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Review Article

Fullerenes in dentistry: A review on unlocking their therapeutic potential in oral medicine

Fatima Injela Khan[1]*, Ashish Aggarwal[1], Nitin Upadhyay[1], Sowmya Gujjar Vishnurao[1], Navendra Jha[1]

[1] *Dept. of Oral Medicine and Radiology, Institute of Dental Sciences, Bareilly, Uttar Pradesh, India*

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ABSTRACT

Fullerenes are a family of carbon allotropes that have demonstrated great potential in oral medicine. They have a distinct cage-like structure and take the shape of hollow spheres, ellipsoids, or tubes with special structural and physicochemical features. When fullerenes are spherical, they are known as buckyballs, and when they are cylindrical, they are known as carbon nanotubes or buckytubes. Due of their flexible construction, they can be used in a variety of settings, including medication delivery, gene therapy, diagnostics, and oral illness treatment. Fullerenes have the ability to conjugate or encapsulate medicinal substances, allowing for the regulated and targeted administration of drugs to tissues afflicted by diseases including mouth cancer and periodontal disease. When treating infections and long-term inflammatory disorders in the oral cavity, their capacity to improve drug stability and bioavailability is very advantageous. Functionalized fullerenes improve biosensing platforms and imaging methods in diagnostics, facilitating the early detection of illnesses and oral malignancies. There are still obstacles to overcome in order to maximize their biocompatibility, toxicity profiles, and delivery methods for clinical application, despite their enormous potential. This review aims in revolutionizing the detection and treatment of numerous oral disorders, and ongoing research endeavours to fully investigate the therapeutic potential of fullerenes in oral healthcare.

1. Introduction

Nanomedicine is the science of employing nanoparticles to preserve and enhance human health as well as prevent, diagnose, and treat disease.[1] Due to its valency, carbon may form a wide variety of allotropes, or structurally distinct forms, such as T-carbon, diamond, graphite, graphene, carbon nanotubes, and so on.[2] The 1985 discovery by Harold W. Kroto, Robert F. Curl, and Richard E. Smalley of Carbon fullerenes, a unique carbon allotrope with a polygonal structure composed entirely of 60 carbon atoms; for this discovery, they were granted the 1996 Nobel Prize in Chemistry.[3]

The most prevalent member of the fullerene family, fullerene, was first prepared on a preparatory scale in 1990 using resistive heating of graphite (Kraetschmer et al 1990).[1] The only component of fullerene molecules is carbon, which is arranged into hollow spheres, ellipsoids, or tubes. Another name for spherical fullerenes is "Buckyballs".[2] High symmetry is a significant characteristic of the C60 molecule, commonly referred to as "Buckminsterfullerene."[3]

The molecule is mapped onto itself by 120 symmetrical operations, such as rotation around an axis and reflection in a plane. According to Taylor et al. (1990), this makes Carbon 60 (C_{60}) the most symmetrical molecule.[2] There are 12 pentagons and 20 hexagons on the C_{60} fullerene surface.

* *Corresponding author.*
E-mail address: fatimainjelakhan23@gmail.com (F. I. Khan).

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Every ring has been fused, and every double bond has been conjugated. They behave chemically and physiologically as electron-deficient alkenes rather than electron-rich aromatic systems, despite their high conjugation (Fowler and Ceulemans 1995).[4] Numerous scientists predicted a number of technological possibilities based on the distinct physical and chemical characteristics of these novel carbon forms.[3]

Owing to the diverse forms and characteristics of fullerene compounds, the materials are incorporated into human bodies to augment biological functions.[5] Nanocarbon fullerene materials have been studied and used in dentistry among other medical fields since the discovery of fullerene.[3] Pharmaceuticals, dentistry prophylaxis, and diagnostics all use nanocarbon fullerene materials.[5]

2. Structure and Properties of Fullerenes

Fullerenes, in their most common form, resemble soccer balls due to their symmetrical structure composed of hexagons and pentagons (C_{60}).[5] Because of their spherical form, which provides a high surface area that is beneficial for functionalization, they are appropriate carriers for medicinal drugs.[4] Among the essential characteristics of fullerenes that are especially pertinent to oral medicine are:

1. High antioxidant activity: Reactive oxygen species (ROS) can be neutralized by fullerenes, thus protecting tissue from the damaging effects of oxidative stress.
2. Hydrophobic nature: Their adaptability for drug delivery can be increased by functionalizing them to improve their solubility.
3. Photodynamic properties: Fullerenes produce singlet oxygen in response to light, which is harmful to cancer cells, bacteria, and fungus.
4. Stability: Because of their stable molecular structure, they are less prone to break down in physiological settings, resulting in long-lasting therapeutic effects.[6]

3. Applications of Fullerene in Oral Medicine

3.1. Antimicrobial activity

Compounded with photoactivation, fullerene derivatives have the ability to generate singlet oxygen and other reactive oxygen species. [5]These ROS have the ability to destroy bacterial nucleic acids, proteins, and cell walls, which results in microbial death. Broad-spectrum antibacterial activities of fullerenes can target fungi, bacteria, and both Gram-positive and Gram-negative bacteria.[6]

1. Dental caries prevention: To inhibit the growth of Streptococcus mutans, responsible for cavities, fullerene-based chemicals could be added to toothpaste, mouthwashes, or dental coatings.[5]
2. Treatment of Periodontal Disease: Derivatives of fullerene may be able to lessen the bacterial burden particularly Porphyromonas gingivalis and prevent Periodontitis.[3]
3. Antifungal Effects: Oral fungal infections, like Candida albicans-caused oral thrush, may be treated with fullerene-based medications.[6]
4. Wound Healing and Oral Ulcers: Fullerene-based materials have anti-inflammatory qualities that make them potentially helpful in encouraging wound healing following ulcers or oral surgery.[2]

3.2. Antioxidant therapy

Fullerenes has the potential to react with oxygen species, including superoxide O2 and hydroxyl radicals OH, which can destroy macromolecules such as proteins, lipids, and DNA without consuming any energy.[3] Since, they are thought to be the most effective radical scavenger in the world, they are referred to as radical sponges. Reactive oxygen species (ROS) are often released into the oral cavity by food, smoking, germs, and other environmental variables.[7]

1. Management of periodontal disease: Fullerene-based antioxidants have the ability to mitigate oxidative damage and inflammation in cases of periodontitis.[6]
2. Protection of oral cells from oxidative damage derivatives of fullerene may shield these cells from damage caused by reactive oxygen species (ROS), released by lifestyle factors such as smoking, poor diet, or infections hence reducing the likelihood of cell mutations and the formation of precancerous or cancerous lesions.[7]
3. Treatment of oral ulcers and mucositis: High levels of oxidative stress are linked to mucositis, or inflammation of the mucous membranes also known as aphthous stomatitis.[8] Treatments based on fullerene may be able to alleviate these excruciating diseases by lowering ROS and encouraging tissue repair.[2]
4. Dental materials and coatings: Long-lasting antioxidant protection could be achieved by incorporating fullerene nanoparticles into dental products like sealants and fillings.[8] Preventing problems or subsequent infections may assist preserve the health of the oral tissues surrounding it.[9]

3.3. Antiviral therapy

Fullerenes have demonstrated potential in the treatment of oral viral infections, including herpes simplex virus (HSV) infections and lesions related to the human papillomavirus (HPV).[10]

1. Herpes simplex virus (HSV) Infections: HSV-1 frequently results in mouth lesions and cold sores. Because fullerenes block the entry, replication, and spread of the virus, they may be utilized to treat HSV infections.[8]

2. Human papillomavirus (HPV) lesions: Oral diseases such as warts as well as precancerous conditions are linked to HPV. Fullerene derivatives could be investigated as topical therapies for HPV-related lesions in the oral cavity due to their capacity to impede viral protein activity and disrupt viral replication.[7]
3. Prevention of viral Infections in immunocompromised patients: Fullerene-based antiviral therapies may offer an additional line of defence in immunocompromised patients, such as those receiving chemotherapy or those who are HIV positive, by lowering viral loads and shielding these patients from opportunistic infections.[10]
4. Post-operative antiviral protection: Patients are more susceptible to viral infections following oral or dental treatments; consequently, topical lotions or materials coated with fullerene may help shield surgical areas from viral infections while they heal.[8]

3.4. Drug delivery systems

Fullerenes usage as drug delivery vehicles is among their most promising uses in oral medicine.[9] Fullerenes has a distinct structure that enables them to pass across biological membranes, allowing for the targeted delivery of medicinal medicines to the oral tissues that are impacted.[10]Drug delivery using them has been investigated for diseases such fungal infections, oral malignancies, and chronic inflammatory disorders.[11]

1. Treatment of genetic oral diseases: Gene therapy may be utilized to treat hereditary disorders of the oral cavity, such as specific forms of periodontal disease or amelogenesis imperfecta, an illness that affects tooth enamel. Corrective genes could be sent to afflicted cells via fullerene-based vectors, aiding in the restoration of normal function.[10]
2. Regeneration of oral tissues: In patients with advanced periodontal disease, fullerenes can transfer genes that support the repair of injured oral tissues, such as gum or bone. For example, introducing genes that encode growth factors (like VEGF or BMPs) may promote tissue regeneration and repair, so averting tooth loss and enhancing oral health in general.[11]

3.5. Diagnosis and treatment of oral cancer

Advanced imaging technologies that can be used to identify mouth cancer early on may find uses for fullerenes.[4] They can be functionalized with imaging agents to improve contrast in several imaging modalities and improve the visibility of malignant tissues.[6]

1. Nanoparticle-based imaging: For application in imaging techniques including computed tomography (CT), magnetic resonance imaging (MRI), and fluorescence imaging, fullerenes can be coupled with fluorescent molecules or contrast agents. This facilitates accurate tumor localization in the oral cavity, enhancing early identification and directing biopsies or surgeries.[12]
2. Fluorescent markers: Fluorescent dyes can be used to functionalize fullerenes, allowing for the real-time tracking of malignant cells during diagnostic processes. By binding to cancer-specific receptors, these fullerene-based fluorescent markers can produce strong contrast in imaging and facilitate the differentiation of malignant from healthy tissues.[11]
3. Biosensing and biomarker detection: Biosensors can be equipped with functionalized fullerene derivatives to identify particular cancer biomarkers in blood or saliva. To enable non-invasive early diagnosis, fullerene-based sensors, for example, can be designed to detect proteins, DNA mutations, or other molecular markers linked with oral cancer.[13]

3.6. Photodynamic therapy (PDT)

Photodynamic therapy (PDT) is one of the most promising uses of fullerenes in the treatment of oral cancer.[12] In photodynamic therapy (PDT), cancer cells are killed by reactive oxygen species (ROS) produced by a photosensitizer, a light-activated medication, when exposed to a certain light wavelength.[10]

Fullerenes as photosensitizers: In photodynamic therapy, fullerenes, especially C60, can function as effective photosensitizers.[13] Under light irradiation, fullerenes release reactive oxygen species (ROS), which cause oxidative damage to cancer cells and ultimately result in their demise. The ability of fullerenes to produce ROS in a regulated and restricted way reduces the harm they do to nearby healthy tissues.[14]

3.6.1. Advantages of fullerenes in PDT[2]

1. Selective targeting: Fullerenes have the potential to be functionalized in order to selectively target cancer cells, minimizing harm to healthy tissues and improving the accuracy of PDT in the treatment of oral cancer.
2. Lower side effects**:** Conventional radiotherapy and chemotherapy can have serious adverse effects, including as harm to the teeth, bone, and mucosa of the mouth. Because fullerene-based PDT is extremely targeted and non-invasive, it can lessen these negative effects.
3. Minimal Invasiveness: PDT using fullerenes is an alternative for less intrusive treatment than surgery or radiation since it can be done as an outpatient procedure.

3.7. Targeted drug delivery

In individuals with oral cancer, fullerenes can act as nanocarriers for anticancer medications, enabling targeted and regulated delivery to the tumor location.[14]

1. Encapsulation of chemotherapeutic agents: Chemotherapeutic medications can be conjugated or encapsulated by fullerenes, which shields them from degradation and delivers them only to cancer cells. By increasing the medications' effectiveness and lowering their systemic side effects, this raises their therapeutic index.[11]
2. Functionalization for targeting: Fullerenes can be functionalized with Ligands (such as peptides or antibodies) to bind and recognize cancer-specific receptors on oral cancer cells. This reduces the toxicity of the medications to healthy tissues by ensuring that they are administered exactly to the tumor site.
3. Controlled release: Therapeutic doses of the medicine can be sustained at the tumor site and treatment outcomes can be enhanced by designing fullerene-based drug delivery systems to release the drug gradually.[13]

3.8. Gene therapy

The use of fullerenes in gene therapy, a method that includes introducing therapeutic genes to cancer cells in order to fix genetic flaws or cause cancer cell death, is also being investigated.

1. Delivery of siRNA or DNA: In order to repress oncogenes or increase the expression of tumor suppressor genes in oral cancer cells, small interfering RNA (siRNA) or DNA can be delivered via fullerenes. This strategy may be able to stop the spread of cancer or maybe stop tumor growth altogether.
2. Protection of Genetic Material: Fullerenes shield genetic material in the mouth cavity from being broken down by nucleases. Additionally, they enhance the effectiveness of gene therapy by facilitating the uptake of genetic material by cancer cells.

3.9. Combination therapies

Due to their ability to integrate several therapeutic modalities, fullerenes provide the potential for combination therapy.[14] For instance, fullerene-based nanoparticles can enhance the overall therapeutic effect by delivering genes and chemotherapeutic medicines at the same time.

Chemotherapy and PDT: Chemotherapy and fullerene-based photodynamic treatment (PDT) can increase the killing of cancer cells. Fullerenes increase the chance of total tumor elimination by acting as photosensitizers and chemotherapeutic drugs in a single therapy approach.[15]

3.10. As an X-ray contrast agent

As X-ray contrast agents, the fullerene derivatives are useful. C60 fullerenes have been suggested as MRI contrast agents.[8]Their complexes with gadolinium, also known as gadofullerene, which include Gd3 + ions trapped inside the fullerene cage, show great promise for both in vitro and in vivo NMR imaging. After it is introduced, the heavy radioactive metal that is poisonous cannot escape the fullerenes cage. This characteristic implies the use of fullerenes as in vivo radiotracers.[2]

4. Safety and Toxicology Concerns[16]

1. The use of fullerenes in oral medicine is still in its experimental stages, despite its encouraging promise. Safety and toxicity problems are still present. Due to their inherent hydrophobicity, fullerenes have a limited bioavailability and may accumulate in tissues other than those intended for them.
2. The results of toxicological research on fullerenes have shown that they can cause oxidative stress and harm cellular components. Before fullerenes are widely used in oral medicine, their pharmacokinetics and biocompatibility must be carefully evaluated due to the possibility of fullerene buildup in tissues.

5. Current Challenges and Future Directions

The clinical application of fullerenes in oral medicine faces several challenges. These include:

1. Toxicity: addressing issues regarding fullerene safety and long-term implications, particularly with repeated or high-dose applications.[17]
2. Regulatory approval: Early-stage or preclinical trials are currently being conducted on fullerene-based therapies, although regulatory frameworks for their use in humans have not yet been developed.[18]
3. Functionalization: One of the main areas of ongoing study is creating functionalized fullerene molecules with improved stability, solubility, and targeted delivery capabilities.[17]
4. Cost: The cost of producing fullerenes and their derivatives makes them difficult to scale up for general use in therapeutic settings.[19]

However, Fullerenes appear to have a bright future in oral medicine. Technological developments in materials science and nanotechnology may help remove these obstacles, increasing the usefulness and accessibility of fullerene-based therapies.[20]

6. Conclusion

Fullerenes possess unique characteristics such as antioxidant, antibacterial, and drug transport capabilities, which make them highly promising in the field of oral medicine. Early results are promising, especially in the areas of photodynamic treatment, tissue regeneration, and targeted drug delivery, even though their application is currently mainly experimental. However, more investigation is required to address toxicity-related worries and create fullerene-based remedies for oral health issues that are safe, efficient, and affordable. Fullerenes could be very important in oral medicine down the road if these obstacles can be resolved.

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None.

8. Conflict of Interest

None.

References

1. Kanaparthy R, Kanaparthy A. The changing face of dentistry: nanotechnology. *Int J Nanomedicine*. 2011;6(1):2799–804.
2. Kerna NA, Flores JV, Pruitt KD, Nwokorie U, Holets H. The Potential and Promising Application of Fullerenes in Pain Management and Anaesthesia. *EC Anaesth*. 2020;6(11):14–8.
3. Bhakta P, Barthunia B. Fullerene and its applications: A review. *J Indian Acad Oral Med Radiol*. 2020;32(2):159–63.
4. Bakry R, Vallant RM, ul Haq MN, Rainer M, Szabo Z, Huck CW, et al. Medicinal applications of fullerenes. *Int J Nanomedicine*. 2007;2(4):639–49.
5. Yadav BC, Kumar R. Structure, properties and applications of fullerenes. *IJNA*. 2008;2(1):15–24.
6. Fernandes NB, Shenoy RU, Kajampady MK, Dcruz CE, Shirodkar RK, Kumar L, et al. Fullerenes for the treatment of cancer: an emerging tool. *Environ Sci Pollut Res*. 2022;29(39):58607–27.
7. Sharoyko VV, Shemchuk OS, Meshcheriakov AA, Vasina LV, Iamalova NR, Luttsev MD, et al. Biocompatibility, antioxidant activity and collagen photoprotection properties of C60 fullerene adduct with L-methionine. *Nanomedicine*. 2022;40(1):102500.
8. Hou W, Shi G, Wu S, Mo J, Shen L, Zhang X, et al. Application of fullerenes as photosensitizers for antimicrobial photodynamic inactivation: a review. *Front Microbiol*. 2022;13(1):957698.
9. Chen Z, Ma L, Liu Y, Chen C. Applications of functionalized fullerenes in tumor theranostics. *Theranostics*. 2012;2(3):238–50.
10. Fiorito S, Serafino A, Andreola F, Togna A, Togna G. Toxicity and biocompatibility of carbon nanoparticles. *J Nanosci Nanotechnol*. 2006;6(3):591–9.
11. Aoshima H, Kokubo KE, Shirakawa S, Ito M, Yamana S, Oshima T. Antimicrobial activity of fullerenes and their hydroxylated derivatives. *Biocontrol Sci*. 2009;14(2):69–72.
12. Yadav J. Fullerene: properties, synthesis and application. Research and Reviews. *J Phys*. 2017;6(3):1–6.
13. Fillmore HL, Shultz MD, Henderson SC, Cooper P, Broaddus WC, Chen ZJ, et al. Conjugation of functionalized gadolinium metallofullerenes with IL-13 peptides for targeting and imaging glial tumors. *Nanomedicine (Lond)*. 2011;6(1):449–58.
14. Nancy A. Buckyballs Could Be Plentiful in the Universe; 2010. Available from: https://www.universetoday.com/76732/buckyballs-could-be-plentiful-in-the-universe/.
15. Mitchell DR, Brown RM, Spires TL, Romanovicz DK, Lagow RJ. The synthesis of megatubes: New dimensions in carbon materials. *Inorg Chem*. 2001;40(12):2751–5.
16. Chen YW, Hwang KC, Yen CC, Lai YL. Fullerene derivatives protect against oxidative stress in RAW 264.7 cells and ischemia-reperfused lungs. *Am J Physiol Regul Integr Comp Physiol*. 2004;287(1):21–6.
17. Mroz P, Pawlak A, Satti M, Lee H, Wharton T, Gali H, et al. Functionalized fullerenes mediate photodynamic killing of cancer cells: Type I versus Type II photochemical mechanism. *Free Radic Biol Med*. 2007;43(5):711–9.
18. Li YF, Chen C. Fate and Toxicity of metallic and metal-containing nanoparticles for biomedical applications. *Small*. 2011;7(21):2965–80.
19. Pai P, Nair K, Jamade S, Shah R, Ekshinge V, Jadhav N. Pharmaceutical applications of carbon tubes and nanohorns. *Curr Pharm Res*. 2006;1(2):11–5.
20. Shetty NJ, Swati P, David K. Nanorobots: Future in dentistry. *Saudi Dent J*. 2013;25(1):49–52.

Author biography

Fatima Injela Khan, Post Graduate Student https://orcid.org/0009-0006-9708-3253

Ashish Aggarwal, Professor & Head https://orcid.org/0009-0002-4347-740X

Nitin Upadhyay, Professor https://orcid.org/0009-0005-6600-1561

Sowmya Gujjar Vishnurao, Professor https://orcid.org/0000-0002-6441-0426

Navendra Jha, Post Graduate Student https://orcid.org/0009-0009-3858-9053

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