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NOVEL DRUG DELIVERY SYSTEM FOR THE TREATMENT OF VARIOUS CANCERS

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ABSTRACT

Cancer is one of the world's most devastating diseases. The estimated number of incident cases of cancer in India for the year 2022 was found to be 14,61,427 (crude rate: 100.4 per 100,000). In India, one in nine people are likely to develop cancer in his/her lifetime. Lung and breast cancers were the leading sites of cancer in males and females,respectively.

However, better understanding of tumor biology and improved therapeutic outcomes.

Nanotechnology has the potential to revolutionize cancer diagnosis and therapy. In this review, drug delivery system including liposomes, nanoparticles, micelles in developing novel drug delivery for various types of cancers therapeutics are discussed. Various nanocarriers have been introduced to improve the therapeutic efficacy of anticancer drugs. The current treatments of conventional dosage form for cancer treatment are discussed.

Recently, targeted drug delivery systems for anti-tumor drugs have demonstrated great potential to lower cytotoxicity and increase therapeutic effect.

This paper provides an overview of breast cancer, lungs cancer, uterus cancer, skin cancer, oral cancer , stomach cancer, bone cancer and blood cancer. Also includes conventional therapies, potential of novel drug technology in management of cancers andrational approaches for targeting cancers.

Keywords: Breast Cancer, Drug Delivery Systems For Breast Cancer, Lung Cancer, Drug Delivery Systems For Lung Cancer, Uterus Cancer, Drug Delivery Systems For Uterus Cancer, Skin Cancer, Drug Delivery Systems For Skin Cancer, Oral Cancer, Drug Delivery Systems For Oral Cancer, Stomach Cancer, Drug Delivery Systems For Stomach Cancer, Bone Cancer, DrugDelivery Systems For Bone Cancer, Blood Cancer.

I. INTRODUCTION

A very serious disease in which cells in one part of the body start growing and form lumps in a way that is not normal. A disease in which abnormal cells divide uncontrollably and destroy body tissue[1]. Cancer is the second leading cause of mortality worldwide. Therefore, cancer is a serious problem affecting the health of all human societies[2]. Unfortunately, it is a variety disease at the tissue level and this variety is a major challenge for its specific diagnosis,followed by efficacy of treatment[3,4] . In main, the highest percentage of cancer types occur in prostate, lungs and bronchus, colon and rectum, and urinary bladder, respectively in human, cancer prevalence is highest in the breast, lung and bronchus, colon and rectum, uterine corpus and thyroid respectively[2]. This data indicates that prostate and breast cancer constitute a major portion of cancer in men and women, respectively[5].For children, the highest percentage types of cancer disease are blood cancer, and cancers related to the brain[6,7].

In the past few decades, considerable attention has been focused and development of novel drug delivery system (NDDS) for herbal/chemical drug. The novel carriers should ideal fulfil two pretrequisites. Firstly it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, I should channel the active entity of herbal/ chemical including prolonged release dosage, forms are unable to meet none of these. In phyto-formulation research, developing nanodosage forms (Polymeric, nanoparticles, nanocapsules, liposomes, solid, lipid nanoparticles, phytosomes and nanoemulsion etc.) have a number of advantages for herbal/ chemical drugs, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of stability, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation etc.[8]. The development of efficienrt drug delivery system(DDS) that optimize thepharmacological action of drug received great attention during the last twenty years. One of these recent approaches is the use of nanoparticles technology, which has many advantages over the controlled release, including the improvement of drug solubility and stability enhancement of efficacy, and reduction of toxicity. Nanoparticles(NPs) are solid, colloidal particles that vary in size ranging from 10nm to less than 1000nm. However, the preferential size of a nanomedicines is less than 300nm, in which the drug is loaded dissolved passively absorbed chemically bound to the surface of the polymer[9].Chemotherapy is an essential line of defense against cancer. However, these drug do not act selectively on tumor sites and can also act on healthy

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tissues. Whether for chemo or other systemic therapy, low intratumoral accumulation leads to the administration of higher doses. Above two short comings could both generate systemic toxicity which is associated with severe side effects[10,11]. Cancer is among the most devastating disease and the root cause of more than25% deaths worldwide[12]. Lung, breast, colorectal and stomach cancers are the most diagnosed malignancies, globally, accounting for more than 40% of all cases. According to WHO, men have a 25% higher standardized cancer incidence rate than women. Cancer kills 04 million people in India each year, making it the third leading causes of death. In addition to chemotherapy and surgery, radiation therapy, hormone therapy, hormone therapy, and immunotherapy may be used to treat cancer. Chemotherapy is the standard treatment for most disseminated cancer. Cancer chemotherapy attempts to destroy cancer cells while inflicting little or no harm on healthy tissues[13].

Types of Cancer-

- **Breast Cancer:-**

According to National Cancer Institute of the U.S., breast cancer is the second common cancer seen in women and it begins in breast tissue, usually the ducts and lobules.

Breast cancer shows no symptoms in the early stages; therefore screening tests often fail todetect the disease at this time. The following changes may occur with breast cancer growth:

- A lump in or near the breast
- A change in the size of shape of the breast
- A change in the skin of breast , areola, or nipple[14].

Breast cancer is a deadly disease that can metastasize to distant organs such as bones, liver, lungs and brain. This type of metastasis is usually the cause of breast cancer's incurability. If detected early , breast cancer has an excellent prognosis and a high survival rate. Breast cancer is exacerbated by risk factors such as sex, age, family history and an unhealthy lifestyle[15]. Breast cancer can be classified into two types namely histological and molecular subtypes. The molecular subtype is further classified into Luminal A (ER- positive, PR positive, HER2 negative, Ki-67 protein low), Luminal B (ER-positive, PR negative, HER2 negative, high Ki-67 protein), Basal like breast cancer(ER negative, PR negative, and HER2- negative, K5 114 *), HER2- enriched (ER negative, PR negative, HER2 positive, high Ki-67 protein), normal breast like (adipose tissue gene signature*), and claudin low (ER negative, claudin negative, low E- cadherin). On the other hand, histological subtypes are broadly classified into two types, namely in-situ carcinoma, and invasive infiltrating carcinoma. In-situcarcinoma is further divided into ductal and lobular where ductal is further sub-classified into cribriform, papillary and solid. Invasive infiltrating carcinoma was further divided into tubular,ductal lobular, invasive lobular, infiltrating ductal, mucinous, and medullary[16].

The treatment options for breast cancer depend on its type and stage at which it is first diagnosed. Currently available options include chemotherapy, surgery, immunotherapy, genetherapy, and hormonal therapy. Among these ,chemotherapy is the most preferred method for cancer treatment . Chemotherapy is defined as the use of cytotoxic agents to prevent cancer cells from growing and spreading and eliminate them. However, Chemotherapeutic agents are equally responsible for unwanted toxicity to normal tissues. The majority of chemotherapeutics come with the disadvantages of low bioavailability, the short circulation time of their active pharmaceutical ingredients, and toxicity to normal cells. Injectable nanomedicines are being explored to overcome these challenges, to increase effectiveness while reducing potential side effects[17].

- Stages of Breast Cancer –

A) Stage 0: In Situ

A secondary microscopic discovery of abnormal tissue development in the lobular breast is called as in situ lobular cancer. Neither breast progresses to anotherinvasive breast cancer, but the probability of a successive invasive breast cancer increases by about 7% over 10 years[18].

B) Stage I and Stage II : Early- Stage Invasive

Stage I is the earliest stage of invasive breast cancer, where the tumor size ranges upto 2cm without affecting any lymph nodes. The cancer cells spread to a distant location from the original location, which surrounds the breast tissue [19]. In stage II, also known as invasive breast cancer, the tumoe may be 2-5 cm in size. It usually spreads to the lymph node under the arm. Stage II breast cancer present with

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a slightly new type of disease. At this stage,cancer cells migrate outside the breast tissues, and the tumor brcomes bigger than in stage I. However, stage II indicated to that the disease has not spread to distant organgs[19].

C) Stage III : Locally Advanced

Stage III is locally advanced breast cancer and the tumoe size of the breast tissue exceed 5 cm in diameter. It is extensively found in the underaem lymph nodes.It is a new foem of invasive breast cancer, a new form of invasive breast cancer, and cancer cells usually do not spread futher in the body. The tumor is huge at this stage,which may extend to thr chest wall or the skin of the breast[19].

D) Stage IV: Metastatic

Stage IV occurs when the tumor has spread to distantb parts of the body. The affected areas include the brain, liver,bones, and lungs. The cancer can spread tomore than one part of the body[19].

- **Treatment for Breast Cancer:**

Liposomes:

About 40 yrs ago, British haematologist Prof. Alec D. Bangham described conventional liposomes as spherical phospholipid vesicles composed of bilayer membrane that surrounds an aqueous interior. Both lipophilic and hydrophilic drugs can be entrapped into liposomes because of their biphasic character. Lipophilic drugs are very poorly soluble in water, hence entrapped in the lipid bilayers of liposomes. Hydrophilic drugs may be entrapped inside the aqueous care of liposomes or located in the external water phase. The preparation procedureand bilayers composition of liposome affects the percentage entrapment of hydrophilic drug[20]. The combination of doxorubicin and cyclophosphamide utilizing non-PEGylated liposomes were used for the treatment of metastatic breast cancer[21]. Combined delivery ofquercetin and vincristine via liposomal delivery has been delivered for enhanced estrogen- receptor-negative breast cancer treatment. Studies demonstrate the synergistic effect of both encapsulated chemotherapeutic drugs[22]. Nanoliposomal short-chain ceramide inhibits agonist-dependent translocation of neurotensin receptor 1 (NT5R1) to structured membrane microdomains, in breast cancer cells. Generally,it reduces NTSR1 interaction with Galphag/11 subunits within structured membrane microdomains, consistent with diminished NTS- induced translocation of NTSR1 into membrane microdomains. Thus, ceramide based liposomal formulations have the potential to inhinbit NTS-dependent breast cancer progression[23].

Micelles:

Polymeric micelles (PMS) are colloidal particles prepared from conjugates of water- soluble polymers with phospholipids or long chain fatty acids and other surfactants. Micelles are used for the delivery of water-insoluble chemotherapeutic drugs. They were first proposed by pawl Ehrlich for targeted drug delivery to diseased cells. Micelles accumulated at poorly vascularized tumors and enhance permeability and retention and increase the half- life of anticancer agents[24].Amphiphilic methoxy-poly(ethylene glycol) grafted polyphosphazene with glycine ethyl ester side groups (PPP-g-PEG/GlyET) has been synthesized and utilized for nthe preparation of doxorubicin loaded polymeric miceller systems. Doxorubicin loading, sustained release with significant higher uptake in Adriamycin- resistant humans breast cancer MCF-7 cell line[25].Genexol-pm is an FDA-approvedpolyethylene glycol-polylactide (PEG-PLA) polymeric micelle of paclitaxel used to treat breast cancer[26].In another study of the use of Paclitaxel pm formulation in metastatic breast cancer patients, the Genexol-pm response rate was observed to be 58.5% compared to plain drugs that are in clinical trial phase I and Phase II. However ,in SK-BR-3 cells, antibody –decorated NPs have shown 53.4%and 38.6% higher cellular uptake than the plain micelles in phase I andII, respectively[27].

- **Lungs Cancer:**

Worldwide lungs cancer is the leading cause of cancer-related deaths with adismal 5 year survival rate of only 15%. Every year in the united states approximately 220,000 individuals are diagnosed with lungs cancer of which 85% of the cases are classified as non- small-cell lungs carcinoma (NSCLC)[28].Lung cancer is heterogenous disease that arise when genetic and epigenetic alternation happens in lung epithelium[29]. “Osimertinib is a new- generation EGFR protein inhibitor that has shown efficacy in people with locally advanced NSCLC as well as in these with whose tumor has metestasized to the central nervous system”. The carriers in DPSs may deliver drugs in a different way: transdermal (eg. membrane), implantable (eg.stents, implants),parenteral (eg. hypodermic needle) or pulmonary (eg. liposomes solid lipid and polymer particles)[30,31]. Lung cancer is categorized into two categories based on histological assessment, which are

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1) Small cell lung cancer(SCLC)

2) Non-small cell lung cancer (NSCLC)[32].

In developing countries, NSCLC is very common primarily due to smoking and it accounts for at least 85% of cases of lung cancer, whereas, SCLC accounts for the rest of the 15% cases[33]. NSCLC is further categorized into three sub-categories i.e.,a) Adenocarcinoma(AD)

b) Large cell carcinoma (LC) c)Squamous- cell carcinoma(SCC)[34].Causes of Lungs cancer:

The main cause of lung cancer(and cancer in general) include carcinogens(such as those in tobacco smoke), ionizing radiation, and viral infection. This exposure cause cumulative changes to the DNA in the tissue lining the bronchi of the lungs (the bronchial epithelium). As more tissue becomes damaged, eventually a cancer develops[35]. Smoking, especially of cigarettes is the main cause of lung cancer. Smoke from cigarette contains approximately 73 known cancer- causing agents, including benzo(a)pyrene[36]. Professor George G. chen from Chinese universities of Hong Kong, china presented in 5th world congress on cell and steam cell research about thromboxane in smoking-induced lung carcinogenesis[37]. Exposure to radon is estimated to be the second-leading cause of lung cancer, accounting for an estimated 21,000 lung cancer deaths each year (range of 8,000 to 45,000). Radon is a tasteless, colourless and odourless gas that is produced by decaying uranium and occur, naturally in soil and rock. The majority of these deaths occur among smokes since there is a greater risk for lung cancer when smokes also are exposed to radon[38]. Lung cancer can also be caused by occupational exposures, including asbestos, uranium and coke(an important fuel in the manufacture of iron in smelters, blast furnaces and foundries). The combination of asbestos exposure and smoking greatly increases the risk of developing lung cancers[39].

- **Treatment for lung cancer:**

Polymeric nanoparticles:

A dry powder formulation of doxorubicin (DOX) encapsulated in NPs was developed by Azarmi et al. This vector was produced by method of polymerization emulsion and then dried. After being redissolved in deionized water,the particles had an average size of 173±43nm. The DOX- loaded NPs showed enhanced cytotoxicity compared to free DOX[40].

Liposomes:

Anabousi et al. carried out in vitro assessment of transferring-conjugated DOX- loaded liposomes as drug delivery systems for inhalation therapy of lung cancer[41].Nanotechnology had emerged on the commercial scale when the first product using NPs, Abraxane, an injectable suspension of albumin NPs with bound paclitaxel was used for cancer therapy and became available in 2005[42]. Paclitaxel(PTX) is a drug commonly used for lung cancer, however, it has serves limitations, which include the development of peripheral neurotoxicity, which may lead to treatment suspension and therapy failure[43]. Zhu et al worked on a liposomal dry powder(LDP) of docetaxel(DTX) as LC therapeutics. DTX encapsulated in folic- acid-conjugated liposomes demonstrated significant cytotoxicity and excellent tumor targeting properties[44].In both pharmacological and pharmacokinetic terms the re-dispersed liposome obtained after the redipersion liposomes obtained after the redispersion of inhaleddry powders differ from the initial liposomes .A study by Gandhi et al show that by using the lyophilisation process, gemeitabin HCI could be effectively integrated into LDP[45].

Nanoparticles:

In lung cancer treatment ,liposomes may be promising delivery system for drug and genes. The drug of choice for the treatment of NSCLC for the last two decades, cisplatin, is implicated in the development of nephrotoxicity in 20% of patients receiving high doses[46].

Methotrexate (MTX) has poor tumor retention ability due to its high water solubility ,which likely contributes to its slow or poor therapeutic response in patients.However, golg nanoparticle conjugates of MTX have high tumor retention and enhanced therapeutice efficacy bin a lewis lung carcinoma mose model[47].Solid lipid nanoparticle (SLNs) are a newly emerging surrogate to the traditional colloidal delivery system. SEM (scanning electron microscopy) and TEM (Tranissions electron microscopy) analysis have revealed the spherical shape of solid-lipid nanopaeticle and their size, ranging from 50-1000nm,the safety profile ofSLNs was attributed to their biocompatible lipids that are highly tolerable by the lungs antibody[48]. The polymer used for lung cancer treatment includes alginic acid, chitosan,gelatin,polycaprolactone, polyactide-co-glycolide and polylactin acid. However, on suppliementing these polymeric Nano particles with sulphide bond. It regulates the released of the therapeutic drug[49].

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➢ **Uterus Cancer:**

Uterus cancer incidence is highest in north America and northern Europe, intermediate in southern Europe and temperature south America and lowest in Southern and Eastern Asia and most Africa[50]. Nano-sized drug delivery systems (NDDS) are gaining widespread intersted among scientists as a promising and innovative strategy in combination therapy to increase the effect of co-delivered chemotherapeutic drugs due to their enhanced retention and permeability,as well as their extention blood circulation time, controlled drug released , and prevention of drug degradation[51].Endometrial cancer, or uterine cancer, is a malignancy arising from the endometrium. Women al-in-40 lifetime risk of being diagnosed with endometrial cancer, the fourth most common malignancy among women. Uterine cancer is the most common gyneological malignancy inn the united state[52].Most studies have found that the increased relative risk of developing endometrial cancer for women taking tamoxifenis two to three times higher than that of an age matched population[53].

Uterine fibroid lesions were initially knows as the "uterine stone". In the second century AD ,they were called scleromas .The term fibroid was first introduced in the 1860s.Uterine fibroids are the most common pelivic tumor among women of reproductive age, affecting more than 70% of women world wide ,particulary women of color[54,55]. The uterine is the place where the child grows during pregnancy. The uterus is the size and shape of a hollow and inverted poor[56]. The uterus has two layer myometrium is the layer of muscle tissue and forns most of the uterus . The endometrium is the inner layer or inner lining[57].

- Stages of uterus:

1. Stage I – Limited to the uterus

IA – Limited to the endometrium, no invasion or invasion of the than less half of the myometrium.

IB – Invasion of more than half of the myometrium.

2. Stage II – Invasion into the cervical stroma.
3. Stage III – Extenison into pelvis or vagina. IIIA – Invasion into the serosa or adnexa. IIIB – Vaginal or parametrial involvememt.

IIIC – spread to pelvic (IIIC1) or para-arotic lymph nodes (IIIC2)IV .Stage IV- Extension into bladder/ rectum or distant metastasis

IVA – Extension into bladder/ bowel mucosa.

IVB- Distant metastasis into omental or inguinal lymph nodes [58].

- Causes of Uterus Cancer:

Being postmenopausal, or reaching menopause(after age55). A thickened wall lining (endometrial hyperplasia).

Never having children.

Starting periods early(before age 12). Having high Blood Pressure(BP) or Diabetes.Being overweight or obese.

Family history of ovarian, uterine, or bowel cancer[59].

Treatment for Uterus Cancer:

Disulfiraam has been used safely in the clinic for many years to treat alcoholism and has shown potential anti-tumour activity as it can include apostasis in some cell lines and reduce cell growth in certain tumours[60]. One group compared five cycles versus ten cycles of treatment with cyclophosphamide, doxorubicin and cisplatin at a frequency of one cycle for every four weeks. The result showed that ten cycles of treatment induced higher toxicity myelo suppression, hospital admission for nadir fever, nephrotoxicity and neurotoxicity than the five cycles of treatment while causing on improvement to the number of complete response and survival[61].

Liposomes:

Doxorubicin belongs to a class of drug called antracycline, a cytostatic antibiotic used to treat various types of cancers such as break cancer, lymphoma, leukemia and ovarian cancer[62]. Antracycline was used as the first line treatment for ovarian cancer before the introduction of taxanes. Doxorubicin is a topoisomerase II inhibitor and promotes tumor cell DNA fragmentation. Its antitumor activity and drug toxicity can also be resulted from the formation of oxygen free radicals when doxorubicin is reduced inside the cell[63].

Lipid Based Nanocarriers:

Zhang et al. used both in HeLa cells and mouse cervical cancer models, folic acid(FA) modified, cisplatin-(CIS)-loaded nanostructured lipid carriers(NLCs) for cervical cancer chemotherapy, showing its efficacy in selective

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release in tumor cells that highly express FA receptors. Moreover, the FA-CIS-NLC-targeted transfer CIS to cancer cell increases its antitumor power[64].

Solid Lipid nanoparticle:

Paclitaxel is a chemotherapeutic agent used in the treatment of lung cancer, breast cancer, cervical cancer caused by the HPV virus, this drug is a microtubule stabilizing and inhibits the G2 or M cell phases of the cell cycle causing the cell death[65,66]. Doxorubicin is an effective anticancer drug, which induces caspase-dependent apostosis in cancer cells through oxidative DNA damage due the topoisomerase II inhibition[67,68].

Nanoemulsion:

Melphalan is an anticancer drug that has been used in the treatment of ovarian cancer, breast cancer and multiple myeloma, this medicine is used in pharmaceutical tablet and injectable forms[69]. The pharmacokinetic study showed prolonged levels of platinum and gadolinium in the blood with nanoemulsions in mice. Nanoemulsions exhibited less toxicity, increased the survival time of mice compared to an equivalent treatment of cisplatin[70].

- **Skin Cancer:**

Skin is known as the most prominent human body organ with approximately 1.8 m. square surface area. Skin mainly serves as a protective barrier against ultraviolet (UV) radiation, mechanical injury, chemicals and microorganisms [71,72]. Present time, skin cancer is a global public health challenge and its burden is continuously rising that may lead to profound effects on both the global economy and manpower. Skin primarily comprises of two major layers, the epidermis and dermis. The epidermis is the outermost layer of skin that consists of melanocytes, keratinocytes, merkel cells and Langerhans cells[73]. However, when the cells within the skin epidermis undergo neoplastic changes, this results in skin cancer[71]. Several internal and external factors are responsible for this deadly disease[74,75]. External factors include infectious organisms, unhealthy diet, pesticides, environmental toxins, and tobacco while internal factors include inherited genetic mutations, immune conditions and hormones. These factors may act together or in series to develop cancer [74]. There are several stages in cancer progression which is generally established with tumor size, extend of primary tumor and spreading capability to nearby lymph nodes or other organs. Diagnosis and staging are essential elements to initiate therapy. The conventional cancer treatment methods include surgery, radiation and chemotherapy. Several differences in normal and cancer biology render cancer therapy as a multidisciplinary task. Targeted therapy based on distinct tumor type aiming to maximize efficacy and minimize toxicity has remained extremely challenging. Targeted therapy has not been particularly effective in treating certain tumors[76].Apart from skin cells in stratum basale and squamous keratinocytes that are affected,

skin cancer could also originate from the skin melanocytes. Skin melanocytes are melanin- producing cells located in the stratum basale. Melanin, the skin pigment, acts as a natural sunscreen due to its protein structure that could scatter UVB light[77].Histological classification includes 100 different types of cancer that are classified into 6 major categories: i.e. carcinoma, sarcoma, myeloma, leukemia, lymphoma and mixed types[78]. According to the federal research US and development programme agency, the National Nanotechnology involves the development of carriers devices or systems sized in 1 to 100 nm range althoughthis limit can be extended up to 1000nm[79]. These biometric features, together with their surface-to-volume ratio and the possibility of modulating their properties, raised the interest of the high use in biomedical application with potential applications in imaging, diagnosis and therapy[80]. Early detection and treatment are crucial as the treatment is more difficult when the melanoma has metasized[81]. Nanomedicine has an enormous potential to improve the selectivity in targeting neoplastic cells by allowing the preferential delivery of drugs to tumours owing to the enhanced and retention effect(EPR). Furthermore, specific binding of drugs to targets in cancer cells or the tumor microenvironment increases the effectiveness ofpermeability the specific treatment of cancer cells, while leaving healthy cells intact. Nanoparticles(NPs) can also improve the solubility of poorly water-soluble drugs, modify pharmacokinetics, increase drug half-life by reducing immunogenicity, improve bioavailability and diminish drug metabolism. They can also enable a tunable release of therapeutic compounds and the simultaneous delivery of two or more drugs for combination therapy[82,83].

Treatment for Skin Cancer:

Liposomes:-

A study by Haung et al. used a combination of paclitaxel(PTX) and TRAIL with a Liposomal drug delivery system to achieve an increase in anti-melanoma effect, targeted drug delivery (hence, reducing toxicity) and tumor microenvironment responsiveness[84]. New opportunities were developed by Muthu and Feng that developed

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theranostic liposomes, with the possibility of loading a wide variety of diagnostic NPs along with anticancer drug in combination with Vitamin E TPGS coating. Liposomes can also be modified to incorporate a magnetic element for use in monitoring their movement within the body using MRI or to entrap gases and drugs for ultrasound-controlled drug delivery[85,86,87]. Other than a combination of chemotherapy drugs, systemic chemotherapeutic agents are also currently being implemented with immunotherapy for the effective treatment of skin cancer. Moreover, 5-FU is a potent chemotherapeutic medication that can be administered systemically or topically against skin cancer and pre-cancer lesions[88]. In this regard, 5-FU was paired therapeutically with cetuximab, an immunoglobulin G (IgG) antibody with an inhibitory effect on EGFR affinity. Cetuximab is essentially an IgG 1 monoclonal antibody. In the treatment of cancer, it inhibits EGFR through high-specific bond, which leads to inhibition of EGFR tyrosine kinase activity and, hence the interruption of the cell cycle. Petrilli et al. formulated a topical treatment of cetuximab functionalized liposomal complex encapsulating5-FU for skin cancer[88].

Nanoparticles:

Paramagnetic metals, such as gadolinium(Gd) or manganese (Mn), normally used in contrast agents, can also easily be incorporated into micelles for imaging applications.Polymeric nanospheres are insoluble colloidal nano or micro particulates possessing a polymeric core with sizes ranging from about 10 to 1000nm. They are mostly designed as pH sensitive drug delivery systems intended for oral delivery in order to survive in the strongly acidic environment of the stomach[89]. Consistent results demonstrating the cytotoxic effects were observed in a bioengineered melanoma model in which piplartine- loaded NE-C-OA caused a decrease in cell number and disorganization of the epidermis. However, the importance of targeted delivery of piplartine via topical route should be emphasized. This study also revealed that piplartine killed nano- tumor cells in the 3D cancer cell model[90]. Different types of drugs, including proteins and DNA as well as smaller drug molecules, have been linked to the surface chemistry of AUNP, inducing a therapeutic effect in several types of tumors, including melanoma. Gold nanoparticles are also excellent labels for biosensors, because they can detected by numerous techniques, such as optical absorption, fluorescence and electric conductivity[91]. Several techniques such as the use of chemical enhancers (i.e., oleic acid, 1-dodecylazacyclohepatan-2-one or azone, dimethyl sulfoxide, propylene glycol and ethanol) and the application of an electric field (e.g., iontophoresis, sonophoresis and electroporation) have, therefore, been developed to successfully overcome skin barriers and to reach skin malignancies by favouring drug penetration into deep layers of the epidermis[92]. Sodiun alginate, a linear and anionic polysaccharide is used as a polymer in Metformin (MET) and Doxorubicin (DOX). The developed nano-system has co-delivered a combination of MET/DOX into melanoma tumors for treatment tumours for treatment of melanoma[93]. Alpha- terpineol is usedin treatment of skin cancer. Polymer used for incorporation of this drug is Poly(methyl methacrylate) (PMMA) is a synthetic polymer having widespread applications in biological systems[94].

Nanofiber has also been explored for skin cancer treatment as it provides the functional domain in flexibility design[95]. Thus, it releases a therapeutic payload at the goal site when it reacts to the surroundings. In this context, Janani et al. prepared Molybdenum oxide-polycaprolactone nanofiber (MOL-PCL Fibres) containing NPs as ascaffold[96].

- **Oral Cancer:**

Oral cancer is diagnosed worldwide in approximately 350,000 patients every year. Its incidence varies widely among different geographical areas accounting under 5% ofall cancer diagnoses in Erope and the United states, whereas in developing countries its incidence is higher , due to smoking and drinking habits associated with poor socioeconomic status[97]. Oral cancer is the sixth most common malignancy worldwide[98]. Among a wide variety of human oral cancers, the most significant in terms of overall morbidity and mortality is squamous cell carcinoma of the head and neck (HNSCC)[99]. Oral cancer refers to malignancies developing in oral cavity[100].

Oral cancer refers to tumour that occur in the lips, hard palate, upper and lower alveolar ridges, anterior two-thirds of the tounge, sublingual, buccal mucosa, posteriordeltoid muscle of molars and oral cavity[101].

- Causes of Oral Cancer:

The most important carcinogens in tobacco smoke are the aromatic hydrocarbon bezpyrene and the tobacco-specific nitrosamine (TSNS) namely 4- (nitrosomethylamino)-1-(3-pyridyl)-1-butanone(NNK) and N' nitrosonornicotine (NNN)[102].

Alcohol use is a second independent major risk factor for the development of OC[103]. Methanol and Propan-2-ol are toxic to consume, while ethanol along with water and glucose are the main constituents of alcohol

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containing beverages[104].

High risk human papilloma viruses(HPVs) are etiologic agents for anogenital tract cancers and have been detected in head and neck squamous cell carcinomas(HNSCCs)[105].

Betal quid chewing, with and without tobacco is carcinogenic[106]. The combine habbits of BQ chewing and smoking were considered serious risk factors for oral cancer[107].

➢ **Stomach Cancer:**

As an " Unplanned triumph", its incidence declined dramatically in the twentieth century. Yet on a global scale stomach cancer remains one of the most common causes of cancer death.There are several classifications of gastric adenocarcinoma It distinguishes between two main groups: (1) the intestinal type with glandular epithelium composed of absobtive cell and globlet cells and (2) the diffuse type with poorly differentiated small cells in a dissociated noncohesive groeth pattern[108].

- Causes:

Helicobacter Pylori(H.Pylori) infection plays a crucial role in the development of gastric cancer. There are two major pathways for the development of gastric cancer by H.Pylori infections: the indirect action of H.Pylori on gastric epithelial cells through inflammation, andthe direct action of the bacteria on epithelial cells through the induction of protein modulation and gene mutation[109,110]. Almost 10% of the carcinomas throughout the world are monoclonal proliferations of Epstein-Barr virus(EBV) carrying tumor cell[111].

➢ **Bone cancer:**

Bone is a highly active and dynamic connective tissue, which provides vital organ protection, mechanical support, locomotion, and structural body framework[112,113]. Tumor metastasis to bone frequently results in pain, hypercalcemia, anemia, increased susceptibility to infection, skeletal fractures, compression of the spinal cord, spinal cord, spinal instability, and decreased mobility. Bone cancer pain is usually first described as dull in character and constant in presentation, and this pain gradually intensifies with time[114].

- **Causes:**

Allogeneic hematopoietic stem-cell transplantation (HSCT) is a carative advanced, relapsed, or refractory non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (H2), and chronic lymphocytic leukemia (CLL)[115]. Post tranp-lant lymphoproliferative disorder (PTLD) is a heterogenous group of malignant diseases presenting after transplant and caused by i9atrogenic suppression of T-cell function. The most common form of PTLD is related to Epstein-Barr virus (EBV) disease (EBV-PTLD), which present as B-cell proliferation and is referred to a post-allogeneic hematopoietic stem cell transplant (HSCT) EBV-PTLD. Post-HSCT EBV-PTLD is a life threatehing complication and was estimated to effect approximately 4,3 in 1000 reciplents a decade ago (78 of 18014 patients from 234 transplant canters) with an attributable mortality of 84.6% [116]. Described, a bone dysplasia with many clinical features similar to PDB, which they named EEO (MIN 174810). This disease 40 of 90 members in five generation of a large family from Nor theren/reland and showed a clear pattern of autosomal dominant transmission. Radiographs showed generalized and focal skeletal abnormalities, which were associated with elevated serum alkaline phosphatase and urinary hydroxyproline values, bone pain at affected sites, tooth loss, and progressive loss of hearing. Nuclear inclusion bodies similar to these found in PDB were also identified in osteoclast from affected bone[117]. In a study of relationship between biochemical markers of arthritis and the radiographical grading of osteoartheitis (OA) in kness, a significant relationship was found between the joint space width and radiographic knee oa. The joint space width decreased with increasing Kellgren-Lawrence grade. Pyridinoline and TIINP-1 exhibited a significant relationship of the Kellgren –lawrnce grade but only urinary pyridinoline had a significant correlation[118].

➢ **Blood Cancer:**

The therapy of gliomas, the common brain neoplasms of adults, is often impeded by their high resistance to chemotherapeutic agents although some entities such malignant oligodendrogliomas and oligoastrocytomas exhibit response rates of up to 70% [119]. Many different mechanisms may account for this chemoresistance, including reduced blood supply to the tumor, up regulation of antiapoptotic pathways, enhanced DNA repair machanisms, and subsequent elimination of the applied drugs [120]. One of the central questions in the brain metastasis field is the extent of breakdown of the blood-brain barrier (BBB), the protective lining of blood vessels in the brain, to form a blood-tumor barrier (BTB). An argument can be made that the BBB is compromised once a metastasis forms in the brain, as they are diagnosed by the imaging gadolinium uptake . Injection of Evans Blue dye into mice harboring experimental brain metastases turned these lesions variably blue[121].

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- **Causes:**

Blood cancer is often diagnosed late and claims more lives than breast or prostate cancer each year (Blood Cancer UK). Nearly a third of patients diagnosed via an emergency admition hospital. Survival of route has worse outcomes than patientswho presented via other routes (Kane et al., 2017) [122].

The satisfactiory causes of blood cancer are unidentified and in most case its unsettled why blood cancer has developed. Research into possible causes is going on all the time. Like other cancers , blood cancer isn't transferable and can't be approvedon to other people. There are several of factors that may amplify a person's risk of budding blood cancer. Having a scrupulous hazard factor dosen't denote you will definitely get this category of disease and personnel lacking any recognized risk factorscan still developed it[123].

Sr. No.	Drugs	Novel Drug Delivery System Used	Disease	Reference
1.	Doxorubicin and Cyclophosphamide	Liposomal drug deliverysystem	Metastatic breast cancer	21
2.	Quercetin and vincristine	Liposomal drug deliverysystem	Breast cancer	22
3.	Ceramide	Liposomal drug deliverysystem	Breast cancer	23
4.	Doxorubicin	Colloidal drug deliverysystem, Polymeric nano-particledrug delivery system, Liposomaldrug deliverysystem	Breast cancer, Lung cancer,Uterus cancer, Bone cancer,Oral cancer, Gastric cancer	25,40,63,126, 128,132
5.	Paclitaxel	Colloidal drug deliverysystem, Nanoparticle drug deliverysystem, Solid li[id nanoparticle drugdelivery sysetem	Breast cancer, Lung cancer,Uterus cancer, Oral cancer,Gastric cancer	26,43,65,66, 131,132
6.	Ambraxane	Nanoparticle drug deliverysystem	Lung cancer	42
7.	Docetaxel	Liposomal drug deliverysystem, Nanoparticle drug deliverysystem	Lung cancer,Oral cancer,Gastric cancer	44,130,132
8.	Gemcitabin hydrochloride	Liposomal drug delivery system	Lung cancer	45
9.	Cisplatin	Nanoparticle drug delivery system/Gene deliverysystem, Lipid based nanoparticle	Lung cancer,Uterus cancer	46,64
10.	Methotrexate	Nanoparticle drug deliverysystem	Lung cancer	47
11.	Disulfiran	Nanoparticle drug delivery system	Uterus cancer	60
12.	Doxorubicin and Cisplatin	Solid lipid nano-carriers drug delivery system	Uterus cancer	61,67,68
13.	Melphalan	Nano-emulsion drug delivery system	Ovarian cancer	69
14.	Paclitaxel and TRAIL	Liposomal drug delivery system	Skin cancer	84
15.	5-FU	Liposomal drug delivery system,	Skin cancer, Oral	87,88,130,132

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		Nanoparticledrug delivery system	cancer, Gastric caner	
16.	5-FU and Cetuximab	Liposomal drug delivery system	Skin cnacer	88
17.	Piplartine	Nanoparticle drug delivery System	Skin cancer	90
18.	Metformin and Doxorubicin	Nanoparticle drug delivery System	Skin cancer	93
19.	Alpha-terpineol	Nanoparticle drug delivery System	Skin cancer	94
20.	Molybdenum	Nanoparticle drug deliverysystem	Skin cancer	96
21.	Methotrexate, doxorubicin, cisplatin		Bone cancer	124,1
22.	Bisphosphates		Bone cancer	125,1
23.	Alzarin		Bone cancer	127,1
24.	Aluminium phthalocynine chloride	Liposomal drug deliverysystem	Oral cancer	129

II. CONCLUSION

In conclusion, drug delivery appears to be a promising approach for a better effective melanoma therapy. Nanotechnology offers opportunities to achieve drug targeting with newly discovered cancer-specific targets. Effective targeting would require a better understanding of the targeting system. Over the past decade tremendous progress has been made in the elucidation of molecular signalling pathways and their ligands in breast cancer. The growing field of nanotechnology in combination with advanced molecular biology of cell signalling pathways may make possible the development of an entire new generation of specific therapy for breast cancer. Among all the treatment approaches studied in the current research, nanotechnology has received much attention in terms of skin cancer treatment. Liposomes, the most well-established lipid vesicles are shown to provide various advantages in topical drug delivery. Lung cancer in never-smokers is the seventh most lethal cancer world wide,and its incidence will increase in the upcoming years, as the tobacco burden is falling rapidly in many countries. EC is the most common gynaecologic malignancy in developed countries. As treatment planning has been changing overtime, pre- operating imaging evaluational to follow novelties in treatment, in order to offer the appropriate information to surgeons And oncologists for optimal management of patients .The COVID-19 pandemic has already had a profound effect on cancer treatment paradigms. As a Vulnerable population, cancer patient require more caution in the COVID-19 era. AIthough many aspect of SARS-COV-2 and cancer remain unclear, there is no conclusive evidence indicating that antineoplastic treatment aggravates COVID-19 disease. Uterine cancer is the third most prevalent cancer in women globally and is especially dominant in developing countries due to a lack of screening, prevention and control programs. We clearly demonstrated that HA exerts an inhibitory effect on PA NC-1 cell cycle arrest slowing down the cell cycles progression and also modulates the expression of BCI-2 family proteins. The bottleneck to development of oral liposomes lies in the poor understanding of the absorption mechanisms. Following the transit of liposomes from stomach to small intestine, liposomes and gradually broken down. Despite tremendous improvements and progress in cancer operations and adjuvant medications, stomach cancer allied mortality remains high, indicating that there is still scope for research in advancing therapy. To conclude, the recent advancements in the therapeutic strategies against bone tumors are encouraging, paving the way for the standardization of new treatments. Through the interdisciplinary approach of medicine, material science and nanotechnology, bone metastases and sarcomas can be successfully fought against. Researches have reported a volume of information about the novel drugs plays a major roles in the treatments of blood cancer.

In conclusion, the nanotechnology platform has immense potential, and recent in vitro and/or in vivo findings

show that it is an emerging branch of science with numerous applications in drug delivery and therapies.

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