

A Review of the Latest Developments and Trends in Biosensors Based on Carbon Nanotubes for Use in Medical Diagnosis

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Recent days, there have been notable advancements in the field of nanotechnology for various applications. Carbon nanotubes (CNTs) are materials originating from graphite sheets, these graphite layers resemble an indestructible hexagonal mesh structure that is constantly rolled up, with carbon molecules appearing at the apexes of the hexagonal structures. The single-walled carbon nanotubes, double-walled carbon nanotubes, and multi-walled carbon nanotubes are distinguished by the number of carbon layers they contain. The commonly used techniques for creation of CNTs is chemical vapor deposition, electric arc deposition, and laser deposition method. The distinctive qualities of CNTs are high flexibility, and greater chemical inertness. The CNTs are widely used for water purification, medication delivery, and sensing. These materials to make it different molecules or antigens is made possible by surface functionalization, and these are directed towards target cells for immunological therapeutic impact.

Keywords: Antibacterial; Biosensors; Carbon nanotubes; Drug target; Drug delivery.

Nanostructured materials, which form the basis of nanotechnology, are gaining attention in the sector. Nanomaterials are smaller than 100 nm. Access to a wide range of novel magnetic, electrical, mechanical, and optical properties is made possible by this diverse collection of materials. Among the promising class of nanomaterials are nanotubes. Carbon nanotubes are currently by far the most important group, despite the fact that numerous other nanotubes based on boron and molybdenum have been widely

reported. One or more are ranging in diameter of nano-meters, are found within carbon nanotubes. Iijima¹ early experimental observation of CNTs using TEM, subsequent gives the situation enabling the synthesis of significant amounts of CNTs. One way to think of carbon nanotubes is as cylindrically rolled-up graphite sheets. CNTs have a diameter of roughly 100 nm.²

Three distinct techniques like arc discharge, laser ablation, and chemical vapor deposition can be used to create CNTs. The high

temperature (>3000 °C) required to evaporate carbon atoms into a plasma and generate both SWCNTs and MWCNTs is used in the arc discharge process. While MWCNTs does not require the presence of a catalytic agent, individual SWCNTs synthesis necessitates the presence of a catalytic agent. The high converting ratio and high level of purity for the final goods are guaranteed by the graphite purity.

Khan *et al.*³ successfully synthesized carbon nanotube (CNTs) to create nanostructured brushes. In order for cross-linking properties, the oleic acid was used for functionalized CNTs after being salinized using (3- aminopropyl) triethoxysilane, great properties, unique electrical architectures are just a few of the exceptional physical and chemical qualities that CNTs display. With the high usefulness of these CNT, the Scientists are very interest. CNT are utilized for a variety of purposes, like biomolecules, drugs, specific organs, as well as in biosensor analysis and diagnostics.

This paper reviews the various clinical uses of CNTs like biosensors, drug targeting and illness diagnostics. The applications of electrochemical, DNA-based, piezoelectric, and gas sensors are briefly described. There is also discussion of some of CNTs' antifungal and antibacterial properties.

Biomedical applications of CNTs

Because of their many beneficial qualities, which include being higher biocompatible over another materials, having speed moment of electron transfer kinetics. Additionally, they have metallic and semi-conductive qualities that make them a good material for different uses. Additionally, CNTs are important in the development of sensors that can identify different harmful germs and aid in cancer curation. CNTs exhibit a variety of antibacterial properties.^{4,5} Fig. 1 indicated the various synthesis methods of CNTs. Below is a brief discussion of each of these CNT applications is shown in Fig. 2.

Sensors based on CNTs

The CNTs are very useful for many biosensor uses because they have many great qualities for helping to immobilize proteins, a large surface area. MWCNTs are very hopeful for use in biosensors because they can help proteins stick to surfaces while keeping their natural activity.⁶

Saxena and Srivastava⁷ explained in their book chapter, the CNT based gas and vapour sensors response faster and monitors industrial safety in chemical, pharmaceutical, and stable sensor for industries, environmental monitoring, biomedicine, homeland security, and many other areas. Kumar *et al.*⁸ explained in their book, the CNT based chemiresistive sensors have been frequently used in different government and public sectors to detect the toxic and inflammable substances due to their high sensitivity and low operating temperature. MWCNTs integration in biosensor assembly is provided in Fig. 3.

Electrochemical biosensor

Electrochemical biosensors are self-contained devices that are built in. Biological recognition elements (bio-receptors) are linked to electrode, it turns to recognise into an understandable electrical signal. Because they are specific, quick, portable, and cheap⁹, biosensors open up a lot of interesting possibilities for screening in the emergency room, monitoring at the bedside, or self-testing at home. Electrochemical biosensors can be broken down into three groups: amperometric, potentiometric, and conductometric.¹⁰

These days, an electrochemical sensor is developed using an insulating base with an electrode coating on its surface.¹¹. Nanoscale CNTs exhibit a variety of enhanced properties, making them very suitable for the creation of electrochemical biosensors. Advances in this discipline have continuously surfaced during the last two centuries. Screen-printed carbon electro transducers (SPCEs) were transformed using MWCNTs, which had superior qualities to naked SPCEs. CNT exhibits remarkable properties when combined with other materials, such as polymers and nanoparticles, which further distinguishes and advances the material. Using an electroactive adducts, Beden *et al.*¹² created electrochemical sensor for dopamine analysis at subnanomolar levels. The MWCNTs/Au were mixed for sensor to increase their behaviour. When the electrode was altered using nanohybrids, the sensors responded more effectively. This demonstrated a low recognition limit, an excellent wide linear range. Fig. 4 is the schematic representation of electrochemical biosensor.

Using MWCNTs on the glassy carbon electrode (GCE) surface, Gutierrez *et al.*¹⁴ showed

to detect albumin, glucose, and amino acids both qualitatively and quantitatively. The limit at which their probe could detect glucose (Gutierrez *et al.*¹⁴). By using functionalized MWCNTs in sensing, Liu *et al.*¹⁵ have able to decrease the fabrication time and enhance the detection limit of sensing. Mercapto- α -cyclodextrin structure was created by Kan *et al.*¹⁶ and anchored onto MWCNTs. The sensor's low detection limit, high sensitivity, and selectivity all demonstrated strong analytical performance. Quercetin was detected using the sensor that was constructed. Using anchoring nanocomposites as an electron transfer interface, Palisoc *et al.*¹⁷ created a very sensitive nanosensor. MWCNT and Ag nanoparticles are the nanocomposites utilized here. In addition to the nanocomposite, a strong interface was developed using nafion membrane. The sensor was used to find heavy metals in vegetable samples, including cadmium and lead. Heavy metal traces in actual samples can be detected by the developed sensor.

Using amine-functionalized MWCNTs, Revathi *et al.*¹⁸ created nonenzymatic based electrochemical sensor. Hydrogen peroxide was determined selectively using a variety of amine forms. The results demonstrated that the various types of amine functionalization have a significant impact on how well a biosensor function. The signal acquisition modules process data received from the transducer and display the results. A schematic of this procedure is shown in Fig. 5.¹⁹

MWCNTs/Cu-Ni nanosensor was created by Wang *et al.*²⁰ to detect two N_2 bases. In an actual sample sensor was perfectly used to identify both bases. Ahammad *et al.*²¹ created a MWCNT sensor with lead pencil to detect hydroquinone and catechol at the same time. The sensor was used to analyse actual samples. It was discovered that the sensor had good repeatability and reproducibility. The developed sensor uses pencil graphite, which is significantly less expensive than glassy carbon electrode (GCE), in place of GCE.

A nickel-anchored MWCNT-based sensor was created by Wang *et al.*²² to detect phenol. The electroless plating technique was used to fix the nickel onto the MWCNT. In actual sample analysis, the sensor demonstrated exceptional stability, repeatability, sensitivity, and selectivity.

A bilirubin sensor based on MWCNT was independently developed by Thangamuthu

*et al.*²³. The graphene-based sensor outperformed the MWCNT-modified SPE electrode in terms of sensitivity, linear range, and detection limit. By using the specially constructed sensor in blood data for inspection of bilirubin, sensor's feasibility is confirmed. Using nafion iconic membrane prevented the interference. Rahmawati *et al.*²⁴ created an electrochemical sensor creating Fe and MWCNT from iron dust. Sonochemical technique using an ultrasonic horn was employed to create the nanocomposite from iron sand. The viability of using nanocomposites in the design of electrochemical biosensors was determined by a number of investigations. The synthesized nanocomposite demonstrated superior electron transfer kinetics and a wide surface area, according to all studies. Consequently, it is simple to develop an electrochemical biosensor using the produced nanocomposite.

A pencil graphite electrode-based nanosensor was described by Sevgi Guney *et al.*²⁵. MWCNTs and polymer, specifically meldonium imprinted polymer, were used to modify the electrode. Meldonium might be detected by the designed sensor. By contrasting the analytical outcomes of MWCNTs and p-MWCNTs, they were able to verify that the produced sensor's high sensitivity and specificity are made possible by the use of p-MWCNT. The sensor was used in actual samples to identify meldonium at trace levels in human urine samples. According to the comparison analysis, the created nanosensor outperforms the current biosensors in terms of quick reaction and convenience of use.

A nanosensor using MWCNT and cobalt phthalocyanine (CoPc) on a pencil graphite electrode was created by Laís Sales Porto *et al.*²⁶. In the pharmaceutical industry, the developed sensor was used to determine pyridoxine effectively. It was discovered that the sensor has great selectivity, quick reaction, ease of preparation, and ease of use in the pharmaceutical sector. The created sensor may turn out to be the most effective substitute for measuring vitamin B6 levels. Eshaghi *et al.*²⁷ created biosensor for detection of the anti-cancer medications Erlotinib HCl (ETHC) and CPT (capecitabine) on the surface of PGE using MWCNT and polyurethane as a nanocomposite. For both medications, it was discovered that the sensor had a low detection limit up to the molar

range. Aptamer was coupled with nanocomposites in an electrochemical nanosensor created by Liu *et al.*²⁸ to detect α -estradiol with specificity and sensitivity. The used nanocomposites were carbon nanotubes and gold nanoparticles, which serve as an immobilization matrix and a sensing interface for the biorecognition component, or aptamer. To measure cholesterol, Basu *et al.*²⁹ developed a nanosensor through Poly-L-Lysine-MWCNTs mounted on graphene. The minuscule amounts of cholesterol in femtomolar can be detected by the sensor.

In order to monitor the humidity level, Kim *et al.*³⁰ created a nanosensor based on carbon nanotubes (CNTs) embellished on Ag electrode. Humidity-sensor, core shell materials were used, the humidity level was also ascertained by measuring the resistance. High electrical efficiency was demonstrated by the designed sensor, which was independent of frequency and voltage. Chokkareddy *et al.*³¹ created electrochemical-sensor employing CuO and MWCNTs. Furthermore, docking, redox, and nucleophilic investigations were carried out. The coffee sample's chlorogenic acid was detectable by the sensor. In order to determine the catechol, resorcinol, and dihydroxybenzene isomers simultaneously, Yang *et al.*³² created CNT electrode, and they improved the created interface's conductivity. The three analytes' detection limits fall within the micromolar range. The created nanosensor demonstrated remarkable stability, anti-interference capabilities, and reproducibility. The analytes in actual samples can be detected by the nano-sensor. Using electrodes modified by carbon nanotubes, Shetty *et al.*³³ developed biosensor. Methdilazine (MDH), an antihistamine medication, was determined electrochemically using impassive sensor modified with MWCNT in phosphate buffer solution (PBS) at pH 9.0. Several voltammetric approaches were used to examine the effects of concentration, metal ions, excipients, scan rate, pH, accumulation time, and other factors on the MDH voltammetric behavior. A very low detection limit value between $0.1 \times 10^{-7} \text{ M}$ and $0.3 \times 10^{-6} \text{ M}$ was discovered. It was possible to identify the amount of methdilazine in urine and other samples using the sensor's exceptional response and quick results.

The sensor for identifying mefenamic acid and flufenamic acid was created by Shetty *et al.*³⁴. In order to create RuTiO₂/MWCNTs-CPE electrode

identification and measurement of flufenamic acid (FFA) and mefenamic acid (MFA) medications, a mixture of ruthenium-doped TiO₂ and MWCNTs. Very low quantity of 0.68 nM for FFA and 0.45 nM for MFA were displayed by sensor. Using MWCNT on carbon paste electrode adorned with bismuth nanoparticles, Manasa *et al.*³⁵ recently created electro-chemical sensor for sensitive and specific measurement of gallic acid at neutral pH. Gallic acid was successfully extracted in clove and green trees, with a detection of $1.6 \times 10^{-7} \text{ M}$, prepared sensor demonstrated a broad linear dynamic range. Perfect detection, under neutral pH were only a few advantages of the developed sensor. Cetirizine (CTZ) was measured electrochemically utilizing a carbon sensor made of MWCNTs and Ru-TiO₂ nanoparticles. Voltammetry methods like square wave voltammetry, and cyclic voltammetry are used to electrochemically analyse CTZ in order to quantify the heterogeneous rate constant and the amount of proton transfer in the oxidation (Fig. 6).

Piezoelectric sensor

By utilizing MWCNT's electromechanical characteristics, Khan *et al.*³⁶ created polydimethyl

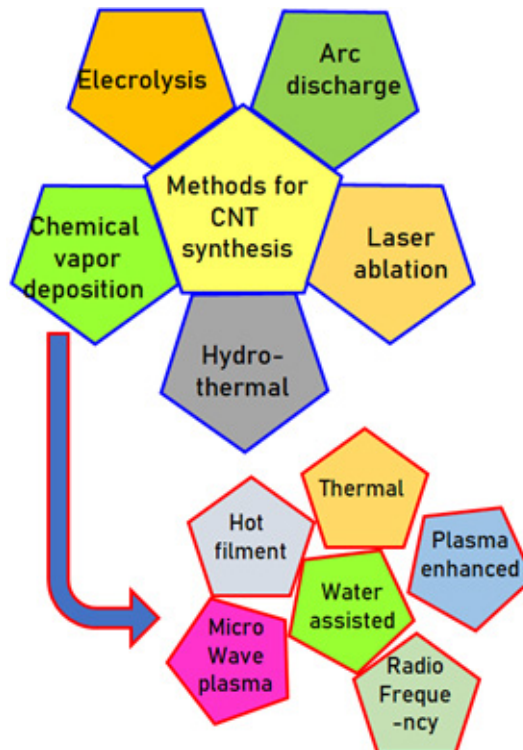


Fig. 1. Various synthesis methods of CNTs

siloxane (PDMS) sensor. Furthermore, SEM studies indicates the spray coating approach can produce a homogenous and compact network of CNTs. When creating stretchable sensors, compactness and homogeneity are crucial. Ali *et al.*³⁷ developed piezoresistive sensor using graphene, CNT, and graphene-CNT composites. The sensitivity and the percentage drop in resistance were found to be higher than those of pure graphene but lower than those of pure CNTs. Park *et al.*³⁸ prepared the same wearable sensor based on MWCNT using PDMS. They have used this sensor for two purposes, (1) strain sensing for tissue characterisation, and (2) robotic hand development. Additionally, they discovered that the sensor is very specific, biocompatible, simple to manufacture, small, flexible, and affordable.

Stretchable sensors based on MWCNTs were created by He *et al.*³⁹ using thermoplastic urethane as the substrate. Wet spinning was used to produce the fibers. Since the stretchy sensor is

built into gloves and bandages, it has been used to measure a wide range of human functions. The outcomes are outstanding and could be used in strain-based textile sensors of the future. Another stretchy sensor based on MWCNTs on PDMS substrate was created by Ramalingame *et al.*⁴⁰ and demonstrated the capacity to sense pressure directly without the need for deformation materials. They are perfect for gait monitoring in insole applications because of their excellent flexibility and compactness. Fig. 7 shows (a) a schematic of the steps used to make Ag NP/MWCNT sensors, (b) a photograph of the samples that were made, and (c) optical pictures of the samples that were made⁴². The steps used for making of Ag/MWCN strain sensors are shown in Fig. 8.⁴³

Gas sensor

Different gas sensors are developed to fulfil the needs of a variety of applications, including industrial, environmental, and medical. The use of nanomaterials as sensing interfaces in

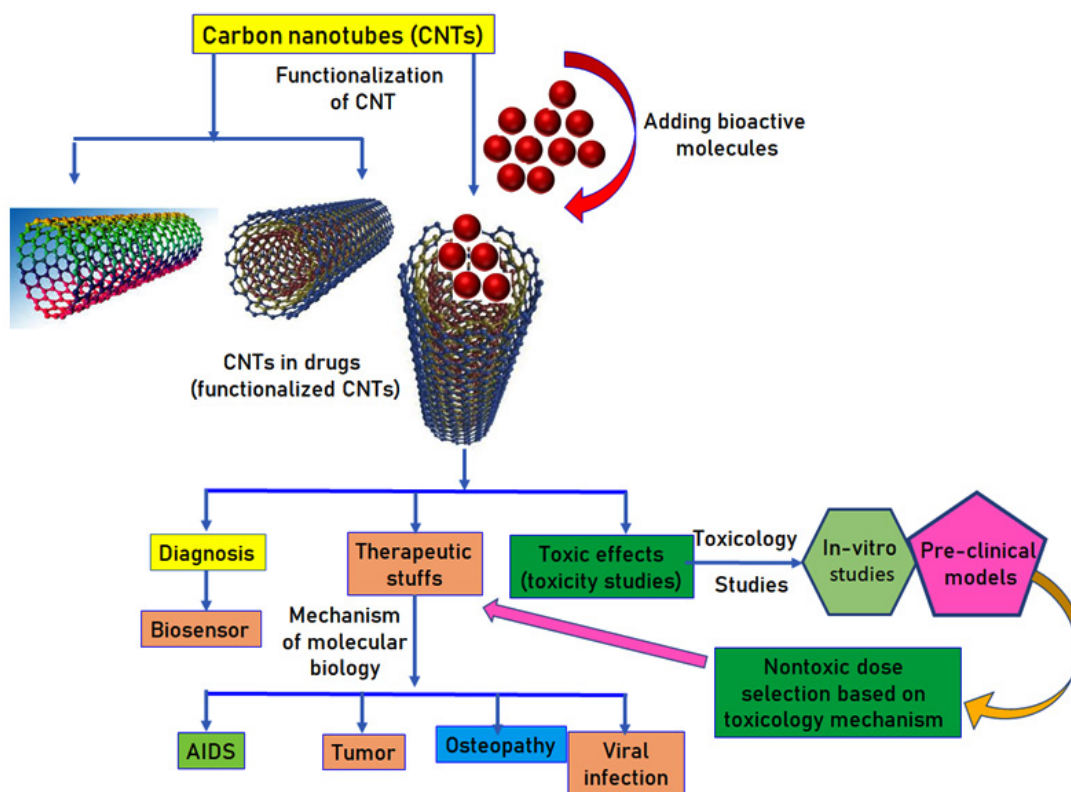


Fig. 2. Different biomedical application of CNTs.

gas sensors provides a clear benefit in terms of both selectivity and sensitivity. For the detection of ammonia gas, Hieu *et al.*⁴⁴ created sensor for the purpose of identification of NH_3 gas. Even at room temperature, the sensor's responsiveness was significantly improved. The ammonia gas sensor was created by Abdulla *et al.*⁴⁵ by immobilizing polyaniline polymer using functionalized MWCNTs. When compared to the unaltered electrode, the created sensor demonstrated good analytical performance in terms of reaction time,

recovery, and stability. A field-effective transistor-type sensor based on MWCNTs was described by Kim *et al.*⁴⁶ for the selective detection of NO_x . Gold was placed over the formed surface after MWCNTs were secured to the silicon wafer's surface. At various gate source voltages, the proposed sensor has the inherent ability to detect NO_x gas.

The sensor's working principle is based on resistivity, that decreases as absorbed NO_x gas increases. In order to detect methane gas, Cismaru *et al.*⁴⁷ created radio frequency gas sensor

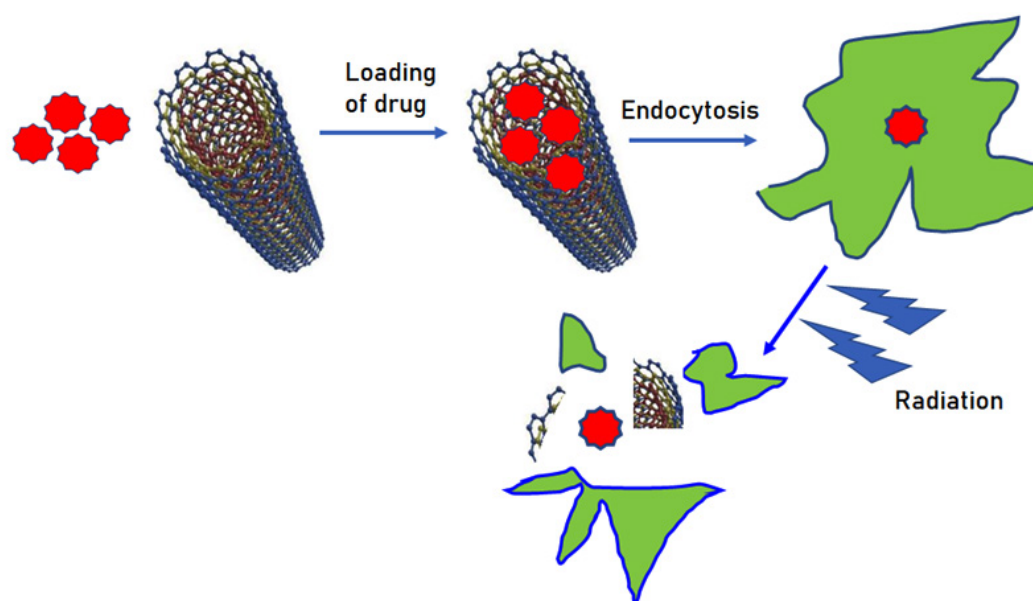


Fig. 3. MWCNTs integration in biosensor

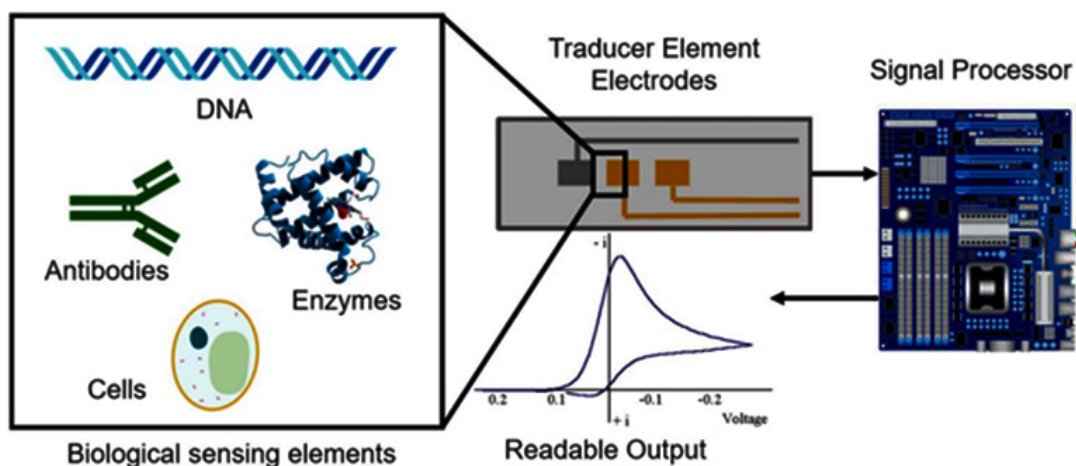


Fig. 4. Diagram of electrochemical biosensor, transducer, and signal processor.¹³

through electro magnetic resonator with a couple made of MWCNT. They demonstrated results using a small device size that clearly demonstrate MWCNT's capabilities in a sensing application. Dilonardo *et al.*⁴⁸ took advantage of MWCNT's gas sensing capabilities. In this work, the surface of Ag and palladium were coated with MWCNTs. A variety of contaminants could be detected by the manufactured sensor. In comparison to gold nanoparticles, the MWCNTs that were adorned on surface of palladium demonstrated superior sensing behaviour.

Sensor for detection of NH_3 was created by Hussein *et al.*⁴⁹, and used OH-MWCNT as sensor, the sensor evaluates capacity to detect ammonia gas selectively at room temperature. For ammonia sensing, Mahajan *et al.*⁵⁰ used ZnO, MWCNT, and reduced graphene oxide. Another functional membrane that is a part of the sensing platform is polypyrrole. ZnO serves as a filler in this method. When it came to ammonia gas, the designed

sensor was extremely sensitive. MWCNTs/NOA 63 energizing them using supercapacitor, Song *et al.*⁵¹ created NO_2 gas detection system. Sensor was able to adhere to skin imperfections. Consequently, sensor may evolve wearable gadget which detects NO_2 gas. George *et al.*⁵² developed Ag/MWCNTs that were anchored onto poly (3,4 ethylene dioxythiophene) and polystyrene.

Duong *et al.*⁵³ developed MWCNT/ WO_3 sensor for identification of NH_3 gas. Hydrothermal method was used to create the nanocomposites for ammonia gas detection. The CNT/ WO_3 electrode exhibited gas sensing capabilities. Kim *et al.*⁵⁴ proposed gas detection system with H_2SO_4 , and NH_3 all at once. MWCNTs were tethered to a dye-functionalized matrix for the sensor. Fig. 9 indicates the schematic diagram of working principle of gas sensor.⁵⁵ Fig. 10 gives an information about the gas-sensing mechanism of the SWCNT-based sensors depicting the chemisorption of the analyte molecules.⁵⁶ Fig 11 provides the gas-sensing

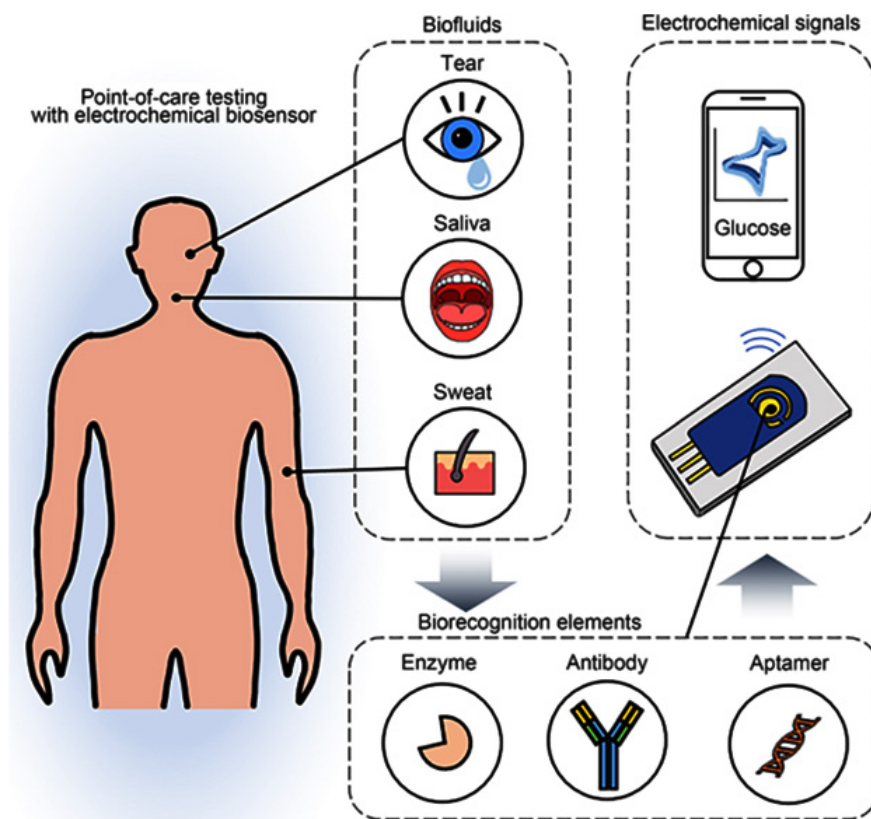


Fig. 5. The diagram of electrochemical systems.¹⁹

mechanism along with the energy band diagram showing the adsorption of ammonia gas leading to corresponding charge transfer.⁵⁷

Drug targeting

Drug targeting and controlled release are two applications for multiwalled carbon nanotubes. Potent therapeutic drug is administered to a specific area for a prolonged amount of time, this is known as targeted drug delivery. With the

hydrophobic properties the bloodstream remains long time, carbon nanotubes are utilized in drug delivery. Because carbon nanotubes can control a variety of stimuli, including magnetic, electric, and temperature changes, among others, they have been used for targeted and controlled medication delivery.

Meherjuoi *et al.*⁵⁸ examined the different nanotubes used to administer the medication

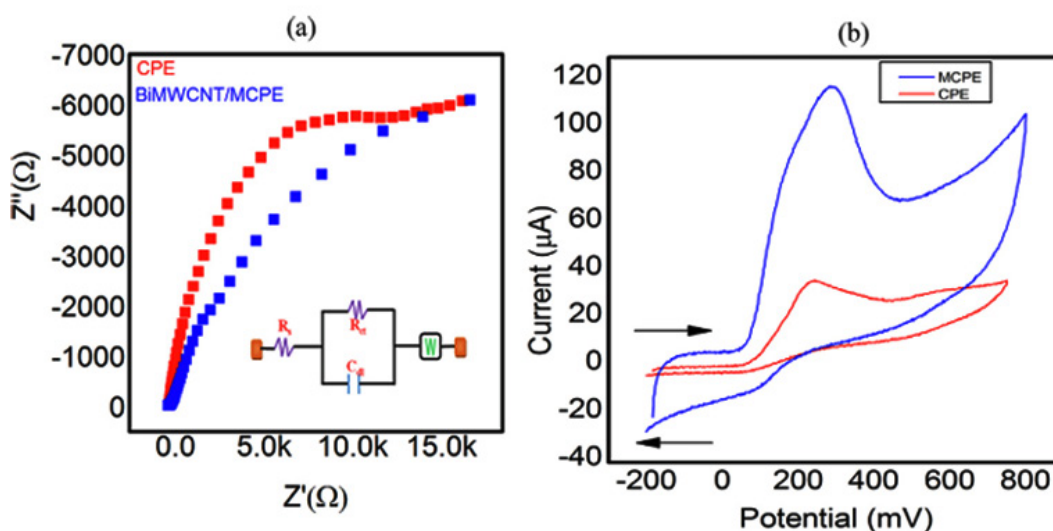


Fig. 6. (a) Nyquist plot, and (b) cyclic voltammograms plot.³⁵

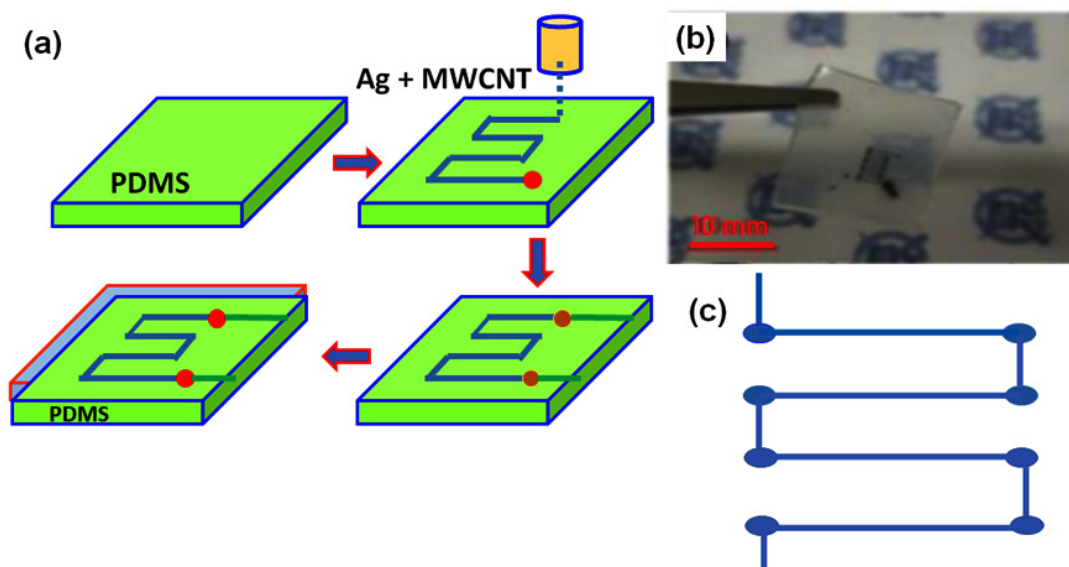


Fig. 7. (a) Fabrication process of Ag/MWCNT sensor, (b) picture, (c) optical images.⁴²

cisplatin. By using Ag stimulator in CNTs generates a molecular dynamic phenomenon. The function of MWCNT and pH in drug administration of duxorubicin was explained by Seyfoori *et al.*⁵⁹ The medicine was administered to U-87 glioblastoma cells using a created nanohybrid technology, and it was discovered that this method limited the growth of cancer cells. In order to access electrical properties, Im *et al.*⁶⁰ created a transdermal patch employing polymer-MWCNT. Through the influence of heating, the scientists have used perfect capabilities of CNTs to expedite medical causes. Mandal *et al.*⁶¹ evaluated the effectiveness of biodegradable, biocompatible nanocomposite hydrogel and MWCNT for the sustainability of diclofenac sodium. A better

alternative to the transdermal formulation was the polymer composite of MWCNTs, which produces diclofenac sodium. An electro responsive polymer-MWCNT hybrid was developed by Servant *et al.*⁶² For the assessment of the controlled released profile, they have used the hydrophilic drug model of radiolabelled sucrose applied with an electric field.

Cancer diagnosis and treatment

Wang *et al.*⁶³ found that, in comparison to larger multiwalled carbon nanotubes (39.5 nm average diameter), narrow multiwalled nanotubes (09.2 nm average diameter) had a better affinity of tissue, particularly for non-reticular endothelium tissues. Through the release method of enzymatic breakage in invitro breast

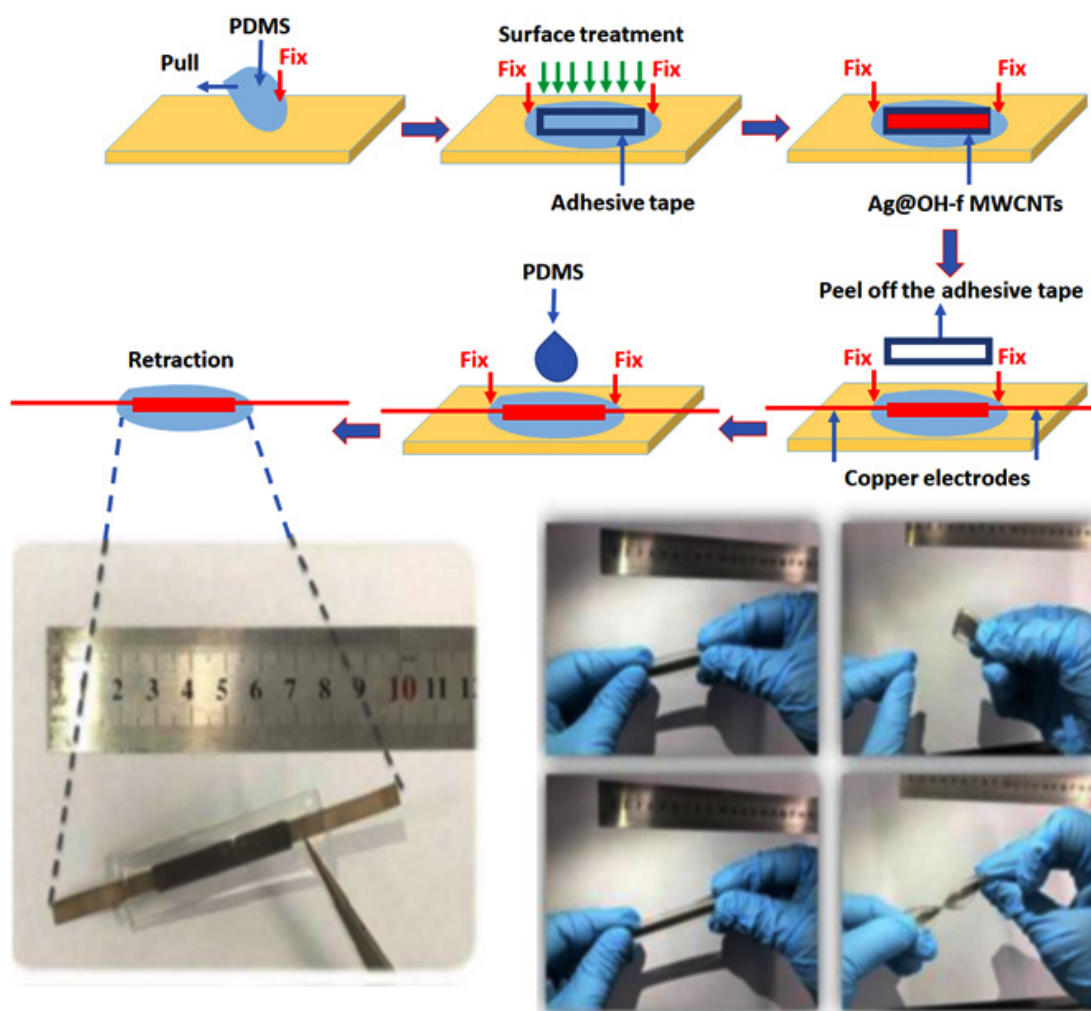
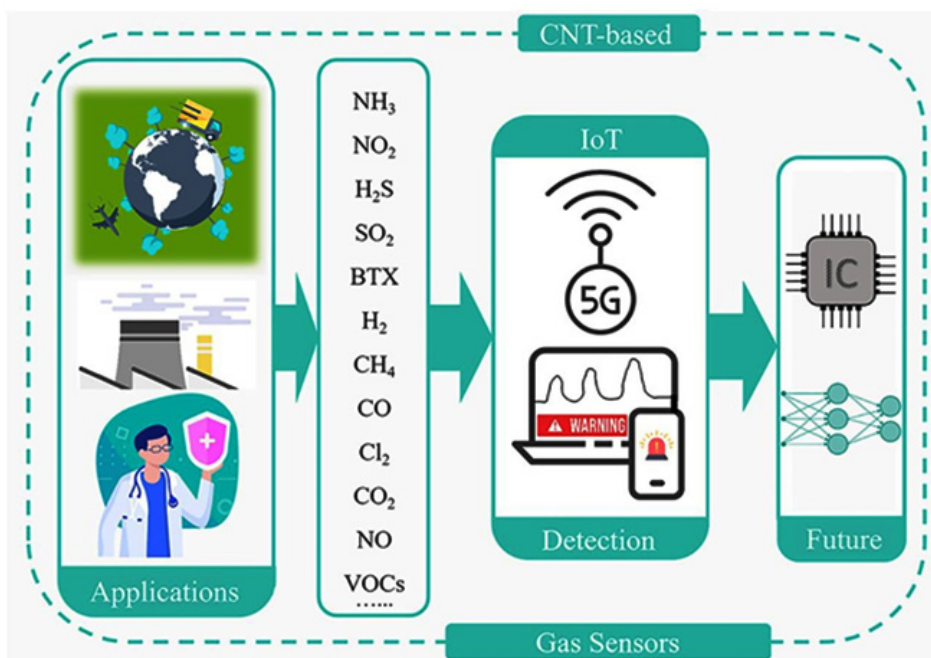
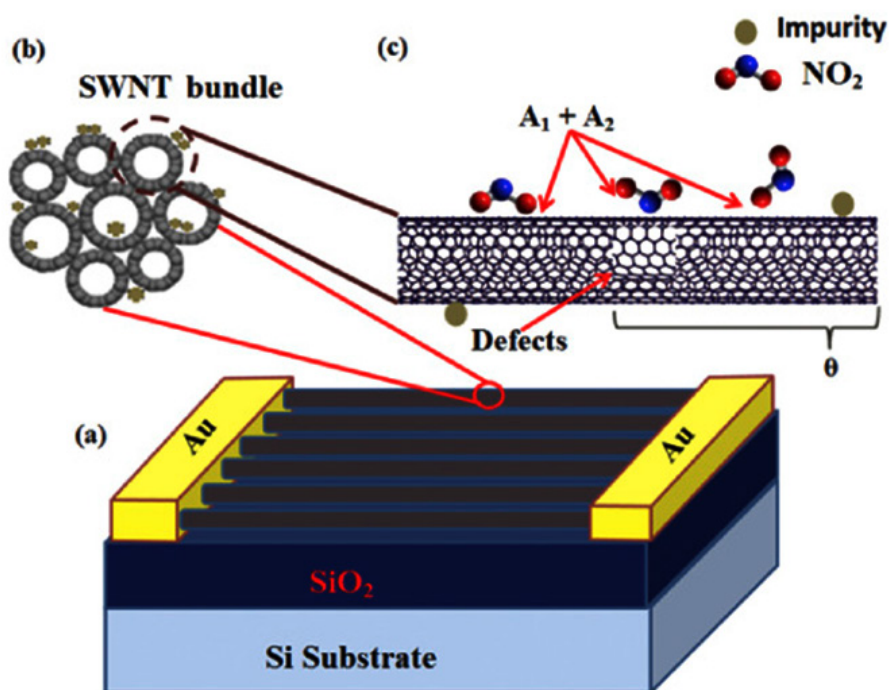


Fig. 8. Flow of the fabrication process of the Ag/MWCNT based strain sensors.⁴³

Fig. 9. Working principle of gas sensor.⁵⁵Fig. 10. SWCNT-based gas sensors.⁵⁶

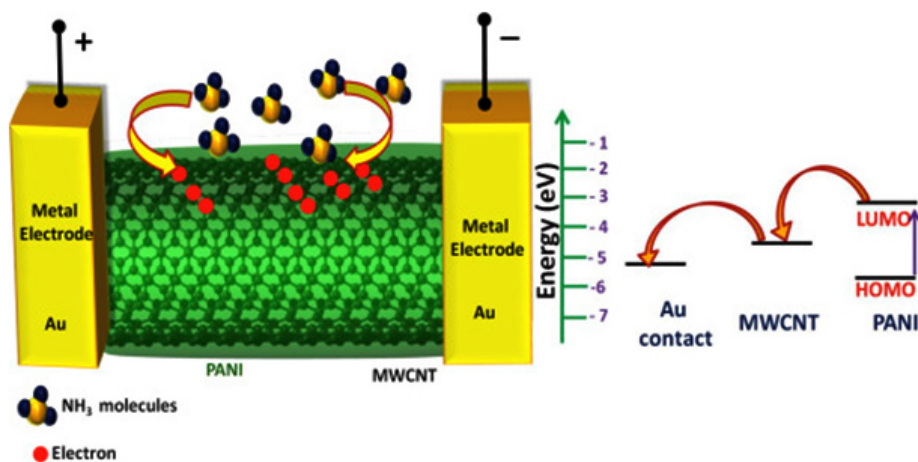
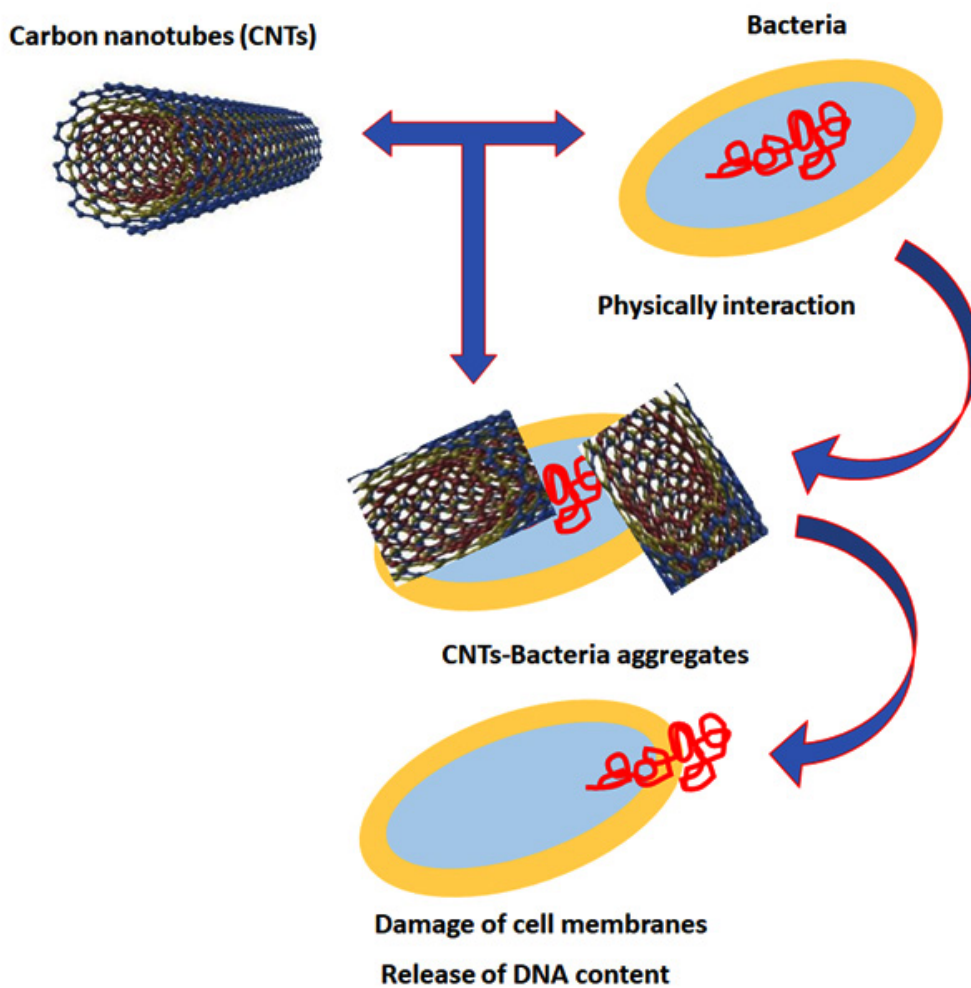
Fig. 11. NH_3 Gas identification procedure.⁵⁷

Fig. 12. Schematic representation of antibacterial activity of CNTs.

cells, Samori *et al.*⁶⁴ administered the anticancer medication methotrexate with the use of MWCNT. The doxorubicin (DO_x) was delivered at lesser pH using dendrimer-MWCNT. Proteins, and DNA can be carried by MWCNT since these macromolecules are readily broken-down by enzymes found inside or outer surface of CNT. Guo *et al.*⁶⁵ created carrier cationic in calutumor xenografts, apoptotic siRNA over polo-like kinase (siPLK1) is administered by direct intertumoral injections using multiwalled carbon nanotubes (NH3p).

Antibacterial activity of CNTs

MWCNTs can demonstrate their antibacterial properties in a number of ways. However, the precise mechanism behind MWCNTs' antibacterial properties is still unknown. First, a tight contact with the membrane surfaces causes a change in the integrity of the cell membrane.⁶⁶ Second, causing the production of ROS, which eventually results in DNA damage and cell death.⁶⁷ Third, the antibacterial properties of MWCNTs may potentially be significantly influenced by impurities.

Furthermore, derivatives that have been studied have reportedly demonstrated greater action against positive gram bacteria relatively less activity over negative gram.⁶⁸ The antibacterial action of SWCNTs in conjunction with iron oxides over *E. coli* bacteria has been documented through Engel *et al.*⁶⁹ The antibacterial effectiveness against several bacteria, including *Shigella flexneri*, *Salmonella* species, *E. coli* examined by membrane filters treated with carbon nanotubes.⁷⁰ Additionally, it has been shown by Rananga and Magadzu⁷¹ that MWCNT treated with Ag has increased antibacterial behaviour. The antibacterial properties of Ag- Fe_3O_4 -MWCNT have been shown by Bhaduri *et al.*⁷²

Zhu *et al.*⁷³ conducted a research to show that MWCNT with a carboxyl group had antibacterial action. There have been reports of antibacterial action against *S. aureus* and *E. coli* using a polyaniline/graphene/carbon nanotube nanocomposite. MWCNT shown superior antibacterial activity compared to pristine MWCNTs, according to Zardini *et al.*⁷⁴ Both four-gram positive and four-gram negative bacteria were shown to be susceptible to their antimicrobial

activity. MWCNTs were utilized by Vecitis *et al.*⁷⁵ to filter the water in order to eliminate bacteria and destroy viruses.

The antibacterial properties of carbon nanoparticles are demonstrated in Fig. 12. After entering the bacterial nuclei, MWCNTs interact with the DNA to form ROS, which eventually causes cell death. The antibacterial property is enhanced by the combined action of MWCNTs and chitosan. The antibacterial properties of MWCNTs are also significantly influenced by their aspect ratio and orientation.⁷⁶

CONCLUSION

The structure of CNT is cylindrical, the MWCNT are having large strength and large surface area. Since carbon nanotubes have demonstrated special benefits, they are serving vehicle for efficient movement of biomolecules like lectins, antibiotics substances. Carbon nanotube-based biosensors have demonstrated improved sensitivity, repeatability, dependability, and affordability. The application of MWCNTs in biosensing technology increases its sensitivity, specificity, and suitability for use in cancer treatment and illness detection. Numerous analytes, including pyridoxine, dopamine, ascorbic acid, uric acid been detected using MWCNT biosensors, additionally, it demonstrated antibacterial properties. Therefore, in order to improve human health more examinations are required for effective utilization of CNT sensors.

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Conflict of interest

The author(s) do not have any conflict of interest.

Data Availability

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not Applicable

Author Contributions

Lingala Syam Sundar: Conceptualization, Methodology, Writing – Original Draft; Madhuri Desai: Data analysis, Data Collection; Nandala Thippa Reddy Ravi Kumar: Writing – Review & Editing.

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