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Aptamers as Targeting Agents: Revolutionizing the Delivery of Plant Bioactive Compounds for Cancer Treatment

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ABSTRACT

Cancer represents a significant public health challenge, being one of the leading causes of illness and death globally. The urgent need for innovative, effective, and less toxic therapeutic strategies is paramount. Natural products, particularly plant bioactive compounds, have shown notable anticancer properties but face challenges, such as poor solubility and low bioavailability. This review explores the innovative role of aptamers in enhancing the delivery of these compounds. Aptamers, with their unique properties, offer a promising solution to the challenges faced by natural compounds, facilitating targeted drug delivery and improving therapeutic outcomes. By leveraging the specificity and binding affinity of aptamers, we can revolutionize the delivery of plant bioactive compounds, ultimately advancing cancer treatment and improving patient care. The integration of nanotechnology further enhances the potential of aptamer-guided delivery systems, marking a significant advancement in cancer therapy.

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Introduction

Cancer represents a significant public health challenge and ranks as one of the leading causes of illness and death globally, being the second leading cause of mortality worldwide. In 2015, cancer accounted for approximately 8.8 million fatalities with around 70% of these deaths occurring in low- and middle-income countries. The annual incidence of new cancer cases is expected to increase from 14.1 million in 2012 to 21.6 million by 2030. The economic burden of cancer is equally substantial; in 2010, the total annual economic cost was estimated to be around 1.16 trillion USD, posing a threat to economies across all income levels and leading to financial hardship for individuals and families. The insidious nature of cancer stems from the unregulated growth and division of abnormal cells that invade adjacent tissues and spread to distant organs, a primary driver of cancer-related deaths [1]. Consequently, the urgent need for innovative, effective, and less toxic therapeutic strategies is paramount. Historically, natural products have served as a rich source for cancer treatments. Among the estimated 250,000 plant species, over a thousand have demonstrated notable anticancer properties [2]. Plant bioactive compounds have been shown to inhibit cancer cells by promoting cell differentiation, enhancing immune responses, suppressing nitrosation and nitration, regulating steroid hormone metabolism, and preventing DNA damage. Recent studies indicate that these compounds manifest their anticancer activity through various cellular signaling pathways at multiple levels, including post-translational modifications, protein synthesis, and intracellular communication [3, 4]. Several bioactive molecules derived from medicinal and dietary plants, such as quercetin, curcumin, resveratrol, and epigallocatechin-3-gallate, have been reported to effectively combat various types of cancer by inhibiting the activation of oncogenic pathways at the cellular level [5-7]. These compounds are particularly attractive due to their high potency, minimal toxicity, and ability to overcome drug resistance, offering a promising alternative or adjunct to conventional therapies. Despite their immense therapeutic promise, the clinical translation of many plant bioactive compounds is often hindered by challenges such as poor solubility, low bioavailability, and non-specific distribution in the body. These limitations can lead to suboptimal therapeutic outcomes and increased toxicity, underscoring the need for innovative strategies to enhance the delivery and efficacy of these valuable natural products in modern medicine [8, 9]. This review explores the innovative role of aptamers in enhancing the delivery of plant-based therapeutics. Aptamers, with their unique properties, offer a promising solution to the challenges faced by natural compounds, facilitating targeted drug delivery and improving therapeutic outcomes. By leveraging the specificity and binding affinity of aptamers, we can revolutionize the delivery of plant bioactive compounds, ultimately advancing cancer treatment and improving patient care [10]. Nanotechnology has emerged as a transformative force in addressing these complex challenges in biomedicine, particularly in cancer therapy and drug delivery. Nanomaterials, encompassing a range of structures, such as nanoparticles, (NPs) nanorods, and nanospheres, possess unique physicochemical characteristics due to their size (typically ranging from 1-100 nm), high surface-to-volume ratio, and tunable surface chemistry. These attributes enable them to overcome the limitations of traditional drug formulations by enhancing drug solubility, improving pharmacokinetics, and enabling targeted delivery. Nanomaterial-based drug delivery systems can encapsulate therapeutic agents, protecting them from degradation, prolonging their circulation time, and facilitating their accumulation within tumor sites through mechanisms, such as the enhanced permeability and retention (EPR) effect [11, 12]. Various nanomaterials, including inorganic forms, such as gold NPs (AuNPs) and silica NPs, and organic structures, such as liposomes, micelles, and polymeric NPs, provide flexible platforms for drug delivery due to their compatibility with biological systems and high drug loading capacities.

This capability of precisely deliver therapeutic payloads directly to diseased tissues or cells marks a significant advancement in cancer treatment [13]. This review delves into how aptamers, as precision targeting agents, are poised to revolutionize the delivery of these valuable plant bioactive compounds for cancer treatment. Aptamers, with their unique properties—including high specificity, tunable binding affinity, and structural stability—offer an innovative solution to overcome the delivery challenges faced by natural products [14]. By leveraging the specific molecular recognition capabilities of aptamers, often in conjunction with nanomaterial carriers, we can facilitate targeted drug delivery to cancer cells, thereby improving bioavailability, minimizing systemic toxicity, and ultimately enhancing therapeutic outcomes. This exploration highlights the cutting-edge strategies employing aptamers to unlock the full therapeutic potential of nature against cancer, paving the way for more effective and patient-centric oncology approaches.

Aptamer-based Drug Carriers for Delivery

Overview of aptamers

Aptamers are a new class of high-affinity nucleic acids that bind to proteins and were first identified in the early 1990s. These short, single-stranded molecules, including DNA, ribonucleic acid (RNA), or synthetic xeno nucleic acid (XNA)—exhibit a remarkable capacity to selectively and strongly attach to specific target molecules. Typically made up of 25 to 80 nucleotides, aptamers function similarly to antibodies in their targeting capabilities. However, they present several advantages over antibodies, including a shorter production time, lower manufacturing costs, greater ease of modification, improved thermal stability, a broader range of potential targets, and importantly, a lack of variability between batches [10].

Systematic evolution of ligands by exponential enrichment (SELEX): The process of aptamer generation

Aptamers are produced using an in vitro molecular evolution method called SELEX, which was independently introduced in 1990 by Tuerk and Gold, as well as Ellington and Szostak. The traditional SELEX process involves three main steps: Selection, partitioning, and amplification. It begins with the synthesis of a library of oligonucleotides, usually containing up to 10^{15} unique sequences. Each sequence consists of random nucleotides (20–50) flanked by two conserved primer-binding sites that enable polymerase chain reaction (PCR) amplification through primer annealing. In the selection phase, the library is incubated with target molecules for a set period. After this incubation, unbound sequences are separated from those that have successfully attached to the target using various techniques. The sequences that bind to the target are then amplified using PCR for DNA SELEX or reverse transcription-PCR for RNA SELEX. The resulting PCR products create a new sub-pool for the next selection rounds. After multiple rounds of selection, the enriched sequences are sequenced, and their binding affinities are evaluated. This entire process can take from several weeks to months to identify specific aptamer candidates, and the success rates are often low. To overcome these difficulties and improve efficiency, various modified SELEX methods have been developed to reduce the selection time and increase the hit rates [15, 16].

Advances in SELEX and aptamer applications

The SELEX process has undergone significant modifications to address its limitations and expand the practical applications of aptamers. For instance, the characterization of aptamers during selection, the diversity of target molecules, and the modifications aptamers can undergo have all advanced. These improvements have broadened the utility of aptamers in both in vitro and in vivo applications. Aptamers generally possess a preferred size ranging from 15 to 45 nucleotides, with molecular weights ranging from 5-15 kDa. Their binding affinities range from pico- to micromolar levels, making them highly versatile tools [17].

Applications of aptamers in targeted drug delivery

The utilization of aptamers in targeted drug delivery has been thoroughly investigated, especially for administering therapeutic substances, such as chemotherapeutics, small interfering RNAs, microRNAs, toxins, and natural compounds. Aptamers, functioning as targeting ligands, are frequently linked to the surfaces of nanoparticle platforms, which serve as carriers for therapeutic payload. It is important to note that while aptamers significantly enhance targeting specificity, the nanoparticle aspect of these delivery systems is vital for boosting overall therapeutic effectiveness. NPs can encapsulate therapeutic agents, shielding them from degradation and promoting their accumulation at tumor sites through mechanisms, such as the EPR effect. The combination of aptamers with nanomaterials results in efficient delivery systems that improve the accuracy of drug delivery in bioanalysis and biomedicine [16, 18].

Nanomaterial Carriers in Aptamer-guided Therapeutic Strategies

Following the discussion on aptamers as highly specific targeting agents, it is crucial to understand the role of nanocarriers in translating this specificity into effective therapeutic delivery, particularly for plant bioactive compounds in cancer treatment. Nanomaterials, owing to their unique physiochemical characteristics, including small size, high surface-to-volume ratio, and adjustable functionality, effectively overcome many limitations associated with traditional drug delivery methods, including poor solubility, low bioavailability, and non-specific biodistribution of therapeutic agents. When integrated with aptamers, these nanocarriers form sophisticated delivery systems that enhance the precision and efficacy of drug targeting. Various types of nanomaterials serve as promising platforms for aptamer-guided delivery, broadly categorized into inorganic and organic systems:

Inorganic nanomaterials: These include materials, such as AuNPs, silica NPs, carbon nanomaterials (carbon nanotubes, graphene), and quantum dots. They offer robust structures, excellent surface functionalization capabilities for aptamer conjugation, and often possess intrinsic therapeutic or imaging properties. For instance, AuNPs are highly biocompatible and can be precisely engineered for drug loading and controlled release, while also enabling optical tracking [19]. Silica NPs provide high porosity and surface area, making them ideal for encapsulating a wide range of therapeutic payload [20].

Organic nanomaterials: This category encompasses biocompatible and biodegradable systems, such as liposomes, polymeric micelles, dendrimers, exosomes and DNA nanostructures [21]. These carriers mimic biological structures, offering excellent biocompatibility, reduced immunogenicity, and efficient encapsulation of both hydrophilic and hydrophobic drugs. Liposomes, for example, can protect encapsulated plant bioactive compounds from degradation and facilitate their accumulation in cancer tissues via the EPR effect [22]. Polymeric micelles provide sustained release profiles, while DNA nanostructurs offer a stimuli-responsive release mechanism [23]. The synergistic integration of aptamers with these diverse nanomaterial carriers is pivotal. Aptamers direct the nanocarrier system to specific cancer cells or tumor microenvironments, while the nanocarrier component protects the therapeutic payload (e.g. plant bioactive compounds), enhances its stability, improves solubility, prolongs systemic circulation, and facilitates controlled release at the target site. This combined approach significantly boosts the therapeutic index of plant bioactive compounds, minimizing off-target effects and maximizing anti-cancer efficacy.

Plant-based therapeutics: Current status and future perspectives

Curcumin

Curcumin, the active ingredient of turmeric (*Curcuma longa*), is a naturally occurring polyphenol compound renowned for its diverse biological functions, which encompass anti-inflammatory, antioxidant, and anticancer effects. Despite its therapeutic promise, curcumin encounters considerable obstacles in clinical application due to its low bioavailability, rapid metabolism, and poor solubility in water [24].

Curcumin plays a significant role in the treatment of various cancers and has been extensively studied for its synergistic effects alongside its analogs in enhancing anti-cancer activity [25]. Innovative strategies, such as the use of aptamers as targeting agents, are currently being investigated to improve the administration and effectiveness of curcumin in cancer therapy.

By utilizing aptamers, which can selectively bind to cancer cells, researchers aim to improve the targeted delivery of curcumin, thereby maximizing its therapeutic effects while minimizing side effects. This approach represents a promising advancement in the field of cancer therapeutics, leveraging the natural benefits of curcumin through enhanced delivery mechanisms [26]. Curcumin is extensively utilized for the treatment of various diseases, including cancers, such as those affecting the lungs and prostate [27]. A study conducted by Maryam Hashemi et al. explored the use of AS1411 aptamer-targeted poly lactic-co-glycolic acid (PLGA) NPs to enhance the delivery and therapeutic efficacy of curcumin, a plant-based compound with well-documented anticancer properties, in combination with mitoxantrone (MTX) for breast cancer treatment. The study addressed the major limitations of curcumin, such as poor water solubility and low bioavailability, by encapsulating it in PLGA NPs and functionalizing the system with the AS1411 aptamer for targeted delivery. The results demonstrated that PLGA-curcumin-aptamer NPs exhibited superior cytotoxicity against breast cancer cell lines (Michigan Cancer Foundation7 [MCF7] and 4T1) compared to untargeted NPs or free curcumin, highlighting the enhanced therapeutic potential of aptamer-targeted delivery systems. Furthermore, the combination of PLGA-curcumin aptamer with MTX showed a significant synergistic effect, reducing the IC_{50} values and improving cancer cell inhibition while minimizing effects on normal cells. This investigation highlights the possibilities of using NPs that are modified with aptamers in revolutionizing the delivery of plant-based therapeutics, such as curcumin, for cancer treatment, offering a promising strategy to enhance their efficacy and specificity [28]. A compelling example of aptamers revolutionizing plant-based therapeutic delivery is seen in the development of aptamer-functionalized curcumin/CTX-loaded lipid-polymer NPs (CTX-LPNs) for targeted prostate cancer therapy. These NPs co-deliver curcumin, a plant-derived agent, with cabazitaxel, employing a dual-targeting strategy where the A10-3.2 aptamer targets prostate-specific membrane antigen (PSMA). This innovative approach achieved strong synergistic effects, notably an optimal 2:5 curcumin ratio yielding a combination index (CI=0.41), and demonstrated enhanced targeting specificity with superior cellular uptake in PSMA-positive lymph node carcinoma of the prostate (LNCaP) cells compared to PSMA-negative prostate cancer, grade 3 (PC-3) cells. Critically,

these aptamer-functionalized NPs showcased significant clinical relevance through improved pharmacokinetics, extending the half-life of both curcumin (12.3±0.8 h) and cabazitaxel (13.2±1.1 h), along with superior tumor accumulation and reduced systemic toxicity, evidenced by normal liver and kidney function markers and maintained body weight, unlike free drug solutions. This work powerfully exemplifies how aptamers can transform the efficacy of plant-based therapeutics through precise targeting and synergistic drug combinations [29].

Lawsone

Lawsone (2-hydroxy-1,4-naphthoquinone), a bioactive compound derived from *Lawsonia inermis* (henna), has demonstrated significant anticancer potential due to its ability to inhibit the growth of various cancer cell lines, including ovarian, lung, colorectal, and hepatocellular carcinoma (HCC) cells [30]. This investigation highlights the promising therapeutic properties of lawsone; yet its clinical use remains limited by its poor aqueous solubility and low bioavailability, which hinder its effective delivery and therapeutic efficacy. To address these challenges, Gheshlaghi et al. (2025) successfully developed AS1411 aptamer-functionalized solid lipid NPs (SLNs) loaded with lawsone, utilizing chitosan coating for enhanced stability and aptamer conjugation. This innovative targeted delivery system demonstrated markedly improved cellular uptake and superior cytotoxicity in nucleolin-positive colon adenocarcinoma cells (C26) compared to free lawsone or non-targeted SLNs, while showing minimal impact on nucleolin-negative normal cells (Chinese Hamster Ovary [CHO] cells). The LWS-SLN-Chit-Apt formulation also exhibited a sustained drug release profile, effectively overcoming lawsone's inherent delivery challenges and showcasing the transformative potential of aptamers in revolutionizing the targeted delivery and therapeutic efficacy of plant-based anticancer agents [31].

Silybin

Silybin (also known as silibinin, with the chemical formula C25H22O10) is a powerful plant-derived anticancer agent. This compound is a well-known dietary supplement extracted from the seeds of *Silybum marianum* (L.) Gaertn, commonly referred to as milk thistle. The extract from milk thistle, known as silymarin, has a long-standing history in traditional medicine and is commonly utilized to avert and manage liver ailments, such as viral hepatitis, liver cirrhosis resulting from alcohol misuse, and liver injury induced by medications and industrial toxins. Moreover, it demonstrates notable antioxidant characteristics by neutralizing hydroxyl radicals and preventing lipid peroxidation, acting as a chain-breaking antioxidant. Over the last twenty years, in addition to its liver-protective and antioxidant properties, silybin has displayed remarkable anti-cancer and cancer-preventive effectiveness in preliminary studies involving cell cultures and animal models of various epithelial cancers, including those impacting the skin, bladder, colon, prostate, and lungs [32, 33]. PLGA NPs offer a foundational solution, encapsulating streptavidinbiotin NPs (SBN) to improve bioavailability and enable sustained, pH-responsive release. Optimized SBN-PLGA NPs exhibit favorable characteristics, such as a diameter of 138.57 nm and 70.19% entrapment efficiency, addressing initial delivery hurdles. The crucial advancement lies in integrating aptamers for active targeting. Specifically, the 5TR1 aptamer, designed to bind the MUC1 protein overexpressed on colorectal cancer (CRC) cells, transforms the delivery system. This aptamer-functionalized SBN-PLGA-5TR1 nanocomplex acts as a precise guidance system, directing the therapeutic payload directly to MUC1-positive CRC cells (C26, HT29 cells). This targeted delivery facilitates efficient cellular uptake and localized SBN release within the tumor microenvironment. Consequently, in vitro studies demonstrate significantly enhanced cytotoxicity against CRC cells, with a concomitant reduction in toxicity towards healthy, MUC1-negative cells (CHO cells). This differential effect highlights the aptamer's indispensable role in substantially improving the therapeutic index and specificity of plant-based therapeutics. Aptamer-guided nanocarriers thus represent a transformative approach, revolutionizing the precise and effective delivery of natural anticancer compounds [34].

Thymoquinone

Thymoquinone is a natural compound primarily found in the seeds of *Nigella sativa*, commonly known as black seed. It possesses a wide range of biological activities, including antioxidant, anti-inflammatory, immunomodulatory, and anticancer properties. Thymoquinone has been shown to lower blood pressure and blood sugar levels, and it exhibits cytotoxic effects against various cancer cell lines [35]. AS1411 nanodroplets loaded with thymoquinone were developed to specifically target breast cancer cell lines MDA-MB-231 and HCC1395. Murphy and colleagues compared the effects of thymoquinone alone and an untargeted formulation. The nanodroplets were designed using perfluoropentane and lipids, creating a core-shell structure. The AS1411 aptamer was attached to the lipid layer to enhance targeting. Results showed that the AS1411 nanoemulsion had significantly

higher cellular uptake in the first four hours compared to the untargeted version, although both formulations demonstrated substantial uptake over time, which may affect the specificity of the study. While there was a slight increase in cytotoxicity in MDA-MB-231 cells with the targeted formulation, it was not statistically significant in HCC1395 cells. However, both formulations significantly enhanced the cytotoxic effects of thymoquinone compared to the free compound, indicating the potential therapeutic value of targeted nanoemulsions in breast cancer treatment [36].

Epigallocatechin 3-gallate (EGCG) (epigallocatechin gallate from green tea)

EGCG is a bioactive phenolic compound found in green tea. It has been extensively researched for its properties as an antioxidant, anti-inflammatory agent, and its potential to inhibit tumor growth and carcinogenesis. EGCG achieves these effects by influencing various molecular signaling pathways, such as AMP-activated protein kinase (AMPK), autophagy, endothelial nitric oxide synthase (eNOS), nuclear factor kappa B (NF-kB), and by inducing epigenetic modifications, such as DNA methylation and histone alterations [37]. A groundbreaking strategy for targeted cancer therapy using aptamer-functionalized NPs for the delivery of EGCG was developed by Alizedeh et al. [38]. Chitosan-coated silica NPs (SiO_2@CS) were synthesized and loaded with EGCG, a polyphenol with anticancer properties. The AS1411 aptamer, known for its high affinity to nucleolin (overexpressed in some cancer cells), was then conjugated to the NPs, enabling targeted delivery to SKOV-3 ovarian cancer cells. The resulting SiO2@CS-EGCG-aptamer NPs exhibited a spherical core-shell morphology with a size of approximately 100 nm. In vitro studies demonstrated that these aptamer-functionalized NPs significantly enhanced the internalization of EGCG into SKOV-3 cells compared to NPs without the aptamer. Furthermore, the targeted NPs exhibited superior cytotoxicity, inducing a higher rate of apoptosis in the cancer cells. Mechanistically, the SiO_2@CS-EGCG-aptamer NPs halted the cell cycle at the G0/G1 phase and reduced the expression levels of extracellular signalregulated kinase 2 (ERK2) and human telomerase reverse transcriptase (*hTERT*) gene, which are involved in cancer cell proliferation and survival. These findings suggest that aptamer-conjugated NPs hold great promise for targeted delivery of plant-based therapeutics, offering enhanced efficacy and reduced side effects in cancer treatment. The study provides a strong foundation for further in vivo investigations to validate the therapeutic potential of this targeted nanocarrier system [38].

Apigenin

Apigenin, a dietary flavonoid known as 4′, 5, 7-trihydroxyflavone, has gained considerable attention as a health-promoting compound in recent years due to its low toxicity and unique effects on normal and cancerous cells compared to other flavonoids. This edible flavonoid, derived from plants, has garnered significant scientific interest for its potential health benefits, particularly in modulating inflammation, oxidative stress, and various biological functions. Furthermore, apigenin's anti-cancer properties are supported by its ability to influence multiple cell signaling pathways, including those related to tumor suppressor genes, angiogenesis, programmed cell death, cell cycle regulation, inflammation, and pathways, such as phosphoinositide 3 kinase/protein kinase B (PI3K/AKT), NF-κB, mitogenactivated protein kinase/extracellular signalregulated kinase (MAPK/ERK), and signal transducer and activator of transcription 3 (STAT3) [39, 40]. Dhara et al. (2023) significantly contributed to the field of targeted cancer therapy by demonstrating the enhanced therapeutic potential of apigenin, a plant-derived flavonoid, through its delivery via phosphorothioated amino-AS1411 aptamer-functionalized PEGylated nanoliposomes (nanostructured lipid carriers [NLCs]). The AS1411 aptamer, specifically targets nucleolin receptors overexpressed on HCC cells, revolutionizes the delivery of this potent plant-based therapeutic. The aptamer conjugation addressed critical limitations of apigenin, such as poor solubility and bioavailability, leading to superior in vitro cytotoxicity, increased apoptosis, and cell cycle arrest at the G2/M phase in HCC cells compared to free apigenin or non-functionalized nanoliposomes. Furthermore, in vivo studies in HCC-induced rats revealed remarkably improved pharmacokinetic profiles, characterized by prolonged circulation, reduced systemic clearance, and precise intratumoral accumulation of apigenin within neoplastic liver tissues. This targeted delivery translated into significant antitumor effects, including a drastic reduction in tumor volume and hepatic altered foci lesions, while maintaining a favorable safety profile with minimal toxicity to normal cells. Consequently, this work stands as a compelling example of how aptamers can serve as innovative targeting agents to amplify the efficacy and specificity of plant-based therapeutics for cancer treatment, thereby expanding their clinical utility [41].

Paclitaxel (from the pacific yew tree)

Paclitaxel, a potent anticancer agent derived from the bark of the Pacific Yew tree, was first isolated in 1967 and has since been extensively studied for its efficacy

against various cancers, including breast, lung, and ovarian cancers. It functions by targeting tubulin, disrupting microtubule dynamics, and inhibiting cell division, which is crucial for cancer cell proliferation. Despite its effectiveness, challenges such as chemoresistance and the high demand for natural extraction have prompted research into synthetic and microbial production methods. Recent advancements include nanoparticle-assisted drug delivery systems that enhance therapeutic effectiveness and reduce side effects, highlighting the ongoing need for innovative approaches in cancer chemotherapy [42]. A notable example of utilizing paclitaxel in targeted cancer therapy is the development of aptamer-coated paclitaxel-polylactide conjugates (Ptxl-LA100). These conjugates were successfully synthesized with controlled molecular weights and narrow molecular weight distributions (Mw/Mn=1.03). The NH2-modified A10 aptamer, which targets PSMA, demonstrated a remarkable 5.2-fold selective binding to PSMA-positive LNCaP cells compared to PSMA-negative PC-3 cells. Furthermore, the aptamer-conjugated nanoconjugates exhibited a time-dependent internalization that increased by 5.7-fold over a period of six hours. Importantly, these aptamer-functionalized nanoconjugates maintained their targeting capability even after lyophilization and subsequent reconstitution, indicating significant potential for clinical translation. The research also highlighted several key advantages of aptamers over traditional antibody-based targeting methods. These advantages include superior stability against variations in pH and temperature, non-immunogenicity, and minimal batch-to-batch variability. These findings underscore the transformative potential of aptamer-guided delivery systems in revolutionizing cancer therapeutics with paclitaxel. This robust platform could be readily adapted for delivering various plant bioactive compounds, enhancing tumor selectivity and therapeutic efficacy [43].

α-Mangostin (αMG)

αMG is a natural xanthone extracted from the pericarps of the mangosteen fruit (*Garcinia mangostana*) and is well-known for its notable anti-cancer properties. It has been thoroughly studied for its ability to interfere with various stages of carcinogenesis, including initiation, promotion, and progression. The compound exhibits multiple mechanisms of action, such as modulating carcinogenic biotransformation, inducing growth arrest and apoptosis in cancer cells, suppressing angiogenesis and metastasis, and enhancing the efficacy of clinical chemotherapy drugs while reducing their toxic side effects. Despite promising preclinical findings, the translation of αMG into clinical applications remains limited, highlighting the need for further research to establish its pharmacokinetics, toxicology, and potential therapeutic uses in cancer prevention and treatment [44, 45]. A recent study demonstrated the potential of aptamers in enhancing the delivery of plant bioactive compounds for cancer treatment, specifically utilizing αMG against breast tumor spheroids. In this research, αMG, a natural compound known for its antitumor properties, was encapsulated into lipidic NPs. Crucially, these αMG-loaded NPs were then conjugated with a CD44 thioaptamer, acting as a highly specific targeting agent. This strategic combination allowed for the targeted delivery of αMG to MCF-7 breast tumor spheroids, which express CD44. The CD44 thioaptamer-tagged NPs achieved significant spheroid disaggregation and a reduction in tumor size at remarkably low αMG concentrations, a more pronounced cytotoxic effect than untagged NPs or free αMG, likely due to enhanced cellular uptake and a more potent impact on cell viability and adhesion. This approach highlights how aptamers can revolutionize cancer therapy by improving drug selectivity, minimizing systemic toxicity, and potentially targeting difficult-to-treat cancer stem cells [46].

Resveratrol

Resveratrol is a naturally occurring polyphenolic compound primarily found in the skins of grapes, berries, and peanuts. It has attracted considerable interest due to its potential health benefits, especially regarding cancer prevention and treatment. Resveratrol demonstrates a diverse array of biological activities, including antioxidant, anti-inflammatory, and anti-cancer effects. Mechanistically, it influences various cellular pathways that regulate cell proliferation, apoptosis, and metastasis. Research has demonstrated that resveratrol can inhibit the growth of cancer cells by inducing cell cycle arrest and promoting apoptosis through the modulation of key signaling pathways such as NF-κB, PI3K/AKT, and MAPK. Additionally, resveratrol has been shown to enhance the efficacy of conventional chemotherapeutic agents, making it a promising candidate for combination therapies. Despite its potential, the clinical application of resveratrol is limited by its low bioavailability, necessitating ongoing research to develop effective delivery methods and formulations that can maximize its therapeutic effects in cancer treatment [7, 47, 48]. To address this, resveratrol-loaded gold NPs (RVT@PVP-GNPs) were developed, significantly enhancing its cellular uptake and anti-tumor efficacy. Further improving targeted delivery, these NPs were conjugated with the AS1411 aptamer, which serves as a highly specific targeting agent. The AS1411 aptamer selectively binds

to nucleolin, a protein overexpressed on the surface of many cancer cells, including pancreatic cancer cells. This aptamer-mediated active targeting facilitated efficient delivery of RVT to tumor sites, leading to substantial, dose-dependent tumor volume suppression in vivo, while notably minimizing systemic accumulation and damage to healthy organs, such as the kidneys, thereby demonstrating the potential of aptamers in revolutionizing targeted delivery of plant bioactive compounds for cancer treatment [49].

Quercetin

Quercetin is a naturally occurring flavonoid found in various fruits and vegetables, particularly in onions, apples, and berries. It has garnered attention for its potential anti-cancer properties, primarily through its ability to inhibit cell proliferation across various cancer cell lines, including breast, prostate, and colon cancer. Quercetin induces cell cycle arrest in the G1 phase by modulating cyclins and cyclin-dependent kinases, while also promoting apoptosis and autophagy through the activation of caspases and the modulation of essential signaling pathways, such as PI3K/AKT/mechanistic target of rapamycin (mTOR). Additionally, it alleviates oxidative stress by neutralizing reactive oxygen species and inhibits metabolic pathways crucial for cancer cell survival, particularly glycolysis [50]. Aptamer-functionalized drug delivery systems have emerged as promising platforms for the targeted delivery of plant bioactive compounds for cancer treatment. Specifically, aptamer-functionalized quercetin thermosensitive liposomes (AQTSL) utilize the AS1411 aptamer to selectively bind to nucleolin, which is over-expressed on tumor cell membranes. This innovative approach combines the advantages of high drug loading, sustained release, and prolonged circulation from PEGylated liposomes with enhanced active targeting and cellular internalization facilitated by the aptamer. Additionally, the thermosensitive nature of the liposomes allows for temperature-controlled quercetin release, enabling a synergistic chemo-thermotherapy effect, where local hyperthermia triggers drug release and directly inhibits tumor growth. In preclinical models, aptamer-functionalized quercetin thermosensitive liposomes (AQTSL) combined with mild hyperthermia (42 $^{\circ}$C) has shown a significant tumor growth inhibition by 75%, outperforming non-targeted systems and demonstrating superior efficacy due to the aptamer's ability to precisely deliver the plant bioactive compound to cancer cells while minimizing systemic toxicity, thus paving the way for personalized and effective cancer therapies [51].

Conclusion

The integration of aptamers as targeting agents in the delivery of plant bioactive compounds represents a significant advancement in cancer therapeutics. Aptamers offer high specificity and binding affinity, which can enhance the targeted delivery of therapeutic agents, thereby improving their efficacy and reducing off-target effects. The combination of aptamers with nanomaterials not only addresses the challenges of poor solubility and low bioavailability associated with many plant-derived compounds but also facilitates controlled release and prolonged circulation time. This innovative approach holds significant potential to improve cancer treatment by maximizing the therapeutic benefits of natural products while minimizing adverse effects. The promising results from recent studies highlight the significant potential of aptamer-guided delivery systems in enhancing the effectiveness of plant-based therapies. Looking ahead, several avenues warrant exploration to fully realize the potential of aptamer-based delivery systems in cancer therapy. First, further research is needed to optimize the design and synthesis of aptamers to enhance their stability, binding affinity, and specificity for various cancer targets. Additionally, the development of multifunctional nanocarriers that can co-deliver multiple therapeutic agents, including chemotherapeutics and plant bioactive compounds, could provide synergistic effects and improve treatment outcomes. Moreover, clinical trials are essential to validate the safety and efficacy of these novel delivery systems in human patients. Investigating the pharmacokinetics and biodistribution of aptamer-functionalized NPs will be crucial in understanding their behavior in vivo and ensuring their clinical applicability. Finally, expanding the range of plant bioactive compounds explored in conjunction with aptamers could lead to new therapeutic options for various cancer types. By utilizing the distinctive characteristics of aptamers and the vast array of bioactive compounds derived from plants, researchers can pave the way for more effective, targeted, and personalized cancer therapies that improve patient outcomes and quality of life.

Ethical Considerations

Compliance with ethical guidelines

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Conflict of interest

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