Fullerenes: Bucky Balls in the Therapeutic Application

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Abstract In 1985, when Kroto found the third allotropic structure of carbon after diamond and graphite. A study on fullerene C_{60} began, and it has shown an increasing significance in biological research. Fullerenes were determined to be innocuous at first, but their unusual cage architecture and solubility in organic solvents made them susceptible to derivatization via addition and redox reactions. These carbon spheres are currently being investigated internationally for a variety of nanomedicine applications. The extraordinary electrical characteristics of these molecules make them promising candidates for diagnostic, therapeutic, and theranostic uses. This chapter focused on the many biological applications of fullerenes and their derivatives.

Keywords Carbon nano structure · Fullerene · Characteristic · Biomedical applications · Therapeutic applications

1 Introduction

Carbon is a common element that occurs in nature in several forms (polymorphs), including graphite and diamond. Fullerenes are the fourth allotrope of carbon. In contrast to the stretched solid-state geometries of graphite and diamond, fullerenes are spherical molecules that are soluble in a range of organic solvents. This characteristic

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may be employed for a range of chemical processes. The empirical formula C_N, where N specifies the number of carbon atoms, is used to derive the chemical formula of fullerenes with a closed mesh network. A fullerene is a carbon cage structure with a merged pentagon and hexagon ring system. In 1970, Japanese scientist Eiji Osawa suggested the term buckyball for the first time. Richard Smalley and his group created the first fullerene chemical, buckminsterfullerene, in 1985 (C_{60}-fullerene). The newly discovered molecule was named after the architect who constructed a geodesic dome with a similar structure, Richard Buckminster Fuller [41, 42].

Since their discovery in 1985, fullerenes have attracted a great deal of attention in a range of scientific fields. Physical, chemical, and biological examinations of the properties of fullerenes have shown positive findings. It is anticipated that their size, hydrophobicity, three-dimensionality, and electrical topologies make them fascinating subjects for biological applications [15]. Their unusual carbon cage structure and extensive derivatization potential make them an intriguing therapeutic option. Despite the low solubility of carbon spheres under physiological circumstances, there is a rising interest in studying their biological uses [7, 80]. The photochemical, electrochemical, and physical properties of the fullerene family, namely C_{60} fullerene, may be used in a variety of medical fields. Fullerene may fit into the hydrophobic cavity of HIV proteases, preventing substrates from accessing the active region of the enzyme. It has antioxidant and radical-scavenging properties [43]. In addition, when fullerene is exposed to light, it may produce substantial quantum yields of singlet oxygen. Additionally, it may be functionalized with a range of medications and biological molecules to treat various diseases [55, 61]. This chapter of the book focuses on the general properties of fullerene and its efficacy in various medicinal applications.

2 Overview and General Characteristics of Fullerene

Fullerenes named Buckminster fullerenes or Buckyballs are one of the carbon allotropes. This is because of its symmetrical cage structure and various sizes (C_{60}, C_{76}, etc.), fullerenes have unusual chemical and physical characteristics. The C_{60}-Fullerene is the most common in the synthesized form and can be prepared by various different methods [2, 21]. In general, C_5-C_5 single covalent bond (12 pentagons), and $C_5 = C_6$ double bonds (20 hexagons) make up the structure. Each fullerene indeed contains $2n + 20$ carbon atoms where 'n' represents the number of hexagons.

These carbon structures are primarily manufactured using laser vaporization of pure carbon, electrical arc discharge heating of graphite, and resistive arc heating. Initially, it was identified via laser vaporization of carbon in an inert environment (helium). This procedure generated a minimal quantity of C_{60} Fullerene. Subsequently, another technique for generating fullerene included establishing an electrical arc between graphite rods in an inert environment. However, to boost the manufacturing rate, lasers were used to irritate polycyclic hydrocarbons (PAHs). This fullerene synthesis method relies on polycyclic aromatic hydrocarbons (PAHs) which

already contain the necessary carbon scaffolds. In flash vacuum pyrolysis conditions, these PAHs molecules "wrap up" to create fullerenes when laser-irradiated at a 337 nm wavelength [54, 58].

Due to the hydrophobic character of simple fullerenes and the fact that they are exclusively soluble in organic solvents, they are not useful for different medicinal applications. However, it is readily functionalizable by covalent and non-covalent conjugation. Depending on the derivitization and exohedral and endohedral derivatization makes them more lipophilic or hydrophilic than basic fullerenes [10, 15, 58]. In this intence, the carbonic nanoparticle (buckyball) behaves differently depending on its surroundings. Because of the molecule's dual nature among reactive oxygen species, this is the case. When exposed to light, the C_{60}-fullerene has the capacity to create reactive oxygen species. This effect is known as "photodynamic treatment" (PDT). Many scientists have used this phenomena to develop specific anti-cancer therapies [49, 50, 56]. On other hand, it reduces ROS, which is a neuro-protective agent [17]. This action's mechanism remains a mystery, and additional inquiry is needed. Because this molecule lacks water solubility and many organic solvents, it is difficult to use it in biological applications. Since hydrophilicity is of higher value in biological systems than hydrophobicity, several ways have been devised to enhance the hydrophilicity and water solubility of materials. Fullerenes can be encapsulated in cyclodextrins [18, 70], polyvinylpyrrolidone micelles [11], liposomes, and other special carriers, as well as chemically modified by hydrophilic substances like amino acids [66, 91] and carboxylic acids, polyhydroxyl groups (fullerenols) [22, 72], among other things, to create two-phase colloidal solutions, as well as fullerene derivatives and fullerene polymers.

3 Fullerenes: Therapeutic Applications

3.1 Biosensor

C_{60}-fullerene is a fundamental component that is utilized for biosensing applications. There are various scientific shreds of evidence already established on this. Here, some scientifically established reports are emphasized and enlightened. Saeedfar et al. [69] developed a potentiometric nano biosensor for the detection of urea by using C_{60}-fullerene [69]. An unique strategy for the quick alteration of fullerene for subsequent enzyme attachment to generate a potentiometric biosensor is provided. The novel strategy is that the urease enzyme was immobilized onto the carboxylated (-COOH) fullerene by replacing hydroxyl group (–OH) in the presence of "N, N'-dicyclohexylcarbodiimide (DCC), or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC)" and the resultant bio-conjugate was applied to confirm the catalytic hydrolysis of urea in solution. The biomaterial was then placed on top of a pH specific screen-printed electrode consisting of a non-plasticized poly (n-butyl acrylate) (PnBA) membrane enclosed with a hydrogen

ionophore. This pH-selective membrane is intended to function as a potentiometric urea biosensor when C_{60}-urease is deposited on the PnBA membrane. The optimal pH and phosphate buffer concentration for the urea biosensor were 7.0 and 0.5 mM, correspondingly. The linear response range of the biosensor was in the region of $2.31*10^3$ M to $8.31*10^5$ M. The cations (Na^+, K^+, Ca^{2+}, Mg^{2+}, and NH^{4+}) had no discernible effect on the response of the urea biosensor. The combination of a fullerene-urease bio-conjugate with a high-adhesion acrylic membrane decreased the leaking of the urease enzyme and increased the urea biosensor's stability for up to 140 days. In another study, Tortolini et al. [81] carboxylated gold nanoparticle conjugated fullerol as a novel electrochemical nano biosensor for the detection of polyphenolic compounds [81]. The scientists used a screen-printed electrode (SPE) as a gold substrate to make a biosensor that could find polyphenols in real wine samples. The Folin–Ciocalteau technique was used as a spectrophotometric reference method to compare their results. They suggested a biosensor called Trametes Versicolor Laccase (TvL) that uses a screen-printed electrode (SPE) as a gold substrate. For the first time, they exhibit the DET of their proposed improved biosensor in the absence of redox mediators using scanning tunneling microscopy (STM) to characterize its surface. In contrast, Uygun et al. [84] synthesized a novel chemical biosensor to detect Fetuin-A levels in blood samples [84]. Fetuin-A (Alpha-2 HS glycoprotein) is encoded by the AHSG gene [59]. It is a 64-kDa glycoprotein that is secreted from both the liver and adipose tissue, responsible for a novel link between obesity and associated problems [82]. For achieving this goal, they created an Electrochemical Impedance Spectroscopy (EIS) based antifetuin-A (Anti-HFA) modified biosensor system and tested it in actual blood samples. The detection electrode was developed by the nanostructure that comprised gold as the core and the surface was decorated by 4-amino thiophenol (4-ATP), Fullerene, and PAMAM-NH2 (G5) as different layers. Thereafter, Anti-HFA was immobilized onto the surface of the resultant particles. Herein, Gold screen-printed electrodes (AuSPE) were used as the transducer. The authors used the ELISA technique for sample detection. In a recent study, Li et al. [46] designed a photochemical biosensor by implying methylene blue-sensitized C_{60}-fullerene for ultrasensitive DNA detection. In this work, photoactive C_{60}-fullerene nanoparticles were changed on the electrode surface to generate an initial photocurrent signal. A signal amplification technique was also utilized to hybridize with DNA2 to transform many DNA duplexes into immobilized methylene blues as the sensitizer, hence producing efficient sensitization toward the C_{60}-fullerene and enhancing the photo-current for quantitative DNA detection [51].

3.2 Targeted Anti-cancer Therapy

Fullerenes are used as anti-cancer therapy. Due to its unique characteristics, many scientists used fullerenes as the drug-conjugated carrier to deliver the drug molecules to the target site. Fullerene has excellent conjugation and loading capacity of the drug molecules as a carrier. Hence, drug-conjugated fullerene is an efficient targeted

anti-cancer delivery system. For instance, Shi et al. [74] depicted docetaxel-loaded polyethyleneimine fullerene with a surface passivated by folic acid that was able to target the prostate cancer cells (PC3 cells) actively [74]. The size and zeta potential of the resultant nano-structure were ~140 nm and ~13.7 mV respectively. Their data reflected that after administration of the resultant nano-structured conjugate against cancer cells, early apoptosis and late apoptosis increased by 1.18–1.88 folds compared with free docetaxel. As similar, Panchuk et al. [61] synthesized doxorubicin (DOX) conjugated C_{60} fullerene nano-system that was used against different kinds of cell lines (HCT116: Human colon adenocarcinoma cell line, MCF7: Human Breast cancer cell line,) [61]. DOX is a well-known anti-cancer drug molecule that inhibits topoisomerase II [79]. They reported that DOX conjugation with C_{60} fullerene results in a 1.5–2 fold increase in DOX toxicity towards numerous human solid tumor cell lines as compared with free DOX. In contrast, this hydrophobic drug molecular moiety is encapsulated by 'Buckysome'S' hydrophobic interiors. Paclitaxel (PTX) is another essential anti-cancer drug molecule that acts as a microtubule de-polymerizing agent. There is scientific evidence that PTX-conjugated fullerenes may be utilized to deliver chemotherapy drugs in a targeted manner. Zakharian et al. (2004) developed a PTX-functionalized C_{60}-antibody combination for the targeted therapy of cancer. They also produced PTX conjugated C_{60}-fullerene for biological activity. In this work, they revealed that PTX directly was not conjugated with fullerene, since as stated that two–OH (hydroxyl) alteration might lose the biological activity. Hence, they employed an ester (–COOC–) or amide ($–CONH_2$) linkage that may be broken by biological processes [36, 92]. In contrast, Partha et al. [64] generated PTX-loaded self-assembled C_{60} fullerene or buckysome (100–200 nm) amphiphilic spherical nano-structure against breast cancer (MCF-7 cell line) [64]. The buckysome was constituted of AF-1 molecules, which are C_{60} fullerene modified with a Newkome-like dendrimer unit with 18–COOH groups. However, the structure of AF-1 was previously established by authors in another study [63]. Herein, the authors ensure that there are six groups connected to each fullerene in an octahedral configuration with C2v symmetry in the AF-1 monomer. A dendritic moiety comprising 18 carboxylic acid groups sits atop the molecule. C_{12} esters are found in pairs at the other five locations (dodecyl malonates). It seems that dodecyl malonates occupy five extra sites on the fullerene, which are oriented octahedrally to the dendritic group. It is more soluble at higher pH values because of the lower electrophilicity of the carboxylic acid groups (pKa 7.5). When the pH is less than 3, the molecule precipitates out of the solution. The self-assembled complex structures were generated at 700 °C, and were morphologically observed as vesicular structures. However, they demonstrated the cellular absorption of these novel buckysomes implanted with the hydrophobic fluorescent dye Dil "(1,1′-Dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate)". The schematic representation of the study was also depicted in Fig. 1.

In another study, Kepinska et al. [39] developed pH-responsive doxorubicin conjugated C_{60}-fullerenes nano- complex as targeted anti-cancer therapy against breast cancer (MCF7 cell line) [39]. They illustrated that DOX was released gradually from the synthesized DOX-fullerene nanoconjugate under a lower pH in the extracellular

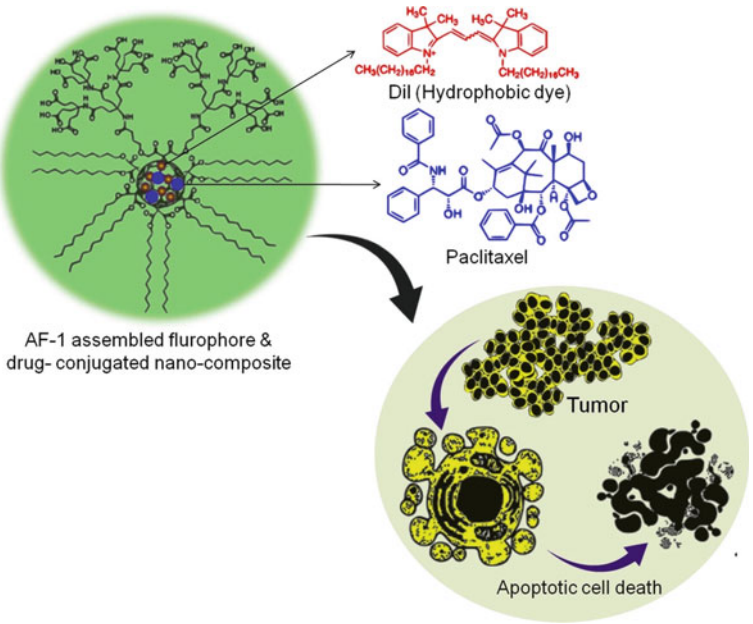

Fig. 1 Schematic depiction of Paclitaxel loaded self-assembled C_{60} fullerene or buckysome containing hydrophobic dye encapsulated AF-1 assembled nanostructure was administered against MCF7 breast cancer cell line. Paclitaxel is an anti-cancer drug molecule and the hydrophobic dye (Dil: 1, 1′-Dioctadecyl-3, 3, 3′,3′-teramethylindocarbocyanine) was encapsulated for cellular tracking and bio-imaging purpose [63]

environment of the cancer cell. The authors reported that the size and zeta potential of the fullerene- DOX nano-complex was ~280 nm and −24 mV respectively. Also, they ensured that the fullerene-DOX complex leads to a threefold increase in cytotoxicity against the MCF7 cell line as compared with free DOX. Similarly, Chen et al. [13] synthesized novel metallofullerenol molecules (e.g., $Gd@C_{82}(OH)x$, where X is the number of hydroxyl group) which has a specific nanostructure that comprises several tens of molecules as magnetic cores Gadolinium (Gd) and close-caged carbon nanosheets with surface passivated hydroxyl groups (–OH) [13]. The synthesized metallofullerenol nanoparticles had anti-tumor activity against liver cancer. The hydrated particles were 22 nm (average) in size and the authors used this nanoparticles against the tumor-bearing mice at a dose level of 10^7 mol/kg which seems to be a very potent anti-cancer activity (~60%). Toxicant tumor inhibition is increased by 26% when the dosage is increased by one order of magnitude (10^7mol/kg). The resultant particles show a great ability to boost immunity and interfere with tumor invasion in normal muscle cells, practically without harm in *invivo* and *invitro*. Aside with prioritising tailored anti-cancer treatment, the product has lower toxicity. As a result, the scientists ensured that just around 0.05% of the applied dose was found in tumour tissues. This implies the nanoparticles have high antitumor effectiveness

without causing harm to cells. According to research results, the tumor chemotherapeutics with great effectiveness and low toxicity may be possible using fullerene derivatives with the correct surface modifications and sizes.

3.3 Photodynamic Therapy

In photodynamic therapy, aberrant cells are destroyed by using light-sensitive drugs in concert with a light source. Oscar Raab, who was the first to conduct a scientific study on photosensitized reactions in 1898, who introduced the photodynamic therapy concept of employing a dye as a photosensitizer in the photodynamic process [1]. Lipson and his colleague developed hematoporphyrin derivatives by combining hematoporphyrin chloride with hydrochloric acid and sulfuric acid. The invention of hematoporphyrin derivatives as photosensitizer laid the groundwork for photodynamic treatment also know as photodynamic therapy.[37].

Many scientists develop C_{60} fullerene which was used as a photosensitizer [25] for the treatment of anti-cancer therapy. In addition, a radiolabelled isotope was used to conjugate with C_{60} fullerene for cancer treatment and as well as diagnosis. Consequently, Ji et al. (2005) developed radiolabelled fullerol [^{125}I-C_{60}(OH)] that comprises a very stable covalent Carbon-Iodine bond in-vivo system [35]. They illustrated the bio-distribution of the resultant nano-composite that was active against five different tumor-bearing mice models, such as "human lung giant-cell carcinoma PD, mouse H22 hepatocarcinoma, human colon cancer HCT-8, and human OS732 osteosarcoma and human gastric cancer MGC803". The accumulation ratios of radiolabelled fullerol [^{125}I-C_{60}(OH)] in mouse H22 tumor to normal muscle tissue (T/N) and blood (T/B) at 1, 6, 24, and 72 h demonstrate that radiolabelled fullerol [^{125}I-C_{60}(OH)] accumulates gradually in H22 tumor and persists for an extended period of time (e.g., T/N: 3.41, T/B: 3.94 at 24 h). For the other four tumor models, the T/N ratio at 24 h ranges between 1.21 and 6.26, while the T/B ratio varies between 1.23 and 4.76. Furthermore, the radiolabelled fullerol [^{125}I-C_{60}(OH)] buildup in tumors is primarily caused by the increased permeability and retention effect (EPR) and phagocytosis of mononuclear phagocytes. Consequently, radiolabelled fullerol [^{125}I-C_{60}(OH)] might be used as a photosensitizer in photodynamic treatment for some types of tumors. Notably, their bio-distribution study of the radiolabelled fullerol ensured that the nano-composite was deposited into the liver, skin, kidney and bone for all types of tumor-bearing mice. The schematic representation of the study was also depicted in Fig. 2. Notably, the figure implies that the administered product with low dose was bio-available into the liver tissue as compare to the large amount. Besides, the resultant product also accumulated into the spleen, kidney & bone tissue.

There was another example where fullerene used as a photosensitizer including MRI imaging that was used as an anticancer agent. Liu et al. [49] synthesized a novel photo-sensitizer (PEG-conjugated-C_{60} fullerene-DTPA) for MRI bioimaging that was also used as an anticancer agent by PDT (Photodynamic therapy) [49].

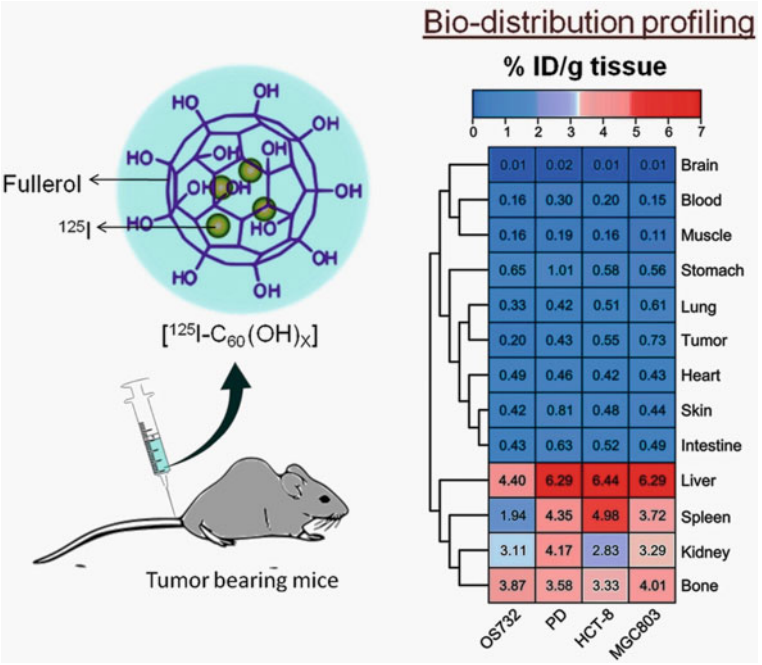

Fig. 2 Schematic representation of the bio-distribution profiling of radiolabel fullerol complex [^{125}I-C_{60} $(OH)_X$] (X = Number of the hydroxyl groups). They used five different tumor cell line successfully implanted into the mouse. After that, 100 μL of aqueous solution of radiolabelled fullerol [^{125}I-C_{60} $(OH)_X$] was administered through tail vein for the bio-distribution study. The results of the distribution were denoted as % ID/g that implies percent of injected dose per gram tissue. ID: Injectable dose

The strategy of the work is depicted in Fig. 3. PEG-conjugated-C_{60} fullerene-DTPA was prepared by adding Diethylenetriaminepentaacetic Acid (DTPA) to the terminal group of polyethylene glycol (PEG). C_{60} fullerene has a cage-like structure & the Gadolinium (Gd+) metal ions were coupled with the PEGylated fullerene via the metal chelation technique. In addition, they also used $^{59}FeCl_3$ solution as a precursor chemical for radiolabelled imaging. After administration of the resultant nano-composite into the tumor-bearing mice through an intravenous route, the photodynamic therapy & MRI tumor imaging were evaluated significantly. A large amount of nano-structure was entrapped & deposited into the tumor enriched site having a passive targeting phenomenon (EPR: Enhanced Permeation & Retention Effect) and showed anti-cancer activity while illuminating with light as an external environmental stimulus. Notably, reactive oxygen species (O2•–) was also generated with or without metal ion (Gd+) chelation. Also, they ensured that there was similar MRI imaging was found with the use of PEG-conjugated-C_{60} fullerene-DTPA and

MAGNEVIST®, in both cases. MAGNEVIST® is a marketed product of gadopentetate dimeglumine, an injectable formulation that is the N-methylglucamine salt of the gadolinium complex of diethylenetriamine penta-acetic acid.

Similarly, Morz et al. [55] synthesized six unique different kinds of functionalized fullerenes with 1, 2, or 3 hydrophilic or 1, 2, or 3 cationic groups used as a photosensitizer in photodynamic treatment of anti-cancer therapy [55]. The functionalized nano-fullerenes absorb the light which is given by an external stimulator to sensitize them that resulting to produce ROS in the specific area of the applied field in the tumor. Herein, they used three different mouse cancer cell lines, such as J774, LLC, and CT26. The apoptosis was triggered 4–6 h after illumination by the monopyrrolidinium fullerene (photosensitizer), which was the most active against all cell lines tested. Moreover, they ensured that A Type I mechanism for phototoxicity was seen when dichlorodihydrofluorescein was used as a ROS probe and caused diffuse intracellular fluorescence. The same groups of scientists develop a novel delivery system for their previous product N-methylpyrrolidinium-fullerene, a functionalized nano-fullerene that was used against colon adenocarcinoma in 2011

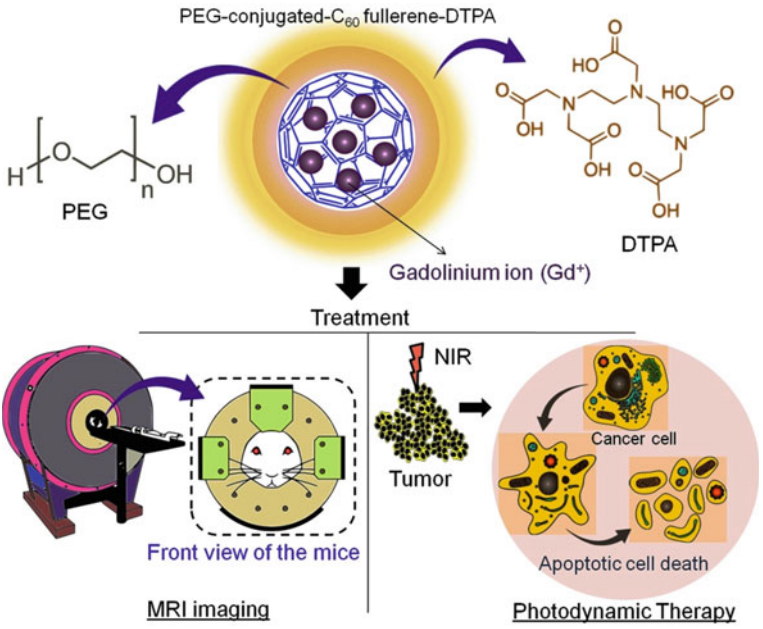

Fig. 3 Schematic representation of C_{60}-fullerene containing novel nano-composite (PEG-conjugated-C_{60} fullerene-DTPA) which used as photodynamic therapy against cancer. The nanostructure is able to use both purposes; such as MRI (Magnetic Resonance Imaging) purpose and photodynamic therapy where NIR (Near infrared light) was used as external stimulator. Herein, the gadolinium ion (Gd+) was coupled to composite for radiolabel imaging as well as induced to produce ROS into the intracellular level. DTPA: Diethylenetriaminepentaacetic Acid [49]

[56]. They developed micelles loaded with N- methylpyrrolidinium-fullerene that was administered via the intraperitoneal route for photodynamic therapy.

Liu et al. (2010) developed a novel pullulan-functionalized C_{60} fullerene as photodynamic therapy against hepatoma [50]. Pullulan, a water-soluble polymer, is conjugated at the surface of C_{60}-fullerene with amino-spacer moiety ($–NH_2$). The amine groups ($–NH_2$) come from ethylene diamine which was used as a precursor chemical for amine functionalization. Pullulan is passivated with the amino group and then the resultant complex was anchored to C_{60} through the terminal amine group of pullulan. When illuminated with light, the C_{60} end-group conjugated with pullulan results to produce a superoxide anion. The pullulan functionalized C_{60}conjugates effectively inhibited the development of HepG2 hepatoma cells with asialoglycoprotein receptors invitro, but in HeLa cells without the receptors showed reduced suppression efficacy. In comparison to HeLa cells, this conjugate exhibits a strong affinity for HepG2 cells.

In another study, Guan et al. [23] designed a novel phototheranostic agent that was used for effective tumor targeting, imaging & treatment [23]. They developed a tri-malonate derivative of fullerene shaped as nano-vesicles for effective tumor targeting & treatment. The functionalized fullerene nano-vesicles were comprised of C_{70} fullerene, 1,10-Diamino-4,7-dioxadecane (OEG2), and Chlorin e6 (Ce6). Herein, Ce6 was conjugated at the surface of the core composite that was made up of C_{70} fullerene. OEG2 was used as a space or linker molecule to conjugate Ce6 moiety as surface anchoring. The resultant developed molecular assembly was formed as a vesicle (the average size of the vesicles was 64.5 ± 6.5 nm) into the water/DMSO solution. The product had some beneficial advantages, such as high loading efficiency of Ce6 (~57wt %), effectively absorbed near-infrared light, better cellular internalization capacity & last but not least potentially biocompatible that excreted out from the body. This is because of its wide π-conjugated aromatic domains, chlorin e6 (Ce6) is a frequently applied photosensitizer because of its enhanced absorption in the near-infrared (NIR) light area and increased singlet oxygen ($^1O_2$) quantum yield [45, 47, 87]. The strategy of the work was illustrated in Fig. 4.

3.4 Alzheimer

Alzheimer's disease impairs numerous brain processes, including memory retention and logical thinking, in a gradual manner. Memory and other mental processes are gradually lost when brain cell connections and cells deteriorate and die. The primary signs and symptoms are a lack of concentration and disorientation. Although there is no cure, medications and other treatment options may help alleviate symptoms for a while. The most fundamental approach for brain-related diseases is to deliver the drug molecules into the brain across the blood–brain barrier. Most of the cases the bare drug molecules can't reach across the blood–brain barrier (BBB) into the systemic circulation of the brain. Hence, the drug delivery system is an important aspect of the treatment of brain-related diseases. Kraemer et al. [40] showed that

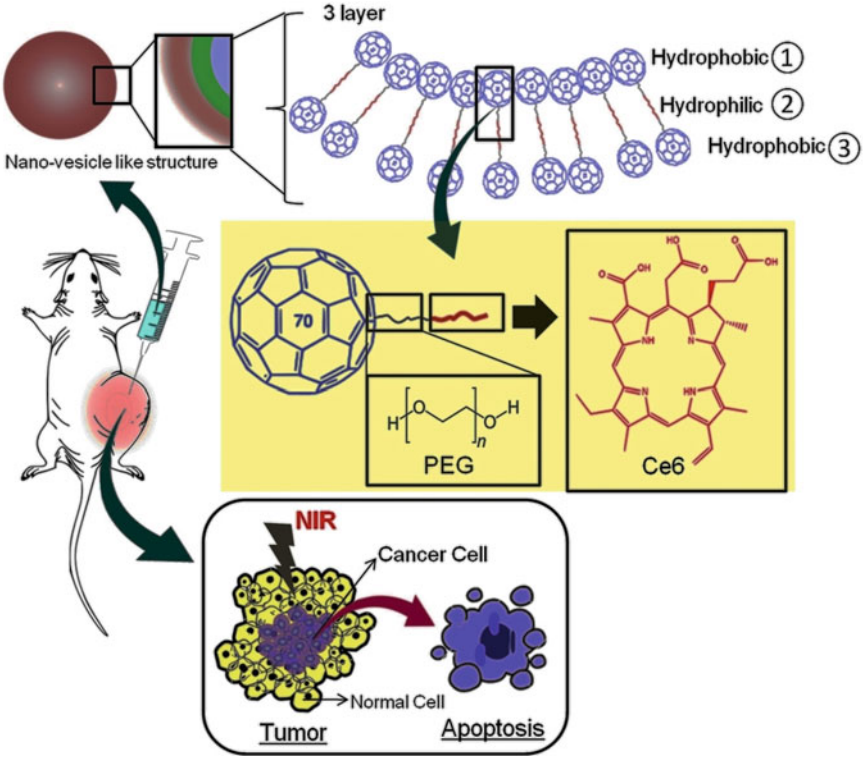

Fig. 4 Depiction as a schematic representation of novel nano-vesicular structure used as photothermal therapy against cancer. The nano-composite structure was comprised of C_{70}-fullerene-PEG- Ce6 molecule as a unit. Subsequently, the two units make together bilaterally that build up 3 layers (Hydrophobic-hydrophilic-hydrophobic) into the inner structure. The nano-bodies are biocompatible in nature and Chlorine (Ce6) was used as the photosensitizer

C_{60} fullerene is another hydrophobic carrier to deliver drug molecules into the brain [39]. Makraova et al. [52] illustrated the comparative study of the affectivity of the different components such as amyloid-$ß_{25\text{-}35}$ (1.6 nmol/1 μL), and hydrophilic colloidal dispersion of C_{60} fullerene (0.46 nmol/1 μL), and colloidal dispersion of C_{60} fullerene before administration of amyloid via intra-hippocampal microinjections [52]. Deposition of amyloid-$ß_{25\text{-}35}$ in hippocampal pyramidal neurons was avoided by administering a modest dose of C_{60} fullerene in an aqueous molecule of colloidal solution before the amyloid peptide. Anti-amyloid medicines that combine antioxidant and anti-aggregation capabilities might be developed using functionalized C_{60}. Moreover, the molecular interaction between C_{60} fullerene and amyloid ß was also established by computational structure biology & bioinformatics study by Xie et al. [90]. Amyloid deposits have a role in the pathogenesis of many neurodegenerative disorders, including Alzheimer ‘s disease. The inhibition of ß-sheet production has been proposed as the primary Alzheimer’s disease therapy. Nanoparticles may

inhibit or induce the fibrillation of amyloid-ß peptides, based on their physicochemical characteristics, according to emerging research. Nevertheless, the fundamental molecular mechanism remains elusive. In this study, it has been demonstrated that replica exchange molecular dynamics (REMD) simulations indicate that fullerene (C_{60}) nanoparticles (fullerene: peptide molar ratio greater than 1:8) may significantly inhibit the production of ß-sheets in amyloid-$ß_{(16–22)}$ peptides. Fullerene@peptide interaction indicates that the greater inhibition of ß-sheet formation by C_{180} is a result of the strong hydrophobic and aromatic-stacking interactions of the hexagonal fullerene rings with the Phe- rings as compared to the pentagonal rings. Strong interactions between fullerene (C_{60}) nanoparticles and amyloid-$ß_{(16–22)}$ peptides significantly inhibit the peptide–peptide interaction required for ß-sheet production, hence retarding amyloid-$ß_{(16–22)}$ fibrillation. Overall, their research demonstrates the importance of hexagonal rings of C_{60}-fullerene in the inhibition of amyloid-$ß_{(16–22)}$ fibrillation and provides novel insight into the creation of Alzheimer's disease therapy possibilities. Vorobyov et al. (2014) depicted that C_{60} fullerene has a neuroprotective activity that seems like a protective role for Alzheimer's disease [86]. Similarly, Gonçalves et al. (2016) suggested five potential C_{60}-fullerene derivatives as new drugs against Alzheimer's disease [77]. Herein, they suggest five potential Alzheimer's disease treatments based on fullerene (C_{60}) derivatives. Human acetylcholinesterase (HssAChE) inhibitors were developed to prevent the fasciculin II (FASII) binding site to the drugs. Herein, they emphasize computational structural biology, docking, and molecular dynamics simulations which demonstrate a stable complex formation with their proposed compounds. New human acetylcholinesterase inhibitors based on C_{60}-fullerene derivatives may take advantage of an area created by many residues (Asp74, Trp286, Tyr72, Asp74, Gln291, Trp286, Tyr341, and Pro344). Moreover, there are two miraculous properties of C_{60}-fullerene is that it may be both a potent ROS generator and a ROS scavenger due to its very delocalized double bond structure [34, 93]. Under UV or visible light, C_{60}-fullerene reaches a metastable triplet excitation state in order to form superoxide anion ($•O_2$) and singlet oxygen ($^1O_2$) by electron transfer or energy transfer [68]. C_{60}-fullerene can produce ROS in the biological system & acts also as a scavenger of ROS a dark state by this process. A group of scientists also illustrated the fact of the dual-state nature of C_{60} fullerene [17]. Du et al. [17] synthesized a novel switchable nano delivery system that was comprised of C_{60}-fullerene. The scheme of the study was that the nanocomposite produced ROS in the presence of NIR (Near-infrared region) that was stimulated externally and as well as decreased ROS at a dark state. C_{60}-fullerene and the amyloid-peptide targeting peptide KLVFF were coupled to photothermal conversion nanoparticles (UCNP@C_{60}-pep), which were utilized to treat Alzheimer's disease [45, 47] Förster resonance energy transfer (FRET) from UCNPs to C_{60} would create ROS to target amyloid-peptide, resulting in oxygenation and inhibiting aggregation under NIR light. During the night, C_{60}–fullerene would scavenge excess ROS and maintain intracellular redox homeostasis at a reasonable level to prevent phototoxicity at nontarget locations. ROS-generating and ROS-quenching capabilities of the resultant nano-structure may be turned on and off using NIR light in this manner. The novel model *Caenorhabditis elegans* (C. elegans) strain CL 2006, a frequently used

model for Alzheimer's disease research, exhibited impressive neuro-protection on this platform [3, 4]. For "image-guided treatment," their product might be employed for both up-conversion luminescence and magnetic resonance imaging (MRI). The schematic representation of the study was depicted in Fig. 5.

However, disruption of the cholinergic system is also responsible for Alzheimer's disease [24]. A recent study depicts that solution with C_{60}-fullerene (solvated C_{60}-fullerene) can significantly improve memory impairment that reflects as a treatment for Alzheimer's disease. The particle size of C_{60}-fullerene in the solution was ~120 nm and the zeta potential was 12.22 ± 5.98 mV. Herein, the researchers wanted to compare the efficacy of solvated C_{60}-fullerene with donepezil (a piperidine derivative that acts as an inhibitor of acetylcholinesterase, dose 2 mg/kg in oral route) that is conventional medicine, in enhancing spatial memory in amnesic male Wistar rats while the administered dose of solvated C_{60}-fullerene was 21 g/mL given in intranasal route. Moreover, Scopolamine HCL is an alkaloid, used as an anticholinergic agent, that induces memory impairments, cognition disorders, and learning problems in rodents and human beings, was administered for developing Alzheimer's disease in

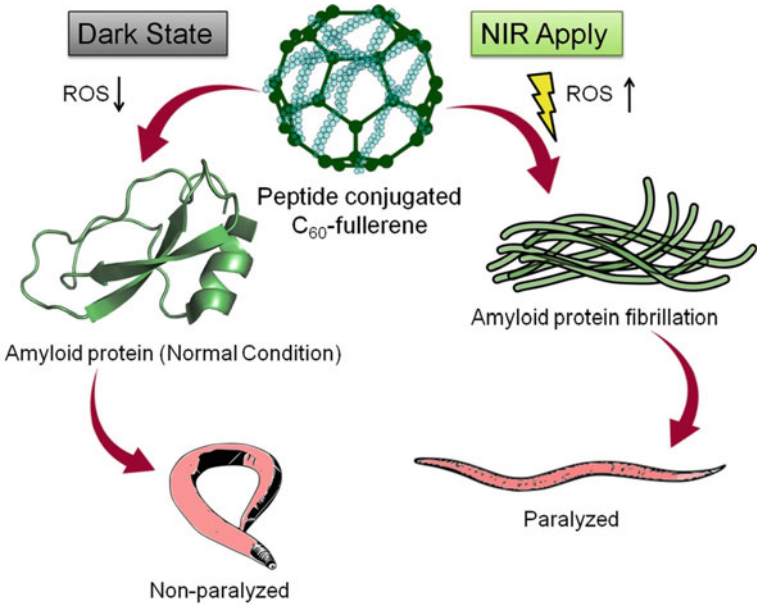

Fig. 5 Schematic depiction of the effectiveness after administration of peptide conjugated C_{60}-fullerene for Alzheimer's disease. Herein, the novel peptide conjugated C_{60}-fullerene was delivered against Alzheimer's disease. The nano-peptide conjugate produces ROS in the intracellular environment after inducing it by NIR (Near Infrared) light. Similarly, these conjugates also scavenge the ROS at a dark state which implies they decrease the elevated ROS level. Elevation of ROS is the most responsible phenomenon which results in amyloid b fibrillation. The crystal structure of amyloid B was taken from Protein Data Bank (PDB ID: 1AAP, resolution: 1.5 Å). The crystal was characterized by XRD method

the animals (dose: 2 mg/kg/i.p.). Some theoretical pieces of evidence also proved that C_{60}-fullerene binds with the P-gp protein that implying it can be effluxed from the cell [75]. For clarification of this aspect, they administered solvated C_{60}-fullerene with the presence and absence of P-gp inhibitor, Verapamil HCL (Dose: 25 mg/kg). In addition, they also showed the expression level of three key genes of Alzheimer's disease, such as Sirtuin 6, SELADIN1, and Auaporins, as well as their total antioxidant capabilities (TACs), after administering solvated C_{60}-fullerene. Selective Alzheimer's Disease Indicator 1 (SELADIN-1) gene expression protects neurons from various damages, such as toxicity effects of Amyloid- protein, oxidative stress, and cell death, by inhibiting caspase-3, which is involved in the apoptotic process, including being involved in Alzheimer's disease [31, 73]. Aquaporins are especially expressed in the organs including the kidney, brain, and secretory glands that build water channels in their cell membranes [57, 85]. SIRtuins (SIRTs) play a critical role in cell proliferation, metabolism, apoptosis, DNA repair, cancer, and lifespan. SIRT6 may have a role in the regulation of neurodegenerative processes [78]. Furthermore, it has been shown to protect cells against oxidative stress-induced damage. SIRT6 is a key player in a broad variety of Alzheimer's Disease triggers, including inflammation, aging, oxidative stress, and DNA damage, thus it lacks could exacerbate neuro-degeneration and the other way around. They ensured that C_{60}-fullerene successfully improves memory impairment that reflects as a treatment for Alzheimer's disease.

3.5 Diabetes

Diabetes is a condition that develops while blood glucose is increased in systemic circulation, commonly known as blood sugar or hyperglycemia. Insulin, a hormone produced by the pancreas, aids in the transport of glucose from food into cells, where it may be utilized for energy. Diabetes mellitus is another well-recognized cause of male sexual dysfunction and impairments of male fertility [26]. C_{60} fullerene has antioxidant properties and it could be used for type-1 diabetes or diabetes mellitus. For instance, Bal et al. (2010) developed hydrated C_{60}-fullerene that was used as a bio-antioxidant and could alleviate testicular dysfunction caused by streptozotocin-induced diabetes in rats [8]. Streptozotocin-induced diabetic murine models develop type-1 diabetes, due to the cytotoxic glucose analogue streptozotocin (STZ) that is toxic to pancreatic β-cells and causes insulin deficiency. STZ methylates DNA, causing DNA fragmentation and killing pancreatic β-cells. Besides, type-1 diabetes is characterized by a reduction in reproductive activity due to hyperglycemia-induced oxidative stress and histological changes in the testes [20]. They ensured that after oral administration of the resultant nanocomposite, the relative weights of the right cauda epididymis, seminal vesicles, prostate, sperm motility, and epididymal sperm concentration were considerably lower in diabetic rats than in controls, but were regained in the fourth group treated with C_{60}HyFn ($p < 0.001$).

Li et al. [46] developed an amino-functionalized Gadofullerene nano-composite that was used against diabetes mellitus [46]. They illustrated that the particles were

accumulated into the pancreas and liver tissue after administration through intraperitoneal (i.p.) administration of C57BL/6 J mice. They ensured that the level of the main oxidoreductase of superoxide dismutase, catalase, and glutathione peroxidase in serum was increased significantly for the administration of gadofullerene nanoparticles. Also, the nanoparticles dramatically reduced the mRNA expression level of inflammatory markers in the pancreas, such as Nf-κb, Tnf-α, IL-1ß, and IL-6, implying that amino-functionalized Gadofullerene nano-composites reduced pancreatic inflammation in diabetic rats. Furthermore, insulin-mRNA expression in the pancreas of diabetic mice was found to be 2.8 times greater than that in normal non-diabetic mice, which was considerably reduced by amino-functionalized Gadofullerene nano-composites in diabetic animals. Demir et al. (2020) illustrated the affectivity of C_{60}-fullerene nanoparticles combined with curcumin against hyperglycemia with kidney failure in diabetic rats [16]. After administration of the nanocomposite into the oral route, malondialdehyde level was increased compared to bare C_{60}-fullerene and free curcumin (C_{60}: 34.141 ± 2.6, free curcumin: 34.75 ± 1.59 & C_{60}- fullerene-curcumin with streptozocin: 36.29 ± 4.8 nM/g) and the level of GSH was also reduced compared than bare C_{60}-fullerene and free curcumin (C_{60}: 168.93 ± 16.46, free curcumin: 166.19 ± 7.22 & C_{60}-fullerene-curcumin with streptozocin: 137.98 ± 8.54 μM/g) that implies oxidative stress was produced significantly into the cell.

3.6 Anti-viral Therapy

There are some shreds of evidence established that implies C_{60}-fullerene has antiviral activity [14, 53]. Schinazi et al. [71] synthesized bis(monoscuccinamide) derivative of p,p/- bis(2-aminoethyl) diphenyl-C_{60} fullerene compound that is biologically active against Human Immunodeficiency Virus (HIV-1 and HIV-2) while the EC_{50} was ~6 and ~3 μM against 3/-azido-3/-deoxythymidine resistant HIV-1 [71]. Notably, they ensured the virucidal properties of the synthesized fullerene complex by virus inactivation assays. Similarly, they also mentioned the tolerance or non-toxic dose maximum of up to 100 μM for peripheral blood mononuclear cells and H9, Vero, and CEM cells (It is a cell line of lymphoblastic cells that came from a child who had acute lymphoblastic leukemia).

This is the 1st study report that implies fullerene derivatives may be the choice of a drug candidate against the influenza virus. Shoji et al. [76] designed 12 different types of fullerene derivatives that could be used against the influenza virus [76]. The derivatives were designed by the various specialized moiety attached to the surface of C_{60}-fullerene. Among all derivatives of fullerene, they identified only 8 distinct fullerene derivatives which significantly inhibited the endonuclease activity of the PA N-terminal domain or full-length PA protein in vitro. Influenza A virus is made up of three subunits: the PA, the PB1, and the PB2 subunits, and especially the N-terminal domain of the PA subunit is capable of performing endonuclease activity. Their in-silico computational biology reports reveal that C_{60}-fullerene can actively

bind at the distinct active location of the PA endonuclease protein. Furthermore, in vitro, the PA endonuclease domain digested M13, mp18 circular single-stranded DNA, and they looked to see whether any of the fullerene derivatives might suppress this activity. Also, their molecular cell-biology data ensured that fullerene derivatives significantly inhibited the digestion of M13 mp18 at a dose of 10 mM. An inhibitory effect on the protease specific to the human immunodeficiency virus HIV-1 has been anticipated theoretically since 1993 and has been shown experimentally since then [19]. A dissociation constant of 10^{-3} to 10^{-6} mM was calculated while using the binding free energy of 8–12 kcal/mol. There are numerous scientific pieces of evidence were established since 1995 which imply that multiple C_{60} derivatives have been synthesized and tested against HIV-1 protease [10, 62].

3.7 DNA Cleavage Activity

There is so much fundamental scientific evidence established that relies upon fullerene derivatives can cleave the oligonucleotide chain. This activity occurred in the presence of light and also, and this phenomenon was established on animal microbial cell lines (Salmonella) [6] and plasmids (pBR322) [65]. There are different types of C_{60}-functional derivatives are present that could cleave DNA molecules after exposure to light in the presence of super-coiled plasmid DNA (pBR322 DNA). While exposed to the light, the fullerene compounds were shown to split a 182-base pair fragment at guanine residues. The parts of fullerene after being excited, are sensitized production of $^1O_2$, and the resultant $^1O_2$ react with the oligonucleotide as ROS, which are the anticipated mechanisms for oligonucleotide scission. Later, Boutorine and his colleagues breakthrough the discovery and established that the fullerene-oligonucleotide complex that could build a duplex with a hairpin from single-stranded DNA, a double-stranded DNA, and the hairpin double-stranded DNA [50]. They ensured that the fullerene-DNA complex system was cleaved at guanine residues while exposed to the light, and as a result, ROS was generated. In general, there are two different pathways of DNA photo-clevaging phenomenon that occurred at guanine sites. Scientific research findings suggest that guanosine oxidation may be caused by singlet oxygen ($^1O_2$) production and energy transfer from the fullerene triplet state to bases [29, 67]. Photo-irradiation causes fullerenes to transition from a singlet state to a triplet state. DNA-intercalators and minor groove binders have been added to fullerenes to increase their affinity for nucleic acid molecules. DNA covalently bonded to a fullerene core should enhance activity and selectivity against target DNA [48]. The investigators demonstrated that another fullerene-oligonucleotide preferentially cut DNA at guanine residues positioned close to the fullerene terminal of the oligonucleotide [32]. They developed a hydrophilic group, homocalix[arene], that was actively conjugated into the surface of the C_{60}-fullerene, and the resultant complex was able to cleave DNA. They examined the potential intermediary of $^1O_2$

by contrasting the responsiveness of the fullerene-oligonucleotide with an identically coupled eosin-oligonucleotide, which is known to increase the generation of $^1O_2$ which helps to treat various diseases.

In this contrast, Bergamin et al. [9] synthesized new hybrid compounds consisting of an oligonucleotide chain and a trimethoxyindole (TMI) unit used as a minor groove binder to increase the efficacy, sensitivity, and integrity of the triple helix [9]. Due to steric and electrostatic interactions that hinder optimal contact with double-stranded DNA, this innovative approach needs considerable improvement, particularly the improvement of the spacer link between TMI and C_{60}. On the other hand, DNA may be attached to a monolayer with cationic groups at the ends capable of linking the double helix phosphates, which had previously been intercalated by C_{60}-fullerene. Fullerene and its derivatives may be used as photo-probes in the investigation of genic transcription [30] onward glutathione-S-transferase [73]. As well as, in the case of fullerols, towards P450-cytochrome-dependent monooxygenases, plasmatic reticulum enzymes of hepatic cells, and mitochondrial ATPase in the process of oxygenation [83]. Nitric oxide synthase (NOS) suppression by fullerene derivatives is a recent finding worth noting. A vital physiological transmitter, nitric oxide is an extremely reactive radical molecule. Even at low amounts, though, it may be harmful to humans. Trimalonic derivatives of C_{60}-fullerene have been shown to inhibit all three kinds of NOS, neural, epithelial, and inducible, after the revelation that fullerols may reduce bronchospasm generated by the system xanthine/xanthine oxidase [44, 88]. A particular type of derivative of C_{60}-fullerene "(C3-tris-malonyl-C_{60}-fullerene and D3-tris-malonyl-C_{60}-fullerene derivatives)" seems to limit electron transmission between subunits through a reversible deformation of the dimer interface, and all three nitric oxide synthase isoforms of the enzyme are inhibited in a completely reversible manner by dilution [88].

3.8 Fullerenes with Anti-bodies

Fullerenes conjugated antibodies are also a developing system that achieving successfully delivers antibodies and as well as to detects a particular system precisely [12, 28]. Hendrickson et al. [27] developed anti-C_{60}-fullerene that can recognize free fullerene and modified water-soluble derivatives present in solution and multi-component biological samples [27]. Eight anti-fullerene antibody clones were produced when animals were immunized with a compound of fullerene C_{60} carboxylic derivative and thyroglobulin generated by carbodiimide activation. The antibody-fullerene binding was found to be specific. The study was performed with ELISA technique for the detection of water-soluble protein–conjugated fullerene, fullerene aminocaproic acid, fullerenol, and pure fullerene in solution. Water–organic combination suitable with immunoassay was suggested to dissolve very hydrophobic free fullerene C_{60}. 2 mg/L of free C_{60}-fullerene could not be detected in the solution. Organ homogenates from rats, intraperitoneally or intra-gastrically fed fullerene, were also identified by ELISA. Extracting fullerenes from a biological sample using

toluene is followed by evaporation and dissolving in a water-organic medium to limit the effect of biometrics on the assay findings. The interactions between fullerene and antibodies were established by Osipov et al. [60]. X-ray analysis and molecular modelling of the Fab-fullerene complex will be used to determine the structural parameters of epitopes that particularly detect insoluble antigens, uncover the unique characteristics of immune complex formation as well as also determined the structure of the anti-C_{60}fullerene antibody Fab-fragment (Fab-C_{60}). It has been shown by computer-assisted docking to evaluate the enthalpy and entropy value in particular the π- π stacking interactions with aromatic amino acid residues of the anti-binding pocket and therefore the Solvent Accessible Surface Area (SASA) value of the hydrophobic surface of C_{60}-fullerene, regulate the binding of C_{60} to FabC_{60} fullerene. By using X-ray crystallography, they were able to resolve the structure of the CDR H3 loop of FabC_{60} (which interferes with C_{60} binding at the antigen-binding site, leading to poor antibody affinity for C_{60}). Antigen-binding site interactions with aromatic residues are mediated by enthalpy and entropy, particularly, by π-π stacking interactions with aromatic residues and decrease of the solvent-accessible area of the hydrophobic surface of C_{60}. The PDB identifier for the apo-FabC_{60} binding structure is 6H3H.

4 Current Clinical Studies, Marketed Formulations and Patents

A small market exists for C_{60}-fullerene as an antioxidant in cosmetics, but there are no fullerene-based commercial products that have made a substantial effect. Radical sponge® (BioResearch Corporation) and LipoFullerene® were made from C_{60}/PVP and squalane-dissolved C_{60} respectively [38, 89]. These preparations were deemed safe due to their lack of cytotoxicity and pro-oxidant activity when exposed to light under a microscope [5]. When LipoFullerene® enters the skin's cells, it functions as a radical scavenger, preventing mitochondrial damage and DNA breakage. Photocytotoxicity, reverse mutagenicity of bacteriophage, and skin penetration into the human skin are also not important biological harmful consequences [38, 89]. For the treatment of inflammatory acne vulgaris, which has been linked to oxidative stress in recent clinical investigations, fullerene gel (Zelens®) is effective [33]. There are some patented formulations regarding C_{60}-fullerene are enlisted in the Table 1.

5 Conclusion and Future Aspect

After its discovery, C_{60}-fullerene has become an emergent carbon molecule with several chemical and biological uses. Effective functionalization characteristics make them more reactive and capable of conjugating diverse biological and chemical

Table 1 Patents list belonging to C_{60}-fullerene formulations as a therapeutic products

Sl. No	Patent No	Inventor names	Product description	Current assignee
1	CN104127872B	Wang Chunru, Zhen Mingming, Shu Chunying, Wang Taishan, Li Jie, Zhang Guoqiang	Metal fullerene nanometer monocrystalline particle is in the application of preparing in the agent of specific tumor blood vessel blocking	Beijing Fullcan Biotechnology Co., Ltd. & Chifeng Funakang Biotechnology Co., Ltd.
2	CN111514306A	Wang Chunru, Li Lei, Zhen Mingming	Fullerene nanoparticles for enhancing anti-tumor immunotherapy	Beijing Fullcan Biotechnology Co ltd & Institute of Chemistry of CAS
3	JP2017521454A	Chunru Wang, Mingming Zhen, Chunying Shu, Taishan Wang, Taishan Wang, Jie Li Jie Li, Guoqiang Zhang, Guoqiang Zhang	Tumor treatment method with metal fullerene single-crystal nanoparticles selectively destroying tumor blood vessels	–
4	CN108478598B	Wang Chunru, Zhou Yue, Zhen Ming	Water-soluble fullerene nano material and preparation method and application	Beijing Fullcan Biotechnology Co ltd & Institute of Chemistry of CAS
5	US9233166B2	Hongjie Dai, Zhuang Liu, Xiaolin Li and Xiaoming Sun	Supramolecular functionalization of graphitic nanoparticles for drug delivery	Leland Stanford Junior University
6	KR101725613B1	Eunsung Lee, Sol Kim	Photosensitizer for photodynamic diagnosis or therapy and photodynamic therapy using the same	–
7	CN108853142A	Wang Chunru, Zhen Mingming, Zhou Yue, Bai Chunli	Water-soluble fullerene nanoparticle inhibits the application in tumor growth drug in preparation	Beijing Fullcan Biotechnology Co ltd. & Institute of Chemistry of CAS
8	US20090214101A1	Lon J. Wilson Jared M. Ashcroft Michael G. Rosenblum	Targeted nanostructures for cellular imaging	William Marsh Rice University
9	KR101503573B1	Lee Eun-seong, Kwak Dong-seop	Hyalronated fullerene, preparing method of the same, and biological use of the same	–

components as therapeutic possibilities. This conjugation makes the compounds more soluble in water and less poisonous. Multiple studies have been presented to illustrate the many therapeutic uses. Although further study needs to be conducted on the use of functionalized fullerenes in the biosensor, anticancer, drug delivery, and photodynamic treatment.

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