IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

RECENT ADVANCES IN NANOTECHNOLOGY IN TREATMENT OF CANCER

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ABSTRACT

Nanotechnology advancements are also anticipated to lay the groundwork for the creation of innovative therapies and a broad range of cancer diagnostic techniques.The most often reported cancers were stomach, skin (non-melanoma), and breast (lung, colon, rectum, and prostate instances). The most often utilized conventional anti-cancer treatments, in addition to surgery, are radiotherapy and chemotherapy. These, however, do not differentiate between healthy and cancerous cells. Targeted cancer therapy and additional therapeutic modalities have developed over time. However, each approach has its drawbacks, and the related medical expenses are hefty and have a negative impact on patients' quality of life. The treatment of cancer uses a variety of nanomaterials. Materials with a size of 1–100 nm exhibit unique optical.

KEY WORDS
Nanotechnology, nanoparticle, cancer therapy, cancer, nanomedicine, drug delivery.

INTRODUCTION

CANCER-

Cancer is a widespread, intricate, and diverse illness. With around 9.5 million cancer-related deaths per year, cancer is emerging as a major global source of morbidity and mortality as the population ages [(1).] Therefore, there is an urgent need for research into the development of cancer medicines. The three main cancer treatments—surgery, chemotherapy, and radiotherapy—often result in unfavorable outcomes and adverse effects [(2, 3).] More potent treatments have become available to get around these restrictions as a result of growing oncology research advancements, including immunotherapy, gene therapy, photothermal therapy, photodynamic therapy, chemodynamic therapy, sonodynamic therapy, and nanomaterial-based chemotherapy [(4–9).] Because of its low toxicity, high specificity, and outstanding absorption, nanomaterial-based chemotherapy stands out among them as a possible treatment for cancer [(10).]

Depending on the type of cancer involved, the normal symptoms vary greatly. Some typical signs include:

• A bulge or lump within the body

• Unaccounted-for weight reduction • Fatigue

• Fever

• Sweaty nights

• Constant cough

• Trouble swallowing

• Modifications in bowel or bladder patterns

• Pain, particularly in the joints, bones, or back

• Dizziness

• Unexpected bruising or bleeding

The primary causes of cancer are:

• **Tobacco use :**
which is the greatest factor in cancer deaths. It is responsible for roughly 22% of cancer fatalities.

• Diet and obesity:
Breast, colon, and pancreatic cancer have all been related to obesity and poor diet, respectively.

• **Physical inactivity :**
Excessive inactivity raises the risk of a number of cancers, including breast, colon, and endometrial cancer.

• **Abuse of alcohol:**
Abuse of alcohol raises the chance of developing a number of cancers, including liver, mouth, and throat cancers.

• **Specific infections:**
Some diseases, including hepatitis B and C, Epstein-Barr virus, and human papillomavirus (HPV), can raise the chance of developing cancer.

• **Ionizing radiation exposure:**
Ionizing radiation exposure, such as that from nuclear radiation or X-rays, can raise the chance of developing cancer.

• **Environmental contaminants:**
Asbestos and arsenic are two toxins that might raise the risk of developing cancer.

PRINCIPLES OF NANOTECHNOLOGY

Use of nanotechnology to improve therapeutics is no longer novel, in fact, there has been a steady increase in nanotechnology research as the benefts become more apparent [11, 12]. Currently approved cancer nanomedicines are predominantly liposomal formulations and drug conjugates (protein, polymer, and/or antibody) focused on improving pharmacokinetics and pharmacodynamics (PK/PD) of the free drug and utilizing passive targeting. Tere are many clinical studies currently investigating nanomaterials for therapeutic and diagnostic applications, including imaging modalities [13, 14]. Passive targeting for tumors is based upon the enhanced permeation and retention (EPR) efect, where NPs can preferentially accumulate within tumor [15]. Many tumors have leaky blood vessels with apertures suitable for NPs to pass through and accumulate within the tumor tissue [16]. However, the EPR efect is not the end-all solution: passive targeting does not eliminate drug action in healthy tissues nor the side efects that accompany systemic distribution [17]. Tere are physiological obstacles that prevent NPs from reaching their target, even without a diseased state, and can become even more complex to navigate for cancer patients [18]. Protein and lipid adsorption, blood fow rate, coronas, and phagocytic cells can reduce stability and delivery capability [19–20]. Interstitial pressure and extracellular matrices can also limit access to a tumor [21, 22].

SOME OF THE POTENTIAL BENEFITS OF NANOTECHNOLOGY

1. Medical :-
Nanoparticles can be utilized to diagnose diseases, produce novel medical implants, and deliver medications to specific parts of the body. The way we treat illnesses could be completely changed by this, and millions of people's quality of life could be raised.

2. Power :-
The creation of new, more effective energy sources like solar cells and fuel cells may be facilitated by nanotechnology. This might lessen our dependency on fossil fuels and aid in the fight against climate change.

3. Environmental protection includes :-
New techniques for removing pollution and identifying and monitoring environmental dangers could be developed using nanotechnology. This might aid in preserving our planet's resources.

4. Producation :-
The development of new, stronger, and lighter materials could be facilitated by nanotechnology.

THE FOLLOWING ARE SOME SPECIFIC INSTANCES OF HOW NANOTECHNOLOGY IS BEING APPLIED TO THE CREATION OF NOVEL CANCER TREATMENTS

• Nanocarriers :
Nanocarriers are nanoparticles that can be utilized to more efficiently transport medications to cancer cells. Nanocarriers can be created to deliver medications gradually over time or to target particular cancer cells. This may aid in minimizing the negative consequences of cancer treatment.

• Nanorobots :
These tiny robots can be used to directly kill cancer cells or to deliver medications to cancer cells. Although they are still in the early phases of development, nanorobots have the potential to completely change the way cancer is treated.

• Cancer immunotherapy :
Nanoparticles are being employed to create new cancer immunotherapies. Immunotherapies function by stimulating the body's defenses against cancer cells. Nanoparticles can be utilized to deliver medications or immune cells to cancer cells.

HERE ARE SOME INSTANCES OF HOW NOVEL CANCER DIAGNOSES ARE BEING CREATED USING NANOTECHNOLOGY:

Nanosensors
Naosensors are minuscule instruments that can be used to find cancer cells. It is possible to create nanosensors that can identify particular proteins or chemicals linked to cancer[10,11]. This can assist doctors in making an earlier cancer diagnosis and monitoring the effectiveness of cancer treatment.

Nanoimagery:
Nanoimaging is a method for imaging cancer cells that makes use of nanoparticles. Doctors can use nanoimaging to more clearly see cancer cells and to monitor how the cancer cells are reacting to treatment

ADVANCES IN NANOTECHNOLOGY FOR TARGETED DELIVERY:-

Cancer treatment based on nanomaterials shows advantages over using free drugs, particularly for targeted delivery. Compared to free drugs, targeted delivery exhibits reduced toxicity, decreased degradation, increased half-life, and enhanced capacity [23,24]. Recent advances have been made in nanomaterial-based targeted drug delivery systems, including in active or passive targeting. Active targeting is achieved using antibodies or small moleculeconjugated nanoparticles, whereas passive targeting occurs through enhanced permeability and retention effects. Active targeting displays great potential and acted as an alternative strategy to passive targeting and the ability of tumor localization in active targeting was improved by increased efficiency and retention [25]. Compared with traditional chemical therapies, nanomaterial-based drugs display increased specificity, improved bioavailability, lower cytotoxicity, better loading capacity, and a longer half-life. To date, many nanomaterials for cancer treatment have been developed based on remarkable advances in nanoscience, technology, and cancer pathology. However, few nanomaterial-based drugs have been intensively studied and utilized in clinical practice. Nanomaterials can be broadly classified into several categories are shown in fig 1.

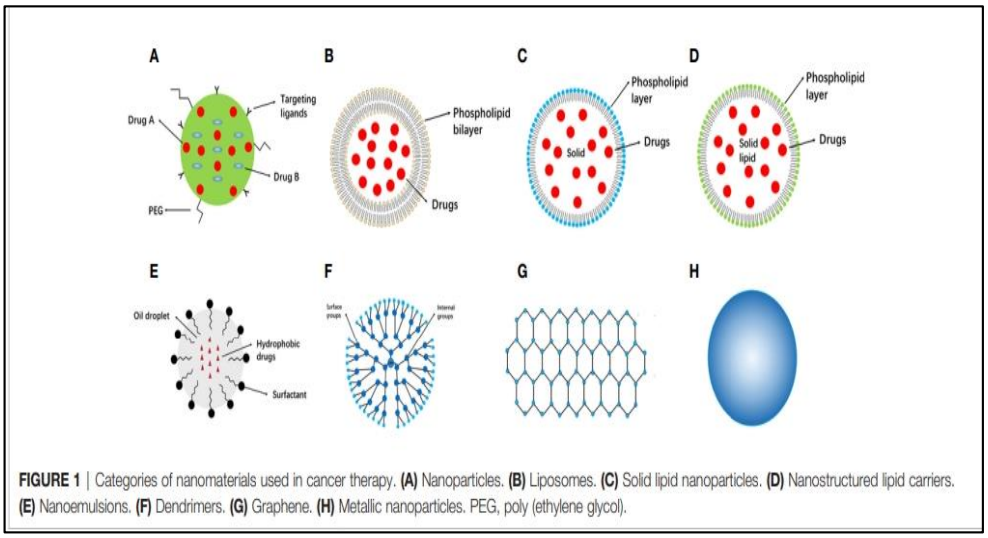

FIGURE 1 | Categories of nanomaterials used in cancer therapy. **(A)** Nanoparticles. **(B)** Liposomes. **(C)** Solid lipid nanoparticles. **(D)** Nanostructured lipid carriers. **(E)** Nanoemulsions. **(F)** Dendrimers. **(G)** Graphene. **(H)** Metallic nanoparticles. PEG, poly (ethylene glycol).

Fig 1 : classification of several categories of nanomaterial.

NANOMATERIALS IN CANCER THERAPY

Several well-studied nanoparticles are listed in Supplementary in above table [26–31]. Chemical drugs can be delivered and sustainably released to target sites by Polymeric nanoparticles (PNPs) (10 to 1000 nm) [32]. Nanoparticle components have olved over the past few decades; they were initially manufactured from non-biodegradable polymers, including polymethyl methacrylate and polyacrylates [33, 34]. Because they cause chronic inflammation and toxicity, one challenge to using these types of PNPs is their timely removal. To overcome this difficulty, biodegradable polymers such as polylactic acid, poly (lactic-co-glycolic acid), and poly (amino acids) have been fabricated [35], which exhibit excellent advantages depending on their structures and properties. PNPs protect drugs from degradation, improve loading ability, and increase stability [36]. However, metal nanomaterials are not considered for cancer treatment because renal and brain toxicity and denaturation of enzymes may be caused by excessive heavy metal element in-take [37, 38].

SOME OF NANOMATERIAL USED IN CANCER THERAPY ARE AS FOLLOW :

A. **MONOCLONAL ANTIBODIES NANOPARTICLES –**

Antibody drug conjugates are created through the integration of mab's and cytotoxic pharmaceuticals to boost the therapeutic potency of anticancer therapies. Depending on the antigens produced in cancer cells, less toxicity and more specificity can be achieved [39]. Several antibody-drug conjugate methods boost therapy efficacy in breast cancer [38,40].

The most well-known and promising kind of mAb treatment for cancer is immune checkpoint blocking is shown in below fig.2. To govern immune cell responses to antigen, immune cell activation and regulation must combine a number of costimulatory and coinhibitory signals [41,42]. Immune checkpoints are inhibitory receptors and pathways that are in charge of self-tolerance and modifying immune responses in response to tissue injury [43].

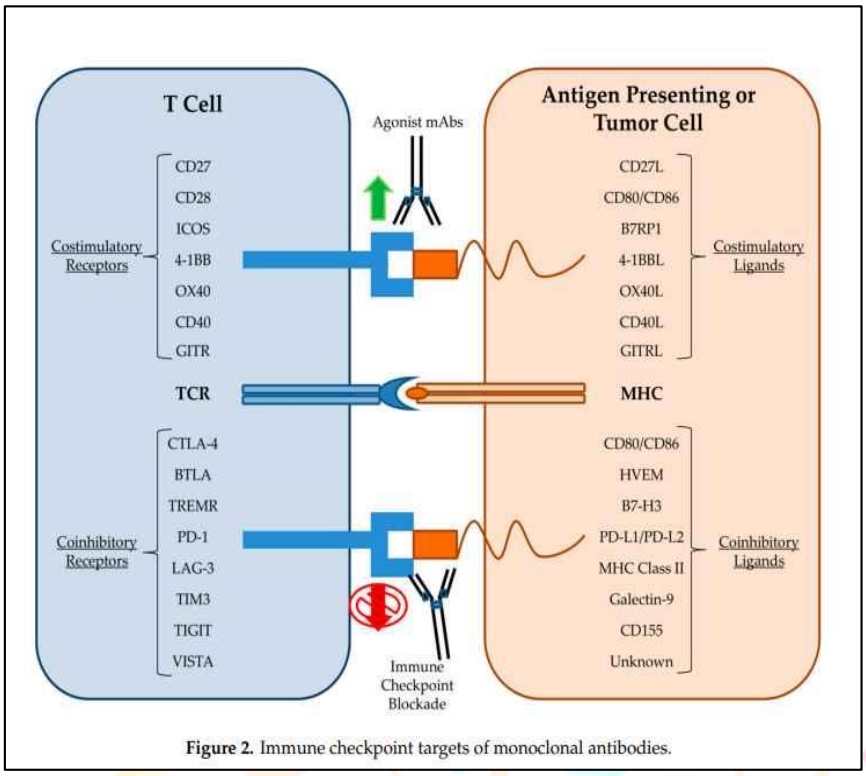

Figure 2. Immune checkpoint targets of monoclonal antibodies.

B. LIPID BASED NANOMATERIAL:

Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers are the three fundamental types of lipid-based nanomaterials. Liposomes, which ranged in size from 20 nm to 1 mm, were the first microcosmic phospholipid bilayer nanosystems [44]. Both hydrophilic and hydrophobic drugs can be delivered depending on the form of the liposome structure [45]. Drugs are shielded from degradation by the central cavity of liposomes [46] The core chamber of the liposome protects medications against degradation. Because liposome membranes may be phagocytized by the mononuclear phagocyte system, often known as human guards, they should be modified to im[rove their half-life [47].

This can be achieved through polyethylene glycol conjugation. For example, PEG-liposomes carry]ng doxorubicin (DOX) were developed and applied to treat Kaposi sarcoma [48]. In cancer chemotherapy, drug effectiveness is impacted by bioavailability, and DOX liposomes have lower bioavailability than free DOX, indicating that bioavailability should be enhanced during liposome design [49]. A new PEGylated liposome carrying cobimetinib and ncl240 displayed an enhanced cytotoxic effect through synergistic effects, leading to higher efficacy [50]. Moreover, liposomes loaded with floxuridine and irinotecan exhibited better effects on advanced solid tumors, whereas a new liposome containing multilayer sirna molecules and that co-delivered DOX displayed better DOX efficacy, decreasing the tumor mass in breast cancer [51, 52].

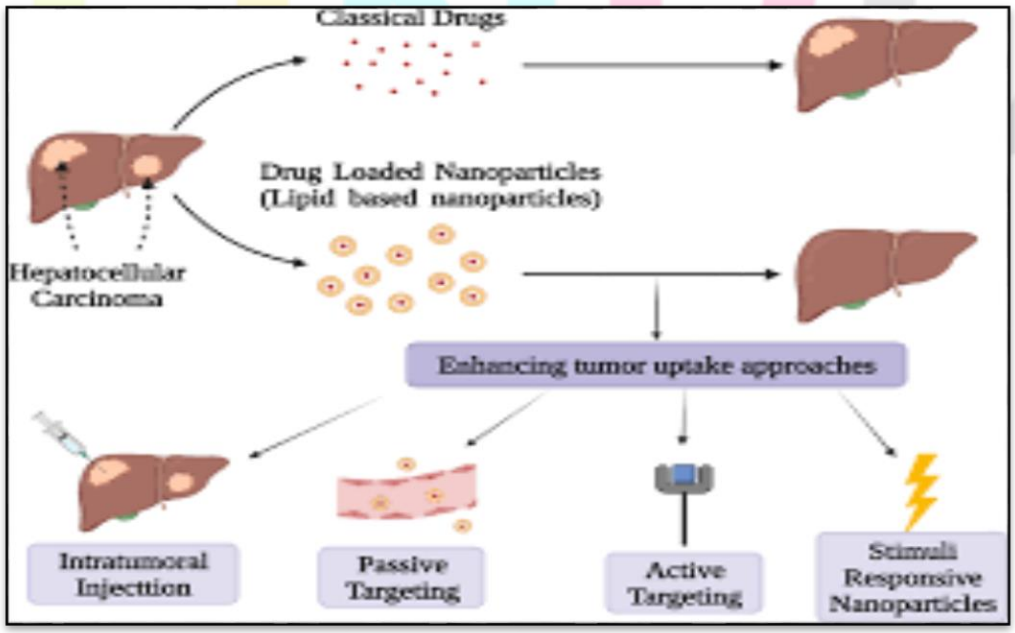

Figure 3. showing mechanism lipid based nanoparticle used in cancer treatment

C. NANOEMULSIONS :

Nanoemulsions (NEs) are colloidal nanoparticles with an aqueous phase, emulsifying agents, and oil [53]. NEs are widely utilized drug nanocarriers. They have a lipophilic surface and solid spheres; three typical NE types are water-inoil NE systems, oil-in-water NE systems, and bi-continuous NE [54]. Compared with most lipid-based nanomaterials, NEs show the advantages of optical clarity, excellent biodegradability, and improved molecule release profiles.

NEs can also be used in immune therapies. A modified NE loaded with interferon-g inhibited the viability of MCF-7 breast cancer cells and enhanced the activity of phagocytes. These results indicate the potential of these NEs for cancer therapy [55]. A new NE carried baicalein and paclitaxel was produced enhanced oxidative stress and decreased glutathione levels in MCF-7/Tax cells, providing a suitable approach for increasing the sensitivity of cells to paclitaxel.

Compared to conventional paclitaxel production, baicalein-paclitaxel NE displayed higher anticancer efficacy in-vivo [56, 57]. These studies indicate that applying elaborately fabricated NEs is useful for managing multi-drug resistance.

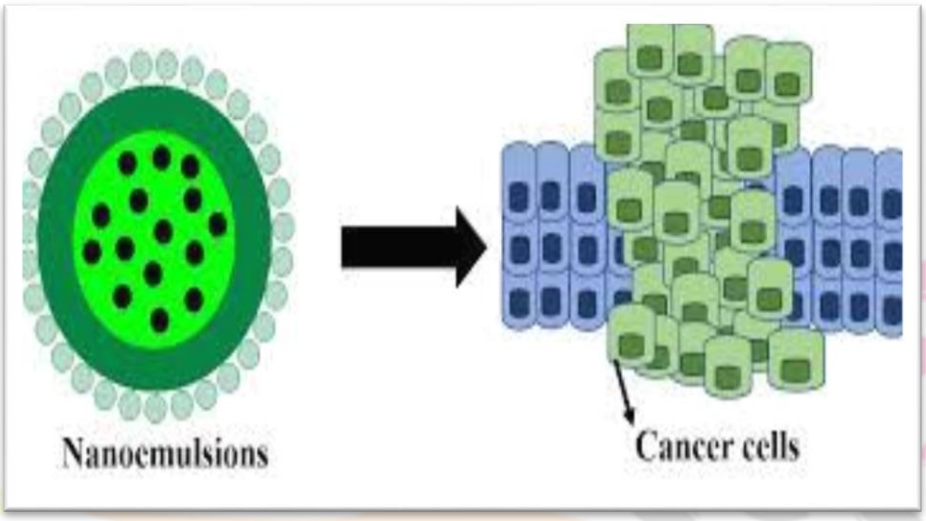

Figure 4. showing mechanism of nanoemulsion

D. DENDRIMERS :

Dendrimers (1-15 nm) are distinguished by their highly branched surface topographic structure [58, 59]. Dendrimer molecules comprise three distinct parts: an internal the core, branches, and a covering surface. Polyamidoamine (PAMAM), polypropylenimine, 5-aminolevulinic acid, and triethanolamine are a few dendrimers that have been reviewed for cancer therapy [60]. Fluorescence was created by the carbon dots, and targeting of avb3 integrin receptors by arginine-glycine-aspartic acid ligands resulted. TPGS demonstrated exceptional cancer-inhibiting specificity cells [61].

Furthermore, DOX has been successfully employed to treat colon cancer. TRAIL and DOX plasmids were carried in a dendrimer nanocarrier, which established updated anticancer effects when compared to modified carriers being held only the TRAIL or DOX plasmids [62]. A PAMAN nanocarrier is being developed and employed to treat liver cancer predicated on the dendrimer. PAMAN dendrimers without decoration exhibit inefficient cellular internalization, low transfection efficiency, and unstable encapsulation; however, the competitive characteristics of nanomaterials exhibit many advantages in combination therapy [63, 64].

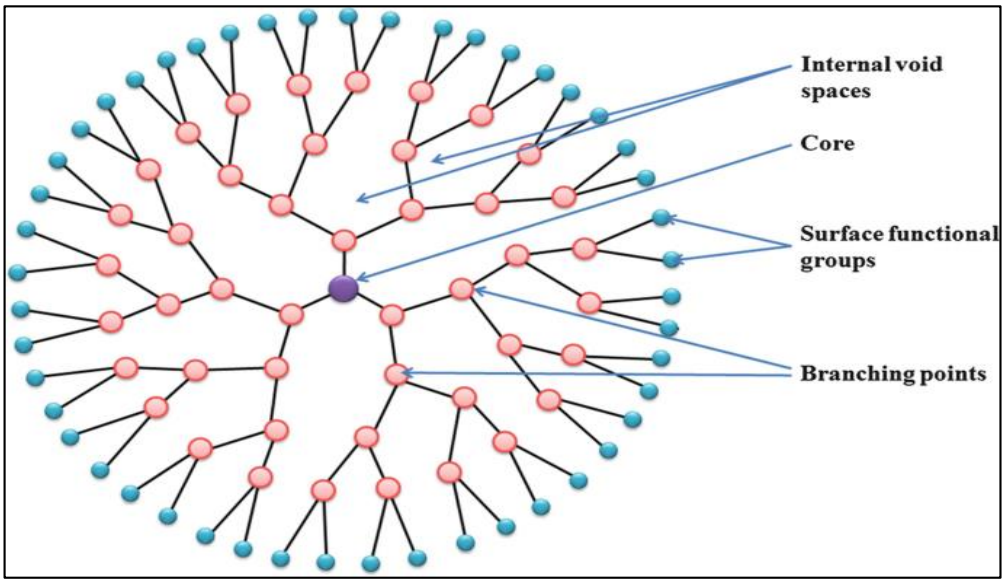

Figure 5 : Structure Of Dendrimers.

E. GRAPHENE :

Because of its important mechanical and electronic characteristics, graphene has been widely studied in cancer therapy [65]. Based on their composition, structure, and characteristics, single-layer and multi-layer graphene, graphene oxide (GO), and reduced graphene oxide have been defined [66]. Graphene shows unique mechanical and electrochemical advantages. Optical transmittance, high density, and hydrophobicity are outstanding properties [67, 68]. In addition, high drug-carrying ability and thermal conductivity are important properties in cancer theragnostic[69, 70]. However, the poor solubility of graphene causes toxicity and prevents its manufacture [71]. Hence, more bioavailable graphene-based nanomaterials are needed. A classical GO molecule is composed of functional oxygen groups, carbonyl groups, and epoxy groups [72].

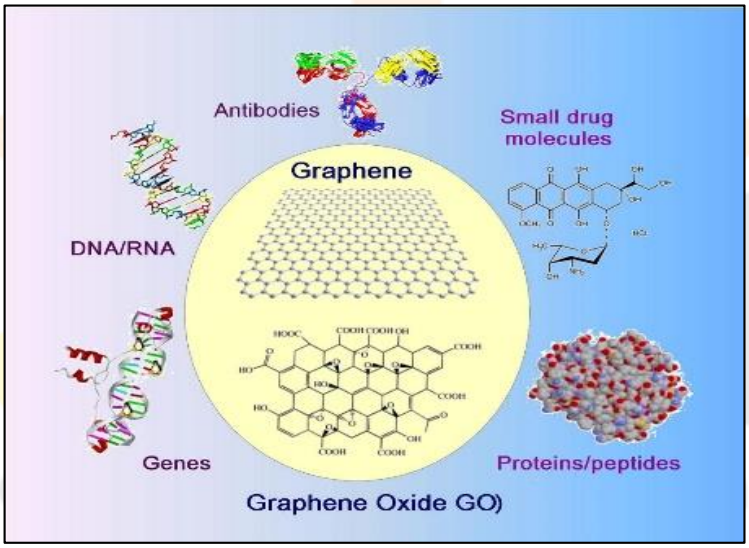

Figure 6 : Basic Structure Of Graphene

HISTORICAL PERSPECTIVE OF CANCER TREATMENT

There are several approaches towards cancer treatment including surgery, radio- and chemotherapy, and most recently targeted immunotherapy.

i.SURGERY :

Historically, Maimonides in AD 1190 appears to be the frst to document surgery as a method to remove tumours [73]. It was not until the nineteenth and early twentieth centuries that major advances were made in cancer surgery, especially after anaesthesia became available in 1846. Halsted developed the radical mastectomy during the last decade of the nineteenth century [74]. Most

women with breast cancer nowadays have the primary tumour removed followed by adjuvant therapy that may include radiation, chemotherapy, targeted, or hormonal therapy. Progress in cellular, molecular and imaging techniques in the twentieth century was instrumental in the advancement of surgical techniques. For example, ultrasound (sonography), computed tomography (CT scans), magnetic resonance imaging (MRI scans) and positron emission tomography (PET scans) have replaced the exploratory surgeries used previously to diagnose cancer. Advances in surgical techniques also include laparoscopic, thoracoscopic surgeries, endoscopy, lasers, cryoablation and radiofrequency ablation [75].

ii.RADIOTHERAPY :

Shortly after the discovery of X-rays by Wilhelm Rontgen in 1895, radiotherapy as a treatment option for cancer started to emerge. Currently, almost half of all patients with cancer are treated with radiation. Ionising radiation induces DNA damage leading to cancer cell death, but it has toxic efects on normal tissue [76]. Few years after its discovery, radiation therapy was found to cause cancer. Radiation carcinogenesis was established in human populations, and the dose–response relationship was described in radiation leukaemia [77]. Advances in radiation physics and computer technology in the twentieth century made it possible to aim radiation more precisely at tumours. For example, conformal radiation therapy (CRT) allows three-dimensional anatomical information of the tumour and surrounding healthy tissues, thus facilitating the establishment of three-dimensional conformal radiotherapy (3D-CRT) and radiation beams are delivered to the tumour from several directions. Intensitymodulated radiation therapy (IMRT) allows the intensity of the beams to be adjusted, thus delivering high dose to the cancer while decreasing the dose reaching the surrounding normal tissue [78].

iii.CHEMOTHERAPY

The discovery of chemotherapy was a result of observations that soldiers in World War II exposed to nitrogen mustard had low white blood cells count. This led to the discovery that intravenous nitrogen mustard slowed the growth of lymphomas and leukaemia in patients refractory to radiotherapy [79].Chemotherapy was developed in response to findings that troops exposed to nitrogen mustard during World War II had low white blood cell counts. This led to the finding that intravenous nitrogen mustard inhibited the development of lymphomas and leukaemia in radiotherapy-resistant individuals. The first rationally designed nucleotide analogue chemotherapeutic drugs were created [80, 81]. Farber developed aminoopterin, which was the forerunner to methotrexate, which is still widely used today.

Combination chemotherapy was shown to be more effective than single drugs. Some kinds of leukaemia and lymphoma that develop extremely quickly react very effectively to combination treatment. For example, remission induction treatment for acute myeloid leukaemia (AML) comprises of 4-5 rounds of intense chemotherapy that commonly contains cytarabine (Ara-C), the foundation of many therapeutic regimens, combined with etoposide and anthracycline [82].

iv.TARGETED THERAPY

Advances in our comprehension of cancer biology and the human genome have brought about in therapies that target specific molecular pathways required for cancer cell survival, growth, progression, and metastasis. Cancer medicines that are targeted are designed to disrupt a specific component of the complex network of altered signalling channels that leads to uncontrolled cell proliferation [83]. Molecular targeted therapies have shown remarkable success in the treatment of several cancer types including breast, leukaemia, colorectal, lung and ovarian cancers [84].

Growth factor antagonists and growth factor receptor inhibitors are effective targeted treatment techniques for suppressing cancer cell development and metastasis and sensitising cancer cells to dying by cytotoxic anticancer drugs. Her2 antibodies that target EGFR, IGF-1R, VEGFR, and PDGFR are examples [85].

Targeted immunotherapy has proven successful in many types of cancer. It harnesses the immune system to attack cancer cells. Cancer immunotherapy includes monoclonal antibodies, cancer vaccines, immune checkpoint inhibitors, CAR T cell therapy and immune system modulators. Limitations of cancer immunotherapy include resistance, escape of cancer cells from the immune response and issues related to delivery methods. Some of these issues could be resolved by using nanocarriers as vehicles because of their increased surface areas, targeted delivery, controlled surface and release chemistry, enhanced permeation and retention efect [86].

NANOPARTICLES DELIVERY FOR CANCER TREATMENT

1. TARGETING CANCER CELL :-

The foremost aim of chemotherapeutic drugs for targeting cancer cells is to kill the cancer cells and to minimise the side efects [87]. In order to accumulate nanoparticle delivery systems including liposomes, polymeric-drug conjugates, micell Active targeting makes use of the highly expressed surface receptors on cancer cells by sustaining their engagement with the targeting ligands. In the earlier investigation on the active targeting of nanoparticles, several ligands composed of proteins (antibodies), nucleic acids, peptides or carbohydrates were employed [88]. AR systems and polymeric NPs, passive targeting mostly relies on the physiological properties of the tumour. Rapidly developing tumours with enhanced vascular permeability and compromised lymphatic drainage frequently cause cancer and increase the permeability and retention (EPR) efect of nanosystems in that disease. Active cancer-targeting uses adding certain moieties to improve the delivery of nanoparticle systems to the tumour site [89].

2. TARGETING THE MICROENVIRONMENT :-

Tumour microenvironment has been implicated in cancer growth and metastasis. With a better understanding of tumours, it is now known that they develop in a microenvironment that is very heterogeneous, complex, and made up of TAMs, CAFs, immune cells,

and ECM components. Recent research shows that one key tactic in preventing cancer growth, invasion, and metastasis is altering the tumour microenvironment and its aberrant composition. With the development of nanotechnology in the drug delivery feld, creative strategies to combat the cancer threat have emerged [90, 91]. However, it has emerged that the complexity of the tumour microenvironment has a signifcant, though debatable, impact on the control of nanochemotherapeutics' higher tumoural penetration and, consequently, their biological effects [92]. nanotechnology ofers a fexible tool by permitting the delivery of either a solitary or combinations of chemotherapeutics together with numerous targeting ligands to specifcally target overexpressed receptors or enzymes or a reductive environment, a characteristic of the tumour microenvironment [93, 94].

3. NP AND IMMUNOTHERAPY :-

Cancer immunotherapy, which activates body's own immune system has become a viable method for treating a variety of cancers. By triggering a signifcant immune reaction against the tumour, this treatment not only destroys tumour cells but Table also stops them from getting back. High immune-mediated toxicity, inefective and untargeted delivery of cancer antigens to immune cells, and of-target side efects are only a few of the daunting obstacles that therapeutic cancer immunotherapy must overcome. However, nanoparticle-mediated proposed system various ways to get beyond those restrictions and can thereby increase the efectiveness of immunotherapy. The primary problem in cancer immunotherapy is to deliver antigens for the subsequent development of an immune response [95]. To cause naive T-cell diferentiation and activation as well as antigen presentation by the APCs for later CD8+and CD4+T cell activation, sufcient antigen and pretreatment are needed [96, 97].

APCs are immune cells that deliver antigens to the class I and class II MHC molecules on the surface of killer cells so that they can connect with T cell receptors [98].

4. NP AND DRUG RESISTANCE:-

The most frequent reasons for chemotherapy failure, innate or acquired drug resistance, severely restricts the therapeutic results of chemotherapy. Recent developments in nanotechnology have ofered substitute methods for addressing tumour medication resistance. Drug-loaded nanoparticles (NPs) are superior to free drug forms in a number of ways, including decreased cytotoxicity, prolonged blood circulation and greater tumour accumulation. However, due to the multiple pathophysiological hurdles present in the tumour microenvironment, such as intertumoral dispersion, penetration, intracellular trafcking, etc., nanoparticulate medicines have currently only minimally increased the overall survival rate in clinical studies. To increase the therapeutic efectiveness of nanomedicine, smart NPs with stimulus-adaptable physical and chemical characteristics have been developed in considerable detail. At the level of the tumour tissue, the drug resistance mechanism is highly intricate. Commonly regarded as the main drug resistance factors are given below, tumour heterogeneity, tumour microenvironment (TME), drug transporter and multidrug resistance, cancer stem cells (CSCs), epithelial-mesenchymal transition (EMT) and tumour metastasis all contributes to the of target efect in the use of chemotherapy. Additionally, drug efux caused by drug transporters compromises the delivery of cellular chemotherapeutics, resulting in low therapeutic doses [99–101]. Furthermore, the survival compensation efect may be strengthened by low pH, a hypoxic tumour microenvironment, and other anti-apoptotic chemicals [102]. Other resistant factors include gene mutations and genomic instability, epigenetic alterations including DNA methylation and protein acetylation, suppression of apoptotic signalling, and overexpression of anti-apoptotic molecules, in addition to the fve medication resistance factors described [103].

Representative list showing diferent mechanisms along with drugs, molecular targets and cancer type associated with cancer drug resistance are as follow -

Resistance mechanism	Cytotoxic drugs	Type of cancer	Target	Reference
Microseminoprotein, prostate-associated (MSMP) gene upr	Vascular endothelial growth factor receptor 1/2/3 (VEGFR1/2/3) inhibitors	Ovarian cancer	Hypoxia, triggering mitogenactivated protein kinases (MAPK) signaling	**[104]**
Activated PDGFR	Histone deacetylase inhibitors, phosphatidylinositol 3-kinase, anti-VEGF drugs	Prostate cancer	Platelet-derived growth factor receptor (PDGFR	**[105]**
Tumour heterogeneity	Tyrosine kinase inhibitors	Prostate cancer	Epidermal growth factor receptor (EGFR) T790M mutation	**[106]**
Drug inactivation	Platinum drug	Lung cancer	Thiol glutathione	**[107]**
Reduced drug uptake	5-Fluorouracil (5-FU) and miR-21 inhibitor oligonucleotide (miR21i	Colon cancer	Micro-RNA-21 (miR-21)	**[108]**
DNA repair alternation	Platinum (carboplatin or cisplatin) and taxol (paclitaxel)	Ovarian cancer	DNA repair pathways	**[109]**

Inhibition in apoptotic pathways and autophagy	Epirubicin, tamoxifen, herceptin, and vinorelbine	Breast cancer	Autophagy	**[110]**
Epithelial to mesenchymal transition (EMT)	Wingless and Int-1 (Wnt) signaling inhibitors	Ovarian cancers	Wnt/β-catenin signaling pathway	**[111]**
Epithelial to mesenchymal transition (EMT)	Nivolumab	Ovarian cancers	EMT/stroma-related gene expressio	**[112]**

CONCLUSION :

Like most other scientific advances that have revolutionized medicine over the past decades, cancer nanomedicine must also mature before its full impact can be realized. Improving our understanding of tumour heterogeneity and identifying EPR markers will enable selection of patients maximally responsive to nanotherapies. A full understanding of nano–bio interactions, systemic transport of NPs to tumour cells and targeting of NPs to the TME or premetastatic niche will lead to safer and more efficacious nanotherapeutics. Addressing the challenges of controllable, reproducible and scalable NP synthesis, as well as NP screening and evaluation, will facilitate clinical development. Although most approved nanomedicines have used existing drugs as payloads, we expect the next generation of nanomedicines to increasingly incorporate new molecular entities (for example, kinase inhibitors24) and novel classes of therapeutic agent (for example, siRNA, mRNA and gene editing).

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