



## Review

# A review on allopathic and herbal nanofibrous drug delivery vehicles for cancer treatments

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## ABSTRACT

Drug delivery empowered with nanotechnology manifests to be a superior therapy to cancer. Electrospun nanofibers cocooning anti-cancerous drugs have shown tremendous cytotoxicity towards various tumor cells, including breast, brain, liver, and lung cancer cells. This pristine drug delivery system, according to literature, desists showing any undesirable effects on other parts of the body and bestows several other benefits. From nature-derived Curcumin to laboratory-made Doxorubicin, literature proclaims many such drugs used in nanofibrous drug delivery. Also, multi-drug delivery has been reported to exhibit enhanced properties. The present review exhibits the unrealized potential of nanofibrous drug delivery in chemotherapy.

## 1. Introduction

Cancer continues to be one of the most perplexing public health and well-being issues on the planet. As of 2018, cancer is the cause of 9.6 million deaths, and the number of new cases has shot up to 18.1 million worldwide [1, 2]. While genetics may play a role in cancer growth, only a little over 5 percent of cases worldwide are due to unfortunate genetic mutations [3, 4]. The World Health Organization (WHO) predicts over 13 million deaths due to cancer by 2030, which depicts the alarming rate of cancer making its presence felt across the globe [5].

Cancer treatment aims to show a path to cure the deadly disease and live everyday life. When a complete solution is not feasible, treatment will shrink or prolong the growth of the tumor, enabling one to hold on for an extended time. Cancer therapy options include surgery, chemotherapy, bone marrow transplant, radiation therapy, and immunotherapy, to name a few. However, these methods face major criticism due to the lack of drug bioavailability at the targeted site, which causes a wide range of side effects, including death [6, 7, 8].

To overcome the aforementioned challenges, many scientists and researchers have worked to develop targeted or site-specific drug delivery systems. Extensive research is needed because the novel drug delivery system demonstrates exceptional vigor in combating issues that plague its traditional counterpart. With such valor from scientists and researchers around the globe, cancer would be reduced to an old chestnut in the years to come. Nanotechnology truly has the potential to

be humanity's savior in the struggle against such a terrible disease, as well as the future of medical sciences.

Numerous approaches for the delivery of sedates have been approved or are in progress. For cancer treatment, nanostructures such as liposomes, dendrimers, and micelles have been used as managed delivery vehicles. Various biomaterials have shown drug delivery capability, but only a few have been tested on human patients. This is due to the pharmaceutical industry's aversion to researching new biomaterials that have never been used in drug production before, although the cost of testing is minimal. Biomaterials are essential to understand drug action and delivery systems using *In-vitro* models better. The study of drug delivery to tumor cells necessitates the creation of 3D tumor models, and biomaterials have been crucial in the construction of such models [9].

Drug confinement results in greater stability, tailored administration, and fewer adverse effects for patients, both of which are reasons of merit to use the encapsulation process instead of other traditional ones. Various drug delivery vehicles with varying surface physico-chemical properties, sizes, targeting methods, and architectures have been developed to date [10, 11, 12].

Nanofibrous drug delivery appears to be the quintessential solution to problems linked to cancer therapy. Electrospinning is used to produce polymeric nanofibers from biocompatible and biodegradable polymers to design a polymer matrix for drug conveyance and tissue engineering. It possesses peculiar properties such as low density, a high surface area-

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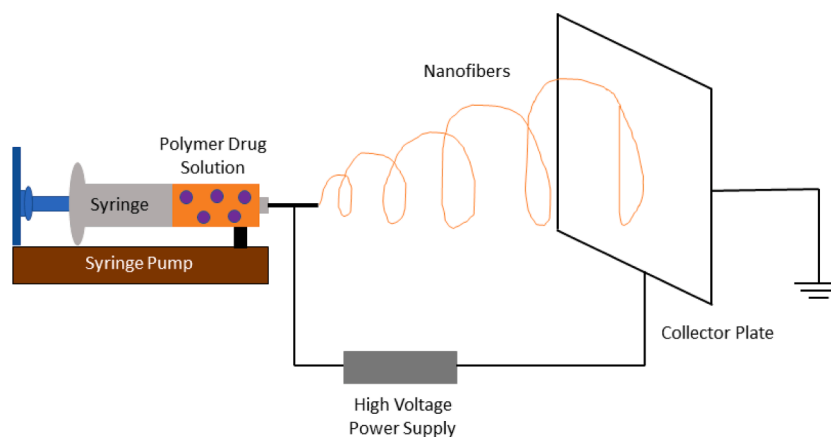


Fig. 1. Schematic representation of electrospinning process

to-mass ratio, and a significant pore depth as a result of its very high surface-to-weight ratio in comparison to conventional nonwovens [13]. Recently many studies have reported on the possible cure for cancer tumors using a range of anticancer drugs (modern medicine and herbal) with nanofiber-based drug carriers. These *In-vivo* and *In-vitro* trials demonstrate the efficacy of drug-loaded nanofibers in cancer care [14, 15, 16]. The treatment methods are designed with a single drug or multiple drugs with simultaneous and sequential release using allopathic and herbal drug molecules [17, 18]. We reviewed all recent research advances in chemotherapy utilizing nanofiber-based drug carriers for allopathic, natural, and hybrid medicine in this study.

## 2. Fabrication technique of electrospun nanofiber based drug carrier

Electrospinning is an efficient procedure used in the synthesis of nanofiber matrix [19]. Nanofiber matrices can be used in drug delivery, bio-sensors, affinity membranes, cosmetics, tissue engineering, cell regeneration, filtration processes, and textile. In this process, strong electric fields are applied between the needle tip and collector, producing continuous polymer fibers ranging from micrometers to nanometers. These ultrafine fibers are fabricated from one or many polymer solutions or melts.

As previously mentioned, the fibers hold a large surface-area-to-volume ratio and are utilized to prepare drug delivery systems [20]. The high surface area causes enhanced interpenetration, and the bio-adhesive intensity helps increase contact time with the mucus membrane, ensuring optimal drug dose presence at the target site. Clinical conditions are improved, and the likelihood of chemoresistance is minimized, resulting in simple administration and termination, as well as cost savings and ease of service [21]. Recent studies show that electrospun matrices can also be used in post-surgical chemotherapy to avoid the relapse of the tumor. Aside from these benefits, nanofibers have several others, including cost-effectiveness, ease of processing, high encapsulation performance, high drug loading capability, multi-drug delivery, and managed drug release profiles [22].

A pipette to contain the polymer solution, two electrodes, and a DC voltage supply is used in the electrospinning operation. The jet is electrically charged, and a voltage difference exists between the collector and the pipette tip. This potential gap attracts the solution from the pipette and directs it to the collector. During electrospinning, the polymer fluid is expanded as it passes through the collection plate as the jet leaves the needle tip. The molecular chains get entangled as the polymer solution stretches, stopping the electrically driven jet from splitting apart and maintaining a steady solution stream. Fig. 1 depicts the electrospinning phase. Several parameters must be configured when fabricating nanofibers, and Table 1 lists the parameters that influence

nanofiber geometry.

## 3. Electrospun nanofibrous drug delivery system for chemotherapy

Several permutations and combinations have been formulated with chemotherapeutic agents and are successful in cancer care against many tumors. Studies on widely used anticancer medications such as Doxorubicin (DOX), 5-Fluorouracil (5-FU), and Paclitaxel (PTX) revealed that they were successful against tumors. Nature-derived chemotherapeutic agents like Curcumin (CUR) and Quercetin (QUE) also showed prospectivity. However, it should be noted that all electrospun nanofiber-mediated drug delivery approaches for cancer therapy are currently in preclinical and clinical trials.

### 3.1. Recent developments in cancer treatments using natural anti-cancer drugs

Natural agents have been considered for the anti-cancer study. Several medicinal plants from all over the world contain drugs that could be potentially used for tumor therapy. Studies are being conducted by using these natural drug encapsulated nanofibers for cancer therapy. A list of recent studies with nanofiber drug carriers using these herbs for cancer treatment is shown in Table 2.

#### 3.1.1. Camptothecin (CPT)

Camptothecin (CPT) is a drug that is naturally occurring and is found in the bark and stem of a tree species called *Camptotheca acuminata*, mainly grown in China and Tibet. Though it can induce cancer cell death, it has low aqueous solubility, making its use impracticable. Hence nanofibers are used to overcome this issue [34].

One of the first studies with this drug was done on encapsulated CPT in Peptide Amphiphile (PA) nanofibers, and its antitumor activity in breast cancer cells was investigated. *In-vitro* studies show that when CPT is encapsulated in PA, it displays excellent antitumor potential [34].

Another research on the effect of Polycaprolactone (PCL) nanofibers loaded with CPT showed that the drug release occurred in two stages. For the first 10 h, there was a burst release (17%), followed by a gradual release for the next 70 h [35]. As shell-sheddable CPT-based nanofibers were studied on human ovarian cancer cells, it was discovered that as the pH increased, the rate of drug decomposition increased, proving that this system was also suitable for cancer drug delivery [36].

Most recent studies were made using CPT-loaded DNA nanofibers to test its activity against lung cancer cells. The initial release was found to be very rapid and followed first-order kinetics for 2 h. It then followed zero-order kinetics and, like the previous, also proved the successful and effective loading of the drug [37].

**Table 1**  
Parameters affecting nanofiber geometry in the electrospinning process

S. No	Parameter	Remarks
<b>1</b>	<b>Solution Parameters</b>	
i	Surface Tension	Due to the possible difference, the charges on the polymer must be high enough to tolerate any surface tension of the solute in the jet to be removed. However, no conclusive correlation with fiber morphology was discovered [23].
ii	Polymer Solubility	The higher the molecular weight, the less soluble it is and the longer it takes to dissolve. The enthalpy of a solute-solvent mixture is equal to the square of the difference in solubility parameters [24]. Polymer solubility affects fiber morphology.
iii	Viscosity	Low viscosity leads to the formation of smooth but beaded fibers. Good solvents have high intrinsic viscosity [25]. Fiber diameter increases with increased viscosity.
iv	Volatility	High volatility leads to solvent evaporating even before the jet reaches the collector, forming porous fibers [23].
v	Conductivity of Solution	Conductivity helps to overcome surface tension. Reagents are added to improve conductivity. Higher conductivity helps to form finer fibers [23].
vi	Molecular weight	The polymer chain size and viscosity are also affected. The greater the molecular weight, the smaller the entanglements [26]. The diameter of the fiber increases as the polymer's molecular weight rises.
vii	Dielectric effect of solvent	The greater the dielectric property, the fewer beads shape and the smaller the diameter of the fabric. The electrospinning jet's bending volatility also rises [27].
<b>2</b>	<b>Process Parameters</b>	
i	Voltage	Higher voltages initiate the electrospinning process [28]. At even higher voltages, thick fibers are formed. Lower voltages favor the formation of finer nanofibers [23].
ii	Feed rate	The feed rate is proportional to the fiber diameter and the scale of the beads. A slower feed rate is preferred so that the solvent will evaporate [23].
iii	Effect of collector	The collector plate is electrically grounded to ensure a safe potential difference between the source and the collector. Nonconductors can collect charges on the plane, resulting in fewer fiber deposits [29, 30].
iv	Diameter of Pipette Orifice/ Needle	Clogging and the number of beads in electrospun fibers is reduced by having a limited internal diameter [31].
v	Distance between tip and collector	Lesser distance implies that the jet has to travel lesser to reach the collector plate, not giving it sufficient time to evaporate, forming intra-bonding layers and beads [28, 32]. Larger distances allow more stretching of fibers which decreases the fiber diameter [33].
<b>3</b>	<b>Ambient Parameters</b>	
i	Humidity	High humidity affects fiber morphology when water condenses on the fiber surface, increasing the size and depth of the shaped circular pores [23].
ii	Type of atmosphere	Under strong electrostatic fields, different gasses behave differently [23].
iii	Pressure	Lower pressures (below ambient pressure) cause erratic jet formation and solution bubbling at the needle tip. Electrospinning is impractical at extremely low pressures due to the direct discharge of electrical charges [23].
iv	Temperature	Higher temperature helps decrease the diameter of fibers but may not be suitable for proteins and enzymes-based fiber [23].

CPT demonstrated anti-tumor efficacy against brain, breast, lung, and ovarian cancer cell lines. Furthermore, CPT displays anti-HIV efficacy because it disrupts the infectious factor's consciousness and is present in many retroviruses [46].

### 3.1.2. Curcumin (CUR)

Curcumin is a naturally occurring bioactive phenolic agent contained in turmeric that has anti-cancer effects [17].

Curcumin was introduced into nanofibers made of poly (lactic-co-glycolic) acid (PLGA) in early studies by Sampath et al., and its anti-cancer effect on A431 carcinoma cells was tested. The release was continuous with no burst effect for at least 8 days [38]. To treat breast cancer, electrospun curcumin-loaded nanofibers demonstrated remarkable initial rapid release, followed by sustained and continuous-release, indicating that it is safe for use in therapies [39]. Another treatment for breast cancer was a novel drug delivery system using chitosan (CS) nanofibers loaded with curcumin. In the first 24 h, there was a visible burst discharge, accompanied by a slow-release [40]. Recently, in a study of the delivery of curcumin and chrysin (CH) using electrospun PLGA-PEG nanofibers, also on breast cancer cells, the *In-vitro* findings demonstrated a lengthy and continuous drug release with no burst release [17].

Curcumin finds its way in several medical applications because of its good antimicrobial, antioxidant, anti-cancer, anti-inflammation, and anti-infective properties [40].

### 3.1.3. Quercetin (QUE)

Quercetin is a polyphenolic compound that is found in plants, like apples or tea. It has the potential to stop or hinder the growth of the tumor cells [47].

In one of its earliest studies, Vashisth et al. developed a method for Quercetin release utilizing biodegradable Poly(lactide-co-glycolide)-Polycaprolactone (PLGA/PCL) nanofibers. It was carried out on human

hepatocellular carcinoma cells. In the *In-vitro* release study, the fabricated nanofibrous matrix of PLGA/PCL gave a desirable and sustained drug release. The aqueous permeability, system degradation, and diffusion were also enhanced. The drug was released in a blast at first and followed a subsequent slow release later [41]. A similar study was conducted by Ş. Eskitoros-Togay, where the nanofiber matrix was generated by combining PCL with PLGA, Polyethylene Oxide (PEO), and Polylactic Acid (PLA). In all circumstances, Quercetin was encapsulated, and the tests were on MCF-7 breast cancer cells. The maximal release of Quercetin from the PCL/PEO blended nanofiber matrix was also demonstrated. This system also showed a two-stage release of Quercetin [42]. Quercetin was also studied by Peng et al. with Sodium Alginate (SoA) and Chitosan nanofibers to treat colon cancer. The release mechanisms are discussed using different drug release models. The Quercetin release was a complicated discharge pattern consisting of erosion, diffusion, and swelling [43]. In another study, Quercetin was encapsulated in Polyethylene glycol and Cellulose Acetate (CA) nanofibers, and the system showed a rapid release initially, which released 85.3% of the drug in the first 6 h, and then it took 24 h to release the remaining drug [44].

Quercetin is a biologically active compound and has remarkable anti-inflammatory, antioxidant, anti-tumor activities [44].

### 3.1.4. Emblica Officinalis (EO)

Emblica Officinalis, also called Indian Gooseberry or Amla, is a drug vastly used in modern medication and is one of the most important medicinal plants in the Indian traditional medical system, i.e. Ayurveda. It is obtained by natural means, through plant extracts, and shows incredible therapeutic properties and shows minimal side effects. It is sour, bitter, and a bit astringent. However, it is very fibrous.

Gajanan et al. incorporated EO into PCL nanofibers and observed that it had sound antiproliferative effects against the human breast cancer cell lines.

**Table 2**

Scientific evidence for the potential application of natural anti-cancerous drugs using nanofibers

Excipient	Drug (s)	Application	Ref.
PA	CPT	<i>In-vitro</i> and <i>In-vivo</i> on breast cancer cells	[34]
PCL	CPT	<i>In vitro</i> on C2C12 cancer cells	[35]
PEG	CPT	<i>In-vitro</i> and <i>In-vivo</i> on breast and ovarian cancer cells	[36]
DNA	CPT	<i>In-vitro</i> on A549 cancer cells	[37]
PLGA	CUR	<i>In-vitro</i> on carcinoma cancer cells	[38]
CS	CUR	<i>In-vitro</i> on MCF-7, HEP G2 and L929 cancer cells	[39]
CS	CUR	<i>In-vitro</i> on breast cancer cells	[40]
PLGA-PEG	CUR/CH	<i>In-vitro</i> and <i>In-vivo</i> on breast cancer cells	[17]
PLGA-PCL	QUE	<i>In-vitro</i> on Hepatocellular carcinoma (HepG2) cancer cells	[41]
PCL/PEO/PLA/PLGA	QUE	<i>In-vitro</i> on breast cancer cells	[42]
SoA/CS	QUE	<i>In-vitro</i> on colon cancer cells	[43]
CA/PEG	QUE	<i>In-vitro</i> on HeLa tumor and SH-4 skin cancer cells (melanoma)	[44]
PCL	EO	<i>In-vitro</i> on MCF-7 cancer cells	[45]

Preclinical examinations have revealed that the drug possesses cardioprotective, antipyretic, analgesic, antianaemia, wound healing, anti-diarrheal, nephroprotective, and neuroprotective properties along with radio-modulatory, chemo-modulatory, chemopreventive, antioxidant, anti-inflammatory effects, which are also highly essential in the treatment of cancer [48]. EO cannot be used directly as it may lead to overdosage and toxicity, which is why an excellent drug carrier is needed to deliver it to the tumorous sites [45].

### 3.2. Recent developments in cancer treatments using allopathic anti-cancer drugs

Allopathic drugs have made a name for themselves in nanofiber drug delivery for the treatment of cancer cells. They have been researched upon more than natural drugs and have been showing promising results. Combinations of natural and allopathic drugs in carriers have been experimented upon too [49, 50]. They could be used for commercial purposes to treat the disease. The list of the most used drugs in cancer treatment encapsulated in various polymers is given in Table 3.

A mixture of two or more medications may be electrospun by adding additional polymers into the device that could be used to deliver and discharge the drugs, with an intermediary layer(s) serving as isolation for both the sheath as well as the core materials. Dual drug administration can show superior anti-cancer effects and improve the quality of therapy [51–54].

The list of the most used drugs in cancer treatment encapsulated in various polymers is given in Table 3.

#### 3.2.1. 5-Fluorouracil (5-FU)

5-Fluorouracil was founded in 1956 (used for medical purposes in 1962). Many cancers like stomach, colon, and breast cancer, are treated using this drug [86]. Its effectiveness and extensive usage put it on the World Health Organization's List of Essential Medicines [87].

One of the earliest studies was developing a dual drug delivery system of 5-FU and Oxaliplatin (OX) primed polylactide nanofibers used to diagnose colon cancer. A sustained drug release was attained, which led to superior tumor growth suppression [22]. A similar study using a Polycaprolactone (PCL) nanofibers-based drug delivery system with a dual drug combination of 5-FU and Paclitaxel (PTX) was performed to treat prostatic and breast cancer. A consistent drug release pattern was observed for 25 days [55]. In another study, 5-FU was loaded in PCL/Chitosan nanofibers and was tested as a treatment for colorectal

**Table 3**

Scientific evidence for the potential application of allopathic anti-cancerous drugs using nanofibers

Excipient	Drug(s)	Application	Ref.
PLA	5-FU/OX	<i>In-vitro</i> and <i>In-vivo</i> on colorectal cancer cells	[22]
PCL	5-FU/PTX	<i>In-vitro</i> on prostatic and breast cancer cells	[55]
PCL/CS	5-FU	<i>In-vitro</i> on colorectal cancer cells	[15]
PBAT	5-FU/CUR	<i>In-vitro</i> on colorectal cancer cells	[56]
P(NIPAAAM-AAm-VP)	DOX	<i>In-vitro</i> on A-549 lung cancer cells	[57]
PLGA	DOX/CPT	<i>In-vitro</i> and <i>In-vivo</i> on HeLa cervical cancer cells	[58]
PLGA/GEL	DOX/CPT	<i>In-vitro</i> on HepG-2 liver cancer cells	[59]
PEG-PCL	DOX/CUR	<i>In-vitro</i> on HeLa cervical cancer cells	[50]
PEO/CS	DOX	<i>In-vitro</i> on lung cancer cells	[60]
PLLA	DOX	<i>In-vitro</i> and <i>In-vivo</i> on breast cancer cells	[61]
PLGA/GEL	DOX	<i>In-vitro</i> on Caco-2, 4T1 and 431 cancer cells	[62]
PCL	DOX	<i>In-vitro</i> on carcinoma cells, cervical cancer cells, and breast cancer cells	[63]
PLGA	PTX	<i>In-vitro</i> on C6 Glioma cancer cells	[64]
PEO/CS	PTX	<i>In-vitro</i> on prostate cancer cells	[16]
PU	PTX	<i>In-vitro</i> and <i>In-vivo</i> on CT-26 colon cancer cells	[65]
PLLA	PTX	<i>In-vitro</i> on HepG-2 cancer cells	[66]
PCL	PTX	<i>In-vitro</i> on liver cancer cells	[67]
PLGA	PTX/BFA	<i>In-vitro</i> on HepG-2 cancer cells	[68]
SA	PTX	<i>In-vitro</i> and <i>In-vivo</i> on A549 lung cancer cells	[69]
SnO2	PTX	<i>In-vitro</i> on liver cancer cells	[70]
CA	PTX	<i>In-vitro</i> on Gastric adenocarcinoma SGC7901 cancer cells	[71]
PLA	PTX	<i>In-vitro</i> and <i>In-vivo</i> on Glioblastoma brain tumor cells	[72]
PLGA/CS	PTX	<i>In-vitro</i> and <i>In-vivo</i> on prostate cancer cells	[73]
PLA/PEG	PTX	<i>In-vitro</i> and <i>In-vivo</i> on Fibrosarcoma HT1080 cancer cells	[74]
PCPP-CA-PHM	PTX	<i>In-vitro</i> on breast cancer cells	[75]
PLLA	CIS	<i>In-vitro</i> on lung spc-a-1 cancer cells	[76]
PLGA	BCNU, Irinotecan, and CIS	<i>In-vitro</i> and <i>In-vivo</i> on Glioblastoma multiforme brain cancer cells	[77]
PCL/CS	CIS	<i>In-vitro</i> on MCF-7 breast cancer cells	[78]
PCL/PU	TMZ	<i>In-vitro</i> on U-87 MG glioblastoma cancer cells	[79]
PCL/PU	TMZ	<i>In-vitro</i> on Glioblastoma cancer cells	[80]
PVA	DTX	<i>In-vitro</i> on breast cancer cells	[81]
PLA	DTX	<i>In-vitro</i> and <i>In-vivo</i> on breast cancer cells	[82]
PEG-PLLA	BCNU	<i>In-vitro</i> on Glioma C6 cancer cells	[83]
Cellulose	Metformin	<i>In-vitro</i> on Melanoma cancer cells	[84]
PLA - HA	GEM	<i>In-vitro</i> on pancreatic cancer cells	[85]

cancer. Korsmeyer-Peppas drug release kinetics was followed by the nanofiber matrices through permeation or diffusion [15]. In recent studies, many researchers attempted to develop a dual drug therapy with herbal and allopathic drugs. This helped reduce the side effects caused by the allopathic drugs and use the goodness of natural drugs. 5-FU and Curcumin-loaded Poly(Butylene-Adipate-co-Terephthalate) (PBAT) nanofibers had been synthesized to treat colorectal cancer. There was a burst release initially for around 8 min, followed by which there was a sustained drug release [56].

The nanofibers encapsulated with 5-FU showed favorable results in tackling tumors of prostate, colorectal, and breast cancer. This revealed the ability of the drug-electrospun fibers to be implantable and a simple local drug delivery mechanism.

### 3.2.2. Doxorubicin (DOX)

Doxorubicin is a medication on the World Health Organization's Registry of Essential Medicines, [87] extensively used to treat bladder, breast cancer, and Lymphoma. In the United States, DOX got its approval in 1974 for medical usage [88].

The earliest research studies showed the results of fabricated Poly(N-sopropylacrylamide-co-acrylamide-co-vinylpyrrolidone) P(NIPAAM-AAm-VP) loaded in DOX nanofibers, which aimed at finding a treatment for lung cancer. The release rate of DOX declined during the release period as the drug content in the fibers increased [57]. Following this, a dual drug delivery system was presented by Mengxia Chen et al., which consisted of Doxorubicin hydrochloride (DOX-HCl) and Hydroxycamptothecin. The multiple drug combination was loaded into PLGA nanofibers to treat HeLa cervical cancerous cells. This system demonstrated a prolonged release behavior and better antitumor result than their single-drug counterparts [58]. In another work, DOX-HCl and CPT encapsulated PLGA/Gelatin blended nanofiber systems were investigated to treat liver cancer. CPT showed a rapid release due to hydrophilic Gelatin (GEL), whereas DOX indicated a continued release behavior [59].

Some studies also compared the effect of drug deliveries between natural and allopathic drugs. For diagnosis of HeLa cervical cancer cells, Poly (ethylene glycol)/Poly (ε-caprolactone) (mPEG-PCL) was loaded together with DOX and Curcumin. The studies initially showed that the DOX release was significantly faster than that of Curcumin, but later the release of the former slowed down. The multi-drug-loaded system showed a high cytotoxicity effect [50]. Multi-drug systems are mainly studied to obtain more optimum and favorable results. Polyethylene oxide (PEO)/Chitosan-loaded DOX nanofibers were synthesized to find treatment for lung cancer. The scientists discovered that a pH of 5.3 resulted in a greater opioid release than a pH of 7.4. This occurred due to reduced interaction between the DOX and the PEO/Chitosan nanofibers [60]. For the treatment of breast cancer, Polylactic Acid (PLLA) nanofibers that contained DOX were produced. The nanofibers showed a sudden surge in the release rate for the first 10 days, then a prolonged release over 39 days [61].

PCL (Polycaprolactone) is another very commonly used polymer in drug delivery. Upon being examined with DOX, Hydroxyapatite (nHA) nanofibers loaded with it were tested on Caco-2 (human colorectal adenocarcinoma cells), 4T1 (mice breast cancer cells), and 431 cancer cells. The dual drug delivery system demonstrated a more significant cytotoxic impact as contrasted to that of single-drug treatment. The drug was initially released in a burst, followed by prolonged discharge for around 55 h [62].

Recently Preethi et al. developed PCL nanofiber systems encapsulating DOX to treat cervical, carcinoma, and breast cancer cells. It was discovered that the release of the drug happened over a significant amount of time (almost 9 days), which was close to that of multi-walled carbon nanotubes [63].

DOX-loaded systems that are electrospun into nanofibers have high cytotoxic characteristics. That is why they are researched heavily upon. They showed favorable results in treating many cancers.

### 3.2.3. Paclitaxel (PTX)

Paclitaxel, also known as Taxol, is an anticancer medication well known for its widespread usage as a chemotherapy drug and treating various cancers such as lung cancer, breast cancer, cervical cancer, and others. It is also on the World Health Organization's List of Essential Medicines [87, 89]. In 1991, it was licensed for medicinal use. PTX has a lot of side effects similar to any other chemotherapeutic drug, which include numbness, severe muscle pain, and hair fall. [89].

This drug is one of the most studied for anti-cancer nanofiber drug delivery. One of the earliest studies tested it on C6 Glioma cells. PLGA nanofibers were tested with PTX. The rate of release of the PLGA nanofibers loaded with PTX was much faster compared to that of PLGA microfibers. About 80% of PTX was released from 20% PTX loaded Poly

(bis (p carboxyphenoxy) propane) anhydride and PCPP-SA (Sebacic Acid) (20:80). The PCPP-SA were polymer discs released after around 37 days, and 20% of the PTX has released *In-vitro* after the first two days [64]. On synthesizing electrospun porous nanofibers loaded with PTX for chemotherapy against prostate cancer, initially, a burst discharge was found in the release profile. This was due to the PTX drug's diffusion-controlled distribution and the electrospun nanofibers' improved water adsorption. The drug molecule showcased faster diffusion into the aqueous medium from the matrix. 48 h later, it did not take much time to attain equilibrium [16]. To treat gastrointestinal cancer and the related stenosis using chemotherapy, Polyurethane (PU) nanofibers loaded with PTX were synthesized. The PTX release from the nanofiber membrane (NFM) was examined for almost 30 days. Even though the regulated release of the PTX drug from such a thin membrane under the harsh gastrointestinal environments (like digestive enzymes, bile acid) is hardly attainable, it showed a steady release, and there was no initial burst either. It remained the same for the first 10 days and 20 days after that in a buffer of PBS with some Bile extract [65].

Wanyun Liu et al. prepared a setup of poly (L-lactide) electrospun nanofibers and encapsulated them with PTX and fullerenes, which are water-soluble for drug delivery. The experiment was carried out to treat liver cancer. The release rate of PTX increased when the contents of the fullerene nanoparticles C70- TEG's increased. The higher the content of C70- TEG's, the higher was the percentage release of the drug from the nanofiber mats. Samples with the most C70- TEG content showed a release of almost 83% of its total drug in 72 h, while those with the least C70- TEG content released 72%. The faster release of PTX may be credited to nanoparticles that came under the nanofiber surface when the content of C70 particles was increased [66].

The drug and gene delivery of biodegradable Polycaprolactone (PCL) nanofibers were studied extensively to treat liver cancer. The amount of PTX released from PCL nanofiber was 10% at 1-day incubation based on the cumulative release curve. At 16-day post-incubation, PTX was released to approximately 20% and observed a much gentler and constant release which could be credited to the drug diffusion localized in the PCL nanofibers [67].

Multiple drug systems also showed promising results. Dual drug release of PTX and Brefeldin A (BFA) was examined to treat liver cancer. HepG-2 cells were taken as the sample on which the system was tested. It was observed that the release of PTX from composite nanofiber Paclitaxel /poly (lactic co glycolic acid)@Brefeldin A Polymeric Micelles (PTX /PLGA@BFA- PM) was quickly reached within 12 h, compared to that with nanofiber PTX/PLGA. This rapid release behavior of PTX from PTX/PLGA@BFA-PM can be credited to more PTX on or near the fibers' surface. The release rate of BFA from nanofiber BFA/PLGA was much faster than that from the composite nanofiber PTX/PLGA@BFA-PM. At 72 h, the rate of accumulated drug release reached 72.9% and 20.7% for BFA/PLGA and PTX/PLGA@BFA-PM, respectively. The prolonged-release mechanism has decelerated the rate of release of the drug from the composite nanofiber. The rate of release of the BFA from micelle was faster than that from the electrospun nanofibers [68].

The antitumor impact of Succinic Acid (SA) nanofibers loaded with PTX were investigated to treat lung cancer. Initially, the nanofibers' release of PTX in a slow, continuous fashion was displayed in a non-obvious manner as PTX release needed the ester bond hydrolysis between PTX and SA, which varied from delivery systems with a physical frame of the drugs. The fibers became thinner and shorter as the degradation proceeded [69].

Orchestrated hollow mesoporous SnO<sub>2</sub> nanofibers functionalized with folate as a targeting carrier of drugs aided in enhancing PTX's antitumor effect in the treatment of liver cancer. Both SnO<sub>2</sub> nanofibers with Paclitaxel (SNFP) and folate functionalized mesoporous SnO<sub>2</sub> nanofiber (SFNFP) had greater rates of dissolution than compared to pure PTX. This is due to the structure of SFNFP, which is mesoporous. The SNF primarily restricted the size of the PTX particles, which were in a non-crystalline environment [70].

Recent studies describe the release of PTX using cellulose acetate (CA) nanofibers. The release rate of PTX was found to be greater during the first 12 h of release. Later, it slowed down, and the cumulative release concentration and release rate of PTX from Cellulose Acetate/Paclitaxel/ Rectorite (CA/PTX/REC) mats seemed to have reduced compared to CA/PTX. It was concluded that the rectorite could successfully reduce the quantity of PTX discharged from the fibers. This meant that PTX could be reabsorbed and prevented by the rectorite (layered) framework, which could be used to prolong PTX release [71].

Another study demonstrated the release of PTX to treat Glioblastoma using Polylactic Acid (PLA) nanofibers. When the diameter of the fiber decreased, the release rate also decreased. Encapsulation efficiencies were also good for PTX-scaffolds. The polymer used resulted in substantially different PTX release speeds, which are strongly associated with scaffold degradation. Only a trace amount of PTX was liberated *In-vitro* from PLA scaffolds, which is congruous with literature, where release trials were conducted in the absence of proteinase [72].

To ensure that there was a targeted release of PTX against prostate cancer cells, the use of carriers like chitosan, PLGA and zeolites were researched upon. Swelling occurring under acidic pH and the relative decomposition of synthesized zeolites and nano-metallic organic frameworks (NMOFs) were observed. This gave a quicker release of PTX. In the PLGA/chitosan nanofibers, there was a surge in the release of the drug initially caused due to the PTX molecules being released from the surface of the nanofibers. An evident change in the velocities of sedate release at different times was noted [73].

PTX drug was loaded into PLA/PEG to diagnose Fibrosarcoma HT1080 cells. The results revealed that fibers containing PEG discharged more PTX and had a longer release duration than fibers containing PTX but lacking PEG. This initial rate rise culminated in an average increase in Paclitaxel drug release in the accumulated model [74].

Another very recent study shows the effect of ovata dietary fibers loaded with PTX for breast cancer therapy. PCPP-CA-PHM nanofibers happened to show a restricted release of the sedate for a prolonged period compared to other nanofibers. Similarly, triaxial acid nanofibers, PVA-chitosan-poly lactide, showed regulated release of the drug too [75].

PTX provides a broad range of uses and is compatible with a variety of opioid carriers. The drug's release differed from one to the other, though the release is often simpler if there is a carrier rather than the drug being issued directly. PTX is a hydrophobic substance that has triggered many issues, and many of the studies here have been successful and are focused on solving this major annoyance.

### 3.2.4. Cisplatin (CIS)

Cisplatin is one of the drugs which is used to treat brain tumors and lung cancer. This drug was discovered in 1845 and got its license for medical usage in 1978. It also had made its way into the World Health Organization's List of Essential Medicines [87, 90]. There are several downfalls in delivering this drug to the body, though, including several deadly side effects, among them being neurotoxicity, and nephrotoxicity. Therefore, carriers that can aid in minimizing side effects and inhibiting the growth of tumors are used for the same [90].

Cisplatin loaded in Poly(lactic acid) (PLLA) composite nanofibers were tested against the spc-a-1 tumor cells (human lung). The release rate of the drug was found to be stable and prolonged. In three out of the four cases observed, there was no initial burst release. Regulated release of Cisplatin could be achieved for a longer time [76]. Like DOX, multi-drug-loaded systems were also studied in Cisplatin. One of them showed the supply of 3 drugs- Irinotecan, Carmustine, and Cisplatin loaded into Poly[(d,l) lactide-co-glycolide] nanofibers in the cerebral cavity. Cisplatin was shown to have a burst release within the first four days (PLGA nanofibers), followed by a moderate discharge lag. This occurred from days 4 to 14. Then there was a prolonged and faster release for another two weeks. Eventually, the concentration gradually decreased [77]. Recently, chitosan-grafted-poly(N-vinyl caprolactam)

(PNVCL) nanofibers were used to coordinate the regulated release of Cisplatin. There was some shrinkage in the fibers, which facilitated the faster release of Cisplatin. Close to the fiber surface, the drug was released in a blast at first. Later, the rate of release slowed down because of the diffusion mechanism from the nanofibrous matrix [78].

There has not been any progress on this compound in electrospun nanofibrous drug carriers, despite it being a potential anticancer drug.

### 3.2.5. Temozolomide (TMZ)

Temozolomide is a medication that is prescribed for use in the management of brain tumors. It has been shown to work efficiently on being injected directly into the body. However, it also leads to severe side effects like injection site reactions like pain, irritation, warmth, hair loss, and body pain. It got approved for medical usage in 1999 [91].

Irani et al. worked on two different systems with Temozolomide (TMZ) and obtained interesting results. The first on a drug delivery mechanism of chitosan/TMZ nanoparticles encapsulated in PCL-PU nanofibers was to pursue a solution for Glioblastoma cells. The release rate of TMZ medication in these nanofibers was found to be in a relaxed manner than in CS-TMZ-NP-loaded nanofibers. A burst release was found in both instances [79]. The second research demonstrated that PCL-PU nanofibers could transmit TMZ medication for extended periods to Glioblastoma cells. Various nanofibrous formulations were orchestrated to achieve a sustained release of TMZ after the initial burst release of the same [80].

TMZ is still new in the market but has many applications. TMZ loaded nanofibers have been in limited talks concerning the research aspect. The drug has successfully had a regulated release with drug carriers. Hence, the administrative systems of multi-drug mixtures of Temozolomide with electrospun drug carriers should be considered in the future.

### 3.2.6. Docetaxel (DTX)

Docetaxel/Taxotere, a chemotherapeutic medication on the World Health Organization's List of Essential Medicines, can diagnose various cancers, including head, breast, throat, and prostate cancer. After receiving a patent in 1986, Docetaxel got its approval for medical use in 1995 [82, 92].

There have been very few studies conducted on this drug. One of them explains drug delivery using Polyvinyl Alcohol (PVA) nanofibers encapsulated with Docetaxel. Tests were carried out to find a treatment for breast cancer. The accumulated drug release revealed that a blast (nearly 30.6 percent) was detected within the first few hours. Later, the rate of release steadily slowed. This may be due to the polymer partially congealing. This prevented water from diffusing through the polymeric structure. In 6 h, the release rate was almost as high as 97.1 percent [81]. Also, in another study, a cure for breast cancer relapse, explored the therapeutic usage of PLA nanofibers loaded with DTX. The sedate release profiles show an initial burst release (less than 12 h), and then the release gradually decreased. This data proved that DTX/PDLLA had a remarkable *In-vitro* anti-tumor cytotoxicity [82].

In terms of nanofiber drug delivery, docetaxel has fewer applications. Additionally, docetaxel is available as a generic medication.

### 3.2.7. Bis-chloroethyl nitrosourea (BCNU)

BCNU, also known as Carmustine, is a chemotherapeutic drug that finds its usage in treating myeloma, lymphoma, and glioma. The drug got its approval in 1996 for medical use.

While PEG-PLLA ultrafine fibers were investigated for diagnosing Glioma G6 cells, it was realized that the release rate increased as the BCNU compound's structure increased. For the first 30% of cumulative drug release, there was a linear relationship between the percentage of accrued drug release and the square root of time. After that, the relationship deviated from linearity. BCNU drug release in BCNU/PEG-PLLA fibers started rapidly and accompanied a constant release rate due to diffusion [83].

Some other applications of BCNU are that it is a nitrogen mustard  $\beta$ -chloro-nitrosourea compound and is utilized as an alkylating agent. Carmustine can form interstrand crosslinks in DNA as an alkylating agent, preventing replication and transcription of DNA.

### 3.2.8. Metformin

Glucophage (also known as Metformin) is a drug that is used to treat type 2 Diabetes. It also has anti-cancer applications and is a part of the World Health Organization's List of Essential Medicines. First discovered in 1922, it was used as a medication in 1995 [87, 93].

Nurani and his team assessed the potential of its anti-metastatic properties on melanoma cells using cellulose nanofiber gel. In the first hour itself, almost 70% of the drug was released. Later it gradually slowed down. Almost 98% of the drug was discharged at 6.5 pH at the end of 3 h [84].

The primary use of Metformin is the treatment of diabetes and not of many scopes in anti-cancer treatment. It was the fourth most used drug in the United States in 2017, with over 78 million prescriptions.

### 3.2.9. Gemcitabine (GEM)

Gemcitabine, also known as Gemzar is a drug that finds its use in chemotherapy medication to diagnose cancers like testicular, breast, and ovarian. This drug received its patent in 1983 and was put to medical use in 1995 [94]. It is also a part of the World Health Organization's List of Essential Medicines [87].

A research was conducted in which PLA-Hyaluronic acid (HA) electrospun fibrous membranes filled with GEM with a core-shell structure were used. Sol-electrospinning technique was used to assure the GEM was released over an extended period. It was studied on cells from pancreatic cancer. The cumulative time required for the GEM medication to be released could be altered by varying the thickness of the core, which allowed the drug to be delivered for three weeks. Localized drug distribution is successful in restraining the development of liver, colorectal, and cervical cancer tumors. Additionally, it was discovered to mitigate the adverse consequences of chemotherapeutics [85].

GEM is known to have severe side effects when given through traditional chemotherapeutic means. Hence studies are being conducted to check its potential after being encapsulated in a carrier to overcome this issue [85].

## 4. Conclusion and future prospects

Year by year, the number of lives lost due to cancer is alarming. For the ones who fight it successfully, there is a severe traumatizing impact left behind due to all the painful side effects and weaknesses caused throughout the treatment and recovery process. There is a need to find other less harmful alternatives for the same. Considering the potential of various drugs and their delivery, there is hope that this feat is not too far from being achieved. The use of nanotechnology for drug delivery has been one of the methods which could be approved for harmless medication soon. This is because, along with reducing the tumor volume, the terrible side effects are also taken care of. The amount of drug released can be controlled, thus preventing toxicity and damage to healthy cells. High surface area, extended drug release, high encapsulation efficiency, biocompatibility, and cost-effectiveness are properties that are the most desirable ones in a potential anti-cancer drug carrier. Electrospun nanofibers are one such example of drug carriers that have successfully fulfilled most of these properties.

We studied the various potential delivery systems for anti-cancer drugs. Natural drugs are showing the way for efficient drug delivery. They are available in nature, hence reducing synthesis costs. However, they have not been extensively studied upon. Allopathic drugs have given a lot of tested and verified results in favor of curbing tumor growth. In most of the studies, it was found that the initial release rate was very high, but later it was followed by a comparatively slower

release.

As an extension of these studies, more testing must be done on mice, later on other animals, and finally on humans. There is a long way to go before a cure without side effects is achieved with the help of modern science.

Now that less harmful treatment alternatives are being researched, there can be further investigation on easier and comfortable means of delivery. For example, using oral means to deliver the drug instead of injecting it into the body is less painful and easier to consume. Also, Artificial Intelligence (AI) could be incorporated into studies, and technology could be developed where nanofiber-drug combinations are automatically suggested by the smart systems based on the drug to be used, release concentration, type of tumor, and the type of release site. This review focuses on delivering many anticancer drugs into different electrospun nanofibers, intending to uncover the ultimate cure for this deadly disease.

## Declaration of Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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