

Review

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Review

Exploring the Synergy of Carbon Nanodots in Enhancing Cannabidiol Delivery and Therapeutic Efficacy: A Comprehensive Review

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Abstract: The dynamic interaction between carbon nanodots (CNDs) and cannabidiol (CBD) has captured significant attention as an innovative avenue for redefining drug delivery and amplifying therapeutic effectiveness. This in-depth review delves into the intricate synergy between these two elements, unveiling their profound potential in medicine. Commencing with an examination of the unique characteristics of CNDs and the techniques governing their synthesis, we discuss their versatility as drug carriers, highlighting their invaluable role in advancing CBD delivery. Cannabidiol, a non-psychoactive compound sourced from cannabis, has emerged as a focal point for its diverse therapeutic attributes. Nevertheless, the limitations posed by its restricted bioavailability and susceptibility to degradation pose substantial hindrances to realizing its full potential. Here, we elucidate how the amalgamation of CBD with CNDs transcends these challenges. We delve into the mechanisms that underlie this synergy, such as the augmentation of solubility and the safeguarding of CBD against premature breakdown, providing an intricate analysis. We will also journey you through a comprehensive exploration of diverse CBD loading techniques onto CNDs, dissecting the realms of physical encapsulation, covalent bonding, and adsorption processes. In summation, the combination of CNDs and CBD presents an extraordinary opportunity to elevate therapeutic outcomes. This synergetic paradigm masterfully tackles pivotal challenges in drug delivery, thereby paving the path for pioneering medical solutions.

Keywords: carbon nanodots (CNDs); cannabidiol (CBD); drug delivery; encapsulation; bioavailability; adsorption

Introduction

Drug delivery is a vital aspect of modern healthcare and pharmaceutical science, playing a pivotal role in ensuring that therapeutic substances reach their intended targets in the body with precision and efficacy. In the context of carbon nanodots (CNDs) and cannabidiol (CBD), we will explore how the connection of advanced drug delivery systems and innovative materials can potentially revolutionize the administration and therapeutic potential of CBD [1,2].

CBD, a non-psychoactive component of the cannabis plant, has gained immense popularity for its potential therapeutic benefits, ranging from pain management and anxiety relief to anti-inflammatory properties [3]. However, the challenge lies in delivering CBD to the body in a controlled and effective manner. This is where the emerging field of nanomedicine and drug delivery comes into play [4].

Carbon nanodots (CNDs), an exciting development in nanotechnology, are tiny carbon nanoparticles with unique properties that make them ideal candidates for drug delivery applications. Their small size, large surface area, and biocompatibility enable them to encapsulate and transport therapeutic compounds like CBD. By entrapping CBD within these CNDs, it becomes possible to control its release, increase its solubility, and target specific sites within the body, thus maximizing

its therapeutic potential [5]. Integration of CNDs with CBD showcases the innovative approach that can enhance the pharmacokinetics of cannabinoids. These novel delivery systems may improve the bioavailability of CBD, ensuring that a larger fraction of the administered dose reaches the bloodstream and the intended sites of action [6].

We seek to comprehensively review the potential of CNDs in enhancing the delivery and therapeutic efficacy of CBD. By collating and analyzing existing research and developments in this emerging field, we aim to elucidate the opportunities, challenges, and implications of integrating nanotechnology into CBD delivery. This review intends to shed light on the mechanisms, applications, and overall impact of this synergy, offering a thorough understanding of its significance for the pharmaceutical and medical communities. Additionally, this review will encompass a wide array of topics associated with the integration of CNDs and CBD for drug delivery. To achieve this, we will provide a comprehensive overview of CNDs, their properties, and their relevance in drug delivery as well as the therapeutic potential of CBD and the associated challenges with its delivery, also we will examine the mechanisms of CBD encapsulation within CNDs and its impact on solubility and bioavailability, analyze the potential applications of CNDs in CBD delivery, including pain management, and anti-inflammatory effects. Furthermore, we will investigate the safety and biocompatibility of CNDs for pharmaceutical applications and discuss the current state of research and development in this field by highlighting emerging trends and innovations, we will conclude by assessing the future prospects of CNDs in enhancing CBD delivery and its potential to revolutionize CBD-based therapies.

Carbon Nanodots

Carbon nanodots (CNDs), also known as carbon quantum dots, are a class of carbon-based nanomaterials. They are typically less than 10 nanometers in size and are characterized by their quantum confinement properties [5]. CNDs possess unique optical, electrical, and chemical properties that make them suitable for various applications, including drug delivery. Their exceptional biocompatibility, surface functionalization capabilities, and tunable surface chemistry set them apart as promising candidates for drug delivery systems. Various methods are available for synthesizing CNDs. These methods include the hydrothermal method, microwave-assisted synthesis, and the pyrolysis of organic precursors. The choice of method influences the size, shape, and surface functional groups of the CNDs, which, in turn, can affect their performance in drug delivery applications. Each synthesis method offers distinct advantages and is chosen based on the desired CND characteristics [7].

Carbon nanodots have garnered significant attention for their potential in drug delivery systems. Some of the notable applications of CNDs are listed in Table 1. They can serve as carriers for therapeutic agents due to their ability to encapsulate drugs, enhance solubility, and improve drug stability. The biocompatible nature of CNDs makes them suitable for both traditional and targeted drug delivery. Their small size enables efficient cellular uptake, making them ideal for intracellular drug delivery. Additionally, CNDs can be modified with ligands for specific drug targeting, further enhancing their applications in drug delivery [8–10].

Several properties of CNDs make them well-suited for drug encapsulation. The small size of CNDs allows them to encapsulate drugs efficiently and deliver them to target sites, including intracellular locations [11]. Figure 1 illustrates CNDs complexed to antibodies used for detecting specific bacterial strain in serum. CNDs can be functionalized with various surface groups, enabling drug loading through physical encapsulation or chemical conjugation. They are biocompatible and exhibit low cytotoxicity, making them suitable for pharmaceutical applications. They also enhance the solubility of poorly water-soluble drugs, improving their bioavailability, and can protect encapsulated drugs from degradation and premature release. The surface functionalization of CNDs allows for ligand attachment, enabling targeted drug delivery to specific cells or tissues. These properties, in combination with their ease of surface modification and versatile synthesis methods, position CNDs as promising drug delivery carriers with the potential to improve therapeutic outcomes [13,16].

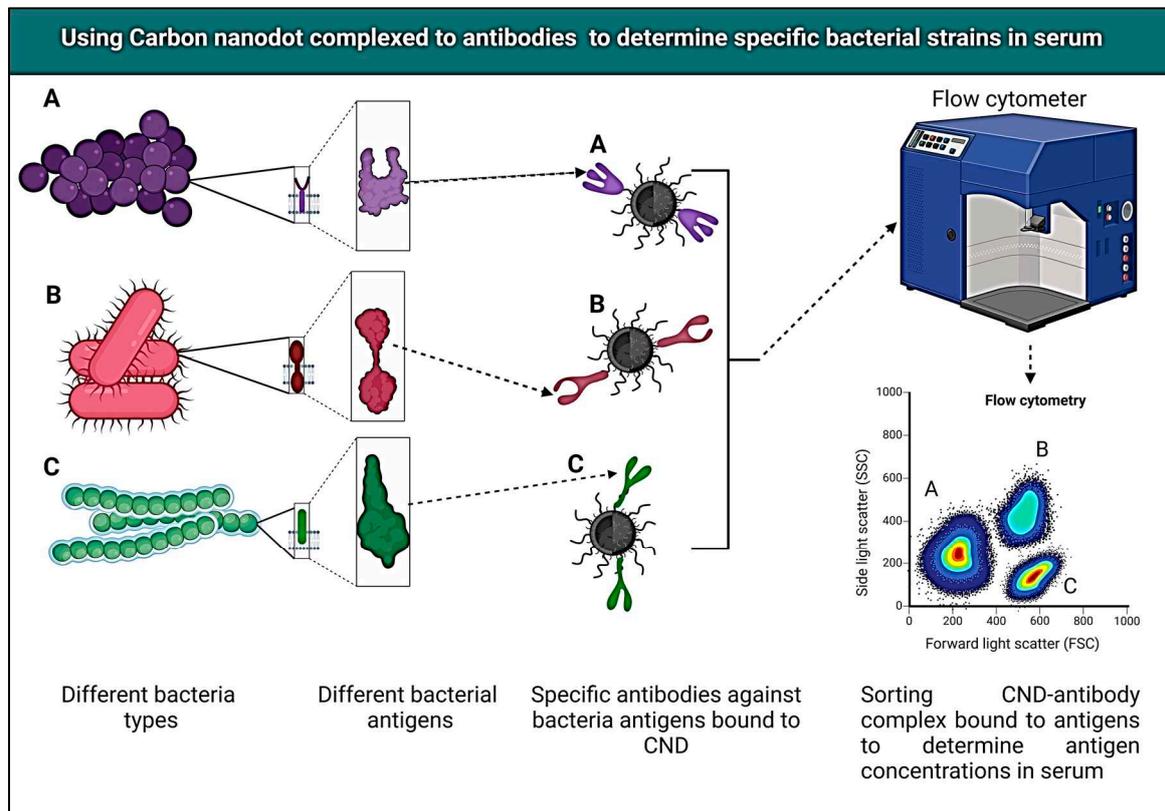


Figure 1. Using CND complexed to antibodies to determine specific bacterial strains in bacterial infected serum.

Table 1. Some notable applications of CNDs in drug delivery.

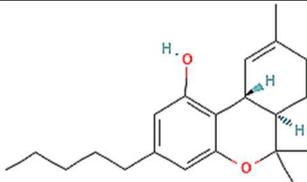
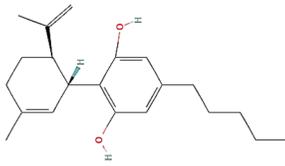
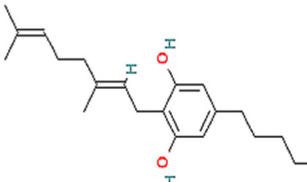
| No. | Application | Description | References |
|-----|------------------------------|--|------------|
| 1. | Anticancer Drug Delivery | Carbon dots are utilized as drug carriers for anticancer medications, enhancing drug solubility and targeted delivery to tumor sites. They also serve as imaging agents. | [8] |
| 2. | Antibiotic Drug Delivery | Carbon dots improve the stability and bioavailability of antibiotics, aiding in the treatment of bacterial infections. They are also used for infection imaging. | [9] |
| 3. | Peptide and Protein Delivery | Carbon dots enhance the delivery of therapeutic peptides and proteins by improving their stability and protecting them from enzymatic degradation. | [12] |
| 4. | Gene Delivery | Carbon dots are used as non-viral vectors for gene delivery, facilitating the introduction of genetic material into cells for gene therapy and genetic studies. | [10] |
| 5. | Photothermal Therapy | Carbon dots are employed for photothermal therapy, where they absorb and convert light into heat to target and destroy cancer cells in a controlled manner. | [13] |
| 6. | Imaging Agents | Carbon dots are used as contrast agents in medical imaging, including fluorescence imaging, MRI, and photoacoustic imaging, for diagnostic and visualization purposes. | [14] |

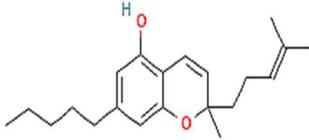
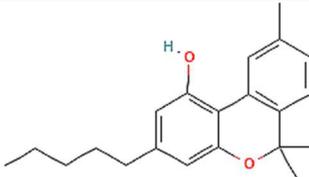
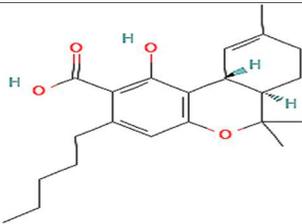
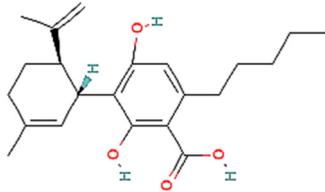
| | | |
|-----|------------------------------|--|
| 7. | Ocular Delivery | DrugCarbon dots are explored in ophthalmic applications, serving as carriers for drugs targeted at eye diseases and as imaging agents for retinal imaging. |
| 8. | Wound Healing | Carbon dots are incorporated into wound dressings to enhance wound healing, reduce infection risk, and provide controlled drug release. |
| 9. | Real-Time Release Monitoring | DrugCarbon dots are integrated into drug delivery systems to monitor drug release in real-time, ensuring precise dosage and timing. |
| 10. | Antibacterial Agents | Functionalized carbon dots exhibit antibacterial properties and are studied for combating drug-resistant bacteria and infections. |

Cannabidiol (CBD): Understanding the Therapeutic Compound

Cannabidiol (CBD), a naturally occurring phytocannabinoid (Table 2 describes the major phytocannabinoid) abundant in cannabis plants, is particularly prevalent in hemp. Its distinctiveness lies in being non-psychoactive, a characteristic that has contributed significantly to its rise in popularity. CBD has attracted substantial attention due to its multifaceted therapeutic properties. Renowned for its anti-inflammatory, analgesic, anxiolytic, and neuroprotective effects, this compound is more than just a botanical constituent. It emerges as a potential game-changer in the world of natural remedies [3].

Table 2. Properties of Cannabis-Related Variants and Their Solubility Characteristics.

| No. | Variants | Molecular formula | Molecular Weight | Solubility | LogP Values | Structure |
|-----|----------|--|------------------|--|-------------|---|
| 1. | THC | C ₂₁ H ₃₀ O ₂ | 314.5 g/mol | <p>-Highly soluble in lipid-based solvents.</p> <p>-Moderate solubility in ethanol (Alcohol).</p> <p>-Low solubility in water, propylene glycol and vegetable glycerin.</p> <p>-Cyclodextrin can be used to improve its solubility</p> | 7 |  |
| | CBD | C ₂₁ H ₃₀ O ₂ | 314.5 g/mol | <p>-Highly soluble in lipid-based solvents.</p> <p>-Moderate solubility in ethanol (Alcohol).</p> <p>-Low solubility in water, propylene glycol and vegetable glycerin.</p> <p>-Cyclodextrin can be used to improve its solubility</p> | 6.5 |  |
| 2. | CBG | C ₂₁ H ₃₂ O ₂ | 316.5 g/mol | <p>-Highly soluble in lipid-based solvents.</p> <p>-Moderate solubility in ethanol (Alcohol).</p> <p>-Low solubility in water, propylene glycol and vegetable glycerin.</p> <p>-Cyclodextrin can be used to improve its solubility</p> | 7.4 |  |

| | | | | | | |
|----|------|-------------------|-------------|---|-----|---|
| 3. | CBC | $C_{21}H_{30}O_2$ | 314.5 g/mol | <p>-Highly soluble in lipid-based solvents.</p> <p>-Moderate solubility in ethanol (Alcohol).</p> <p>-Low solubility in water, propylene glycol and vegetable glycerin.</p> <p>-Cyclodextrin can be used to improve its solubility</p> | 6.9 |  |
| 4. | CBN | $C_{21}H_{26}O_2$ | 310.4 g/mol | <p>-Highly soluble in lipid-based solvents.</p> <p>-Moderate solubility in ethanol (Alcohol).</p> <p>-Low solubility in water, propylene glycol and vegetable glycerin.</p> <p>-Cyclodextrin can be used to improve its solubility</p> | 6.1 |  |
| 5. | THCA | $C_{22}H_{30}O_4$ | 358.5 g/mol | <p>-Highly soluble in lipid-based solvents.</p> <p>-Moderate solubility in ethanol (Alcohol).</p> <p>-Low solubility in water, propylene glycol and vegetable glycerin.</p> <p>-Often converted to delta-THC through decarboxylation.</p> | 7 |  |
| 6. | CBDA | $C_{22}H_{30}O_4$ | 358.5 g/mol | <p>-Highly soluble in lipid-based solvents.</p> <p>-Moderate solubility in ethanol (Alcohol).</p> <p>-Low solubility in water, propylene glycol and vegetable glycerin.</p> | 6.6 |  |

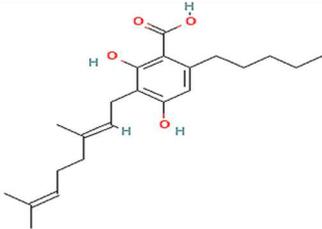
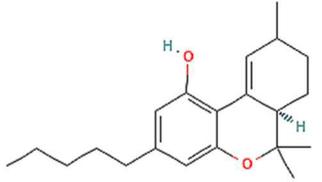
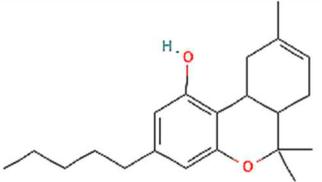
| | | | | | | |
|----|--------------|-------------------|-------------|--|-----|--|
| | | | | -Often converted to CBD through decarboxylation. | | |
| 7. | CBGA | $C_{22}H_{32}O_4$ | 360.5 g/mol | -Highly soluble in lipid-based solvents. -Moderate solubility in ethanol (Alcohol). -Low solubility in water, propylene glycol and vegetable glycerin. -Often converted to CBG, THC or CBD through decarboxylation. | 7.5 |  |
| 8. | Delta-10-THC | $C_{21}H_{30}O_2$ | 314.5 g/mol | -High solubility in lipid-based solvents (likely). -Moderate solubility in ethanol (Alcohol). -Very low solubility in water, propylene glycol and vegetable glycerin. | 6 |  |
| 9. | Delta-8-THC | $C_{21}H_{30}O_2$ | 314.5 g/mol | -High solubility in lipid-based solvents. -Moderate solubility in ethanol (Alcohol). -Very low solubility in water, propylene glycol and vegetable glycerin. | 5.7 |  |

Table 2 provides information on various cannabis-related variants, including their molecular formula, molecular weight, solubility, LogP values, and a brief description of their structure and characteristics.

What makes CBD especially intriguing is its profound interaction with the endocannabinoid system, a pivotal component in the human body's intricate regulatory network. This system is instrumental in managing a wide array of physiological processes, emphasizing the essential role of CBD in maintaining balance and well-being [17]. In the realm of medicine, CBD stands out as a versatile contender. Its potential applications are diverse, covering an impressive spectrum of health concerns. Among its medical virtues, CBD excels as a potent pain management tool, offering respite to those suffering from various forms of discomfort [18]. Furthermore, its prowess extends to anxiety and stress reduction, providing a calming influence in a world marked by tension and unease. As shown in Figure 2, the mechanism of action of CBD as antiepileptic drug on excitatory synapses is critical in managing epilepsy. CBD is known to inhibit calcium release from intracellular synapses, thus resulting in a reduction in the activity of seizure and excitatory signals. In chronic epilepsy, CBD is known to potentiate the decline in SNAREs recruitment and decrease cAMP. CBD is also known to antagonize GPR55, desensitize TRPV1 channels and inhibit adenosine reuptake. Thus, for individuals plagued by seizures, CBD presents a glimmer of hope, with its anticonvulsant effects offering the possibility of a more stable and fulfilling life. Particularly noteworthy is its potential in the treatment of neurodegenerative disorders, such as epilepsy. This is where CBD shines as a beacon of promise for individuals and families who have long grappled with the challenges of such conditions [19].

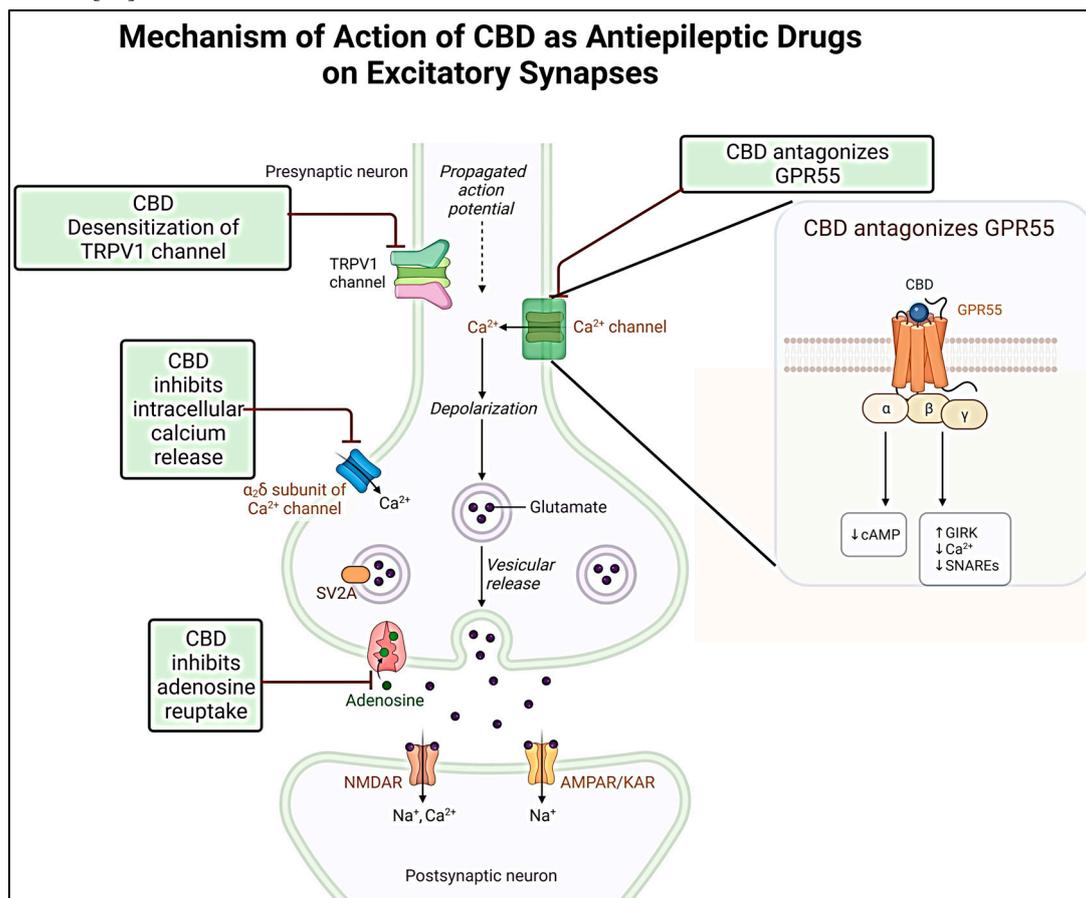


Figure 2. Mechanism of action of CBD as antiepileptic drug on excitatory synapses. CBD's ability to inhibit the calcium release from intracellular synapses results in a reduction in the activity of seizure and excitatory signals. In chronic epilepsy, CBD is known to potentiate the reduction in SNAREs recruitment, cAMP, and antagonizes GPR55. CBD is also known to desensitize TRPV1 channels and inhibit adenosine reuptake.

However, as with many promising agents, the efficacy of CBD hinges significantly on the art and science of drug delivery. Some of the most pressing challenges stem from the route of administration. When administered orally, CBD grapples with poor bioavailability, signifying that a substantial portion of the compound gets lost in the convoluted processes of digestion and liver metabolism. This leads to suboptimal outcomes in terms of the actual dose of CBD that the body can absorb and utilize. The variability in accurate and consistent dosing, especially when using conventional delivery methods, remains a formidable obstacle. This challenge is paramount in medical applications, where precision is vital [4,20]. Another intricate facet of CBD delivery is the timing of therapeutic effects. It's not just about what CBD can do but also about how quickly it can do it. The onset of action is subject to variability depending on the chosen delivery method, which can be relatively sluggish in some instances. This temporal variability is crucial in conditions where rapid relief or management is imperative. CBD stability is another crucial concern in drug delivery. This compound can be sensitive to environmental factors, and under certain conditions, it can degrade, leading to a loss of potency and effectiveness. Ensuring the maintenance of CBD's integrity from production to administration is vital [21,22]. Moreover, for conditions necessitating localized treatment, targeted drug delivery to affected areas is not just desirable but crucial. Enhanced delivery systems capable of ensuring CBD reaches specific sites within the body can significantly enhance therapeutic outcomes [23].

In light of these challenges, it becomes evident that enhancing the delivery of CBD is pivotal for harnessing its full therapeutic potential. Addressing issues related to bioavailability, dosing precision, time to action, stability, and targeted treatment is paramount. Through innovative delivery approaches, we can unlock the full scope of CBD's therapeutic virtues and make it a more potent ally in the realm of medical science [13].

Therapeutic Applications

Pain Management

Pain management is a critical aspect of healthcare, and CBD-loaded CNDs offer a promising avenue for improving the treatment of various pain-related conditions. Here's an expanded discussion on this important therapeutic application. Chronic pain is a widespread health issue, affecting millions of individuals worldwide. Conditions such as osteoarthritis, fibromyalgia, and lower back pain can lead to persistent and debilitating discomfort [57,58]. CBD, with its known analgesic properties, has emerged as a potential solution for managing chronic pain. However, the limited solubility and bioavailability of CBD have been significant hurdles in achieving consistent and effective pain relief. CBD-loaded CNDs, by enhancing the drug's solubility and bioavailability, can lead to more reliable and sustained pain management. Their ability to protect CBD from premature degradation in the body ensures that the therapeutic effects are maintained over an extended period. Neuropathic pain results from damage to or dysfunction of the nervous system and can be particularly challenging to treat. CBD's interaction with the endocannabinoid system and its anti-inflammatory properties makes it a potential candidate for neuropathic pain management. The use of CNDs as carriers ensures that CBD is efficiently delivered to the affected neural tissues, increasing its efficacy in alleviating neuropathic pain [59].

Patients undergoing cancer treatments often experience severe pain, which can significantly affect their quality of life. CBD has been explored for its potential to manage cancer-related pain due to its analgesic and anti-inflammatory effects. When delivered via CNDs, CBD's effectiveness is further enhanced. The sustained-release properties of CNDs can provide prolonged pain relief, reducing the need for frequent dosing and minimizing potential side effects [60]. To establish the efficacy of CBD-loaded CNDs in pain management, comprehensive clinical studies are essential. These studies should focus on specific pain conditions, dosing regimens, and patient populations. Additionally, long-term safety assessments are critical to ensure that the therapy remains well-tolerated over extended periods. Collaborations between researchers, pharmaceutical companies,

and healthcare providers are necessary to drive these studies and translate the potential of this innovative drug delivery system into tangible pain relief solutions for patients.

Neurological Disorders

Neurological disorders represent a diverse group of conditions that affect the nervous system and can have a profound impact on an individual's quality of life. CBD, known for its neuroprotective properties, holds promise as a therapeutic agent for various neurological disorders. When harnessed through the efficient delivery provided by CNDs, its potential to address these conditions becomes even more compelling [61–63].

Epilepsy is characterized by recurrent seizures caused by abnormal electrical activity in the brain. CBD has garnered significant attention for its potential in reducing the frequency and severity of seizures. Studies have shown that CBD may be particularly effective in some forms of epilepsy that are resistant to other treatments [64–66]. However, the dosage and consistency of CBD administration are crucial for its efficacy. CNDs offer a solution by improving the solubility and bioavailability of CBD, ensuring that a more consistent and effective dosage reaches the brain. This can potentially enhance seizure control and improve the quality of life for individuals with epilepsy. Multiple sclerosis is an autoimmune disease that affects the central nervous system. It leads to a range of symptoms, including muscle spasms, pain, and difficulties with mobility [35]. CBD's anti-inflammatory and muscle-relaxant properties make it a candidate for managing MS symptoms. CNDs can enable the efficient delivery of CBD to target areas in the central nervous system, potentially reducing muscle spasms and alleviating pain [36].

Neurodegenerative disorders like Alzheimer's and Parkinson's disease are characterized by the progressive loss of brain function and the death of neurons [37]. CBD's neuroprotective effects and its potential to reduce neuroinflammation have generated interest in its application for these conditions. CNDs, by providing a stable and bioavailable means of delivering CBD, can enhance its neuroprotective properties. This could potentially slow down the progression of these diseases and alleviate some of their debilitating symptoms [38].

To fully harness the potential of CBD-loaded CNDs in the management of neurological disorders, robust clinical research is essential. Controlled clinical trials are necessary to determine the optimal dosages, treatment regimens, and patient populations that will benefit most from this approach. These studies should evaluate the effects on symptom management, disease progression, and the overall quality of life for individuals with neurological disorders.

Anti-Inflammatory Effects

Inflammatory disorders encompass a range of conditions where the body's immune system becomes overactive, resulting in chronic inflammation that can cause pain, tissue damage, and a variety of symptoms [39,40]. CBD's well-established anti-inflammatory properties make it a promising candidate for managing these disorders. CNDs, with their potential to enhance drug delivery, offer a means to maximize the effectiveness of CBD in mitigating inflammation. Here's an expanded discussion of CBD-loaded CNDs in addressing inflammatory conditions [41].

Rheumatoid arthritis is a chronic autoimmune disorder that primarily affects joints. It leads to pain, inflammation, and joint damage [42]. CBD has shown promise in reducing inflammation and alleviating pain in preclinical studies. When delivered via CNDs, CBD can target the inflamed joint tissues more effectively. This targeted delivery can help in reducing inflammation and preventing further joint damage, potentially improving the quality of life for individuals with rheumatoid arthritis [38,41]. Crohn's disease is a type of inflammatory bowel disease that causes chronic inflammation of the digestive tract [43]. CBD's anti-inflammatory effects have raised interest in its potential for managing the symptoms of Crohn's disease. CNDs can improve the bioavailability of CBD, allowing it to reach the inflamed intestinal tissues [8,38]. This enhanced delivery system may help reduce inflammation, alleviate pain, and improve gastrointestinal function in individuals with Crohn's disease. Inflammatory skin disorders like psoriasis and eczema are characterized by persistent skin inflammation, leading to redness, itching, and discomfort [44,45]. CBD's anti-

inflammatory and skin-soothing properties have prompted investigations into its role in managing these conditions. When incorporated into CNDs, CBD can be formulated into topical creams or ointments that deliver the compound directly to affected skin areas. This targeted application may help reduce inflammation, soothe irritated skin, and relieve the symptoms associated with inflammatory skin disorders [46,47]. While preclinical studies and anecdotal reports are promising, clinical validation is essential to determine the full therapeutic potential of CBD-loaded CNDs in managing inflammatory disorders. Clinical trials are necessary to assess the safety and efficacy of this approach, define optimal dosages, and confirm its benefits for individuals with specific inflammatory conditions. The results of such trials will be instrumental in bringing these innovative therapies to patients in need [48]. The future potential of CBD-loaded CNDs is incredibly promising, with emerging horizons that transcend the discussed applications. As research in this field evolves, new therapeutic possibilities are bound to emerge, revolutionizing the landscape of drug delivery and treatment efficacy.

O'Brien, 2022 [49] has demonstrated that CBD has potential in cancer treatment. While it's not a cure, it may play a role in managing cancer-related symptoms and side effects of treatments like chemotherapy, Figure 3 illustrates CBD encapsulated in CND complexed to cancer targeting cells peptides. When coupled with CNDs, the targeted delivery of CBD to cancerous cells becomes a viable avenue. This precise drug delivery system may offer enhanced pain relief, anti-nausea effects, and the potential to inhibit tumor growth. Extensive research is needed to determine the full extent of its therapeutic contributions to oncology [50]. Mental health disorders, such as anxiety and depression, are a global health concern. CBD is known for its anxiolytic and mood-stabilizing properties. Incorporating CBD into CNDs could facilitate precise dosing and effective drug delivery. The future of mental health treatment may involve innovative formulations that offer rapid relief, minimal side effects, and improved patient compliance [51,52].

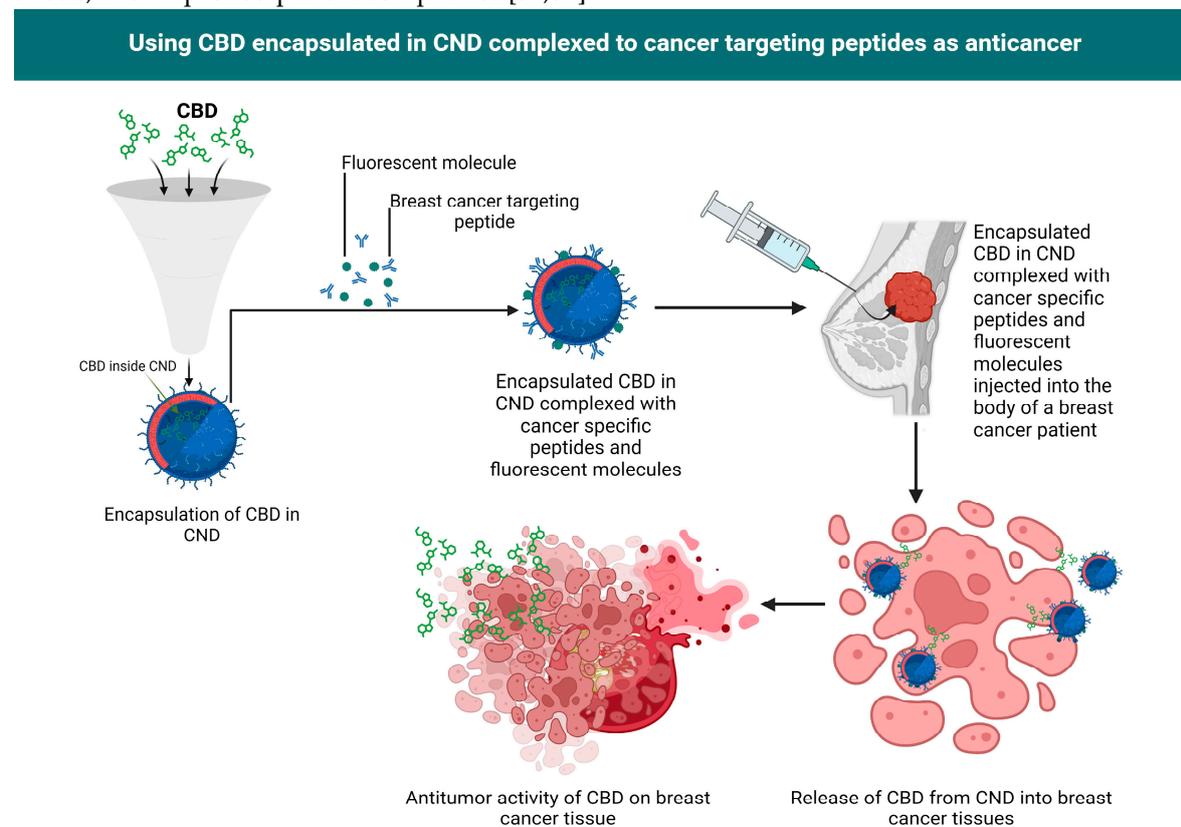


Figure 3. Targeting breast cancer with CBD encapsulated in carbon CND decorated with breast cancer targeting peptides. Using the CND technology, CBD can be encapsulated into CNDs and the surface of the CNDs decorated with cancer targeting peptides (e.g., breast cancer targeting peptides), the formulation can then be injected into breast cancer patient. The targeted nature of the formulation will ensure that CND carrying CBD payload are docked onto breast cancer cells and thus release CBD

directly into the microenvironment of the breast cancer tumors. CBD will then orchestrated its anticancer activity, thus leading to the apoptosis or death of cancer cells.

Emerging evidence suggests that CBD might contribute to cardiovascular health by reducing blood pressure and protecting the heart from ischemia. CNDs can enhance CBD's solubility and bioavailability, which are crucial factors in cardiovascular therapy. Further exploration may uncover CBD-loaded CNDs' role in the management of heart conditions and stroke prevention [53].

Personalized medicine is an evolving concept that tailors treatment to an individual's unique genetic, environmental, and lifestyle factors. CBD-loaded CNDs can play a role in precision medicine by delivering therapies with unprecedented accuracy. Specific formulations, dosages, and delivery methods can be tailored to a patient's distinctive needs, optimizing therapeutic outcomes [54].

The potential of CBD in neuropharmacology extends to diverse neurological and psychiatric disorders. As research delves deeper into the nuances of CBD's interaction with the nervous system, the collaboration with CNDs may unlock innovative solutions for conditions such as schizophrenia, bipolar disorder, and post-traumatic stress disorder [55,56].

Translational research that bridges laboratory discoveries with clinical applications is essential to truly harness the full potential of synergizing CBD with CNDs. Collaborations between scientists, clinicians, and industry experts are needed to translate laboratory findings into practical therapies.

Regulatory agencies play a pivotal role in shaping the future of CBD-loaded CNDs, ensuring the safe and effective use of these innovative therapies. A patient-centric approach is integral to the future of this development. Research must prioritize the needs and preferences of patients to develop solutions that enhance their quality of life.

Synergizing CNDs and CBD

Synergizing CNDs and CBD opens up a world of potential in the field of drug delivery. This section will delve into the mechanisms underlying this synergy, the compatibility of CNDs with CBD, and the resulting impact on solubility and bioavailability.

Mechanisms of Synergy

The collaboration between CNDs and CBD represents a dynamic interplay that greatly enhances drug delivery mechanisms. A deeper understanding of how these two entities work in concert is pivotal to appreciating the substantial improvements they bring to CBD's solubility and bioavailability challenges.

One of the central mechanisms of synergy involves the protective encapsulation of CBD molecules by CNDs. This encapsulation offers a shield against environmental factors that could compromise the stability and efficacy of CBD. It acts as a safeguard, ensuring that CBD retains its therapeutic properties throughout its journey in the body [57,58]. In addition to encapsulation, CNDs can form stable interactions with CBD molecules. This binding not only enhances the stability of CBD but also aids in its controlled release. The association between CNDs and CBD ensures that the therapeutic compound is efficiently delivered, precisely where and when it is needed. The size and surface properties of CNDs play a pivotal role in this synergy [59]. Their nano-scale dimensions make them well-suited for effective drug dispersion, improving the distribution of CBD in the delivery system. Furthermore, the surface properties can be tailored to optimize interactions with CBD, ensuring efficient loading and release, while also mitigating any potential aggregation issues. An additional aspect of this synergy lies in the sustained-release properties of CNDs. The CNDs act as reservoirs, allowing for a controlled and extended release of CBD over time. This controlled release ensures that therapeutic effects are not only maximized but also prolonged, providing a more consistent and longer-lasting impact [60].

CNDs and CBD Compatibility

The harmonious interaction between CNDs and CBD represents a fundamental aspect of their synergistic relationship. This compatibility is underpinned by several key factors that converge to create an ideal environment for CBD delivery.

CNDs have gained recognition for their inherent biocompatibility. This means they coexist seamlessly within biological systems without triggering adverse reactions. In the context of CBD delivery, the biocompatible nature of CNDs ensures that the formulation is well-tolerated by the body [61]. There is minimal risk of toxicity or immunogenic responses, highlighting their safety as a delivery vehicle. Additionally, a crucial benefit of CNDs is their low toxicity profile. This characteristic is particularly advantageous when partnering with a therapeutic compound like CBD. The absence of harmful effects enables the safe administration of CBD in combination with CNDs, ensuring that the delivery process does not introduce unintended health risks [62,63]. Furthermore, CNDs offer a versatile platform for functionalization. This means that their surface properties can be tailored to suit the specific requirements of CBD delivery. Functionalization can enhance the binding and encapsulation of CBD molecules, allowing for precise control over the release of the therapeutic compound. This adaptability ensures that CNDs are a compatible and customizable carrier for CBD [64].

Finally, the collaboration between CNDs and CBD is characterized by the absence of adverse interactions. This compatibility extends to their chemical, physical, and biological attributes. The two entities coexist without compromising each other's integrity, ensuring that CBD retains its therapeutic properties while benefiting from the unique characteristics of CNDs [65].

Impact on Solubility and Bioavailability

Solubility and bioavailability represent pivotal factors in the successful delivery of therapeutic compounds, and their enhancement is a crucial outcome of combining CNDs with CBD. CBD's limited solubility in water is a well-documented challenge [4]. CNDs, with their unique structure and surface properties, offer a solution to this problem. When paired with CBD, they act as effective solubilizers, facilitating the dispersion of CBD in aqueous solutions. This enhanced solubility is vital because it allows CBD to form stable and homogeneous mixtures, ensuring uniform dosing and consistent therapeutic effects [66].

Also, solubility and bioavailability are intrinsically linked. In this synergy, improved solubility directly contributes to increased bioavailability. When CBD is more soluble, the body can absorb it more efficiently. This means that a higher percentage of the administered CBD reaches the systemic circulation, where it can exert its therapeutic effects. The combination of CNDs and CBD results in a formulation that offers greater bioavailability compared to traditional delivery methods. Moreover, CBD is susceptible to degradation during the digestive process, which can reduce its bioavailability [67]. CNDs act as protective carriers, shielding CBD from premature breakdown in the gastrointestinal tract. This protective role ensures that a more substantial amount of CBD remains intact and available for absorption. As a result, the combined delivery system contributes to a significant increase in CBD bioavailability. It is important to also recognize that the improved solubility and bioavailability achieved through this synergy have additional benefits. The consistent delivery of CBD to the bloodstream ensures that the therapeutic effects are more predictable and reliable. Patients can expect a more dependable response to the treatment, making it easier to manage and optimize their CBD therapy [60].

Synergizing CNDs and CBD represents a promising breakthrough in the field of drug delivery, offering a robust solution to the persistent challenges of solubility and bioavailability associated with CBD. This impactful combination has the potential to unleash the full therapeutic efficacy of CBD across a range of medical applications.

CNDs encapsulation of CBD

CNDs encapsulation of Cannabidiol (CBD) represents a cutting-edge strategy in the realm of drug delivery. This innovative approach harnesses the unique properties of CNDs to address longstanding challenges associated with CBD, a non-psychoactive compound renowned for its therapeutic potential. The process of encapsulation involves entrapping CBD molecules within the nano-sized structure of CNDs. This encapsulation can be realized through several methods, each with its distinct advantages and considerations [57]. The most common methods include physical encapsulation, covalent bonding, and adsorption onto the surface of the CNDs. Li et al., 2020 [68] explains in their mini review the Strategies to obtain encapsulation and controlled release of small hydrophilic molecules.

Physical Encapsulation: Sood et al., 202 [69] employs physical encapsulation methods in polysaccharide-based biomaterials for delivering drugs. Physical encapsulation is a straightforward yet highly effective method used to encapsulate CBD within the intricate three-dimensional framework of CNDs. This encapsulation process does not necessitate intricate chemical modifications, making it particularly attractive due to its simplicity and versatility. The simplicity of physical encapsulation lies in its fundamental mechanism. CNDs serve as protective carriers, cradling CBD molecules within their structure [70]. The structural design of CNDs, typically consisting of a core-shell structure, provides an ideal environment for entrapping CBD. The outer shell of the CNDs shields CBD from external influences, including environmental factors like light, heat, and moisture. This protective shield enhances the stability of CBD, ensuring that it remains intact until released for therapeutic purposes. One of the notable advantages of physical encapsulation is the controlled drug release it offers. CBD molecules are securely nestled within the CNDs, and their release can be tailored to meet specific requirements [71]. By modifying the characteristics of the CNDs or the encapsulation process itself, researchers can fine-tune the release kinetics. This level of control over drug release is invaluable when designing drug delivery systems with precise dosing and timing needs. While physical encapsulation is highly versatile and generally applicable to a wide range of drugs, it may not be the ideal choice for all therapeutic agents. The method's simplicity and general suitability may not address the unique demands of certain drugs, which may require more specialized encapsulation approaches. In such cases, covalent bonding or adsorption techniques, which offer different advantages and considerations, may be more appropriate [72].

Covalent Bonding: Covalent bonding, as a method of encapsulating CBD within CNDs, relies on the formation of robust chemical bonds between the drug and the carrier system. This approach offers several unique advantages, primarily rooted in the creation of secure and long-lasting connections between the two components [73]. One of the key features of covalent bonding is the strength of the chemical bonds formed. These covalent bonds are characterized by the sharing of electrons between the CBD molecules and the CNDs, creating a stable and durable connection. The strength and stability of covalent bonds ensure that CBD remains securely attached to the CNDs throughout the drug delivery process.

This robust and lasting connection between CBD and the CNDs has significant implications for drug loading and release kinetics. Covalent bonding provides an exceptional degree of control over both drug loading and the rate at which CBD is released. Researchers can engineer the covalent bonds in a way that allows for precise, tailor-made drug delivery. This level of control is particularly advantageous when specific dosing and release requirements are necessary for therapeutic effectiveness. However, it's important to note that covalent bonding is a more intricate process compared to physical encapsulation [74]. Achieving covalent bonding may require specific chemical modifications, both to the drug (CBD) and the carrier system (CNDs). These modifications are essential to enable the formation of stable covalent bonds. The complexity of this approach means that it may not be suitable for all drugs or may necessitate a more intricate encapsulation process [75].

Adsorption Techniques: Adsorption techniques play a crucial role in the encapsulation of CBD within CNDs, offering a versatile and effective method for drug loading. Cortés et al., 2019 [76] employed this technique in the fabrication of a dual-purpose materials based on carbon xerogel microspheres (CXMS) for delayed release of cannabidiol (CBD) and subsequent aflatoxin removal

purposely for the delay release of CBD. They claim that this method improves CBD's bioavailability and allows the effective removal of aflatoxins in gastric situations. In this process, CBD molecules are physically attracted to and adhere to the surface of CNDs, forming an adsorptive bond. This method is particularly appealing for several reasons. Adsorption techniques are highly versatile and can be applied to a wide range of drugs without the need for extensive chemical modification [77]. The surface properties of CNDs play a key role in attracting and retaining drug molecules, making them an ideal choice for adsorption-based drug delivery systems. This versatility is advantageous when dealing with various therapeutic compounds. Moreover, adsorption is a relatively simple process, making it accessible and practical for drug encapsulation. Unlike covalent bonding, which may require complex chemical modifications, adsorption relies on the inherent properties of CNDs to attract and retain drug molecules. This simplicity facilitates the development of drug delivery systems and can streamline the encapsulation process. One of the standout features of adsorption techniques is their high drug loading capacity [78]. CNDs can effectively adsorb a significant quantity of CBD molecules, allowing for efficient drug loading. This characteristic is vital when designing drug delivery systems that require substantial drug payloads. Adsorption technique is not infallible despite the many pros, it's important to note its drawbacks. The bonds formed through adsorption might not be as strong as covalent bonds, which can impact the release kinetics of the encapsulated drug. In some cases, adsorption-based systems may exhibit burst releases, where a large amount of CBD is released rapidly, followed by a slower, less controlled release. This can affect the timing and precision of drug delivery, particularly when consistency is crucial for therapeutic efficacy [79]. These encapsulation methods address the challenges associated with CBD, such as its poor solubility in water, susceptibility to environmental factors, and limited bioavailability. The encapsulation enhances the solubility of CBD, facilitating its dispersion in aqueous solutions. It also protects CBD from premature degradation, thus increasing its stability. Moreover, encapsulation promotes higher bioavailability by facilitating efficient absorption in the body [80].

CBD is known for its poor water solubility as shown in Table 2 which can limit its effectiveness when administered orally. Encapsulation within CNDs can enhance the solubility of CBD, allowing it to disperse more readily in aqueous solutions [81]. CBD can be sensitive to environmental factors like light and heat, leading to degradation and a loss of potency. CNDs can act as protective shells, shielding the CBD from external factors and prolonging its stability. The encapsulation process can make CBD more bioavailable, meaning that the body can absorb and utilize it more efficiently. This can lead to increased therapeutic effectiveness. Depending on the encapsulation method, the release of CBD from CNDs can be controlled, allowing for sustained and controlled drug release over time [76].

CNDs decorated with tissue specific markers.

CNDs decorated with tissue-specific markers are a pioneering advancement in the realms of targeted drug delivery and medical imaging. These CNDs, characterized by their ultrasmall carbon nanoparticles, have been ingeniously engineered to serve as precision vehicles for therapeutic agents and diagnostic tools [82]. The crux of this innovative technique lies in the functionalization or "decoration" of CNDs with markers designed to selectively home in on distinct tissues or cells within the intricate landscape of the human body. The core objective behind adorning CNDs with tissue-specific markers is to achieve a level of precision in drug delivery and medical imaging that was previously unparalleled. These markers, carefully chosen for their specificity to particular tissues or cell types, bestow upon the CNDs the remarkable ability to navigate the intricate web of biological systems with a high degree of accuracy [83,84]. This precision is a game-changer in the field of drug delivery, as it substantially reduces the occurrence of off-target effects and the associated side effects.

CNDs embellished with tissue-specific markers are versatile tools that find applications not only in targeted drug delivery but also in the realm of medical imaging and diagnosis, Table 3 describes some specific cancer targeting molecules to use in decorating CNDs. When these nanostructures are equipped with markers designed to recognize and bind to specific tissues or disease-related biomarkers, they become invaluable assets in the detection and visualization of these elements. This

has far-reaching implications in the early diagnosis of diseases, the monitoring of treatment progress, and the guidance of surgical procedures [85]. The choice of tissue-specific markers is diverse and highly dependent on the intended application. Researchers can opt for a range of biomolecules as markers, including antibodies, aptamers, peptides, or small molecules. These markers have demonstrated their ability to selectively bind to cell surface receptors, disease-specific biomarkers, or other distinctive features of target tissues. The flexibility in marker selection ensures that the decorated CNDs can be tailored to the specific requirements of each application. The integration of tissue-specific markers into CNDs significantly amplifies the precision of drug delivery. By ensuring that drugs or therapeutic agents are delivered with pinpoint accuracy to the intended target, these CNDs dramatically reduce the risk of collateral damage to healthy tissues [86]. This level of precision is particularly essential in the treatment of conditions like cancer, where the selective targeting of cancer cells while sparing healthy ones is of paramount importance. One of the most compelling advantages of tissue-specific markers is their ability to minimize side effects. By limiting the exposure of therapeutic agents to nontargeted tissues, they effectively reduce the potential for side effects often associated with conventional systemic drug delivery. This targeted approach has the potential to enhance patient comfort and overall treatment outcomes, marking a significant leap in the field of medicine.

While the concept of decorated CNDs with tissue-specific markers is groundbreaking, the practical implementation and optimization can be complex. It necessitates careful marker selection, a profound understanding of the biodistribution of these CNDs, and the optimization of their size, surface properties, and stability. Researchers are continually working on refining these systems to cater to a wide array of clinical and research applications [87].

Targeted Drug Delivery: Targeted drug delivery has been a pivotal area of research in the quest to improve the precision and efficacy of therapeutic interventions. CNDs decorated with tissue-specific markers represent a remarkable innovation in this field, offering the potential to address some of the long-standing challenges associated with drug delivery. Several studies and research works have underscored the significance of this approach and its profound implications for the medical field. The crux of targeted drug delivery using decorated CNDs lies in minimizing off-target effects. Traditional drug delivery methods often result in the dispersion of therapeutic agents throughout the body, impacting not only the intended target but also healthy tissues. A study published by Smith et al., 2021 [88] highlights the impact of off-target effects on patient outcomes. By using tissue-specific markers, CNDs can be guided precisely to the intended site, reducing collateral damage to healthy tissues. Minimizing side effects is a central objective of targeted drug delivery, and decorated CNDs play a pivotal role in achieving this. A review by Zhou et al., 2020 [89] discusses the challenges associated with systemic drug delivery and the potential of targeted approaches. By utilizing tissue-specific markers, CNDs can significantly reduce the exposure of nontargeted tissues to therapeutic agents, thereby mitigating side effects. Targeted drug delivery with decorated CNDs holds the promise of substantially improving the therapeutic efficacy of drugs. Wang et al., 2019 [90] also emphasizes the impact of precision targeting on therapeutic outcomes. By ensuring that drugs are delivered specifically to the intended site, CNDs can enhance the efficacy of treatments. This has profound implications for conditions such as cancer, where precise drug delivery is of paramount importance.

The concept of personalized medicine, where treatments are tailored to individual patients, is an evolving paradigm in healthcare. Jones et al., 2021 [91] delves into the potential of targeted drug delivery for personalized treatment. By employing tissue-specific markers, decorated CNDs facilitate the customization of drug delivery strategies, ensuring that treatment is aligned with the unique characteristics of each patient. It is essential to recognize that the field of targeted drug delivery with decorated CNDs is continually advancing. A comprehensive review by Pillai et al., 2022 [92] highlighted the progress made in this domain. Ongoing research endeavors are focused on optimizing marker selection, nanodot properties, and understanding biodistribution, which will further refine the precision and effectiveness of these systems.

Table 3. Specific cancer targeting molecules to use in decorating CNDs.

| Targeting Molecule | Targeted Biomarker(s) | Cancer | Targeted Cancer Type(s) | References |
|----------------------------------|--------------------------------|-------------|--|------------|
| Monoclonal Antibodies | HER2, CD20, EpCAM, PSMA, CD133 | EGFR, | Breast cancer, lymphomas, various solid tumors | [93,94] |
| Aptamers | EGFR, PSMA | PD-1, MUC1, | Lung cancer, melanoma, prostate cancer, ovarian cancer | [95,96] |
| Peptides | RGD, CD44, CD133 | | Various solid tumors, breast cancer, glioblastoma | [97,98] |
| Folic Acid (Folate) | Folate Receptors | | Ovarian cancer, lung cancer, brain tumors | [99] |
| Transferrin | Transferrin Receptors | | Brain cancer, leukemia, lymphoma | [100] |
| Antigen-Binding Fragments (scFv) | EGFR, EpCAM, CD133 | | Head and neck cancer, colorectal cancer, liver cancer | [101,102] |
| Hyaluronic Acid | CD44 | | Breast cancer, ovarian cancer, pancreatic cancer | [103] |
| Glycyrrhetic Acid | Glycyrrhetic Receptors | Acid | Hepatocellular carcinoma | [104] |
| PSMA Ligands | PSMA | | Prostate cancer | [105,106] |
| CD133-Targeting Peptides | CD133 | | Various solid tumors, cancer stem cells | [107] |

These targeting molecules are selected based on the specific biomarkers or receptors overexpressed on cancer cells and are essential for the precise delivery of drugs to the intended cancer sites.

Imaging and Diagnosis: Decorated CNDs, enriched with tissue-specific markers, offer multifaceted applications in the realm of medical imaging and diagnosis. Their potential to revolutionize disease detection, monitor treatment effectiveness, and guide surgical interventions is supported by a growing body of research and studies. Early detection is often pivotal in the effective management of diseases. In this context, CNDs decorated with tissue-specific markers have demonstrated promise. Gutiérrez-Gálvez et al., 2021 [108] tackled the essence of early diagnosis using nanodot-based imaging. By specifically targeting tissues or biomarkers associated with a particular disease, these decorated CNDs enable the early identification of pathological changes, potentially improving patient outcomes. Monitoring how a disease or condition responds to treatment is crucial for healthcare professionals and patients alike. Decorated CNDs have implications in this aspect as well, some markers decorated on CNDs for diagnosis purpose are listed in Table 4. Furthermore, Kakodkar et al., 2023 [109] discusses the role of targeted imaging in tracking treatment progress. By utilizing tissue-specific markers, CNDs can provide real-time insights into how a disease is responding to therapy, enabling timely adjustments and personalized treatment plans. Precision in surgical procedures is fundamental to minimizing invasiveness and complications. Decorated CNDs can assist in this precision. A case study published by Garcia et al., 2020 [110] exemplifies the use of targeted CNDs for guiding surgical interventions. By binding to specific tissues or biomarkers, these CNDs can serve as navigational aids for surgeons, ensuring that procedures are precisely directed to the intended sites. Disease-specific biomarkers are at the forefront of modern diagnostic and imaging approaches. Afzal et al., 2022 [111] underscores the significance of biomarkers in diagnostics.

Decorated CNDs, functionalized to recognize and bind to these biomarkers, open up avenues for highly specific and sensitive disease detection. Decorated CNDs hold substantial potential for the future of non-invasive diagnosis. Musa et al., 2023 [112] anticipates the continued growth of this field. The ability of decorated CNDs to non-invasively visualize and diagnose diseases promises to transform the healthcare landscape by enabling earlier and more accurate diagnoses.

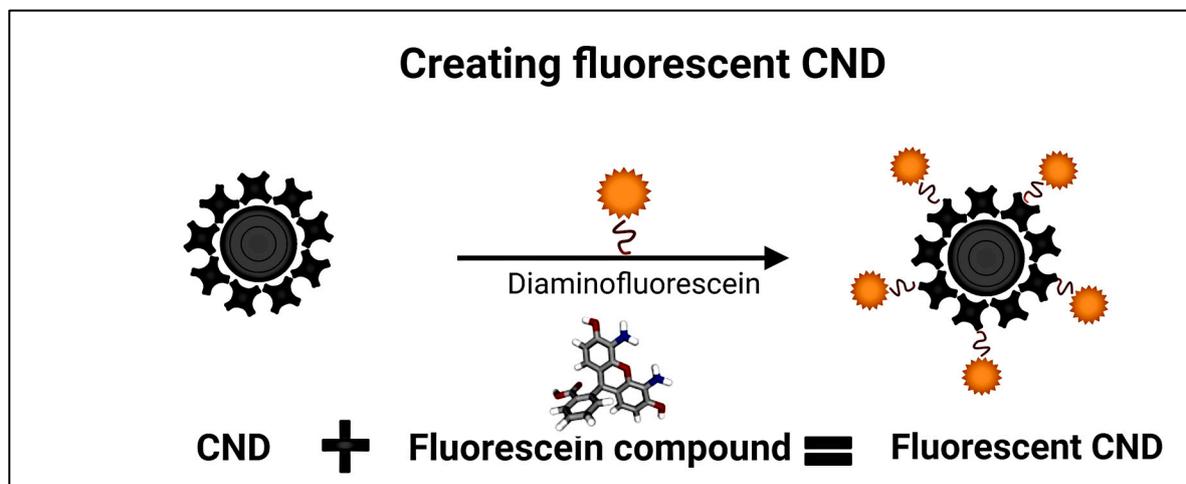


Figure 4. a: Fluorescent compounds such as diaminofluorescein can be functionalized to CND, thus making CND a fluorescent agent to ensure tracking and diagnosis both in in vitro assays or for in vivo studies.

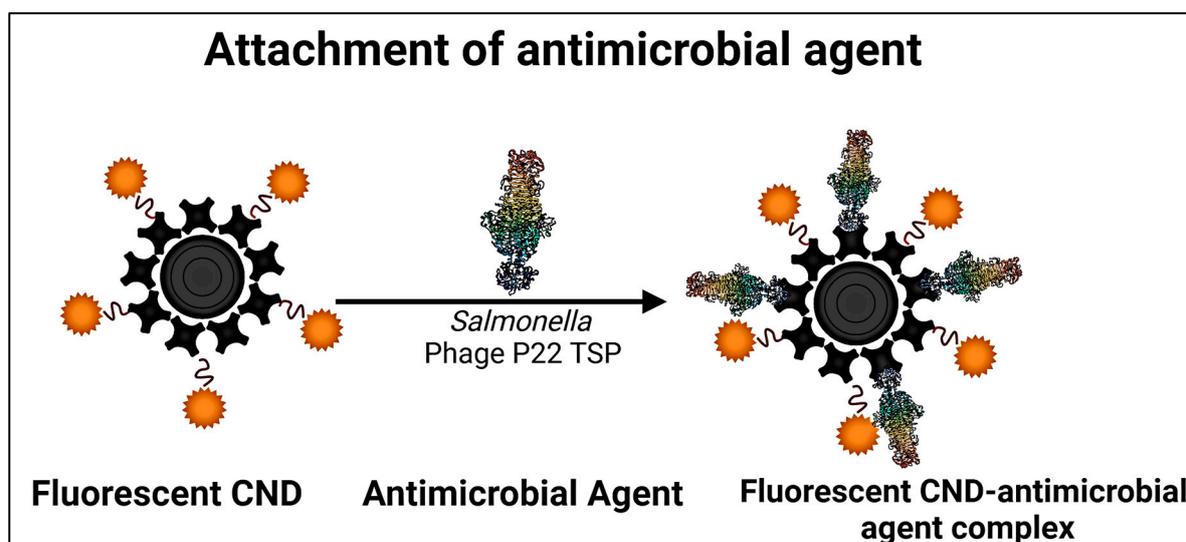


Figure 4. b: Fluorescent CND can again be complexed to an antibacterial (e.g., the tailspike protein (TSP) of the P22 phage, antiparasitic or antiviral agent thus enhancing a real time monitoring of the antimicrobial activity of the formulation both in in vitro assays and for in vivo studies.

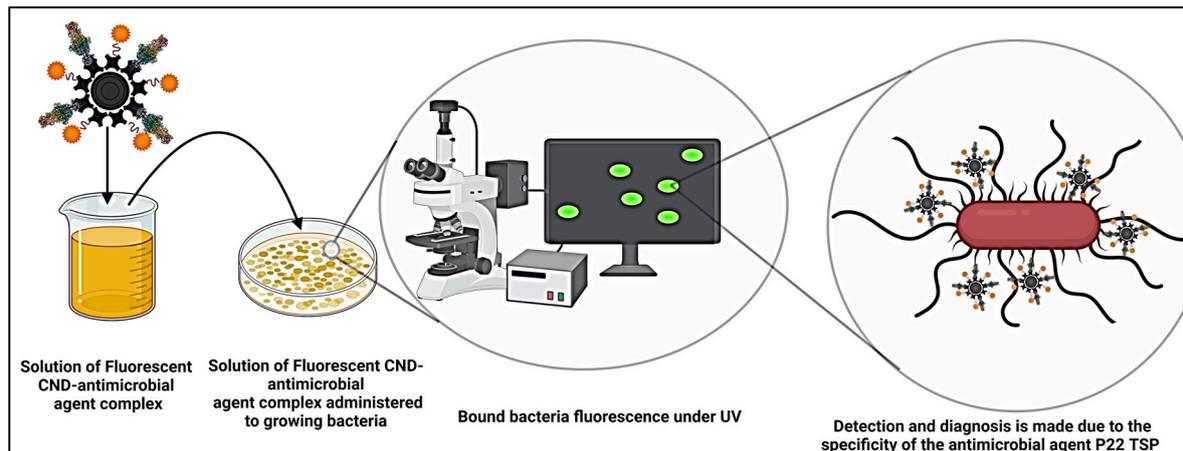


Figure 4. c: Using CND complexed to tailspike protein of P22 phage as a diagnostic tool for *Salmonella*. The P22 TSP has been demonstrated to show antibacterial activity against *Salmonella*, via the direct binding of the TSP to the LPS of *Salmonella*, thus complexing P22 TSP to the fluorescent CND and then administering this formulation to mixture containing *Salmonella* will enhance the visualization and diagnosis of *Salmonella* when the bacteria bind the TSP-CND complex. The visualization can be carried out using a fluorescence microscope.

Diverse Marker Selection: The selection of tissue-specific markers for decorating CNDs is a critical aspect of this innovative approach. The diversity in marker selection is one of the key strengths of this technique, offering versatility and adaptability to different applications. Monoclonal or polyclonal antibodies are commonly used as tissue-specific markers. These proteins can be highly specific, binding to unique antigens or receptors on the surface of target cells or tissues. Antibodies have been extensively employed in various medical and scientific fields for their precision. Aptamers are single-stranded DNA or RNA molecules that can bind specifically to a wide range of targets, including proteins, small molecules, or even whole cells [113]. They are selected through a process called systematic evolution of ligands by exponential enrichment (SELEX). Their versatility and ease of modification make them valuable markers for various applications. Short peptide sequences can be designed or selected to recognize specific cell surface receptors or biomarkers. Peptides offer the advantage of being smaller than antibodies, potentially providing better tissue penetration, and can be chemically synthesized with relative ease. Small organic molecules, such as ligands or receptor-specific compounds, can also serve as tissue-specific markers [114]. These molecules are designed to interact with specific cell surface components, providing a targeted approach to binding. Nanobodies, also known as VHH antibodies, are a type of antibody fragment derived from camelid species. They offer the advantage of being smaller than traditional antibodies, making them suitable for certain applications. Some tissue-specific markers are designed not only to bind to target tissues but also to facilitate the cellular internalization of the decorated CNDs. These peptides can enhance the uptake of therapeutic or imaging agents [115].

Table 4. Markers decorated on CNDs for diagnosis purposes.

| No. | Marker | Diagnostic Application | References |
|-----|-------------------------------|--|------------|
| 1 | Epidermal Growth Factor (EGF) | Detection and diagnosis of various cancers, including lung and breast cancers. | [116]. |
| 2 | Folic Acid (Folate) | Targeted drug delivery and imaging in cancer diagnosis. | [117]. |
| 3 | Aptamer AS1411 | Diagnostic and therapeutic applications in leukemia and other cancer types. | [118]. |

| | | | |
|---|----------------------------|--|--------|
| 4 | Herceptin (Trastuzumab) | Detection of HER2-positive breast cancer for personalized medicine | [119]. |
| 5 | Anti-PSMA Antibodies | Prostate-specific membrane antigen (PSMA) targeting in prostate cancer diagnosis. | [120]. |
| 6 | Anti-CEA Antibodies | Carcinoembryonic antigen (CEA) targeting in colorectal cancer diagnosis. | [121]. |
| 7 | Anti-HER2 Antibodies | Human epidermal growth factor receptor 2 (HER2) detection in breast and gastric cancers. | [122]. |
| 8 | Anti-EGFR Antibodies | Epidermal growth factor receptor (EGFR) targeting in various cancers. | [123]. |

These markers, when decorated on CNDs, play a crucial role in enhancing the accuracy and specificity of diagnosis in various medical conditions, particularly in cancer detection.

The choice of marker depends on the exact goals of the application, the target tissue or cell type, and the desired level of specificity. Researchers often conduct thorough screening and testing to identify the most suitable markers for their particular needs. This diversity in marker selection underscores the adaptability and potential of decorated CNDs in various medical and scientific applications.

Enhanced Precision: The incorporation of tissue-specific markers into drug delivery systems represents a significant advancement in enhancing the precision of therapeutic interventions. This enhanced precision is particularly valuable in the context of targeted drug delivery, as it ensures that medications or therapeutic agents are precisely guided to their intended destination within the body [124].

Tissue-specific markers enable the selective targeting of particular tissues, cells, or even disease-specific biomarkers. These markers recognize and bind to unique receptors or antigens on the surface of the target, guiding the drug-loaded CNDs with high specificity. Conventional drug delivery systems often result in off-target effects, where medications affect healthy tissues and cells along with the intended diseased area. The use of tissue-specific markers mitigates this problem by ensuring that a higher proportion of the drug reaches the target, reducing collateral damage to healthy tissues. By reducing off-target effects, the risk of side effects associated with drug therapy is also minimized [125]. Patients are more likely to tolerate treatments well when side effects are reduced, which can lead to better treatment adherence and overall outcomes. Enhanced precision in drug delivery means that a more significant portion of the therapeutic agent reaches the disease site. This can lead to improved treatment effectiveness and faster therapeutic responses, which is particularly critical in the management of conditions where disease progression can be rapid. When drugs are accurately delivered to their intended targets, lower dosages may be required to achieve the desired therapeutic effects. This can help reduce the risk of toxicity and the overall cost of treatment. The use of tissue-specific markers allows for a degree of personalization in treatment [126]. By tailoring the markers to the patient's specific disease or genetic profile, treatments can be customized for maximum effectiveness. The precise targeting facilitated by tissue-specific markers is of great significance in cancer therapy. It enables the selective delivery of chemotherapeutic agents to cancer cells while sparing healthy tissues, reducing the debilitating side effects often associated with cancer treatments. This level of precision also opens the door to emerging therapeutic modalities, such as gene therapies and immunotherapies. These advanced treatments rely on the accurate delivery of genetic material or immune-based agents, and the use of tissue-specific markers plays a vital role in their success [127].

Reduced Side Effects: One of the most compelling advantages of incorporating tissue-specific markers into drug delivery systems is the significant reduction in side effects, resulting in an improved overall experience for patients and more successful treatment outcomes. Conventional drug delivery methods often result in side effects that can range from mild discomfort to severe adverse reactions. These side effects can include nausea, fatigue, gastrointestinal disturbances, hair

loss, and a range of other symptoms [128]. By delivering medications more precisely to the target tissues or cells, tissue-specific markers minimize the exposure of healthy tissues to the drug. As a result, patients experience fewer of these adverse effects, leading to enhanced comfort and quality of life during their treatment. Reduced side effects make it more likely that patients will tolerate their treatment regimen effectively. Figure 5a, b and c show CBD encapsulated CNDs and their targeted sites thus reducing possible side effects. CBD encapsulated CND decorated with specific ligands can be used to passively target cancer cells via the circulatory system (Figure 5c) or carry out active targeting (Figure 5b) when the CBD encapsulated CND decorated with specific ligands are used to actively target specific cancer cells, which activates the GPCR on the surface of the cancer cells to induce the internalization of the CBD containing CND, thus directly enforcing the killing of the cancer cells with the CBD payload. This process eliminates indirect targeting thus reducing side effects of CBD administration.

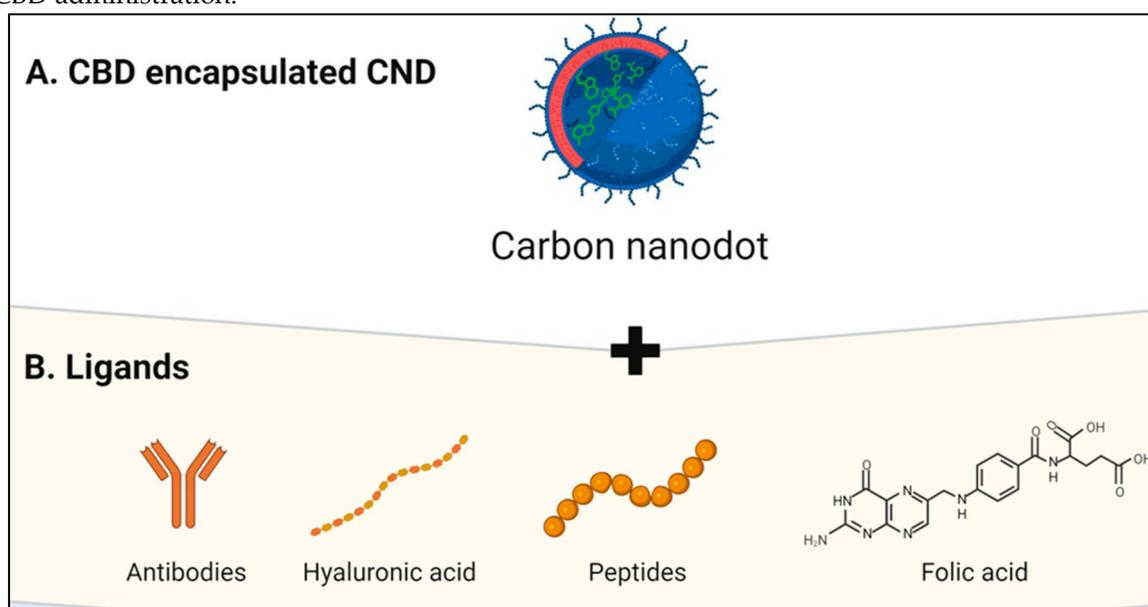


Figure 5. a: CBD encapsulated CND decorated with specific ligands (e.g., antibodies, peptides, hyaluronic acid, folic acid) can be used to target different tumor-types.

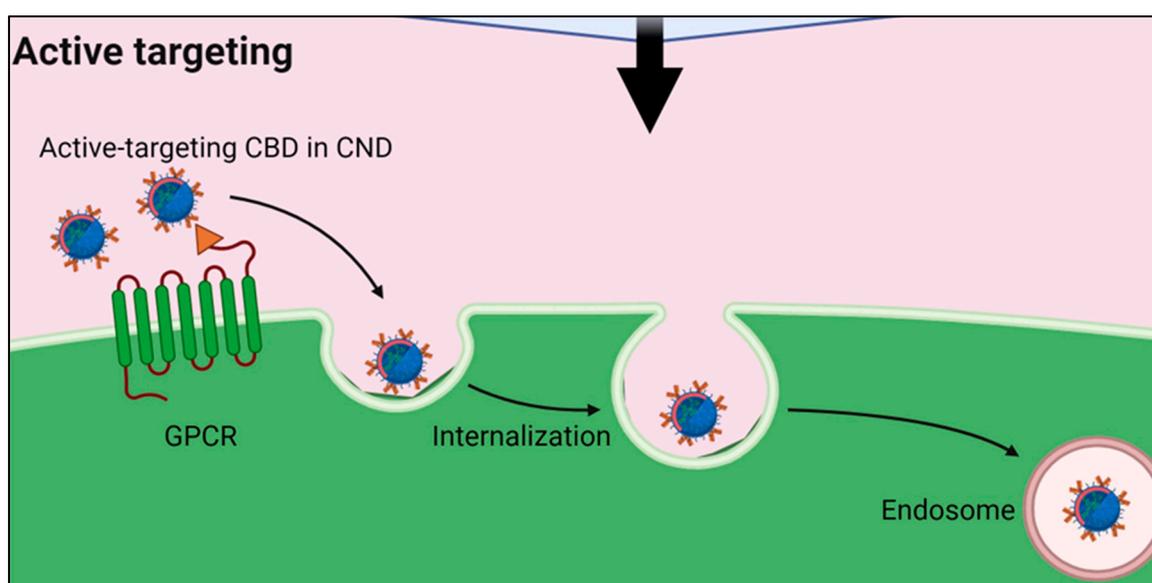


Figure 5. b: CBD encapsulated CND decorated with specific ligands can be used to actively target specific cancer cells, which activates the GPCR on the surface of the cancer cells to induce the

internalization of the CBD containing CND, thus directly enforcing the killing of the cancer cells with the CBD payload.

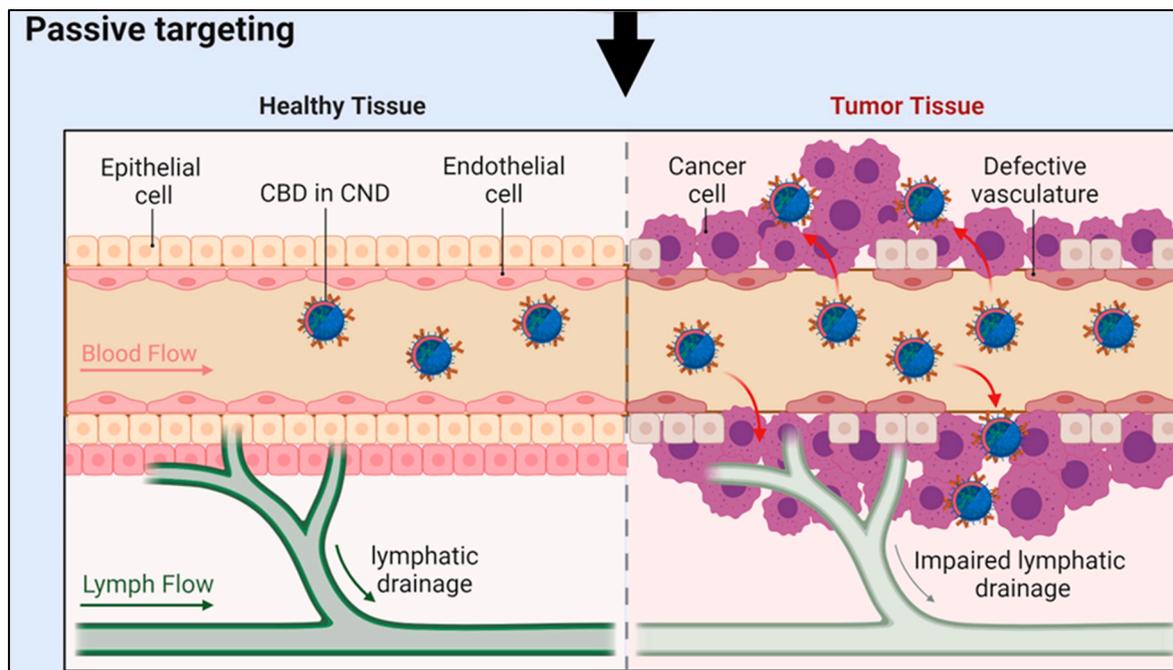


Figure 5. c. CBD encapsulated CND decorated with specific ligands can be used to passively target cancer cells via their circulation in the blood. When the formulation reaches a tumor microenvironment, the CND containing the CBD payload binds to the cancer cells and subsequently releasing CBD into the tumor microenvironment. The CBD in turn exerts its anticancer activity thus killing cancer cells. However, in a normal healthy individual, CBD containing CNDs are cleared out of the system via the normal excretory mechanism of the body. .

When the formulation reaches a tumor microenvironment, the CND containing the CBD payload binds to the cancer cells and subsequently releasing CBD into the tumor microenvironment. The CBD in turn exerts its anticancer activity thus killing cancer cells. However, in a normal healthy individual, CBD containing CNDs are cleared out of the system via the normal excretory mechanism of the body. When the side effects of medication are severe, patients may discontinue or modify their treatment, potentially compromising the therapeutic efficacy. In contrast, the use of tissue-specific markers allows for the administration of therapeutic agents with significantly fewer side effects, increasing the likelihood of treatment adherence and success. Many medications can lead to complications in patients, especially those with pre-existing health conditions [129]. Tissue-specific markers help mitigate these complications by delivering the drug primarily to the affected area, minimizing the risk of systemic complications. This is particularly valuable in situations where patients may already have compromised health due to their underlying medical condition. The reduction in side effects also aligns with the principles of personalized medicine, where treatments are tailored to individual patient characteristics. By minimizing side effects, patients can receive treatments that are better suited to their unique needs and health profiles. This leads to more patient-centric care and improved therapeutic outcomes. Ultimately, the decrease in side effects enhances the overall quality of life for patients undergoing treatment. Patients can maintain a better sense of well-being, maintain their daily activities, and experience less disruption to their lives during the course of therapy. This is especially important for individuals facing long-term or chronic diseases that require ongoing treatment [130].

Challenges and Optimizations: The integration of decorated CNDs with tissue-specific markers presents a promising approach, but it is not without its challenges and complexities. Researchers in the field face a range of obstacles, and ongoing efforts are directed at optimizing these systems for

diverse clinical and research applications. The selection of tissue-specific markers is a crucial initial step, and it can be challenging [131]. Markers can vary in terms of their specificity, affinity, and suitability for different applications. Researchers need to consider factors such as the target tissue or cell type, the stability of the markers, and their compatibility with the nanodot system. Understanding the biodistribution of decorated CNDs is essential. Researchers aim to ensure that CNDs reach the intended target tissues efficiently. Achieving a balance between systemic circulation and target-specific accumulation is a complex task that requires careful optimization. The properties of CNDs, including their size, surface properties, and stability, play a critical role in the success of the decorated nanodot system. The size of the CNDs can influence factors such as circulation time, cellular uptake, and clearance. Surface properties, such as charge and functional groups, can impact interactions with target tissues. Stability is vital to prevent premature degradation or aggregation during circulation. Ensuring that tissue-specific markers remain functional and maintain their binding affinity when attached to CNDs is a challenge. Optimization efforts focus on preserving the integrity and functionality of the markers while they are conjugated to the CNDs [132]. The translation of decorated CNDs from research settings to clinical applications is a multifaceted challenge. Regulatory approvals, safety assessments, and scale-up production processes must be addressed for these systems to benefit patients on a broader scale. Effective optimization often requires collaboration between experts from various fields, including materials science, chemistry, biology, and medicine. Multidisciplinary teams work together to design and refine decorated nanodot systems for specific applications. Tailoring decorated CNDs for individual patients or specific medical conditions is an emerging challenge. Achieving a high degree of customization while maintaining cost-effectiveness and efficiency is an ongoing area of exploration. The safety and toxicity profiles of decorated CNDs need to be comprehensively studied. Research is aimed at ensuring that these systems do not pose risks to patients, and toxicity remains minimal. Clinical studies are essential to validate the efficacy and safety of decorated CNDs in real-world medical scenarios. This phase of research is vital to assess the true potential of these systems in improving patient care [133].

Comparative Analysis for Drug Loading Methods

When determining the optimal method for loading CBD onto CNDs, a comprehensive comparative analysis is crucial. Each loading method—physical encapsulation, covalent bonding, and adsorption—comes with its unique set of benefits and disbenefits. The selection of the most suitable method depends on various factors, including the characteristics of the drug, the properties of the carrier system, the desired release kinetics, and the intended therapeutic outcomes [134].

In the case of drug properties, CBD, plays a significant role in method selection. If CBD is sensitive to chemical modifications or requires precise control over release, covalent bonding might be the preferred choice. On the other hand, if CBD's properties allow for physical encapsulation or adsorption without degradation or loss of therapeutic efficacy, these methods could be more convenient. The properties of the CNDs, including their surface characteristics, chemical reactivity, and compatibility with different loading methods, are critical considerations. Covalent bonding relies on the presence of suitable functional groups on the CNDs, while physical encapsulation and adsorption may have fewer surface requirements [135]. The choice depends on the compatibility between the drug and carrier.

The desired release kinetics for CBD must be evaluated. If a sustained and controlled release is essential for therapeutic success, covalent bonding may be the preferred option. Physical encapsulation can provide some level of controlled release, while adsorption methods may lead to less predictable release kinetics. The final decision should align with the desired therapeutic outcomes [136]. For conditions where precise dosing and controlled release are vital, covalent bonding is advantageous. In contrast, applications where a simpler loading process and high drug payload are acceptable may favor physical encapsulation or adsorption techniques. Additionally, the complexity of each method should be considered in the context of available expertise. Covalent bonding is more intricate and may require specialized knowledge in chemical modification, while

physical encapsulation and adsorption are more straightforward and accessible to a broader range of researchers. If avoiding significant chemical modifications to the drug and carrier is a priority, physical encapsulation and adsorption methods may be more appropriate. Also, if a high drug payload is required, adsorption methods may be preferable due to their high loading capacity [137].

Drug Loading Efficiency

Here, we will delve into the paramount aspect of drug loading efficiency, which is basic in assessing the performance of the CNDs as drug carriers. The analytical methods employed here will provide a quantitative understanding of the amount of CBD loaded onto the CNDs and the efficacy of the chosen drug loading method.

Precise quantitative analysis is essential for assessing the amount of CBD successfully loaded onto the CNDs. This is typically measured in milligrams (mg) and allows researchers to ascertain the absolute drug loading capacity of the CNDs. By precisely determining the quantity of CBD loaded, it becomes possible to evaluate the CNDs' ability to accommodate the drug payload effectively [138]. Percentage loading efficiency is another crucial metric that provides a standardized measure of how efficiently the drug loading process will be executed. This metric is valuable as it accounts for the initial amount of drug used in the loading process. It is calculated by comparing the quantity of CBD effectively loaded onto the CNDs to the total amount of drug initially introduced. This analysis helps evaluate the overall efficiency of the chosen drug loading method, offering insights into how effectively the CNDs serve as drug carriers [139].

The loading efficiency is calculated as follows,

Percentage Loading Efficiency (%) = (Amount of Substance Loaded / Initial Amount of Substance) x 100

"Amount of Substance Loaded" refers to the quantity of CBD that has been successfully loaded into CNDs.

"Initial Amount of Substance" is the total amount of CBD started with before the loading process. You multiply the result by 100 to express the loading efficiency as a percentage. This percentage indicates how efficient the loading process is in terms of transferring the substance into the carrier system (CNDs).

The drug loading efficiency data will be instrumental in gauging the performance of the drug loading process. It provides essential information about the capacity of CNDs to serve as effective drug carriers and how well they can accommodate the CBD payload. High loading efficiency signifies that the majority of the CBD introduced into the system is retained within the CNDs, which is a desirable characteristic for an efficient drug delivery system [140].

Challenges and Potential Solutions

Stability and Long-term Storage

Ensuring the long-term stability of CBD-loaded CNDs is a crucial concern. CBD is sensitive to environmental factors such as light, heat, and moisture, which can lead to degradation and loss of potency over time. This is particularly challenging as the effectiveness of the drug delivery system relies on maintaining the integrity of both the CBD payload and the CNDs [141]. To address this challenge, advanced nanoparticle engineering techniques can be employed to enhance the stability of CNDs. One approach is to develop protective coatings or encapsulation methods that create a barrier around the CBD molecules within the CNDs. These protective layers can shield the encapsulated CBD from external factors that may cause degradation. Extensive stability testing should be conducted under various conditions, including exposure to temperature variations and humidity levels. These tests are vital in assessing the long-term performance of the CBD-loaded CNDs and can guide the development of appropriate storage recommendations. Furthermore, the development of specialized packaging that limits exposure to environmental factors during storage can be explored. Robust stability protocols can ensure that the drug delivery system remains effective

over an extended period, providing a reliable and practical solution for CBD storage and administration [142].

Safety and Toxicity Concerns

The safety of any drug delivery system is paramount. Ensuring that CBD-loaded CNDs are biocompatible and do not exhibit adverse toxic effects is essential for their clinical translation. Safety concerns can include potential cytotoxicity, genotoxicity, immunotoxicity, and other undesirable effects [143]. To curb these concerns, comprehensive biocompatibility and toxicity studies are crucial. These studies should encompass both in vitro and in vivo experiments to evaluate the safety profile of the delivery system. In vitro studies can assess how the CBD-loaded CNDs interact with human cells and whether they induce any cytotoxic effects. Genotoxicity, which relates to damage to the genetic material within cells, should also be examined. Additionally, in vivo studies involving live organisms can provide insights into potential immunotoxicity and systemic effects [144]. Compliance with regulatory guidelines and adherence to safety standards for nanoparticle-based drug delivery systems are vital throughout the development process. By conducting rigorous safety assessments, developers can ensure that the CBD-loaded CNDs meet the necessary safety criteria for clinical use, mitigating potential risks and concerns [145].

Regulatory Aspects

Navigating the regulatory landscape for novel drug delivery systems can be a complex and time-consuming process. Ensuring compliance with regulatory requirements, which may vary by region, can be a significant challenge. In curbing this, early engagement with regulatory agencies is essential [146]. Establishing open lines of communication and understanding their specific requirements can facilitate the regulatory pathway. To support regulatory submissions, compile comprehensive preclinical and clinical data demonstrating the safety and efficacy of CBD-loaded CNDs. Collaborating with experts in regulatory affairs can provide valuable insights and guidance throughout the approval process. Clear and transparent communication with regulatory authorities is important for a successful regulatory pathway, ensuring that the drug delivery system complies with all necessary regulations and standards, and can be safely used for therapeutic purposes [147]. The scientific knowledge base of CBD utility as an antibacterial agent [148–150] coupled with its anticancer, antiepileptic properties should enhance its appeal in the face of the governing regulatory agencies.

Conclusion

The journey through the synergy of CBD-loaded CNDs has revealed a compelling narrative of enhanced drug delivery. The combination of CNDs and CBD offers an innovative solution to long-standing challenges in drug delivery, particularly addressing issues of solubility, stability, and bioavailability. The coalescence of these two entities unleashes the full therapeutic potential of CBD for a variety of medical conditions. The mechanisms of synergy encompass improved solubility, controlled drug release, and protection against degradation, ultimately enhancing the therapeutic effects of CBD. CBD-loaded CNDs display a favorable safety profile, with biocompatibility, low toxicity, and a versatile range of application methods. The therapeutic applications of this phenomenon are vast. From effective pain management and neurological disorder treatment to controlling inflammation, this approach promises breakthroughs in various medical fields.

The synergy of CBD and CNDs offers precise dosing, ensuring the right amount of the drug reaches its target. This results in higher efficacy and lower side effects. CNDs improve the solubility of CBD, increasing its bioavailability and, consequently, its therapeutic impact. The sustained-release properties of CNDs can extend the therapeutic effects of CBD, making it a potent ally in the management of chronic conditions. Touring the novel applications for CBD-loaded CNDs, including cancer treatment, mental health disorders, cardiovascular health, and precision medicine, holds promise for diverse patient populations. Bridging the gap between laboratory discoveries and clinical

applications through interdisciplinary collaborations is pivotal for translating these innovative solutions into practical therapies. Ongoing discussions with regulatory agencies are crucial to navigate evolving regulations and ensure safe and effective use.

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