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REVIEW PAPER

Fullerene nanoparticle as new therapeutic agent for the nervous system disorders

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ABSTRACT

Neurodegenerative diseases and brain tumors are significant medical ailments that impact the brain. Administering therapeutic drugs to the brain is more challenging compared to other organs or systems. The existence of the blood-brain barrier (BBB) poses significant complexities and challenges in delivering drugs to the brain. This study explores the potential of Fullerene nanoparticles as a novel therapeutic agent for delivering drugs to the brain and their neuroprotective roles within the central nervous system. Novel drug delivery methods have been devised to surmount obstacles posed by BBB and accomplish targeted drug delivery to the brain. Carbon nanostructures are an excellent option for delivering drugs into the brain because they have favorable biocompatibility and can easily penetrate BBB. Furthermore, these nanocarriers has the potential to serve as a therapeutic agent inside the central nervous system, exhibiting neurogenerative properties in some cases. Additionally, their impact on the proliferation of neurons and their ability to counteract the formation of amyloid plaques is particularly remarkable. Carbon-based nanomaterials, including zero-dimensional fullerene (C60), one-dimensional carbon nanotubes (CNTs), and two-dimensional graphene, have shown significant potential in the area of nanomedicine. This is attributed to their unique blend of chemical and physical characteristics, as well as their hydrophobic surfaces. Fullerene nanoparticles have the potential to greatly improve the treatment of brain illnesses by serving as both carriers and therapeutic agents.

Keywords: *Fullerenes, Nanotechnology, Neuroprotection, Oxidative stress*

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INTRODUCTION

The blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier serve as obstacles to the transport of drugs into the brain. Drugs with low molecular weight, high lipophilicity, and favorable partition coefficients are able to permeate these barriers. Nevertheless, a significant number of medications fail to attain these characteristics, hence posing challenges in the treatment of brain disorders. Despite the use of invasive methodologies, these treatments exhibit low patient compliance and acceptability owing to their intricate and expensive nature. Current research is focused on developing nanoparticles (NPs) that can effectively penetrate the blood-brain barrier (BBB), as particles smaller than the BBB may traverse the membrane [1]. Fullerenes, the third carbon allotrope, were first identified in 1985. They consist of a truncated icosahedron structure composed of 60 carbon atoms. Due of their symmetrical structure, stiffness, and stability, they have been widely explored in different domains. Nevertheless, the limited solubility of these substances in water-based solvents restricts their use in the field of biomedicine [2]. In recent times, scientists have created a range of fullerenes that are soluble in water and compatible with living organisms. These include hydrolyzed fullerenes (fullerenols), carboxyfullerenes,

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aminated fullerenes, fullerenes modified with peptides, and endohedral metallofullerenes such as Gd@ [3]. Fig. 1 demonstrates the versatile use of fullerene-derivative nanoparticles in many biomedical applications, such as radiotracers [4, 5], MRI contrast agents for metallofullerenols, and drug delivery systems. The production of these nanoparticles derived from fullerene has enabled a more thorough understanding of their characteristics and possible uses in several domains [6-9].

The actions of Fullerene nanoparticles in the central nervous system (CNS) are very intriguing; however they do not function as an ideal drug carrier. Carbon-derived nanostructures have been discovered to have a function in the process of neuro-regeneration and the formation of neurites. Neuro-regeneration refers to the process of repairing and restoring neurons that have been damaged or lost due to neurodegenerative illnesses. Carbon structures possess neuro-regenerative properties that have the potential to advance the treatment of neurodegenerative illnesses [10]. The study reports the ability of fullerenes to counteract the formation of amyloid aggregates, suggesting their potential as a future treatment for amyloid-related illnesses such as Alzheimer's disease. Carbon-based nanostructures possess neuroregenerative properties, making them beneficial in the treatment of neurodegenerative conditions such as Alzheimer's and Parkinson's disease. Fig. 2 depicts the activities of different carbon nanostructures in Alzheimer's and Parkinson's disease. To find out

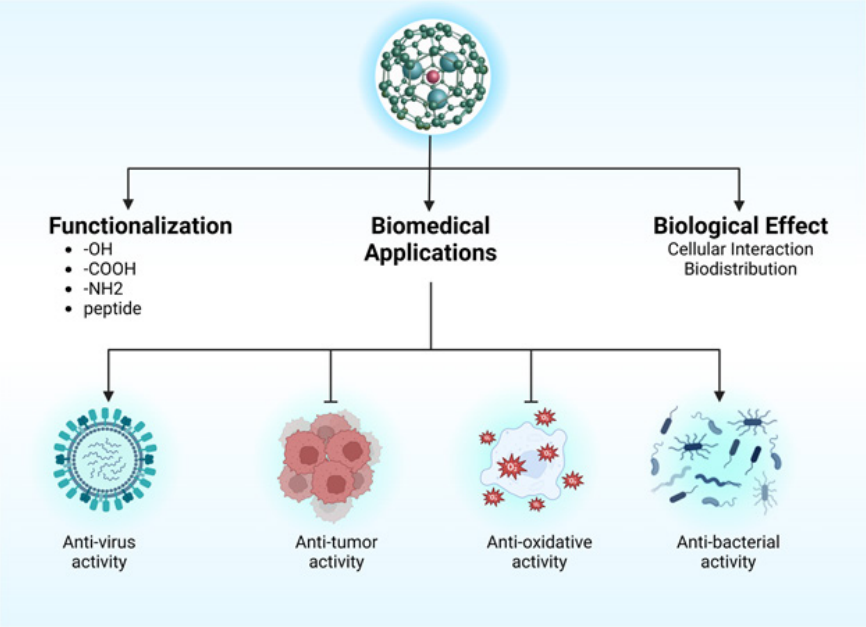

Fig.1. Nanopharmaceuticals using fullerene-based nanoparticles for disease treatment

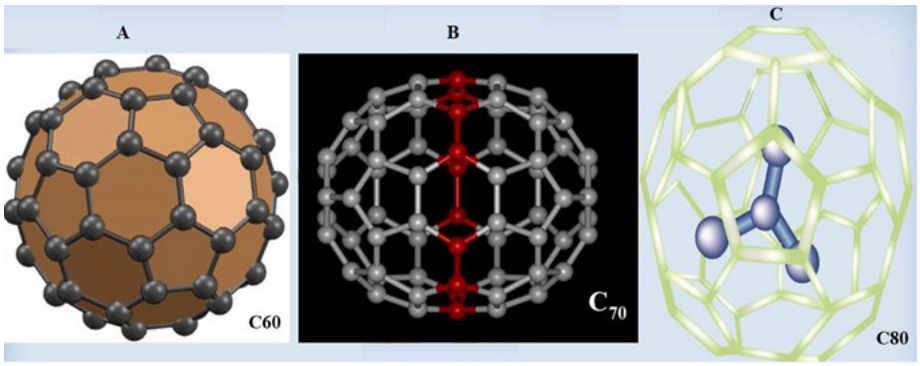

Fig. 2. Illustrations of fullerene formations. (A) Unoccupied C60 fullerene cage, (B) unoccupie d C70 fullerene cage, and (C) C80 endohedral fullerene encapsulating gadolinium (175, 176)

if carbon nanostructures are safe in a biological system, tests have been done both *in vivo* and *in vitro* to see if they are biocompatible and toxic [11, 12]. The purpose of this review is to introduce our Fullerene nanoparticle as a recently developed therapeutic agent for the treatment of diseases that affect the neurological system.

General characteristics of fullerene

Carbon displays several allotropes, such as diamond, graphite, and other variants. Fullerene is the third structural type of carbon, exhibiting different arrangements of its atoms [13]. Research on this carbon allotrope and its derivatives started thirty years ago with Kroto and his colleagues, who identified fullerene as a new type of carbon with distinct properties. Buckminsterfullerene (C60) is a symmetrical polyhedron consisting of 60 carbon atoms. These atoms are arranged in pentagons connected by single C5-C5 connections and hexagons connected by double C5-C6 bonds. The C60 fullerene molecule has a diameter of 0.7 nm, making it a significant member of the carbon nanomaterials (CNMs) family. The discovery of C60 fullerene has generated significant attention in medicinal chemistry owing to its considerable potential as a physiologically active molecule [14].

Fullerenes are extensively used in many biological applications due to their distinctive geometrical forms, innovative photophysical features, and excellent radical scavenging effectiveness [11, 15]. Buckminster fullerenes have strong radical scavenging properties due to their capacity to neutralize numerous radicals per each fullerene molecule. Nevertheless, the radical scavenging activity can only be applied to a biological system if the water solubility of the fullerene is enhanced [16]. Empty cage fullerenes, seen in Fig. 2A & B, exhibit distinctive electrochemical characteristics and possess a broad spectrum of potentially advantageous biological qualities. Another kind of fullerene has the capability to encapsulate metals inside its structure (Fig. 2C) [17]. The inclusion of the π electron moiety in fullerenes enhances intermolecular interactions, but it also renders them insoluble in the majority of typical solvents. The unfavorable characteristics of these molecules, such as their limited solubility in polar solvents and tendency to form aggregates in aqueous solutions, may be remedied via chemical or supramolecular methods [18]. The solubility of fullerenes in polar fluids is improved by incorporating them into ionic and nonionic groups, thereby addressing the limits posed by C60 [19, 20]. Jiang et al. used radical polymerization using vinylpyrrolidone to create a nanoball structure of fullerene derivatives that exhibit excellent water solubility [21]. C60 and its derivatives are highly regarded as effective vehicles for drug delivery due to their exceptional fluorescence characteristics and little toxicity. The C60 molecule has been extensively used in photodynamic therapy (PDT) [22]. Furthermore, C60 fullerene has been regarded as a powerful therapeutic agent for the management of illnesses such as cancer, diabetes, Parkinson's, and Alzheimer's [23, 24].

Antioxidative activity of fullerenes

Fullerenes, which are often referred to as "free radical sponges," possess a one-of-a-kind structure that allows them to ensnare many radicals inside a single molecule. This unique structure enables fullerenes to possess powerful antioxidant activity that safeguards against cytotoxicity brought on by intracellular oxidative stress. As a result of their ability to behave as both oxidants and antioxidants in biological systems, these sponges may exhibit some paradoxical features. One of the factors that lead to the development of diseases is the production of free radicals inside cells. These free radicals include reactive oxygen species (ROS) and reactive nitrogen species. Through a process known as the Fenton reaction, reactive oxygen species (ROS) such singlet oxygen and hydrogen peroxide are able to produce oxygen radicals like superoxide. These organisms have the ability to interact with large molecules and change their function, which has the potential to have negative effects on a variety of biological processes. However, the usage of antioxidants, such as vitamins A and C, is mostly focused on non-prescription supplements with the purpose of promoting general well-being and reducing the effects of aging. Research has shown that antioxidants may minimize damage and slow the progression of disease pathology. On the basis of its capacity to absorb electrons and disseminate them via the three-dimensional p-conjugated structure that is scattered throughout its surface, the carbon cage of empty cage fullerenes (Fig. 2) [17] may have antioxidant activity. This is because the carbon cage is typically composed of carbon 60 and carbon 70. They have the ability to scavenge

free radicals, which has led to their potential as a new method for treating a wide variety of diseases and pathologies. Some of these diseases and pathologies include multiple sclerosis (MS) [13], neurodegenerative diseases [25], anti-HIV activity [26], cancer [27], radiation exposure [28], ischemia [29], osteoporosis [30], general inflammation [31], and selective antimicrobial agents against bacteria [32]. It is interesting to note that mice and rats that are given water-solubilized carboxylated fullerenes on a continuous basis had considerably longer lifespans when compared to littermate controls. There are almost an infinite number of ways in which side groups may be added to the carbon cage in order to induce functionality [33, 34]. This might lead to the discovery of possible solutions to some of the most perplexing issues in contemporary medicine.

Fullerene-based materials as neuroprotective agents

Oxidative stress is a factor in neurological disorders such as ischemia and neurodegenerative diseases [35-37]. It leads to a decrease in mitochondrial function, heightened oxidative harm, and alterations in the antioxidant defense system [38, 39]. Scientists are now engaged in the development of innovative neuroprotective medications, using fullerene-based substances because of their remarkable antioxidant qualities, which provide a diverse array of neuroprotective capacities [40, 41].

Carboxyfullerenes, which are a kind of fulllerene-derivatives that may dissolve in water, have shown their ability to protect the nervous system in different experimental models. Research has shown that malonic acid derivatives of C60, namely C63((COOH)2)3, reduce the occurrence of excitotoxic neuronal death in cortical neurons when exposed to NMDA, AMPA, or oxygen-glucose deprivation. The in vivo findings have further shown that the administration of carboxyfullerenes in a transgenic mouse model for familial amyotrophic lateral sclerosis resulted in a delay in the development of symptoms and mortality, as well as an improvement in functional performance when compared to animals treated with saline [42]. The study conducted by Makarova et al. [43], focused on the use of fullerene derivatives to treat Alzheimer's disease. The researchers found that when beta-amyloid peptide 25-35 was injected directly into the hippocampus, it inhibited the production of beta-amyloid 25-35 deposits in the pyramidal neurons of the hippocampus, hence preventing neurodegeneration. The occurrence of focal cerebral ischemia results in substantial generation of intravascular free radicals, which may be alleviated by the use of free radical scavengers and antioxidants [44, 45]. The research conducted by Huang et al.[46] , investigated the impact of hexasulfobutylated C60 on focal cerebral ischemia in vivo. The results demonstrated the favorable benefits of this compound in lowering the size of the infarcted area.

Lin et al. [47], did research investigating the effects of carboxyfullerene as a pharmaceutical treatment for rat brain damage. The carboxyfullerene was supplied either by intravenous injection or intracerebroventricular infusion, 30 minutes before to the occurrence of transient ischemia-reperfusion. Despite the absence of any observable protection, the intracerebroventricular injection had a substantial effect in reducing the size of the infarcted region and mitigating oxidative harm. Nevertheless, these defensive benefits were associated with unfavorable alterations in behavior, indicating possible undesirable consequences when delivered in a living organism.

According to the research conducted by Zha et al. [48], fullerene derivatives have a dual impact that varies depending on the concentration used. Water-soluble polyhydroxy fullerene has a biphasic effect on hippocampus neuronal viability. At low concentrations, it enhances viability and safeguards neurons against oxidative damage. Conversely, at high concentrations, it diminishes neuron viability and triggers apoptosis. This prompts inquiries on the toxicity concerns associated with C60 and its use in nanomedicine. Additional investigation is required to comprehend the dual behaviors that are influenced by the concentration. Lin et al. [49], conducted a research to assess the neuroprotective effects of carboxyfullerene in living organisms. The researchers used iron injection to deliberately cause degeneration of the nigrostriatal dopaminergic pathway. After the administration of iron, there was a noticeable occurrence of oxidative damage and a reduction in the amount of dopamine present, which was noticed after a period of 7 days. Co-infusion with carboxyfullerene prevented the occurrence of this damage, and no detrimental effects were seen in the nigrostriatal dopaminergic system.

Lao et al. [50] showed that fullerene derivatives, namely polyhydroxylated C60(OH)22 and malonic acid C60(C(COOH)2)2, have the ability to shield against nitric oxide-triggered cell death in rat cerebral micro vessel endothelial cells treated with sodium nitroprusside. This indicates that these derivatives could be potentially used in the treatment of disorders related to nitric oxide. The protective effects of fullerene derivatives have been attributed to their ability to scavenge free radicals [51]. Ali et al. [52] proposed that the C3 malonic acid C60 derivative functions as a mimic of superoxide dismutase and is found in mitochondria, which is a primary location for the generation of reactive oxygen species. Cai et al. [53] postulated that these compounds had the potential to serve as neuroprotective agents for the treatment of Parkinson's disease. The scientists conducted research where they exposed human neuroblastoma cells to MPP1, which is a cellular representation of Parkinson's disease. Then, they examined the impact of C60(OH)24 on MPP1-induced mitochondrial dysfunction and oxidative stress to determine its protective effects. The findings have shown that the polyhydroxylated fullerene derivative has strong efficacy in scavenging radicals, hence safeguarding mitochondria. This supports the notion that fullerene derivatives have the potential to serve as neuroprotective agents [54, 55].

Role of fullerenes in Alzheimer's disease (AD)

Alzheimer's disease (AD) gradually impairs the cognitive functions of the brain, including memory retention and logical thinking. It leads to diminished concentration and a feeling of perplexity. Although a permanent solution is unavailable, there are pharmacological and therapeutic options that may provide temporary relief from symptoms. The transportation of medicine molecules across the blood-brain barrier is the principal approach used in the treatment of brain-related illnesses. Most of the time, bare medication molecules are incapable of entering the systemic circulation of the brain. Hence, the medication delivery mechanism plays a crucial role in the management of neurological illnesses [56]. Water-soluble derivatives of Buckminster fullerene, which are molecules with antioxidant properties, have been linked to AD due to the presence of neurofibrillary manifestations such amyloid β plaques. The goal of therapeutic interventions is to hinder the formation of Aβ aggregates, which may lead to neuronal dysfunction and cognitive impairment via inhibition. While Fullerene C60 has shown the capacity to hinder the creation of Aβ fibrils, it is crucial to acknowledge that its restricted solubility and cytotoxicity remain significant issues [57]. Kraemer and colleagues have provided data indicating that C60 fullerene may serve as a hydrophobic carrier for delivering medicinal chemicals to the brain [58]. Makraova et al. [43] performed a comparative investigation on the effectiveness of several substances, such as amyloid-ß25-35 and C60 fullerene, by injecting them into the hippocampus at doses of 1.6 nmol/1 µL and 0.46 nmol/1 µL respectively [43]. Xie et al. [59] conducted research which has shown that administering a low dosage of C60 fullerene may effectively inhibit the accumulation of amyloid-ß25-35 in hippocampus pyramidal neurons. This implies the need for the creation of pharmaceuticals that possess both antioxidant and anti-aggregation properties to combat amyloid-related conditions. A documented molecular connection exists between C60 fullerene and amyloid ß [59]. Amyloid deposits have a substantial influence on neurodegenerative illnesses, such as AD. The main treatment for AD includes suppressing the formation of ß-sheet proteins. Fullerene (C60) nanoparticles, have shown the ability to either hinder or stimulate the formation of amyloid-ß peptide fibrils, depending on their physicochemical properties. Nevertheless, the precise molecular process is still unknown. The results from replica exchange molecular dynamics simulations demonstrate that C180 nanoparticles effectively suppress the formation of ß-sheets in amyloid-ß [16–22] peptides. This inhibition is attributed to the robust hydrophobic and aromatic-stacking interactions between the hexagonal fulllerene rings of the nanoparticles and the peptide rings. This interaction inhibits the process of amyloid-ß [16–22] fibrillation. The study emphasizes the significance of hexagonal rings in preventing the formation of amyloid-ß [16–22] fibrils and offers fresh perspectives on potential therapeutic approaches for AD. C60 fullerene has neuroprotective properties, perhaps acting as a safeguard against Alzheimer's disease [60]. In their study, Gonçalves et al. [61] suggested five C60-fullerene derivatives with the potential to serve as novel pharmaceuticals for the treatment of AD. The authors suggest five prospective therapies for

AD using fullerene (C60) derivatives. They created inhibitors for human acetylcholinesterase in order to hinder the binding of FASII to medications. The researchers use computational structural biology, docking, and molecular dynamics simulations to demonstrate the creation of stable complexes with their molecules. The derivatives of C60-fullerene may effectively use residues and function as both a powerful generator and scavenger of reactive oxygen species (ROS) owing to its delocalized double bond structure [62, 63]. When exposed to UV or visible light, C60-fullerene generates superoxide anion (•O2) and singlet oxygen [1O2] via electron or energy transfer [64]. C60-fullerene, a chemical present in plants, has a dual-state nature by being capable of generating reactive oxygen species (ROS) and functioning as a scavenger in a dark state [65]. Du et al. [65] devised an innovative nano delivery device using C60-fullerene that can be switched on and off. The technology generated reactive oxygen species (ROS) inside the near-infrared region (NIR) and reduced ROS levels in a condition of darkness. The study used a combination of C60-fullerene and KLVFF, a peptide that targets amyloid-peptides, together with photothermal conversion nanoparticles (UCNP@ C60-pep) for the treatment of AD. The process of Förster resonance energy transfer (FRET) from upconversion nanoparticles (UCNPs) to fullerene (C60) generates reactive oxygen species (ROS) that selectively act on amyloid-peptide, oxidizing it and preventing its aggregation when exposed to near-infrared (NIR) light. C60-fullerene removes excessive reactive oxygen species (ROS) at nighttime, so preserving the balance of redox inside cells and facilitating the nano-structure's ability to both generate and neutralize ROS [66, 67]. The Caenorhabditis elegans strain CL 2006, a commonly used model for AD research, exhibited significant neuroprotective effects on this platform [57, 68, 69]. Fig. 3 illustrates the use of the product in image-guided therapy using up-conversion

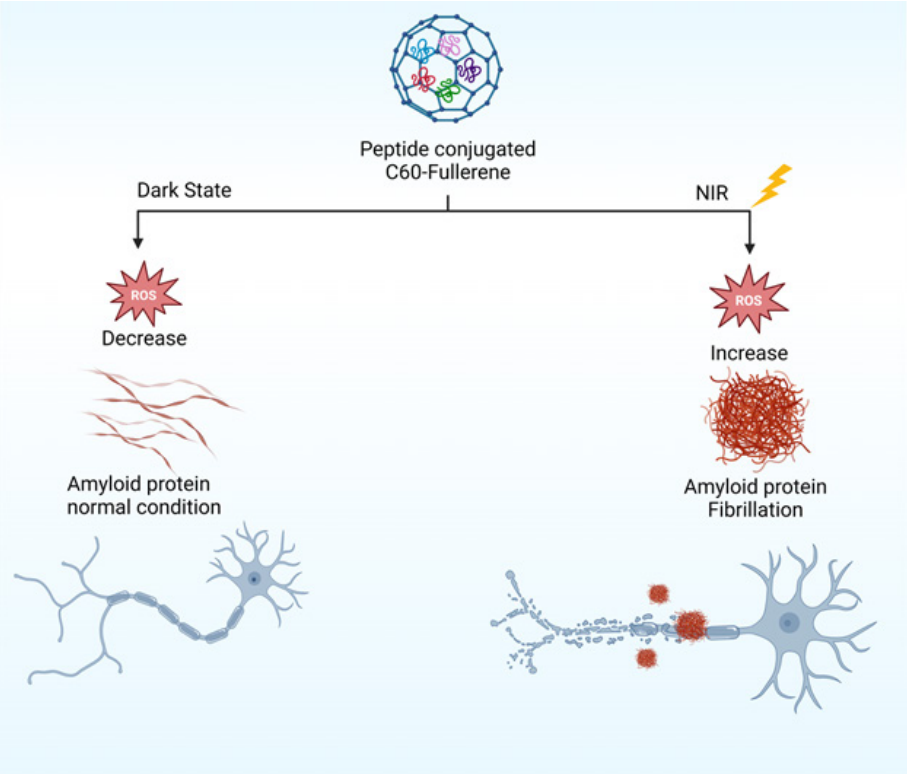

Fig.3. Illustration representing the efficacy after the application of peptide-conjugated C60-fullerene for the treatment of Alzheimer's disease. In this study, a new peptide-conjugated C60-fullerene was administered as a treatment for Alzheimer's disease. The nano-peptide conjugate generates reactive oxygen species (ROS) inside the intracellular milieu upon stimulation with near-infrared (NIR) light. Likewise, these conjugates also remove the reactive oxygen species (ROS) when they are not exposed to light, resulting in a reduction of the high ROS levels. The elevation of reactive oxygen species (ROS) is the primary factor that leads to the fibrillation of amyloid beta. The crystallographic arrangement of amyloid B was obtained from the Protein Data Bank (PDB ID: 1AAP) at a resolution of 1.5 Å. The crystal was analyzed using the X-ray diffraction (XRD) technique

luminescence and MRI [63].

AD is also associated with the disturbance of the cholinergic system [70]. Research has shown that the presence of solvated C60-fullerene may greatly enhance memory impairment, suggesting a possible therapeutic use for AD. The solution, which has particles about 120 nm in size and a zeta potential of 12.22 ± 5.98 mV, was tested against the common drug donepezil to see how well it helped male Wistar rats with amnesia remember where things they had seen before. The research further discovered that Scopolamine HCL, an alkaloid used as an anticholinergic drug, causes memory deficits, cognitive abnormalities, and learning difficulties in both mice and humans. The research further discovered that C60-fullerene forms a bond with the P-gp protein, indicating its potential to be expelled from cells [71]. The research investigated the impact of solvated C60-fullerene on AD, by comparing its effects with Verapamil HCL, a P-gp inhibitor. Additionally, it unveiled the levels of expression of crucial genes associated with AD, such as Sirtuin 6, SELADIN1, and Auaporins, together with their overall antioxidant capabilities. The research revealed that the expression of the SELADIN-1 gene safeguards neurons against harm, oxidative stress, and cellular demise by impeding caspase-3, a key apoptotic mechanism [72, 73]. Aquaporins are specifically found in the kidney, brain, and secretory glands, where they form water channels in their cell membranes [74, 75]. SIRTs play a vital role in several cellular processes such as cell proliferation, metabolism, apoptosis, DNA repair, cancer, and longevity. SIRT6, in particular, has the potential to regulate neurodegenerative processes [76]. The compound C60-fullerene, which is present in the C. fullerensis plant, has demonstrated the ability to safeguard cells against damage caused by oxidative stress. This is significant because oxidative stress is a major contributor to the development of AD, as it is associated with inflammation, aging, and DNA damage. Furthermore, C60-fullerene has been proven to enhance memory impairment, suggesting its potential as a therapeutic intervention.

Glutathione has been linked to both the pathophysiology of Alzheimer's disease and Parkinson's disease, and vitamin E has been linked to a lower chance of acquiring this pathology in relation to Alzheimer's disease. Oxidative damage leads to a reduction in GSH levels inside mitochondria, whereas individuals with Alzheimer's disease have a decline in the frontal brain. Insufficient amounts of vitamin D may lead to aberrant neurological development, resulting in the loss of dopaminergic neurons in the brains of individuals with Parkinson's disease. Neurodegenerative disease development is associated with deficits in Vitamin B [77].

Role of fullerenes in Parkinson's disease (PD)

Loss of dopamine-releasing neurons in the brain's substantia nigra causes motor function degradation in PD, a chronic disorder affecting more than 6.3 million individuals globally (Fig. 4)

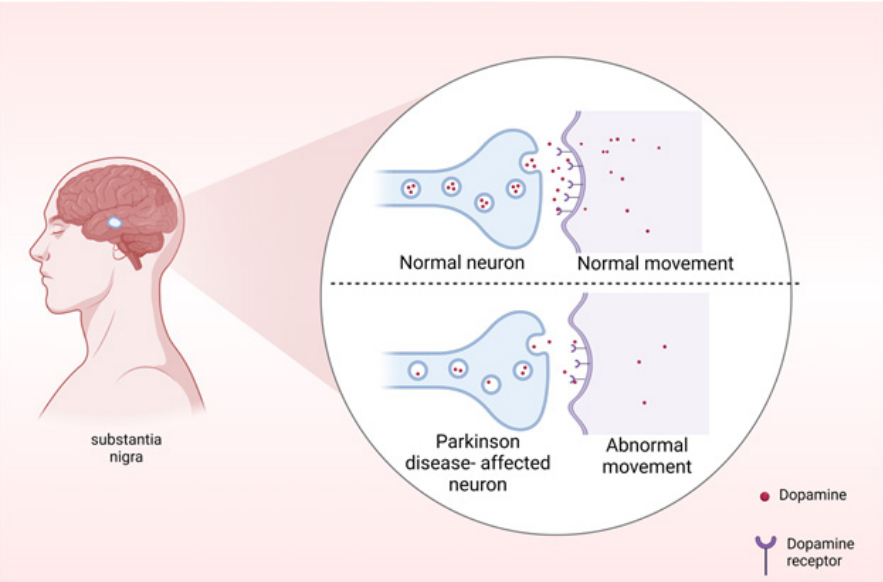

Fig.4. Comparison of dopamine levels between a healthy neuron and a neuron damaged by Parkinson's disease.

[78]. In many cases, the delay in diagnosing the condition adds another layer of difficulty to its care. C60 fullerene derivatives might be a game-changer in the fight against PD; they are a novel substance with strong antioxidant capabilities [79]. The pathophysiology of many acute brain injuries is associated with elevated levels of oxygen radical species and nitric oxide, which are also associated with PD [80]. Fullerenes' ability to react with free radicals of reactive oxygen species (ROS), such as hydroxyl and superoxide, gives them neuroprotective characteristics. Absorbing ROS and decreasing cell death *in vitro*, is a superb antioxidant [81, 82].

Though some patients choose for antagonist, anticholinergic, or monoamine oxidase inhibitor (MAO) medications, the mainstay of care for PD is levodopa (L-DOPA). Administering L-DOPA in a regulated and rapid manner is essential for treatment. Inhibitors of monoamine oxidase (MAO), decarboxylase, dopamine, and carrier-mediated transport (CMT) are further groups of PD medications [83]. However, there is now minimal therapy available since the causes and course of neurodegenerative illnesses are yet unknown [84, 85]. The BBB, cerebrospinal fluid barrier (CSF), and P-glycoproteins are examples of blood-brain barriers that impede the entrance of molecules. There is a lot of hope for the development of new drug delivery carriers as means of treating PD [84]. It is common practice to add ligands to fullerene nanocarrier systems in order to improve their permeability, bioavailability, cellular absorption, and therapeutic agent targeting capabilities.

The polyhydroxylated derivative of fullerene has shown protective properties in human neuroblastoma cells caused by PD, by decreasing the levels of reactive oxygen species and mitigating oxidative damage to proteins and DNA. It functions as a stimulant for phase-2 enzymes, safeguarding the levels of glutathione and γ-glutamyl cysteine ligase. Electron spin resonance (ESR) investigations have showed that polyhydroxy fullerene is an effective scavenger for hydroxyl, superoxide, and lipid radicals. This substance has mitochondrial protective properties as an antioxidant, which it does via both indirect means by promoting antioxidant activity and direct means by scavenging free radicals [86]. Reina et al. investigated the possibility of fullerenes (C36, C35 E, E=N, and B) as nanovesicles for delivering neuroprotective medicinal drugs, with a specific focus on their use in the treatment of PD. Temperature impacts on these interactions were assessed using ab initio molecular dynamics. The research used pristine , boron , and nitrogen N fullerenes to conduct density functional theory calculations in the vapor phase. The objective was to investigate the collaborative mechanism of the physical, chemical, and electrical properties of Anti-Parkinson's medications. Nevertheless, the potential effectiveness of this system as a drug carrier seems improbable owing to chemisorption being the underlying interaction mechanism. The examined complexes exhibited the lowest electron affinity [87]. Frazao et al. devised a novel nano system for PD treatment, using fullerene as a nano system to enhance the rate at which L-DOPA is absorbed and maintain consistent therapeutic plasma levels. This technique offers uninterrupted dopamine stimulation and less negative effects whether administered via the skin or orally. Fullerene has the ability to enter the gastrointestinal system and skin. The absorption patterns were predicted using Density Functional Theory (DFT), which matched the classical molecular dynamics of how levodopa spreads around the molecule [88]. The research conducted by Stetska et al. examines the therapeutic effectiveness of an aqueous solution containing fullerene in a water rat model. The results demonstrate that this solution boosts the motor activity of the distal colon when stimulated, as well as increases the levels of glutathione [89].

Frazao and colleagues conducted research on the adsorption of L-DOPA onto four different levels of C60 fullerene in order to explore its potential for oral and transdermal delivery. The researchers developed a novel nanosystem aimed at enhancing the delivery of L-DOPA for the treatment of Parkinson's disease. To increase the permeation rate of L-DOPA and to achieve stable therapeutic plasma levels, fullerene can be used as a nanosystem. It provides continuous dopamine stimulation and fewer side effects after transdermal and oral administration. In order to enhance the permeation rate of L-DOPA and maintain consistent therapeutic plasma concentrations, fullerene may be employed as a nanosystem. This approach offers sustained dopamine delivery and reduced adverse reactions following transdermal and oral dosing [88]. Also, in another study the therapeutic potential of pristine C60 fullerene aqueous solution (C60 FAS) was explored by Stetska et al. in the 6-OHDA

model using water rats. Results indicated that C60 FAS was able to enhance the index of stimulated distal colon motor activity and increase glutathione levels [89].

Role of fullerenes in amyotrophic lateral sclerosis (ALS)

While there is a wealth of research publications focusing on the development of therapeutic nanoparticles for AD and PD, there is a scarcity of published techniques for other neurodegenerative illnesses such as ALS and MS [90]. Motor neuron disease, or ALS, is a neurodegenerative condition marked by the gradual loss of muscle function caused by the deterioration of motor neurons in the primary motor cortex, brain stem, and spinal cord. The manifestation of ALS exhibits significant variability and is influenced by four key factors: the first affected body location, a combination of upper and lower motor neuron involvement, the speed of disease development, and cognitive decline. Early signs may manifest as minor, although they are often disregarded. The diagnosis of ALS is mostly based on clinical evaluation, with electromyography (EMG) being the key diagnostic test. Performing laboratory testing and imaging, such as MRI, is essential to rule out other possibly more manageable conditions [91].

Amyotrophic lateral sclerosis (ALS) is an incurable condition characterized by elevated levels of oxidative stress, neurotoxicity, and inflammation in sufferers. The medications Riluzole and Edaravone have been authorized by the US food and drug administration (FDA) [92]. Nanomedicines have been created to treat ALS by facilitating efficient medication delivery via the blood-brain barrier and exhibiting neuroprotective properties [93]. Fullerene derivatives, in the form of nanoparticles, has a strong ability to remove free radicals as a result of their double bond structure, which enables them to capture many radicals on a single fullerene molecule [94, 95]. Several studies have shown the beneficial benefits of the neuroprotective compound fullerene [96]. Studies conducted on cortical neurons in mice and animals with ALS have consistently shown that fullerene has neuroprotective properties against the potential damage induced by glutamate receptor agonists, such as kainic acid [97]. Because of their ability to scavenge free radicals, carboxyfullerenes have also shown promise as neuroprotectants [98, 99].

Role of fullerenes in ischemic stroke (IS)

A cerebral stroke occurs when there is an obstruction in the blood circulation to the brain, resulting in insufficient supply of oxygen and nutrients. IS is a complex condition marked by reduced energy supply, disruption of ionic gradients, breakdown of the blood-brain barrier, buildup of calcium, swelling caused by increased blood vessel permeability, excessive nerve cell stimulation, oxidative damage, impaired mitochondrial activity, inflammation, and cell death [100, 101]. Two primary strategies have been used for the treatment of stroke, namely recanalization (thrombolysis) and neuroprotection [102]. The progress in nanomedicine is transforming our comprehension and management of IS by addressing cerebral blood deficit and mitigating reperfusion adverse effects, which lead to substantial tissue damage. Adopting this empowering strategy is essential for safeguarding the integrity of the blood-brain barrier and preserving brain tissue that can still be saved [103]. Fullerene (C60) nanoparticles have been recognized as a powerful scavenger of free radicals and as a means of shielding neurons from harm caused by reperfusion [104]. The many derivatives of fullerenes have extensive applications in ischemic tissue for their potential to reduce ROS and maintain tissue function after ischemia [55]. The size, structure, and surface of fullerenes may impact their antioxidant properties and biological activity, which may either help cells survive oxidative stress or promote cell death [105-107]. Also, the antioxidant properties of fullerene have made it extensively used for medicine delivery to the brain. Fullerene may efficiently pass across BBB when combined with a physiologically active component, enabling precise delivery of drugs to specific targets [108]. Water-soluble derivatives of fullerene have more potency than fullerene itself as a medication delivery method in the CNS [109]. The non-covalent adsorption of several chemotherapeutic drugs onto the surface of fullerene enhances the polarity of C60, hence improving its passage across the blood-brain barrier and enabling targeted drug administration in the brain [12, 107]. The intravenous injection of hexasulfobutylated fullerene (C60 FC4S) in Long-Evans rats before and during Middle cerebral artery occlusion (MCAO) resulted in the elevation of nitric oxide levels and reduction in LDH levels and total infarction volume. This effect is likely due to its role as a scavenger of free radicals [110]. Administering carboxyfullerene by intracerebroventricular

infusion in rats subjected to MCAO stroke reduced the extent of cerebral infarction and avoided the increase in lipid peroxidation and decrease in GSH levels caused by temporary ischemia/reperfusion. Nevertheless, several instances shown detrimental consequences including fatalities [111]. Based on these studies, Vani et al. [112] demonstrated that polyhydroxylated fullerene or fullerenol (OH-F) derivatives provided protection to rat brain cells against ischemia/reperfusion injury and prevented oxidative/nitrosative damage in the brain using an MCAO model. These derivatives acted as a strong scavenger of free radicals [112]. Furthermore, Fluri et al. [113] documented that the administration of fullerenol and glucosamine-fullerene conjugate (GlcN-F) resulted in a decrease in cellular harm and inflammation after a stroke. Fullerenol functioned as a radical scavenger in this instance, whereas the glucosamine derivative decreased inflammation [113].

Role of fullerenes as a potential therapy in Multiple sclerosis (MS)

Multiple sclerosis (MS) is a neurological disorder that disrupts the transmission of nerve impulses in the nervous system by causing damage to the myelin sheath, which is a protective layer around axons [114]. This condition is categorized as an autoimmune disease because the immune system targets and kills myelin cells. MS development is influenced by variables such as genetics and the environment. patients diagnosed with MS have reduced levels of antioxidants and elevated amounts of lipid peroxidation products, while healthy ones show greater antioxidant levels [115]. Activated microglia and macrophages enhance the generation of ROS, leading to the degradation of myelin and neurons. The treatment consists of administering immunosuppressive medications, namely monoclonal antibodies or neuroprotective pharmaceuticals [116, 117]. Using a variety of indicators, including leukemia inhibitory factor (LIF) produced by astrocytes, nanoparticles are utilized to diagnose multiple sclerosis [118, 119]. LIF has shown effectiveness in the treatment of inflammatory demyelination in allergic encephalomyelitis, and its nanoformulation as PLGA nanoparticles, known as LIF-NP, has shown promise for the eradication of myelin damage [118]. After injecting animals with myelin protein, Basso and colleagues synthesized a nanoformulation of a water-soluble fullerene called ABS 75 and an antagonist for the NMDA receptor. This synergy's antioxidant properties significantly retarded the progression of MS [120]. Iron oxide nanoparticles have been utilized to color macrophages in an effort to see multiple sclerosis. To hasten the regeneration of damaged axons and halt the degenerative course of multiple sclerosis, researchers have explored the use of cutting-edge technologies, such as produced magnetic nanoparticles (karyobots and cytobots) [121]. Experimental models of multiple sclerosis have shown that nanoformulations of immunosuppressant medications, such as tacrolimus MPEG-PLA nanoformulation, provide site-specific delivery of the drug with improved effectiveness and tolerance [122, 123].

Role of fullerenes in HIV-1-associated neurocognitive disorders (HAND)

Cognitive dysfunctions, such as HIV-1 associated dementia and HIV-1 encephalitis (HIVE), may occur when brain structures and cells are damaged or killed [124]. Antiretroviral drugs effectively manage HIV symptoms, but they are unable to impact cognitive abilities due to their inability to penetrate the blood-brain barrier [125]. Atazanivir® was delivered via solid spherical nanoparticles, which enabled it to cross the blood-brain barrier. Additionally, it may be combined with a transactivating transcription peptide to inhibit the removal of ritonavir from cells [126, 127]. There is evidence indicating that C60-fullerene has antiviral properties, since the viral genetic material is enclosed inside a conical structure made up of 1500 individual protein units [128-130]. The proteins are organized into hexamers and pentamers, which contribute to the distinctive structure of the bare core. The capsid shields viral RNA from host immune sensors and facilitates the transportation of reverse-transcribed viral DNA into the nucleus of the host cell [131]. A bis (monosuccinamide) derivative of p,p/-bis(2-aminoethyl) diphenyl-C60 fullerene molecule was synthesized by Schinazi et al. [132] and has been shown to be physiologically active against HIV-1 and HIV-2. Regarding the 3/-azido-3/-deoxythymidine resistant HIV-1, the EC50 was around 6 and 3 μM [132]. Through viral inactivation experiments, the virucidal characteristics of the fullerene complex were validated, and it has shown a tolerance of up to 100 μM for H9, Vero, and CEM cells as well as peripheral blood mononuclear cells.

According to the first research report, fullerene derivatives have the potential to be a viable therapeutic option for combating the influenza virus. Shoji et al. [133] created a total of 12 distinct derivatives of fullerene, out of which only eight were shown to effectively suppress the endonuclease activity of the PA N-terminal domain or full-length PA protein in laboratory tests. The Influenza A virus is composed of three subunits: PA, PB1, and PB2. The N-terminal region of the PA subunit has the ability to carry out endonuclease activity [133]. Computational biology investigations shown that C60-fullerene may effectively bind to the active site of the PA endonuclease enzyme. The PA endonuclease domain demonstrated the ability to digest M13, mp18 circular single-stranded DNA, and fullerene derivatives in an in vitro setting. The digestion of M13 mp18 was severely hindered by the presence of fullerene derivatives at a concentration of 10 mM [134]. The inhibitory action on the protease specific to the human immunodeficiency virus HIV-1 has been predicted since 1993 and confirmed by experimental evidence since that time [135]. Multiple C60 derivatives have been produced and tested against HIV-1 protease since 1995, based on many scientific data [136].

Role of fullerenes in prions disease

Prion disorders are neurodegenerative illnesses that gradually worsen over time. They are defined by the buildup of the scrapie isoform (PrPSC) of the normal cellular prion protein (PrPC) outside of the neurons, which leads to significant loss of these cells. Implementing strategies to decrease microglial activation may have therapeutic advantages [137]. Indications including neurodegeneration, amnesia, and cognitive deficits. The blood-brain barrier renders conventional pharmaceutical interventions for prions ineffective. Dendrimers, with the ability to traverse the blood-brain barrier, serve as valuable nanoformulations for specifically targeting neuroblastoma cells. Solassol and colleagues have shown the potential of cationic PAMAM dendrimers in inhibiting the production of prions by binding to them [138, 139]. In research conducted by Ye et al, [140] it was shown that pretreatment with C60-OH significantly reduced the activation of microglia in response to PrP (106–126]. C60-OH increased the activity of antioxidant enzymes even more by turning on Nrf2, which is a nuclear factor. The findings indicate that C60-OH shields neuronal cells from the harmful effects of PrP [106–126] by activating the Nrf2 pathway [140].

Role of fullerenes in brain cancer cells

Primary brain cancer agents frequently demonstrate ineffectiveness in clinical trials due to challenges in penetrating the formidable blood brain barrier (BBB), leading to insufficient concentrations at the intended site, as well as the limited duration of action of low-molecular mass therapeutic agents, which fail to sustain optimal levels within cancerous cells [141, 142]. In a study, it was introduced that a nanoconjugate containing fullerenes is loaded with a biocompatible linker and monomethyl fumarate (MMF). The nanoconjugate provides medication release that is dependent on pH, significant permeability to cancer cells, and compatibility with blood. Nanomedicine makes MMF work better on neuroblastoma cells by increasing the amount of MMF that can be accessed in the plasma and making it stay in the body longer. The preclinical results of the nanocarrier indicated that it may safely and effectively transport MMF to neuroblastoma cells. This has potential implications for treating brain cancer [143].

Role of fullerenes in Huntington's disease (HD)

Huntington's disease is a hereditary neurological disorder characterized by a mutation in the huntingtin gene, which is inherited in an autosomal dominant manner. The outcome is a decline in both physical and cognitive abilities, accompanied by mental symptoms and increased oxidative stress [144, 145]. Increased ROS levels, impaired cellular activity, and neuronal death are symptoms of the syndrome. Involuntary motions are the primary factor contributing to motor dysfunction [146]. The presence of markers in plasma, brain tissue, lymphoblasts, and cerebrospinal fluid demonstrates that oxidative stress plays a crucial role in the development of HD [147]. Currently, there are no established therapies available for HD, leaving patients with no other option than to focus on managing and alleviating their symptoms. Studies have shown that antioxidant substances such as ascorbic acid, α-tocopherol, and idebenone have the ability to reduce or prevent oxidative damage in neurons [148, 149]. Recent advancements in diagnostic and therapy strategies, including the use of

nanotechnology and cutting-edge technology, have been employed to address HD [150]. Bolshakova, et al., conducted a study to investigate the neuroprotective effects of C60(OH)30 and C120O(OH)44 fullerenols in a Drosophila transgenic HD model. Supplementation with these fullerenes was shown to decrease oxidative stress and neurodegenerative processes in the brains of the flies. This suggests that fullerenes have neuroprotective characteristics in this particular paradigm [151].

Role of fullerenes in epilepsy

Epilepsy, which afflicts more than 40 million individuals worldwide, is a devastating condition that affects the CNS. It occurs due to an unevenness in the electrical activity of neurons, mainly regulated by calcium ions [152, 153]. Antiepileptic drugs (AEDs) are often used for seizure management; however, they may induce a spectrum of side effects, ranging from mild CNS dysfunction to fatality. Drug-resistant epilepsy is seen in 30% of individuals with epilepsy, and nanotechnology, namely fullerenes, has emerged as a promising remedy [154, 155]. Proposed nano-strategies aim to hinder various calcium channel types in the brain and enhance the brain's ability to use conventional AEDs in individuals who are resistant to treatment. Exploring the use of nanocarriers to interact with calcium channels in the brain and transport AEDs across the blood-brain barrier might be a promising avenue for future research in epilepsy therapy [156].

Fullerenes as a potential therapy for diabetic neuropathy

Hyperglycemia, or elevated blood glucose levels in the systemic circulation, is a common symptom of diabetes. The pancreas secretes the hormone insulin, which helps move glucose from meals into cells where it is used as fuel. It also results in problems with fertility and male sexual dysfunction [157]. Because of its antioxidant qualities, C60 fullerene may be used to treat type 1 diabetes or diabetic mellitus. Rats with testicular dysfunction were given hydrated C60-fullerene as a bioantioxidant by Bal et al. (2011) [158]. Type-1 diabetes is brought on by streptozotocin's cytotoxic glucose analogue, STZ, which methylates, shreds, and destroys pancreatic β-cells in diabetic mouse models. Because of the oxidative stress and histological alterations in the testes brought on by hyperglycemia, type 1 diabetes also lowers the rate of reproduction [159]. Following the ingestion of the nanocomposite, diabetic rats exhibited significant reductions in the relative weights of the right cauda epididymis, seminal vesicles, prostate, sperm motility, and epididymal sperm concentration in comparison to the control group. However, these effects were reversed in the fourth group that received treatment with C60HyFn.

An amino-functionalized Gadofullerene nanocomposite was created by Li et al. [160] to treat diabetes. The C57BL/6 J mice were given the particles intraperitoneally, and the pancreatic and liver tissue absorbed them. The blood levels of glutathione peroxidase, catalase, and oxidoreductase were raised by the nanoparticles. Additionally, they decreased the expression of inflammatory markers such Tnf-α, IL-1ß, IL-6, and Nf-κb in the pancreas. The insulin-mRNA expression in diabetic mice was shown to be 2.8 times higher than that in normal, non-diabetic animals; however, the nanoparticles drastically decreased this expression. In their 2020 study, Demir et al. [24] investigated the impact of C60-fullerene nanoparticles mixed with curcumin on hyperglycemia and renal failure in rats with diabetes. When contrasted with bare C60-fullerene and free curcumin, the nanocomposite significantly raised malondialdehyde levels and decreased GSH levels, indicating that the cell was subjected to substantial oxidative stress. These nanoparticles, when combined with curcumin, may have beneficial effects on the health of diabetic rats, according to the research. According to recent research, it has been shown that fullerene C60 has the ability to hinder the production of TNF-α protein in the hippocampus. This might possibly alleviate pain and prevent brain damage in individuals with diabetes [161].

Fullerene toxicity

Fullerene safety evaluation is challenging due to a lack of controlled structure-activity studies, inadequately defined or uncharacterized initial compounds, and a lack of research on different cage sizes, which are more likely to be approved by the US FDA [162]. The FDA Nanotechnology Task Force's 2007 research underscores the importance of biodistribution analysis in assessing nanomaterials in products, but most studies focus on immediate results, neglecting long-lasting effects and the complexity of *in vitro* testing due to

exposure to various cell types [163, 164]. Research was conducted where young Largemouth bass were exposed to nonderivatized C60, a substance that cannot dissolve in water, resulting in significant controversy [165]. Despite the widespread public perception of fullerenes as harmful substances, the authors neglected to include a control group in order to determine whether the observed effects were due to the presence of large aggregated particles, tetrahydrofuran pollutants, or the chemical properties of C60 [166]. The group released later research discreetly, disclosing that the first 'toxicity' was caused by contaminants in the samples [167]. The first Oberdorster work faced criticism due to potential experimental artifacts; however, subsequent investigations conducted on mice [168] and rats [169] demonstrated that comparable C60 preparations significantly enhanced the longevity of these animals [170, 171].

The recommendation is to categorize nanoscale materials based on size, chemical composition, surface structure, solubility, ability to form, and inclination to aggregate. The Nanotechnology Characterization Laboratories of the National Cancer Institute are beneficial for characterizing nanoscale materials and establishing standards. Research on carbon nanomaterials, such as carbon nanotubes, nanohorns, graphene, fullerenes, and their derivatives, is limited due to their early development [172]. Prioritizing chronic exposure, genotoxicity, carcinogenicity, and reproductive toxicity is crucial for converting these compounds into human systems. The distinctive qualities, lower manufacturing costs, improved scalability, and potential medical applications of fullerene nanomaterials have sparked extensive study [173]. Although there were early worries about toxicity, newer investigations indicate very little indication of harm. Advancements in contemporary medicine via the fullerene area need more comprehensive characterization and study to address long-term toxicity data [17, 174].

CONCLUSION

The text provides a concise overview of the latest advancements in the study of fullerenes as distinctive nanopharmaceuticals for the treatment of diseases. Fullerene-based nanomaterials have the potential to be innovative therapeutic agents. Biomedical uses of these materials mostly revolve around their capacity to hinder tumor development, reduce microbial activity, serve as radical scavengers, and restrict viral growth. Many studies have been done on the creation, characterization, functionalization, disease treatment effects, biological effects, and toxicity of fullerene derivatives. Nevertheless, further fundamental and practical investigation must be conducted prior to their use in clinical environments.

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CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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