Fullerene Nanoarchitectonics Against Infectious Diseases: A Review

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Abstract

Nanoscience is an advancing interdisciplinary field, creating a revolutionary shift across various domains of bio-engineering including biomedicine. In particular, stimuli-responsive and self-assembly the nanomaterials are at the forefront of the current research arena, emphasizing their unique physicochemical properties over their macroscopic counterparts. With the advent of "Nanoarchitectonics", conventional nanomaterials are being applied as promising biomaterials in healthcare. For instance, the concept of "nanoarchitectonics" has enabled the synthesis of increasingly complex fullerene structures, to mimic the intricate architecture of biological systems, emerging as a pivotal candidate for the strategies of next-generation therapy. This allows us to develop a promising alternative nano system to conventional antibiotics, especially in combating multidrug-resistant (MDR) bacterial and fungal species. Additionally, fullerenes are being actively explored for their therapeutic potential in radical scavenging and enzyme inhibition. In this regard, the review aims to elucidate the critical role of fullerenes in infectious biology, with a focus on current trends, antimicrobial therapies, and the underlying mechanisms of action. Furthermore, the challenges posed by drug-resistant pathogens like bacteria, fungi, and epidemic viruses are critically examined. Existing research gaps and limitations in the current landscape of fullerene-based technologies are highlighted, with a discussion of future directions and potential breakthroughs in the field.

Keywords: *Fullerene; functionalization; ROS production; radical scavenging; photodynamic inactivation; cytotoxicity*

1. Introduction – Fullerene, as an emerging nanomedicine in the advanced biomedical application and antimicrobial strategies:

At nanoscale dimension, carbon is primarily characterized by a covalently bound, tetrahedral structure exhibiting distinct properties. They are known for their versatility, which is partially due to the multi-molar interaction of its atoms at their different hybridization rates. These nanoparticles are less than 100 nm in size, exhibiting a superior optical and surface-volume ratio than their macro counterparts, which is influenced by the hybridization shift [1,2]. For example, diamond and graphite are two different forms of carbon with diamond possessing an organized crystalline lattice structure by the sp^3 hybridization. Under low pressure and extreme temperatures, this sp^3 hybridization shifts to sp^2 interaction resulting in a change of spatial arrangement. The addition of tightly stacked such sp^2 hybridized layer gives rise to the graphite [3,4]. This shift in hybridization alters the intra-molecular bond configuration, resulting in a change of their structural properties. Since then, various hybridization techniques have been employed to harness the carbon in a broad range of applications including electrical, optical, and biomedical sectors [5,6]. The exploration of carbon nanostructures began in the mid-90 s, with the first extensively studied nanostructure being "nano-diamond" - synthetically produced through the detonation of diamond and graphite with the goal of preserving the original properties in these nano structures [7]. Other carbon nanostructures, such as nanotubes, nanorods, onion rings, fullerene, and graphene compounds are currently under extensive exploration for various applications including imaging, super-conductivity and toxicity studies [8–10].

Among the allotropes of carbon, fullerenes are the third allotropy characterized by their caged structure [11]. Dr. Kroto first discovered fullerene while analyzing the long-chain polymerization of carbon in the interstellar space. He observed, when graphite on subjected to laser ablation, carbon atoms self-assembled to form the carbon core with 60 molecules in a caged structure popularly known as "Soccer ball" or "Buckyball" and widely known as C_{60}. Later following the discovery of $C_{60,}$ other fullerenes

such as $C_{70,}$ C_{84} were synthesized each exhibiting unique properties [12,13]. In the interstellar nebulae, fullerenes have also been discovered in diffused matter, exhibiting emission in infrared region [14,15]. Of all fullerenes, buckminsterfullerenes are the most stable one accounting for its highly symmetrical, cage structure imitating icosahedral with pentagons and hexagons. In their pristine form, these fullerenes exhibit a zero-order dimension, with characteristic extended π-π stacking owing to their supramolecular assemblies. This leads to the formation of an array of nano to macro structures, each having different physico-chemical potentials [16,17].

In carbon biology, the concept of nanoarchitectonics, involving the regulated arrangement or pre-designated configuration of the intra-molecular moieties facilitates the production of different latticed structures. Thereby creating different order of symmetries including zero-dimensional (0D), one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D) forms [18,19]. Nanoarchitectonics facilitates the modification at an atom/molecular level with utmost structural precision to architect the functional molecular systems [20,21]. For instance, regulated production of carbon fullerenes under optimized environmental conditions can produce higher hierarchical structures from low-ordered fullerene sphere and, nanorods to intricate 3D complexes such as fullerene onion rings, micelles, and nanosheets [22]. The concept of fullerene-nanoarchitectonics in biology, pertains to synthesis of biomolecules and biomaterials within the biological system, which are constantly subjected to environmental stimuli and cellular dynamics at the sub-micron level. So, by synthesizing the fullerenes which can be stabilized, self-assembled, self-repaired and self-adjusted under these dynamic conditions may exactly mimic the biological processes.

The concept nanoarchitectonics underlies most of fullerene applications such as a nano-carriers for drug deliveries, nano-conjugates with environmental stimuli, and tissue engineering [23]. Despite of all these advantages, fullerene in biological application is still an underdeveloped one. This is due to the insolubility of fullerene in an aqueous medium and its tendency to aggregate causing significant

toxicity towards living cells, and a potential pollutant. Aggregated fullerene may exhibit characteristics similar to that of compressed fullerene known for their solid and insoluble structures called aggregated diamond nano rods which is of environmental concern too. However, various functionalization techniques were actively employed to produce different fullerene derivatives that are more soluble in the polar solvents.

In the field of infectious biology, fullerene is extensively employed in anti-microbial, immunomodulatory studies and onco-therapies. In response to the urgent need of alternatives to traditional antibiotics, the use of fullerene against multi-drug resistance (MDR) species has been done parallelly to its exploration on the supramolecular chemistry. Studies on antibiotic-resistant bacteria including *Methicillin Resistant Staphylococcus aureus* (MRSA), *Escherichia coli,* and *Pseudomonas* species were seen to be appreciatively effective [24–26]. Furthermore, the fullerene conjugated with current antibiotics against the same resistant species is known to re-sensitize the bacterial species resulting in the effective killing. When these caged structures on integrated with drugs, resist the efflux pumps of bacteria by increasing the porosity of the membrane and effectively transmitting the antibiotics to an inner surface of the cell, thereby enhancing the efficacy of antibiotics [27,28]. Functionalized fullerene has also been employed as an anti-viral agent with its mode of action including viral entry blockage, enzyme inhibition and virion disruption [29]. Water-soluble fullerenes have the added advantage of causing less host toxicity and less aggregation [30]. The properties such as radiation excitation, nucleosidase activity, membrane flux disruption, and radical scavenging are some of the phenomena that have been widely employed for the microbial disruption [31,32]. But, the hindrances such as the biodegradability of fullerene, target specificity and fullerene-target interaction are very crucial as they directly influence the efficiency of the therapies [33,34].

Despite the routine use of fullerene functionalization for enhancing solubility in aqueous solutions, surface-modified fullerenes sometimes exhibit low solubility. Consequently, the bio-absorption

remains a significant challenge, prompting the exploration on computational analysis of fullerene-microbial membrane or compound to enhance better specificity [35,36].

In this regard, review intends to give a comprehensive overview on the antimicrobial activity of C_{60} (Figure 1) and its research gap in various fields accentuating more on the mode of approach, functionalization and applications. The current prospects of fullerene employment in various sectors of infectious biology, therapeutics and theragnostic approaches have been highlighted with the experimental evidences and possible outcomes for the future applications. All the previous reviews elaborated on the particular technique of fullerene against MDR bacteria or virus. Whereas, this reviews compressively elaborates the existing antibacterial mechanism of fullerene against both bacterial and pathogenic virus has been put forth. Addition to the mechanism of action, the various fullerene assemblies and their properties has been briefly discussed in the view of nanoarchitectonics.

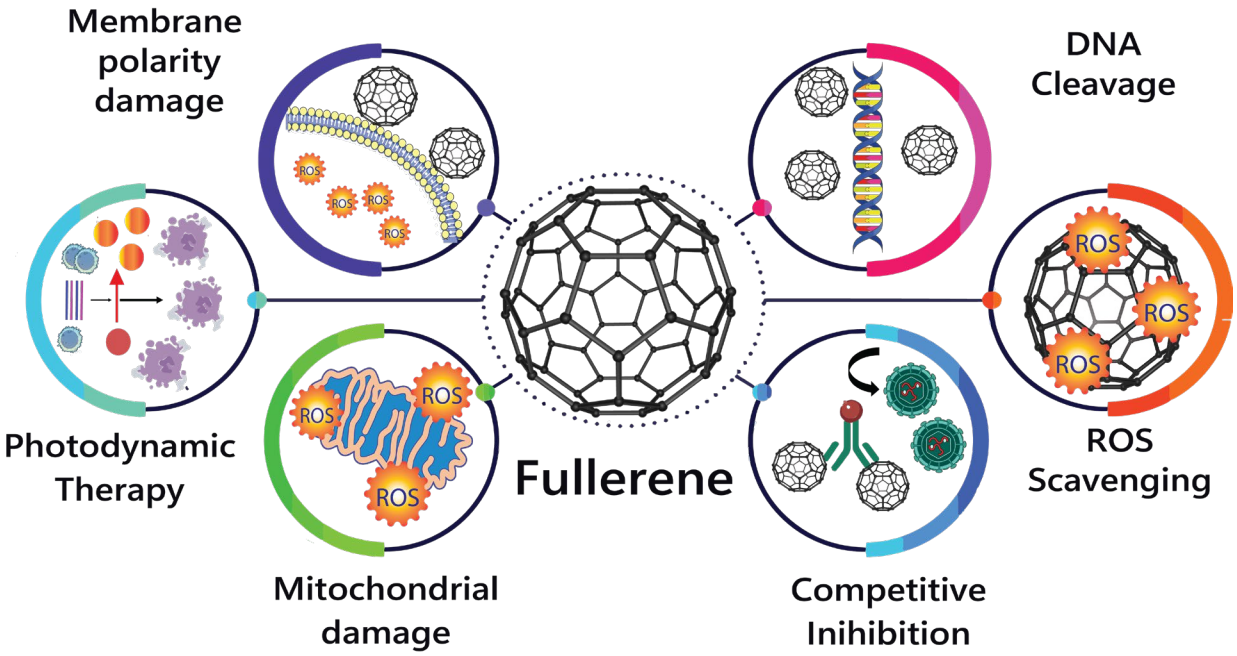

Figure 1. The applications of fullerene in the biomedical sector, emphasizing its role as photo inducer, radical scavenger.

2. The nano structural advantage of fullerene – deciphering physio-chemical properties in aiding the revolutionary applications in carbon biology

C_{60} fullerene, with a polyhedral structure, and a molecular weight of approximately 720.64 g/mol, are typically produced through the laser ablation or arc deployment of graphite and carbon soot. Under the high temperature, and reducing pressure in an inert atmosphere, the nanostructures formed are known as fullerene. In general, the production ratio of fullerene under inert conditions may be enhanced by the suitable metal catalyst such as palladium and silver, contributing to metal conjugation [37]. The spatial arrangement of fullerene is influenced by $\pi - \pi$ stacking. These fullerenes follow the zero-order kinetics, the unique property defines their structural ability and makes them amenable to precise atomic-level manipulation. Thus, being actively utilized in the field of nanoarchitectonics [38,39]. Additionally, fullerenes are extremely hydrophobic and prefer non-polar solvents like benzene and alkanes solution, hence making their usage restricted in polar solvents. However, the presence of double bonds makes it easy to conjugate it with functional groups such as -OH, -COOH, and NH_2 making fullerenes more hydrophilic. These modifications have opened up avenues for tailoring fullerenes to specific applications. For example, the incorporation of a greater number of hydrogen bonds through short oligopeptides attached to fullerene core can fundamentally alter the dynamics of these moieties and structural modifications with hierarchical development for desired structures [40]. These are some of the key manipulations that can be done in fullerene to get targeted assemblies, and more of these phenomena are detailed below.

2.1 Dissolution of hydrophobic fullerenes- a key for potential inducer of anti-microbial activity

The solubility of fullerenes highly depends on the molecular interaction with other compounds over its surface chemistry specifically, towards the electron exchange on fullerene, determining its stability as well as solubility [41,42]. Typically, low-polar solvents like benzene, xylene and toluene have good dissolution with fullerene, whereas highly polar solution has lower solubility. In aqueous solvents,

fullerene often forms small aggregates and suspensions as they are hydrophobic in nature [43]. The hydrocarbon, amine and certain nitrogen groups are regarded as the highly reactive groups with fullerene, to the extent of forming covalent bonds [44]. These functional groups on conjugation to the fullerene core, makes it more soluble. The, research on increasing the solubility of C_{60} by supramolecular approach was started in the late 90s [45]. At present, the hydrophobicity of C_{60} fullerene is near to no problem, as various surface modifications were successfully established for diverse functions. Numerous methods such as solvent replacement, solvent displacement, for fullerene synthesis were based on the precipitation of fullerene dispersion in different polar solvents [46].

2.2 Photonic potential of fullerene - a cutting-edge strategy of using fullerene as nanomedicine

The presence of a double bond in the fullerene contributes to their high reactivity and photoexcitation properties [47]. Fullerenes possess a high molar absorbance coefficient in visible light and are capable of producing triplet-excited photons, which in turn produce unstable intermediate ions. These ions have a high affinity towards free electrons, causing irreversible chelates**.**

Another property of fullerenes is their strong photo-absorbing capacity, high in UV and moderate in the visible region. These excited fullerenes, inside the biological membrane, collide with environmental oxygen and produce singlet oxygen moieties through photo process II. Other reactive species such as hydrogen peroxide, and free radicals are produced by photo process I. Both can result in lipid peroxidation and membrane damage, which in turn, cause a potential threat to biomolecules and nucleic acid. This principle finds practical application in Photo Dynamic Inactivation (PDI). The PDI, Photothermal Therapy (PTT) and magnetic bead applications are some of the promising stimuli responsive methods to be explored in biological sector [48,49]

2.3 Unveiling the environmental remediation of fullerene as a bio toxicant

Environmental degradation and toxicity of fullerene, remains as a area of uncertainty requiring further investigation, as a nanomaterial discharge into the environment is always on threat based on the range. Numerous research focusing on the environmental studies shows that medial range discharge has an implicative impact on molecular biology of marine animals [50]. Subsequently, efforts have focused on elucidating the toxicity of C_{60} pertaining to environmental discharge and human health worldwide, but only limited data on environmental remediation has been obtained. Under industrial applications, fullerene are routinely used for the wastewater separation and broadly claimed as biocompatible. The Bretschger and team worked on the *Shewanella oneidensis*- an environmental bacterium, employed as a model organism for the C_{60} tracer studies, incorporating lactate as a tracer molecule [51,52]. Growth static is seen in the initial stages, but eventually remission of the growth cycle is recorded, suggesting fullerene internalization does not affect the central core metabolism of the organism, stating the safe digestion of fullerene by the organism[53]. This phenomenon may have two possible reasons:

- Change in membrane structure accordingly to efflux the excess fullerene out of the system.
- Restoration of growth occurs once the organism is adapted to fullerene.

In another study conducted by Indeglia and team worked on the fresh water algae and invertebrate *Raphidocelus subcapitata* and *Ceriodaphnia dubia* respectively. The LC_{50} value was found to be much a higher than the commercially available fullerene containing chemicals, rendering fullerene as a biodegradable agent [54]. However, some of the biological processes of invertebrate *Ceriodaphnia dubia* was seen compromised, even though effects are not detrimental to the population. The compromised biological effects were of species specific and not chronic.

Even though fullerene is claimed to be biocompatible and less toxic in terms of bio-degradation and growth retention, physio-chemical properties of fullerene is having greater influence. The bio-availability of industry available fullerene and lab grown fullerene are differed in their structural

conjugation and so their chemical state. The fullerene degradation highly depends on the solubility in aqueous environment, in turn connected with their alloy states. In this regard, it's safe to conclude that environmental degradation of fullerene research depends on multiple factors and solid techniques to quantify the effects are rare, and conclusions are yet to be drawn.

3. Nanoarchitectonics of fullerene – Newer perspective architecture for molecular dynamics

Pertaining to fullerene biology, fullerene assemblies, and fullerene composites are the domain of interest. Similarly, the large exploring area is the stimuli responsive compounds. The concept of nanoarchitectonics in a nut shell arises from the fusion of material chemistry at nanoscale units to build a functional biological system. Architecting the structures through arranging atoms and molecules as building blocks known as self-assembly or targeted assembly [55]. Nanobiology helps in the coordination of elements, molecules to form self-assembly/self-organized, nano/microfabricated, material processes which can be best utilized in molecular system buildings. Self-assembly process is best explained as a technique consists of two processes namely nucleation and crystal growth [56]. When the mechanism of nucleation is controlled, the desired structural changes can be incorporated, by different techniques such as phase separation, catalysis replacement etc.,[55]. Therefore, the self-assembly is a new avenue of nanoarchitectonics revamping the material chemistry. Similar to self-assembly, stimuli responsive compounds are best suited for the dynamically changing biological environment causing internal change sensing the outer environment which are used in PDT and PTT.

Atomic level manipulation, molecule building are being explored with the help of nano chemistry. The supramolecular assembly, annular space concepts help to create an atomically precise nano structures leading to the development of a material, useful in biological systems. Because, confiding the atomic structures in the prescribed molecular state helps in enhancing the solid-state dynamics and solvent reactivity thereby suitable for changing environment of biological system. For instance, Matsuno et al., studied peapod arrangement of fullerene (Carbon nanotubes trapped fullerene) arranged in

cylindrical space by weak Vander walls force and CH-π bond. Although bounded by weak inter-molecular forces, these peapods exhibit strong bond association carrying out multiple interactions to the dynamic outer environment in solvent phase [11,57]. These peapods, therefore, can be best used as a nanodevices showing adaptability to the complex biological systems. Similar to atomic manipulation, other basic concepts of nanoarchitectonics such as atomic switches, and coordination chemistry are used for the manipulation of thermal fluctuation (Figure 2), a basic dynamic observed in the biological environment, in-turn can be replicated to produce macroscopically sophisticated biological systems [58]. The atomic switches play a main role in the demonstration of complex biological systems, the inorganic synapses which were designed with these switches, profoundly imitate the mammalian synaptic movements. Based on the atomic switches, Song and his team worked on Ag_2S, found out, on stimulation the short time plasticity became long time plasticity leading to permanent change of the memory cells [59,60]. Similar to atomic switches, as mentioned before self-assembly is another key phenomenon for making biomimetic systems [61]. When hydrophilic fullerenes are synthesized by liquid-liquid interface precipitation (LLIP) systems, these self-assembled fullerene derivatives showed good uptake by neural stem cells (NSC). The self-assembled fullerene depends on size showed the upregulation of neural genes, therefore helps in neural cell line differentiation. Such fullerene assemblies can be best utilized as nanodevices for the neural systems [62]. Considering fullerene as nanocarrier, starting materials of self-assemblies are crucial as they are directly connected with the synthesis of different structures and sizes. Therefore, Rasovic and his team utilized, diffusion – limited aggregation created a strong association bond within the controlled space leading to the self-assembled structures. The non- covalent forces between these interactions within confined space determines the structure and size of the fullerene assemblies [63]. This work opens new avenues in the search for control of material chemistry in soft matter structures through tuning of nanoscale building blocks. Conjugate nanoarchitectonics is another excellent field exploring the facile molecular organization of different combinations to achieve precise target molecules. Such fullerene assemblies are found in its

applications as bio sensors, bio – imaging, *in vitro* tracking, diseases diagnosis [64], targeted gene expression [65], scaffold building and cellular differentiation [66]. Fullerene assemblies as a cellular scaffold holds a significant potential as differentiation substrates [67], for example when fullerene nanowhiskers were aligned by rotational flow in air-water surface, seeded cells shown to produce cellular polarity of bone differentiated cells [68].

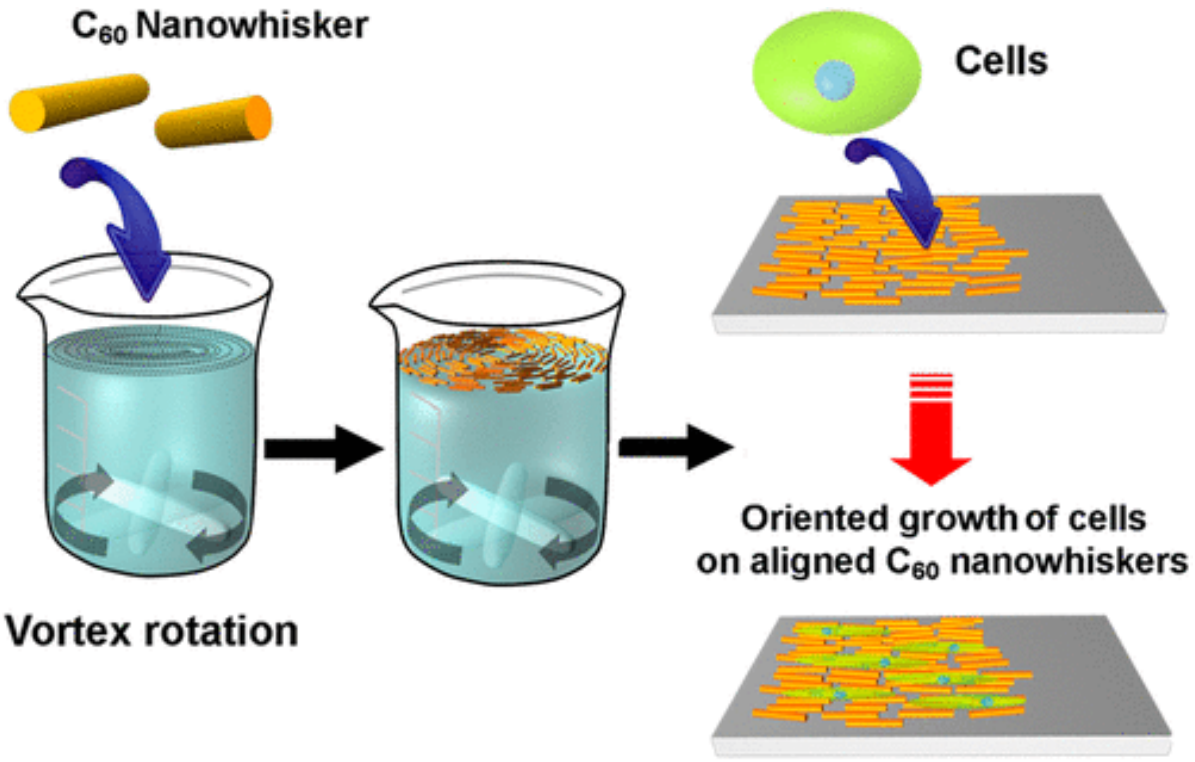

Figure 2. Self-assembly of fullerene nano whiskers in the air-water suspension, influenced by the direction of rotation. It shows that cells seeded onto the self-assembled nano whiskers showed the polarity preferences determined by the direction of oriented nano whiskers. Reproduced with permission from [67]. Copyright 2015 American Chemical Society.

The molecular mechanism behind these polarity preferences arises from the mechanotransduction of nano whiskers enhancing the focal adhesions of seeded cells (Figure 3). Therefore, it is acceptable that tunable topographical features of nanopatterned fullerene can be translated into the finely tuned

manipulation of cell−material interactions, influencing cell spreading, orientation, focal adhesions, and eventually self-renewal of targeted cells [69].

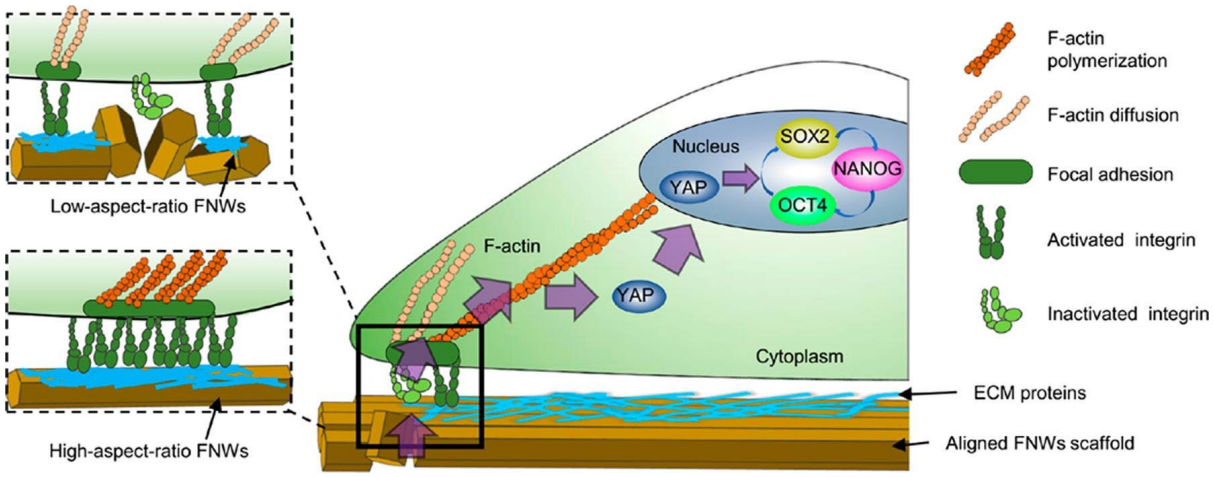

Figure 3. FNWs nanopatterned scaffolds control the hematopoietic Mesenchymal stem cells (hMSC) self-renewal process by mechanotransduction. High-aspect-ratio FNWs provide protein nanopatterns that allow the elongation of focal adhesion parallel to the long axes of FNWs, while low-aspect-ratio FNWs prevent maturity of focal adhesions due to small unit of surface area for ECM protein adsorption promoting hMSC multipotency retention. Reproduced from reference [69]. Copyright 2020 American Chemical Society.

Thereby paving a revolutionary change in stem cell therapies. In this aspect, fullerene being a zero-dimensional structure, an ideal candidate for nanoarchitectonics. These self-assembled structures being the fundamental units possess an innate ability for spatiotemporal regulation, shape shifting making them an indispensable tool to design biomimetic systems and living like creatures.

4. Applications of Fullerene as a renowned nanobiotic- elucidating critical strategies and newer phenomena

Exploration of fullerene as a biomedical agent has rapidly progressed since the late 1990s. Recent advancements in understanding the fullerene biology broaden their application in both therapeutic and environmental aspects. The antimicrobial properties of fullerenes are due to the fact that they are membranotropic substances, easily penetrating the membrane of microorganisms, thereby interacting with cellular structures. These fullerenes exhibit the property of photoexcitation that generate a reactive singlet oxygen (SO), interact with nucleus, and affect membrane instability which causes cell death [70], widely used antimicrobial therapy. Fullerene is regarded as one of the most exploring fields in terms of MDR species and few of these key advancements are discussed below (Table 1)**.**

S. No	Compound conjugation	MDR species	Mode of action	References
1	Pyridinium fullerene Proline fullerene Piperidium fullerene	HIV	Inhibition of viral replication	[71]
2	Fullerene	*Acinetobacter baumanni* *Pseudomonas aeruginosa*	Down regulation of chemotaxis	[72]
3	Polyaniline- fullerene	*Mycobacterium tuberculosis*	MPT64 diagnosis	[73]
4	Ag-C_{60}-Cl Cu-C_{60}-Cl	*Escherichia coli* *MRSA*	Induction of ROS	[74]
5	Pyrrol-fullerene	HIV	Impairs virus maturation	[75]
6	Fullerene	*Salmonella typhi*	Membrane polarity damage	[76]
7	Sulfur doped fullerene	*Pseudomonas aeruginosa*	Neutralization of Tox A	[77]
8	Fullerene-Porphyrin	HIV	Singlet production	[78]

Table 1: The summarization of recent analysis of fullerene formulations against multi-drug resistant bacterial and viral species

4.1 Target with precision – Fullerene as a combustible nanobot in photodynamic therapy

The research into PDI started in 1993, focusing on the principle of singlet oxygen induction and enzyme inhibition by the photoexcitation of fullerenes. Fullerenes on light induction, the fullerene-conjugated cells, subjected to the type II photo process, an oxygen-dependent photo excitation state. In which the excited fullerenes will be converted into triplets- an unstable intermediate that immediately interacts with the oxygen and produces singlet oxygen, a highly reactive oxygen species known as ROS. This single oxygen can induce a series of destructive cascades in a biological cell through random oxidation of biomolecules leading to cellular death. During the studies of Tokuyama in 1993, a similar effect was seen in light irradiated cells and neutral effect in non-irradiated cells. Cells that are irradiated in dark were neutral similar to the non-irradiated cells. From then, the fullerenes were regarded as the photo absorbers and have 'strong potential for photodynamic damage to biological systems' [79]. Further studies revealed that an increase in ROS production can also occur independent of oxygen availability collectively called as type I photo process, where cytochrome-C plays a major role. These fullerenes are known to cause a down regulation in cytochrome by suppressing the superoxide dismutase, which in turn releases more of super-oxides into the environment, thereby making the biomolecules more vulnerable to the ROS attack and creates oxidative stress to the cell [80].

The aforementioned concept forms the basis for the research on PDI of bacteria as a therapy. The overuse of antibiotics over past decades led us to multi-drug resistance microorganisms. These super bacteria are said to mark the end of the "antibiotic era", and left us with no defense. This is where the PDI comes into play [81].

It has been known as early as from last century that light illuminations are enough to kill certain microorganisms by generating free radicals. The points to be considered are the selection of dye specific to microorganisms and the light source. Second, the target precision to carry out the whole

work with less damage to the host cell [82]. From then, this was used as an ideal alternative for antibiotic defense with the additional advantage of not risking of evolving resistant genes in bacteria, as well as the permissible level of cytotoxicity to host cells [83]. The PDT is now a upcoming method where even the more toxic bacterial species and toxins such as hemolysin from *Streptococcus* species, *Mycobacterium and Salmonella,* are known to be sensitive for destruction of cellular membrane [84]. On combination with metal nanoparticles such as silver, fullerene composites exhibited more than 90% of inhibition for the most of sepsis forming bacterial species including *E. coli, Bacillus* and pathogenic fungi [85]. The detailed molecular insights are provided below:

4.1.1 ROS fallouts inside the cell – A Mechanistic Insights into fullerene-induced cytotoxicity

The basis of PDI relies on two components namely: photosensitizing dye and visible light for illumination. These dyes can be directed towards the targeted tissues upon light illumination and initiate the photo process followed by production of free radicals and singlet oxygen. Increases in ROS are capable of inhibiting various secondary signaling molecules like serine and tyrosine kinases, in turn, affect the net biosynthesis of the cell. Consequently, the reactive species are also responsible for inducing random oxidation leading to cell wall disruption, cell membrane damage, alteration in cellular transport, nucleic acid disruption, inhibition of protein biosynthesis, inhibition of enzymatic pathways, peroxidation of lipids, and leakage of cellular components. This aftermath awakens the stress response of cell and simultaneous increase in ROS fallouts in stress-induced programmed cell death causing irreversible changes to make the bacterial cells disrupted [86].

Mostly used Photo Sensitizers (PS) are porphyrins [87] but they come with the cost of some side effects such as chemical heterogeneity and low light penetration [88]. At, some instances, the aggregation of porphyrins causes low yield of triplet excitation, thereby affecting the efficiency of PDI. The aggregated porphyrins, also known to show cutaneous cytotoxicity and off-target effect, therefore the interest is drawn towards fullerenes. Because, unlike other PS, fullerenes are biocompatible and

produce ROS even in the absence of oxygen (type–I process) [89]. Precisely, the process starts with treating the infected area with photosensitizers of choice, followed by illuminating the locality, with the visible light. Depending on the penetration, the activity of cell death is seen. Since the host cell and bacterial cell shows the same reaction towards PDI, specificity towards bacterial cells has to be done with the utmost precision to avoid host cell loss. Application of PS in a particular area helps in this focusing of target, while penetration of visible light will further aid in fine-tuning of the target site. Thereby reducing the PDI effects in nearby host tissue [90].

Once illumination occurs, the PS becomes excited on the light collision. These excited PS produce highly reactive ROS like hydrogen peroxide, super-oxide or singlet oxygen based on the type of process initiated and the availability of oxygen. Despite the reactive species produced, all are known to initiate the random oxidation of enzymes and proteins leading to microbial cell death. Further, the elimination of bacterial dead cells and toxins, if any, is achieved by the host immune system.

Both the PS and PDI efficiency directly depend on the microenvironment. PS in inorganic solvents are much more excited than the aqueous solvents, this is because the former one attacks in the synergistic effect of both photosystems, whereas the latter depends on the type-I system alone [91]. More upgradation and different strategies were employed for increased efficiency and quality as this PDI is mugged with various factors. For instance, the off-target effect of PDI can occur or the host cells may take up the PS; both of these may turn into deleterious for the host tissues.

In this accordance, the change in efficiency of treatment is also depends on the bacterial cell constituents, for example, the gram-positive bacteria are found to be more sensitive to PDI destruction than gram-negative bacteria [92]. This is because of the presence of a less porous cell wall and peri-plasmic space in gram-negative bacteria, making it resistance towards PDI. Under environmental stress or starvation, an increase in toxicity makes the microbes to modify their membranes with trans fatty acids as dominant. This cis/trans ratio variation makes the membrane more rigid, thereby decreasing the membrane fluidity and transmembrane transportation [93]. Experimental evidence using the water

suspension fullerene was employed to alter the cellular metabolism of *Pseudomonas putida* (Gram-negative) and *Bacillus subtills* (Gram-positive). The test organisms were treated with a low level of fullerene suspension, a markedly lower expression of unsaturated fatty acids has been recorded and increased expression of trans-saturated fatty acids [94,95]. This spontaneous defense mechanism also increases the phase-transition temperature, giving the ultimatum of increased resistance to warmer environments and blockage of toxic metals and loss of essential nutrients from inside the cell. This may be the reason for the protective mechanism of gram-negative organisms against fullerene. However, *B. subtilis* shows bacterio-static effect at low concentration followed by cell membrane disruption and cellular leakage at higher concentration and the same was replicated in *P. putida* when treated with higher fullerene concentration [96].

In order to penetrate the rigid cell wall of gram-negative bacteria, fullerenes of different charge are being employed. These charged fullerenes are easily bound to the lipid membrane of gram-negative bacteria through electrostatic attraction and were shown to kill the gram-negative bacteria very effectively. This might be due to the presence of more oxygen double bond nature of charged fullerene, thereby making it extremely reactive. Another interesting approach for gram-negative bacteria were the use of cationic fullerenes, which seemed to increase the porosity of gram-negative bacterial membranes [97,98].

The charge-based approach has an added advantage of bacterial cell selectivity, since the bacterial cells are more negatively charged than mammalian cells [99]. The positively charged fullerene can aid in competitive uptake of more fullerenes by bacterial cells than by mammalian cells. This enhanced targeted delivery will also minimize the host cell damage. Thus, designing a cationic fullerene having a more positive charge group will effectively kills the gram-negative organism [100]. The charge-based approaches need the functionalized fullerene, which is of great deal with much more versatility to take part in the various biomedical applications, a few of these experiments are discussed below.

4.1.2 Functionalization of fullerene – bridging applications through surface chemistry

Surface functionalization of fullerenes is a rapidly expanding field with numerous applications conjugating different fullerenes for various purposes [101]. In general, glycolated fullerenes are predominately used in the field of viral inhibition and bacterial toxicity [102]. Among various functionalizations, poly hydroxylated fullerenes serve as radical sponge against toxin-producing bacteria and neurodegenerative diseases [103,104]. Fullerene conjugates are also been synthesized and reviewed for their cytotoxic activities on cancer cells [105,106]. Fullerenes with cyclodextrins induce ROS, whereas hydroxylated fullerenes scavenge ROS, functionalization with ketone can be targeted to nucleotide cleavage.

The cationic fullerenes are charged assemblies, typically functionalized through cycloproponation or by addition of pyrrolidine [107]. These modified fullerenes not only reduce off-target effect but also enhance the solubility of fullerenes thereby facilitating high tissue penetrance. Apart from these two additions, the functionalization with –OH, amino peptides and sugars exists, but these are used in stringent way than the former mentioned one.

As previously discussed, the charged fullerenes are effective against the gram-negative organisms. However, the maximum efficiency can be achieved with the increasing number of charged groups bound to the fullerene cage. When the mono and di cationic fullerenes were treated against the gram-negative rods, the decrease in viability was seen with the increasing order of charge groups in fullerene [108]. The antimicrobial activity is attributed to the electrostatic binding of charged fullerenes onto the lipid membrane of the bacterial cell wall causing membrane instability of microbial cell and the DNA cleavage. Pyrrolidine-conjugated fullerene effectively enhances the production of ROS and peroxidation of membrane, thereby inducing membrane leakage. All this evidence confirms that the charge carried by fullerene is directly proportional to their anti-bacterial activity. The bacterial cell wall being more negative readily uptakes the cationic fullerenes, thereby increasing the fullerene accumulation within the cell [24].

Another critical consideration in pyrrolidine functionalization is the position of cationic charge which will influence the efficiency of the fullerene. The charged groups in fullerene cage and found the efficiency of ROS induction increased, similarly the presence of more dipole aids in increased inactivation of *E. coli* [109,110].

Cyclopropronation of fullerene alters the surface chemistry to increase the properties such as hydrophilicity, conductance, and bio-compatibility. This can be achieved through the bingel reactions, where the deprotonated functional group are conjugated with the pre-treated nucleophilic fullerene. The molecule, thus by the electron transfer a functional group are covalently bound to the fullerene cage. The cyclopropronation was best used to bound peptides, sugars and quaternary ammonium to the fullerene structures. The cyclopropronated fullerenes are known to be utilized for their cidal activity against bio-film forming pathogens. Fullerene conjugated with ammonium cations are hypothesized to easily transverse the fullerene moieties to cross the bacterial cell wall. It can bind to lipid rafts and thereby disrupts the plasma membrane gaining access to the inside for further accumulation. Similar to this hypothesis, Zhang and his team designed the fullerene containing five cationic groups with two quaternary ammonium salts constructs were added with potassium iodide. The cytotoxic activity was seen better in the UV region than the white light, this may be due to the phenomenon that photons capture particular wavelength for better excitation. Therefore, his work again proves the significance of choosing the right light source for getting maximum bactericidal activity. The addition of iodide also increases the cidal activity. It may be because of two reasons, one may be, on excitation, these iodides would have acted as electron donor for oxidized carbon intermediates, thus more the electrons being utilized by the system more the production of ROS will be. The ultimatum of the situation was the random oxidation of enzymes and sugars, leading to cellular leakage. The second reason is, that iodide radical itself would have excited and started its own saga of ROS production and other cytotoxic molecules including hydrogen peroxide, HO^- leading to cellular disruption. This above concept opened

the new arena of using the PDT for the anti-biotic resistive species as they exhibit a similar regression in growth curve in accordance with their anti-biotic sensitive counterparts [111].

Similar to above experiment, potassium iodide is routinely used to potentiate fullerene treatment against the resistant strains. Under some circumstances, when the fullerene fails to impregnate the bacterial cell wall, the addition of potassium iodide will help in the membrane instability and fullerene internalization [112]. Moreover, the addition of potassium iodide will induce more of free iodide, in turn producing more of excited tri-iodide causing an influx of electrons to the bacterial cell leading to more bactericidal activity [91,97].

To the above regard, the fullerenopyrrolidine (iodide bonded) are used as a photosensitizer to treat a biofilm of *enterococcal*, which are known for causing a nosocomial infection of catheters, oral and teeth. These enterococci are the reason for the failure of endodontic surgeries. A rise in the resistant strains to the available antibiotics is making the situation even worse. Therefore, PDI are used to re-sensitize the bacteria to antibiotics. With slight modification to the Vecchio's work, Wozniak used the fullerene not as a monotherapy but as a synergistic effect with rose bengal. There is no increase in the bacterial count was observed in the Rose Bengal-fullerene (RB- FL) treated cells illuminated by the green light. However, regression was less in fullerene-illuminated cells. They hypothesize that this may be due to the production of singlet oxygen along with ROS. Bacterial inactivation by PDI plays an important role in the re-sensitizing of bacteria to their resistant antibiotics. Streptomycin, gentamycin, and ciprofloxacin, which are initially resistant to the bacteria, are being re-sensitized for bacterial disruption. This may be due to the phenomenon that these iodide fullerenes increased the permeability of lipoteichoic acid resulting in the increased influx of antibiotics to the cell. Thus confirming, the disruption of biofilm along with modification of extracellular matrix followed by destruction of bacteria by a synergistic effect of fullerene on antibiotics [113].

4.2 Modulation of membrane electron flux – A key hydrophobic play of fullerene and its impact

The membrane instability caused by fullerene is actually due to the disruption of electron potential of plasma membrane, possibly through two main mechanisms:

1. **Binding to peroxidase enzymes**: By binding to the peroxidase enzymes, fullerene oxidizes enzymes to make it bind to the lipid rafts causing an increased membrane permeability and lipid peroxidation.
2. **Affecting Electron Channel and Membrane Potential Homeostasis**: Fullerene disrupts the homeostasis of electron channels and membrane potential.

These two phenomena are widely used in the anti-tumor activity against the *Helicobacter pylori*. This bacteria in particular is extremely resistant to the fluctuating pH thereby gaining entry to the acid-filled enteric cavity. More than 70% of gastric cancers and peptic ulcers are caused by this acid-producing bacteria, increasing resistance towards antibiotics and pH-induced drugs [114]. The fullerene of different functionalized assemblies was subjected against *H. pylori* (Figure 4). The internalized fullerene structures cause significant changes in the proton motive leading to increased membrane permeability and collapse of channel transport, followed by microbial death [115]. However, the low pH environment of the host gut changes the cellular permeability results in less internalization of fullerene moieties. Under such circumstances, fullerene cages conjugated with C=O/C-O have a better affinity towards peroxidases substrates. Therefore, such fullerenes show good internalization and increased induction of peroxidation, disrupting lipid homeostasis of the membrane followed by cellular leakage and bio-film inhibition [116].

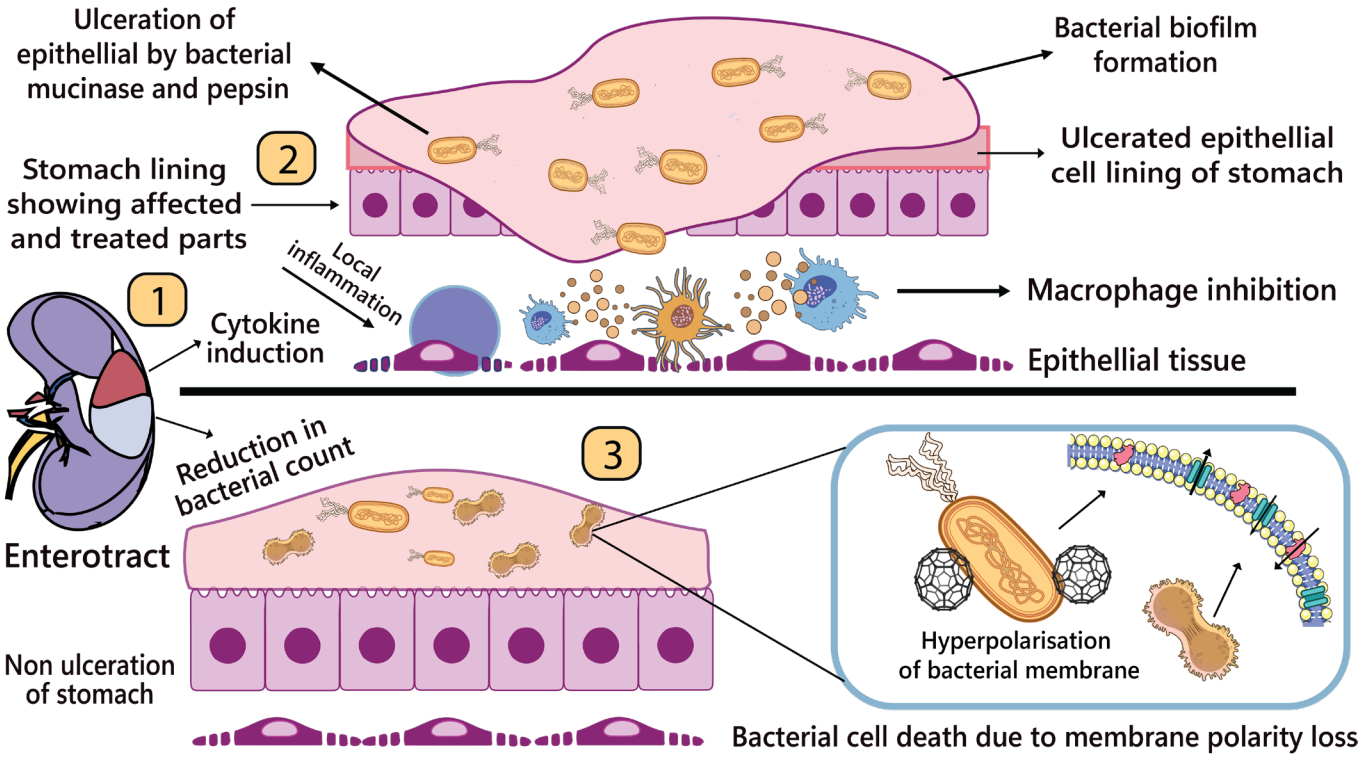

Figure 4. Schematic representation explaining the pathophysiology and therapeutic effects of fullerene treating gastric ulcers caused by *Helicobacter pylori*. 1) Enterotract showing the infected area having inflammation and treated area showing reduced inflammation, 2) epithelial cells of stomach infected with bacterial biofilm causing local invasion and inflammation. 3) Fullerene treated area showing lysed bacteria and non-ulcerated epithelial lining, molecular mechanism of bacterial death caused due to the fullerene integration onto bacterial membrane and increased permeability.

In above explained cases, the affinity of fullerene to the substrate influences the efficiency of cytotoxicity. Specificity and bonding ligands are regarded as the major contributors of the cytotoxicity. Therefore, the fullerene induced membrane damage and ROS induction will be a potential target for restricting the growth of microorganisms, thereby providing a therapeutic alternative for the bacterial carcinogenicity such as nano-formulated vaccines and drug conjugated fullerenes.

4.3 A fullerene as a ROS adducts – Impact of caged structure as radical absorbers in antioxidant therapies

Oxidative stress is one of the major critical factors causing increased cytotoxicity. The ROS, superoxide molecules produced from the various cellular processes (cellular respiration) are responsible for the random oxidation of enzymes, radicles and electrons leading to the disruption in cellular homeostasis. In general, both innate and exogenous anti-oxidants such as vitamins, carotenoids, and polyphenols, work together to mitigate this oxidative stress within cells. The excessive production of ROS, mitochondrial dysfunction, and endoplasmic reticulum (ER)-mediated cell loss are pathophysiological features common to numerous neurodegenerative diseases, brain disorders, and certain microbial diseases [117,118]. Fullerene in its non-irradiated state acts as a radical sponge [119], the electron acceptor arm readily accepts the free radical either by "C-addition" or by "H-abstraction" depending on the percentage of hydroxylation [120]. Thereby preventing the increased oxidation load of the cell. This phenomenon is applied as an alternative for anti-oxidants and used as an anti-bacterial fullerenol [121]. Bacterial meningitis is one of the fatal diseases characterized by the brain inflammation and increased permeability in the blood-brain barrier [122]. The toxin produced by meningitis organisms resides in the subarachnoid space of the Central Nervous System (CNS) triggers the pro-inflammatory cytokines and immune chemokines, leading to an increased influx of the neutrophils, prostaglandins, microglial cells and endothelial cells. This ultimatum results in the increased permeability in blood-brain barrier, loss of ion homeostasis and inflammation. When the meningitis was induced on the fullerene pre-treated mice by directly inoculation through intra-cerebral injection, showed no signs of neuropathic effect [123]. The radical scavenging was evident by the reduction of inflammation and induction of anti-inflammatory chemokines. Although the fullerene showed neuroprotective effect, since they were not irradiated, the ROS induction and bacterial clearance was not possible. Under these circumstances, the bacterial clearance solely depends on the

host defense mechanism and half-life of the fullerene formulations to retain the anti-inflammatory effect.

However, there is evidence stating the involvement of fullerene assemblies in the immunomodulatory activities. The maturation of dendritic cell, T-cell proliferation and mast cell accumulation in fullerene treated mice shows the immune enhancement and promotion of the host humoral and cellular immunity [124,125]. This could possibly aid in the bacterial clearance by host immunity and thereby fullerene acting as an adjuvant in antibacterial therapies. Similarly, fullerene is also known to demonstrate neutrophils modulation. For instance, fullerene is employed to inhibit the growth of toxin producing organisms such as *Streptococcus pyogenes*. *S. pyogenes* belongs to the *Streptococcus group A* organism, collectively known as GAS (Group A Streptococcus), which causes necrosis fasciitis, and streptococcal toxic shock syndrome by producing serine proteases and inducing oxidative stress. This is mostly associated with the toxic-induced inflammation and filtration of neutrophils gaining systemic access for further spread [126,127]. Similar to the above concept, Tsao studied a carboxy fullerene treatment on mice infected with necrotic *S. pyogenes* showed, survival rates increased by 80%. This improvement was attributed to the fullerenes' ability to reduce oxidative load and neutralize bacterial toxins. Additionally, carboxy-fullerenes modulated neutrophil activity, enhancing the host immune response and inhibiting protease production [128].

Out of all derivatives, the hydroxy fullerenes or fullerenol are the most appropriate candidate for the radical scavenging, since they are water soluble and shows increased activity in the aqueous solvent. This is best suited for the biological application and has been extensively explored. Fullerene treated against macrophages cell lines showed accumulation of particles but less cytotoxicity and increased in proliferation by ROS scavenging [129] . This experiment serves as proof for the ROS quenching even though nanoparticles ingestion was seen. The fullerene formulations containing amino groups were localized around lysosomes showing its prominent role in absorbing ROS. Although, bond formation and quenching depend on the structure configuration of fullerene formulation, the fullerenol was seen

to be shown good quenching ability due to its π stacking and hydroxyl availability. The anti-oxidant nature of fullerenol has been long back established as a protective shield against host- toxicity, Tsai et al., demonstrated the regression of cellular injury due to hydrogen peroxide effect in the bronchial asthma model of mice [130]. Since then, these fullerenols have been exhaustively studied in the neuro-protective and bactericidal activities.

Fullerenol is widely employed in the field of cosmetology and dermatology. The fullerene conjugates easily cross the human keratinocytes through endocytic cellular transport. The internalization of fullerene near the mitochondria, a ROS producing organelle, possibly explains the role of fullerene in ROS scavenging. Consequently, a greater number of dermal formulations are in the consideration for the epidermal diseases and anti-tanning creams [131]. One such is, the Pyrrolidone-fullerenol which is used in open human clinical trials for treating the facial erythematous pustules and papules caused by *Propionibacterium acnes*. This bacterium triggers the pro-inflammatory cytokines and chemokines causing localized inflammation and erythema. In order to chelate the inflammatory chemokines and their superoxide, the PVP formulated hydrogel was employed to reduce the lipids. The reduction in papules were seen, which is due to the infiltration of neutrophil and reduction of oxidative stress [132,133]. Apart from the neuroprotectivity, there are evidence that water soluble fullerene protects the DNA from enzyme degradation. When hydroxylated fullerenol tagged with the naked DNA, presence of intact DNA in agarose gel proved that this fullerenol inhibited the restriction action of enzymes. Further, it also inhibited the thermal degradation of DNA. The fullerenol binds to the DNA forming aggregates shielding the active motif sites of enzymes, thereby inhibiting the degradation. This may act as the precursor for gene delivery research. There are evidences of fullerene delivery of drugs at the intramuscular and intra-dermal level, this approach can also be best suited for the m-RNA vaccine deliveries, liposomal enzyme target and gene therapies [134,135].

Despite numerous reports on the bio-compatibility of fullerene, host cytotoxicity is one of the crucial parameters to be considered [136,137]. While reports on fullerene sequestration by healthy cells and

associated host toxicity are limited, the dose dependency of nanoparticles for bioactivity must be considered. The report on hydroxylated fullerene to Peripheral Blood Mononuclear Cells (PBMC), shows the presence of fullerenol in the mitochondrial membrane leading to radical scavenging, thereby reducing the effect of cell death. Although fullerenol is an electron donor and inclusion of such fullerenols causes depolarization of the membrane, still no chances of necrosis or apoptosis have been seen [138]. This may be due to the fact membrane depolarization causes influx of ions and an increase in ROS leads to radical scavenging by synthesized fullerenol. This experiment verified that cytotoxicity and compatibility are dose-dependent, despite of lodging of fullerenols in PBMC does not induce either cell death or necrosis.

4.4 Molecular mimicry of caged structure - Competitive inhibition strategy for anti-viral and anti-bacterial applications

In the field of glycobiology, oligosaccharides and glycolipids are pivotal in numerous complex biosynthetic processes. These glycol-conjugates are known to play a mediating role and as a secondary messenger in bio-synthesis processes [139] and are found to be crucial in protein folding and motif recognition thereby marking its influence in most of the biological events [140,141]. These carbohydrate–receptor interactions were explored exhaustively in the field of enzymology. Since then, a myriad of synthetic ligands has been experimented especially in competitive inhibition of protein molecules [142], secondary signaling molecules, decoy ligands, and reversible inhibition [143]. Thus, the data accumulated shows the promising future of fullerene in molecular manipulation, disease biology, and delivery strategies.

“Lectins” are multimeric proteins and cell surface glycans having a high affinity predominately for carbohydrates. Avidity of such binding depends on the either multi-valency or multitude of ligand bindings popularly known as “cluster effect of glycoside” [144]. This carbohydrate–protein interaction

causes a conformational change which are more crucial for bacterial and viral entry, cellular proliferation, and cancer metastasis [145,146].

Years of research in glyco-dynamics revealed that the "cluster effect of glycoside" depend on the amplitude of multivalency of carbohydrate-lectin interaction. Therefore, it is wise to be reminded only a few alterations from the natural way in the substrate-transition dynamics are negligible. Hence, the orientation, distance, spatial arrangement of functional group, and stearic interference all account for the final yield of inhibition effect of the designed decoy [147,148]. Factors to be considered are:

- The binding affinity of interaction is variedly differed in its monovalent form and multivalent form.
- The multivalent form has more enhanced recognition of its lectin counterparts than the monovalent form.

Based on the above concept, Cecioni et al., employed glycoclusters of *Pseudomonas* as a target binding for fullerene structure. It was modulated as a multivalent fullerene loaded with 12 iminosugar, functionalized at equidistant intervals from each other. These fullerenes exactly mimic the glycoclusters, belongs specifically to the LecA, family of lectins. LecA or PA-IL belongs to the organism *Pseudomonas*, known to cause predominantly a nosocomial infection, rarely an opportunistic infection and lung issues in the patients of cystic fibrosis. Against this organism, the designed the dodecavalent fullerene decorated with the galactose and glucose residues does competitive ligand interaction with the PA-IL. The galactose showed more affinity than glucose, because structurally, the binding capacity is more influenced by the distance between neighboring moieties as well as the bonded moiety to that of the core. This approach on carbohydrate-bacterial lectin had spurred the effort towards inhibition of microbial entry by using competitive binding where the synthesized fullerene acts as decoys [140].

A similar effort was made for the inhibition of *E. coli*. These uropathogenic bacteria exploit the mannose receptors of a host cell for their entry. *E. coli* in general infects host through a lectin-mediated

pathway, Fimbriae H (FimH) – an adhesion molecule found in the pili that binds to the mannose surface receptor of the host cell facilitating entry through endocytosis. So, the glycolated fullerenes were decorated with 12 mannose receptors and named as sugar balls. In the Hemagglutination Inhibition Assay there was a decrease in the agglutination rate of FimH to the guinea pig erythrocytes, when excess of glycol-conjugated fullerene was added. Thus, the reverse in agglutination further confirms the competitive inhibition of glycolated fullerene [149]. In addition to the equidistance concept, the spacer and spatial arrangement of glycosidic linkages are more important in controlling the duration and affinity of the ligand and receptor linkages.

Similar to the above work, same glycofullerenes were employed in the blocking of viral entry [150]. The surface of viruses is mostly seeded with the glycocalyx ligands, which form receptor-ligand interaction with the host cell glycol-conjugates. This leads to the internalization of viral particles by receptor-mediated endocytosis**.**

The construction of fullerene decoy for viral conjugates follows the same principles of bacterial inhibition with factors affecting are position of the functional group, charge of the fullerene addicts, and orientation. As general rules, positive and amphiphilic fullerenes exhibit more virucidal activity [151]. Similar to FimH experiment, Luczkowiak synthesized a glycolated dendrons to form the sugar balls consisting of 36 mannose receptors equipped with two spacers to block the entry of Ebola virus by effective binding to the dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN) cell receptors in the host [150]. These DC-SIGN receptors and C-type lectins are found on the surfaces of dendritic cells, alveolar macrophages and circulating serum immune cells. They possess a high affinity for sugar residues, predominantly for the mannose [152,153]. The glycoprotein(gp) -2 surface protein on the Ebola virus encounters these receptors thereby gaining the entry through endocytosis. The positive results on the Isothermal Titration Calorimetry (ITC) showed that designed fullerenes are readily bound to that of concanavalin A confirms the recognition of fullerenes by lectin receptors. The *in-vitro* assay demonstrated that an increase in valency decreases the inhibition activity [150].

A similar approach can be used for the inhibition of other viruses like Human immunodeficiency virus (HIV) [152,154] and HSV Herpes Simplex Virus (HSV) [155] which uses same surface receptor endocytosis for their entry".

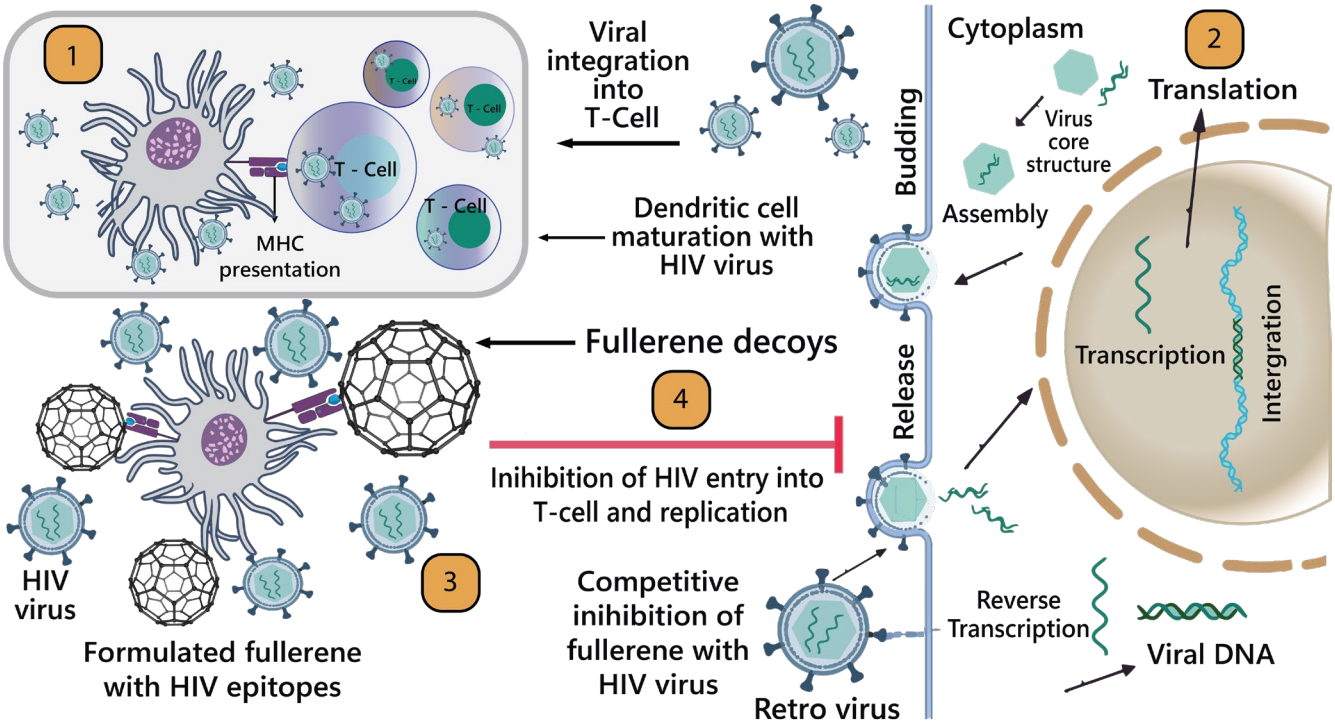

Figure 5. Illustration depicts the competitive inhibition strategy of formulated fullerene controlling viral entry of retrovirus into T-cell. 1) MHC presentation of dendritic cell engulfing HIV virus to T-cell. Retrovirus invades T- cell by trans dendritic cell maturation causing increase in infected T- cell population, 2) Internalization and replication of virus inside the cell, 3) Formulated fullerene binds to dendritic cell instead of HIV virus due to shared epitope shape, 4) Competitive binding of formulated fullerene inhibits trans entry of HIV virus into the cell, thereby effectively controlling the replication of retrovirus into the cell.

The HIV epitopes of gp-120 and gp-48 were often used as a target cluster for these fullerene decoys, in one such approach the fullerene derivative with tryptophan at its periphery were synthesized and tested for stearic interferences. In SPR analysis, this amino-acid decorated fullerene assemblies showed the increased affinity and slower detachment than the Pradimicin-A, a routinely used non-

peptide anti-viral drug. This high affinity of fullerene assembly towards HIV, aids in the competitive binding as a decoy (Figure 5) [156]. In addition to surface receptor targeting, some fullerene assemblies can penetrate membranes and inactivate enzymes. The proline conjugated fullerene is shown to be a dual inhibitor of the reverse transcriptase enzyme and protease enzyme, where both are responsible for the viral entry and proliferation. These formulated fullerene conjugates showed superior enzyme inhibition and high affinity towards HIV titer, highlighting their potential as effective antiviral agents [157].

It should be noted that the topological arrangement and spatial distribution of the glycolated fullerenes influence the efficiency of binding, as do the charge and hydrophobicity. However, the precise idea on binding affinity still needs further exploration [149,150]. Rather than the HIV, similar study on the influence of hydrophobicity and amphiphilicity of the charged functional groups over the binding capacity of fullerene through Vesicular Stomatitis Virus (VSV) was done. The VSV belongs to the Rhabdoviridae family, and interacts with the L-selectin of host leukocytes to gain entry. This VSV is known to affect the equine and other grazing animals. The comparative analysis, on the sulphated fullerene and amphiphilic fullerene showed that sulphated fullerene has enhanced cidal activity than its counterpart. This may be due to that fact that sulphate in core imparts negative charge, which in turn increases its electrostatic potential towards the viral epitope, thereby enhancing binding affinity [156]. As explained above, the specificity and π-π conjugation of fullerene cage which helps in ligand binding are being thoroughly exploited in the field of infectious biology. The fact that these fullerenes are less toxic and easily taken up by host cells are an added advantage. Fullerene constructs as inhalers, intra-dermal drugs and adjuvants are under consideration. These formulations, holds promising future as anti-viral therapeutics over the conventional drugs [145].

4.5 Mechanistic understanding on catalytic activity of fullerene – Molecular probes on DNA

Fullerenes are known for their nucleosidase activity, which is often attributed to the action of excited triplet electrons rather than being a distinct process [158]. This is because the precise components of Deoxyribose Nucleic Acid (DNA) cleavage by fullerene exposure and its mechanism are yet to get a clarity. When Yamakoshi and his team worked on the role of super radicals in the process of DNA cleavage on the pBR322 supercoiled DNA, cleavage with the presence of radiation initiator-nicotinamide adenine dinucleotide hydrogen (NADH) and quencher radical. Cleavage was recorded only in the presence of the initiator and intact DNA in the quencher treated nucleotide. This may be due to the fact that on radiation the fullerene binds to the DNA may induce the super oxides, which in turn causes nucleosidase activity [91]. When the same experiment was extrapolated with the involvement of photo-induction strategized that positively charged fullerene will readily bind to the negatively charged DNA. The irradiation is enough for denaturation of nucleotides, a saturation of hydrogen bonds in DNA was seen, the nick of DNA strand was found to be duration-dependent and pH-dependent, ideal pH was found to be 8 [159]. Here the light irradiation provides the adequate energy for the induction of super oxides by fullerene, similar to radiation initiator. In both the experiments, when source of excitation is absent (under radical quencher, dark conditions) the DNA cleavage did not happen, despite fullerene being bounded to the DNA groove.

It is hypothesized that the fullerenes have better affinity to bind towards the guanine residue of nucleic acid (Figure 6). This targeted approach was employed as an anti-viral therapy against the influenza virus [160]. Influenza virus is an enveloped Ribo Nucleic Acid (RNA) virus known for its recent pandemics and endemics in the region of South Asia. The toxicity of the viruses depends on the two toxins, namely: neuraminidase and heme agglutinin protein found in the capsid of these viruses. Even though antiviral agents like oseltamivir are employed to inhibit the viral entry and neutralization of toxins, these agents have exerted their own host toxicity and rising resistance is seen [161,162]. In this

regard Shoji and co-workers, designed 12 different fullerenes and subjected to the PA subunit of the influenza polymerase enzyme, for the comparative analysis of nucleic acid disruption.

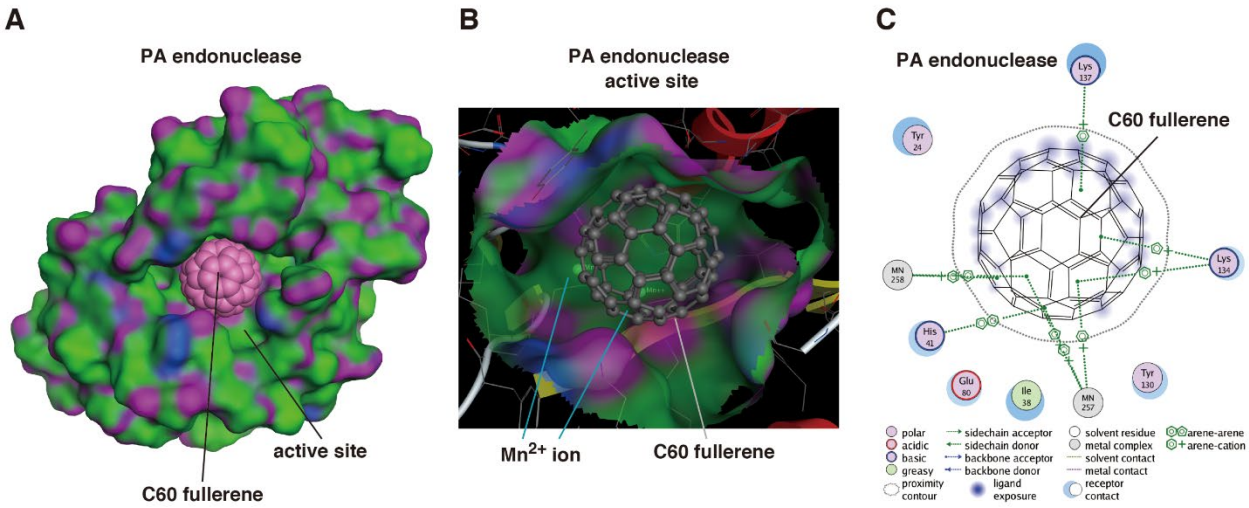

Figure 6. Simulation of C60 fullerene docked with PA endonuclease. (A) Docking simulation analysis of C60 fullerene with the PA endonuclease domain of influenza. The surface of the pocket of PA endonuclease is shown in green and purple. The pink ball indicates the carbon atoms in the fullerene. (B) The fitting of the fullerene to the active pocket of PA endonuclease. PA endonuclease is depicted as a ribbon structure. The α-helix and β-strands are shown in red and yellow, respectively. The fullerene is shown as a gray stick structure. The manganese ions in PA endonuclease are behind the fullerene. (C) Two-dimensional analysis of the interactions between fullerene and PA endonuclease. The fullerene is shown in the center with the key and with the interacting amino acids shown around it. MN indicates the Mn2+. Reproduced from reference [160]. Available under CC- BY XX. Copyright 2013 PLOS Shoji et al.

The experiment revealed that in endonuclease activity the fullerene conjugated with tetramethyl pyrrolidinium di-iodide was found to exert maximum binding followed by the cleavage [163]. The virucidal activity was because of the RNA disruption followed by inhibition of the virion's proliferation. Though the role of superoxide anion in DNA cleavage is still under the debatable radar mostly, it has been a part of cellular disruption after fullerene irradiation, [88]. Now fullerenes are being

actively explored as an enhancer or adjuvant usually conjugated with other metal oxides or probes to achieve heightened cytotoxicity. The fullerene composites formulated with, the porphyrin, cyclodextrin, hyaluronic acid is being used as a photo-induced DNA cleavage construct. The presence of porphyrins and cyclodextrins helps to overcome the poor insolubility of fullerene in aqueous environment. As expected, the constructs are shown to cleave the supercoiled DNA to the fragments evident from agarose gel electrophoresis [164].

4.6 Augmentation of fullerene as immunologic enhancers for anti-microbial activity

As soon as the numerous research on the anti-microbial activity of fullerene is known, it has become a boon to treat most of multidrug-resistant microbes precisely towards bacteria. On the other hand, parallel research utilizes these fullerenes as an adjuvant to augment the host immune attack against the multi-drug-resistant species in conjunction with the routine antibiotics. The strategy is based on the fact that fullerene conjugated with antibiotics avoids ion channels rather than entering through lipid membrane. Which gives access to the cell's interior leading to cellular disruption. While fullerene directly did not exert its toxic activity towards microbial species, this indirect approach has been widely considered in the field of infectious diseases, onco therapy and photo radiation inhibition some of them are mentioned in the table 2.

S.no	**Fullerene composition**	**Acts as therapy for**	**Biological activity of fullerene**	**Reference**
1	Teicoplanin Ψ glycolate fullerene conjugates	Vancomycin resistance *Entercoccus faecalis van^{+}, Staphylococcus aureus*	Multivalent glycolated fullerene forms a bond with the bacterial cell wall, helping the antibiotic	[165]

			to enter the cell membrane	
2	Chitosan-glycine-fullerene conjugate	*Propionibacterium vulgaris*	Growth inhibition was equivalent to *Streptomyces,* radical scavenging	[166]
3	C_{70} pyrrolidinium iodide.	Human Immunodeficiency Virus	Impairment of Gag and Gag-Pol, assembly defect and impaired maturation	[167]
4	Fullerene-liposome	H1N1 -influenza virus	ROS production, virucidal effect	[168]
5	Fullerene-tetrapeptide tuftsin	Immuno- modulation	Resistant to chemical degradation, enhanced chemotaxis	[169]
6	Poly-hydroxylated fullerenol	HCV recombinant protein	Enhanced interferon production	[125]
7	Curcumin- pristine fullerene	Diabetes	Reduced cholesterol biosynthesis, increased expression of anti-apoptosis, stabilizing fatty acids and maintenance of tissue architecture	[170]

8	Fullerene-pyrrolidone-tris acid	Immunomodulation on inflammatory disorders	Suppression of T-cell immunity and IL-4 production	[171]
9	Polyhydroxylated fullerene	Shielding effect against high-energy electrons	Reduces the potassium efflux, reduces oxidation of thiol groups in membrane	[172]
10	Fullerenol as vaccine adjuvant	Hepatitis C virus	Immuno-modulator, increases T-cell proliferation, increase humoral immunity	[173]
11	Fullerene nano films	Cocktail of cancer cell lines	Suppression of SMAD pathway, reversing of EMT	[174]

Table 2: List of studies, where fullerene is employed as an adjuvant for the enhanced activity.

4.7 Role of fullerenes as therapeutic nanobot in degenerative diseases, auto-immune disorders and metabolic disorders

Apart from their role in infectious biology, fullerenes are being actively experimented in allergic diseases, cancer biology, wound healing, and cosmetic sectors. Although fullerene studies in immunomodulatory contexts remain relatively rare, the research in auto-immune disorder is gaining momentum with these fullerenols. Notably, research in anaphylaxis and hypersensitivity has proven that fullerene can stabilize the mast cells and pro-inflammatory cytokines *in vivo*, highlighting the

importance of employing them as therapeutic agents [175]. However, the fullerene functionalization is directly known to influence the efficiency of outcome. Specifically, the stabilization of mast cells varies with the type of covalent bonding used in the fullerene. For instance, hydroxylated fullerenes have been synthesized and tested for their effects on suppressing pro-inflammatory histamines and cytokines in arthritis-induced mice [176]. On subjecting, such formulated fullerenes were happened to arrest the degranulation of mast cells by ROS scavenging and thereby inhibiting the tissue hyperplasia and joint inflammation. To further elucidate the interaction between the mast cells and fullerenes, the same fullerene has been introduced into the mast cell deficiency mice, which again showed the amelioration of the disease inhibition. However, the interaction of fullerene cage with other immune cells and inflammatory cells such as osteoblast and osteoclast require more study. This hypothesis was further confirmed by Piotrowski and co-workers on experimenting the PEGylated fullerene against human osteoblast in the *in vitro* cultures. The positive correlation to the osteoblast differentiation revealed the enhanced viability of cells treated with fullerene are much more efficient than the control group [177]**.** The difference in viability of both the groups are due to the fact, that fullerene treated cells possess low ROS load, thereby surpassing the ROS induced cell death. Such fullerenes hold the promising future in the field of bone regeneration, implant tissue regeneration and osteointegration.

ROS scavenging is also widely employed in the neuroprotection of human cells, especially in the degenerative disorders [178–180] . For example, in the case of Parkinson's disease, aggregation of α-synuclein and production of ROS are the pathophysiology to be concerned [181]. Whereas, in case of Alzheimer's diseases similar scenario arises, but the aggregates are the tau protein of amyloid origin. In recent years a greater number of researchers have used various carbon nanoparticles to address the issue with aggregates, as these nanostructures are better at crossing the Blood Brain Barrier (BBB) [182]. Simultaneously, fullerenes are used as a radical sponge. Studies using primates, and drosophila insist that the alleviation of ROS lessens the pathophysiology of Parkinson's disease (Figure 7). [182]. These fullerene cages mimic the catalytic domain of Super Oxide Dismutase (SOD), thereby effectively

eliminating the singlet oxygen. The collective effect of these elimination results in the improved motor skills, and increased efflux of dopamine in striated muscles, thereby lessening the parkinsonism [179].

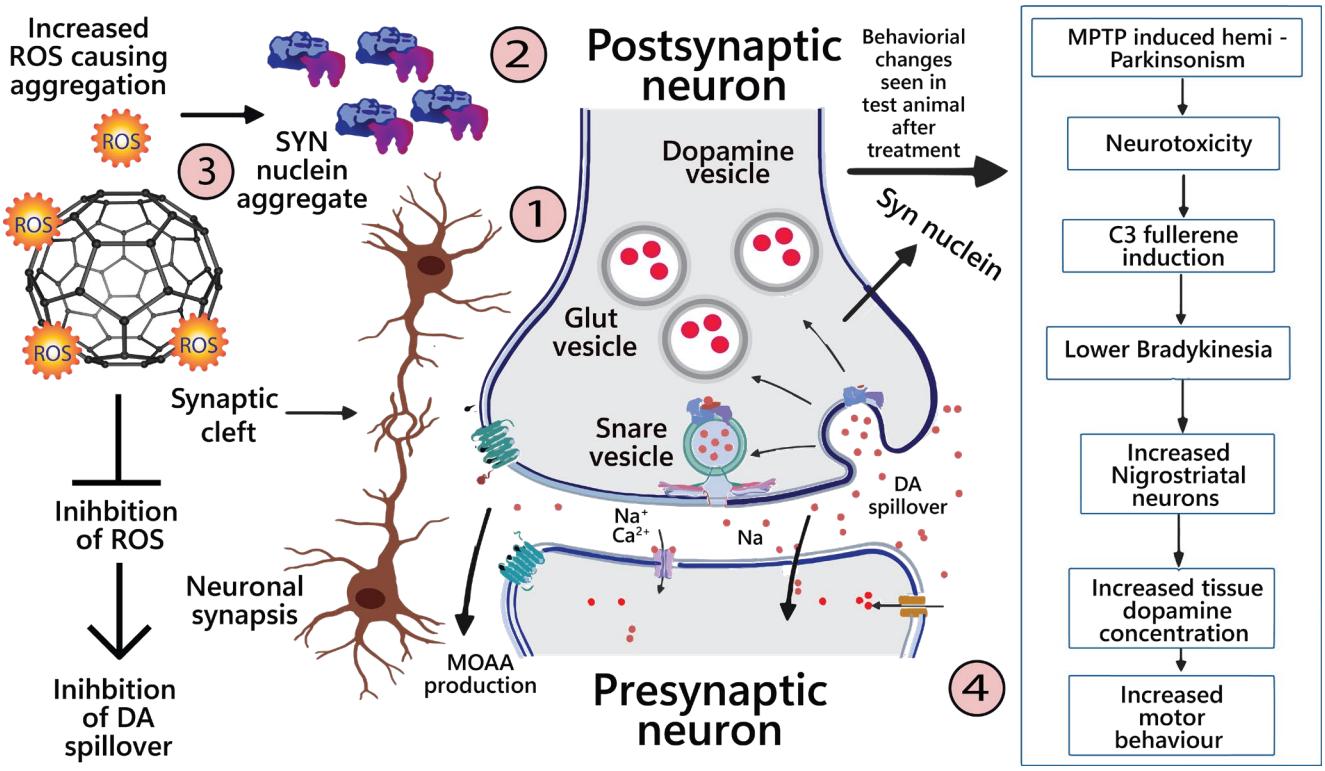

Figure 7. Illustrates the loss of α-syn nuclein protein in synaptic cleft, one of the pathophysiology expressions in Parkinson diseases. 1) Synaptic Cleft formed between pre and post synaptic neuron of substantia nigara, 2) Synaptic cleft showing the loss of α-syn nuclein protein due to aggregation leads to dopamine spillover in the extracellular space. 3) Radical scavenging of ROS by the fullerene cages, thereby inhibiting the syn nuclein aggregation, 4) Prognosis of therapeutic fullerene in treated monkeys showing better behavioral changes. DA – Dopamine. MOAA – Monoamine Oxidase - Neurotoxic product.

Other than infectious diseases another wide field that exploits the cytotoxic activity of fullerenes are in cancer therapies. Enhanced cytotoxicity is seen when fullerene derivatives are irradiated by the photo-radiation, pH or by conjugated with other chemotherapeutics like doxorubicin, and paclitaxel [158,183]. The mechanism by which it exerts cell toxicity is pretty much similar to that of PDI in microbial

cells and addition of chemotherapeutic agents exerts a synergistic effect against the cancer cells [184]. A higher acidic environment and increased epithelial leakiness of cancer cells helps in the selective uptake of these fullerene agents, thereby reducing the bystander effect. But still, site-specificity and solubility of fullerene targets are hindrances where more insights are needed [185].

The duality of fullerenes once again became an indispensable role in radiobiology with fullerenols being tested for a cytoprotective role against irradiated cells. In this accordance, Grebowski tested hydroxylated fullerenes employed for the scavenging of ROS in the cancer cell lines, mice and Wistar rats. Fullerenol pretreated mice were radiated and found to have neuroprotective effects [186]. They were compared with the chemo cytoprotective drug called amifostine showing similar outcomes. The *in-vitro* assay on fullerenol-treated cell lines shows the increased gene expression of anti-apoptotic and cytoprotective genes. Moreover, the stability of mitochondrial imbalance, and membrane channel homeostasis was seen [187]. This initiative will be further employed for the healing purpose of radiation burns, and compensation of cell loss during radiotherapy.

Despite of insufficient knowledge and uncertainties in toxicity, fullerenes are still considered as an indispensable boon when it comes to material chemistry, tissue engineering, infectious biology and pharmacology [188]. The patents in the field of dermatology and cosmetics, for treating the side effects of skin laser treatment, acne treatment and hair growth in hairless mice are some of the future therapies showing promising results [189]. Recently, water-soluble fullerene using as a nanomedicine in Parkinson's has been patented, and more of this kind of fullerene has been explored to the core in cancer and has been in process of patents [190,191].

5. Conclusion

In the field of carbon biology, fullerenes have been of significant importance. With its unique properties, fullerene chemistry attracted researchers from various fields. From, the discovery of fullerenes in the mid-90s, till now they have been regarded as an active exploration area in more of

energy capacitor domains. However, in last decade only, fullerene in biology geared its experimentation starting from adjuvants to alternatives of antibiotics. Thanks to the development of nanoarchitectonics as it makes the fullerene biology more of standard in the field of medical sector. For instance, the fullerene assemblies with that of antibiotics, acted as adjuvants surpassing the bacterial barriers for safe delivery of the drugs. During the 21st century, the irradiation therapy such as PDT have been routinely used with fullerene as a photosensitizer replacing porphyrins. The hydrophobic nature of fullerenes poses a great hindrance to its application in hydrophilic environment such as microfluidics and bio-medical diagnostics. The potential for surface modification through self-assembly allows for functionalization, making fullerenes more applicable. Functionalized fullerene has been proven to be efficient by numerous researchers, moreover the fullerene composites and metal conjugates helps in the membrane disruption and bacterial inhibition.

Along, with metal conjugates fullerene-antibiotics composition is also an upcoming technique to minimize the rising bacterial resistance. Unlike, antibacterial technique, antiviral activity of fullerene focuses on the epitope docking causing effective entry blockage by competitive inhibition. More experiments on fullerene formation by lectins conjugation, polysaccharide conjugation served as an epitope binder. The antiviral activity of fullerene has an added advantage of being the biocompatible on functionalization, elucidating no to less immunogenic but effective in viral blockage. On contrary to antibacterial activity, no disruption of virus is seen rather the disruption of replication via entry blockage reducing the viral load. Some of the above-mentioned skin formulations containing fullerene and antioxidant compounds per sees the fullerene as huge in infectious sector.

Hence, exploration of fullerene pertaining to its surface biology at molecular level may bring more insights into the antimicrobial tendency of fullerene in turn may garner much of promising therapies in the near future. Moreover, exploration of nanoarchitectonics pertaining to nanoscale structural regulation and hydrogen bond behavior will throw more insights into the dynamics of fullerene and membrane interactions, in turn, strengthen our understanding in formulations of therapies. This review

focused on the various approaches of fullerene derivatives, employed for the anti-microbial activity of infectious diseases, highlighting the current approaches and future areas of exploration. Additionally, this review hereby highlights that less exploration pertaining to surface manipulation in the view of nanoarchitectonics i.e., very few attempts has been made in recent decade for the production of stimuli responsive fullerene. More of research relating to fullerene is happening in material chemistry rather than in the biological sector. With this research gap and also as the limitation of this study, we propose that fullerene exploration will be an effective alternative in terms of infectious biology. Furthermore, insights into the surface chemistry of fullerene cages with different conjugation foresees exciting applications in radiobiology and oncotherapies.

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References:

(1) Liberman-Martin, A. L. The Emergence of Zerovalent Carbon Compounds from Structural Curiosities to Organocatalysts. *Cell Rep Phys Sci* **2023**, *4* (8), 101519. https://doi.org/10.1016/j.xcrp.2023.101519.

(2) Kroto, H. W.; Allaf, A. W.; Balm, S. P. C60: Buckminsterfullerene. *Chem Rev* **1991**, *91* (6), 1213–1235. https://doi.org/10.1021/cr00006a005.

(3) He, H.; Sekine, T.; Kobayashi, T. Direct Transformation of Cubic Diamond to Hexagonal Diamond. *Appl Phys Lett* **2002**, *81* (4), 610–612. https://doi.org/10.1063/1.1495078.

(4) Falcao, E. H.; Wudl, F. Carbon Allotropes: Beyond Graphite and Diamond. *Journal of Chemical Technology & Biotechnology* **2007**, *82* (6), 524–531. https://doi.org/10.1002/jctb.1693.

(5) Rashid, M.; Zaid Ahmad, Q.; Tajuddin. Trends in Nanotechnology for Practical Applications. In *Applications of Targeted Nano Drugs and Delivery Systems*; Elsevier, 2019; Vol. 1, pp 297–325. https://doi.org/10.1016/B978-0-12-814029-1.00011-9.

(6) Kang, Z.; Lee, S.-T. Carbon Dots: Advances in Nanocarbon Applications. *Nanoscale* **2019**, *11* (41), 19214–19224. https://doi.org/10.1039/C9NR05647E.

(7) Shenderova, O. A.; Zhirnov, V. V.; Brenner, D. W. Carbon Nanostructures. *Critical Reviews in Solid State and Materials Sciences* **2002**, *27* (3–4), 227–356. https://doi.org/10.1080/10408430208500497.

(8) Dai, D.; Li, Y.; Fan, J. Room-Temperature Synthesis of Various Allotropes of Carbon Nanostructures (Graphene, Graphene Polyhedra, Carbon Nanotubes and Nano-Onions, n-Diamond Nanocrystals) with Aid of Ultrasonic Shock Using Ethanol and Potassium Hydroxide. *Carbon N Y* **2021**, *179*, 133–141. https://doi.org/10.1016/j.carbon.2021.04.038.

(9) Tiwari, S. K.; Kumar, V.; Huczko, A.; Oraon, R.; Adhikari, A. De; Nayak, G. C. Magical Allotropes of Carbon: Prospects and Applications. *Critical Reviews in Solid State and Materials Sciences* **2016**, *41* (4), 257–317. https://doi.org/10.1080/10408436.2015.1127206.

(10) Zhao, C.; Kang, J.; Li, Y.; Wang, Y.; Tang, X.; Jiang, Z. Carbon-Based Stimuli-Responsive Nanomaterials: Classification and Application. *Cyborg and Bionic Systems* **2023**, *4* (4), 00–22. https://doi.org/10.34133/cbsystems.0022.

(11) Matsuno, T.; Isobe, H. Trapped yet Free inside the Tube: Supramolecular Chemistry of Molecular Peapods. *Bull Chem Soc Jpn* **2023**, *96* (5), 406–419. https://doi.org/10.1246/bcsj.20230052.

(12) Iwamoto, T.; Watanabe, Y.; Takaya, H.; Haino, T.; Yasuda, N.; Yamago, S. Size- and Orientation-Selective Encapsulation of C_{70} by Cycloparaphenylenes. *Chemistry – A European Journal* **2013**, *19* (42), 14061–14068. https://doi.org/10.1002/chem.201302694.

(13) Diederich, F.; Ettl, R.; Rubin, Y.; Whetten, R. L.; Beck, R.; Alvare, M.; Anz, S.; Sensharma, D.; Wudl, F.; Khemani, K. C.; Koch, A. The Higher Fullerenes: Isolation and Characterization of C_{76}, C_{84}, C_{90}, C_{94}, and $C_{70}O$, an Oxide of D_{5h}-C_{70}. *Science (1979)* **1991**, *252* (5005), 548–551. https://doi.org/10.1126/science.252.5005.548.

(14) Omont, A. Interstellar Fullerene Compounds and Diffuse Interstellar Bands. *Astron Astrophys* **2016**, *590* (A & A), A52. https://doi.org/10.1051/0004-6361/201527685.

(15) Galazutdinov, G. A.; Shimansky, V. V.; Bondar, A.; Valyavin, G.; Krełowski, J. C_{60}^{+} – Looking for the Bucky-Ball in Interstellar Space. *Mon Not R Astron Soc* **2017**, *465* (4), 3956–3964. https://doi.org/10.1093/mnras/stw2948.

(16) Shrestha, L. K.; Shrestha, R. G.; Hill, J. P.; Tsuruoka, T.; Ji, Q.; Nishimura, T.; Ariga, K. Surfactant-Triggered Nanoarchitectonics of Fullerene C_{60} Crystals at a Liquid–Liquid Interface. *Langmuir* **2016**, *32* (47), 12511–12519. https://doi.org/10.1021/acs.langmuir.6b01378.

(17) Emelyantsev, S.; Prazdnova, E.; Chistyakov, V.; Alperovich, I. Biological Effects of C60 Fullerene Revealed with Bacterial Biosensor—Toxic or Rather Antioxidant? *Biosensors (Basel)* **2019**, *9* (2), 81. https://doi.org/10.3390/bios9020081.

(18) Ariga, K.; Nishikawa, M.; Mori, T.; Takeya, J.; Shrestha, L. K.; Hill, J. P. Self-Assembly as a Key Player for Materials Nanoarchitectonics. *Sci Technol Adv Mater* **2019**, *20* (1), 51–95. https://doi.org/10.1080/14686996.2018.1553108.

(19) Ariga, K.; Li, M.; Richards, GaryJ.; Hill, JonathanP. Nanoarchitectonics: A Conceptual Paradigm for Design and Synthesis of Dimension-Controlled Functional Nanomaterials. *J Nanosci Nanotechnol* **2011**, *11* (1), 1–13. https://doi.org/10.1166/jnn.2011.3839.

(20) Ariga, K.; Jia, X.; Song, J.; Hill, J. P.; Leong, D. T.; Jia, Y.; Li, J. Nanoarchitectonics beyond Self-Assembly: Challenges to Create Bio-Like Hierarchic Organization. *Angewandte Chemie International Edition* **2020**, *59* (36), 15424–15446. https://doi.org/10.1002/anie.202000802.

(21) Minami, K.; Song, J.; Shrestha, L. K.; Ariga, K. Nanoarchitectonics for Fullerene Biology. *Appl Mater Today* **2021**, *23*, 100989. https://doi.org/10.1016/j.apmt.2021.100989.

(22) Choucair, M.; Stride, J. A. The Gram-Scale Synthesis of Carbon Onions. *Carbon N Y* **2012**, *50* (3), 1109–1115. https://doi.org/10.1016/j.carbon.2011.10.023.

(23) Ariga, K.; Leong, D. T.; Mori, T. Nanoarchitectonics for Hybrid and Related Materials for Bio-Oriented Applications. *Adv Funct Mater* **2018**, *28* (27), 1702905. https://doi.org/10.1002/adfm.201702905.

(24) Mashino, T.; Nishikawa, D.; Takahashi, K.; Usui, N.; Yamori, T.; Seki, M.; Endo, T.; Mochizuki, M. Antibacterial and Antiproliferative Activity of Cationic Fullerene Derivatives. *Bioorg Med Chem Lett* **2003**, *13* (24), 4395–4397. https://doi.org/10.1016/j.bmcl.2003.09.040.

(25) Hong, L.; Luo, S.-H.; Yu, C.-H.; Xie, Y.; Xia, M.-Y.; Chen, G.-Y.; Peng, Q. Functional Nanomaterials and Their Potential Applications in Antibacterial Therapy. *Pharm Nanotechnol* **2019**, *7* (2), 129–146. https://doi.org/10.2174/2211738507666190320160802.

(26) Behren, S.; Westerlind, U. Novel Approaches To Design Glycan-Based Antibacterial Inhibitors. *European J Org Chem* **2023**, *26* (1), 202200795–202200808. https://doi.org/10.1002/ejoc.202200795.

(27) Nurzynska, A.; Piotrowski, P.; Klimek, K.; Król, J.; Kaim, A.; Ginalska, G. Novel C60 Fullerenol-Gentamicin Conjugate–Physicochemical Characterization and Evaluation of Antibacterial and Cytotoxic Properties. *Molecules* **2022**, *27* (14), 4366. https://doi.org/10.3390/molecules27144366.

(28) Zhilenkov, A. V.; Khakina, E. A.; Troshin, P. A.; Inchagova, K. S.; Deryabin, D. G. Synthesis and Antibacterial Activity of Hybrid Supramolecular Complexes Based on Tetracycline/Doxycycline and Water-Soluble C60-Fullerene Derivatives. *Pharm Chem J* **2017**, *50* (10), 637–641. https://doi.org/10.1007/s11094-017-1505-7.

(29) Martínez-Gualda, B.; Sun, L.; Rivero-Buceta, E.; Flores, A.; Quesada, E.; Balzarini, J.; Noppen, S.; Liekens, S.; Schols, D.; Neyts, J.; Leyssen, P.; Mirabelli, C.; Camarasa, M.-J.; San-Félix, A. Structure-Activity Relationship Studies on a Trp Dendrimer with Dual Activities against HIV and Enterovirus A71. Modifications on the Amino Acid. *Antiviral Res* **2017**, *139*, 32–40. https://doi.org/10.1016/j.antiviral.2016.12.010.

(30) Kraevaya, O. A.; Novikov, A. V.; Shestakov, A. F.; Ershova, E. S.; Savinova, E. A.; Kameneva, L. V.; Veiko, N. N.; Schols, D.; Balzarini, J.; Kostyuk, S. V.; Troshin, P. A. Water-Soluble Fullerene-Based Nanostructures with Promising Antiviral and Myogenic Activity. *Chemical Communications* **2020**, *56* (70), 10203–10206. https://doi.org/10.1039/D0CC03928D.

(31) Shershakova, N. N.; Andreev, S. M.; Tomchuk, A. A.; Makarova, E. A.; Nikonova, A. A.; Turetskiy, E. A.; Petukhova, O. A.; Kamyshnikov, O. Y.; Ivankov, O. I.; Kyzyma, O. A.; Tomchuk, O. V.; Avdeev, M. V.; Dvornikov, A. S.; Kudlay, D. A.; Khaitov, M. R. Wound Healing Activity of Aqueous Dispersion of Fullerene C60 Produced by "Green Technology." *Nanomedicine* **2023**, *47*, 102619. https://doi.org/10.1016/j.nano.2022.102619.

(32) Hana Kubatova; Eva Zemanova; Karel Klouda; Karel Bilek; Jana Kadukova. Evaluation of Effects of C60 Fullerene and Its Derivatives on Selected Microorganisms. *Journal of Materials Science and Engineering B* **2013**, *3* (7), 409–417. https://doi.org/10.17265/2161-6221/2013.07.001.

(33) Witte, P.; Beuerle, F.; Hartnagel, U.; Lebovitz, R.; Savouchkina, A.; Sali, S.; Guldi, D.; Chronakis, N.; Hirsch, A. Water Solubility, Antioxidant Activity and Cytochrome C Binding of Four Families of Exohedral Adducts of C60 and C70. *Org Biomol Chem* **2007**, *5* (22), 3599. https://doi.org/10.1039/b711912g.

(34) Bai, Y.; Wu, X.; Ouyang, P.; Shi, M.; Li, Q.; Maimaiti, T.; Lan, S.; Yang, S.-T.; Chang, X.-L. Surface Modification Mediates the Interaction between Fullerene and Lysozyme: Protein

Structure and Antibacterial Activity. *Environ Sci Nano* **2021**, *8* (1), 76–85. https://doi.org/10.1039/D0EN00645A.

(35) Sharoyko, V. V; Iamalova, N. R.; Ageev, S. V; Meshcheriakov, A. A.; Iurev, G. O.; Petrov, A. V; Nerukh, D. A.; Farafonov, V. S.; Vasina, L. V; Penkova, A. V; Semenov, K. N. In Vitro and In Silico Investigation of Water-Soluble Fullerenol C60(OH)24: Bioactivity and Biocompatibility. *J Phys Chem B* **2021**, *125* (32), 9197–9212. https://doi.org/10.1021/acs.jpcb.1c03332.

(36) Hsu, P.-C.; Jefferies, D.; Khalid, S. Molecular Dynamics Simulations Predict the Pathways via Which Pristine Fullerenes Penetrate Bacterial Membranes. *J Phys Chem B* **2016**, *120* (43), 11170–11179. https://doi.org/10.1021/acs.jpcb.6b06615.

(37) Chung, D. D. L. Review Graphite. *J Mater Sci* **2002**, *37* (8), 1475–1489. https://doi.org/10.1023/A:1014915307738.

(38) Ariga, K. Nanoarchitectonics: What's Coming next after Nanotechnology? *Nanoscale Horiz* **2021**, *6* (5), 364–378. https://doi.org/10.1039/D0NH00680G.

(39) Ariga, K.; Li, J.; Fei, J.; Ji, Q.; Hill, J. P. Nanoarchitectonics for Dynamic Functional Materials from Atomic-/Molecular-Level Manipulation to Macroscopic Action. *Advanced Materials* **2016**, *28* (6), 1251–1286. https://doi.org/10.1002/adma.201502545.

(40) Shrestha, L. K.; Ji, Q.; Mori, T.; Miyazawa, K.; Yamauchi, Y.; Hill, J. P.; Ariga, K. Fullerene Nanoarchitectonics: From Zero to Higher Dimensions. In *Chemistry - An Asian Journal*; 2013; Vol. 8, pp 1662–1679. https://doi.org/10.1002/asia.201300247.

(41) Prylutskyy, Yu. I.; Petrenko, V. I.; Ivankov, O. I.; Kyzyma, O. A.; Bulavin, L. A.; Litsis, O. O.; Evstigneev, M. P.; Cherepanov, V. V.; Naumovets, A. G.; Ritter, U. On the Origin of C_{60} Fullerene Solubility in Aqueous Solution. *Langmuir* **2014**, *30* (14), 3967–3970. https://doi.org/10.1021/la404976k.

(42) Jensen, A. W.; Wilson, S. R.; Schuster, D. I. Biological Applications of Fullerenes. *Bioorg Med Chem* **1996**, *4* (6), 767–779. https://doi.org/10.1016/0968-0896(96)00081-8.

(43) Hashikawa, Y.; Murata, Y. Water in Fullerenes. *Bull Chem Soc Jpn* **2023**, *96* (9), 943–967. https://doi.org/10.1246/bcsj.20230135.

(44) Tanzi, L.; Terreni, M.; Zhang, Y. Synthesis and Biological Application of Glyco- and Peptide Derivatives of Fullerene C60. *Eur J Med Chem* **2022**, *230*, 114104. https://doi.org/https://doi.org/10.1016/j.ejmech.2022.114104.

(45) Ruoff, R. S.; Tse, D. S.; Malhotra, R.; Lorents, D. C. *Solubility of Cm in a Variety of Solvents*; 1993; Vol. 97. https://pubs.acs.org/sharingguidelines.

(46) Mchedlov-Petrossyan, N. O. Fullerenes in Aqueous Media: A Review. *Theoretical and Experimental Chemistry*. Springer January 1, 2020, pp 361–391. https://doi.org/10.1007/s11237-020-09630-w.

(47) Pobłocki, K.; Drzeżdżon, J.; Kostrzewa, T.; Jacewicz, D. Coordination Complexes as a New Generation Photosensitizer for Photodynamic Anticancer Therapy. *International Journal of Molecular Sciences*. MDPI August 1, 2021. https://doi.org/10.3390/ijms22158052.

(48) Cai, G.; Yang, Z.; Chen, Y.-C.; Huang, Y.; Liang, L.; Feng, S.; Zhao, J. Magnetic Bead Manipulation in Microfluidic Chips for Biological Application. *Cyborg and Bionic Systems* **2023**, *4* (4), 23. https://doi.org/10.34133/cbsystems.0023.

(49) Dixit, M.; Shrestha, L. K.; Ariga, K.; Pati, F. Carbon-Based Nanoarchitectonics in Advancing Cardiac Tissue Bioprinting: A Review. *ACS Appl Nano Mater* **2024**, *7* (21), 24638–24652. https://doi.org/10.1021/acsanm.4c04441.

(50) Meethalepurayil, V. K. C.; Velu, K.; Dhinakarasamy, I.; Shrestha, L. K.; Ariga, K.; Rene, E. R.; Vijayakumar, G. K.; Mani, R.; Radhakrishnapillai, A.; Tharmathass, S. D.; Prasad, S. Insights into the Molecular Response of *Dioithona Rigida* to Selenium Nanoparticles: *De Novo* Transcriptome Assembly and Differential Gene Expression Analysis. *Sci Technol Adv Mater* **2024**, *25* (1), 2379758. https://doi.org/10.1080/14686996.2024.2379758.

(51) Bretschger, O.; Obraztsova, A.; Sturm, C. A.; In, S. C.; Gorby, Y. A.; Reed, S. B.; Culley, D. E.; Reardon, C. L.; Barua, S.; Romine, M. F.; Zhou, J.; Beliaev, A. S.; Bouhenni, R.; Saffarini, D.; Mansfeld, F.; Kim, B. H.; Fredrickson, J. K.; Nealson, K. H. Current Production and Metal Oxide Reduction by Shewanella Oneidensis MR-1 Wild Type and Mutants. *Appl Environ Microbiol* **2007**, *73* (21), 7003–7012. https://doi.org/10.1128/AEM.01087-07.

(52) Meshulam-Simon, G.; Behrens, S.; Choo, A. D.; Spormann, A. M. Hydrogen Metabolism in *Shewanella Oneidensis* MR-1. *Appl Environ Microbiol* **2007**, *73* (4), 1153–1165. https://doi.org/10.1128/AEM.01588-06.

(53) Tang, Y. J.; Ashcroft, J. M.; Chen, D.; Min, G.; Kim, C.-H.; Murkhejee, B.; Larabell, C.; Keasling, J. D.; Chen, F. F. Charge-Associated Effects of Fullerene Derivatives on Microbial Structural Integrity and Central Metabolism. *Nano Lett* **2007**, *7* (3), 754–760. https://doi.org/10.1021/nl063020t.

(54) Indeglia, P. A.; Georgieva, A. T.; Krishna, V. B.; Martyniuk, C. J.; Bonzongo, J.-C. J. Toxicity of Functionalized Fullerene and Fullerene Synthesis Chemicals. *Chemosphere* **2018**, *207*, 1–9. https://doi.org/10.1016/j.chemosphere.2018.05.023.

(55) Ariga, K. Nanoarchitectonics: The Method for Everything in Materials Science. *Bull Chem Soc Jpn* **2024**, *97* (1), uoad001. https://doi.org/10.1093/bulcsj/uoad001.

(56) Harano, K. Self-Assembly Mechanism in Nucleation Processes of Molecular Crystalline Materials. *Bull Chem Soc Jpn* **2021**, *94* (2), 463–472. https://doi.org/10.1246/bcsj.20200333.

(57) Ariga, K. Confined Space Nanoarchitectonics for Dynamic Functions and Molecular Machines. *Micromachines (Basel)* **2024**, *15* (2), 282. https://doi.org/10.3390/mi15020282.

(58) Ariga, K.; Shionoya, M. Nanoarchitectonics for Coordination Asymmetry and Related Chemistry. *Bull Chem Soc Jpn* **2021**, *94* (3), 839–859. https://doi.org/10.1246/bcsj.20200362.

(59) Ohno, T.; Hasegawa, T.; Tsuruoka, T.; Terabe, K.; Gimzewski, J. K.; Aono, M. Short-Term Plasticity and Long-Term Potentiation Mimicked in Single Inorganic Synapses. *Nat Mater* **2011**, *10* (8), 591–595. https://doi.org/10.1038/nmat3054.

(60) Avizienis, A. V.; Sillin, H. O.; Martin-Olmos, C.; Shieh, H. H.; Aono, M.; Stieg, A. Z.; Gimzewski, J. K. Neuromorphic Atomic Switch Networks. *PLoS One* **2012**, *7* (8), e42772. https://doi.org/10.1371/journal.pone.0042772.

(61) Song, J.; Kawakami, K.; Ariga, K. Localized Assembly in Biological Activity: Origin of Life and Future of Nanoarchitectonics. *Adv Colloid Interface Sci* **2025**, *339*, 103420. https://doi.org/10.1016/j.cis.2025.103420.

(62) Wong, C.-W.; Tsai, K.-C.; Shrestha, L. K.; Ariga, K.; Hsu, S. Effects of Hydrophilic Fullerene Nanoarchitectured Structures on the Behaviour of Neural Stem Cells. *Nanoscale* **2022**, *14* (31), 11152–11161. https://doi.org/10.1039/D2NR01817A.

(63) Rašović, I.; Piacenti, A. R.; Contera, S.; Porfyrakis, K. Hierarchical Self-Assembly of Water-Soluble Fullerene Derivatives into Supramolecular Hydrogels. *Small* **2024**, *20* (42), 2401963–2401975. https://doi.org/10.1002/smll.202401963.

(64) Prylutska, S. V. USING OF C60 FULLERENE COMPLEXES WITH ANTITUMOR DRUGS IN CHEMOTHERAPY. *Biotechnol Acta* **2014**, *7* (3), 9–20. https://doi.org/10.15407/biotech7.03.009.

(65) Wang, H.-H.; Li, M.-J.; Wang, H.-J.; Chai, Y.-Q.; Yuan, R. P–n-Sensitized Heterostructure Co_3O_4 /Fullerene with Highly Efficient Photoelectrochemical Performance for Ultrasensitive DNA Detection. *ACS Appl Mater Interfaces* **2019**, *11* (26), 23765–23772. https://doi.org/10.1021/acsami.9b05923.

(66) Vacik, J.; Lavrentiev, V.; Novotna, K.; Bacakova, L.; Lisa, V.; Vorlicek, V.; Fajgar, R. Fullerene (C60)–Transitional Metal (Ti) Composites: Structural and Biological Properties of the Thin Films. *Diam Relat Mater* **2010**, *19* (2–3), 242–246. https://doi.org/10.1016/j.diamond.2009.10.016.

(67) Krishnan, V.; Kasuya, Y.; Ji, Q.; Sathish, M.; Shrestha, L. K.; Ishihara, S.; Minami, K.; Morita, H.; Yamazaki, T.; Hanagata, N.; Miyazawa, K.; Acharya, S.; Nakanishi, W.; Hill, J. P.; Ariga, K. Vortex-Aligned Fullerene Nanowhiskers as a Scaffold for Orienting Cell Growth. *ACS Appl Mater Interfaces* **2015**, *7* (28), 15667–15673. https://doi.org/10.1021/acsami.5b04811.

(68) Hsieh, F.-Y.; Shrestha, L. K.; Ariga, K.; Hsu, S. Neural Differentiation on Aligned Fullerene C_{60} Nanowhiskers. *Chemical Communications* **2017**, *53* (80), 11024–11027. https://doi.org/10.1039/C7CC06395D.

(69) Song, J.; Jia, X.; Minami, K.; Hill, J. P.; Nakanishi, J.; Shrestha, L. K.; Ariga, K. Large-Area Aligned Fullerene Nanocrystal Scaffolds as Culture Substrates for Enhancing Mesenchymal Stem Cell Self-Renewal and Multipotency. *ACS Appl Nano Mater* **2020**, *3* (7), 6497–6506. https://doi.org/10.1021/acsanm.0c00973.

(70) Allison, R. R. Photodynamic Therapy: Oncologic Horizons. *Future Oncology*. Future Medicine Ltd. January 1, 2014, pp 123–142. https://doi.org/10.2217/fon.13.176.

(71) Yasuno, T.; Ohe, T.; Kataoka, H.; Hashimoto, K.; Ishikawa, Y.; Furukawa, K.; Tateishi, Y.; Kobayashi, T.; Takahashi, K.; Nakamura, S.; Mashino, T. Fullerene Derivatives as Dual Inhibitors of HIV-1 Reverse Transcriptase and Protease. *Bioorg Med Chem Lett* **2021**, *31*, 127675. https://doi.org/10.1016/j.bmcl.2020.127675.

(72) Skariyachan, S.; Gopal, D.; Kadam, S. P.; Muddebihalkar, A. G.; Uttarkar, A.; Niranjan, V. Carbon Fullerene Acts as Potential Lead Molecule against Prospective Molecular Targets of Biofilm-Producing Multidrug-Resistant *Acinetobacter Baumanni* and *Pseudomonas Aerugenosa* : Computational Modeling and MD Simulation Studies. *J Biomol Struct Dyn* **2021**, *39* (3), 1121–1137. https://doi.org/10.1080/07391102.2020.1726821.

(73) Bai, L.; Chen, Y.; Bai, Y.; Chen, Y.; Zhou, J.; Huang, A. Fullerene-Doped Polyaniline as New Redox Nanoprobe and Catalyst in Electrochemical Aptasensor for Ultrasensitive Detection of Mycobacterium Tuberculosis MPT64 Antigen in Human Serum. *Biomaterials* **2017**, *133*, 11–19. https://doi.org/10.1016/j.biomaterials.2017.04.010.

(74) Ibrahim, A. A.; Khan, T.; Nowlin, K.; Averitt, J.; Pathiraja, G.; LaJeunesse, D.; Obare, S. O.; Dellinger, A. L. A Rapid One-Step Synthesis of Silver and Copper Coordinated Chlorine Functionalized Fullerene Nanoparticles with Enhanced Antibacterial Activity. *Nanoscale Adv* **2024**, *6* (23), 5833–5852. https://doi.org/10.1039/D4NA00732H.

(75) Martinez, Z. S.; Castro, E.; Seong, C. S.; Cerón, M. R.; Echegoyen, L.; Llano, M. Fullerene Derivatives Strongly Inhibit HIV-1 Replication by Affecting Virus Maturation without Impairing Protease Activity. *Antimicrob Agents Chemother* **2016**, *60* (10), 5731–5741. https://doi.org/10.1128/AAC.00341-16.

(76) Skariyachan, S.; Parveen, A.; Garka, S. Nanoparticle Fullerene (C60) Demonstrated Stable Binding with Antibacterial Potential towards Probable Targets of Drug Resistant *Salmonella Typhi* – a Computational Perspective and *in Vitro* Investigation. *J Biomol Struct Dyn* **2017**, *35* (16), 3449–3468. https://doi.org/10.1080/07391102.2016.1257441.

(77) Darabpour, E.; Doroodmand, M. M.; Halabian, R.; Imani Fooladi, A. A. Sulfur-Functionalized Fullerene Nanoparticle as an Inhibitor and Eliminator Agent on *Pseudomonas Aeruginosa* Biofilm and Expression of *ToxA* Gene. *Microbial Drug Resistance* **2019**, *25* (4), 594–602. https://doi.org/10.1089/mdr.2018.0008.

(78) Sharma, D.; Rai, M.; Singh, A.; Gaur, R.; Sengupta, D. Fullerene (C $_{60}$ & C $_{70}$)- *Meso* -Tris-4-Carboxyphenyl Porphyrin Dyads Inhibit Entry of Wild-Type and Drug-Resistant HIV-1 Clades B and C. *J Med Virol* **2025**, *97* (2), 1–11. https://doi.org/10.1002/jmv.70181.

(79) Tokuyama, H.; Yamago, S.; Nakamura, E.; Shiraki, T.; Sugiura, Y. Photoinduced Biochemical Activity of Fullerene Carboxylic Acid. *J Am Chem Soc* **1993**, *115* (17), 7918–7919. https://doi.org/10.1021/ja00070a064.

(80) Nakajima, N.; Nishi, C.; Li, F. M.; Ikada, Y. Photo-Induced Cytotoxicity of Water-Soluble Fullerene. *Fullerene Science and Technology* **1996**, *4* (1), 1–19. https://doi.org/10.1080/10641229608001533.

(81) Wang, H.; Li, B.; Sun, Y.; Ma, Q.; Feng, Y.; Jia, Y.; Wang, W.; Su, M.; Liu, X.; Shu, B.; Zheng, J.; Sang, S.; Yan, Y.; Wu, Y.; Zhang, Y.; Gao, Q.; Li, P.; Wang, J.; Ma, F.; Li, X.; Yan, D.; Wang, D.; Zou, X.; Liao, Y. NIR-II AIE Luminogen-Based Erythrocyte-Like Nanoparticles with Granuloma-Targeting and Self-Oxygenation Characteristics for Combined Phototherapy of Tuberculosis. *Advanced Materials* **2024**, *36* (38), 1–10. https://doi.org/10.1002/adma.202406143.

(82) Hamblin, M. R. Fullerenes as Photosensitizers in Photodynamic Therapy: Pros and Cons. *Photochemical & Photobiological Sciences* **2018**, *17* (11), 1515–1533. https://doi.org/10.1039/c8pp00195b.

(83) Hamblin, M. R.; Hasan, T. Photodynamic Therapy: A New Antimicrobial Approach to Infectious Disease? *Photochemical & Photobiological Sciences* **2004**, *3* (5), 436–450. https://doi.org/10.1039/b311900a.

(84) Alavi, M.; Ashengroph, M.; Mozafari, M. R. Interaction of Carbon Nanotubes, Capped Carbon Nanotubes, CNT2–5, C60, C70, HO-C60, [C60]2, and [C60]3 Fullerenes with Virulence Factors of Gram-Negative and Gram-Positive Bacteria: Potential Applications for 3D-Printed Scaffolds. *Inorganics (Basel)* **2024**, *12* (3), 77. https://doi.org/10.3390/inorganics12030077.

(85) Biswas, K.; Mishra, A. K.; Rauta, P. R.; Al-Sehemi, A. G.; Pannipara, M.; Sett, A.; Bratovcic, A.; Avula, S. K.; Mohanta, T. K.; Saravanan, M.; Mohanta, Y. K. Exploring the Bioactive Potentials of C60-AgNPs Nano-Composites against Malignancies and Microbial Infections. *Int J Mol Sci* **2022**, *23* (2), 714. https://doi.org/10.3390/ijms23020714.

(86) Hou, W.; Shi, G.; Wu, S.; Mo, J.; Shen, L.; Zhang, X.; Zhu, Y. Application of Fullerenes as Photosensitizers for Antimicrobial Photodynamic Inactivation: A Review. *Front Microbiol* **2022**, *13*, 957698. https://doi.org/10.3389/fmicb.2022.957698.

(87) Vagos, M. R.; Gomes, M.; Moreira, J. M. R.; Soares, O. S. G. P.; Pereira, M. F. R.; Mergulhão, F. J. Carbon Nanotube/Poly(Dimethylsiloxane) Composite Materials to Reduce Bacterial Adhesion. *Antibiotics* **2020**, *9* (8), 1–15. https://doi.org/10.3390/antibiotics9080434.

(88) Liosi, K.; Stasyuk, A. J.; Masero, F.; Voityuk, A. A.; Nauser, T.; Mougel, V.; Solà, M.; Yamakoshi, Y. Unexpected Disparity in Photoinduced Reactions of C_{60} and C_{70} in Water with the Generation of $O_2^{\bullet-}$ or $^1O_2$. *JACS Au* **2021**, *1* (10), 1601–1611. https://doi.org/10.1021/jacsau.1c00239.

(89) Galstyan, V. “Quantum Dots: Perspectives in next-Generation Chemical Gas Sensors” – A Review. *Anal Chim Acta* **2021**, *1152*, 238192. https://doi.org/10.1016/j.aca.2020.12.067.

(90) Armstrong, Z. T.; Kunz, M. B.; Zanni, M. T. Ultrafast Fluctuations in PM6 Domains of Binary and Ternary Organic Photovoltaic Thin Films Probed with Two-Dimensional White-Light Spectroscopy. *J Phys Chem Lett* **2021**, *12* (37), 8972–8979. https://doi.org/10.1021/acs.jpclett.1c02234.

(91) Yamakoshi, Y.; Umezawa, N.; Ryu, A.; Arakane, K.; Miyata, N.; Goda, Y.; Masumizu, T.; Nagano, T. Active Oxygen Species Generated from Photoexcited Fullerene (C_{60}) as Potential Medicines: $O_2^{-\bullet}$ versus $^1O_2$. *J Am Chem Soc* **2003**, *125* (42), 12803–12809. https://doi.org/10.1021/ja0355574.

(92) Kashef, N.; Huang, Y.-Y.; Hamblin, M. R. Advances in Antimicrobial Photodynamic Inactivation at the Nanoscale. *Nanophotonics* **2017**, *6* (5), 853–879. https://doi.org/10.1515/nanoph-2016-0189.

(93) Ingram, L. O. Adaptation of Membrane Lipids to Alcohols. *J Bacteriol* **1976**, *125* (2), 670–678. https://doi.org/10.1128/jb.125.2.670-678.1976.

(94) Fang, J.; Lovanh, N.; Alvarez, P. J. J. The Use of Isotopic and Lipid Analysis Techniques Linking Toluene Degradation to Specific Microorganisms: Applications and Limitations. *Water Res* **2004**, *38* (10), 2529–2536. https://doi.org/10.1016/j.watres.2004.03.006.

(95) Kaneda, T. *Iso-and Anteiso-Fatty Acids in Bacteria: Biosynthesis, Function, and Taxonomic Significancet*; 1991; Vol. 55.

(96) Fang, J.; Lyon, D. Y.; Wiesner, M. R.; Dong, J.; Alvarez, P. J. J. Effect of a Fullerene Water Suspension on Bacterial Phospholipids and Membrane Phase Behavior. *Environ Sci Technol* **2007**, *41* (7), 2636–2642. https://doi.org/10.1021/es062181w.

(97) Vecchio, D.; Gupta, A.; Huang, L.; Landi, G.; Avci, P.; Rodas, A.; Hamblin, M. R. Bacterial Photodynamic Inactivation Mediated by Methylene Blue and Red Light Is Enhanced by Synergistic Effect of Potassium Iodide. *Antimicrob Agents Chemother* **2015**, *59* (9), 5203–5212. https://doi.org/10.1128/AAC.00019-15.

(98) Hamblin, M. R. Antimicrobial Photodynamic Inactivation: A Bright New Technique to Kill Resistant Microbes. *Curr Opin Microbiol* **2016**, *33*, 67–73. https://doi.org/10.1016/j.mib.2016.06.008.

(99) Merchat, M.; Bertolini, G.; Giacomini, P.; Villaneuva, A.; Jori, G. Meso-Substituted Cationic Porphyrins as Efficient Photosensitizers of Gram-Positive and Gram-Negative Bacteria. *J Photochem Photobiol B* **1996**, *32* (3), 153–157. https://doi.org/10.1016/1011-1344(95)07147-4.

(100) Jori, G.; Fabris, C.; Soncin, M.; Ferro, S.; Coppellotti, O.; Dei, D.; Fantetti, L.; Chiti, G.; Roncucci, G. Photodynamic Therapy in the Treatment of Microbial Infections: Basic Principles

and Perspective Applications. *Lasers Surg Med* **2006**, *38* (5), 468–481. https://doi.org/10.1002/lsm.20361.

(101) Ganesh Kumar, V.; Velu, K.; Vineeth Kumar, C. M.; Sorna Lakshmi, A. Functional Nanostructured Materials and Processes: An Introduction. In *Pulsed Laser-Induced Nanostructures in Liquids for Energy and Environmental Applications*; Yong Choi, M., Theerthagiri, J., Kumari, M. L. A., Manickam, S., Min, A., Eds.; Elsevier, 2024; pp 3–21. https://doi.org/10.1016/B978-0-443-13379-4.00001-8.

(102) Hoyos, P.; Perona, A.; Juanes, O.; Rumbero, Á.; Hernáiz, M. J. Synthesis of Glycodendrimers with Antiviral and Antibacterial Activity. *Chemistry – A European Journal* **2021**, *27* (28), 7593–7624. https://doi.org/10.1002/chem.202005065.

(103) Xiao, L.; Hong, K.; Roberson, C.; Ding, M.; Fernandez, A.; Shen, F.; Jin, L.; Sonkusare, S.; Li, X. Hydroxylated Fullerene: A Stellar Nanomedicine to Treat Lumbar Radiculopathy via Antagonizing TNF-α-Induced Ion Channel Activation, Calcium Signaling, and Neuropeptide Production. *ACS Biomater Sci Eng* **2018**, *4* (1), 266–277. https://doi.org/10.1021/acsbiomaterials.7b00735.

(104) Golomidov, I.; Bolshakova, O.; Komissarov, A.; Sharoyko, V.; Slepneva, E.; Slobodina, A.; Latypova, E.; Zherebyateva, O.; Tennikova, T.; Sarantseva, S. The Neuroprotective Effect of Fullerenols on a Model of Parkinson's Disease in Drosophila Melanogaster. *Biochem Biophys Res Commun* **2020**, *523* (2), 446–451. https://doi.org/10.1016/j.bbrc.2019.12.075.

(105) Chaudhuri, P.; Paraskar, A.; Soni, S.; Mashelkar, R. A.; Sengupta, S. Fullerenol−Cytotoxic Conjugates for Cancer Chemotherapy. *ACS Nano* **2009**, *3* (9), 2505–2514. https://doi.org/10.1021/nn900318y.

(106) Skivka, L. M.; Prylutska, S. V.; Rudyk, M. P.; Khranovska, N. M.; Opeida, I. V.; Hurmach, V. V.; Prylutskyy, Y. I.; Sukhodub, L. F.; Ritter, U. C60 Fullerene and Its Nanocomplexes with Anticancer Drugs Modulate Circulating Phagocyte Functions and Dramatically Increase ROS Generation in Transformed Monocytes. *Cancer Nanotechnol* **2018**, *9* (1), 8. https://doi.org/10.1186/s12645-017-0034-0.

(107) Huang, Y.-Y.; Sharma, S. K.; Yin, R.; Agrawal, T.; Chiang, L. Y.; Hamblin, M. R. Functionalized Fullerenes in Photodynamic Therapy. *J Biomed Nanotechnol* **2014**, *10* (9), 1918–1936. https://doi.org/10.1166/jbn.2014.1963.

(108) Spesia, M. B.; Milanesio, M. E.; Durantini, E. N. Synthesis, Properties and Photodynamic Inactivation of Escherichia Coli by Novel Cationic Fullerene C60 Derivatives. *Eur J Med Chem* **2008**, *43* (4), 853–861. https://doi.org/10.1016/j.ejmech.2007.06.014.

(109) Mizuno, K.; Zhiyentayev, T.; Huangv, L.; Khalil, S.; Nasim, F. Antimicrobial Photodynamic Therapy with Functionalized Fullerenes: Quantitative Structure-Activity Relationships. *J Nanomed Nanotechnol* **2011**, *02* (02), 1–9. https://doi.org/10.4172/2157-7439.1000109.

(110) Palacios, Y. B.; Durantini, J. E.; Heredia, D. A.; Martínez, S. R.; González de la Torre, L.; Durantini, A. M. Tuning the Polarity of Fullerene C $_{60}$ Derivatives for Enhanced Photodynamic Inactivation †. *Photochem Photobiol* **2021**, *97* (6), 1431–1444. https://doi.org/10.1111/php.13465.

(111) Zhang, Y.; Dai, T.; Wang, M.; Vecchio, D.; Chiang, L. Y.; Hamblin, M. R. Potentiation of Antimicrobial Photodynamic Inactivation Mediated by a Cationic Fullerene by Added Iodide: *In Vitro* and *in Vivo* Studies. *Nanomedicine* **2015**, *10* (4), 603–614. https://doi.org/10.2217/nnm.14.131.

(112) Huang, L.; Bhayana, B.; Xuan, W.; Sanchez, R. P.; McCulloch, B. J.; Lalwani, S.; Hamblin, M. R. Comparison of Two Functionalized Fullerenes for Antimicrobial Photodynamic Inactivation: Potentiation by Potassium Iodide and Photochemical Mechanisms. *J Photochem Photobiol B* **2018**, *186*, 197–206. https://doi.org/10.1016/j.jphotobiol.2018.07.027.

(113) Woźniak, A.; Kruszewska, B.; Pierański, M. K.; Rychłowski, M.; Grinholc, M. Antimicrobial Photodynamic Inactivation Affects the Antibiotic Susceptibility of Enterococcus Spp. Clinical Isolates in Biofilm and Planktonic Cultures. *Biomolecules* **2021**, *11* (5), 693. https://doi.org/10.3390/biom11050693.

(114) Shirani, M.; Pakzad, R.; Haddadi, M. H.; Akrami, S.; Asadi, A.; Kazemian, H.; Moradi, M.; Kaviar, V. H.; Zomorodi, A. R.; Khoshnood, S.; Shafieian, M.; Tavasolian, R.; Heidary, M.; Saki, M. The Global Prevalence of Gastric Cancer in Helicobacter Pylori-Infected Individuals: A Systematic Review and Meta-Analysis. *BMC Infect Dis* **2023**, *23* (1), 543. https://doi.org/10.1186/s12879-023-08504-5.

(115) Zolfaghar Karahrudi, N.; Taherpour, A. *Theoretical Study of Electron Transfer Process Between Fullerenes and Membrane Cells of Helicobacter Pylori*; 2016; Vol. 11. www.electrochemsci.org.

(116) Zhang, J.; Chen, Z.; Kong, J.; Liang, Y.; Chen, K.; Chang, Y.; Yuan, H.; Wang, Y.; Liang, H.; Li, J.; Mao, M.; Li, J.; Xing, G. Fullerenol Nanoparticles Eradicate *Helicobacter Pylori* via PH-Responsive Peroxidase Activity. *ACS Appl Mater Interfaces* **2020**, *12* (26), acsami.0c05509. https://doi.org/10.1021/acsami.0c05509.

(117) Estevez, A. Y.; Erlichman, J. S. The Potential of Cerium Oxide Nanoparticles (Nanoceria) for Neurodegenerative Disease Therapy. *Nanomedicine* **2014**, *9* (10), 1437–1440. https://doi.org/10.2217/nnm.14.87.

(118) Heckman, K. L.; DeCoteau, W.; Estevez, A.; Reed, K. J.; Costanzo, W.; Sanford, D.; Leiter, J. C.; Clauss, J.; Knapp, K.; Gomez, C.; Mullen, P.; Rathbun, E.; Prime, K.; Marini, J.; Patchefsky, J.; Patchefsky, A. S.; Hailstone, R. K.; Erlichman, J. S. Custom Cerium Oxide Nanoparticles Protect against a Free Radical Mediated Autoimmune Degenerative Disease in the Brain. *ACS Nano* **2013**, *7* (12), 10582–10596. https://doi.org/10.1021/nn403743b.

(119) Djordjevic, A.; Srdjenovic, B.; Seke, M.; Petrovic, D.; Injac, R.; Mrdjanovic, J. Review of Synthesis and Antioxidant Potential of Fullerenol Nanoparticles. *J Nanomater* **2015**, *2015* (1), 1–15. https://doi.org/10.1155/2015/567073.

(120) Ueno, H.; Yamakura, S.; Arastoo, R. S.; Oshima, T.; Kokubo, K. Systematic Evaluation and Mechanistic Investigation of Antioxidant Activity of Fullerenols Using β -Carotene Bleaching Assay. *J Nanomater* **2014**, *2014* (1), 1–7. https://doi.org/10.1155/2014/802596.

(121) Petrovic, D.; Seke, M.; Srdjenovic, B.; Djordjevic, A. Applications of Anti/Prooxidant Fullerenes in Nanomedicine along with Fullerenes Influence on the Immune System. *J Nanomater* **2015**, *2015* (1), 565638-565638,. https://doi.org/10.1155/2015/565638.

(122) Akhtar, M. J.; Ahamed, M.; Alhadlaq, H. A.; Alshamsan, A. Mechanism of ROS Scavenging and Antioxidant Signalling by Redox Metallic and Fullerene Nanomaterials: Potential Implications in ROS Associated Degenerative Disorders. *Biochimica et Biophysica Acta (BBA) - General Subjects* **2017**, *1861* (4), 802–813. https://doi.org/10.1016/j.bbagen.2017.01.018.

(123) Tsao, N.; Kanakamma, P. P.; Luh, T.-Y.; Chou, C.-K.; Lei, H.-Y. Inhibition of *Escherichia Coli* -Induced Meningitis by Carboxyfullerence. *Antimicrob Agents Chemother* **1999**, *43* (9), 2273–2277. https://doi.org/10.1128/AAC.43.9.2273.

(124) Wang, B.; Yang, D.; Sun, B.; Wei, X.; Guo, H.; Liu, X.; Ying, G.; Niu, R.; Zhang, N.; Ma, Y. An Anti-Tumor Nanoparticle, [Gd@C₈₂(OH)₂₂]_N, Induces Macrophage Activation. *J Nanosci Nanotechnol* **2011**, *11* (3), 2321–2329. https://doi.org/10.1166/jnn.2011.3610.

(125) Liu, J.; Feng, X.; Chen, Z.; Yang, X.; Shen, Z.; Guo, M.; Deng, F.; Liu, Y.; Zhang, H.; Chen, C. The Adjuvant Effect of C60(OH)22 Nanoparticles Promoting Both Humoral and Cellular Immune Responses to HCV Recombinant Proteins. *Materials Science and Engineering: C* **2019**, *97*, 753–759. https://doi.org/10.1016/j.msec.2018.12.088.

(126) Silversides, J. A.; Lappin, E.; Ferguson, A. J. Staphylococcal Toxic Shock Syndrome: Mechanisms and Management. *Curr Infect Dis Rep* **2010**, *12* (5), 392–400. https://doi.org/10.1007/s11908-010-0119-y.

(127) Chuang, Y.-Y.; Huang, Y.-C.; Lin, T.-Y. Toxic Shock Syndrome in Children. *Pediatric Drugs* **2005**, *7* (1), 11–25. https://doi.org/10.2165/00148581-200507010-00002.

(128) Tsao, N.; Luh, T. Y.; Chou, C. K.; Wu, J. J.; Lin, Y. S.; Lei, H. Y. Inhibition of Group A Streptococcus Infection by Carboxyfullerene. *Antimicrob Agents Chemother* **2001**, *45* (6), 1788–1793. https://doi.org/10.1128/AAC.45.6.1788-1793.2001.

(129) Biswas, R.; Manley, B. J.; Xiao, L.; Siringan, M. J.; Crichton, R. A.; Stein, J. B.; Dawar, A.; Lee, K. B.; Jin, L.; Li, X.; Zhang, J. Reactive Oxygen Species Scavenging Capacity of Functional Fullerenes in Solution and in Macrophage Cells. *ACS Appl Nano Mater* **2024**, *7* (15), 18036–18044. https://doi.org/10.1021/acsanm.4c03467.

(130) Tsai, M.-C.; Chen, Y. H.; Chiang, L. Y. Polyhydroxylated C60, Fullerenol, a Novel Free-Radical Trapper, Prevented Hydrogen Peroxide- and Cumene Hydroperoxide-Elicited Changes in Rat Hippocampus In-Vitro. *Journal of Pharmacy and Pharmacology* **1997**, *49* (4), 438–445. https://doi.org/10.1111/j.2042-7158.1997.tb06821.x.

(131) Rondags, A.; Yuen, W. Y.; Jonkman, M. F.; Horváth, B. Fullerene C $_{60}$ with Cytoprotective and Cytotoxic Potential: Prospects as a Novel Treatment Agent in Dermatology? *Exp Dermatol* **2017**, *26* (3), 220–224. https://doi.org/10.1111/exd.13172.

(132) Inui, S.; Kokubo, K. *Inhibition of Sebum Production and Propionibacterium Acnes Lipase Activity by Fullerenol, a Novel Polyhydroxylated Fullerene: Potential as a Therapeutic Reagent for Acne Safety Evaluation View Project Radical Scavenging Ability of Fullerene View Project*; 2012. https://www.researchgate.net/publication/233802771.

(133) Inui, S.; Aoshima, H.; Nishiyama, A.; Itami, S. Improvement of Acne Vulgaris by Topical Fullerene Application: Unique Impact on Skin Care. *Nanomedicine* **2011**, *7* (2), 238–241. https://doi.org/10.1016/j.nano.2010.09.005.

(134) Hadad, A.; Azevedo, D. L.; Caetano, E. W. S.; Freire, V. N.; Mendonça, G. L. F.; Neto, P. L.; Albuquerque, E. L.; Margis, R.; Gottfried, C. Two-Level Adsorption of Ibuprofen on C 60 Fullerene for Transdermal Delivery: Classical Molecular Dynamics and Density Functional Theory Computations. *Journal of Physical Chemistry C* **2011**, *115* (50), 24501–24511. https://doi.org/10.1021/jp2066277.

(135) Kazemzadeh, H.; Mozafari, M. Fullerene-Based Delivery Systems. *Drug Discovery Today*. Elsevier Ltd March 1, 2019, pp 898–905. https://doi.org/10.1016/j.drudis.2019.01.013.

(136) Nielsen, G. D.; Roursgaard, M.; Jensen, K. A.; Poulsen, S. S.; Larsen, S. T. In Vivo Biology and Toxicology of Fullerenes and Their Derivatives. *Basic and Clinical Pharmacology and Toxicology*. September 2008, pp 197–208. https://doi.org/10.1111/j.1742-7843.2008.00266.x.

(137) Shah, P.; Lalan, M.; Jani, D. Toxicological Aspects of Carbon Nanotubes, Fullerenes and Graphenes. *Curr Pharm Des* **2020**, *27* (4), 556–564. https://doi.org/10.2174/1381612826666200916143741.

(138) Lichota, A.; Piwoński, I.; Michlewska, S.; Krokosz, A. A Multiparametric Study of Internalization of Fullerenol C60(OH)36 Nanoparticles into Peripheral Blood Mononuclear Cells: Cytotoxicity in Oxidative Stress Induced by Ionizing Radiation. *Int J Mol Sci* **2020**, *21* (7), 2281. https://doi.org/10.3390/ijms21072281.

(139) Bertozzi, C. R.; and Laura L. Kiessling. Chemical Glycobiology. *Science (1979)* **2001**, *291* (5512), 2357–2364. https://doi.org/10.1126/science.1059820.

(140) Cecioni, S.; Oerthel, V.; Iehl, J.; Holler, M.; Goyard, D.; Praly, J. P.; Imberty, A.; Nierengarten, J. F.; Vidal, S. Synthesis of Dodecavalent Fullerene-Based Glycoclusters and Evaluation of Their Binding Properties towards a Bacterial Lectin. *Chemistry - A European Journal* **2011**, *17* (11), 3252–3261. https://doi.org/10.1002/chem.201003258.

(141) Nierengarten, I.; Nierengarten, J. F. Fullerene Sugar Balls: A New Class of Biologically Active Fullerene Derivatives. *Chemistry - An Asian Journal*. John Wiley and Sons Ltd 2014, pp 1436–1444. https://doi.org/10.1002/asia.201400133.

(142) Zhou, S.; Trochimczyk, P.; Sun, L.; Hou, S.; Li, H. Sugar-Functionalized Fullerenes. *Curr Org Chem* **2015**, *20* (14), 1490–1501. https://doi.org/10.2174/1385272820666151207194235.

(143) Mintzer, M. A.; Dane, E. L.; O'Toole, G. A.; Grinstaff, M. W. Exploiting Dendrimer Multivalency To Combat Emerging and Re-Emerging Infectious Diseases. *Mol Pharm* **2012**, *9* (3), 342–354. https://doi.org/10.1021/mp2005033.

(144) Lundquist, J. J.; Toone, E. J. The Cluster Glycoside Effect. *Chem Rev* **2002**, *102* (2), 555–578. https://doi.org/10.1021/cr000418f.

(145) Xu, P.-Y.; Li, X.-Q.; Chen, W.-G.; Deng, L.-L.; Tan, Y.-Z.; Zhang, Q.; Xie, S.-Y.; Zheng, L.-S. Progress in Antiviral Fullerene Research. *Nanomaterials* **2022**, *12* (15), 2547. https://doi.org/10.3390/nano12152547.

(146) Rambaruth, N. D. S.; Dwek, M. V. Cell Surface Glycan–Lectin Interactions in Tumor Metastasis. *Acta Histochem* **2011**, *113* (6), 591–600. https://doi.org/10.1016/j.acthis.2011.03.001.

(147) Rísquez-Cuadro, R.; García Fernández, J. M.; Nierengarten, J.; Ortiz Mellet, C. Fullerene-sp ^{2} -Iminosugar Balls as Multimodal Ligands for Lectins and Glycosidases: A Mechanistic Hypothesis for the Inhibitory Multivalent Effect. *Chemistry – A European Journal* **2013**, *19* (49), 16791–16803. https://doi.org/10.1002/chem.201303158.

(148) Durka, M.; Buffet, K.; Iehl, J.; Holler, M.; Nierengarten, J.; Vincent, S. P. The Inhibition of Liposaccharide Heptosyltransferase WaaC with Multivalent Glycosylated Fullerenes: A New Mode of Glycosyltransferase Inhibition. *Chemistry – A European Journal* **2012**, *18* (2), 641–651. https://doi.org/10.1002/chem.201102052.

(149) Durka, M.; Buffet, K.; Iehl, J.; Holler, M.; Nierengarten, J. F.; Taganna, J.; Bouckaert, J.; Vincent, S. P. The Functional Valency of Dodecamannosylated Fullerenes with Escherichia Coli FimH—towards Novel Bacterial Antiadhesives. *Chemical Communications* **2011**, *47* (4), 1321–1323. https://doi.org/10.1039/c0cc04468g.

(150) Luczkowiak, J.; Muñoz, A.; Sánchez-Navarro, M.; Ribeiro-Viana, R.; Ginieis, A.; Illescas, B. M.; Martín, N.; Delgado, R.; Rojo, J. Glycofullerenes Inhibit Viral Infection. *Biomacromolecules* **2013**, *14* (2), 431–437. https://doi.org/10.1021/bm3016658.

(151) Bosi, S.; Da Ros, T.; Spalluto, G.; Balzarini, J.; Prato, M. Synthesis and Anti-HIV Properties of New Water-Soluble Bis- Functionalized[60]Fullerene Derivatives. *Bioorg Med Chem Lett* **2003**, *13* (24), 4437–4440. https://doi.org/10.1016/j.bmcl.2003.09.016.

(152) van Kooyk, Y.; Geijtenbeek, T. B. H. DC-SIGN: Escape Mechanism for Pathogens. *Nat Rev Immunol* **2003**, *3* (9), 697–709. https://doi.org/10.1038/nri1182.

(153) Ji, X.; Olinger, G. G.; Aris, S.; Chen, Y.; Gewurz, H.; Spear, G. T. Mannose-Binding Lectin Binds to Ebola and Marburg Envelope Glycoproteins, Resulting in Blocking of Virus Interaction with DC-SIGN and Complement-Mediated Virus Neutralization. *Journal of General Virology* **2005**, *86* (9), 2535–2542. https://doi.org/10.1099/vir.0.81199-0.

(154) Geijtenbeek T. B. H. and van Kooyk, Y. DC-SIGN: A Novel HIV Receptor on DCs That Mediates HIV-1 Transmission. In *Dendritic Cells and Virus Infection*; Steinkasserer, A., Ed.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2003; pp 31–54. https://doi.org/10.1007/978-3-662-06508-2_2.

(155) Klimova, R.; Andreev, S.; Momotyuk, E.; Demidova, N.; Fedorova, N.; Chernoryzh, Y.; Yurlov, K.; Turetskiy, E.; Baraboshkina, E.; Shershakova, N.; Simonov, R.; Kushch, A.; Khaitov, M.; Gintsburg, A. Aqueous Fullerene C_{60} Solution Suppresses Herpes Simplex Virus and Cytomegalovirus Infections. *Fullerenes, Nanotubes and Carbon Nanostructures* **2020**, *28* (6), 487–499. https://doi.org/10.1080/1536383X.2019.1706495.

(156) Donskyi, I.; Drüke, M.; Silberreis, K.; Lauster, D.; Ludwig, K.; Kühne, C.; Unger, W.; Böttcher, C.; Herrmann, A.; Dernedde, J.; Adeli, M.; Haag, R. Interactions of Fullerene-Polyglycerol Sulfates at Viral and Cellular Interfaces. *Small* **2018**, *14* (17), 1800189. https://doi.org/10.1002/smll.201800189.

(157) Pochkaeva, E. I.; Podolsky, N. E.; Zakusilo, D. N.; Petrov, A. V.; Charykov, N. A.; Vlasov, T. D.; Penkova, A. V.; Vasina, L. V.; Murin, I. V.; Sharoyko, V. V.; Semenov, K. N. Fullerene Derivatives with Amino Acids, Peptides and Proteins: From Synthesis to Biomedical Application. *Progress in Solid State Chemistry* **2020**, *57*, 100255. https://doi.org/10.1016/j.progsolidstchem.2019.100255.

(158) Wang, L.; Wang, Y.; Hao, J.; Dong, S. Magnetic Fullerene-DNA/Hyaluronic Acid Nanovehicles with Magnetism/Reduction Dual-Responsive Triggered Release. *Biomacromolecules* **2017**, *18* (3), 1029–1038. https://doi.org/10.1021/acs.biomac.6b01939.

(159) Kumar, A.; Rao, M. V.; Menon, S. K. Photoinduced DNA Cleavage by Fullerene–Lysine Conjugate. *Tetrahedron Lett* **2009**, *50* (47), 6526–6530. https://doi.org/10.1016/j.tetlet.2009.09.027.

(160) Shoji, M.; Takahashi, E.; Hatakeyama, D.; Iwai, Y.; Morita, Y.; Shirayama, R.; Echigo, N.; Kido, H.; Nakamura, S.; Mashino, T.; Okutani, T.; Kuzuhara, T. Anti-Influenza Activity of C60 Fullerene Derivatives. *PLoS One* **2013**, *8* (6), e66337. https://doi.org/10.1371/journal.pone.0066337.

(161) Ugbaja, S. C.; Mtambo, S. E.; Mushebenge, A. G.; Appiah-Kubi, P.; Abubakar, B. H.; Ntuli, M. L.; Kumalo, H. M. Structural Investigations and Binding Mechanisms of Oseltamivir Drug Resistance Conferred by the E119V Mutation in Influenza H7N9 Virus. *Molecules* **2022**, *27* (14), 4376. https://doi.org/10.3390/molecules27144376.

(162) Toovey, S.; Rayner, C.; Prinssen, E.; Chu, T.; Donner, B.; Thakrar, B.; Dutkowski, R.; Hoffmann, G.; Breidenbach, A.; Lindemann, L.; Carey, E.; Boak, L.; Gieschke, R.; Sacks, S.;

Solsky, J.; Small, I.; Reddy, D. Assessment of Neuropsychiatric Adverse Events in Influenza Patients Treated with Oseltamivir. *Drug Saf* **2008**, *31* (12), 1097–1114. https://doi.org/10.2165/0002018-200831120-00006.

(163) Kobayashi, T.; Yasuno, T.; Takahashi, K.; Nakamura, S.; Mashino, T.; Ohe, T. Novel Pyridinium-Type Fullerene Derivatives as Multitargeting Inhibitors of HIV-1 Reverse Transcriptase, HIV-1 Protease, and HCV NS5B Polymerase. *Bioorg Med Chem Lett* **2021**, *49*, 128267. https://doi.org/10.1016/j.bmcl.2021.128267.

(164) Chen, Y.; Zhao, D.; Liu, Y. Polysaccharide–Porphyrin–Fullerene Supramolecular Conjugates as Photo-Driven DNA Cleavage Reagents. *Chemical Communications* **2015**, *51* (61), 12266–12269. https://doi.org/10.1039/C5CC04625D.

(165) Tollas, S.; Bereczki, I.; Sipos, A.; Rőth, E.; Batta, G.; Daróczi, L.; Kéki, S.; Ostorházi, E.; Rozgonyi, F.; Herczegh, P. Nano-Sized Clusters of a Teicoplanin ψ-Aglycon-Fullerene Conjugate. Synthesis, Antibacterial Activity and Aggregation Studies. *Eur J Med Chem* **2012**, *54*, 943–948. https://doi.org/10.1016/j.ejmech.2012.06.054.

(166) Ghabdian, Y.; Taheri, A.; Jahanian-Najafabadi, A. Development of Novel Topical Formulation from Fullerene with Antibacterial Activity against *Propionibacterium Acnes*. *Fullerenes, Nanotubes and Carbon Nanostructures* **2021**, *29* (2), 163–173. https://doi.org/10.1080/1536383X.2020.1825388.

(167) Castro, E.; Martinez, Z. S.; Seong, C.-S.; Cabrera-Espinoza, A.; Ruiz, M.; Hernandez Garcia, A.; Valdez, F.; Llano, M.; Echegoyen, L. Characterization of New Cationic *N* , *N* -Dimethyl[70]Fulleropyrrolidinium Iodide Derivatives as Potent HIV-1 Maturation Inhibitors. *J Med Chem* **2016**, *59* (24), 10963–10973. https://doi.org/10.1021/acs.jmedchem.6b00994.

(168) Chun-Xian Du. The Antiviral Effect of Fullerene-Liposome Complex against Influenza Virus (H1N1) in Vivo. *Scientific Research and Essays* **2012**, *7* (6), 706–711. https://doi.org/10.5897/SRE11.1927.

(169) Xu, Y.; Zhu, J.; Xiang, K.; Li, Y.; Sun, R.; Ma, J.; Sun, H.; Liu, Y. Synthesis and Immunomodulatory Activity of [60]Fullerene–Tuftsin Conjugates. *Biomaterials* **2011**, *32* (36), 9940–9949. https://doi.org/10.1016/j.biomaterials.2011.09.022.

(170) Demir, E. Therapeutic Effect of Curcumin and C60 Fullerene against Hyperglycemia-Mediated Tissue Damage in Diabetic Rat Lungs. *J Bioenerg Biomembr* **2021**, *53* (1), 25–38. https://doi.org/10.1007/s10863-020-09861-5.

(171) Hirai, T.; Yoshioka, Y.; Udaka, A.; Uemura, E.; Ohe, T.; Aoshima, H.; Gao, J.-Q.; Kokubo, K.; Oshima, T.; Nagano, K.; Higashisaka, K.; Mashino, T.; Tsutsumi, Y. Potential Suppressive Effects of Two C60 Fullerene Derivatives on Acquired Immunity. *Nanoscale Res Lett* **2016**, *11* (1), 449. https://doi.org/10.1186/s11671-016-1663-7.

(172) Grebowski, J.; Kazmierska, P.; Litwinienko, G.; Lankoff, A.; Wolszczak, M.; Krokosz, A. Fullerenol C60(OH)36 Protects Human Erythrocyte Membrane against High-Energy Electrons.

Biochimica et Biophysica Acta (BBA) - Biomembranes **2018**, *1860* (8), 1528–1536. https://doi.org/10.1016/j.bbamem.2018.05.005.

(173) Vesnina, L. É.; Mamontova, T. V; Mikitiuk, M. V; Bobrova, N. A.; Kutsenko, L. A.; Iaroshenko, G. A.; Kaĭdashev, I. P. [Fullerene C60 Exhibits Immunomodulatory Activity during Adjuvant-Induced Arthritis in Rats]. *Eksp Klin Farmakol* **2012**, *75* (8), 15—20. https://doi.org/europepmc.org/abstract/MED/23012990.

(174) Sosnowska, M.; Kutwin, M.; Koczoń, P.; Chwalibog, A.; Sawosz, E. Polyhydroxylated Fullerene C60(OH)40 Nanofilms Promote the Mesenchymal–Epithelial Transition of Human Liver Cancer Cells via the TGF-B1/Smad Pathway. *J Inflamm Res* **2023**, *16*, 3739–3761. https://doi.org/10.2147/JIR.S415378.

(175) Ryan, J. J.; Bateman, H. R.; Stover, A.; Gomez, G.; Norton, S. K.; Zhao, W.; Schwartz, L. B.; Lenk, R.; Kepley, C. L. Fullerene Nanomaterials Inhibit the Allergic Response. *The Journal of Immunology* **2007**, *179* (1), 665–672. https://doi.org/10.4049/jimmunol.179.1.665.

(176) Dellinger, A. L.; Cunin, P.; Lee, D.; Kung, A. L.; Brooks, D. B.; Zhou, Z.; Nigrovic, P. A.; Kepley, C. L. Inhibition of Inflammatory Arthritis Using Fullerene Nanomaterials. *PLoS One* **2015**, *10* (4), e0126290. https://doi.org/10.1371/journal.pone.0126290.

(177) Piotrowski, P.; Klimek, K.; Ginalska, G.; Kaim, A. Beneficial Influence of Water-Soluble PEG-Functionalized C60 Fullerene on Human Osteoblast Growth In Vitro. *Materials* **2021**, *14* (6), 1566. https://doi.org/10.3390/ma14061566.

(178) Parimi, J. L.; Sadhu, S.; Mukherjee, S.; Bhati, S.; Manchikanti, P.; Dhara, S. Potentialities of Nanomedicine and Nanocarriers for Infectious Disease Treatment. In *Nanotechnology for Drug Delivery and Pharmaceuticals*; Elsevier, 2023; pp 165–185. https://doi.org/10.1016/B978-0-323-95325-2.00022-5.

(179) Dugan, L. L.; Tian, L.; Quick, K. L.; Hardt, J. I.; Karimi, M.; Brown, C.; Loftin, S.; Flores, H.; Moerlein, S. M.; Polich, J.; Tabbal, S. D.; Mink, J. W.; Perlmutter, J. S. Carboxyfullerene Neuroprotection Postinjury in Parkinsonian Nonhuman Primates. *Ann Neurol* **2014**, *76* (3), 393–402. https://doi.org/10.1002/ana.24220.

(180) Wu, H.; Liao, H.; Li, F.; Lee, J.; Hu, P.; Shao, W.; Li, X.; Ling, D. Bioactive ROS-scavenging Nanozymes for Regenerative Medicine: Reestablishing the Antioxidant Firewall. *Nano Select* **2020**, *1* (3), 285–297. https://doi.org/10.1002/nano.202000021.

(181) Azizi-Lalabadi, M.; Hashemi, H.; Feng, J.; Jafari, S. M. Carbon Nanomaterials against Pathogens; the Antimicrobial Activity of Carbon Nanotubes, Graphene/Graphene Oxide, Fullerenes, and Their Nanocomposites. *Adv Colloid Interface Sci* **2020**, *284*, 102250. https://doi.org/10.1016/j.cis.2020.102250.

(182) Polidori, M. C.; Griffiths, H. R.; Mariani, E.; Mecocci, P. Hallmarks of Protein Oxidative Damage in Neurodegenerative Diseases: Focus on Alzheimer's Disease. *Amino Acids* **2007**, *32* (4), 553–559. https://doi.org/10.1007/s00726-006-0431-x.

(183) Butowska, K.; Kozak, W.; Zdrowowicz, M.; Makurat, S.; Rychłowski, M.; Hać, A.; Herman-Antosiewicz, A.; Piosik, J.; Rak, J. Cytotoxicity of Doxorubicin Conjugated with C60 Fullerene. Structural and in Vitro Studies. *Struct Chem* **2019**, *30* (6), 2327–2338. https://doi.org/10.1007/s11224-019-01428-4.

(184) Youn, Y. S.; Kwag, D. S.; Lee, E. S. Multifunctional Nano-Sized Fullerenes for Advanced Tumor Therapy. *J Pharm Investig* **2017**, *47* (1), 1–10. https://doi.org/10.1007/s40005-016-0282-8.

(185) Mehra, N. K.; Jain, A. K.; Nahar, M. Carbon Nanomaterials in Oncology: An Expanding Horizon. *Drug Discov Today* **2018**, *23* (5), 1016–1025. https://doi.org/10.1016/j.drudis.2017.09.013.

(186) Grebowski, J.; Kazmierska, P.; Krokosz, A. Fullerenols as a New Therapeutic Approach in Nanomedicine. *Biomed Res Int* **2013**, *2013*, 1–9. https://doi.org/10.1155/2013/751913.

(187) Cai, X.; Hao, J.; Zhang, X.; Yu, B.; Ren, J.; Luo, C.; Li, Q.; Huang, Q.; Shi, X.; Li, W.; Liu, J. The Polyhydroxylated Fullerene Derivative C60(OH)24 Protects Mice from Ionizing-Radiation-Induced Immune and Mitochondrial Dysfunction. *Toxicol Appl Pharmacol* **2010**, *243* (1), 27–34. https://doi.org/10.1016/j.taap.2009.11.009.

(188) Ershova, E. S.; Sergeeva, V. A.; Chausheva, A. I.; Zheglo, D. G.; Nikitina, V. A.; Smirnova, T. D.; Kameneva, L. V.; Porokhovnik, L. N.; Kutsev, S. I.; Troshin, P. A.; Voronov, I. I.; Khakina, E. A.; Veiko, N. N.; Kostyuk, S. V. Toxic and DNA Damaging Effects of a Functionalized Fullerene in Human Embryonic Lung Fibroblasts. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* **2016**, *805*, 46–57. https://doi.org/10.1016/j.mrgentox.2016.05.004.

(189) Xiao, L.; Takada, H.; Maeda, K.; Haramoto, M.; Miwa, N. Antioxidant Effects of Water-Soluble Fullerene Derivatives against Ultraviolet Ray or Peroxylipid through Their Action of Scavenging the Reactive Oxygen Species in Human Skin Keratinocytes. *Biomedicine & Pharmacotherapy* **2005**, *59* (7), 351–358. https://doi.org/10.1016/j.biopha.2005.02.004.

(190) Fernandes, N. B.; Shenoy, R. U. K.; Kajampady, M. K.; DCruz, C. E. M.; Shirodkar, R. K.; Kumar, L.; Verma, R. Fullerenes for the Treatment of Cancer: An Emerging Tool. *Environmental Science and Pollution Research* **2022**, *29* (39), 58607–58627. https://doi.org/10.1007/s11356-022-21449-7.

(191) Cheng, G.; Liu, Y.; Ma, R.; Cheng, G.; Guan, Y.; Chen, X.; Wu, Z.; Chen, T. Anti-Parkinsonian Therapy: Strategies for Crossing the Blood–Brain Barrier and Nano-Biological Effects of Nanomaterials. *Nanomicro Lett* **2022**, *14* (1), 105. https://doi.org/10.1007/s40820-022-00847-z.

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