biochem. J.*, vol. 335, pt. 2, pp. 433-440, 1998. doi: 10.1042/bj3350433.

2. L. Liu, S. Shan, K. Zhang, Z.Q. Ning, X.P. Lu, and Y.Y. Cheng, "Naringenin and hesperetin, two flavonoids derived from Citrus aurantium up-regulate transcription of adiponectin," *Phytother. Res.*, vol. 22, pp. 1400-1403, 2008. doi: 10.1002/ptr.2472.
3. M.R. Lauro, F. De Simone, F. Sansone, P. Iannelli, and R.P. Aquino, "Preparations and release characteristics of naringin and naringenin gastro-resistant microparticles by spray-drying," *J. Drug Deliv. Sci. Technol.*, vol. 17, pp. 119-124, 2007. doi: 10.1016/S1773-2247(07)50018-6.
4. Sharma, P. Bhardwaj, and S.K. Arya, "Naringin: A potential natural product in the field of biomedical applications," *Carbohydrate Polymer Technol. Appl.*, vol. 2, article 100068, 2021. doi: 10.1016/j.carbpol.2021.100068.
5. F.I. Kanaze, M.I. Bounartzi, M. Georgarakis, and I. Niopas, "Pharmacokinetics of the citrus flavanone aglyconeshesperetin and naringenin after single oral administration in human subjects," *Eur. J. Clin. Nutr.*, vol. 61, pp. 472-477, 2007. doi: 10.1038/sj.ejcn.1602545.
6. R. Choudhury, G. Chowrimootoo, K. Srai, E. Debnam, and C.A. Rice-Evans, "Interactions of the flavonoid naringenin in the gastrointestinal tract and the influence of glycosylation," *Biochem. Biophys. Res. Commun.*, vol. 265, pp. 410-415, 1999. doi: 10.1006/bbrc.1999.1703.
7. A.W. Khan, S. Kotta, S.H. Ansari, R.K. Sharma, and J. Ali, "Self-nanoemulsifying drug delivery system (SNEDDS) of the poorly water-soluble grapefruit flavonoid Naringenin: Design, characterization, in vitro and in vivo evaluation," *Drug Deliv.*, vol. 22, pp. 552-561, 2015. doi: 10.3109/10717544.2013.879792.
8. S.M. Jeon, H.K. Kim, H.J. Kim, G.M. Do, T.S. Jeong, Y.B. Park, and M.S. Choi, "Hypocholesterolemic and antioxidative effects of naringenin and its two metabolites in high-cholesterol fed rats," *Transl. Res.*, vol. 149, pp. 15-21, 2007. doi: 10.1016/j.trsl.2006.08.002.
9. A.L. Steed et al., "The microbial metabolite desaminotyrosine protects from influenza through type I interferon," *Science*, vol. 357, pp. 498-502, 2017. doi: 10.1126/science.aam5336.
10. Y. Wei et al., "The intestinal microbial metabolite desaminotyrosine is an anti-inflammatory molecule that modulates local and systemic immune homeostasis," *FASEB J.*, vol. 34, pp. 16117-16128, 2020. doi: 10.1096/fj.202001072R.
11. Z. Xeng et al., "Microbial Metabolism of Naringin and the Impact on Antioxidant Capacity," *Nutrients*, vol. 14, p. 3765, 2022. doi: 10.3390/nu14123765.
12. A.W. Ghanbari-Movahed, G. Jackson, M.H. Farzaei, and A. Bishayee, "A systematic review of the preventive and therapeutic effects of naringin against human malignancies," *Front. Pharmacol.*, vol. 12, article 639840, 2021. doi: 10.3389/fphar.2021.639840.
13. R. HeidaryMoghaddam, Z. Samimi, S.Z. Moradi, P.J. Little, S. Xu, and M.H. Farzaei, "Naringenin and naringin in cardiovascular disease prevention: A preclinical review," *Eur. J. Pharmacol.*, vol. 887, article 173535, 2020. doi: 10.1016/j.ejphar.2020.173535.
14. S. Raja Kumar, E.S. MohdRamli, N.A. Abdul Nasir, N.H.M. Ismail, and N.A. MohdFahami, "Preventive effect of naringin on metabolic syndrome and its mechanism of action: A systematic review," *Evid. Based Complement Alternat. Med.*, vol. 2019, article 9752826, 2019. doi: 10.1155/2019/9752826.
15. Z. Xeng et al., "Microbial Metabolism of Naringin and the Impact on Antioxidant Capacity," *Nutrients*, vol. 14, p. 3765, 2022. doi: 10.3390/nu14123765.
16. Hixson and J.H. Crowell, "Dependence of reaction velocity upon surface and agitation," *J. Ind. Eng. Chem.*, vol. 23, pp. 923-931, 1931. doi: 10.1021/ie50263a022.

17. K. Rao, M. Imran, T. Jabri, I. Ali, S. Perveen, A.S. Shafiullah, and M.R. Shah, "Gum tragacanth stabilized green gold nanoparticles as cargos for Naringin loading: A morphological investigation through AFM," *Carbohydr. Polym.*, vol. 174, pp. 243-252, 2017. doi: 10.1016/j.carbpol.2017.06.060.
18. Roy, D. Tripathy, A. Chatterjee, and S. Dasgupta, "A spectroscopic study of the interaction of the antioxidant naringin with bovine serum albumin," *J. Biophys. Chem.*, vol. 1, pp. 141-152, 2010. doi: 10.4236/jbpc.2010.12017.
19. V.E. Santo, M.E. Gomes, J.F. Mano, and R.L. Reis, "From nano- to macro-scale: Nanotechnology approaches for spatially controlled delivery of bioactive factors for bone and cartilage engineering," *Nanomedicine*, vol. 7, pp. 1045-1066, 2012. doi: 10.2217/nnm.12.83.
20. R. Singh and J.W. Lillard, "Nanoparticle-based targeted drug delivery," *Exp. Mol. Pathol.*, vol. 86, pp. 215-223, 2009. doi: 10.1016/j.yexmp.2008.12.004.
21. S.A. Low and J. Kopeček, "Targeting polymer therapeutics to bone," *Adv. Drug Deliv. Rev.*, vol. 64, pp. 1189-1204, 2012. doi: 10.1016/j.addr.2012.06.004.
22. P. Lavrador, V.M. Gaspar, and J.F. Mano, "BioinstructiveNaringin-Loaded Micelles for Guiding Stem Cell Osteodifferentiation," *Adv. Healthc. Mater.*, vol. 7, article 1800890, 2018. doi: 10.1002/adhm.201800890.
23. M. Pleguezuelos-Villa, S. Mir-Palomo, O. Díez-Sales, M.A.O. Vila Buso, A. Ruiz Sauri, and A. Nácher, "A novel ultradeformable liposomes of naringin for anti-inflammatory Therapy," *Colloids Surf. B Biointerfaces*, vol. 162, pp. 265-270, 2018. doi: 10.1016/j.colsurfb.2017.11.052.
24. S. Mohanty, A.K. Sahoo, V.B. Konkimalla, A. Pal, and S.C. Si, "Naringinin combination with isothiocyanates as liposomal formulations potentiates the anti-inflammatory activity in different acute and chronic animal models of rheumatoid arthritis," *ACS Omega*, vol. 5, pp. 28319-28332, 2020. doi: 10.1021/acsomega.0c03169.
25. S. Kotta, H.M. Aldawsari, S.M. Badr-Eldin, L.S. Binmahfouz, R.B. Bakhaidar, N. Sreeharsha, A.B. Nair, and C. Ramnarayanan, "Aerosol delivery of surfactant liposomes for management of pulmonary fibrosis: An approach supporting pulmonary mechanics," *Pharmaceutics*, vol. 13, article 1851, 2021. doi: 10.3390/pharmaceutics13111851.
26. Dharmendra Bhati *et al.*, "FUSED AND SUBSTITUTED PYRIMIDINE DERIVATIVES AS POTENT ANTICANCER AGENTS," *Biochemical and Cellular Archives/Biochemical and cellular archives*, vol. 24, no. 1, Jan. 2024, doi: https://doi.org/10.51470/bca.2024.24.1.749.
27. K. J. Mangala *et al.*, "NANOCELLULOSE: A VERSATILE AND SUSTAINABLE CARRIER FOR DRUG AND BIOACTIVE COMPOUNDS," *Biochemical and Cellular Archives/Biochemical and cellular archives*, vol. 24, no. 1, Jan. 2024, doi: https://doi.org/10.51470/bca.2024.24.1.553.
28. Rohit Kumar Trivedi *et al.*, "REVOLUTIONIZING DRUG DELIVERY THROUGH 3D PRINTING TECHNOLOGY: CURRENT ADVANCES AND FUTURE DIRECTIONS," *Biochemical and Cellular Archives/Biochemical and cellular archives*, vol. 24, no. 1, Jan. 2024, doi: https://doi.org/10.51470/bca.2024.24.1.521.
29. H. Rastogi, P. Bhatt, S. Garg, S. Kamboj, V. Deva, and R. Goel, "EXPLORING THE POTENTIAL OF QUANTUM DOTS AS LUMINOUS PROBES FOR TARGETED DRUG DELIVERY AND BIOIMAGING IN CLINICAL DIAGNOSTICS," *Biochemical and Cellular Archives/Biochemical and cellular archives*, vol. 24, no. 1, Jan. 2024, doi: https://doi.org/10.51470/bca.2024.24.1.457.
30. M. shama, "CRISPR-Cas9 gene editing in pharmaceuticals : Current applications and future prospects," *Biochemical and Cellular Archives/Biochemical and cellular archives*, vol. 23, no. S1, Dec. 2023, doi: https://doi.org/10.51470/bca.2023.23.s1.1655.

31. S. Arora, Saiphali, G. Dharmamoorthy Dharmendra Bhati, T. Gupta, and P. Bhatt, “Advancements in peptide-based therapeutics: Design, synthesis and clinical applications,” *Biochemical and Cellular Archives/Biochemical and cellular archives*, vol. 23, no. S1, Dec. 2023, doi: https://doi.org/10.51470/bca.2023.23.s1.1415.
32. M. Singhal et al., "Formulation development and characterization of powder for oral suspension containing H2 blocker drug to combat GERD and peptic ulcer," NeuroQuantology, vol. 20, no. 11, pp. 1258, 2022.
33. S. Ahamed, 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, 2022.
34. V. Ahmed, 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.
35. A. E. Al-Snafi, S. Singh, P. Bhatt, and V. Kumar, "A review on prescription and non-prescription appetite suppressants and evidence-based method to treat overweight and obesity," GSC biol pharm sci, vol. 19, no. 3, pp. 148–155, 2022.
36. B. Baskar, S. Ramakrishna, and A. Daniela La Rosa, Eds., Encyclopedia of green materials. Singapore: Springer Nature Singapore, 2022.
37. P. Bhatt et al., "Nanorobots recent and future advances in cancer or dentistry therapy- A review," Am J PharmTech Res, vol. 9, no. 3, pp. 321–331, 2019.
38. P. Bhatt et al., "Citrus Flavonoids: Recent Advances and Future Perspectives On Preventing Cardiovascular Diseases," in The Flavonoids, 2024, pp. 131-152.
39. P. Bhatt et al., "Functional and tableting properties of alkali-isolated and phosphorylated barnyard millet (Echinochloaesculenta) starch," ACS Omega, vol. 8, no. 33, pp. 30294–305, 2023.
40. P. Bhatt et al., "Plasma modification techniques for natural polymer-based drug delivery systems," Pharmaceutics, vol. 15, no. 8, p. 2066, 2023.
41. P. Bhatt et al., "Comparative study and in vitro evaluation of sustained release marketed formulation of aceclofenac sustained release tablets," Pharma Science Monitor, vol. 9, no. 2, 2018.
42. P. Bhatt et al., "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.
43. P. Bhatt et al., "Artificial intelligence in pharmaceutical industry: Revolutionizing drug development and delivery," The Chinese Journal of Artificial Intelligence, 2023.
44. P. Bhatt et al., "Blockchain technology applications for improving quality of electronic healthcare system," in Blockchain for Healthcare Systems, 2021, pp. 97–113.
45. P. Bhatt, "Mouth Dissolving Tablets Challenges, Preparation Strategies with a Special Emphasis on Losartan Potassium–A Review," World J. Pharm. Pharm. Sci, vol. 7, no. 9, pp. 271-287, 2018.
46. C. Goyal et al., "Estimation of shelf-life of Balachaturbhadrika syrup containing different sweetening agents," Res J Pharm Technol, pp. 5078–5083, 2022.
47. T. Kaur and S. Singh, "Controlled release of bi-layered malvidin tablets using 3D printing techniques," J Pharm Res Int, pp. 70–78, 2021.
48. M. Kaurav et al., "In-depth analysis of the chemical composition, pharmacological effects, pharmacokinetics, and patent history of mangiferin," Phytomed Plus, vol. 3, no. 2, p. 100445, 2023.

49. A. Kumar, 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.
50. M. K. Malik et al., "Significance of chemically derivatized starch as drug carrier in developing novel drug delivery devices," Nat Prod J, 2022.
51. M. K. Malik et al., "Preclinical safety assessment of chemically cross-linked modified mandua starch: Acute and sub-acute oral toxicity studies in Swiss albino mice," ACS Omega, vol. 7, no. 40, pp. 35506–35514, 2022.
52. M. K. Malik et al., "Phosphorylation of alkali extracted mandua starch by STPP/STMP for improving digestion resistibility," ACS Omega, vol. 8, no. 13, pp. 11750–11767, 2023.
53. Pankaj, "Anti-cancer cyclodextrinnanocapsules based formulation development for lung chemotherapy," J Pharm Res Int, pp. 54–63, 2021.
54. Pankaj, "Cyclodextrin modified block polymer for oral chemotherapy," J Pharm Res Int, pp. 21–29, 2021.
55. V. Raghuwanshi et al., "Recent Advances In Nanotechnology For Combating Against Corona Virus Infection," Journal of Pharmaceutical Negative Results, pp. 1811-1820, 2022.
56. K. K. Sahu et al., "Utility of nanomaterials in wound management," in Nanotechnological Aspects for Next-Generation Wound Management, 2024, pp. 101–130.
57. S. K. Sharma 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.
58. S. K. Sharma and P. Bhatt, "Controlled release of bi-layered EGCG tablets using 3D printing techniques," J Pharm Res Int, pp. 5–13, 2021.
59. S. K. Sharma and S. Singh, "Antimicrobial Herbal Soap Formulation," Journal of Pharmaceutical Research International, vol. 32, no. 36, pp. 82-88, 2022.
60. S. Singh et al., "Cardiovascular comorbidity of COVID-19 disease: A review," WJPMR, vol. 8, no. 4, pp. 216–225, 2022.
61. S. Singh et al., "Phytonutrients, Anthocyanidins, and Anthocyanins: Dietary and Medicinal Pigments with Possible Health Benefits," in Advances in Flavonoids for Human Health and Prevention of Diseases, 2024, pp. 23-46.
62. S. Singh et al., "Digital Transformation in Healthcare: Innovation and Technologies," in Blockchain for Healthcare Systems, 2021, pp. 61–79.
63. S. Singh et al., "Alginate based Nanoparticles and Its Application in Drug Delivery Systems," Journal of Pharmaceutical Negative Results, pp. 1463-1469, 2022.
64. R. Johari et al., "Artificial Intelligence and Machine Learning in Drug Discovery and Development," in 2023 12th International Conference on System Modeling& Advancement in Research Trends (SMART), 2023, pp. 556-561.
65. P. Bhatt et al., “Impact of Cross-Linking on the Physicochemical and Physiological Characteristics of Barnyard Millet (Echinochloafrumentacea) Grains Starch,” Stärke/Starch, May 2024, doi: https://doi.org/10.1002/star.202300285.
66. V. Kumar et al., “Ultrasound assisted techniques for starch modification to develop novel drug delivery systems: A comprehensive study,” Journal of bioactive and compatible polymers, May 2024, doi: https://doi.org/10.1177/08839115241249143.
67. Felgines et al., "Bioavailability of the flavanone naringenin and its glycosides in rats," *Am. J. Physiol. Gastrointest. Liver Physiol.*, vol. 279, pp. G1148-G1154, 2000. doi: 10.1152/ajpgi.2000.279.6.G1148.

68. T.Z. Fang, Y.G. Wang, Y. Ma, W.W. Su, Y. Bai, and P.Y. Zhao, "A rapid LC/MS/MS quantitation assay for naringin and its two metabolites in rats plasma," *J. Pharmaceut. Biomed.*, vol. 40, pp. 454-459, 2006. doi: 10.1016/j.jpba.2005.08.003.
69. S.Q. Li et al., "Comparative pharmacokinetics of naringin in rat after oral administration of chaihu-shu-gan-san aqueous extract and naringin alone," *Metabolites*, vol. 3, pp. 867-880, 2013. doi: 10.3390/metabo3040867.
70. M. Lavrador, V.M. Gaspar, and J.F. Mano, "BioinstructiveNaringin-Loaded Micelles for Guiding Stem Cell Osteodifferentiation," *Adv. Healthc. Mater.*, vol. 7, article 1800890, 2018. doi: 10.1002/adhm.201800890.
71. M. Pleguezuelos-Villa, S. Mir-Palomo, O. Díez-Sales, M.A.O. Vila Buso, A. Ruiz Sauri, and A. Nácher, "A novel ultradeformable liposomes of naringin for anti-inflammatory Therapy," *Colloids Surf. B Biointerfaces*, vol. 162, pp. 265-270, 2018. doi: 10.1016/j.colsurfb.2017.11.052.
72. S. Mohanty, A.K. Sahoo, V.B. Konkimalla, A. Pal, and S.C. Si, "Naringinin combination with isothiocyanates as liposomal formulations potentiates the anti-inflammatory activity in different acute and chronic animal models of rheumatoid arthritis," *ACS Omega*, vol. 5, pp. 28319-28332, 2020. doi: 10.1021/acsomega.0c03169.
73. Ahmed, H. Khan, M. Aschner, M.M. Hasan, and S.T.S. Hassan, "Therapeutic potential of naringin in neurological disorders," *Food Chem. Toxicol.*, vol. 132, article 110646, 2019. doi: 10.1016/j.fct.2019.110646.
74. Cassidy and A.M. Minihane, "The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids," *Am. J. Clin. Nutr.*, vol. 105, pp. 10-22, 2017. doi: 10.3945/ajcn.116.136051.