ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 01 | January - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

FULLERENE – A REVIEW ARTICLE

Medicine

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ABSTRACT

Carbon is one in all the foremost abundant elements on earth. Discovery of Fullerene, the third carbon allotrope triggered the world. Biomaterials have become a crucial element in numerous biomedical, preclinical, and clinical applications. Besides, in the new promising field of artificial biomaterial generation, fullerenes are studied as the load in nanocomposite materials, improving their mechanical properties. The potential use of fullerene derivatives in medical field is due to its unique biological behavior. Studies show that it is rapidly absorbed by tissues and excreted by urinary tract which shows reduced toxicity in vitro and in vivo. This review concentrates on development and potential uses of fullerene and its derivatives in medical field.

KEYWORDS

Fullerene, Antioxidant, Photosensitizer, Biosensor.

INTRODUCTION

A Fullerene is a carbon-based molecule that takes the shape of a hollow sphere, ellipsoid, or tube [1]. Fullerene's structure is said to be similar to that of graphite [2]. Fullerene is the third allotrope of carbon. Allotrope is the existence of a chemical element in two or more forms [3]. Fullerene is one of the strongest antioxidants and also known as RADICAL SPONGES [1]. The researchers, Richard E. Smalley, Robert F. Curl and Harold W. Kroto of the University of Sussex in Brighton, United Kingdom, discovered fullerene in 1985 and won a Nobel prize [4]. Fullerenes are frequently used to create a variety of new materials and devices [5]. Because of their small size, mass, high electrical and thermal conductivity, they have amazing structural, mechanical, and electronic properties [6].They have an excellent ability to pierce cell membranes, allowing them to localize in cells and distribute medications under the right conditions. It is also used as a scaffold in human tissue engineering [7]. Fullerenes were first used as structural additions in electronics, optics, polymers, and other nanotechnology-related materials [8]. In the treatment of CNS-related disorders, delivering medications to the central nervous system is a major challenge; fullerene nanoparticles can pass the blood-brain barrier which could be an advantage [5].

TYPES OF FULLERENES:

- Buckyball clusters
- Nanotubes
- Megatubes
- Polymers
- Nano "onions"
- Linked ball and chain
- Fullerene rings

FULLERENE IN MEDICAL DIAGNOSIS

MRI Contrast agents

Gadolinium is used as contrast agents in various diagnostic aids nowadays. But they are toxic to humans, so to prevent its toxicity it is formulated in a chelate. In patients with kidney diseases due to prolonged excretion time these may separate causing toxicity. Fullerene nanoparticles when used along with gadolinium, acted as a stable cage and thus prevented the problem of separation. These new MRI contrast agents also provided physicians new ways to detect atherosclerotic plaque build-up in blood vessel walls. In vitro experiments demonstrated that these contrast agents better delineated tumours at low concentrations. Later experiments showed that the imaging agents remained in tumours far longer than conventional agent and was better able to discern the margins of growing tumour[4].

FULLERENES IN THERAPEUTICS

Fullerenes are scavengers of free radicals. For many disorders like asthma, allergies, and arthritis, they can intercept free radicals and neutralize them before they cause cellular damage. Mast cells are seen in a variety of organs as a result of allergic reactions. Fullerene derivatives are being tested to inhibit these diseases by inhibiting mast cell production. They inhibit the process unlike other treatments which only stops the allergic reaction from progressing. Mast cell mediator release is the fundamental cause of asthmatic episodes. Fullerenes are being studied to see if they can prevent mast cell activation in the lungs, which often leads to an asthma attack. Mast cells are also responsible for the development of arthritis.Thus, fullerenes are being experimented in preventing Arthritis[9].

ANTIOXIDANT

Fullerenes act as an excellent antioxidant due to the chemical properties such as high electron affinity and large number of conjugated double bond. They have the ability to interact with several free radicals before being consumed. They possess many conjugated double bonds and lowest unoccupied molecular orbital which can take up an electron [10]. They are biocompatible and safe within the cell which is major advantage to be used as an antioxidant [3]. They have the ability to localize within the mitochondria in a cell and other cell sites in diseased state where the production of free radicals takes place [2]. These radical scavengers have shown to protect cell growth from various toxins that can induce apoptosis in vitro. Fullerenes are also used as cytoprotective agent against UV radiation. These radiations generate reactive oxygen species in human cells which causes apoptosis of cells. Here fullerenes act as radical sponge against oxidative stress and protects human cells. They can enter depth of human skin epidermis which enables prevention of UV skin-injuries and aging [10].

ANTIVIRAL

Antiviral compounds have been described in a variety of pharmacological actions, drawing medical attention to them. Fullerenes and their derivatives are being experimented for their antiviral effects [2]. One of their most remarkable properties is their capacity to inhibit the replication of the human immunodeficiency virus, which resulted in a decrease in the symptoms of acquired immunodeficiency syndrome. HIV protease inhibition by fullerene compounds has been discovered, preventing HIV replication [3]. The relative position of side chains on fullerenes strongly influences their anti-viral activity [10]. Dendrofullerene has shown to have the highest anti-protease activity. Fulleropyrrolidines with two ammonium groups have been found active against HIV-1 and HIV-2 [2].

GENE THERAPY AND DRUG DELIVERY

Gene therapy is a method to correct a defective gene that causes a disease by using DNA molecule. Carbon nanotubes were used in this therapy where it delivered the DNA to the site before it was destroyed by defense mechanism [8]. Organic cationic compounds, viral carriers, recombinant proteins, and inorganic nanoparticles are set to be the four major groups of drug and gene carriers [2]. Drug delivery means to have a right transport of the drug to the target site [3]. Transport of any compound into the nucleus of an intact cell is a major challenge, as transfer is limited by three membrane barriers which are the cell membrane, the endosomal membrane, and the nuclear membrane [11]. Due to their small size and biological activity fullerenes are classified under inorganic nanoparticles [2]. Fullerene is hydrophobic in nature, by attaching hydrophilic particles they become water-soluble and now can carry drugs and genes [10]. Many anticancer drugs use functionalized carbon nanotubes and tested successfully, for example drugs such as Doxorubicin, Methotrexate, Cisplatin have been tested in vitro and in vivo [8].

 PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr

PHOTOSENSITIZERS IN PHOTODYNAMIC THERAPY

Photodynamic therapy is a photochemical method that uses photosensitizing agents and light irradiation to produce reactive oxygen species in tumour tissue, to induce damage and apoptosis [12]. The properties of fullerene make them potential photosensitizers for their use in photodynamic therapy. Mroz et al investigated the photodynamic activity of fullerenes derivatized with hydrophilic and cationic groups against a range of mouse cancer cell lines [12]. Monocationic fullerene, they discovered, is a highly potent photosensitizer for destroying cancer cells through fast apoptosis [10]. Photodynamic therapy is a non-invasive and nonsurgical treatment for some type of tumors and some of non-malignant diseases [4]. (See Figure 1)

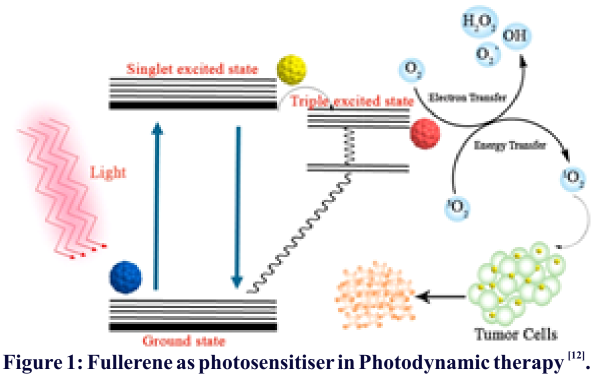

Figure 1: Fullerene as photosensitiser in Photodynamic therapy [12].

When visible light is passed, fullerene gets excited from S0 ground state to a short-lived state, S1, excited state. S1 quickly decay to lower lying triplet state which has a long life timeT1. In the presence of dissolved oxygen, fullerene (T1) is quenched to produce singlet oxygen and catalyse ROS production. A newer approach for cancer treatment implies the combination of fullerene derivatives with other molecules [4]. The combination with several antitumor drugs suggested that these could be a promising approach in cancer therapy, even though further developments in this field requires more advanced investigations [12].

FULLERENE IN ORTHOPEDIC RESEARCH

Cartilage degeneration

Cartilage degeneration is caused by loss of chondrocytes. The procedure involves generating new chondrocytes from progenitor cells. Fullerenes were found to have effect on promotion of primary embryonic limb bud cell chondrogenesis. This effect was proportional to the concentration of the fullerene. The mechanism by which fullerene is able to influence chondrogenesis is still not known. It might be due to its anti-oxidative properties for chondrocytes differentiation [3].

Osteoporosis therapy

It is skeletal disorder with decreased bone density, increased risk of fracture and deterioration of skeletal architecture. Fullerenes have strong affinity to calcium phosphate mineral hydroxyapatite of bone, that it could bring bone promoting agents in destructive bone tissues and thus used in treatment of Osteoporosis [3]. The experiments in rat showed that fullerenes inhibit bone resorption caused by osteoclasts [4].

NEUROPROTECTIVE AGENT

Neuroprotective activity of fullerene derivatives is like their radical scavenging activity. Reports has shown their ability to reduce apoptosis in cortical neurons and to block glutamic acid receptors [4]. They are used in drugs against treatment of Alzheimer's and Parkinson's disease [8]. Free radicals are said to be associated with Cancer, atherosclerosis, Alzheimer's, Parkinson's disease, and a variety of other diseases [3].

BIOSENSORS

A biosensor is an analytical device that combines a biological sensing element or a recognition site with a transducer to detect the presence and count the number of biomolecules, enzymes, microorganisms, organelles, antibodies, and receptors [4]. The recognition site reacts to the presence of biomolecules, which the transducer then translates into quantifiable signals. Here, fullerenes can act as a mediator between the recognition site and the biosensor electrode, speeding up the electron transfer rate caused by analyte and biological component biochemical reactions in the recognition site [13]. Pristine Fullerenes are hydrophobic in nature, but an efficient mediator should be hydrophilic and thus they cannot be used. So, fullerene derivatives are used as mediators in biosensors. They were experimented in glucose biosensing [4].

TOXICITY

It is important to remember that fullerenes are a group of compounds, and toxicity varies depending on the size, composition, surface characteristics, and functionalization of the individual molecules [14]. The solvents used and their by-products, as well as metal contaminants, are to blame for its toxicity. Various toxicity mechanisms have been proposed. One of them is oxidative stress, which is caused by the production of reactive oxygen species and can lead to cell death. Fullerenes may also activate genes involved in the inflammatory process, metalloendopeptidase activity, and immune system response. Phagocytosis, which is caused by the fibrous form of long carbon nanotubes, can have severe consequences. As compact tangles, nanotubes may cause lung fibrosis and cancer, whereas as fibers, they may impact the pleura and produce mesothelioma, similar to asbestos [14]. In dermal fibroblasts, they also cause genotoxicity, cytotoxicity, and apoptosis. Because of its cosmetic applications, dermal toxicity warrants special study. Fullerenes are described as a "double edged sword", safe in low concentrations and toxic in high concentrations [15].

CONCLUSION

Fullerenes were discovered at the end of the last century. The use of fullerene and its derivatives to biological targets has now yielded interesting medical applications. The unique chemical and physical features of the fullerene, notably their photodynamic capabilities, have drawn such attention to them. These, together with the low toxicity are enough to stimulate researchers in chemistry and biology to examine the biological aspects of these interesting molecules. These new researches and advancements are beneficial to both doctors as well as the patients. The high production cost of fullerenes has been the main stumbling block in the past, but now there is a significant drop in price, which will open the door to a plenty of new advancements.

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