International Journal of Experimental Research and Review (IJERR)

ISSN: 2455-4855 (Online) ***Review Article***
Received: 25th June, 2021; **Accepted:** 24th July, 2021; **Published:** 30th August, 2021
DOI: https://doi.org/10.52756/ijerr.2021.v25.002

Graphene: the magic carbon derived biological weapon for human welfare

#Arnob Chakrovorty[1], #Banani Bhattacharjee[1], Rishita Dey[1,2], Asmita Samadder[1]* and Sisir Nandi[2]

[1]Cytogenetics and Molecular Biology Laboratory, Department of Zoology, University of Kalyani, Kalyani, Nadia-741235, India; [2]Department of Pharmaceutical Chemistry, Global Institute of Pharmaceutical Education and Research (Affiliated to Uttarakhand Technical University), Kashipur-244713, India

 # Equal authorship

***Corresponding Author:** asmita.samadder@gmail.com

Abstract

Graphene plays an etiologic role for the new edge drug designing in the area of therapeutic management of myriads of diseases. Several researchers have experimentally validated the use of graphene and its derivative either in chemical form or in their nano-form to provide a longer and better life to the patients suffering from cancer, diabetes, etc. In this review, we have tried to focus on the literature to understand molecular docking-based role of graphene as an anti-cancer and anti-diabetic therapeutic tool which is very pertinent in the extensive arena of pharmacology, from pharmacovigilance to pharmacodynamics and kinetics, that ameliorates and concords with the modern scientific approaches of disease management.

Keywords: Anti-cancer, anti-diabetic, graphene, graphene oxide (GO), therapeutic management.

Introduction

Carbon is an element of life. Carbon exists in many different forms in nature, either in a free state, as an element, or existing in a combined state with other elements, as a compound. With an electronic configuration of 2, 4, carbon can form 4 covalent bonds with other element and also with itself, i.e., with other carbon atoms, forming long-chain carbon compounds, termed as catenation, which augments an uniqueness to its elemental property (Walker and Thrower, 1975; Ergun, 1968). The physical forms or allotropes of Carbon are categorised into two categories; first are the crystalline forms, where the substances have a regular geometric shape, which includes diamond and graphite; and second are the amorphous forms where the structural arrangement have

no definite geometric shape, which includes, coal, lampblack and soot (Walker and Thrower, 1975; Ergun, 1968).

The three most common allotropes of carbon, coal, graphite and diamond, has been known to exist with a substantially vast spectra of application for a considerable period of time, until the notable discovery by Kroto et al. in 1985 where they observed in several experiments that some of the mass spectrum of laser-sublimated graphite samples displayed a peak at 720, which indicated that the sample must be holding 60 carbon-atoms structure (720/12 D 60), i.e., C60 molecule. By validating their results, they successfully added a third member to the family of carbon allotropes, which had 60 carbon atoms and was named as Buckminsterfullerene or simply fullerene (Smalley, 1997; Kademani et al., 2002; Ahmad, 1999; Kroto et al., 1985). In laboratory condition, the C_{60} molecule formed by laser vaporization of graphite showed to possess a hollow sphere structure, with an approximate diameter of 0.7 nm, made of 12 pentagonal and 20 hexagonal rings of carbon with structural similarities to that of graphite, differing by the presence of the pentagonal rings (Smalley, 1997; Kademani et al., 2002; Ahmad, 1999; Dresselhaus et al., 1996). Fullerenes also exist in higher carbon numbers like C_{70}, C_{84}, C_{90}, C_{94}etc, all of which possess 12 pentagonal rings and varying numbers of hexagonal rings which obeys Euler's Theorem, defining that each closed-caged geometry can be composed of a vast number of hexagonal rings but must hold exactly 12 pentagonal rings in order to implement curvature essential to lock the caged structure (Diederich and Whetten, 1992; Diederich et al., 1991; Choudhary, 2012).

While the discoverer of the next interesting member of the carbon allotrope family remains a part of controversy in scientific literature (Monthioux and Kuznetsov, 2006), the discovery itself gained much attention. The 3D (three-dimensional) tube structure formed by the polymerization of Cycloparaphenylene (Carbon nanoring) came into existence and was righteously named as carbon nanotubes (CNT). These CNTs have a diameter ranging from less than 1 nm up to 70 nm, but their lengths are in order of several microns (Iijima, 1991; Kuila et al., 2012; Delgado et al., 2008; Salvetat et al., 1999).

With the proposed hypothesis of Landau and Peierls, it was believed for over 70 years that strictly 2D (two-dimensional) crystals were thermodynamically unstable and could not exist (Peierls, 1935; Landau, 1937) and that the melting temperature of thin films decrease with decreasing thickness, and they become unstable and segregate into smaller fragments (Venables et al., 1984; Evans et al., 2006). Discoveries of carbon allotropes so far, strictly abided by the proposed hypothesis until 2004, when the experimental discovery of graphene flaunted the common wisdom (Novoselov et al., 2004). Experiment validated that these one atom thick 2D sheet of graphite derivative was not only thermodynamically stable but also possess robust crystal quality (Novoselov et al., 2004).

Graphene: a therapeutic weapon

The structure of graphite involves planes of hexagonal carbon rings that form stacking sheets one on top of the other with Van Der Wall forces that holds those stacked sheets together yet allows them to slide over each other (Walker and Thrower, 1975; Ergun, 1968; Pereira et al., 2009). Graphene may thus be defined as the single-layer derivative

of graphite that is one atom thick, which also shows the similar sp^2 hybridization state of each carbon atom which has an additional p-orbital that can form weak delocalized bonds as exhibited by graphite (Walker and Thrower, 1975; Geim and Novoselov, 2010). So graphite may also be defined as stacked layers of graphene sheets held together by Van Der Wall forces. So the question that arises is, what would be the considerations regarding the differentiation of classification of 2D structure from 3D graphite? Electronic structure rapidly evolves with the number of layers, so the 3D limit of graphite is approached at 10 layers (Partoens and Peeters, 2006). The production of graphene involves two processes which often involves either chemical vapour deposition of hydrocarbons on metal substrates, or by thermal decomposition of Silicone Carbide (SiC) substrates (Land et al., 1992; Nagashima et al., 1993; Forbeaux et al., 1998; Berger et al., 2004; Berger et al., 2006).

Graphene oxide (GO) as a potential component in enzyme-assisted and non-enzyme assisted glucose biosensor systems

Graphene oxide (GO) has been taken into consideration due to its unique characteristic of being amphiphilic in nature, having aqueous surface, exceptional surface features, capable of fluorescence quenching and has Raman's scattering property (Chung et al., 2013). Synthesis of GO using Hummer's method includes graphite oxidation which is done by combining graphite, potassium permanganate, and sulfuric acid and mixing the solution followed by sonication producing graphite salts (Gao, 2015). These salts of graphite functions as the GO precursor producing GO which after undergoing thermal and chemical reduction, forms graphene analogue (Park et al., 2009). These chemical procedures extend the interlayer space and base plane (Compton et al., 2010). The following part of this study reviews the beneficial role of graphene, in the arena of drug delivery and the development of biosensors with relevance to requisites of modern pharmacology.

Diabetes mellitus has become a significant health issue, mainly among adults. It is a type of disorder or disease where the blood glucose level rises at an abnormal rate due to deficiency in the secretion of insulin. It is accompanied with thirst and urination at a frequent rate along with several other difficulties including renal failure, diabetic neuropathy and blindness (Jiang et al., 2011).

Therefore, consistent monitoring and detection of blood glucose level of diabetic patients needs to be an important part of diabetes management regime, for which several biosensors are commercially available. Enzymatic biosensors were found to have several drawbacks, including immobilization and quick inactivation of enzyme, which led to the development and more preferred usage of non enzymatic biosensors where glucose oxidation occurs directly with enzyme-free electrode (Jiang et al., 2010; Bo et al., 2011; Wang et al., 2010; Chen et al., 2010; Zhu et al., 2009) (Fig. 1).

Despite the toxicological effect, graphene and its derivatives have therapeutic efficiencies by behaving as a platform for preparing nanoparticles using Au, Pt etc., for non-enzymatic detection of glucose (Krishnan et al., 2019). Molecular docking, a computational method to analyse the binding of ligand with its target, confirms the interaction between GO with several substrates including glucose oxide and glucose oxidase, an enzyme which catalyzes the oxidation of β-D-glucose into H_2O_2 which further auto-catalyzes to yield two free

electrons that are utilised for the detection of glucose in the sample. The docking approach in an enzyme-assisted biosensor system also reveals that graphene oxide interacts with the enzyme glucose oxidase, at a site away from the active binding pocket of β-D glucose, thus behaving as a non-competitive ligand that is meant to function as glucose oxide immobilizer. GO is surrounded by a large number of amino acids such as Arg37, Glu40, Asn41, Asp134, Asn135, Ala138, Tyr139, Leu141, Gln142, Arg145, Ser163, Gly166, Val167, Asn168, Gly169, Arg239, Asp573, Leu576, and Glu577 forming hydrophobic interactions which proves it to have a very strong binding affinity with enzyme. Besides counting its enzymatic mechanism, the docking platform also shows its non-enzymatic approach, which exhibits the propensity of GO to directly interact with glucose having almost the same binding affinity to that of the enzyme. These potential abilities of GO widens its spectra of application, both in enzyme-assisted and non-enzyme assisted biosensor systems, further disclosing its promising role to act as an upgraded “fine-tailored” biosensor of glucose (Sumaryada et al., 2019).

Graphene oxide (GO) as a modified tool for drug delivery in biological systems

The potential role of GO nanoparticles in context of delivery of anticancer drugs has been elucidated by recent researches, where GO has been found to selectively target the tumor cells other than interfering with normal cells. Therefore, a drug delivery system using nanoparticles is nowadays more preferred as it turns down the toxicity and side effects as well as ameliorates functional effectiveness (Torchilin, 2014). Thus, loading of anti-cancer drugs on the surface of GO either covalently or non-covalently produces a better drug delivery activity compared to the prodrug used alone (Kim et al., 2013). On account of the fact that targeting cancer cells with two drugs yield better result compared to one, as single-use of drug needs large quantity to be delivered which will further adverse the situation causing cytotoxic effects, an upgraded way has been approved by researchers where GO has been consecutively loaded with two effective anti-cancer drugs- Cisplatin (Pt) and Doxorubicin (DOX) (Pei et al., 2020). The loading of two different drugs was only made possible due to its large surface area (Bitounis et al., 2013). Cisplatin, used for the treatment of solid cancers like ovarian cancer, cervical cancer, breast cancer, bladder cancer which mainly acts by hampering the repair mechanism of DNA and kills the cell by inhibiting synthesis and Doxorubicin, another drug that is known to cure breast cancer, bladder cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia functions by acting as an intercalating agent and causing double-stranded break and inhibiting replication (Fig. 2).

The preparation of the co-drug delivery system is made by loading PEG (Polyethylene glycol) through covalent modification, then further loading Pt covalently on the PEG functionalized GO followed by non-covalently attaching DOX that forms π- π interactions. When both the drugs are incorporated into PEG functionalized GO, the increased efficacy of the chemotherapeutic treatment is being observed, which makes GO an important candidate to be used in drug delivery system. The results of fluorescence imaging study of CAL-27 cancer cell line incubated separately with both PEG-GO-DOX-Pt and DOX-Pt showed the appropriate delivery of both the drugs in tumour concentrated zone when GO is used as a carrier.

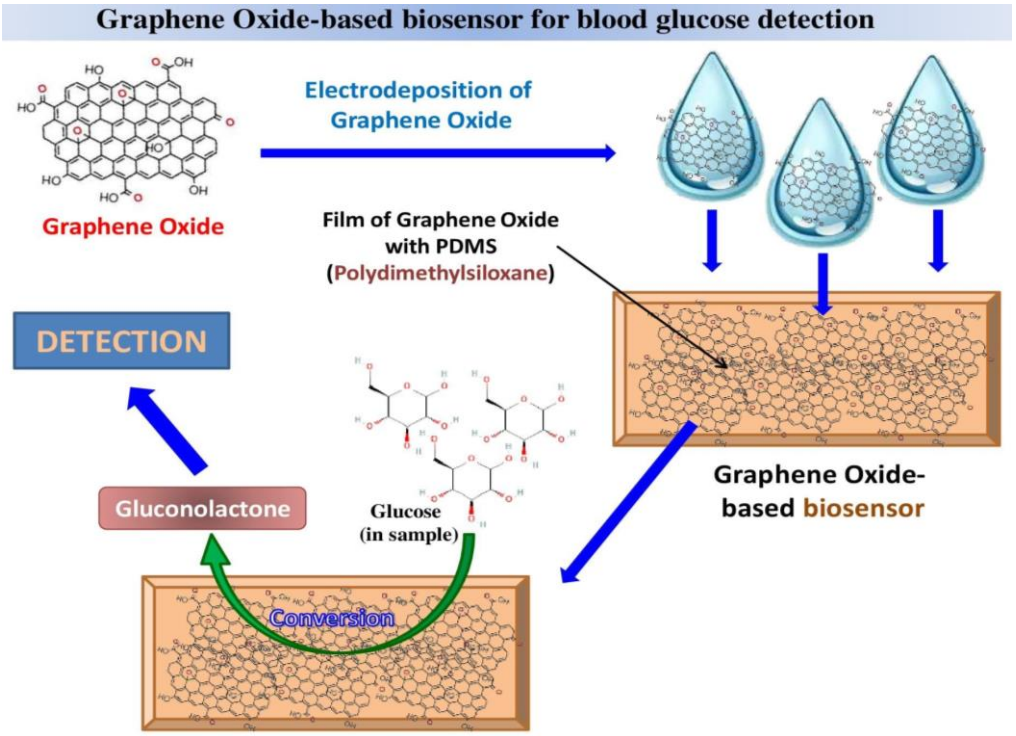

Figure 1. Graphene Oxide-based biosensor for blood glucose detection (non-enzymatic approach).

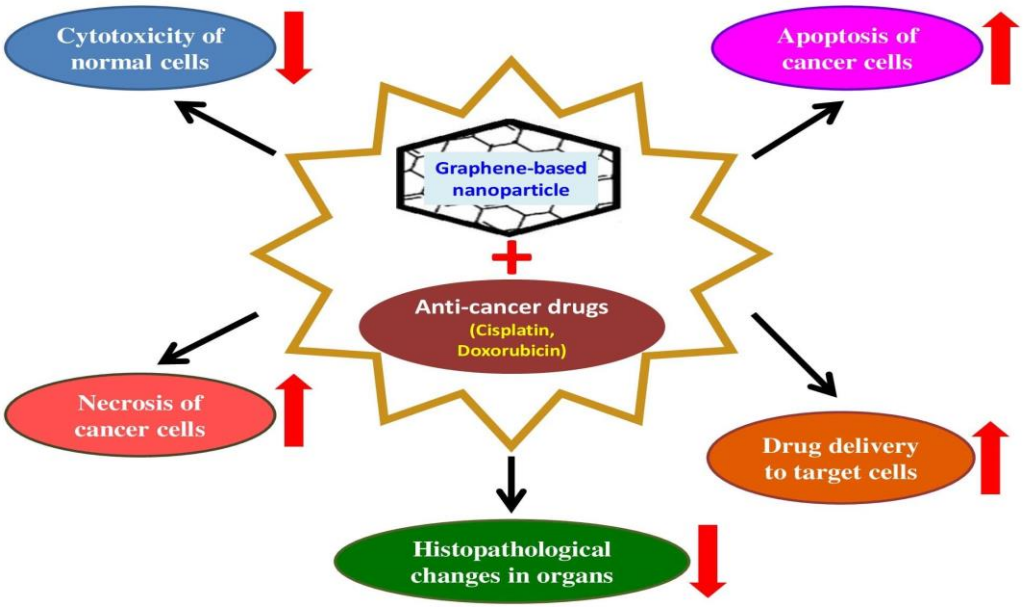

Figure 2. Diagrammatic representation of the benefits associated with the therapeutic usage of graphene-based nano-particles for administration of anti-cancer drugs.

According to apoptotic assay, negligible cell death or apoptotic effect was found in vitro when using only PEG-GO which confirmed the harmless and safe nature of GO nanoparticles in in vitro models. A comparably higher apoptotic and necrotic rate was found in cells incubated with PEG-GO-DOX-Pt that also gives evidence of perfect drug release activity of GO into targeted tumour cells. On the other hand, research related to histopathology showed no significant changes in the histopathological parameters of organs like heart and kidney when using GO as a carrier of dual drugs correlated with the drug quantification analysis value, which showed higher concentration of both the drugs into the target region (Pei et al., 2020). Whereas the release of a combination of two drugs in selected tumorigenic region showed reduced body weight and several histopathological changes in spleen and heart toxicity like cardiac dysfunction associated with thickening of heart muscle (Ling et al., 2015; Pan et al., 2014). Quantifiable data in the reviewed studies showed that the level of both the drugs was found to be less, which proves its agglomeration in different regions. The negligible cytotoxic effect, excellent drug delivery potency, and high surface area confirm the safety of using GO in delivering anti-cancer drugs.

Conclusion

Researchers have been continually undergoing to explore different simple as well as safe strategies to cure and heal disorders. The existence of carbon in various allotropes has intrigued scientific minds, and the eventual “quest for more” has led to the discovery and identification of another form called graphene, a derivative of graphite. The synthesis of graphene oxide has gained importance due to its unique physical and chemical properties and has eventually been validated to functional in several pharmacological applications including the arena of analysis and treatment diseases such as diabetes mellitus and different cancers. Our study focuses on graphene oxide due to its unique ability to not only sense glucose levels in a non-enzymatic manner as well as to be able to act as a major vehicle to drive and deliver anti-diabetic drugs but also for its potentiality to deliver the anticancer drugs at proper tumorigenic site which adds up its efficacious role. Therefore, the versatile nature of graphene oxide has gained importance in many fields due to its distinctive properties and remarkable functionality, which would play a beneficial role in the therapeutic management and monitoring of several diseases of humankind.

Acknowledgement

We are grateful to the respective institutes for providing us basic infrastructure.

Conflict of interest

None to declare.

References

Ahmad, S. (1999). Carbon nanostructures fullerenes and carbon nanotubes. *IETE Tech. Rev.* 16(3-4): 297-310.

Berger, C., Song, Z., Li, T., Li, X., Ogbazghi, A. Y., Feng, R. and De Heer, W. A. (2004). Ultrathin epitaxial graphite: 2D electron gas properties and a route toward graphene-based nan-oelectronics. *J. Phys. Chem. B*. 108(52): 19912-19916.

Berger, C., Song, Z., Li, X., Wu, X., Brown, N., Naud, C. and de Heer, W. A. (2006). Electronic confinement and coherence in patterned epitaxial graphene. *Science*. 312(5777): 1191-1196.

Bitounis, D., Ali-Boucetta, H., Hong, B. H., Min, D. H. and Kostarelos, K. (2013). Prospects and challenges of graphene in biomedical applications. *Adv. Mater*. 25: 2258–2268.

Bo, X., Bai, J., Yang, L. and Guo, L.P. (2011). The nanocomposite of PtPd nanoparticles/onion-like mesoporous carbon vesicle for nonenzymaticamperometric sensing of glucose. *Sens. Actuators B: Chem.* 157(2): 662-668.

Chen, X. L., Pan, H. B., Liu, H. F. and Du, M. (2010). Nonenzymatic glucose sensor based on flower-shaped Au@ Pd core–shell nanoparticles–ionic liquids composite film modified glassy carbon electrodes. *Electrochim. Acta*. 56(2): 636-643.

Choudhary, A. K. (2012). Fullerene chemistry an overview.*Ind. J. Res.* 6: 72.

Chung, C., Kim, Y. K., Shin, D., Ryoo, S.-R., Hong, B. H. and Min, D. H. (2013). Biomedical applications of graphene and graphene oxide. *Acc. Chem. Res*. 46(10): 2211–2224.

Compton, O. C. and Nguyen, S.T. (2010). Graphene oxide, highly reduced graphene oxide, and graphene: versatile building blocks for carbon-based materials. *Small.* 6(6): 711–723.

Delgado, J. L., Herranz, M. A. and Martin, N. (2008).The nanoforms of carbon. *J. Mater. Chem.*18 (13): 1417-1426.

Diederich, F. and Whetten, R. L. (1992). Beyond C60: The higher fullerenes. *Acc. Chem. Res*. 25(3): 119-126.

Diederich, F., Ettl, R., Rubin, Y., Whetten, R. L., Beck, R., Alvarez, M. and Koch, A. (1991). The higher fullerenes: isolation and characterization of C76, C84, C90, C94, and C700, an oxide of D5h-C70. *Science.* 252(5005): 548-551.

Dresselhaus, M. S., Dresselhaus, G. and Eklund, P. C. (1996). Science of fullerenes and carbon nanotubes: their properties and applications. Elsevier.

Ergun, S. (1968).Structure of carbon. *Carbon*. 6: 141–159.

Evans, J. W., Thiel, P. A. and Bartelt, M. C. (2006). Morphological evolution during epitaxial thin film growth: Formation of 2D islands and 3D mounds. *Sur. Sci. Rep.* 61(1-2): 1–128.

Forbeaux, I., Themlin, J. M. andDebever, J. M. (1998). Heteroepitaxial graphite on 6H-SiC(0001): Interface formation through conduction-band electronic structure. *Phys. Rev. B*.162: 406-412.

Gao, W. (2015). The Chemistry of Graphene Oxide in Graphene Oxide. Springer, Berlin. Pp. 61–95.

Geim, A. K. and Novoselov, K. S. (2010). The rise of graphene.*In Nanoscience and technology: a collection of reviews from nature journals*. Pp. 11-19.

Iijima, S. (1991).Helical microtubules of graphitic carbon.*Nature*. 354(6348): 56-58.

Jiang, L. C. and Zhang,W. D. (2010).A highly sensitive nonenzymatic glucose sensor based on CuO nanoparticles-modified carbon nanotube electrode. *Biosens. Bioelectron*. 25(6): 1402-1407.

Jiang, X.Y., Wu, Y.H., Mao, X.Y., Cui, X.J. and Zhu,L. D.(2011). Amperometric glucose biosensor based on integration of glucose oxidase with platinum nanoparticles/ordered mesoporous carbon nanocomposite.*Sens. Actuators B: Chem.* 153-158.

Kademani, B. S., Kalyane, V. L. and Kumar, V. (2002). Scientometric portrait of Nobel laureate Harold W. Kroto. *SRELS J. Info. Mana*. 39(4): 409-434.

Kim, H., Lee, D., Kim, J., Kim, T. I. and Kim, W. J. (2013). Photothermally triggered cytosolic drug delivery via endosome disruption using a functionalized reduced graphene oxide. *ACS Nano*. 7: 6735–6746.

Krishnan, S. K., Singh, E., Singh, P., Meyyappan, M. and Nalwa, H. S. (2019).A review on graphene-based nanocomposites for electrochemical and fluorescent biosensors. *RSC. Adv*. 9: 8778-8881.

Kroto, H. W., Heath, J. R., O'Brien, S. C., Curl, R. F. and Smalley, R. E. (1985). C 60: buckminsterfullerene. *Nature*. 318 (6042): 162-163.

Kuila, T., Bose, S., Mishra, A. K.,Khanra, P., Kim, N. H. and Lee, J. H. (2012). Chemical functionalization of graphene and its applications. *Prog. Mater. Sci.* 57(7): 1061-1105.

Landau, L. D. (1937). Zur Theorie der phasenumwandlungen II. *Phys. Z. Sowjetunion.* 11: 26–35.

Land, T. A., Michely, T., Behm, R. J., Hemminger, J. C. and Comsa, G. (1992). STM investigation of single layer graphite structures produced on Pt(111) by hydrocarbon decomposition. *Surf. Sci.* 264(3): 261-70.

Ling, X., Shen, Y., Sun, R., Zhang, M., Li, C., Mao, J., Xing, J., Sun, C. and Tu, J. (2015). Tumor-targeting delivery of hyaluronic acid-platinum(IV) nanoconjugate to reduce toxicity and improve survival. *Polym. Chem-Uk.* 6: 1541–1552.

Monthioux, M. and Kuznetsov, V. L. (2006). Who should be given the credit for the discovery of carbon nanotubes? *Carbon*. 44(9): 1621-1623.

Nagashima, A., Nuka, K., Itoh, H., Ichinokawa, T., Oshima, C. and Otani, S. (1993). Electronic states of monolayer graphite formed on TiC (111) surface. *Surf. Sci*. 291(1-2): 93-98.

Novoselov, K. S., Geim, A. K., Morozov, S. V., Jiang, D. E., Zhang, Y., Dubonos, S. V., Grigorieva, I. V. and Firsov, A. A. (2004) Electric field effect in atomically thin carbon films. *Science*. 306(5696): 666-669.

Pan, D., She, W., Guo, C., Luo, K., Yi, Q. and Gu, Z. (2014). PEGylated dendritic diaminocyclohexyl-platinum (II) conjugates as pH-responsive drug delivery vehicles with enhanced tumor accumulation and antitumor efficacy. *Biomaterials.* 35(38): 10080-10092.

Park, S. and Ruoff, R.S. (2009). Chemical methods for the production of graphenes. *Nat. Nanotechnol.* 4(4): 217–224.

Partoens, B. and Peeters, F. M. (2006). From graphene to graphite: Electronic structure around the K point. *Phys. Rev. B.* 74(7): 075404.

Peierls, R. E. (1935). Quelques proprietes typiques des corpsessolides. *Ann. I. H. Poincare*. 5(3): 177–222.

Pei, X., Zhu, Z., Gan, Z.,Chen, J., Zhang, X., Cheng, X., Wan, Q. and Wang, J. (2020). PEGylated nano-graphene oxide as a nanocarrier for delivering mixed anticancer drugs to improve anticancer activity. *Scientific Reports*. 10(1): 1-15.

Pereira, V. M., Neto, A. C. H. and Peres, N. M. R. (2009).Tight binding approach to uniaxial strain in graphene. *Phys. Rev. B.* 80(4): 045401.

Salvetat, J. P., Briggs, G. A. D., Bonard, J. M., Bacsa, R. R., Kulik, A. J., Stockli, T. N., Burnham, A. and Forro, L. (1999). Elastic and shear moduli of single-walled carbon nanotube ropes. *Phys. Rev. Lett.* 82(5): 944.

Smalley, R. E. (1997). Discovering the fullerenes. *Rev. Mod. Phys.* 69(3): 723.

Sumaryada, T., Muhammad, S. G., Salahuddin, P., Sugianto, A. and Akhiruddin, M. (2019). A Molecular Interaction Analysis Reveals the Possible Roles of Graphene Oxide in a Glucose Biosensor. *Biosensors*. 9(1): 18.

Torchilin, V. P. (2014). Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. *Nat. Rev. Drug. Discov.* 13: 813–827.

Venables, J. A., Spiller, G. D. T. and Hanbucken, M. (1984). Nucleation and growth of thin films. *Rep. Prog. Phys.* 47: 399–459.

Walker, P. L. and Thrower, P. A. (1975) *Chemistry & Physics of Carbon*. CRC Press.

Wang, X., Hu, C. G., Liu, H., Du, G. J., He, X. S. and Xi, Y. (2010). Synthesis of CuO nanostructures and their application for nonenzymatic glucose sensing. *Sens. Actuators B: Chem.* 144(1): 220-225.

Zhu, H., Lu, X. Q., Li, M. X., Shao, Y. H. and Zhu, Z. W. (2009). Nonenzymatic glucose voltammetric sensor based on gold nanoparticles/carbon nanotubes/ionic liquid nanocomposite. *Talanta*. 79(5): 1446-1453.