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HERBAL MEDICINE MEDIATED CARBON DOTS - CURRENT STATUS AND FUTURE TREND

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ABSTRACT

Interest in using herbal medicine as a precursor for the synthesis of carbon dots (CDs) in growing fast with their unique properties and applications in various fields. There has been an extensive increase in the selection of raw materials for synthesizing carbon dots, and herbal medicine is receiving more attention as a precursor. Herbal medicine-derived carbon dots (HM-CDs) are described as a relatively recent addition to the family of carbon dots, indicating that their use is gaining popularity in the past decade. HM-CDs are noted for their potential in theranostics, which refers to the combination of diagnostics and therapeutics in one system. The unique aspect mentioned is that they can achieve theranostic functions without the need for drug loading. Despite growing interest in HM-CDs there is still a lack of systematic examination of the relevant developments and research results. This suggests a need for comprehensive analysis and consolidation of the existing knowledge. Main objective of this chapter is to provide an overview of the origin and history of HM-CDs, emphasizing their functional properties in medical diagnosis and treatment. An attempt has been made to categorize herbal medicine precursors and analyse the primary methods of synthesizing HM-CDs and their key characteristics. The applications of HM-CDs include medical therapeutics, ion, and molecular detection, bioimaging, and pH sensing which suggests that HM-CDs have a wide range of potential applications in the medical field. Finally, the passage indicates that it will discuss the crucial challenges and prospects for HM-CDs, suggesting that there are ongoing research and development opportunities in this area.

KEYWORDS: Herbal medicine, Carbon dots, Synthesis, Theranostics, Bio-medical applications.

1. INTRODUCTION

Carbon dots (CDs) are nanomaterials < 10 nm that were initially discovered by Scrivens in early 2004. These emerging nanomaterials are noted to have a combination of qualities from traditional semiconductors (inorganic quantum dots) and small molecules (fluorophores). They also exhibit unique properties like photobleaching resistance, photostability, good biocompatibility, and stable physicochemical characteristics. These properties make them useful in various applications, especially in the field of biomedical theranostics.

There are various precursors that have traditionally been deployed in synthesizing CDs. However, these chemical-based syntheses often involve toxic products, which can ultimately hinder their clinical applications. To address the toxicity issue, researchers are exploring green, biomass-based precursors as alternatives possessing lower toxicity, abundant heteroatoms (atoms other than C and H), and good biocompatibility. Many CDs derived from green precursors have been found possessing promise in applications like anti-tumour therapy and antimicrobial agents.

Despite the advantages of green-CDs, they still have limitations, particularly in case of drug loading, which can be a complex process with unpredictable efficiency. The herbal medicines, on the other hand, are considered ideal green precursors for CDs. Medicinal herbs are natural products with high availability and relatively lower toxicity. They are also rich in active components, making them suitable for the acquisition of heteroatoms, which is crucial for biomedical applications. Herbal medicine is highlighted as a direct avenue for acquiring heteroatoms, enabling them with theragnostic features without complex drug delivery systems. CDs derived from herbal medicine (HM-CDs) have gained significant attention in the recent years due to these characteristics.

It has, however, been noted that there is currently no systematic discussion or review of the general knowledge of HM-CDs, indicating a gap in the existing

literature. The basic purpose of the current chapter is to highlight the merits of HM-CDs to suggest that it will provide a comprehensive overview of this emerging field of research.

The concept of CDs has been introduced above by enumerating their unique properties, the shift towards green precursors, and the specific focus on HM-CDs for potential applications in biomedical theranostics, emphasizing the need for their systematic exploration and review. The related descriptions are also mentioned in more detail in the enclosed references [Atabaev, **2018;** Wang, and Tang, **2018**; Zhang, et al, **2018**; Anand, et al, **2019;** Devi, et al, **2019**; Du, et al, **2019**; Kang, and Lee, **2019;** Loczechin, et al, **2019;** Ma, et al, **2019**; Shi, et al, **2019**; Ashrafzadeh, et al, **2020;** Caglayan, et al, **2020**; Cui, et al, **2020**; Dong, et al, **2020**; Pan, et al, **2020**; Tejwan, et al, **2020**; Wang, et al, **2020**; Kumar, et al, **2020**; Radnia, et al, **2020;** Ansari, et al, **2021**].

2. DEVELOPMENT OF HERBAL NANOMEDICINE AT JAMIA HAMDARD

Before delving into the development of herbal medicine-mediated carbon nanodots, it's important to highlight the preceding work involving the development of nanoparticulate forms of herbal species to start with. This initiative took place around 2006 at Jamia Hamdard, Delhi, India, and involved a multidisciplinary approach to investigate the pharmaceutical properties of nanoparticulate formulations of commonly used ingredients in Unani Medicines. These basic ingredients included substances like turmeric, black pepper, Artemisinin, Berberine, Triphala (a combination of fruits from three tree varieties), and Kalaunji (Nigella sativa) to name a few to start with.

Researchers with adequate practical experiences of synthesizing inorganic and organic nano-formulations were entrusted with the task of producing a variety of material samples that were characterized using standard techniques to measure various parameters, including particle size, size distribution, zeta potential, SEM, TEM and XRD. Subsequently, animal trials were conducted based on standard FDA-approved protocols. The facilities and expertise for these characterizations were readily available in-house, owing to several ongoing research programs in different departments associated with targeted drug discovery and delivery from pharmaceutical nano-formulations.

The immediate observations noted from this modest but inquisitive approach of research confirmed the enhanced efficacy of each of these nano-formulations in animal trials. This revelation prompted a closer look at the enhanced efficacy of these nano-formulations for each specific herbal ingredient.

For example, the nanoparticulate formulation of Curcumin from Turmeric, Piperine from Piper nigrum (black pepper), Artemisinin derived from sweet wormwood (Artemisia annua), and berberine were found effective against several disease cells and demonstrated enhanced efficacies in different animal models. These models encompassed various diseases such as liver cirrhosis, ischemic brain damage, and leishmaniasis. Notably, the nanoparticulate samples of Kalaunji from Nigella sativa Linn. exhibited antibiotic properties that were three orders of magnitude superior to ampicillin, a standard antibiotic.

The remarkable outcomes of these herbal nanomedicine formulation research led to the conceptualization of a new discipline known as "herbal nanomedicine." This field was introduced to explore the use of nanotechnology to enhance the therapeutic properties of herbal remedies with promising innovative and potent solutions for a wide range of medical applications.

Having witnessed many nanoherbal formulation studied by the research teams from different schools of Pharmacy, Biochemistry, Industrial Chemistry in Jamia Hamdard in past one and half decade, it was natural to extend the work of herbal nanomedicines in the light of its possible applications in theranostic version as well by exploring the chemical conjugation of carbon nanodots after having success in synthesizing fluorescent carbon dots from different precursors. Attempts made in preparing carbon nanodots not only succeeded in preparing fluorescent CDs, but its conjugation also showed its utility of theranostic applications of herbal nanomedicines along with carbon nanodots.

2.1 Contemporary Development of Fluorescent CDs

Let us start with a brief history of HM-CDs followed by highlighting their development, synthetic methods, and applications in biomedicine. Water-soluble fluorescent CDs were synthesized using watermelon peel as a raw material way back in 2012. These CDs displayed strong blue luminescence and were applied in live cell imaging (HeLa cells). Watermelon peel was used to prepare these CDs, making them the first HM-CDs and the pioneering example of high-performance optical imaging probes. In 2014, HM-CDs were subsequently prepared from ginger, marking the first use of HM-CDs for cell intervention and disease treatment. It was found that these ginger-derived CDs, without drug loading, effectively inhibited human hepatocellular carcinoma cells and slowed tumour growth in nude mice. This marked the beginning of an era of herbal medicine-based disease treatment using CDs. The practical compatibility of herbal medicine is characterized by having multiple components, targeting multiple pathways, and exhibiting co-regulatory properties. This complexity makes herbal medicine an attractive choice for the development of novel therapeutic agents like HM-CDs.

The comparison of chemical-CDs, biomass-CDs, and HM-CDs in the context of biotherapy highlight the advantages and distinctions of HM-CDs in the field of biomedicine.

A historical perspective on HM-CDs involving their emergence as a tool for disease treatment, and their distinctive features in the context of herbal medicine suggests that the multi-component and multi-target nature of herbal medicine makes it a valuable resource for the development of therapeutic agents like HM-CDs, which have shown promise in various biomedical applications as discussed elsewhere [Becraft, et al, **2020**; Wang, et al, **2020**].

The synthesis of CDs, particularly HM-CDs was attempted using *Fermentata (Jiaoshenqu)* as the first herbal formula. Fermentata, known as Jiaoshenqu, is recognized as the first herbal medicine formula used for synthesizing HM-CDs. This development represents an important milestone in the utilization of herbal medicine in CD synthesis. JSX-CDs are emphasized as a noteworthy achievement in the realm of HM-CDs. JSX is a combination of various medicinal components, and the CDs derived from JSX are noted for having a more intricate surface composition and structure when compared to other herbal CD formulations. The majority of reported herbal precursors for HM-CDs are sourced from medicinal plants. These sources include different parts of the plants, such as roots, flowers, leaves, fruits, and seeds. These various plant parts contain diverse active components that play a crucial role in the synthesis of HM-CDs. Although acknowledging the presence of various active components in different plant parts used for HM-CD synthesis, it points out that there is a lack of detailed reports on the specific active ingredients of HM-CDs. This indicates that further research is needed to comprehensively understand the composition and properties of HM-CDs. The role of herbal medicine in the development of HM-CDs and how different parts of medicinal plants are utilized as precursors is highlighted. The complexity and diversity of these plant-based precursors make it necessary to go for more detailed research on the active ingredients and properties of HM-CDs.

The diverse sources for HM-CD precursors, the influence of heteroatom doping on physicochemical properties, and the potential of protein-rich animal drugs are also noted as valuable precursors. In addition to plants, other sources such as hair, honey, egg yolk oil, and mulberry silkworm cocoon have also been used as precursors for HM-CDs. This indicates a growing interest in exploring a wide range of herbal medicine sources, expanding beyond traditional plant-based materials.

The physicochemical properties of CDs are influenced by their structures and photoluminescence mechanisms, which are not fully understood. However, the role of surface state-derived luminescence, which includes surface defects and functional groups emphasize that heteroatom doping, involving elements like nitrogen, sulphur, boron, and metal atoms, is an effective way to engineer the fluorescent properties of CDs. This can result in increased fluorescence intensity that enhances the performance of the CDs.

Herbal medicines are described as rich sources of bioactive compounds, including polysaccharides, proteins, nucleic acids, and phospholipids. These compounds have abundant heteroatoms, such as carbon, hydrogen, nitrogen, and oxygen, which can contribute to the properties of HM-CDs. Importantly, these heteroatoms can be harnessed without the need for additional surface passivation or doping, simplifying the synthesis process.

The protein-rich animal drugs, which are abundant in elements like carbon, hydrogen, oxygen, and nitrogen, may serve as optimal precursors for HM-CD synthesis. The presence of these elements in the precursors can enhance the performance of the resulting CDs, making them valuable materials for specific applications. The diverse sources for HM-CD precursors, the impact of heteroatom doping on CD properties, and the rich chemical complexity of herbal medicines highlight the cumulative potential of these sources for generating unique HM-CDs with valuable properties, making them promising materials for various applications.

3. HM-CDs – Synthesis

There are two main categories of synthesizing CDs such as ‘top-down’ and ‘bottom-up’. Top-down methods involve breaking down larger particles to smaller ones physically and in contrast, bottom-up methods are favoured for being straightforward and cost-effective. The bottom-up methods include hydrothermal, solvothermal, pyrolysis, and microwave-based syntheses. Among these, the hydrothermal synthesis is highlighted as the greenest way to prepare HM-CDs.

3.1 Hydrothermal Synthesis

The hydrothermal synthesis starts with cutting and drying the materials into small pieces or powder followed by subjecting them to a hydrothermal reaction in a Teflon-lined stainless-steel autoclave. This method does not require the addition of organic matter and does not require additional passivation on the surface of CDs to ensure safety and minimum toxicity. The reaction temperature and time are critical factors that affect the physicochemical properties of HM-CDs. Extended studies have been conducted involving different reaction temperatures and times to understand the processes involved better. It notes that the fluorescence intensity, quantum yield (QY), and lifetime of CDs can vary based on these parameters.

The fluorescence intensity of CDs exhibits temperature-dependent behaviour. For example, higher reaction temperatures leading to increased molecular collision frequency, non-radiative transition rate, and constant radiative transition rate, affecting the CDs' fluorescence properties. CDs can potentially function as temperature sensors based on these characteristics.

It is noted from the experimental investigations that CDs derived from different medicinal parts and herbal species can exhibit distinctly different properties. This emphasizes the importance of understanding the source materials and their impact on the properties of the synthesized CDs. The above-described points provide insights into the hydrothermal method for preparing HM-CDs, including the synthesis procedure and the influence of reaction temperature and time on their properties. It underscores the importance of carefully controlling these parameters to tailor the properties of the synthesized CDs for specific applications. The precursor specific synthesis of HM-CDs resulting in varying features due to different herbal sources, particle size variations, and their potential to overcome biological barriers like the blood-brain barrier (BBB) are briefly described in the following.

The source of herbal medicine can significantly impact the properties of HM-CDs. For example, in a comprehensive investigation of synthesizing HM-CDs involving 14 different strains of orange peels, each varietiy of the peal exhibited different QY under the same condition of preparation. This observation suggested that QY may be associated with the amounts of volatile oils in the herbal source. Moreover, CDs prepared from different parts of the same herbal medicine also exhibit divergent performances. For example, HM-CDs from different parts of the same ginkgo tree showed significant differences in their QY possibly due to variations in their constituent compounds. The nanoscale size of HM-CDs, being less than 10 nm in diameter, enhances their permeability, particularly through the blood-brain barrier (BBB). It is also noted that HM-CDs may possess ultra-small size, abundant surface functional groups, and a strong affinity to the endothelial cell membrane of the BBB, potentially allowing for their passage through this barrier. The BBB permeability mechanisms including active and passive transport across the potential might cross the BBB due to their small size and functional groups, but further research is still needed to understand the molecular uptake mechanisms of HM-CDs. The potential of using HM-CDs as carriers for drug delivery to enable the transport of macromolecules across the BBB may be especially relevant for neurological disorders where herbal medicine is often prescribed. The high-temperature pyrolysis is another common approach for synthesizing CDs, where organic substances in the precursors are converted into CDs through heating and carbonization processes.

The role of the herbal source in influencing the physicochemical properties of HM-CDs, the importance of their nanoscale size, and their potential applications in drug delivery, particularly for neurological disorders, highlights the advantage of high-temperature pyrolysis as an alternative synthesis method. Most of these basic issues are included in the referred publications [Yan, et al, **2018;** Yu, et al, **2018;** Zhou, et al, **2018**; Li, et al, **2019**; Mohapatra, and Das, **2019**; Jiang, et al, **2019**; Pal, et al, **2019**; Sagbas, and Sahiner, **2019**; Wang, et al, **2019**; Xia, et al, **2019**; Xiong, et al, **2019**; Yan, et al, **2019;** Zhi, et al, **2019**; Dhenadhayalan, et al, **2020**; Kang, et al, **2020;** Kim, et al, **2020;** Sun, et al, **2020**; Surendran, et al, **2020;** Tejwan, et al, **2020**; Wang, et al, **2020**; Zhang, et al, **2020**; Zheng, et al, **2020**; Zheng, et al, **2020;** Zhu, et al, **2020**; Chen, et al, **2021**; Li, et al, **2021;** Zhang, et al, **2021**].

3.2 Pyrolysis

High-temperature pyrolysis-based synthesis of HM-CDs involves the organic substances present in the herbal medicine precursors to high temperatures in which they are gradually converted into CDs through a series of processes that include heating, dehydration, degradation, and carbonization. This transformation occurs under high-temperature conditions and controlled environment, such as a vacuum or inert atmosphere.

The high-temperature pyrolysis is considered as straightforward, solvent-free, low-cost, and suitable process for large-scale production. This method offers an efficient way to convert herbal medicine into purified HM-CDs. The steps of high-temperature pyrolysis method start by placing precursor in a crucible and heating at a specific temperature using a muffle furnace until it undergoes carbonization. The resulting charred herbal material is then crushed and boiled in deionized (DI) water. The upper liquid portion of the resultant solution is collected and filtered through a 0.22 μm microporous membrane, and the resulting solution is subjected to dialysis for several days to obtain purified HM-CDs.

3.3 Microwave Synthesis

Microwave synthesis is like pyrolysis but with certain advantages. Unlike pyrolysis, microwave synthesis allows for rapidly reaching the desired energy levels and ensures even heating of the precursors. Microwaves (1 mm to 1 m wavelengths) deliver energy to the precursors that leads to the cleavage of chemical bonds. This capability to break chemical bonds through energy makes microwave synthesis suitable for creating uniform HM-CDs. Microwave synthesis is noted for significantly reducing the reaction time during synthesis and improving its overall efficiency. The quick and even heating, along with the ability to break chemical bonds, contributes to these advantages. Alternately, microwave-assisted hydrothermal synthesis has also been attempted in place of traditional hydrothermal synthesis to enhance the process.

Microwave-assisted synthesis provides fast and even heating besides breaking the chemical bonds, making it a more efficient method for producing uniform carbon dots. It can be used as an alternative to both pyrolysis and hydrothermal synthesis, offering advantages in terms of response time and effectiveness as discussed in the enclosed references [Shen, et al, **2018;** Ghosal, and Ghosh, **2019;** Chung, et al, **2021].** The microwave

method could thus be considered as an ideal choice for HM-CD synthesis. Its features like short reaction times, high efficiency, and uniform heating make it well-suited for the rapid synthesis of large-scale HM-CDs.

3.4 Solvothermal Method

The solvothermal synthesis of CDs is a versatile method that allows using various solvents instead of water. The choice of solvent can have a significant impact on the properties of the resulting CDs, as highlighted in the following discussion. The solvothermal method is employed to synthesize CDs, and it offers the flexibility to use different solvents. An illustrative example involves the use of ethanol and water to prepare CDs from papaya, resulting in E-CDs and W-CDs, respectively. It is noted that the choice of solvent has a substantial influence on the properties of the CDs. Specifically, W-CDs synthesized using water displayed superior fluorescence stability. In contrast, E-CDs, which were synthesized in ethanol, exhibited larger particle sizes.

3.5 Comparison of Various Methods

Compared to hydrothermal synthesis, pyrolysis usually requires a higher reaction temperature (~300 ℃). Higher reaction temperature results in shorter reaction time. Dager, et al. prepared a mono-dispersed HM-CDs using the fennel seeds at a constant temperature of 500 °C for 3 h. These CDs were stored for up to 15 months and had excellent colloidal solubility, photostability and environmental stability. In the existing high-temperature pyrolysis, the minimum heating temperature is generally kept around 220 °C. Blue-light CDs are prepared with watermelon peel as a carbon source at this temperature and dissolve in several solvents. Another vital issue is the particle size of HM-CDs synthesized by both of the methods. Characterization studies point out that the hydrothermal synthesis produces narrower size distribution of CDs than those in case of pyrolysis with smaller particle sizes. The experimental results confirm the diameters of HM-CDs prepared by pyrolysis around 5 nm under the existing synthetic conditions. It represents no noticeable difference in the particle sizes of HM-CDs synthesized by the two approaches [Dager, et al, **2019**].

While examining the QY of CDs synthesized through different methods and using various carbon sources following points may be noted. The QY of CDs synthesized through pyrolysis is lower than that of CDs synthesized through hydrothermal methods. The reason for this difference is attributed to the diversity of carbon sources used in pyrolysis. In a specific example of CDs synthesized from lychee seeds showed a high QY of 10.60%, which is an exception to the generally lower QY in pyrolysis synthesis. *Schizonepetae Herba Carbonisata CDs (SHC-CDs)* exhibit the divergent results in two studies on SHC-CDs synthesized under the same conditions. One study reported an average size of 0.8-4.0 nm and a QY of 2.26%, while another reported an average size of 1.29–6.87 nm and a QY of 6.31%. This suggests that the synthesis of these CDs is unstable. Zhang et al., combined pyrolysis with microwave method to synthesize hair CDs with a high QY of 86.06%, which is significantly higher than the QY of citric acid CDs (19.73%). This combination of synthetic strategies appears to be promising and can lead to high-QY CDs. It is noted that skin CDs with a higher QY (51.35%) were prepared using protein-rich materials as precursors. This suggests that materials derived from animals used in herbal medicine may hold promise for the synthesis of high-QY CDs in the future as discussed in the enclosed references [Sun, et al, **2018**; Zhang, et al, **2018**].

To compare with other methods, detailed experiments were conducted to prepare CDs using two different approaches: hydrothermal (H-CDs) and microwave (M-CDs) methods. The results of these experiments revealed significant differences in terms of reaction time, particle size, and fluorescence properties.

The synthesis of M-CDs using the microwave method was notably faster, taking only 5-15 minutes, which is much shorter than the hydrothermal method. Additionally, the M-CDs had relatively smaller particle sizes compared to H-CDs. Despite the shorter synthesis time and smaller particle size, the fluorescence property of H-CDs was found superior to that of M-CDs. This difference in fluorescence can be attributed to two main factors. Firstly, H-CDs exhibited a more regular and uniform morphology, contributing to better fluorescence. Secondly, the luminescence mechanism in H-CDs played a crucial role in enhancing their fluorescence properties. H-CDs had a higher QY and a longer lifetime, resulting in a more robust and intense fluorescence intensity compared to M-CDs.

The microwave method demonstrated exceptional efficiency in preparing CDs derived from orange peel in as little as 1 minute, yielding up to 16.20%. These CDs displayed high green fluorescence and exhibited excitation-dependent emission fluorescence behaviour.

Overall, these results suggest that microwave synthesis may be superior to hydrothermal and pyrolysis methods in terms of both synthesis time and efficiency. However, despite these advantages, the microwave method remains less commonly utilized for the synthesis of HM-CDs.

The experimental studies highlight the contrasting advantages and limitations of hydrothermal and microwave methods for the synthesis of HM-CDs. While microwave synthesis offers faster production at higher efficiency, the hydrothermal method excels in terms of fluorescence properties, especially with regards to QY and fluorescence intensity. The choice of method may depend on the specific application and desired properties of the CDs being synthesized as discussed elsewhere [Hu, et al, **2021**]

Challenges in HM-CD Synthesis

Regardless of the synthesis method used for HM-CDs, one common issue is the uneven distribution of particle sizes. This non-uniformity can affect their physicochemical properties and performance. Another challenge lies in achieving a high QY. HM-CDs tend to have poorer QY, which is a critical factor in their potential application in biomedicine and commercialization.

APPLICATIONS

Significant medical applications of HM-CDs are reported, particularly in the context of haemostasis (the process of stopping bleeding) and the treatment of haemorrhagic diseases. It highlights the specific mechanisms by which HM-CDs derived from herbal medicine precursors address these medical conditions.

It is noted that medical applications of HM-CDs have become a highly active research field contributing to the development of nanomedical science. It emphasizes the importance of avoiding complicated modifications and expensive materials in medical treatments. HM-CDs offer specific efficacy due to their herbal medicine precursors, which can potentially overcome limitations associated with traditional CDs that often rely on loading pharmacophores or acting as drug carriers. For instance, haemostasis charcoal drugs have been there in the traditional Chinese medicine for more than 2000 years. While their haemostatic effects are well-recognized, the specific mechanisms involving small molecule activators have not yet been thoroughly understood. HM-CDs can be prepared from carbonized herbal medicine, and researchers are exploring their specific haemostatic mechanisms.

The specific HM-CDs derived from charcoal drugs like *Junci Medulla Carbonisat, Pollen Typhae Carbonisata, and Schizonepetae Herba Carbonisata* have demonstrated haemostatic effects by activating the internal coagulation system, increasing fibrinogen levels, and potentially increasing platelet counts. HM-CDs can provide herbal medicine with additional haemostatic functions, even when the herbal medicine itself does not possess haemostatic effects. Examples include *egg yolk oil*-CDs (EYO-CDs) and *Phellodendri Cortex Carbonisatus*-carbon dots (PCCCDs), which have shown haemostatic effects by activating coagulation pathways and fibrinogen systems. The use of HM-CDs for haemostasis and the specific mechanisms by which they achieve haemostatic effects offer additional haemostatic function to herbal medicine that may not possess such effects on its own. This research represents an important development in the field of medical applications of nanomaterials as discussed by many [Agrawal, et al, **2018**; Liu, et al, **2018;** Shen, et al, **2018**; Sun, et al, **2018**; Zhang, et al, **2018**; Chen, et al, **2019;** Ghosal, and Ghosh, **2019;** Tejwan, et al, **2020;** Chung, et al, **2021;** Hu, et al, **2021**].

The anti-inflammatory properties of HM-CDs have been found favourable in various inflammatory models.

Inflammation is a fundamental biological process that plays a crucial role in maintaining human health by acting as a natural defence mechanism in the body and serving various protective and reparative functions. This complex process can be categorized into different types, depending on the underlying triggers, such as infection, and whether it is acute or chronic in nature.

Inflammation is a multi-faceted response that involves the activation of various cell types, including nonimmune cells like fibroblasts and vascular endothelial cells, as well as immune cells like neutrophils, tissue macrophages, monocytes, mast cells, and lymphocytes. These diverse cellular components work together to protect the host from pathogens, infections, and toxins. In addition to safeguarding the body, inflammation plays a critical role in tissue repair and regeneration, ultimately contributing to the restoration of cellular haemostasis.

While inflammation is a vital defence mechanism, it can have detrimental effects under certain circumstances. Inappropriate or uncontrolled inflammation can lead to the body's immune system mistakenly attacking healthy tissues, resulting in various disorders. Acute inflammation is typically a less severe and localized response, targeting a specific site in the body. However, in cases where acute inflammation is unable to resolve the underlying issue, chronic inflammation may develop.

Chronic inflammation is characterized by its persistence over an extended period and can be associated with various health problems. It can lead to the development of autoimmune conditions, as the accumulation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) occurs. These reactive species can target and harm healthy host cells, causing illness and disrupting the delicate balance of cellular homeostasis.

Inflammation being a complex and essential process acting as a protective shield for the body against external threats in case it becomes chronic and uncontrolled, it can result in autoimmune disorders and disrupt the delicate equilibrium of cellular health and function. Understanding the various facets of inflammation is critical in the fields of medicine and biology, as it holds profound implications for human health and the development of therapeutic interventions [Chen, et al, **2018**; Jin, et al, **2018;** Leigh, et al, **2020**].

Prior research has indicated that persistent oxidative stress plays a pivotal role in intensifying localized tissue damage, a phenomenon that can ultimately lead to chronic inflammation. This chronic inflammatory state, in turn, is associated with the development and progression of various chronic human diseases. Notable examples of such diseases include diabetes,

neurodegenerative disorders, cancer, pulmonary ailments, ischemic heart disease, liver conditions, cardiovascular diseases, and hepatitis.

Oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract their harmful effects, can be triggered by various lifestyle factors and environmental influences. These factors encompass obesity, excessive alcohol consumption, physical inactivity, exposure to radiation, chronic stress, and cigarette smoking. The resulting surge in ROS production can, in turn, initiate and perpetuate inflammatory responses within the body.

One of the key mechanisms by which ROS exerts its pro-inflammatory effects is through the modulation of the synthesis of numerous inflammatory markers. These markers include chemokines, cytokines, cyclooxygenase-2 (COX-2), and proinflammatory transcription factors. Some of the pivotal transcription factors affected by ROS-induced inflammation include nuclear factor kappa light chain enhancer of activated B-cells (NF-κB), tumour necrosis factor (TNF), p53, nuclear factor erythroid 2-related factor 2 (Nrf2), activator protein 1 (AP-1), hypoxia-inducible factor 1α (HIF-1α), peroxisome proliferator-activated receptor γ (PPAR-γ), and β-catenin/Wnt. The persistent oxidative stress associated with various lifestyle factors can trigger inflammation, which is linked to the development of chronic diseases. These diseases encompass a wide range of conditions affecting different organs and systems in the body. Oxidative stress-induced inflammation influences the expression of key inflammatory markers and transcription factors, playing a central role in the pathogenesis of these diseases. Understanding these molecular mechanisms is crucial for developing strategies to prevent and treat chronic inflammatory diseases [Gupta, *et al*, **2018;** Abete, et al, **2019**; Tu, et al, **2019].**

Cells possess innate mechanisms, both enzymatic and nonenzymatic, to counteract the harmful effects of oxidative stress. These defences are typically effective in maintaining cellular balance under normal conditions. However, in cases of prolonged or exceptionally high levels of reactive oxygen species (ROS), the natural cellular defences may prove insufficient to prevent damage. Therefore, there is a growing interest in developing new approaches to combat inflammation and oxidative stress-related diseases by simultaneously reducing excessive ROS production and enhancing antioxidant defence mechanisms.

In this context, the utilization of nanomaterials has emerged as a highly promising avenue for addressing these challenges and providing innovative solutions for treating chronic disorders. Nanomaterials exhibit a wide range of beneficial properties and have demonstrated significant potential in mitigating high ROS levels and inflammation. They are being explored as an alternative strategy for the treatment of a variety of chronic conditions.

Key attributes and applications of nanomaterials in the context of oxidative stress and inflammation include:

Anti-Inflammatory Effects: Nanomaterials can exert potent anti-inflammatory effects by regulating immune responses and modulating cytokine and chemokine production. These properties make them valuable for mitigating chronic inflammation, which is often a key factor in the progression of many diseases.

Antimicrobial Properties
Some nanomaterials exhibit inherent antimicrobial capabilities, which can be harnessed to combat infections and reduce inflammation associated with microbial agents.

Antioxidant Activity
Nanomaterials can function as antioxidants, scavenging ROS and protecting cells from oxidative damage. This antioxidant capacity is valuable in reducing the oxidative stress associated with many diseases.

Antidiabetic Effects
Certain nanomaterials show promise in regulating blood sugar levels and ameliorating diabetes-related complications, which often involve oxidative stress and inflammation.

Drug Delivery
Nanomaterials can be employed as drug delivery vehicles, facilitating the targeted and controlled release of therapeutic compounds to sites of inflammation and disease.

Treatment of Cardiovascular and Kidney Disorders
Nanomaterials have applications in managing cardiovascular and kidney disorders, as they can help alleviate inflammation and oxidative stress associated with these conditions.

Catalytic Capabilities
Nanomaterials possess unique catalytic properties, enabling them to participate in various chemical reactions and processes that may be beneficial in the context of disease treatment and cellular protection.

The nanomaterials represent a highly promising frontier in biomedical research and clinical applications due to their diverse range of properties and potential applications in the fields of inflammation and oxidative stress management and thus make them invaluable tools for tackling chronic disorders. As researchers continue to explore and develop nanomaterial-based therapies, their significance in the biological and medical sectors is expected to grow, offering innovative solutions for the treatment of a wide range of diseases [Ma, et al, **2020;** Kong, et al, **2022;** Park, et al, **2022**].

Nanoparticles (NPs) are a class of materials that are gaining increasing attention in various fields, including biomedicine. They can be synthesized using a wide range of materials, both organic and inorganic. These nanoparticles exhibit unique properties and are valuable for their diverse applications. Let's explore some of the key types of NPs and their characteristics:

Polymeric NPs
These are NPs composed of biocompatible and biodegradable polymers. Examples include poly(lactic-co-glycolic acid) (PLGA) NPs, which are widely used for drug delivery due to their controlled release properties.

Polyvinylpyrrolidone (PVP) NPs
PVP is a versatile polymer that can be used to create NPs with excellent stability and compatibility with various drugs and biomolecules.

Poly(N-(2-hydroxypropyl) methacrylamide) (PHPMA) NPs
PHPMA-based NPs are known for their biocompatibility and potential for drug delivery and targeted therapy.

Chitosan NPs
Chitosan, derived from chitin, is used to create NPs with mucoadhesive properties, making them suitable for drug delivery to mucosal surfaces.

Dendrimer-Based NPs
Dendrimers, such as polyamidoamine (PAMAM), polypropylene imine (PPI), poly(glycerol-co-succinic acid), and poly-l-lysine (PLL), offer well-defined structures and are utilized for drug delivery and imaging applications.

Liposomal NPs
Liposomes are lipid-based NPs with a lipid bilayer structure. They are excellent drug carriers and can encapsulate both hydrophobic and hydrophilic drugs.

Inorganic NPs
These semiconductor NPs have unique optical properties, including size-dependent fluorescence. They are used in imaging and labeling applications due to their bright and tunable emission.

Carbon-based NPs include single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). They have high aspect ratios and are utilized for drug delivery, imaging, and sensing.

Iron oxide NPs, such as superparamagnetic iron oxide nanoparticles (SPIONs), are used in magnetic resonance imaging (MRI) and magnetic drug targeting due to their magnetic properties.

One of the remarkable features of NPs is their nanoscale size, which enables them to interact with biological systems in unique ways. Their small size, distinctive shape, and surface properties allow for efficient tissue penetration. NPs can be employed for drug delivery, imaging, and therapy through passive or active targeting mechanisms. Passive targeting exploits the enhanced permeability and retention (EPR) effect, which enables NPs to accumulate in tumour tissues with leaky vasculature. Active targeting involves functionalizing NPs with ligands or antibodies that specifically bind to receptors on target cells, increasing their selectivity and efficacy.

NPs, whether organic or inorganic, offer an array of properties and applications in biomedicine. Their ability to be tailored for specific functions, including drug delivery and imaging, positions them as valuable tools in the fields of healthcare, diagnostics, and therapeutics. NPs continue to be a subject of intense research and hold great promise for innovative biomedical applications [Chen, et al, **2021**].

Carbon dots (CDs) are a versatile and promising class of nanomaterials with a wide range of applications particularly in biomedicine. Their unique surface properties and desirable qualities make them valuable tools for numerous applications.

Surface functionalization of CDs comprising of amino, carboxyl, hydroxyl, and similar other groups offers unique opportunity of enhancing their physicochemical properties. For instance, their enhanced optical characteristics, biocompatibility, and targeting ability make them more sensitive and selective in various applications.

Adjustable photoluminescence of CDs makes them valuable for bioimaging and sensing applications. Their fluorescence properties can be tailored to specific wavelengths, enhancing their versatility in imaging.

CDs are highly soluble in water, a crucial feature for their use in biological systems. Their water solubility allows for easy dispersion in aqueous solutions, facilitating applications in drug delivery and imaging.

CDs are known for their low cytotoxicity, ensuring minimal harm to living cells and organisms. This is a fundamental characteristic for their safe use in biomedicine besides their enhanced biocompatibility, making them suitable for various biological applications. They can be used for targeted drug delivery, gene transfer, and cancer therapy without causing significant harm to the body. CDs are biodegradable, which is essential for their use in biomedical applications as they are easily metabolized and eliminated from the body, reducing concerns about long-term accumulation.

CDs find applications in a diverse range of fields, including: fluorescence-based bioimaging (*in vitro/vivo*)**,**

in biosensors for detecting various biomolecules and analytes, in delivering anticancer drugs to target cancer cells, drug and gene delivery for therapeutic applications, in improving the efficiency of photosynthesis in plants, in removing radioactive ions from aqueous solutions, in sea water desalination, in optoelectronic devices such as LEDs and solar cells, catalysis, energy storage and conversions, and in enhancing plant growth and nutrient absorption in agriculture.

The exceptional properties and versatile surface functionalities of CDs make them indispensable tools in biomedicine and various other fields. Their adjustable photoluminescence, water solubility, biocompatibility, and biodegradability have opened a vast array of applications, ranging from bioimaging to environmental remediation, and hold great promise for future innovations in science and technology [Kim, et al, **2018**; Dhenadhayalan, et al, **2020;** Agnol, et al, **2021;** Wang, et al, **2021;** Xiao, et al, **2021;** Đorđević, et al, **2022**; Wang, et al, **2022].**

The synthesis of CDs involves various techniques, which can be broadly categorized into top-down and bottom-up approaches. These approaches offer different advantages and trade-offs, allowing to tailor the attributes of the resulting nanomaterials to meet specific requirements.

Top-Down Synthesis
Top-down techniques involve reducing larger materials to nanoscale particles. While they can yield higher quantities of nanomaterials, they often require aggressive oxidation agents and post-synthesis processes for fine-tuning. Examples of top-down methods include:

Chemical Ablation
This method employs chemical reactions to break down larger carbon sources into nanoscale particles, often using strong acids or other oxidizing agents.

Laser Ablation
Laser ablation uses high-intensity laser beams to fragment carbon-rich materials into nanoparticles. It is a precise technique that offers control over particle size.

Arc Discharge
In arc discharge synthesis, a high electrical current is passed through carbon electrodes in an inert atmosphere, resulting in the vaporization and condensation of carbon into nanoparticles.

Electrochemical Methods
These methods involve using electrical current to disintegrate bulk carbon sources into nanoscale particles. They are known for their simplicity and scalability.

Bottom-Up Synthesis
Bottom-up approaches involve constructing nanoparticles from smaller building blocks, offering better control over morphology and size. However, they may require longer synthesis times and additional effort. Examples of bottom-up methods include:

Hydrothermal Treatment
Hydrothermal synthesis uses high-temperature and high-pressure water to promote the growth of nanomaterials from precursor molecules. This method allows for precise control of size and morphology.

Microwave Treatment
Microwave-assisted synthesis utilizes microwave radiation to accelerate chemical reactions, resulting in rapid nanoparticle formation. It is known for its efficiency and speed.

Solvothermal Treatment
Solvothermal methods involve heating a solvent under high pressure to encourage the crystallization of nanoparticles from precursor compounds.

Reverse Micelle Method
This approach involves using surfactants to create small micelles within a solvent, where nanomaterials can form within these confined spaces.

Pyrolysis
Pyrolysis is the thermal decomposition of organic compounds at elevated temperatures, leading to the formation of carbon nanoparticles.

Template Method
In this method, nanoparticles are formed within a template or scaffold structure, allowing precise control over size and shape.

Chemical Oxidation
Chemical oxidation methods involve the reaction of carbon sources with strong oxidizing agents to produce C-dots.

Purification and Separation
After synthesis, it is often necessary to purify and separate the resulting nanomaterials. Various techniques can be employed, including:

Filtering
Filtration methods use porous membranes to separate nanoparticles from solution.

Centrifugation
Centrifugation involves spinning a sample at high speeds to separate particles based on their density.

Dialysis
Dialysis utilizes semipermeable membranes to remove impurities and excess reactants from the nanoparticle solution.

Freeze Drying and Vacuum Drying
These methods remove solvents from the solution, leaving behind the dry nanoparticles.

Chromatography
Chromatographic techniques can be used to separate nanoparticles based on their size, charge, or other properties.

Ultrasonication
Ultrasonication employs high-frequency sound waves to disperse and disaggregate nanoparticles in solution.

Many syntheses are noted to combine several techniques to produce high-purity nanoparticles tailored for specific applications. Researchers choose the most suitable methods based on their goals and the desired properties of the CDs. The selection of the right synthesis and purification techniques is crucial in achieving the desired quality and characteristics of CDs for their intended applications as discussed in the enclosed references [Arkan, et al, **2018**; Calabro, et al, **2018;** Liu, et al, **2018**; Sharma, et al, **2020**; Wareing, et al, **2021;** Đorđević, et al, **2022;** Barrientos, et al, **2023**].

The utilization of both inorganic and organic molecules for the synthesis of carbon dots has been well-established. However, in recent years, there has been a growing interest in using biomass-based materials as the starting materials for C-dot synthesis, giving rise to what are often referred to as "green CDs." This approach has several advantages and has gained significant attention in the field of nanomaterials. Here, we will delve into the significance of green C-dots and some examples of biomass sources used for their synthesis:

Significance of Green CDs
Green CDs represent a class of nanomaterials that are synthesized from biomass-based materials, and they offer several key advantages over conventional CDs:

Green CDs are known for their excellent biocompatibility, making them ideal for use in various biomedical and biotechnological applications. Their reduced toxicity and compatibility with biological systems enhance their safety and effectiveness in medical settings. The use of biomass materials aligns with sustainable and eco-friendly practices. By repurposing agricultural and food waste, green CD synthesis contributes to reducing environmental impact and waste. Green CDs are often synthesized without the need for heteroatom doping or chemical additives. This simplifies the synthesis process, making it more straightforward and cost-effective.

Biomass Sources for Green CDs
Several biomass materials have been explored for the synthesis of green CDs, including:
Lotus root has been used to create C-dots with unique properties, such as size and fluorescence, making them suitable for various applications. CDs derived from coriander leaves exhibit biocompatibility and have been applied in bioimaging and sensing. Pumpkin-based CDs have been investigated for their potential in drug delivery, sensing, and imaging. Potato-based CDs have shown promise in bioimaging and theranostics (diagnosis and therapy). Lentil-derived CDs are being explored for drug delivery and sensing applications. Garlic is a source of green CDs with potential for drug delivery and bioimaging. Starch-based C-dots have found use in bioimaging and sensing applications.

Some unconventional sources have also been used to create green CDs with their applications in sensing and environmental remediation. CDs derived from polysaccharides exhibit biocompatibility and have applications in drug delivery and imaging. Peach gum-based CDs have been explored for their potential in biomedical applications.

While green CDs offer numerous advantages, there are still challenges and areas for further exploration. These include:
There is much to explore concerning the structure and properties of green CDs to enhance their performance in various applications. Investigating the potential of green CDs in the treatment of inflammatory diseases and understanding their mechanisms of action remains a key area of research.

The synthesis of homogeneous CDs with precise control over their size and surface properties is an ongoing challenge that researchers are actively working to address. Green CDs, synthesized from biomass-based materials, hold great promise in the field of nanomaterials, particularly in biomedicine and environmental applications. Their eco-friendly nature, biocompatibility, and minimal chemical additives make them an attractive choice for a wide range of innovative uses. Ongoing research is focused on further enhancing their properties and exploring new applications [Zhang, et al, **2018;** Tejwan, et al, **2020;** Chahal, et al, **2021**; Feng, et al, **2021;** Sharma, et al, **2021**].

In recent years, there has been a growing body of research highlighting the direct link between chronic diseases and inflammation, with inflammation being recognized as a primary contributor to chronic damage and associated disorders. In this context, carbon dots (C-dots) have emerged as promising candidates with anti-inflammatory properties. Let's explore a specific case involving the use of pharmacological molecules, particularly aspirin, as the starting material for the synthesis of C-dots, and their potential for anti-inflammatory and bioimaging applications:

Aspirin-Based C-Dots (FACDs)
Aspirin, a nonsteroidal anti-inflammatory drug with a long history of therapeutic use, has demonstrated its efficacy in reducing inflammation and is associated with a decreased risk of conditions like cancer and heart disease. However, it comes with certain limitations, including low solubility and potential adverse effects on

the stomach. Building upon the anti-inflammatory properties of aspirin, researchers, led by Xu et al., embarked on the development of fluorescent aspirin-based C-dots (FACDs) with the dual objectives of anti-inflammation and bioimaging.

FACDs were designed to retain the anti-inflammatory properties of aspirin while offering the benefits of improved solubility and reduced side effects. In vitro experiments demonstrated that FACDs exhibited remarkable anti-inflammatory activity. Notably, at a concentration of 100 mg/mL, FACDs displayed superior anti-inflammatory effects compared to aspirin alone. They effectively reduced the expression of key inflammatory markers such as TNF-α and IL-1β. FACDs were further tested in animal disease models. In a carrageenan-induced inflammation model, they were found to significantly lower the levels of prostaglandin E2 (PGE2), a pro-inflammatory molecule. Importantly, the administration of FACDs did not result in any side effects, as confirmed through haematological analyses. Additionally, no signs of toxicity to vital organs such as the liver, gallbladder, or kidney were observed, suggesting the safety of CDs for *in vivo* applications. Beyond their anti-inflammatory properties, FACDs demonstrated excellent bioimaging capabilities. They were effective for cellular imaging both in vitro and in vivo, highlighting their dual functionality for imaging and anti-inflammation.

The findings from this research pointed to the high therapeutic potential of FACDs. By combining anti-inflammatory and bioimaging properties, FACDs represent a versatile and promising tool for future therapeutic applications. This innovation holds the potential to address the limitations associated with traditional aspirin therapy while opening new avenues for the treatment and imaging of inflammatory conditions. Overall, FACDs represent a significant step in harnessing the power of CDs for dual medical applications in anti-inflammation and bioimaging [Leuti, et al, **2020**].

Inflammatory Control using CDs

Gout, a form of inflammatory arthritis, is a condition characterized by the accumulation of monosodium urate (MSU) crystals in the joints due to elevated levels of uric acid in the body. While there are first-line treatments available for gout, they come with certain drawbacks. As a result, researchers are continually exploring and developing novel therapeutic alternatives for the management of inflammatory arthritis and hyperuricemia (high uric acid levels). In this context, CDs derived from various sources have emerged as potential candidates for these novel therapies.

Aurantii fructus immaturus carbonisata-derived C-Dots (AFIC-CDs):

In one of the studies CDs derived from Aurantii fructus immaturus carbonisata, also known as Zhi Shi in Chinese and isolated from citrus plants (AFIC-CDs) were synthesized, characterized, and subjected to *in vivo* and *in vitro* testing to evaluate their potential inhibitory effects on gout and hyperuricemia. AFIC-CDs had a significant impact on the symptoms of gout. It resulted in a marked reduction in paw pressure and volume, which are indicators of inflammation and swelling. AFIC-CD treatment was associated with a reduction in the levels of proinflammatory cytokines produced in response to MSU crystals. This anti-inflammatory effect further supports the potential therapeutic role of AFIC-CDs in gout. *In vitro* studies revealed that AFIC-CDs exhibited negligible cytotoxicity, suggesting their safety for use in biological systems. Inhibition of xanthine oxidase (XOD) was found to reduce uric acid producing enzyme XOD activity in RAW264.7 cells. The inhibition of XOD activity is a key mechanism for reducing uric acid levels.

In animal models of hyperuricemia, AFIC-CDs demonstrated the ability to lower uric acid levels in a time-dependent manner. Different doses of AFIC-CDs were administered, resulting in a dose-dependent reduction in XOD activity in the liver and serum. This reduction in XOD activity contributed to the management of hyperuricemia. Another study conducted showed antigout effects of C-dots prepared from Puerariae lobatae radix (a type of kudzu root) using an animal model of gout.

The C-dots derived from Puerariae lobatae radix were effective in lowering blood uric acid levels in gout model rats. The CDs were found to inhibit the activity of XOD, an enzyme involved in uric acid production. This inhibition contributed to the reduction in uric acid levels. This study observed a decrease in the degree of swelling and pathological damage associated with gouty arthritis in response to CD treatment, indicating their potential in managing the symptoms of gout.

These studies demonstrate the promising potential of CDs derived from Aurantii fructus immaturus carbonisata and Puerariae lobatae radix in the management of gout and hyperuricemia. These nanomaterials have shown anti-inflammatory properties, the ability to reduce uric acid levels, and minimal cytotoxicity, making them candidates for further exploration in the development of novel therapies for gout and related conditions [Wang[1,2], et al, **2019**].

Mesenchymal Stem Cells (MSCs) in Gene Therapy

Mesenchymal stem cells (MSCs) have garnered significant attention in the field of regenerative medicine and are considered a potential clinical therapy for a wide range of diseases. They hold promise in gene therapy, where the delivery of therapeutic genes or small interfering RNA (siRNA) is crucial. CDs and carbon quantum dots have emerged as versatile tools for gene delivery.

Cartilage Tissue Engineering has been explored using

CDs in gene therapy for cartilage tissue engineering. Here, a safe nano vector was created by bio-conjugating CDs with a protein cross-linker called sulfosuccinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC). This bioconjugation allowed for the binding and delivery of small interfering RNA (siRNA), a powerful tool in gene therapy. Tumour necrosis factor-α (TNF-α) is a proinflammatory cytokine that plays a role in local inflammatory processes, particularly in the joints, and has inhibitory effects on chondrogenesis (cartilage formation). The study demonstrated that bio-conjugated CDs effectively inhibited TNF-α and promoted chondrogenesis from MSCs. This strategy facilitated the binding and delivery of siTnfα to MSCs, effectively targeting TNF-α. CDs bio-conjugated with sulfo-SMCC upregulated the expression of cartilage-specific markers (Sox9, Col2a1, and Acan) in MSCs. These markers are associated with cartilage regeneration and the inhibition of inflammation. This suggests that CDs, when used as a delivery system for siRNA, can enhance cartilage regeneration by inhibiting inflammation in MSCs.

The study found that CD-SMCC (CD-sulfo-SMCC) demonstrated favourable biocompatibility, low toxicity, high transfection efficiency, and excellent complexing ability with siRNA. *In vivo* experiments further indicated that CD-SMCC-siTnfα-transfected MSCs accelerated cartilage regeneration.

For centuries, mulberry silkworm cocoon carbonisata (MSCC) has been used in traditional medicine for its potential anti-inflammatory properties. Innovative research explored the anti-inflammatory effects of MSCC-derived carbon dots (MSCC-CDs) using various animal models of inflammation.

MSCC-CDs exhibited significant anti-inflammatory bioactivity in various animal models of inflammation, including ear oedema, vascular permeability, and sepsis induced by phlogistic agents (dimethylbenzene, acetic acid, and lipopolysaccharide, or LPS). The study found that MSCC-CDs could effectively inhibit the serum levels of proinflammatory cytokines TNF-α and IL-6 in an LPS-induced inflammation model, which closely resembles sepsis in humans. MSCC-CDs were also effective in reducing oedema induced by xylene and vascular permeability triggered by acetic acid, further highlighting their anti-inflammatory potential.

These findings demonstrate the biomedical applications of CDs, particularly as potential anti-inflammatory agents. The use of CDs for gene therapy and the anti-inflammatory effects of MSCC-CDs in various animal models offer promising prospects for future therapeutic applications as reported in the enclosed references [Liu, et al, **2019**; Chisari, et al, **2020**; Wang, et al, **2020;** Margiana, et al, **2022**].

Nitric Oxide (NO) and Inflammation

Nitric oxide (NO) is a key signalling molecule that plays a significant role in modulating inflammatory responses, particularly within macrophages. Research has shown that the production of NO by macrophages can have a profound impact on the regulation of inflammation.

In one of the anti-inflammatory studies of CDs derived from molasses reduced generation of NO was induced by lipopolysaccharide (LPS) in RAW264.7 macrophages. While the exact mechanistic insights remain unclear, the study, however, suggested that the cellular uptake and tracking of CDs involved receptor- or non-receptor-mediated endocytosis, as observed through laser scanning confocal microscopy.

Another study focused on CDs synthesized from carob molasses and explored the impact of different surface passivation agents on their anti-inflammatory properties. The surface passivation agents examined included alginate (ALG), polyvinyl alcohol (PVA), and polyethylene glycol (PEG). The authors found that C-dots with PEG or PVA significantly inhibited the production of proinflammatory cytokines, specifically interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), in RAW264.7 cells. In contrast, CDs passivated with ALG increased TNF-α production, thus potentiating the proinflammatory response.

This study's findings underscore the notion that the presence of different functional groups on the surface of CDs can have a significant impact on their applicability in modulating inflammatory responses. In this context, CDs passivated with PVA demonstrated the most robust anti-inflammatory effects, suggesting that surface modifications can tailor their anti-inflammatory properties for specific applications.

These studies shed light on the potential of CDs as anti-inflammatory agents, with the ability to modulate NO production and cytokine expression in macrophages. Moreover, they highlight the importance of surface passivation and functional groups in determining the anti-inflammatory efficacy of C-dots [Ayaz, et al, **2020**; Yavuz, et al, **2020**].

Ibuprofen-Derived CQDs as Anti-Inflammatory Agents

Ibuprofen is a widely used nonsteroidal anti-inflammatory drug (NSAID); however, its clinical use is limited due to side effects, including poor solubility and gastric injury. NSAIDs function by inhibiting cyclooxygenase (COX) enzymes, which in turn reduces the production of inflammatory mediators like prostaglandins. In a novel approach, researchers synthesized carbon quantum dots (CQDs) using ibuprofen as a carbon source and assessed their potential as anti-inflammatory agents in an animal model of inflammation.

Ibuprofen precursor was used to synthesize CQDs in one

of the studies to evaluate the cytotoxicity of the functional CQDs in HeLa cells. Importantly, the CQDs were found to exhibit negligible cytotoxicity, ensuring their safety for potential applications. The functional CQDs demonstrated high stability, solubility, and good biocompatibility. In an animal model of inflammation induced by carrageenan, the CQDs exhibited anti-inflammatory effects. Specifically, they reduced carrageenan-induced prostaglandin E2 (PGE2) serum levels and significantly decreased the number of neutrophils. The CQDs also displayed strong fluorescence for an extended period (60 minutes) in vivo, making them amenable to bioimaging studies. The authors suggested that the anti-inflammatory effects of the CQDs were likely attributed to the functional groups acquired from the carbon source, ibuprofen. These functional groups may have played a key role in modulating the inflammatory response.

This study highlights the potential of CQDs derived from ibuprofen as effective and biocompatible anti-inflammatory agents. By utilizing a well-known NSAID as a precursor for CQD synthesis, researchers have opened new avenues for the development of anti-inflammatory therapeutics with improved safety and biocompatibility. Additionally, the fluorescent properties of these CQDs make them promising candidates for bioimaging applications [Bindu, et al, **2020**; Qu, et al, **2020**].

Anti-Inflammatory/Antioxidant CDs

The intricate relationship between oxidative stress and inflammatory reactions is well-established. Elevated levels of reactive oxygen species (ROS) contribute significantly to secondary damage cascades in various injury scenarios, including spinal cord injury. CDs have garnered attention for their dual antioxidant and anti-inflammatory effects, making them promising candidates for mitigating oxidative stress-induced inflammation and its associated damages.

Recent research explored the potential therapeutic role of selenium (Se)-doped carbon quantum dots (Se-CQDs) in the context of spinal cord injury. In both *in vitro* and *in vivo* experiments, Se-CQDs demonstrated protective effects against spinal cord damage. These effects were manifested as a reduction in inflammation, neuronal cell death, and demyelination, ultimately resulting in improved locomotor function. Further investigations are necessary to elucidate the specific mechanisms and biosafety of Se-CQDs, but their potential for ameliorating spinal cord injuries is noteworthy.

CDs synthesized from laccaic acid exhibit anti-inflammatory properties against lipopolysaccharide (LPS)-induced inflammation in macrophages (RAW264.7 cells). The solvothermal synthesis of CDs from laccaic acid led to the development of nanozymes capable of modulating inflammation.

Nanocomposite hydrogels incorporating CDs are gaining attention for their simple preparation and useful properties. A bio-adhesive, injectable, self-healing hydrogel was reported facilitating the efficient diffusion of catalytic CDs to the target site, which in this case was the skin. The CDs contributed to the relief of oxidative stress and inflammation by removing excess ROS. Such composites represent a novel avenue for injectable drug delivery systems with potential clinical applications.

TNF-α induction can elevate ROS levels in endothelial cells. The beneficial effects of CDs was reported on TNF-α-induced ROS levels and inflammatory molecules in human microvascular endothelial cells.In the context of wound healing, cerium-doped carbon nanodots demonstrated modulating effects on inflammation in a mouse model. These nanodots have potential applications against diseases related to oxidative stress.

Green C-dots derived from Carica papaya leaves were found to possess anti-inflammatory and antioxidant activities. These CDs induced membrane stabilization in hyposaline-treated human red blood cells.

Metal-free CDs synthesized using various precursors, such as ethylenediamine, phenylenediamine, and ethanol, have demonstrated the ability to reduce LPS-induced inflammation in the liver of a mouse model. These CDs were also found to scavenge hydroxyl, superoxide anion, and peroxide radicals.

These studies highlight the critical role of CDs in reducing oxidative stress by scavenging ROS, ultimately leading to the prevention of inflammation and diseases caused by oxidative stress. The versatile applications of CDs in various models and therapeutic contexts underscore their potential in addressing oxidative stress-related health issues as discussed in enclosed references [Gao, et al, **2019**; Zuo, et al, **2019**; Luo, et al, **2020**; Belperain, et al, **2021;** Dong, et al, **2021;** Zhang, et al, **2021;** Dong, et al, **2022;** Gudimella, et al, **2022;** Kong, et al, **2022].**

Anti-Inflammatory and Gastroprotective Properties of C-Dots

Cancer is intricately linked to chronic inflammation, and this section delves into the potential of C-dots, specifically those derived from natural sources, to address gastric health issues, particularly in the context of stomach cancer and ulcers.

Nelumbinis Rhizomatis Nodus Carbonisata (NRNC):

CDs synthesized from NRNC, obtained from the dried nodal rhizome of Nelumbo nucifera, were tested for their efficacy against ethanol-induced gastric ulcers in rats. Ethanol consumption is known to induce oxidative stress and inflammatory responses in animal models. Green synthetic CDs derived from NRNC exhibited no cytotoxicity towards gastric epithelial cells. Notably, CD therapy significantly mitigates the harmful effects of ethanol on the gastric mucosal layer in rats, preventing

gastric ulcer formation. The observed reduction in inflammation in test animals was attributed to the inhibition of proinflammatory markers and a decrease in oxidative stress due to the elevated levels of antioxidant enzymes.

Radix Sophorae Flavescentis Carbonisata

Hu et al. synthesized CDs using Radix Sophorae Flavescentis carbonisata and explored their protective effects against ethanol-induced acute gastric ulcers in rats. The anti-inflammatory effects of C-dots stemmed from their role in downregulating the NF-κB pathway, thereby inhibiting the production of inflammatory markers like IL-6 and TNF-α. The CDs also exhibited antioxidant effects by upregulating the expression of enzymatic and nonenzymatic antioxidants and downregulating the levels of iNOS and the lipid peroxide metabolite malondialdehyde (MDA). These synthesized CDs were well-tolerated with negligible toxicity and good bioavailability.

Glycyrrhizae Radix et Rhizoma (GRR)

A similar study demonstrated the anti-gastric ulcer effects of C-dots derived from Glycyrrhizae Radix et Rhizoma. GRR-C-dots alleviated oxidative stress in the mucosal layer, similar to previous studies. They restored the balance of MDA and superoxide dismutase (SOD) levels. Importantly, gastric NO levels decreased significantly after treatment with C-dots. However, no effects were observed on serum NO levels.

Semi-carbonized Nanodots from Medicinal Herbs

The anti-gastric cancer effects of seven semi-carbonized nanodots derived from various herbs were reported recently. Atractylodes macro cephala-derived nanodots exhibited notable activity against a gastric ulcer animal model. These carbon nanodots offered protective effects, including the inhibition of proinflammatory cytokine production, alleviation of oxidative stress, and an increase in prostaglandin E2 (PGE2) and mucin MUC5AC secretion to safeguard the gastric mucosa. The inhibition rate of the CDs was approximately 90%. Moreover, CD treatment resulted in lower levels of neurotransmitters such as dopamine and 5-hydroxytryptamine in the brain, thereby reducing the neurobiological response induced by stress. Additionally, CD treatment restored normal bacterial diversity and regulated energy metabolism. Accordingly, the semi-carbonized nature of CDs plays a crucial role in their biological properties against stomach ulcers.

These studies collectively demonstrate that green CDs have antiulcer and gastroprotective properties. Their applications are promising as therapeutic candidates in the treatment of gastric cancer and other gastric health conditions. The protective and anti-inflammatory actions of CDs hold potential for mitigating gastric ulcers and related diseases [Hu, et al, **2021**; Liu, et al, **2021;** Lu, et al, **2021;** Luo, et al, **2021;** Zhao, et al, **2021;** Jaroenlapnopparat, et al, **2022**].

CDs in Acute Inflammations and Organ Injuries

Acute inflammatory reactions frequently occur in response to venomous creature stings or bites, such as those from snakes. In addition, studies have shown that snake venom can lead to acute kidney injury. CDs synthesized from natural sources, specifically Phellodendri chinensis cortex, is found effective in preventing acute kidney injury induced by snake venom.

In a study, lyophilized venom from Deinagkistrodon acutus, a highly venomous snake in China, was used to induce acute kidney injury in mice. While a topical antidote exists for this venom, it comes with side effects. The study explored alternative treatments and found that CDs effectively countered kidney inflammatory responses in mice injected with Deinagkistrodon acutus venom. The administration of C-dots resulted in lower expression levels of proinflammatory markers, including monocyte chemotactic protein 1 (MCP-1), IL-1β, and IL-10 in the kidneys. MCP-1 is an important chemokine that plays a role in leukocyte activation and recruitment during inflammatory responses. The study also observed improved kidney function in the mouse model, showcasing the therapeutic potential of C-dots against snake venom-induced kidney inflammation.

The same research team produced CDs using Phellodendri chinensis cortex through the calcination process and noted that these CDs are beneficial on mice with skin conditions mimicking psoriasis, a chronic inflammatory skin disorder typically induced by imiquimod. CDs were associated with a shift in microglial polarization from the M1 to M2 state, leading to anti-psoriasis effects in both cell and animal models.

In one of the studies the protective and anti-inflammatory potential of heme oxygenase-1 (HO-1), an enzyme known for its protective properties was examined. In response to lipopolysaccharide (LPS)-induced acute lung injury, CDs made from L-ascorbic acid were administered in a mouse model. This treatment led to the upregulation of HO-1 expression and modulation of the BTB and CNC homology (BACH) signalling pathways, which resulted in an anti-inflammatory effect and enhanced survival rates. Lower levels of proinflammatory cytokines like IL-6 and TNF-α were observed in the lung tissues of CD-treated mice. This demonstrated the potential of CDs to improve the outcomes of acute lung injury.

Similarly, CDs from Armeniacae Semen Amarum carbonisata were evaluated for their protective effects against LPS-induced acute lung injury *in vivo*. These CDs were associated with a decrease in serum proinflammatory cytokine levels (IL-1β, IL-6, and TNF-α) and an increase in IL-10 levels. They also exhibited antioxidant capacity by increasing glutathione content and superoxide dismutase (SOD) activity. Notably, CDs significantly reduced myeloperoxidase (MPO) activity

and malondialdehyde (MDA) levels in the lung tissues, indicating their ability to mitigate inflammation and enhance antioxidant status.

These studies highlight the therapeutic potential of CDs in addressing acute inflammatory reactions and preventing organ injuries, particularly in the context of snake venom-induced kidney injury, skin conditions like psoriasis, acute lung injury, and pneumonia as reported elsewhere [Zhang, et al, **2019**; Wang, et al, **2021;** Zhang, et al, **2021**; He, et al, **2022**; Zhao, et al, **2022**].

CDs and Non-alcoholic Fatty Liver Disease and Inflammation

Non-alcoholic fatty liver disease (NAFLD) is a group of liver conditions that have been on the rise globally, posing a significant health concern. NAFLD can progress to a more severe inflammatory condition in the liver called non-alcoholic steatohepatitis.

Iron (Fe) accumulation is believed to be a significant contributor to the development of NAFLD. Excess iron in the liver can lead to oxidative stress, inflammation, and cell damage. Considering this, a recent study explored the use of CDs capable of chelating Fe ions in zebrafish.

In this study, CDs were synthesized using iron and egg whites, and their administration resulted in several beneficial effects. These included a reduction in levels of reactive oxygen species (ROS), alleviation of endoplasmic stress, and a decrease in hepatic cell apoptosis. Additionally, C-dot treatment regulated the NF-κB signaling pathway, which plays a key role in inflammation and oxidative stress. This regulation was associated with the CDs' anti-inflammatory and antioxidative effects against NAFLD. The study also noted that the Fe-chelating capability of the synthesized CDs was comparable to other established Fe chelators, such as ethylenediaminetetraacetic acid and deferiprone. Importantly, the C-dots demonstrated excellent biocompatibility both in vitro and in vivo. They were also utilized for real-time monitoring of Fe ions in living organisms.

Anomalous activation of the NF-κB pathway is linked to a variety of disorders. As a result, significant research efforts have been dedicated to finding NF-κB inhibitors. CdTe quantum dots have shown a unique capability to selectively block the NF-κB pathway. This inhibition involves suppressing the activation of IκB kinase alpha/beta (IKKα/β), resulting in the inhibition of both canonical and noncanonical NF-κB signaling pathways, both in vitro and in vivo. CQDs have also demonstrated multifaceted applications, including their potential as anticancer and antiviral agents.

CDs produced using citric acid and glutathione showcased robust anti-inflammatory properties, especially in the context of lipopolysaccharide (LPS)-induced inflammation in J774A.1 cells (macrophages). Their mechanism of action involved the regulation of the NF-κB signaling pathway and the mitigation of reactive oxygen species (ROS) production.

These studies suggest that CDs have the potential to be employed as promising candidates for the treatment of oxidative stress-related inflammatory disorders, particularly in the context of NAFLD and the modulation of the NF-κB pathway [Friedman, et al, **2018;** Wang, et al, **2020;**Yu, et al, **2021**].

Some Examples - Inflammation Reducing CDs

Ulcerative Colitis (UC)

In ulcerative colitis, increased levels of proinflammatory proteins contribute to the inflammatory process. CDs derived from the carbonized product of Rhei Radix et Rhizoma demonstrated their effectiveness in reducing inflammation and mitigating oxidative stress damage. Their mechanism of action involved increasing the levels of anti-inflammatory cytokine IL-10, as well as antioxidant enzymes such as GSH (glutathione), SOD (superoxide dismutase), and CAT (catalase). Simultaneously, they decreased the levels of proinflammatory cytokines IL-6 and TNF-α, as well as oxidative stress markers like MDA (malondialdehyde) and MPO (myeloperoxidase).

Fever and Hypothermia Symptoms

Another study explored CDs synthesized from *Lonicerae japonicae Flos* and their anti-inflammatory effects in an LPS-induced rat model displaying fever and hypothermia symptoms. CDs were found to lower body temperature and reduce the expression of proinflammatory cytokines. This is particularly relevant as previous research has linked fever and hypothermia to TNF-α, making C-dots a promising option for addressing these temperature-related conditions.

Bone Tissue Regeneration

Inflammation is a significant hindrance to bone tissue regeneration, especially when exacerbated by increased levels of reactive oxygen species (ROS). Inhibition of inflammation during bone regeneration is a key challenge. Recent research demonstrated the synthesis of CDs from citric acid, ammonium fluoride, and a small amount of dexamethasone (an anti-inflammatory drug). These CDs exhibited anti-inflammatory properties and showed superior potential for promoting osteogenesis in both normal and inflammatory environments. The anti-inflammatory activity of these CDs is believed to be linked to the presence of functional groups and the bioactive nature of dexamethasone. Additionally, CDs were shown to promote macrophage plasticity from the M1 (proinflammatory) to M2 (anti-inflammatory) phenotype in vivo, further highlighting their anti-inflammatory properties.

Immunosuppressive Sepsis

Another study explored the impact of CDs on macrophage plasticity in an immunosuppressive sepsis mouse model. These C-dots exhibited the ability to downregulate proinflammatory cytokines and upregulate anti-inflammatory cytokines in macrophages. Furthermore, aggregated C-dots were loaded into macrophage lysosomes, displaying excellent antibacterial capabilities. These multifaceted properties, including antibacterial, anti-inflammatory, and immunomodulatory effects, suggest C-dots as a novel approach to treating sepsis.

Anti-frostbite Agent

CDs synthesized from Artemisiae Argyi Folium (AAF) carbonisata were studied for their potential use as an anti-frostbite agent. These C-dots were found to reduce local inflammation by decreasing the expression of inflammatory mediators in mice and lowering blood glucose levels. This research highlights the diverse applications of CDs beyond the treatment of specific diseases.

These studies discussed demonstrate the versatile potential of CDs as anti-inflammatory agents, making them promising candidates for the development of new drugs and therapies in various medical contexts as reported by many [Wu, et al, **2020;** Kong, et al, **2021;** Wan, et al, **2022**; Zhang, et al, **2022;** Li, et al, **2023**].

Conclusion and Future Directions

This comprehensive review highlights the remarkable potential of CDs as anti-inflammatory agents for the treatment of various inflammation-associated diseases, underscoring their promising role as nanomedicines. Over the recent years, research into the anti-inflammatory properties of CDs has gained substantial momentum. Numerous preclinical studies have employed C-dots to target a range of diseases, including those induced by lipopolysaccharides (LPS), gout, cartilage tissue engineering, drug-induced inflammation, spinal cord injury, wound healing, non-alcoholic fatty liver disease (NAFLD), stomach cancer, gastric ulcers, acute kidney and lung injuries, frostbite, psoriasis, fever, hypothermia, and bone tissue regeneration. CDs have consistently demonstrated their protective effects, which involve the reduction of reactive oxygen species (ROS), functioning as antioxidant enzymes, and modulation of inflammatory markers and signalling pathways, most notably the NF-κB cell signalling pathway.

Although significant progress has been made in CD research regarding synthesis techniques, structural characterization, mechanistic insights, and applications, several challenges remain to be addressed before their full potential can be realized. These challenges include the need for improved C-dots with enhanced anti-inflammatory properties and studies on their toxicity, fluorescence properties, and size optimization, especially for *in vivo* applications. Surface engineering using biocompatible polymers and passivation agents is essential to overcome issues like low quantum yield. Research should also focus on the development of CDs from biodegradable and low immunogenic raw materials for use in human applications.

Consistency in CD production from batch to batch remains an issue, and in-depth comparisons of synthesis methods are essential. Advanced characterization techniques are crucial for evaluating structural-functional relationships and properties. Environmentally friendly mass production methods are needed to ensure widespread use, but this should also be considered from a safety perspective.

Further research should explore novel strategies involving C-dot nanocomposites for anti-inflammatory and other biological applications. The development of drug carriers with large surface areas, water solubility, biocompatibility, and low toxicity is essential for efficient drug delivery. Multifunctional CDs that combine gene therapy, chemotherapy, and phototherapy can be developed for comprehensive theranostic applications. Additionally, the application of bioinformatics, computational tools, and artificial intelligence technology can enhance the prediction, optimization, and fabrication of CDs and other nanomaterials.

Studies should transition from cytocompatibility assessments in cell models to long-term studies in experimental animals to determine the effects of prolonged CD use, including potential inflammation, liver and kidney damage, and immunological responses. The goal is to conduct extensive research on CD pharmacokinetics, toxicology, and their effects on the human body, paving the way for clinical trials and broad interdisciplinary collaborations in various scientific fields.

The synthesis of high-quality CDs is a significant challenge, but it holds substantial promise as a biomedicine for the treatment of inflammatory diseases as elaborated by many groups [Jiang, et al, **2018**; Mishra, et al, **2018**; Paloncýová, et al, **2018;** Du, et al, **2019**; Ghosal and Ghosh, **2019**; Jia, et al, **2019;** Liu, et al, **2020;** Tejwan, et al, **2020;** Han, et al, **2020**; Liu, et al, **2020;** Ansari, et al, **2021;** Gifani, et al, **2021;** Luo, et al, **2021;** Wu, et al, **2022**].

Anti-Inflammatory Properties of HM-CDs

Inflammation is a highly intricate biological process that involves a multitude of interconnected pathways and molecular interactions. Herbal medicine has gained recognition for its potential to exert anti-inflammatory effects, primarily due to its unique characteristics, including its multi-component and multi-target nature. However, despite the presence of bioactive substances in herbal medicine with anti-inflammatory properties, the precise mechanisms that underlie these effects still necessitate further exploration.

In this context, some HM-CDs synthesized through pyrolysis have emerged as promising candidates with demonstrable anti-inflammatory effects across various experimental models. Several specific instances illustrate the potential of these HM-CDs in mitigating inflammatory responses as mentioned below.

Mulberry silkworm cocoon-CDs (MSC-CDs) display notable anti-inflammatory effects in a range of experimental models. They exhibit efficacy in reducing inflammation in scenarios such as xylene-induced ear oedema, acetic acid-induced vascular permeability, and lipopolysaccharide (LPS)-induced systemic inflammation. Significantly, they are observed to dose-dependently lower the serum levels of prominent inflammatory markers, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). Radix sophorae flavescentis carbonisata (RSFC)-based CDs RSFC-based CDs have demonstrated their ability to counter ethanol-induced acute gastric ulcers in rats. This protective effect is achieved by inhibiting the release of pro-inflammatory mediators, such as TNF-α and IL-6, through the downregulation of the nuclear factor-kappa B (NF-κB) pathway. Notably, RSFC has a historical application in traditional medicine for the treatment of ulcerative diseases. Lonicerae japonicae floss-derived CDs (LJFC-CDs) reduce the levels of inflammatory markers, including IL-1β, IL-6, and TNF-α, in models involving LPS-induced inflammation. *Aurantii fructus immaturus carbonization-derived CDs* (AFIC-CDs) and *Puerariae lobatae radix CDs* (PLR-CDs) alleviate the joint swelling in the context of gouty arthritis. AFIC-CDs exhibit a dose-dependent reduction in the levels of inflammatory markers, such as IL-1β and TNF-α. Puerariae corylifoliae carbonisata-derived CDs (PCC-CDs) have shown potential in reducing the levels of various inflammatory markers, including IL-6, TNF-α, IL-17A, and IL-23, in a model mimicking psoriasis-like inflammation.

The favourable anti-inflammatory effects exhibited by HM-CDs can be attributed to the formation of intramolecular or intermolecular hydrogen bonds by functional groups on the surface of these particles, including N–H and O–H bonds. These hydrogen bonds play a critical role by interacting with molecules and pathways associated with inflammation, thereby modulating the overall inflammatory response. The formation of hydrogen bonds on the surface of HM-CDs is suggested as a contributing factor to their anti-inflammatory properties.

HM-CDs derived from herbal medicine sources have demonstrated considerable promise in mitigating inflammation across various experimental models. These effects are thought to be closely linked to the formation of hydrogen bonds on the surface of the CDs, which interact with key inflammatory pathways and molecules. The potential of HM-CDs in anti-inflammatory treatments underscores their significance in the realm of medicine and the management of inflammatory conditions, as observed by several research groups [Tasneem, et al, **2019;** Wu, et al, **2020;** Hu, et al, **2021].**

While summarizing the recent findings it raises some important questions and considerations regarding HM-CDs and their future development. For example, HM-CDs derived from various sources, such as fennel seeds, giant knotweed rhizome, pinellia ternata, mustard seeds, papaya, and Purple perilla, have demonstrated sensitivity to pH. Notably, giant knotweed rhizome-CDs efficiently detected Hg^{2+} based on photoluminescence over a pH range from 5.8 to 9.3. This makes them a potential Hg^{2+} fluorescent nanoprobe in both acidic and alkaline environments.

While examining the research advances in HM-CDs, focusing on their synthesis methods and applications definite promise is noted in disease treatment, ion, and molecular detection, bioimaging, and pH sensing. Their unique advantage lies in the potential therapeutic effects without the need for drug loading, thanks to the medicinal value of herbal medicine. HM-CDs have also laid the groundwork for theranostics, a combination of diagnostics and therapeutics.

The careful examination points out that current synthesis methods, particularly hydrothermal synthesis, and high-temperature pyrolysis, have limitations in terms of QY, particle size, and fluorescence intensity stability. The microwave method is suggested as a more efficient and stable alternative for synthesis, which could further expand the applications of HM-CDs. Identifying the active ingredients in HM-CDs is crucial for understanding their mechanisms of action and therapeutic potential. The high-temperature synthesis methods may lead to the decomposition or loss of certain active components of herbal medicine. Therefore, research on preserving the active compounds during CD synthesis is needed. Techniques like high-performance liquid chromatography tandem mass spectrometry (HPLC–MS) are proposed to identify the pharmacodynamic constituents of HM-CDs.

Exploiting the full potential of HM-CDs in various applications needs for more efficient synthesis methods, and the importance of identifying active ingredients to enhance their therapeutic and diagnostic capabilities. It also suggests that HM-CDs have a promising future in the field of nanomedicine and bioimaging [Dager, et al, **2019;** Zhao, et al, **2019;** Chandra, et al, **2019;** Dai, **2019**].

Metabolism and *Bio* distribution of CDs

The metabolim and distribution of nanomaterials, particularly HM-CDs have become a topic of significant interest and concern in the field of biomedical research. While HM-CDs have demonstrated remarkable safety profiles at the cellular level, our understanding of their

behaviour within a living organism is still limited. *In vitro* toxicity tests, which are conducted in controlled laboratory settings, are inadequate to comprehensively assess the safety of HM-CDs within the complex biological system of a living organism.

To address these critical knowledge gaps and to provide a more comprehensive assessment of the safety and functionality of HM-CDs *in vivo*, future studies should aim to answer the associated questions such as: metabolic pathways, biodistribution, effect of different precursors ultimately resulting in long term deposits and chronic effects.

Metabolic Pathways *in vivo*
Researchers need to elucidate the metabolic pathways of HM-CDs within a living organism. Understanding how these nanomaterials are processed, broken down, and excreted is essential to assess their safety and potential impact on the organism's physiological processes.

Distribution *in vivo*
It is crucial to investigate the distribution of HM-CDs within the organism. This involves tracking where these nanomaterials travel, which organs, and tissues they accumulate in, and how they are transported through the circulatory system. Knowledge of their distribution can provide insights into potential interactions and effects on specific body systems.

Effect of Different Herbal Precursors
Different herbal precursors used in HM-CD synthesis may lead to variations in the metabolism and distribution of these nanomaterials *in vivo*. Researchers should explore whether the choice of herbal source affects the behaviour of HM-CDs within the organism, as different herbal extracts contain unique chemical components.

Chronic Toxicity and Long-term Deposits
Long-term treatment with HM-CDs raises questions about whether these nanomaterials can accumulate within the body and cause chronic toxicity over time. Researchers must assess whether HM-CDs deposit in tissues or organs and evaluate their impact on the overall health and well-being of the organism with prolonged exposure.

Accordingly, conducting more comprehensive *in vivo* toxicity tests, distribution studies, and metabolism assessments is essential to fully understand the behaviour and safety of HM-CDs within living organisms. These investigations will not only contribute to our knowledge of the unique functions and potential benefits of HM-CDs but also ensure their safe use in various biomedical applications. Addressing these research questions is crucial to advance our understanding of nanomaterials and their interaction with biological systems.

Realization of Theranostics

The photoluminescent CDs have attracted significant attention in the field of current research of biomedicine. The integration of diagnosis and treatment using HM-CDs holds immense potential, particularly because of the therapeutic effects they offer. However, several challenges and considerations need to be addressed to advance the development of HM-CDs for theranostic applications. Existing studies have primarily focused on the therapeutic effects and bioimaging properties of HM-CDs separately. The potential for combining both aspects into a single, integrated approach, known as theranostics, remains largely untapped.

The success of optimal targeted therapy using HM-CDs relies on ensuring their safety and simplicity. This means that HM-CDs should not pose harm to the organism, and their administration and application should be straightforward. Red-emission CDs are highly desirable for bioimaging applications due to their minimal interference with the biological matrix, superior deep tissue penetration, and reduced autofluorescence background in biological samples. The synthesis of red HM-CDs is crucial for stable and efficient bioimaging. Considering the involvement of aberrant mitochondrial function in various human diseases, the imaging of HM-CDs within mitochondria is a significant area of focus for future research.

Currently, herbal medicine and phytomedicines serve as the primary sources of precursors for HM-CDs. Exploring a wider range of herbal medicines and natural sources is essential for expanding the diversity and functionality of HM-CDs. Additionally, protein-rich materials from animal-based medicines have the potential to act as sources of abundant heteroatoms or functional groups. This exploration can contribute to the improvement of the properties and applications of HM-CDs. Therefore, CDs derived from animal-based medicines represent a crucial area for future research and development.

HM-CDs have shown minimal toxicity, prompting an intriguing question: Can HM-CDs be used to reduce the toxicity of inherently toxic herbal medicines, such as Manchurian dutchman's pipe stem, common monkshood, or aristolochic acid?

In case toxicity reduction is achieved, it raises the question of whether the active ingredients of the herbal medicines will undergo changes during the synthesis process, potentially losing their original efficacy.

If this is a feasible approach, the transformation of toxic herbal medicines into CDs could represent a novel processing tool, offering a solution to mitigate their adverse effects. This could significantly impact the clinical applications of such herbal medicines.

The unique properties of HM-CDs, including their photoluminescence, make them promising candidates for

theranostic applications. However, to realize the full potential of HM-CDs in the field of medicine, several challenges must be addressed, including the safe integration of therapeutic and bioimaging functions, the development of red-emission HM-CDs, mitochondrial imaging, and the exploration of diverse precursors. Additionally, the reduction of toxicity and enhancement of efficiency through the transformation of toxic herbal medicines into CDs could revolutionize the clinical application of such remedies as discussed elsewhere [Shi, et al, **2019**].

Recycling Herbal Residues

The extraction efficiency of herbal medicine is approximately 50%.[160] The residual herbal residues also contain some vital active ingredients. Strategies to recycle herbal residues are underway. In the future, we must attempt to extract CDs from herbal residues, and reuse them in the diagnosis and treatment of diseases, achieving optimal utilization of herbal medicine.

Abbreviations

AFIC-CDs : Aurantii fructus immaturus carbonisata-derived CDs;
APTT : Activated partial thromboplastin time;
BBB : Blood–brain barrier;
CDs : Carbon dots;
E-CDs : Ethanol-papaya CDs;
EYO-CDs : Egg yolk oil CDs;
FIB : Fibrinogen;
H-CDs : Ginkgo fruits-CDs using hydrothermal methods;
H-N-CD : Nitrogen-doped CDs from ginkgo fruits;
HM-CDs : Herbal medicine-CDs;
JMC-CDs : Junci Medulla Carbonisata CDs;
JSX : Jiaosanxian;
LJFC-CDs : Lonicerae japonicae Flos-derived CDs;
M-CDs : Ginkgo fruits-CDs using microwave methods;
MSC-CDs : Mulberry silkworm cocoon-derived CDs;
PCC-CDs : Phellodendri Cortex Carbonisatus CDs;
PTC-CDs : Pollen Typhae Carbonisata-CDs;
QY : Quantum yield;
RSFC : Radix Sophorae;
SHC-CDs : Schizonepetae Herba Carbonisata CDs;
W-CDs : Water papaya CDs

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