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Review Article

Fullerene Derivatives: A Potential Tool In Medicinal Applications

Ms. Aarti Gaikwad*, Ms. Shilpa Godiyal, Dr. Kisan Jadhav, Dr. Vilasrao Kadam

Bharati Vidyapeeth's College of Pharmacy, CBD Belapur, Navi Mumbai, India-400614

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ABSTRACT

The fullerenes and its derivatives are emerging potentially in the field of drug delivery and nano science. This is often all because of its higher stability and ability to deliver drugs and genes to a targeted site. It not only acts as a carrier but also exhibits anti-HIV activity due to its unique physical properties. It is inferred that size, hydrophobicity, three-dimensionality and electronic configurations make them an appealing subject in medicinal chemistry. The present study is acknowledged to explore medicinal and biological applications of fullerene derivatives. It is focused on the competency of fullerene in the area of drug delivery, in diagnostic field and cosmetic formulations. The attachment of both biomedical contrast agents and drugs inside or on the outside of the cage is a further interesting area which allows an early diagnosis and treatment of diseases. The fullerene has further relevant applications in cosmetics, treatment of orthopedic diseases.

INTRODUCTION:

Fullerenes take one of the first places in the area of research in modern nanoscience concerned with carbon-based materials. Fullerenes are the third allotrope of carbon atom after the graphite and diamond. Fullerene molecule is mainly composed of sixty carbon atoms in form of a hollow sphere or ellipsoid, with an important property of high symmetry.[1] The arrangement of the atoms is similar to the shape of the geodesic dome which was invented by architect Buckminster Fuller, hence the name. Buckminsterfullerenes are also known as Buckyball.[1] Buckyballs and other fullerenes because of their chemistry and unusual hollow, cage-like shape are extremely stable and can withstand very high temperatures and pressures. Spherical structure of fullerenes remains intact even after reaction of carbon atoms with other atoms and molecules. Researchers are interested in creating new molecules by adding other molecules to the outside of a buckyball and also trapping smaller molecules inside the cage of a buckyball.[2]

Fullerene family can be exploited in different biological fields due to its very fascinating physicochemical properties. These are insoluble in water, but the addition of suitable functional group makes them soluble. The interaction of organo fullerenes with Deoxyribonucleic acid (DNA), proteins and living cells were discovered by studies on water-soluble fullerene derivatives which were first reported in 1993.[5]

An important property of fullerene molecule is its high symmetry. All the rings are merged; all the double bonds are conjugated. In spite of their extreme conjugation, they behave chemically and physically as electron-deficient alkenes rather than electron-rich aromatic systems. Fullerene can fit inside the hydrophobic cavity of human immunodeficiency virus (HIV) proteases due to which substrates are unable to bind at the catalytic site of the enzyme. Fullerenes have radical scavenging activity; in fact, some water-soluble derivatives are able to reduce reactive oxygen species (ROS) concentrations. On exposed to light, fullerene can produce singlet oxygen in high quantum yields. DNA can be cleaved by this action together with the direct electron transfer from an excited state of fullerene and DNA bases.[3] They can be subjected to extreme pressures, as they regain original shape on pressure release. These molecules can be used as lubricants because they do not combine with each other.[4] Anticancer drugs are unable to differentiate between cancerous cells and living healthy cells henceforth are dangerous to healthy cells. But, intact nature of fullerenes makes them pertinent in anticancer compounds. It is the only molecule composed of a single element to form a hollow spheroid which gives the potential for filling molecules inside and applicable for novel drug-delivery systems.[2]

MEDICINAL APPLICATION OF FULLERENES

Fullerenes as Enzyme inhibitor

HIV protease inhibitor

The replicative cycle of HIV has a number of prospects to target the antiviral drugs against HIV. But the majority of currently available drugs have severe adverse effects and unwelcome drug interactions. Since HIV has high mutation rate and cross-resistance between drugs, it may become difficult to treat same in the near future. The HIV protease inhibition by fullerene has been proposed to be auspicious. The first fullerene derivatives that exhibited anti-HIV activity were reported in 1993.[4] HIV protease is a fundamental enzyme for the virus survival. It is an aspartic protease enzyme similar to mammalian proteases like renin but is specific for HIV proteins. In addition to this, it does not cross-react with human proteases. The HIV protease cleaves a polyprotein shortly after viral budding stage of HIV replicative cycle. The effect of this cleavage is to activate reverse transcriptase (RT), ribonuclease (RNAse), integrase and protease itself. The latter completes the life cycle of HIV-1 and without this step, it is not possible to infect new cluster of differentiation 4 (CD_4) cells. The protease was predicted to be one of the main

possible targets of the antiviral therapy and at the moment molecules that are mostly HIV protease inhibitors are used in clinical medicine. The basic idea behind the design of these inhibitors was to have a fullerene cage which targets the hydrophobic cavity of HIV protease with additional functionalities on the cage to enhance electrostatic interactions with the aspartate units. The active site of HIV protease is a partly-opened with the two amino acidic residues i.e. 25 and 125 aspartate groups, present on the surface of the cavity which catalyzes the hydration of the cleavable peptide bond of the substrate. The approximate diameter of semi opened cavity is about 10 A° which is virtually nearby to the diameter of the fullerene.[6] According to Friedman and coworkers molecular modeling study, the introduction of a fullerene molecule into the catalytic cavity leads to form complex and henceforth the inhibition of HIV protease. As a matter of fact, if the carbon sphere is utterly centered, the distance between its surface and that of the enzyme may acquiesce the generation of van der Waals forces of interactions. The first synthesis of a fullerene derivative which is able to inhibit of HIV protease by adapting accordingly in the active site of the viral protease was synthesized by the same research group. The in vitro study data revealed dissociation rate values with HIV protease around 10^{-6} - 10^{-9}M and the inhibition constant 5.3 mM. During inhibitory studies, the EC50 of the infected peripheral blood mononuclear cells (PBMC) was found to be 7 mM and the non-cytotoxic effect was detected up to 100 mM. The binding constant can be increased up to 1000 times by interpolation of substituents which are able to bring about electrostatic interactions with the two aspartate groups. A broad analysis of the enzyme surface proclaims the presence of two symmetrical channels that are exposed to solvation and cannot be occupied by the side chains of derivative 1. The synthesis of more efficient molecules is based on a better exploitation of the hydrophobic cavity of HIV protease with an increased surface desolvation and the development of stronger bonds. In fact, side chains of derivative 1 lean forward on the outer side and have only a solubilizing function and do not play any role in the interaction.[6]

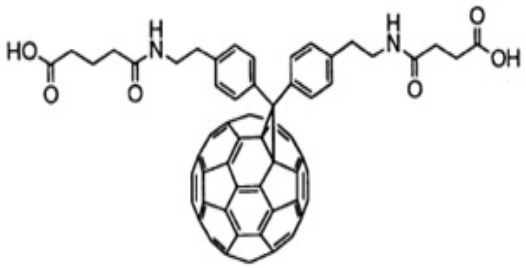


Figure 1: Molecular structure of the fullerene derivative (derivative 1).

In addition to non-polar groups, it becomes easier to insert in those regions, which could increase desolvation. Derivatives 2-4 (Fig. 2) can strongly enhance the desolvation and partially occupy the water-exposed channels. The calculated Ki of derivative 3 was 103 nM, which is 50 times higher than that of derivative 1. The Anti- HIV compound fullerene dendrimer was tested in primary human lymphocytes, acutely infected with HIV-1LAI, with an EC50 of 0.22 mM and it demonstrated to be competent against mutant viruses. Besides, no any apparent cytotoxicity in human PBMC, Vero or CEM cells was evidenced up to 100 mM. According to molecular modeling studies the fullerene core could block the access to the catalytic site of enzyme. From calculations for the intermolecular energy of the minimize model, the interaction between the fullerene moiety and the enzyme results to be energetically favored.[7]

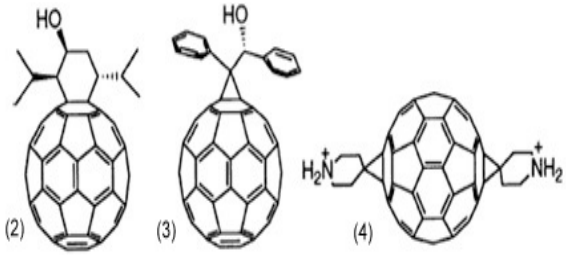


Figure 2: Fullerene inhibitor of HIVP with added non-polar groups (derivatives 2-4).

The provocative approach to fullerene-sugar hybrid for photo-degradation of HIV-1 protease was reported by Toshima and co-workers. The use of sugar was for enhanced interactions between the hybrid and HIV-1 protease through hydrogen bonding. Initially, the hybrid is allowed to complex with HIV-1P, which further photo-irradiated with UV/visible light under neutral conditions in the absence of any other additives which result in the degradation of the virus. In control experiments, the hybrid exhibited significant selectivity toward HIV-1P over other proteins such as bovine serum albumin (BSA) and hen egg lysozyme (Lyso). The photodegradation of the HIV-1 protease was attributed to the action of ROS generated by photoexcited fullerene and dissolved oxygen in solution.[12]

Other Enzyme inhibitor

Fullerene derivative 5 (Fig. 3) has shown inhibitory activity against various enzymes as cysteine proteases (papain, catepsin) and serine proteases (tripsin, plasmin, thrombin).[7]

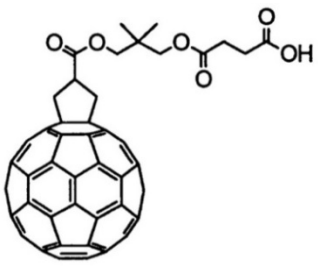


Figure 3: Molecular structure of fullerene derivative 5.

The unique characters of electrophilicity and hydrophobicity are probably key elements for enzyme inhibitory activity. In addition to this high reduction potential contributes to enzyme inhibition. Late examination investigated that the fullerenes can restrain the glutathione-S-transferase and specifically fullerol derivative act towards the plasmatic reticulum enzymes of hepatic cells, mitochondrial ATPase and P450-cytochrome dependent monooxygenases. An applicable advancement in enzyme inhibition by fullerene derivatives identifies with nitric oxide synthase (NOS). Nitric oxide is a highly reactive radical molecule altogether it is an important physiological compound, almost ubiquitary messenger. However, at high concentrations, it may end plainly lethal. After the demonstration, it can be concluded that the fullerols are able to decrease bronchospasm actuated by the systemic xanthine oxidase. The inhibition of all the three forms of NOS (neuronal, epithelial and inducible) has been found by trimalonic derivatives of fullerene, mainly C_3 and D_3 (Fig 4). The inhibition of NOS is multisite and emphatically cooperative and it seems that C_3 inhibits the intersubunit transfer of electrons, presumptively by a reversible distortion of the dimer interface.[7]

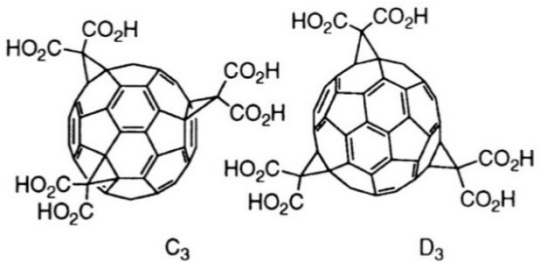


Figure 4: Trimalonic derivatives of C60 (C3 andD3)

Fullerenes as an Antioxidant

The presence of free radical species in a human body is natural, but their overproduction may be detrimental and cause serious diseases. Therefore, there has been broad research on the development of free radical scavengers for biomedical applications. Fullerenes are known for their excellent free radical scavenging abilities, considerably more effective than conventionally used antioxidants. In biological systems, fullerenes may be used to terminate free radical species for the protection against cell damage and death.

Neurodegenerative disorder

The hyper-production of oxygen and nitric oxide radical species prompt the over-excitation of glutamic acid receptors which bring about age of neurodegenerative disorders such as Parkinson's, Alzheimer's and Lou Gehrig's diseases, perhaps due to oxidative stress by oxygen radicals is known to instigate cellular instability by a cascade of events, leading to a programmed cell demise. In these circumstances, the use of radical sponges has

been demonstrated to decrease yet not to eliminate neuronal death. Oxygen radical species such as superoxide (O_2^-) and hydroxyl (^+OH) radicals, usually attack lipids, proteins, DNA and other macromolecules, at the same time fullerenes are better in reacting with these oxygen radical species, henceforth it shows neurological activities. In particular, poly-hydroxylated fullerene derivative fullerenenols or fullerols [C60 (OH) n] have been appeared to be outstanding cell reinforcements. Reducing apoptosis in cortical neurons cultures: with their high solubility and their ability to cross the blood-brain barriers, fullerols have been additionally shown to ingest numerous oxygen radicals per fullerene molecule and to lessen toxicity of free radical harm on neuronal tissue. They have likewise appeared to block glutamate receptors and to bring down the intracellular calcium level. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are influenced more than *N*-Methyl-D-aspartic acid **(**NMDA) and Kainate *(*KA) receptors and the inhibition is dose-dependent with a reduction of neurotoxicity to about 80% at 50 mM.[7]

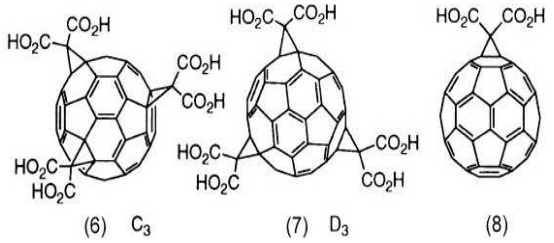


Figure 5: Carboxyfullerenes and fullerene Derivative.

Carboxyfullerenes 6 and 7 (Fig. 5) have demonstrated their efficacy in vivo toward neurodegeneration involved in the amyotrophic lateral sclerosis (ALS) and they restrict oxidative stress induced by iron in the dopaminergic nigrostriatal pathway. Corona-Morales et al. reported the positive action of derivative 6 (Fig. 5) and of ascorbic acid when applied to adrenal chromaffin cell cultures exposed to levodopa, increasing the cell survival and preventing cell demise, including apoptosis.[9] Wang et al. compared the antioxidant power of fullerene derivatives 6-8 (Fig. 5) and tocopherol against $^1O_2$ and ^+OH generated from the xanthine oxidase and Fenton reactions respectively. The fullerene derivative resulted to be the most effective among the examined lipid soluble compounds.[9] An alternate conduct between the behavior of the water-soluble isomers 6 and 7 was observed. The C_3 (derivative 6) was more active than D_3 and this can be explained by noticing that in C_3 all the carboxylic groups are on a similar side of the equator, permitting the inclusion of fullerene into the two-fold lipid layer.[9]

Antiapoptic action of fullerene

Apoptosis is an event where a scheduled death of cell, for the most part, happens due to the transforming growth factor (TGF-b), a dimeric protein. In this course of action, ROS species are discharged meanwhile to stop the damage, or at possibly to decrease it, antioxidant works. Huang demonstrated that fullerene derivatives 6 and 7 (Fig. 5) can prevent apoptosis in hepatic tumor cells Hep3B by neutralization of reactive oxygen species induced by TGF-b.[7] Further experiment emphasizes the antiapoptotic impacts of hexa(sulfobutyl)fullerene derivative in kidney cells presented to an oxidative stress actuated by the ischemic event and following the reperfusion. The drawn out conservation of oxygen took after by an organ reperfusion offers a succession of cell changes that culminate in the apoptosis. The declining of apoptotic cell death level is strictly related to the neutralization of ROS both in vitro and in vivo.[7] Daniela Monti et al explored the defensive action of these derivatives against oxidative stress-induced apoptosis. 2-deoxy-D-ribose (dRib) or TNF-α in addition to cycloheximide were utilized as agents to trigger apoptosis in human peripheral blood mononuclear cells (PBMCs) by meddling with a redox condition of a cell and mitochondrial membrane potential. By retaining the mitochondrial membrane potential trustworthiness, Carboxyfullerenes or C60 tris

(malonic) acid, was able to protect quiescent PBMCs against apoptosis.[10, 11]

Fullerenes used in Cosmetics

Carbon fullerenes have been used in a number of cosmetic products owing to antioxidant properties; thus perceived for their application in the formulation of skin rejuvenation cosmeceutical products.[12] Fullerenes are extremely hydrophobic and this insolubility in aqueous solutions limited their relevance in the initial stages, but by taking advantage of surfactants or surface alterations has aggrandized their capability to solubilize in an aqueous medium and brought more appreciation to their possible cosmeceutical applications.[12] Inui *et al.* assessed the clinical efficacy of fullerene in the treatment of acne vulgaris. They developed a Lipo Fullerene gel, which significantly reduced the number of inflammatory lesions approximately by 23% and 38% after 4 and 8 weeks, respectively.[13] Fullerenes are also used for cytoprotective action against ultra violet A (UVA) irradiation. The UVA radiation (320–400nm) generates reactive oxygen species, which biologically affect human skin cells, prompting cell damage or cell death. By and by the radical scavenging nature of water-dissolvable fullerene specifically Radical Sponge R (fullerene with poly vinylpyrrolidone) was used to secure human ore mammalian cells against oxidative stress, through reactant dismutation of superoxide. Radical Sponge– world's first fullerene-based restorative was hurled in 2005. The capability of Radical Sponge R to go into the profundity of human skin epidermis is because of steadiness towards oxidative decay, makes it more dependable than Vitamin C and engages the anticipation of both UV skin-wounds and skin maturing, without photosensitization and cytotoxicity.[1]

Fullerenes as a Carrier

Drug and gene delivery

The direct delivery of drugs and biomolecules through the cell membrane into cells has acquired increasing attention on the advancement of proficient and safe carriers to transport genes or drugs. The major challenge is the transportation of any compound into the core of a cell which is restricted by three layer barriers (cell membrane, endosomal membrane, and nuclear membrane). Paclitaxel, a standout amongst the most encouraging drugs for a treatment of cancer, was covalently attached to the fullerene confine (Fig. 6) by means of an ester bond, permits the paclitaxel to retain its pharmacological action. Indeed, the hydrolysis of the ester functional group brought about the inferable release of the drug. Besides, it was demonstrated that the derivative 9 has a significant anticancer activity in vitro when administrated with a liposome aerosol formulation, despite the fact that IC_{50} was 1.6 times higher than the homologous formulation containing the drug alone.[14]

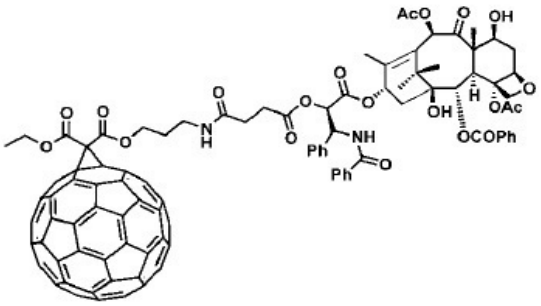


Figure 6: Molecular structures of paclitaxel-fullerene derivative 9

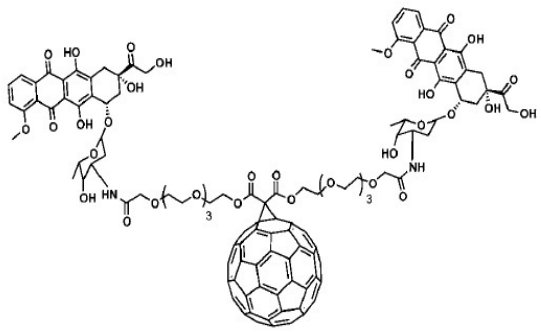


Figure 7: Molecular structures of doxorubicin–fullerene derivative 10.

In a complementary advent, one more compelling anticancer agent doxorubicin was attached to the fullerene moiety (Fig. 7). Doxorubicin is sparingly soluble in water, when conjugated with fullerene its solubility was observed to be increased due to the presence of

two polyethylene glycol chains thus rendering doxorubicin more accessible for bio applications. After incubation with cells, this compound was confined to the cytoplasm and to less degree into the nucleus. In spite of this distinction, the efficiency of doxorubicin was retained. Polyhydroxylated fullerenes called fullerenols or fullerols appeared as potential carriers for delivering anticancer drugs. Indeed, these structures, despite the fact that not flawlessly characterized in the number and the position of the hydroxyl groups, displays the phenomenal favorable position of high dissolvability in polar solvents if contrasted with numerous other C60-derivatives. A multifunctionalized structure can be obtained by binding functional groups with bioactive units resulting in getting high drug loading. A fullerenol model has been utilized to bind cisplatin and doxorubicin.[14] Fullerene has been utilized to deliver anticancer drugs. Additionally, it also delivers other bioactive molecules like coumarin, warfarin. Thrombosis is a major concern which can occur due to fluctuations in concentrations of warfarin in blood. It has been as of late inferred that the biological profile of the warfarin can be modulated by its conjugation to the fullerene. In recent years, it has been observed that fullerenes can infiltrate through the skin, building it's way to new transdermal administration approaches. The interaction with human epidermal keratinocytes was researched to gauge cytokine production and pro-inflammatory response in the presence of fullerene derivatives. Cytokine activity and cell viability were discovered specifically subject to the concentration of the fullerene derivatives.[15] Biochemical studies on the system of transfection demonstrated that the fullerene reagent shapes a defensive sheath around bound DNA, which at last builds the life of DNA in endosomes and subsequently holds their chromosomal incorporation. For the connection of DNA-arrangements, amino fullerenes are generally favored. The unit of DNA in the cytoplasm can be accomplished either by means of loss of its amino groups or loss of the coupling capacity of amines by change into a neutral compound.[1]

Delivery of Nucleic acids

Newly developed techniques in the treatment of hereditary illnesses rely upon cell conveyance of remote nucleic acids, including DNA, RNA, siRNA, LNA, and plasmid DNA (pDNA). Over the most recent couple of years, a ton of consideration has been unified on a progression of proficient strategies that need to experience fundamental criteria: Firmly tie nucleic corrosive successions, Circumvents unfavorable impact, Transfer over the distinctive cell hindrances and defend against the nucleases into the intercellular compartments. After the main transfection strategies in view of liposomes, certain frameworks have been composed and arranged in viral and non-viral vectors. Viral techniques take advantage of the capacity of infections to infuse their hereditary code internal a host cell; however, the dangers of a high resistant reaction are possible. Then again, the non-viral approach depends on the utilization of cationic frameworks like polymers or dendrimers, silica nanoparticles, gluco-nanoparticle or carbon nanotubes to complex and conveys the hereditary material. Relating to the non-viral approach, it is as yet essential to overcoming the low productivity and additionally, the intense invulnerable reaction regularly saw in the utmost of the tried frameworks. Polyfunctionalized fullerenes containing at least one positive charge on their cage have been scrutinized as nucleic acid delivery carriers. This field was spearheaded by Nakamura's group, as orchestrated a twofold gave fullerene transfection subsidiary alongside four positive charges. The subsidiary 11 (Fig. 8) delineates authoritative and conveyance of twofold stranded plasmid DNA (pDNA) into the cells with productivity similar to accessible reagents.[15]

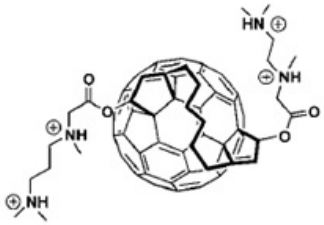


Figure 8: Molecular structure of the cationic fullerene derivative 11.

Also, in the wake of supporting the protein articulation for quite a while, it was observed that the pDNA– fullerene complex was steady in the cytoplasm. Keeping in mind the end goal to comprehend the morphology of the buildings between cationic fullerenes and pDNA, Atomic power microscopy (AFM) examination was performed. Derivative 11 could crease a supercoiled DNA atom into a solitary particle complex with the attachment of DNA twofold strands speaks to just a little increment of the DNA volume. This is positively leveraged as other DNA gathering specialists in light of lipids or dendrimers make bigger and less fundamentally characterized totals.[15]

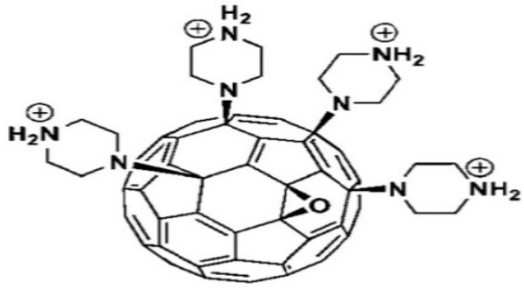


Figure 9: Molecular structure of the tetra (piperazino).

In conclusion, the first in vivo experiment on fullerene derivative explore different avenues were accounted. The cationic tetraaminofullerene (Fig. 9) having high water-solvency was utilized to complex pDNA, and its proficiency and harmfulness were contrasted with Lipofectin, and no intense poisonous quality was found. The in vivo conveyance of insulin-2 gene compared to an expanded plasma insulin level and a diminished blood glucose concentration, showing the high capability of fullerene compound as gene conveyance transporters.[15]

Fullerenes in the treatment of orthopedic disorders

Fullerenes in the osteoporosis therapy

Osteoporosis is a disorder in with a loss of bone strength, reduced bone mineral density and microarchitectural deterioration of skeleton lead to fragile fractures.[11] In addition, the F^- anion is the only known agent that can generate new bone matrix and mineral from formerly inactive areas. As such, F^- is also useful in the treatment of osteoporosis, as it improves bone strength and helps to impede fractures. The traditional agents for osteoporosis treatment, such as bisphosphonate drugs and fluorine anion (NaF), are not efficiently absorbed in the gastrointestinal tract or fairly toxic if orally administered.[7] Thus, the vectored pharmaceuticals targeted at destructive bone tissue may exhibit promising results in this field. Bone tissue is an especially appealing target for vectored pharmaceuticals because of its primary inorganic component, hydroxyapatite (HAP), offers a multitude of binding sites for structurally suitable compounds. As early years reported, functionalized fullerene with diphosphonate groups or amide bisphosphonate and multiple hydroxyl groups, the C60 derivatives C60[C $(PO_3H_2)_2]_2$ and C60 $(OH)_{16}$AMBP conferred a strong affinity to the calcium phosphate mineral hydroxyapatite of bone. Therefore, the fullerene-based bone tissue targeted compound cores demonstrated a promising prospect to be conjugated with traditional bone promotion agents for osteoporosis treatment.[16]

Fullerene derivatives in IVDD therapy

Symptomatic IVDD is strongly implicated as a cause of low back pain, which is one of the most common clinical conditions associated with musculoskeletal disorders, resulting in tremendous socioeconomic burden.[16] Researchers recently performed a study to estimate the therapeutic effects of the fullerol on nucleus pulpsus (NP) cells under

inflammatory induction and on annulus fibrosus puncture-induced disc degeneration in a rabbit model. It was found that the fullerol effectively reversed the matrix degradation of NP cells under either H_2O_2 or IL-1 β induction, and the intradiscal injection of the fullerol prevents the IVDD by not only increasing water and proteoglycan content but also by inhibiting ectopic bone formation.[17]

Fullerene derivatives in bone destruction therapy

In vitro study performed by Liu et al. found that the fullerol nanoparticles inhibits adipogenesis and simultaneously enhances osteogenesis in a bone marrow mesenchymal stem cell line under dexamethasone induction. Further *in vivo* studies were mandatory to confirm the osteogenesis-enhancing potentials of the fullerol.[18] Osteoclasts are multinucleated cells which enter the bone through the blood vessels. Osteoclasts are most likely derived from indistinguishable precursors from macrophage platelets, and they have the ability to dissolve both inorganic and the protein portion of the bone matrix. Every osteoclast expands various cell forms into the network and pumps out hydrogen ions onto the encompassing material, along these lines acidifying and solubilizing it. Hereinafter the hyper-resorption of bone by osteoclasts is another reason for bone destruction.[16]

The studies revealed that the water-soluble fullerene prevents the separation of precursor cells into osteoclasts and osteoclastic resorption in vitro through restraint of receptor activator of NFκB (RANK)-RANK ligand (RANKL) signaling pathway by a coordinate expulsion of ROS and in addition smothering the generation of proinflammatory cytokines. Besides, in their adjuvant-induced ligament bone resorption animal model demonstrate, intra-articular infusion of fullerene fundamentally repressed neighborhood aggravation and joint decimation. Accordingly, fullerene demonstrated another novel component from the opposite side to counteract bone pulverization by osteoclastic concealment and irritation hindrance.[16]

Diagnostic applications of Fullerene

A fullerene cage has the ability to carry metal atom into the interior of the cage which is unstable and hence is called as endofullerenes or metalofullerenes. A few examinations have demonstrated that fullerenes are generally non-harmful and impervious to body metabolism. Biodistribution studies with water soluble derivatives of fullerene reveal that these compounds are initially localized in the liver with a slow clearance rate. Metallofullerenes have a potential in a diagnostic application as they introduce no release of the captured metal atom under *in vivo* conditions, in contrast to metal chelates. Endofullerenes can be applied as magnetic resonance imaging contrast agent MRI, X-ray imaging agent, and radiopharmaceuticals.[1] Noble gases have been encapsulated in Fullerenes, which have no desire to bond with the surrounding carbon atoms but can be used in applications such as magnetic resonance imaging (MRI). Fullerene and other fullerene derivatives with an atom of gadolinium inside were designed by researchers at Rice University and with chemical appendages that make them water-soluble. In typical MRI contrast agents, the metal gadolinium is lined to a non-fullerene molecule, which is normally excreted quickly from the body. These might allow the contrast agent to remain in the body longer, allowing doctors to perform slower studies.[1]

A highly water-soluble derivative Fullerol, was radiolabelled with $67Ga^{3+}$. The results show that radiolabeling yield could reach 97% under the best applied conditions. The radiochemical purity of 67Ga-C60 (OH)x solution kept at 37^0C remained at 88% after 212 hours. Biodistribution study implements data that shows localization of this compound to macrophages, because of the fullerene derivative localized predominately to bone marrow, the liver and spleen with slow clearance and negligible amounts in the blood. The distribution and metabolism study of holmium metallofullerol molecules indicates

significant accumulation in the liver; moreover, they could be detected in the bone. Metallofullerol can be used as a chemotherapeutic agent for treatment of leukemia and bone cancer, as it significantly localized in bone and selectively targeted to tissue rich in macrophages.[1]

Other relevant uses of Fullerenes

Photodynamic Therapy

Photodynamic treatment (PDT) is a rapidly growing treatment for numerous diseases. The therapy involves the administration of nontoxic drugs or dye known as a photosensitizer (PS) which can be applied topically, locally and systemically to a patient bearing a sore. This is followed by the illumination of the sore with visible light in presence of oxygen, which triggers the photosensitizer and results in the formation of cytotoxic reactive oxygen species and eventually leads to cell death and tissue impairment.[2]

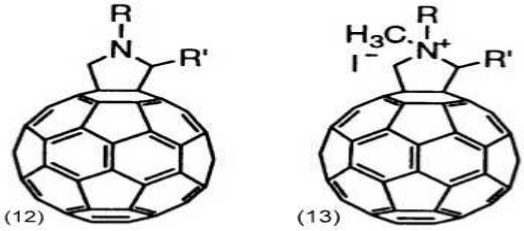
Atsushi Ikeda and colleagues from the Nara Institute of Science and Technology showed that the carbon isotope of fullerene could be delivered into human cancer cells by hollow lipid spheres and used to induce cell death under visible light irradiation. However, the solubility of fullerene in water and transportation of compounds into a cancer cell were few challenges faced by Atsushi Ikeda and coworkers. Moreover, few derivatives of fullerene are water soluble whereas fullerenes which are unmodified give efficiently singlet oxygen. A study carried out by the same group employed different lipids including amino lipids and phospholipids in order to make the lipid layer C60 structures, which are called LMI (60) fullerenes i.e. Lipid Membrane Incorporated C60. The LMI (60) with a cationic surface was found to have a considerably higher PDT activity than the structures with anionic and neutral surfaces; Further study was required to develop PDT photosensitizer with specific tissue distribution properties and upgraded porousness and maintenance impacts of LMI (60) fullerenes and furthermore to tune the lipid film surface utilizing different lipids with modified functional moieties. In future fullerene will be employed not only for cancer therapy but also for bacterial or fungal infections.[2]

Liu et al demonstrated the use of polyethylene glycol (PEG)-conjugated fullerene containing Gd^{3+} ions for photodynamic therapy in combination with MRI. Tumor PDT impact was aided by photosensitizer in order to target tumor and MRI activity. C60-PEG-Gd was infused into tumor-bearing mice and the MRI action was brought into C60-PEG of PDT photosensitizer. The conversion of C60-PEG derivative to a photosensitizer could be done due to the chelate incorporation of Gd^{3+} ions. The formed photosensitizer will find applications in diagnostics and therapeutics.[1]

Antimicrobial action of Fullerene

The insertion of fullerenes into biological membranes has urged many researchers to think about the potential antimicrobial activity of fullerene. The bacteria's like Candida albicans, Bacillus subtilis, Escherichia coli and Mycobacterium avium showed positive results. The efficacy of salts 12 (Fig. 10) against resistant strains of human Mycobacterium tuberculosis was found out to be higher as compared to respective neutral derivatives.[11]

Tsao et al., studied biological effects of the tricarboxyfullerene derivative on twenty different bacteria strains such as Staphylococcus spp., Streptococcus spp. In the study, it was found that all gram positive bacterias are inhibited with MIC5/50 mg/ml, with at least 5 mg/ml for Streptococcus pyogene. The Gram-negative did not have any reaction neither at 500 mg ml. The cell wall of Gram-ve organisms, having an outer membrane consisting of lipoproteins, lipopolysaccharides, and phospholipids is not susceptible to access by fullerenes.[5] This suggests that carboxyfullerenes could be considered as new antimicrobial agents against Gram+ve cocci.[5]



R= -CH_3, R'= -$CH_2OCH_2CH_2OCH_2CH_2OCH_3$
R= -$CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_3$, R'= H
R= -$CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_3$,
R'= -$CH_2OCH_2CH_2OCH_2CH_2OCH_3$

Figure 10: Molecular structures of fullerene derivatives 12 and 13.

By the goodness of the distinctive associations with Gram-positive and Gram-negative microscopic organisms, the bactericide activity was founded on the addition into the microbial cell wall. Additionally, the intercalation of carboxyfullerene into the cell-wall was shown by transmission electron microscopy and hostile to carboxyfullerene restricting assay. Distinctive components, not including the cell film interruption by intercalation of the lipophilic fullerene moiety, can be used to inactivate pathogen specialists. Mashino et al. used two isomers (trans-2 and trans-4) of fullerene-bis (N, N-dimethyl pyrrolidinium iodide) (subordinate 14 and 15, Fig. 11) to think about the bacteriostatic impacts of fullerene derivatives on E. coli and they credit this to the restraint of vitality digestion, by two inverse dosage subordinate systems.[5] At low fullerene level the oxygen take-up is diminished, in actuality, at high fixation, the O_2 take-up is expanded and oxygen is changed over to H_2O_2. Additionally, these fullerene fixations restrain the respiratory chain action.[7] Fullerenes were expected to have antibacterial movement in light of the theory that fullerene could deliver film interruption by inclusion into phospholipids two fold layers. The subsequent film issue, causing changed penetrability, prompts the arrival of metabolites and cell demise. As monomethoxy triethylene glycol (mTEG) substituted fulleropyrollidines indicated finish restraint of Mycobacterium avium at measurements 260 µg/ml and M. tuberculosis at measurements approximately 50 µg/ml. The conceivable clarification for the antitubercular action has been suggested that nearness of carbon confine destabilizes the tubercular cell divider by intercalation in the hydrophobic part.

Pharmacognostic application of Fullerenes

The researchers used a medicinally modified vegetable crop, bitter melon, as a model for investigation of the effects of seed treatment with a fullerene derivative, fullerol [$C_{60}(OH)_{20}$], Additionally on the yield of biomass and fruit characters, and phytomedicine contents and concentration in fruits and plants. It was discovered that bitter melon seeds treated with fullerene expanded the total yield. Nonetheless, a bigger convergence of fullerene reduces the impact. The most astounding biomass expanded up to 54% from this point forward it affirms the assimilation and translocation of the fullerol in plants. All the cucurbitacin-B, lycopene, charantin and insulin were found to increase concerning control. The bitter melon seeds treated with five diverse centralizations of fullerol demonstrated an upgrade in biomass, organic product yield and phytomedicine substance. Fullerol of a proper size and fixation may use to expand the yield of oat and other crops. The future prospect of nanomedicines like fullerene derivatives is fairly bright as it is a low-cost solution to increase the crop production and fruit manifold.[19]

CONCLUSION(S)

Fullerene cages as unique carbon nanostructures apparently offer great opportunities for the exploration of biological and biomedical applications. One significant issue not covered in any detail in is on the potential toxicity or bio-safety of fullerenes, which is still being extensively investigated and intensively debated. Nevertheless, it seems that similar to what has been found in other carbon nanomaterial's such as carbon nanotubes and nanoparticles, the well-functionalized and soluble derivatives of fullerenes are generally less toxic or nontoxic *in vitro* and/or *in vivo*. Since the discovery of carbon nanotubes and more recently graphene sheets, fullerenes has

decreased demand. However, while the nanotubes and sheets are competitors with advantages for some applications, fullerenes remain unique, as they are not only carbon nanomaterials but also molecules, with stoichiometrically defined structures and compositions with less or no toxicity. These characteristics, among others, make fullerenes particularly valuable for at least drug-related biomedical uses. A worth of innovative work exercises everywhere throughout the world has prompted a tremendous number of use situated licenses, crossing an exceptionally wide range of potential business applications, including anticancer medication frameworks utilizing photodynamic treatment, HIV medications, and beautifying agents to back off the maturing of human skin. A strong case can be made for further investigations on various configurations of fullerenes for their applications in biology and medicine which will open the door to a host of other applications.

CONFLICT OF INTEREST

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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