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Review Article

The Application of Fullerene Derivatives in Medicine and Specific Endocrinological Conditions

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Abstract

Fullerene derivatives have select properties that have attracted investigation regarding applications in medicine. For the most part, they have demonstrated high biocompatibility and low toxicity in humans and animals. They have shown antimicrobial, antiviral, and antioxidant properties, and act as an ROS-scavenger. Specific fullerene derivatives are being considered in treating multiple sclerosis, skin disorders, HIV infection, cancer, ischemia, and osteoporosis. They have shown a potential for applications in dermatology, treating acne vulgaris and erythema. Specific fullerene derivatives are used as a synergistic agent in diagnostic imaging, biosensing, drug-delivery, targeted therapy, and theranostic procedures. Exposure to certain fullerene materials can be hazardous to human health, particularly as potential endocrine disruptors. Nevertheless, fullerene derivatives are showing promise in their adjunctive application in medicine and specific endocrinological disorders.

Keywords: *Antioxidant; Biocompatibility; Biosensing; Diagnostic Imaging; Drug-Delivery; Endocrinological Disorders; Fullerene*

Abbreviations

C_{60}: Carbon 60; C60FAS: C60 Fullerene Aqueous Colloid Solution; CNH: Carbon Nanohorn; CNT: Carbon Nanotube; CT: Computerized Tomography; DF-1: Dendrofullerene; HIFU: High-Intensity Focused Ultrasound; HIV: human immunodeficiency virus; MSN: mesoporous silica nanoparticles; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive Oxygen Species; US: Ultrasound

Introduction

Fullerenes applications in medicine

The soccer-ball-shaped nanomaterial can be manipulated by derivatization, dissolution, and functionalization with therapeutic drugs, diagnostic agents, or polymers to develop or improve treatment, diagnosis, and monitoring of specific diseases [1]. The unique structure and properties of fullerene, such as inertness and stability, have made it an attractive research molecule in medicine [2]. Carbon 60 (C_{60})

is the most researched buckyball in medicine due to its high symmetry, ease of availability, and affordability. The buckyball's hollow structure allows for effective trapping of atoms inside it, enabling drug-delivery to the target site [3,4]. *In vitro* and *in vivo* cytotoxicity studies in human and animal cells have demonstrated the non-cytotoxicity or extremely low acute toxicity of C_{60}.

The application of fullerene derivatives in the treatment of specific disorders and diseases

Multiple studies have supported the antimicrobial [5-7], antiviral [8], and antioxidant properties of fullerene [9]. Anionic fullerene is a free radical scavenger with discernable antioxidant properties, attributed to conjugated double bonds and high electron affinity [9]. These properties contribute to its application as a cytoprotective [9-11] and anti-inflammatory agent [12], as well as in the treatment of multiple sclerosis [13], skin disorders [14], HIV infection [15,16], cancer [17], ischemia [18], and osteoporosis [19].

An example of the antiviral property is significant inhibition of reverse transcriptase levels in HIV by dendrofullerene 1 (DF-1) and derivative 2 trans-isomer. Amino acid derivatives of fullerene (Carbon 60-1-Ala) have also been reported to inhibit HIV and hepatitis C virus by binding to the active site of the viral protease [8].

Cationic fullerene derivatives have potential antimicrobial properties [6], possibly attributed to its intercalation into the cell membrane, inhibiting the respiratory chain and photosensitizing effects. Fullerene also inhibits the growth of several microbes (fungi and bacteria), including *Candida albicans, Propionibacterium acnes*, *Malassezia furfur, Staphylococcus epidermidis,* and *Escherichia coli* [7,20-23].

The neuroprotective action of fullerene is attributed to its ability to react with superoxide and hydroxyl radicals, capable of causing cellular damage through oxidation of lipids, DNA, proteins, and other substances. Fullerene is considered a superior free radical-scavenging agent (radical sponges). In humans, reactive oxygen species (ROS) can induce premature apoptosis (programmed cell death) [11,22], causing neurodegenerative diseases, such as Parkinson's [24] and Alzheimer's diseases [24]; thus, the antioxidant property of fullerene makes it a viable therapeutic option.

Fullerene derivatives can protect cells by neutralizing free radical threats [25,26]. This cytoprotectant property is exploited by the cosmetic industry to develop products that protect skin from harmful ultraviolet radiation [26].

Fullerene has potential dermatology applications, especially in treating acne vulgaris and erythema, due to its antioxidant properties [27-29]. In one specific study, fullerene dispersed in a gel matrix was applied to 11 patients with mild to moderate acne vulgaris for 8 weeks [28]. Compared to the adapalene application (loaded in gel), a significant number of patients responded to fullerene. The skin water content of the respondents was also significantly improved without any apparent side effects. In another study, the application of fullerene-loaded hydroquinone (2%) cream provided better recovery from erythema after laser therapy than hydroquinone-only (2%) cream [29].

The anti-inflammatory activity of fullerene is mediated through its ability to neutralize free radicals. Preincubation with fullerenes inhibited the IgE-dependant allergic mediator, which regulates Ag-driven type I hypersensitivity in human mast cells and peripheral blood basophils. This finding offers insights into therapeutic possibilities using fullerene in diseases in which these cells play a critical role [30], such as anaphylaxis, hay fever, certain autoimmune diseases [31], multiple sclerosis [13,32], arthritis [33], and asthma [34,35]. In a mice-model study, fullerene effectively controlled airway inflammation, eosinophilia, and bronchoconstriction by enhancing the production of P-450 eicosanoid metabolite cis-epoxyeicosatrienoic acid [35].

Ischemic injuries comprise 35% of all musculoskeletal system-related injuries. Ischemic–reperfusion injuries in the postoperative setting could lead to severe complications requiring amputation [36]. The ability of fullerene to bind up to six electrons makes it an effective antioxidant with the potential to decrease muscle fatigue syndrome [37]. Two studies explored the potential role of pristine C_{60} fullerene aqueous colloid solution (C_{60}FAS) in preventing and correcting fatigue and ischemic injury in rat skeletal muscle (the soleus muscle and triceps surae, respectively) [33,34].

Bone remodeling, a cyclical process (bone resorption by osteoclasts followed by bone formation by osteoblasts) occurring throughout life, is essential in maintaining bone homeostasis. Excessive osteoclastic activity can disturb bone homeostasis and lead to osteoporosis. Geng., *et al*. (2017) published a study exploring the role of fullerenol, a derivative of fullerene, in osteoporosis. They found that fullerenol inhibited osteoclastic differentiation, maturation, and function, highlighting the potential of fullerene in the management of osteoporosis [38].

The cytotoxic role of fullerene has been explored in several studies. In one such study, researchers_explored the role of novel water-soluble fullerene glycerin derivative. Fullerene exhibited cytotoxicity on cancer cell lines as measured by flow cytometry and MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay [39].

Dysregulation and degradation of the extracellular matrix can lead to a number of diseases, including invasive cancer. Sosnowska., *et al*. (2019) explored the role of fullerene C_{60} on cancer cell lines (HepG2 and C3A). They showed that fullerene C_{60} in the form of nanofilm, which mimics the normal extracellular matrix, can alter the behavior of cancer cells towards normalcy [40].

The addition of fullerene C_{60} in apatite/polymer polyelectrolyte composite has shown potential in surgical and conservative management of periodontal diseases. The composite provides additional phosphorus and calcium ions, strengthening dental structure, providing antimicrobial activity, acting as a drug-delivery system for extended periods, and eliciting minimal side-effects [41].

Fullerene derivatives, in particular C_{60}, have unique electrochemical and physical properties, which can be utilized in various medical applications. Fullerene can bind to the hydrophobic cavity of HIV proteases, inhibiting the access of substrates to the enzyme's catalytic site. Also, it acts as a radical scavenger, reducing ROS concentrations. When exposed to light, fullerene produces singlet oxygen in high quantum yields, cleaving DNA bases [42]". However, according to Kerna and Flores (2020), "the primary antioxidant benefit of fullerene materials might be through the activation of Nrf2" [43]. Rodriguez., *et al*. (2019) noted that a critical role of Nrf2 is in reducing free radical proliferation via increasing endogenous antioxidant enzymes [44].

The application of fullerene derivatives in the treatment of endocrinological disorders and diseases

To date, no significant studies have been performed to correlate the beneficial application of fullerene derivatives (through an oral, dermal, or inhalation pathway) regarding specific endocrine glands or their dysfunction. Nevertheless, specific fullerene derivatives have been shown to act as a synergistic agent, contributing favorably in the treatment of endocrine disorders (e.g. fibroids, benign tumors, and malignant cancers) through their enhanced diagnostic imaging, biosensing, drug-delivery (chemical-tailoring, drug-loading, and drug-nanocarriers), and targeted-therapy— for the most part, without inducing significant toxicity.

Discussion

Fullerene derivatives in diagnostic imaging, biosensing, drug-delivery, and treatment

Fullerene nanoparticles (about 1 nm in size) with a hydrophobic core can permeate the cell membrane and bind mitochondria. This characteristics allows them to carry drugs or genes for targeted-delivery [45,46]. Carbon nanotubes (CNTs) are known to facilitate the targeted delivery of amphotericin B [47]. CNT-facilitated delivery of doxorubicin enhanced the intracellular penetration of the chemotherapeutic drug [48-50]. CNTs and carbon nanohorns (CNHs) of fullerene have potential proteomics, tissue engineering, and bioimaging applications. Their ability to bind and present different antigens has been exploited in designing novel vaccines [51,52].

Fullerenes in diagnostic imaging

C_{60} derivatives are promising as a contrast material in magnetic resonance imaging (MRI). A fullerene gadolinium complex, in which gadolinium ions remain trapped inside the fullerene molecule, known as gadofullerene, has demonstrated potential applications *in vivo* and *vitro* studies. Moreover, as the trapped toxic gadolinium molecule cannot exit the fullerene structure, the complex can be used as a radiotracer in *in vivo* settings [53].

Fullerene has applications in the diagnosis and management of oral cancer. In oral lesions, exosome levels are elevated, which serve as a diagnostic biomarker. Exosomes have been studied using atomic force microscopy with nanoparticles, including fullerene.

According to He., *et al*. (2019), "Composite nanospheres demonstrate potential theranostic application as a multifunctional contrast agent for dual-modality biological imaging and highly efficient synergistic imaging-guided high-intensity focused ultrasound (HIFU) ablation" [54]. Composite nanospheres enhance ultrasound and computerized tomography (CT) imaging.

Wang., *et al*. (2020) validated that the biological targeting synergistic agent can simultaneously achieve tumor-biotargeted multimodal imaging, HIFU synergism, and multimodal image monitoring in HIFU therapy [55]. The biological targeting synergistic agent provided information for the early diagnosis of tumors and multimodal imaging monitoring during HIFU ablation.

Fullerenes in biosensing

The ability of fullerene to flouresce makes it an attractive option in biosensors, often used to study the physiology and pathology of a biological system [46,56,57].

Pirzada and Altintas (2019) noted: "Nanomaterials introduce versatility to the sensing platforms and may even allow mobility between different detection mechanisms" [58].

Liang., *et al*. (2014) wrote: "Nanomaterials can be designed and synthesized in needed sizes and shapes, and they possess unique chemical and physical properties, which make them useful as DNA carriers or assistants, excellent signal reporters, transducers, and amplifiers" [59]. Combined with functional DNAs, nanomaterials contribute to novel assay platforms, highly-sensitive biosensing, and high-resolution imaging.

According to Lee., *et al*. (2019): "Nanomaterials-based biosensing systems provide a significant improvement on healthcare, including rapid monitoring and early detection of infectious disease for public health" [60].

Fullerenes in drug-delivery

Nanotechnology in drug-delivery has resulted in the functionalization of the surface of mesoporous-silica-based nanocarriers with stimuli-responsive groups, nanoparticles, polymers, and proteins [70]. According to Vivero-Escoto., *et al*. (2010), "These nanocarriers work as caps and gatekeepers for controlled release of various cargos is just one of the exciting results reported in the literature that highlights mesoporous silica nanoparticles (MSNs) as a promising platform for various biotechnological and biomedical applications" [61].

Rosenholm., *et al*. (2010) opined: "One of the big challenges of medicine today is to deliver drugs specifically to defected cells" [62]. Nanoparticles can cross physiological barriers to access targeted tissues and enhance cell specificity.

Tang and Chen (2012) concluded: "MSNs as drug delivery systems (DDSs) show significant advantages over traditional drug nanocarriers" [63]. Drug-delivery, using mesoporous silica nanoparticles (MSNs) and their multifunctional counterparts as drug carriers, has overcome specific barriers in targeted cancer therapy.

Anilkumar., *et al*. (2011) stated: "Fullerenes as a unique class of carbon allotropes have been studied extensively for their distinctive material properties and potential technological applications, including those in biology and medicine" [64]. Fullerenes elicit drug-like functions, improving the formulation of established drugs.

Kumar and Raza (2017) noted: "The drug release rate controlling behavior, higher drug loading, immuno-neutrality, substantial biocompatibility, capability to bypass mononuclear phagocytic system, long circulating nature and tissue extraction by virtue of enhanced permeability and retention effect are the major promises of these nanocarriers" [65].

Fullerenes in theranostic procedures and surgeries targeting specific cancers

Zhou., *et al*. (2017) reported: "The fast development of theranostic nanomedicine significantly promotes the development of ultrasound-based biomedicine" [66]. The biological effects and biosafety of silica-based micro/nanoparticles are based on their high biocompatibility and versatile composition and structure regarding ultrasound-based (US-based) theranostic biomedicine.

Likewise, Li., *et al*. (2019) stated that these materials act as highly efficient theranostic agents for targeted multimodal and combined therapy for cancer treatment [67].

Chen., *et al*. (2015) consider the incorporation of nanobiotechnology as a "bloodless scalpel" for successful cancer therapy, minimizing damage to surrounding normal tissues, due to the noninvasive and site-specific therapeutic features of HIFU [68].

Research by Sun., *et al*. (2012) showed that the "successful introduction of superparamagnetic microcapsules into HIFU cancer surgery provided an alternative strategy for the highly efficient imaging-guided non-invasive HIFU synergistic therapy of cancer" [69].

In more recent research, Want., *et al*. (2020) concluded: "This biological targeting synergistic agent can not only provide information for early diagnosis of tumors but also realize multimodal imaging monitoring during HIFU ablation simultaneously with HIFU treatment, which improves the shortcomings of HIFU treatment and has broad application prospects" [70].

Biocompatibility, toxicity, and endocrine disruptor

According to Chen., *et al*. (2013): Due to the intrinsic structural characteristics of elaborately designed MSNs, such as large surface area, high pore volume, and easy chemical functionalization, they have been extensively investigated for therapeutic, diagnostic and theranostic (concurrent diagnosis and therapy) purposes, especially in oncology. Systematic *in vivo* bio-safety evaluations of MSNs have revealed evidence that the *in vivo* bio-behaviors of MSNs are strongly related to their preparation procedures, particle sizes, geometries, surface chemistries, dosing parameters, and administration routes. *In vivo* pharmacokinetics and pharmacodynamics further demonstrated the effectiveness of MSNs as passively or actively targeted drug-delivery systems (DDSs) for cancer chemotherapy [71].

Asefa and Tao (2012) concluded: There is "cytotoxicity of different types of MSNs and the effects of their various structural characteristics on their biological activities . . . synthetic strategies (should be) developed to reduce or eliminate any possible negative biological effects associated with MSNs or to improve their biocompatibility" [72].

In a study on 8-wk-old female Sprague-Dawley rats by Monteiro-Riviere., *et al*. (2012), minor histopathology changes were noted in only one animal, suggesting that fullerol was well tolerated after IV administration to rats [73].

According to Johnston., et al. (2010): Manipulating fullerene water solubility has included the use of surface modifications, solvents, extended stirring, and mechanical processes. However, the ability of these processes to impact fullerene toxicity requires assessment, especially when considering the use of solvents, which particularly appear to enhance fullerene toxicity. The hazards to human health associated with fullerene exposure, are uncertain at this time. Further investigations are required to determine such effects before an effective risk assessment can be conducted [74].

Kerna and Flores (2020) concluded: Experiments conducted with fullerene materials have resulted in low toxicity of tissues and cells. These materials' low toxicity property allows for their application in boosting vitality, longevity, and the immune system in humans, animals, and plants. However, the outcomes in the manufacturing process of experimental-grade nanocarbon onion-like fullerene materials can be inconsistent (even within the same batch), making it challenging to perform reliable assessments and reproducible studies of their biological benefits, biocompatibility, and potential toxicity. Also, their dosage, timing, and duration should be further evaluated and established for therapeutic use in specific conditions [75].

Specific fullerene derivatives may act as endocrine disruptors. Gore (2020) noted, "When neuroendocrine homeostasis is disrupted by environmental endocrine-disrupting chemicals, a variety of perturbations can ensue, particularly when endocrine disruption occurs during critical developmental time periods" [76].

Iavicoli., *et al*. (2013) noted: There is a considerable lack of information on the potential nanoparticle hazard to human health, particularly regarding their possible toxic effects on the endocrine system. Current data support that different types of nanoparticles are capable of altering the normal and physiological activity of the endocrine system. However, a critical evaluation of these findings suggests the need to interpret these results with caution, since research on potential endocrine interactions and the toxicity of nanoparticles is limited [77].

Conclusion

Fullerene is becoming actively researched in medicine due to its unique structure and properties. *In vitro* and *in vivo* cytotoxicity studies in human and animal cells have demonstrated non-cytotoxicity or extremely low acute toxicity of the fullerene allotrope, C_{60}. Numerous studies have revealed the antimicrobial, antiviral, and antioxidant properties of fullerene, as well as its ROS-scavenging properties. Its application may help treat multiple sclerosis, skin disorders, HIV infection, cancer, ischemia, and osteoporosis. Also, fullerene has potential dermatological applications, especially in treating acne vulgaris and erythema, due to its antioxidant properties.

No significant studies have been performed to correlate the beneficial application of fullerene derivatives (through an oral, dermal, or inhalation pathway) in specific endocrine glands or their dysfunction. However, specific fullerene derivatives have been shown to act as a synergistic agent, contributing favorably to the treatment of endocrine disorders, such as fibroids, benign tumors, and cancers, due to diagnostic applications in imaging, biosensing, drug-delivery, targeted-therapy, and theranostic procedures.

Low to no toxicity in tissues and cells have been reported regarding fullerenes experimental applications. However, cytotoxicity of different types of MSNs has been reported. Strategies should be developed to reduce or eliminate any adverse biological effects and improve their biocompatibility. The manufacturing process needs to be refined, and the dose and duration of treatment for specific applications should be determined. Although the hazards to human health associated with fullerene exposure remain uncertain at this time, fullerene derivatives are showing promise in their adjunctive application in medicine and specific endocrinological disorders. Thus, further research to explore their beneficial application in medicine is warranted.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Supplementary Note

As a review, this paper is designed as a brief introduction to fullerenes regarding their application in medicine and specific endocrinological conditions. Other articles have been (or will be) published on the application of specific fullerene materials in the cardiovascular system, respiratory system, gastrointestinal system, neurological system, veterinary medicine, agriculture, pharmacology and toxicology, and other topics. These distinct mini-review articles could have been combined into a much lengthier review or research article. However, to have done so, the subject matter would have resulted in only one publication in one journal to exclude other medical specialties. The purpose of these papers is to disseminate the purported biocompatibility and beneficial effects of fullerenes to the broadest audience of students, researchers, and medical practitioners as possible. The authors hope that the introduction to the application of fullerene derivatives in various and diverse disciplines spawns curiosity and further research regarding fullerene materials. Fullerene materials seem poised to become a vital part of the future of human medicine, veterinary medicine, and agriculture. However, more research is needed to determine any adverse effects of their long-term use. Also, the specific fullerene materials' manufacturing process requires standardization to provide consistent quality and batch samples. Dosage and duration of treatment with fullerene materials for specific conditions need to be established by evidence-based research.

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