A review on human cancer and potential role of MXenes in cancer therapy

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Abstract. Cancer is the second leading cause of death worldwide and is having a serious impact on the global economy. Various treatment modalities are in use to treat cancer but none of the techniques is risk-free. Recently, various nanomaterials such as gold, boron, and other compounds have been investigated for radiotherapy and as anti-cancer drug carriers with promising results. MXenes are 2D novel nanomaterials and their biomedical and anticancer properties are gaining interest due to their high biomedical activity, less bio-toxicity, and photo-responsive nature. However, the biological properties of MXense have not been studied extensively, therefore, limited data is published on its in-vitro and in-vivo anticancer activities, drug loading efficacy, targeted release, and on its photothermal therapy response. In this review, we have discussed the use of nanoparticles and MXenen nanomaterial in cancer therapy. Furthermore, the role of Mxene as a photothermal agent and drug carrier has also been emphasized, along with the present challenges for the use of nanomaterials in the treatment of cancer.

1 Introduction

Recently medical science has been revolutionized by nanotechnologies. This has introduced the Theranostic modality in oncology, by which it is possible to screen the tumor areas and deliver the drug to the targeted sites at the same time [1]. The nanoparticles used, exhibit unique biological, chemical, and physical properties that selectively exhibit the potential to increase the treatment efficacy and limit the side effects on healthy tissues, ultimately leading to increased survival rates of cancer patients [2]. Cancer is the second major cause of death worldwide claiming 8.97 million deaths per year and is likely to become the first in 2060 (~18.63 million deaths yearly) [3]. It is predicted that Asia will be the major prey for cancer diseases as around sixty percent of the world population is residing there and around fifty percent new cancer cases will arise in Asia causing more than fifty percent of global death. [4]. Most of these cancer-related mortalities are reported in poor socio-economic status

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countries due to late-stage presentation, delay in diagnosis, and delay in treatment [5]. Cancer is having an increasingly deleterious effect on the world's economy. Approximately $1.16 trillion was the global yearly cost in 2010 for cancer only [6]. In 2015, the United States spent $183 billion on cancer-related health services, and this figure will rise to $246 billion by 2030, a 34 percent increase [7]. In Brazilian population the average cost of cancer was predicted to be 1.7 percent of GDP per year, with health spendings accounting for 9.5 percent of GDP. It is further expected to rise and may reach approximately INT$ 81 billion in year 2020 [8]. Early detection of pre-cancerous and early stage of cancers, adequate and effective treatment may reduce cancer-related mortality and morbidity. Investing 11 billion dollars in cancer prevention programs in low- and middle-income countries could save 100 billion dollars in cancer care costs [9].

The treatment modalities available for malignancy are surgical, chemotherapy, radiotherapy, chemo radiotherapy, immunotherapy, hormone therapy, and targeted drug therapy [10]. Unfortunately, every modality has its limitations and side effects. So, there is an urgent need to find out effective and safe approach that may increase life expectancy with improving health quality. Nano-medicine provides a flexible network of biocompatible and biodegradable systems capable of delivering in-vivo traditional chemotherapeutic drugs, increasing their bioavailability and tumor tissue concentration, and enhancing their release profile [11]. For various uses, ranging from diagnosis to therapy, nanoparticles can be exploited [11]. Recently, various types of nano materials have been explored for their effectiveness against cancer diagnosis and treatment with promising results. The major advantage of nano materials is their tunable properties, easy surface functionalization, high surface area, and tunable size [12]. Furthermore, some of the nano particles i.e., gold, silver, graphene, and recently 2-D MXenes have shown light-responsive behavior which makes them suitable for targeted drug release using external stimuli. 2-D MXene exhibit exceptional physical and chemical properties which have promised its application in cancer therapeutics (in chemotherapy, radiotherapy, photothermal therapy, photo dynamic therapy) and in cancer diagnosis i.e. imaging techniques [13]. In this review, we have attempted to summarize the use of nanomaterials and 2D MXene in the medical field and especially in cancer diagnosis and therapy.

2 What is cancer?

Cancers are malignant tumors that result from the uncontrolled growth of cells. They invade locally and can metastasize to distant sites, that is why they are difficult to resect by surgery. Cancer is originated from its Latin word "karkinos" (crab) due to its finger-like invading margins [14].

2.1 Types of cancers

In broader terms, approximately 277 different cancerous pathologies have been identified [15] depending upon the cell and organ of origin. The major types of cancers depending on the cell of origin are (1) Carcinoma arises from epithelial cells, (2) Sarcoma arises from soft tissues, (3) Leukemia cancer of the blood and bone marrow where white cells outgrow abnormally, (4) Lymphoma that arises from lymphocytes mainly present in lymph node and other tissues and (5) Melanoma that arises from melanocytes as shown in Fig. 1. Further, Types of major cancers depending on organ site are illustrated in Fig. 2.

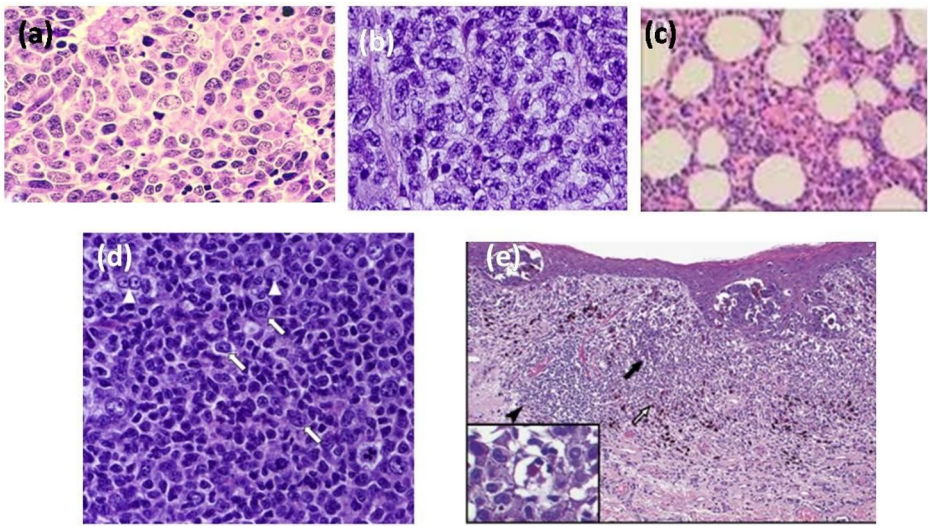

Fig. 1. a) Lung cancer images, large cell lung carcinoma [16], b)Sarcoma New fusion sarcoma [17], c) Leukemia T-cell lymphocytic granular leukemia [18], d) Lymphoma Primary follicular lymphoma [19], e)Melanoma Primary cutaneous melanoma [20] (re-printer with permission).

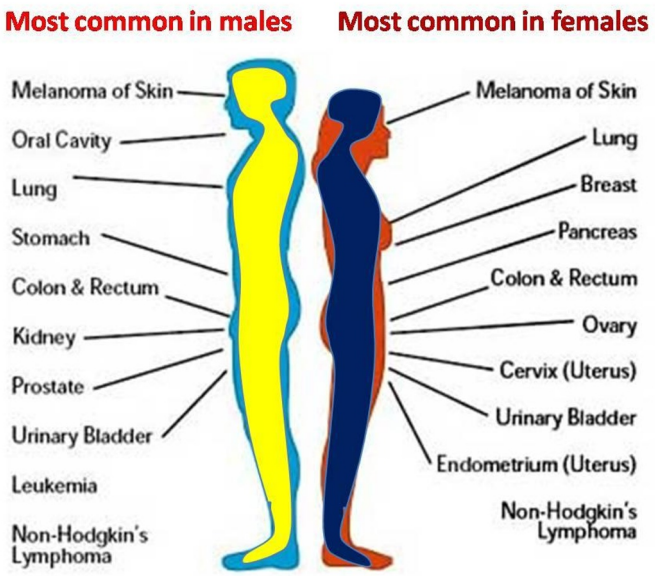

Fig. 2. Most common cancer types in males and females [21].

3 Pathological aspects of cancers

Cancers have multiple aetiological factors including from genetic to molecular level that can affect any human tissue and organ. Certain genetic modifications can contribute to oncogene production and genetic disorders. Three main groups of Genes causing cancers are (1) Tumour suppressor genes: when these lost their function it results in loss of growth inhibitory mechanisms. Mutations can be hereditary (germline mutations) or acquired. For example—

the p53 gene, (2) Proto-oncogenes: cancer occurs when the function of these genes gets enhanced resulting in uncontrolled cell proliferation by coding more growth factors and their receptors or by coding more transcription factors, etc. An example of a proto-oncogene—the Ras gene: mutations in Ras are implicated in 30% of all cancers, including melanoma, lung, and pancreas, and (3) DNA repair genes; cancers occur when the function of these genes is lost and there is an accumulation of mutated genes which results in cancer generation [22].

There is also gender predisposition for many cancers. For example, stomach cancer is two times more common in males similarly are lung and bladder cancers they are most common in males. It might be because of environmental and occupational exposure to carcinogens [22]. Certain infections can also lead to cancer genesis. For example, human papillomavirus (HPV) infection is associated with carcinoma of the cervix, vulva, vagina, penis, and anus. Similarly, carcinoma of the liver is caused by Hepatitis B and C virus. Some bacterial and parasitic infections are also linked with cancers as for Helicobacter Pylori infection [22]. Some external factors responsible may include smoking, alcohol, obesity, lack of exercise, radiation exposure, exposure to industrial or pharmaceutical substances, and environmental pollutants [22].

4 General basis of cancer at cellular level

Hanahan and Weinberg have suggested ‘6 ‘cancer cell phenotypes or hallmarks: which include “cells with limitless proliferative capacity.”(abnormal cell cycle regulation), “environmental independence of cells for growth”, “altered l programmed cell death leading to increase cell survival”, neo “angiogenesis to support growing tumor”, local invasion and then spread ” to distant body parts [23]. The uncontrolled cell growth or metastatic spread may lead to the death of the person [24].

5 Types of cancer treatments in clinical practice

Cancer management needs a multidisciplinary teams(MDTs) and multidisciplinary approach [25]. Cancer therapy requires multiple diagnostic tests, including some form of pathological confirmation, and imaging investigations to assess the extent of the disease. There are different treatment modalities available for cancers as shown in Fig. 3. These modalities depend on the stage of cancer, type and location of cancer, the grade of the tumor, and the suitability for a particular individual. Sometimes the combination of therapies is utilized to maximally benefit the patient. The following are the available treatment modalities with their pros and cons.

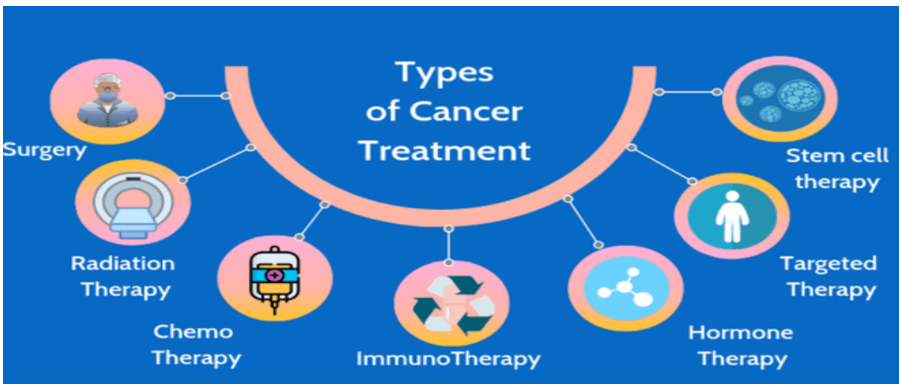

Fig. 3. Types of cancer treatment techniques (adapted from) [26].

5.1 Surgery

Excisional surgery is one of the main modalities of cancer care. Occult neoplastic disease, which persists in situ following curative surgery, is the minimum residual disease (MRD). Tumor removal is increasingly shown to alter MRD growth, leading to peri-operative tumor growth [27]. Malignant tumors were removed by mutilating radical anatomic dissection during the 19th, and for much of the 20th century [28]. Surgery is performed mostly for non-haematologic cancers [10]. Surgery cannot resect the disease when cancer has metastasized to other body parts [10]. Side effects can occur from the type of operation, the surgical technique, and the individual's health status. Surgery has its limitations. It cannot remove the cancers from and near the vital organs [10]. Common complications of surgery include inflammation of the surgical site, dehiscence of the wound, hernia of the incision site, and development of the sinus [29].

5.2 Chemotherapy

Chemotherapy is the use of anticancer drugs (like doxorubicin, paclitaxel, cisplatin) to treat cancers. These drugs either kill or inhibit the growth of tumor cells [10]. Sometimes two or three drugs are used. It is called combination therapy [30]. Despite the increased effectiveness and improved longevity provided by modern therapies, still, chemotherapeutic agents are having serious side effects that are worried some for both doctors and patients.[31]. Using a combination of drugs has improved overall tumor regression response. Multidrug resistance' (MDR) is displayed by some tumor types. A growing number of biomedical studies are aimed at developing chemotherapeutics that can avoid or reverse MDR [32]. More recently, so-called targeted therapies have been developed which aim to specifically inhibit some process of fundamental importance to the cancer cell [22].

Recently, there has been a focus on improving the therapeutic effects of cancer medicine by developing smart targeted drug delivery systems. These anticancer drug delivery systems should preferably hold enough anticancer drugs to avoid phagocytosis, clear transport barriers, and accumulate in the cancerous site and then release anticancer drugs in a controlled manner to affected cells with less adverse effects [33].

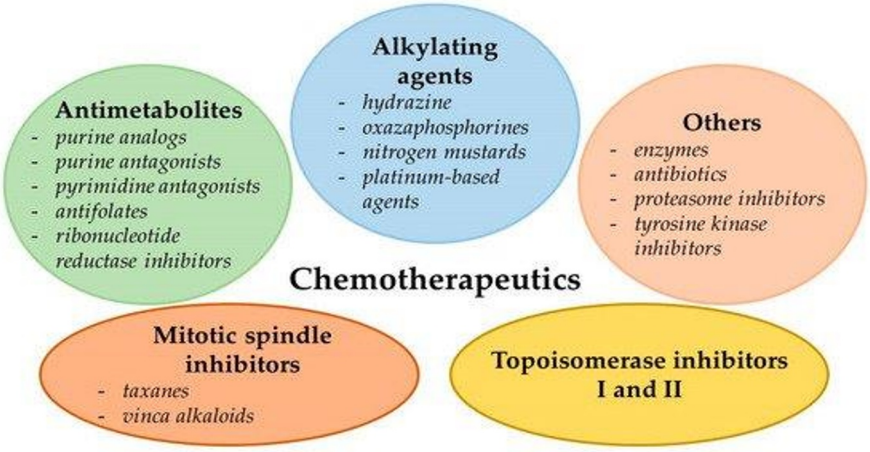

Fig. 4. Types of chemotherapy [32].

5.2.1 Side effects of chemotherapy

Acute chemotherapy-induced nausea and vomiting are being better controlled by recent medication but delayed nausea and vomiting are still difficult to control [31]. Another potential side effect can be seen on skin, hair, bone marrow, kidneys, central and peripheral nervous system [34]. Neutropenia, Diarrhoea (early or late), Thrombocytopenia, Anaemia, Alopecia, Dose-dependent nephrotoxicity, Peripheral neuropathy, and, due to ototoxicity tinnitus and high-tone deafness can occur Serious toxicities which need to limit the dose are hepatic venous-occlusive disease and myelosuppression [35].

Less common toxicities: Hyperpigmentation rarely, pulmonary interstitial fibrosis

5.2.2 Limitations of chemotherapy

Drug resistance is the main limitation of chemotherapy. The dosage of chemotherapy that can be safely administered is inadequate to give the active drug an appropriate concentration at the target tissue site. It can be because of the drug toxicity in other organs, physical barrier between the bloodstream and tumor cells (many tumors have avascular centers), improved drug clearance, de-novo resistance (despite maximum doses, the tumor does not respond), acquired resistance (initial chemotherapy response, then the tumor fails to regress and grows again) or it can be the combination of de-novo and acquired resistance [36].

5.3 Radiotherapy

This treatment approach uses high-energy ionizing radiations to suppress the growth and destruction of tumor cells. This method is used along with other modalities like surgery to either reduce the size of cancer (neo adjuvant therapy) or to minimize the residual disease after surgery (adjuvant therapy). Radiotherapy is an effective treatment modality for non-metastatic cancers [37]. Recently, significant technological development in 3D conformal radiation therapies, such as " stereotactic (body) radiotherapy "(SBRT), "intensity-modulated radiation therapy" (IMRT), and" enhanced imaging system" (i.e., "image-guided radiation therapy", IGRT), have allowed precise delivery of required radiation doses to the targeted tumor while limiting the radiation exposure to unaffected healthy tissues [38]. There are two methods of transmitting radiation to the cancer site, external beam radiation, and brachy therapy. External beam radiation is the most prevalent approach. Brachy therapy is the direct transmission of radiation to the cancer site from within the body by radioactive sources which are enclosed in catheters or seeds. This is routinely used in pelvic cancer treatment [23]. Many tumor forms remain resistant to radiotherapy or recur shortly after treatment due to acquired resistance. The main cause of radiation and chemo-resistance is thought to be cancer stem cells, and tumor heterogeneity plays an important role in acquired radiation resistance [39]. Recently studies are being conducted to develop targeted radiotherapy. To investigate the features of targeted radiotherapy that vary from external beam irradiation, experimental studies will be needed. Targeted radiotherapy of small numbers of tumor cells identified with molecular probes may be a future path [40].

5.3.1 Limitations of radiotherapy

Acute toxicity effects: After the first dose, commonly nausea and vomiting develop within six hours and within the first twenty-four hours parotid glands get affected reversibly and result in dry mouth. At about the fifth day GI inflammation occurs and the patient may experience diarrhea and fever.

Delayed toxicity effects: At about 6 to 8 weeks, anorexia, nausea, sleepiness, and somnolence may occur due to temporary demyelination. Radiation therapy also causes pneumonitis that has a very specific appearance on the X-ray radiograph.

Late toxicity effects: The radiation therapy affects the reproductive system resulting in sub-fertility. It leads to amenorrhoea and menopausal symptoms in females and azoospermia in males. Radiation therapy also affects thyroid and pituitary glands depending on the site of exposure and may result in hypothyroidism and other hormonal problems. In less than twenty percent of cases, a cataract may develop. In the long run, radiation damage may lead to the development of new onset of cancers. With radiotherapy, there is a fivefold increased risk of secondary carcinoma generation. Studies have reported certain brain, rectal and oral cancers as secondary carcinomas. Typically, many of these patients are not treated or undertreated because radiation oncologists are scared of the side effects of full doses of therapy [41].

5.4 Immunotherapy

Immunotherapy is a cancer treatment strategy that helps to combat cancer through the immune system. This is often referred to as biologic therapy, which activates the disease-fighting mechanism to combat cancer inside the patient's body. A large number of immunotherapy trials have been performed to treat cancer, such as monoclonal antibodies that inhibit the action of particular proteins by binding to cancer cells and train the immune system to identify and destroy cancer cells [10]. Interferon alfa (IFN-α) has been used in hairy cell leukemia— CML (chronic myeloid leukemia) with 50–75% hematological remission rates. Side effects of the IFNs include ‘flu-like symptoms (>90%), anorexia, fatigue, deranged liver function tests (LFTs), myelosuppression, and depression (>15%) [42].

5.5 Hormone therapy

Hormone therapy treats cancer by changing the number of hormones in the body to treat some forms of cancer that develop and spread based on these chemicals. This treatment procedure is used to treat breast, reproductive and prostate cancers. Side effects depend on the cancer type, age, sex, and type of medication used [10].

5.6 Targeted Therapy

The targeted cancer treatment focuses on the mechanisms of signal transduction and intracellular signal amplification in tumor cell proteins with critical roles in cell division and cell death. In general, these drugs inhibit some enzymatic proteins within cancer cells which have either mutation or are over-expressed. For example, tyrosine kinase inhibitors like Trastuzumab, Imatinib [43]. Paclitaxel, and trastuzumab once a week for 12 cycles is used as an alternative regimen for breast cancer in lower-risk, node-negative, HER2-positive population [44].

6 Role of nano particles in cancer treatment

Nanoparticles are being used for decades as drug delivery agents in cancer research both in diagnostics and therapeutics [46]. Various strategies have been used to reduce the limitations of cancer treatment. However, nanotechnology has proved itself to be the future of cancer treatment as it has made it possible to screen and treat the cancer areas at the same time, and has enabled targeted drug release [47]. Recently, various nanomaterials such as gold, boron, and other compounds have been investigated for radiotherapy and as anti-cancer drug

carriers, Photothermal Therapy (PTT), and immune-therapies with impressive results [48-50]. GNPs (gold nano particles) can be functionalized for a variety of molecules including drugs, peptides, genes, and antibodies, etc. which makes them highly potential agents for targeted drug delivery [51], PTT [52], radiological investigations [53], and gene delivery agent [54-55].

6.1 Synthesis of various nano particles

These particles can be categorized into two sections: naturally derived and synthetic particles. Nano-particles that contain biological elements such as lipid-based nano-particles are known as naturally derived and can be extracted from plants, bacteria, and yeast, etc. [56] and the ones extracted from metals, inorganic compounds, semiconductor materials, and polymeric nanoparticles are known as synthetic [57]. Different synthesis strategies are given in Fig. 5.

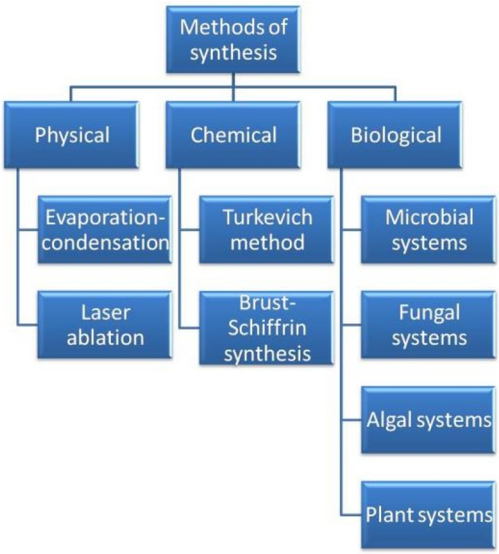

Fig. 5. Synthesis methods of nanoparticles [58].

6.2 Biomedical applications of nanoparticles

The Carbon-based nano materials are being widely used in biological fields due to their good bio-compatible nature and relatively little cytotoxicity. For example., graphene [59], carbon rods [60], and carbon nanotubes (CNTs) [61], further, silver nanoparticles (AgNps) have most widely been used in cancer therapies [62]. Also, they have been used in food technology and industries on a large scale [63]. Silver nanoparticles contain antibacterial, anticancer, and wound healing properties which enhances their utilization in biomedical applications. Figures 6 and 7 show the applications of carbon and Ag nanoparticles.

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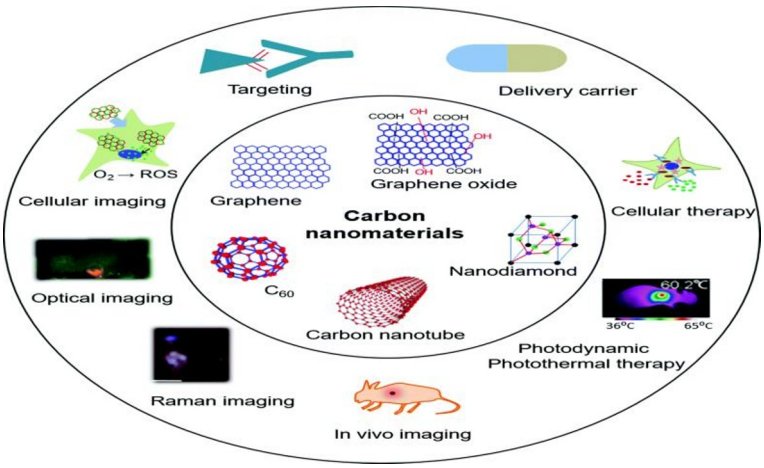

Fig. 6. Biomedical applications of carbon nanoparticles [64] (re-printed with permission).

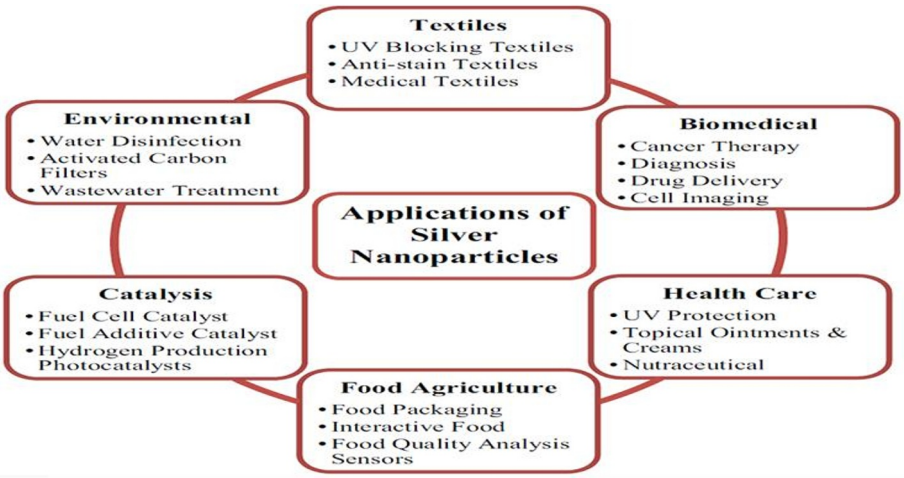

Fig. 7. Silver nanoparticle applications [65] (Re-printed with permission).

6.3 Applications of Carbon Nano particles in cancer therapy

CNTs have been studied on different cell lines. For example, CNTs were studied and found as cytotoxic to neuroblastoma cells [66], in the drug delivery system for release of doxorubicin to lymphoblastic cells [67], vertically aligned, CNTs have been used to differentiate healthy and metastatic colon cells [68]. CNTs has also been used in vitro non-viral gene delivery reagent by transferring siRNA(small interfering RNA) to HeLa cells [69]. Carbon nanomaterials have been successfully tried for chemotherapeutic drug delivery to lymph node and lymphatics, opening a way for the treatment of metastatic tumors [70] and gene delivery [71]. Prostate stem cell antigen-antibody nanotubes were studied for simultaneous ultrasound imaging for cancer and delivering the drug to that sites therapy [72]. Folate single-walled carbon nano tubes effectively enhanced the selective photo thermal destruction of tumor cells .selective photo thermal for cancer cells[73]. CNTs have also been used as a delivery channel for tumor vaccine formulation,[74] and also chemotherapeutic drug carrier [75].

6.3.1 As Drug carrier and Drug delivery

Carbon allotropes known as carbon nanoparticles have gained great importance in cancer biology recently. Culturing CNTs (carbon nano tubes) with various cell lines ensures better apoptosis and cell survival which means they exhibit better therapeutic efficacy [76]. Targeting brain cancer has been a difficult scenario for researchers however, CNTs showed drastically significant results in comparison to chemotherapy. The reason behind the less efficacy of chemotherapy is the blood-brain barrier which interferes with the penetration of drugs into the brain cell, that's why CNTs are considered as safe and effective carriers for drug delivery for brain cancer. SWCNTs are capable of targeting specific cancer cells and limiting their recurrence [66]. Carbon nanotubes (CNTs) due to their extraordinary characteristics, such as small size, high surface area, higher cellular uptake, and ability to attach small and large drug molecules have gained immense attention in the field of drug delivery and healthcare. But its high aspect ratio, the low payload of the drug, potential toxicity at higher amounts, high metallic impurities, and tendency to agglomerate are associated problems [76].

Encapsulation of ionizable and cationic nature lipids with LNP (Lipid-based nano particles) can be more effective to enhance stable and efficient drug delivery due to the negative charge of nucleic acids. Despite the charge, PH effects of LNPs drug delivery agents have also been investigated widely to ensure the efficacy of these agents [77-79]. Gold nano materials have eco-friendly nature which enhances their suitability and demand for biomedical applications such as carriers for delivery of chemo therapeutic drug.

6.3.2 In Photo Thermal Therapy

Various inorganic PTT agents have been widely searched and studied in the recent past. For example Au [80], Ag [81], and Pt [82], and transition metal sulfide or oxide nanoparticles [83-84]. Instead, they show excellent therapeutic potential in animal models their further clinical trials have been restricted due to these agents being non-biodegradable and owe long-term toxicities [85]. Various organic nano agents have been extensively studied to find an ideal photo thermal agent with good biocompatibility and less cytotoxicity [86]. For photothermal therapy of cancer, various mixed dyes, proteins, liposomes, and have fruitfully been tried. [87-88]. Molecular recognition, electronic and optical properties of these gold nano materials (GNPs) are the key features which make them desirable as photo thermal agent [89-91]. Modification in shape and size of GNPs can alter their photochemical and photothermal properties, based on different light wavelengths such as the NIR spectrum [92]. PTT is based on conversion of light energy to heat energy (NIR mostly) for apoptosis and cell necrosis and could be considered as a potential treatment approach for distal cancers also. More studies should be conducted by using different nanoparticles such as carbon, silver, gold, and others to enhance the efficacy of PTT [93].

As compared to gold nanoparticles AgNPs have less potential in photothermal therapy because AgNPs can generate comparatively less heat [94]. This significant difference leads to the gold nanoparticles application on higher scales in cancer photothermal therapy. Both AgNPs and AuNPs are the most potent agents in the arena of therapeutics as compared to other metal nanoparticles. Unfortunately, hyperthermia techniques used for cancer therapies can also cause side effects in vivo [95]. Therefore, targeted nanoparticle-based PTT could be a more suitable and more promising approach to avoid complications and better results [96-97].

6.3.3 In immunotherapy

Lipid-based nanomaterials (LNPs); Lipids being an important component of prokaryotic and eukaryotic cells have an advantage in biomimetic nanoparticles such as liposomal and lipid solid nanoparticles. Due to this biomimetic property these have been employed in several clinical applications including cancer diagnostics and therapeutics [98]. LNPs are mostly studied in cancer immunotherapies using protein/peptide, nucleic acid, and immune-stimulating molecules transportation. Low cytotoxicity because of their biomimetic properties is the key benefit of using these particles. For immunotherapy an attempt was made to inhibit STAT (signal transducer and activator of transcription proteins) pathway which is known to be immunosuppressing by using PH sensitive lipoplex particles for siRNA cytosolic delivery towards suppressor of cytokine signaling 1 (SOCS1). Upon the lipoplex administration subcutaneously, reduced SOCS1 expression was observed in dendritic cells, and increased levels of IL6 and IFN-γ resulting in antitumor activity [77].

Gold nanoparticles have been considered to have great feasibility for cancer immunotherapy. A recent study reported that pegylated IL10 in combination with chemotherapy is in stage III of a scientific trial, only IL10 among the cytokines has yet reached stage III of an experimental trial. It has been observed that Poly Ethyl Glycol (PEG) conjugation increases the half-life of both IL10 & gold nanoparticles and it also inhibits the aggregation of nanoparticles [99].

6.3.4 Role in Gene delivery

Gene delivery recently is emerging as a great approach for several diseases including cancer. Gold nanoparticles can be used as a good gene delivery vehicle as previously described by Xiong et al. 2019 [100]. Xiong demonstrated the use of non-viral vector Au-DENPs for gene delivery for cellular metastasis inhibition, results indicated gold nanoparticles as a powerful vector for gene delivery for multiple diseases.

6.3.5 Anticancer and anti-angiogenic agent

Recently, some in vitro and some in vivo studies have shown the distinguishing anticancer as well as antiangiogenic qualities of silver nano particles (AgNps). In an attempt to explore the response of AgNps against angiogenesis Kalishwaralal et al. observed that, AgNps has stopped the pathway which was involved in angiogenesis [101]. AshaRani et al. while finding out molecular mechanism involved in the anticancer activity of AgNPs observed that intracellular factors, pro-inflammatory response, and gene expression regulation could be influenced by the adsorption of cytosolic proteins on NPs surface [102]. Understanding of mode of action of these nanomaterials is very important, however not a lot of work is done in this aspect. Some studies described modes of action of AgNPs as involvement in gene expression[103], autophagy [104] and signaling pathways [105], ROS production [106], DNA damage [107], lysosomes degradation [108], oxidative stress, and energy supply. Moreover, mitochondrial dysfunction, LDH release, and endoplasmic reticulum stress were also found to be involved in anticancer effects of AgNPs [109] as shown in Fig. 8.

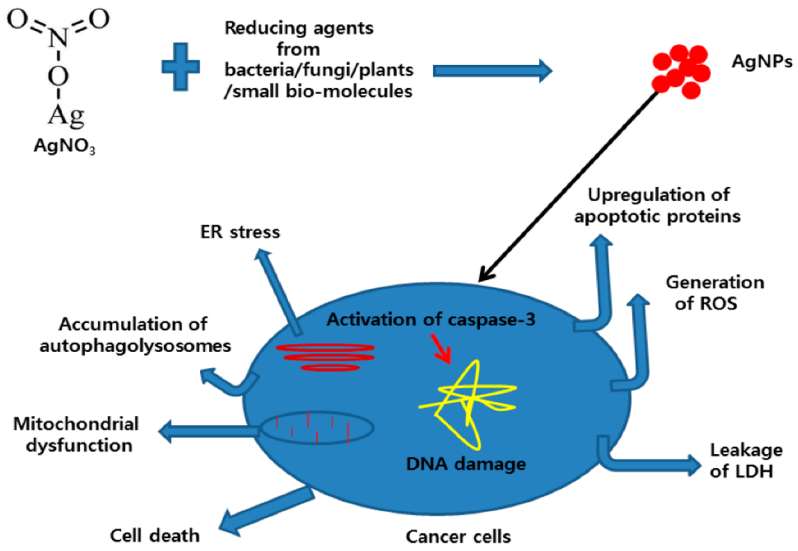

Fig. 8. Mode of action of AgNPs [109] (re-printed with permission).

Thevenot et al. fabricated photocatalytic TiO2 NPs to explore their anticancer photocatalytic activity and were found to be highly cytotoxic through membrane damage of different cell cancer lines including prostate cancer, lung cancer, and melanoma [110]. Another promising material for drug delivery and phototherapy is Cerium oxide. These NPs exhibit the ability to damage only cancer cells without damaging normal cells by oxidative stress and radiations [111]. Ali et al. demonstrated that cerium oxide NPs could enhance ROS production in A375 cells, also these NPs declined the cellular viability and induced DNA damage by chromosomal condensation. Moreover, caspase-3(cysteine-aspartic proteases, cysteine aspartases or cysteine-dependent aspartate-directed proteases) activity was also observed during this study, all these resulted in the programmed death of cancer cells [112]. Copper oxide NPs can also be taken into consideration when thinking about drug delivery and cytotoxic agents. These also can generate ROS and enhance apoptosis meaning that they can be used in cancer therapies and can be synthesized by the green synthesis process[113].

7 MXenes nanoparticles

The MXenes with a general formula of "M_{n+1} Xn Tx", where X is for nitrogen and /or carbon M is any 'transition metal", and T can be any surface functional group are essentially 2-D sheet-like metaloceramics. Their properties lie between metals and ceramics. Owing to versatile chemical and physical characteristics, the MXenes are among the most functional types of nanomaterials over the last decade. All credit goes to their exciting biocompatibility, tunable electronic and optical properties.

7.1 Synthesis of MXenes

MXenes are fabricated by selectively etching the A-element from layered MAX phase, Mn+1AXn precursors. (n=1, 2, or 3, "M" means early d-transition metal, "A" mainly represents a group IIIA or IVA (i.e., group 13 or 14) element and "X" is C and/or N) [114]. Fig. 9 shows the schematic illustration of MXene synthesis.

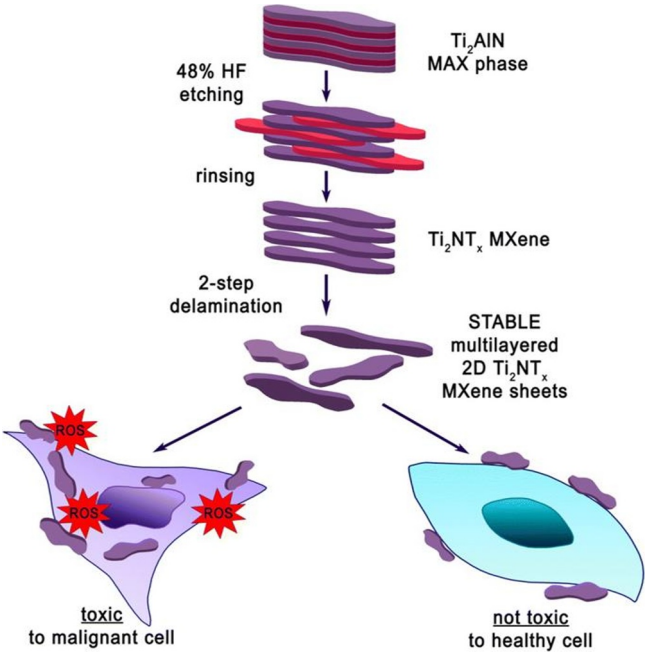

Fig. 9. Flow chart diagram of the synthesis of 2 –D MXene and its cytotoxic potential [115] (re-printer with permission).

This new arena welcomes input from biomedical scientists to develop more useable MXenes to utilize them for various purposes. Apart from other astonishing characteristics, they are unique and guarantee their use for biomedical applications in two ways. Firstly, they have several functional groups such as oxygen and hydroxyl making them able to carry various drugs and secondly, they are found to be cyto compatible ensuring target delivery and less toxicity. Since grapheme, In recent years, MXene nanomaterials have entered an exciting phase.[116].To fight cancers, multiple MXene platforms have been fruitfully synthesized.[117]. Although, MXenes has a large surface area, various surface functional groups, good biocompatibility, excellent mechanical, electronic, and physicochemical properties, still, various problems have to be faced during administration. So, surface modification and functionalization are opted to enhance their viability and usage [118]. One such technique is Self-initiated photo-grafting and polymerization (SIPGP). Brush grafting on the surface of MXenes has been performed in a single step at room temperature under UV irradiation. Chen et al [119] have brush grafted poly (2-(dimethylamino) ethyl methacrylate) (PDMAEMA) through SIPGP. In another method, aryl diazonium is utilized as they are well known in surface chemistry for their ability to form covalent bonds at various surfaces [120]. These techniques are found effective in limiting problems like poor water dispersibility, difficulty to form a stable suspension, and hindrance to the intravenous drug administration route as faced with non-functionalized MXenes. Hydrophilic polymers like soybean phospholipids are used for surface modification. Stability problems have been prevailed after fabricating PEG MXenes [121].

7.2 General properties of MXenes

MXenes exhibit an exceptional blend of electrical, mechanical, optical, magnetic, and topological characteristics which make them suitable for diverse applications [122]. Fig. 10 shows the general properties and applications of MXenes. MXenes have revolutionized

biomedical science and researches is going on for its application in the medical field and especially in photothermal therapy of cancer [123].

Fig. 10. Applications and properties of MXenes [122] (Re-printer with permission).

The pure MXenes are expected to be metallic in nature and semiconductors, as of the MAX phases [124]. Classically, the outer layer of transition metal makes the non-terminated MXenes metallic having a high density of states (DOS) at the Fermi surface. Their electronic properties are mainly determined by outer transition metal as compared to the inner layer of transition metals. Thus the outer layer transition metals surface termination may drastically change the electronic band structure [125]. MXenes exhibit conductivity of metallic type and have no optical gap in dielectric function [126]. MXenes "linear optical properties" like photoluminescence absorption etc and" nonlinear optical properties" like saturable absorption, nonlinear refractive index mainly rely on energy structure and especially on the scattering of linear and nonlinear dielectric function (ε) or refractive index [125, 127]. Moreover, 2 –D MXenes have a wide array of magnetic properties. 2D Cr_2C, Cr_2N, Ta_3C_2, Cr_3C_2 are ferromagnets [128], which could be exfoliated from their MAX phases [129] while 2D Ti_3C_2 and Ti_3N_2 are antiferromagnets. Although most of the MXenes are metals and semiconductors, some of the functionalized MXenes are 2D topological insulators (TI) [130] where electrons transmit along the edge states resulting in dissipation-less transport [131] and are appropriate for low power electronic appliances [131].

7.3 Environmental application

$Ti_3C_2(OH/ONa)_xF2\_x$ MXenes were synthesized by Peng and coworkers [132] by using chemical exfoliation technique and later on alkalization intercalation was done the obtained MXene adsorb more lead Pb(II) than the other heavy metals ions in the same water solution. $Ti_3C_2T_x$ MXene was generated and used to remove copper ions from water by Shahzad and colleagues [133].

7.4 Bio medical applications

7.4.1 Biological activity of MXenes

On reviewing the available literature, MXene exerts its biological activity on living cells by generation of reactive oxygen species This property makes MXenes exert anti-cancer potential due to the already increased baseline amount of reactive oxygen species within cancer cells owing to increase anabolic and catabolic reactions [134]. A.M. Jastrzębska et al [135] studied the biological activity of MXenes in vitro on normal and cancerous cell lines by using MRC-5 normal lung cell and HaCaT normal skin cells while A375(malignant melanoma cell of skin) and A549 (alveolar basal epithelial cell of human)being cancerous cell lines .MXenes exhibited higher cytotoxicity for cancerous cell lines. The underlying mechanism for cytotoxicity was the production of " Reactive Oxygen species(ROS) as MXenes affect oxidative stress [135]. The A 459 cell lines showed the highest cytotoxicity after incubation with MXenes [135].

7.4.2 Bio sensing

Bio sensing is a useful analytical technique employed to detect targeted biomolecules such as Hb in blood or H2O2 in water, this technique is widely being studied [136-137]. Direct Electron Transfer (DET) is a key step being researched between an enzyme and electrode surface. Due to larger surface area, excellent electrical properties, and biocompatibility, MXenes based materials serve advanced and reliable biosensing [138]. Nafion/Hb/MXenes/GC electrode is one such example that has overcome the problem of losing the bioactivity of the enzyme [139]. Ma and coworkers [140] constructed a Ti3C2-based piezoresistive sensor from the three-layered polyimide to detect human bending/release movements such as coughing, swallowing, or joint bending. This MXene-based sensor was used to construct electronic skin and other devices for real-time monitoring of human parameters in <30 ms [140]. Fang and coworkers [141] invented a device that single abnormal nucleotide in human urine. which may indicate gene mutations related to the disease. Zhou and colleagues [142] used MXene based sensors to detect the malathion and organo-phosphorous pesticide. Due to their low-level cytotoxicity, high ratio of 'surface to volume parameter, and superb electrical competence, MXenes have benefits in such applications [142].

7.4.3 Bio imaging

As compared to their application in biosensing there is a huge need to work on MXene applications in bioimaging. MXene quantum dots (MQDs) are mono-dispersed and have a uniform particle size of 1–5 nm used in bioimaging [143]. Owing to consistent nano-scale size, intensive luminescence, and excellent biocompatibility, MQDs have been fabricated before and were found excellent to penetrate the cells via endo-cytosis and are utilized for biological imaging [144-145]. Furthermore, MXene nanoparticles also have the potential to be employed in CT scan, MRI, and Positron Emission Tomography [146-147].

X-rays computed tomography (CT) proves as wonderful tool used in diagnosis. It is non-invasive, has high-resolution power, and can produce 3D images [148]. Mostly Iodine containing contrast agents are used which have short circulation time, high toxicity, and kidney damage. [149]. For safe imaging techniques, more biocompatible materials are being explored and MXenes proved to be the safer potential agent. Tantalum-rich Ta_4C_3 MXenes showed superb results owing to favorable size superb biocompatibility and environmentally safe synthesis techniques [146]. MXenes have also been tried in Photoacoustic (PA) imaging

techniques to visualize tissues. This technique converts optical energy to sound energy but it has a very narrow depth of penetration and needs Laser light.[150] These Laser radiations are harmless non-ionizing and use IR (infra-red) or visible spectrum. [151] Nb_2C_PVP (polyvinylpyrrolidone) was used by Lin and colleagues as a contrast agent for PA and also they found Ta_4C_3 MXenes appropriate to visualize tumors using both CT and photo acoustic imaging techniques [117] The colloidal stability of nano particles is the key factor that enhances their biocompatibility [135, 152].

8 Role of MXene in Cancer therapeutics

MXenes have been used both in vitro and in vivo cancer models. MXenes has opened a new era of theranostics, where one radio-active drug diagnoses the tumor while at the same time the other drug treats the tumor. The need for ideal nanomaterials containing excellent biocompatibility and emerging properties of cancer theranostics applications already began over the past decades. Crop-up properties of MXenes in biocompatibility, optical, and thermoelectrical applications, are emerging in cancer theranostics [153]. The study of MXenes in cancer applications is still in the crop-up stage. Photothermal therapy is an important application of MXene due to its eccentric electric and magnetic properties. Fig. 11 shows the implementation of MXenes in various ontological practices to detect and treat cancer.

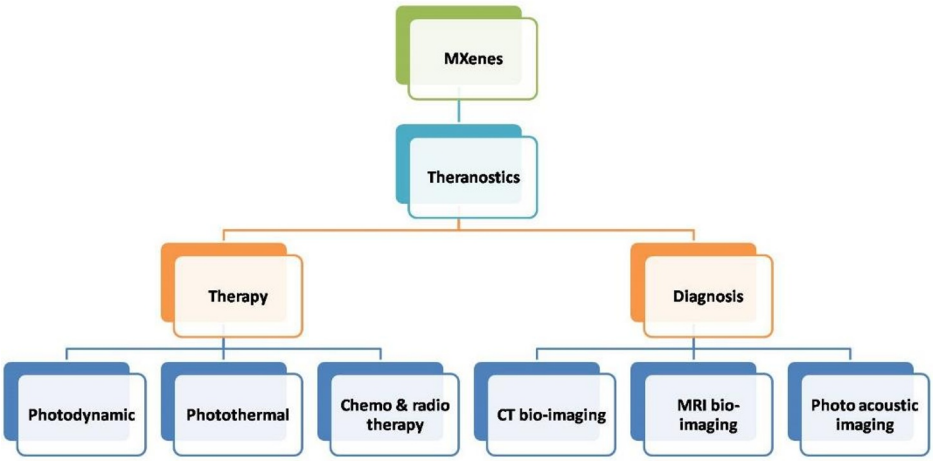

Fig. 11. Role of MXenes in Oncology [13].

8.1 MXene in drug delivery systems for targeted chemotherapy

Chemotherapy is a must-go and crucial step in cancer treatment. Cancer drugs destroy normal cells as well along with cancerous cells and patients suffer from serious side effects. Therefore, it is needed to develop such drug delivery systems that could concentrate more on cancer tissues and promote targeted drug delivery. MXene nano sheets of Ti_3C_2 are said to be promising agents for drug delivery due to unique structure, tunable functionalization [154]. Anti-cancer drug doxorubicin (Dox) was tried as an example by conjugating it onto the surface of Ti_3C_2 via electrostatic adsorption. It was noted that Dox release was significantly enhanced. Having a larger surface area and multiple functional groups, MXenes have the potential for binding large number of drugs for targeted drug delivery [155-156]. Liu and co-authors demonstrated that MXene based drug delivery agents in cancer treatments

can't be controlled elaborately; therefore, they fabricated hetero structured Ti_3C_2-CoNWs nano wires as drug delivery carriers to overcome the limitations. During clinical trials, improvised drug loading capacity and significant photothermal conversion were noted. And it was also observed that PH change can affect the Doxorubicin release. [157]. Al^{+3} ultrathin Ti_3C_2 MXene nanosheets (100) were also tried in another study to treat cancers. The nano sheets demonstrated an excellent mass extinction coefficient (28.6 Lg–1 cm–1 at 808 nm), superior photothermal conversion efficiency (about 558.3 percent), and effective single oxygen production ($^1O_2$) after laser irradiation of 808 nm [158].

A versatile Ti_3C_2-DOX nano platform has been fabricated by surface amendment Ti3C2 nano sheets with hyaluronic acid (HA) and DOX. And due to this combined photothermal and chemo synergistic effect this Ti_3C_2-DOX platform exhibited enhanced biocompatibility, tumor-targeted accumulation, and stimulus-receptive drug release potential and acquires booming cancer cell killing and demolition of cancerous tissue, both in vitro and in vivo. [158]. A new composite platform containing 2D MXene nano material was formulated by using surface nano pore modification technique Li et al. [159] The technique equips MXenes with very well-defined nano pores for the release / targeted drug delivery on demand, better hydrophilic nature/ dispersion, and strong surface chemistry for the target. Comprehensive in vitro and in vivo studies have established the active-targeting capacity of arginine-glycine-aspartic acid (RGD)-targeting Ti_3C_2 MXene in tumors and synergistic chemotherapy (contributed by the mesoporous shell) and photothermal hyperthermia (contributed by Ti_3C_2 MXene core) to entirely eradicate the tumour without any noticeable recurrences. Widespread in vitro-in vivo experiments illustrate targeted and improved cancer therapy and photothermal hyperthermia, by these mesopore-coated 2D Nb_2C MXenes in the NIR-II bio window [160]. While encouraging remarkable results, however, there is still considerable research to be done to explain and confirm the potential benefits for cancer nano medicines of MXene-based PDT. In order to incorporate these 2D materials into clinical use, the assessment of their long-term toxicity is important to fully characterize their safety and effectiveness.

8.2 Photothermal therapy (PTT)

PTT works by utilizing NPs invaded in tumor cells where laser energy converted into heat resulting in ablation of tumor cells. This therapy produces cell necrosis which may induce a pro-inflammatory response, which is deleterious to the success of treatment [161]. Among many proposed treatment options, photothermal therapy is unique and has fewer debilitating side effects, but poor absorption through the skin remained an issue. This problem can be prevailed by utilizing MXene-based materials. Lin and Chen et al have used Nb2C-based material for vastly competent photothermal ablation cells in mice [117]. In another study, MXene (Ti_3C_2) as a PTT platform for cancer treatment was reported. Not only in vitro as well as in vivo studies have shown that both soybean phospho-lipid treated MXene nanosheets and a phase-changeable organic-inorganic hybrid (PLGA/Ti_3C_2) has shown good biocompatibility and efficient photo-response for killing cancer cells. [156]. Li et al also proved excellent light to heat conversion capability of MXene nano sheets. [155]. In another study, hydro-gels-based 3D networks with hundreds-of-micrometer-sized pores of ultrathin Ti_3C_2 and cellulose were developed with excellent photothermal performance and flexible physical properties. It has also been observed that doxorubicin (a chemo therapeutic drug) loaded cellulose/MXene hydrogels were reported as efficient drug carriers as well as showed controlled drug release in water. These hydrogels also showed near infra red-light stimulation properties so these can act as photo thermal as well as chemotherapeutic agents. Such drug loaded cellulose/MXene hydrogels can be strong enough to combat cancer cells more efficiently than either alone chemotherapy or photothermal therapy This study leads to the

fabrication of MXene-polymer-based organic-inorganic hybrid composites for treating the cancers [162].

MXenes have been also studied in combination therapy. Liu and colleagues suggested Ti3C2-based nano platform that targets tumor sites and chemotherapy, PDT and PTT were used synergistically [158].

8.3 Photodynamic therapy (PDT)

PDT is a type of phototherapy that utilizes the production of Reactive Oxygen species (ROS) to kill cancer cells. This treatment modality is yet developing and has restricted tissue invasion. It is used clinically in combination with like radiation therapy, surgery, and chemotherapy [163]. In the mitochondria of every living cell, oxidative phosphorylation is continuously going on and reactive free oxygen radicals are continuously being generated as a by-product. Which is regulated by cell defense mechanisms.[164]. The cancer cells have altered mitochondria function due to abnormal cell cycle regulation and thus have a relatively high concentration of reactive oxygen species as compared to healthy cells.[164] these ROS levels, their type, and site of production determine the cancer cells' viability and later on metastasis to distant body sites. If the ROS levels exceed the threshold levels, it may cause cancer cell death [165]. This phenomenon is depicted in Fig. 12.

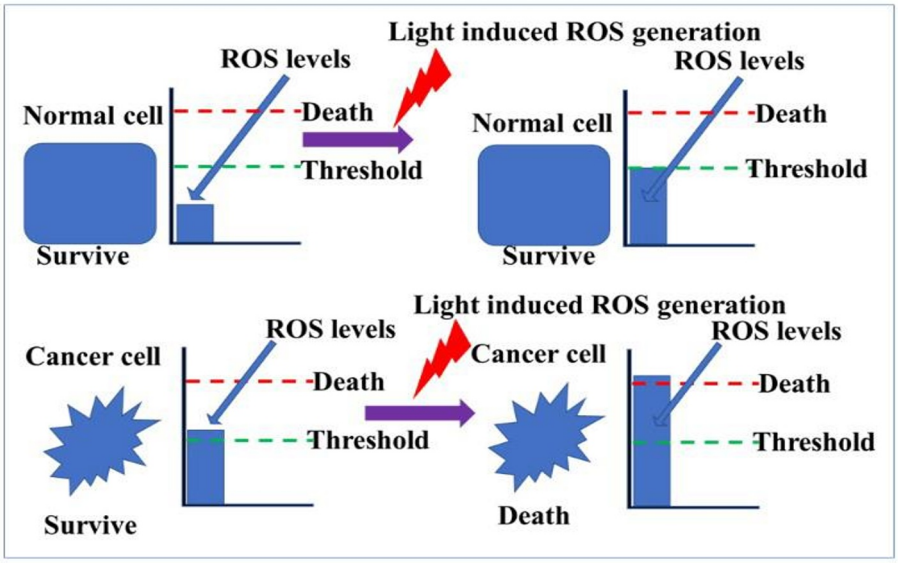

Fig. 12. ROS mediated cell survival and death mechanism and use in PDT (re-printed with permission).

8.4 MXenes in Radiotherapy

Radiation therapy is used for many decades for cancer treatment. It utilizes X-rays, gamma rays, or proton/neutron radiation to produce ROS radicals which damage the cellular DNA leading to mitotic failure and cell death [166]. The MXene synergistic radiation therapy is under trial still very less data is available. But Ti_3C_2Au nanocomposite has been studied in radio photo combined therapy to treat cancer cells with promising results[164].

9 MXene in cancer theranostics

Recent studies showed, MXenes have a very effective role in cancer therapeutics and diagnostics. It has prompted them to explore a new area called theranostics, which aims to effectively combine both the therapy and imaging functions. Furthermore, by enhancing contrast in different imaging methods and providing tailored care, it allows for early detection of the deadly disease. To date, Ta_4C_3, Ti_3C_2, and Nb_2C have all been successfully tested in cancer theranostic applications. To put it another way, superparamagnetic iron oxide nanoparticles (IONPs) embedded in Ti_3C_2 have proved to be the first MXene in a cancer theranostic sample [167].

10 Challenges for MXenes in cancer treatment

Despite the remarkable success in the field of nanotechnology and cancer treatment, nanomedicine in cancer therapy still faces obstacles such as tumor heterogeneity and complexity, lack of understanding of bio-nano interactions, limitations in chemistry, controls, manufacturing, and commercialization. Therefore, it is important to emphasize these aspects to deal with these obstacles. Along with the promising fabrication of High-performance porous MXene-based devices and bringing them into practical applications, much improvement has been achieved in this field of science, still, many challenges remain. Initially, how to get fully adjustable pore composition and shape of developed mesoporous MXenes. Unfortunately, certain porous MXenes have a large distribution of particle size and interpenetrated pores, and the development of reliable and accurate structure-property relationships is extremely challenging. The performance of therapeutic NPs relies on their physiochemical properties. Research on underlying factors in drug delivery systems, internalization & cell targeting, tumor penetration, and efflux, and the efficacy of immunity needs to be studied on a large scale [167-170]. However, the systematic screening of NP properties remains challenging, consequent from the test of rapid, accurate, and reproducible amalgamation of NP libraries with remarkable properties. Contrasted and conventional mass methods, which by and large structure NPs with high polydispersity, microfluidic advancements have as of late stood out for high-speed self-assembly of NPs with smaller size circulation, tunable chemical and physical features and higher batch-to-batch reproducibility [171-172]. Thus, particle replication in non-wetting format (PRINT) innovation has empowered the fabrication of monodisperse NPs with precision in, shape, size, drug loading, chemical composition, and surface functionalization. Such advancements could in the long run encourage NP revelation, undifferentiated from the way high throughput screening of little atoms propelled drug production [173-174].

With the quick rise of nanostructures or biomaterials, in vitro assessment is imperative to distinguish biocompatible applicants before animal testing is carried out. In vitro measures can likewise improve our comprehension of cell-NP interaction. As ordinary in vitro models utilizing cells refined in multiwell plates do not have the multifaceted nature of tissues and command over the liquid stream, such stages may not catch the complex interaction of NPs with physiological obstructions. Ongoing endeavors to create biomimetic 'organ/tumour-on-a-chip' devices may stay away from the impediments of current in vitro models [175-176].

The majority of MXenes are synthesized by down scaling route which has poor control for the preparation factors and thus the poor control of the final product. For theranostic fine-tuning is much needed which is a major obstacle. There is still no work on MXenes' role in Immunotherapy. Further research work needs to be conducted. Current challenges and trends are demonstrated in Fig. 13.

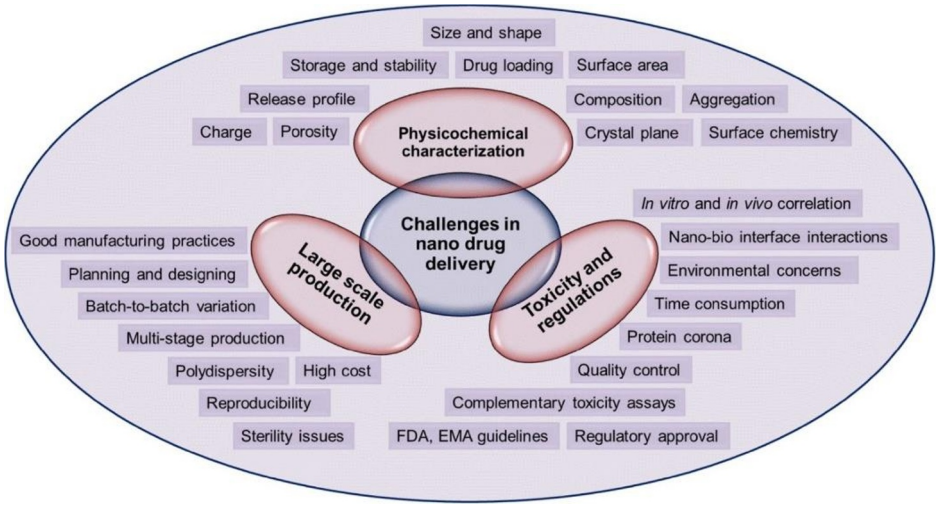

Fig. 13. Current challenges and trends for MXenes in cancer treatment [177] (re-printed with permission).

11 Conclusions

Cancer is among the major cause of human fatality globally. Thus, it has become important to develop new innovative and tailored cancer research strategies for early detection and treatment and to maximally reduce the side effects of therapy. In this regard the biomedical and anticancer properties of MXenes are gaining increasing interest due to their high biomedical activity, less bio-toxicity and photo-responsive nature. According to science direct data base, the publications related to MXenes (keyword used were: MXene cancer) increased from only 3 in 2016 to 164 in 2020. Studies have been conducted to understand the action mechanism and effectiveness of 2-D MXenes towards cancer treatment and detection. The near infrared photothermal response of MXenes made them a viable option to effectively reduce side effects of cancer related treatments without compromising the efficacy of the treatment.

In this review, an attempt has been made to detail the current cancer treatments, their side effects, and available & perspective remedies to avoid extreme side effects. Furthermore, detailed synthesis of MXenes from available literature has been presented related to cancer treatment and special priority has been given to photo thermal treatment due to its minimal side effects and high possibility for targeted chemotherapy and efficient drug release.

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