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Review Article

OVERVIEW OF MITOXANTRONE-A POTENTIAL CANDIDATE FOR TREATMENT OF BREAST CANCER

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ABSTRACT

Anthraquinones are one of the popular classes of aromatic compounds which possess potential anticancer properties by suppressing the nucleic acid formation and proteins essential to the survival of cancerous cells. Mitoxantrone (MT) is an antibiotic and antineoplastic agent belonging to the anthracycline class of compounds which exhibit minimal incident of drug resistance. It is a synthetic anticancer drug, bound to enzyme topoisomerase IIα inhibitor, and intercalates DNA topoisomerase IIα, preventing re-ligations in DNA strands fragmentation and disruption of DNA repair. The expression of this enzyme was used tumor cells marker because of its key function in cell proliferation. The cleavable complex of topoisomerase IIα is hypothesized to damage the DNA and may enhance apoptosis in tumor cell proliferation. The susceptibility of cells to mitoxantrone is associated with cell topoisomerase II α protein and lowered resistance in breast cancer line cell lines to topoisomerase IIα inhibitors. MT is an ABC-transporter in breast cancer, also designated to be associated with "Breast cancer resistance protein" (BCRP) and it is also a cell cycle non-specific anti-cancer drug and P-glycoprotein substrate. Multiple drug resistance is one of the major drawbacks of this drug which can be avoided by reducing the efflux of the drug from cancer cells by formulating drug by using lipophilic carriers. This manuscript discusses about MT's source, chemistry, physicochemical properties, anti-cancer effects of mitoxantrone and possible pathways, Mitoxantrone targeting topoisomerase II inhibitor for cancer therapy and its mechanism, Various Nano formulation development strategy, toxicity profile, and a few patents related information.

Keywords: Breast cancer, Anthraquinone, Mitoxantrone, Nano formulation, Multiple drug resistance

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INTRODUCTION

Cancer is emerging as a major problem globally, both in developed and developing countries. Currently, every year 10 million new cancer cases are diagnosed across the globe [1]. By the end of 2021, cancer rates could rise by 50 % which may account for 15 million new cases and with a projected death fig. of 8.8 million. By 2030, over 21.7 million cancer cases and 13 million cancer deaths are predicted [2–4]. Every year breast cancer affects 2.1 million women and with being frequently reported in the female population [1, 5]). In India, 1.73 million cases were reported in the year 2020, which also contributes to the highest cancer-related mortalities among women [6–8]. Considering high morbidity and mortality associated with breast cancer treatment in the last few decades, cytostatic as well as cytotoxic drugs have been developed [9, 10] the anthraquinone class of antineoplastic agents exhibits better therapeutic efficiency to treat breast cancer compared to that of anthracyclines [11]. Anthraquinone derivatives exhibit antitumor activity by binding to DNA polymerase in tumor cells that results in inhibition of cell growth (cytostatic) or even cell necrosis (cytotoxicity) [12, 13].

Anthraquinone ($C_{14}H_8O_2$) is an aromatic organic compound also known as dioxo anthracene or anthracene Dione [14]. Anthraquinones can be obtained from natural as well as synthetic sources; the compounds of this class have a rigid structure consisting of a flat tricyclic aromatic anthracene which contains two keto groups located at the 9th and 10th positions. The tricyclic anthraquinone core gets embedded in the DNA double helix of abnormal cells, which undergo a specific redox reaction that generates superoxide radical anion (O_2^-) [15]. The bioactive properties of 9,10-anthraquinone (IUPAC: 9,10-dioxoanthracene) are as shown in fig. 1 [16–24]. Anthraquinone compounds have potential anticancer properties as they can inhibit the synthesis of nucleic acid and proteins of cancer cells [25–27].

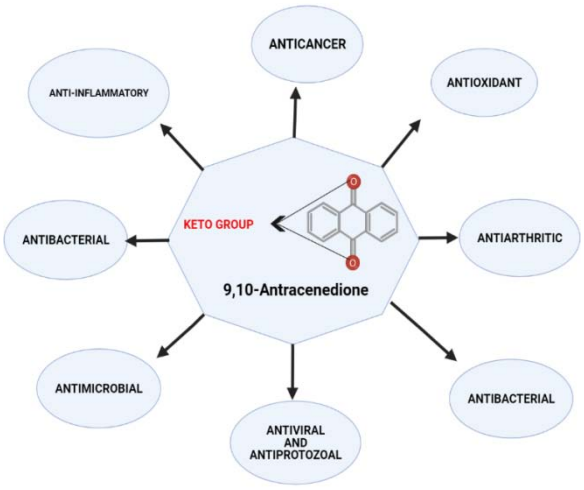

Fig. 1: Bioactive properties of 9, 10 anthracene dione

Anthraquinone derivatives bind to DNA of cancer cells and inhibit the topoisomerase II enzyme, making them as effective cancer cell growth inhibitors [28]. Binding of these derivatives with topoisomerase-II results in a cleavable complex, which induces the breakage of DNA strands, leading to cell death through apoptosis [29]. Food and Drug Administration (FDA) has approved four naturally and synthetic anthraquinone derivatives for cancer treatment which have the capability to interact with the DNA sequence and result in apoptosis [30]. Drugs derived from anthraquinone derivatives currently in use for cancer therapy are Daunorubicin, Doxorubicin, Mitoxantrone, and Amsacrine [31].

One such anthracenedione derivative is Mitoxantrone (MT), a synthetic anticancer agent, which was originally designed as a simplified analogue of the anthraquinone-containing anthracyclines [32, 33]. MT is an antibiotic with an antineoplastic activity that interferes with the growth and metastasis of cancer cells in the body [34, 35]. MT is a doxorubicin analogue and is generally used in combination with other chemotherapeutic agents to improve its antitumor activity, minimize dose-related side effects [36, 37]. Simultaneously Neidhart *et al.*, In 1980, conducted a prospective comparison of antineoplastic agents for breast cancer, mitoxantrone and doxorubicin as therapy for minimally pretreated patients with breast cancer. So MT is the promising antitumor agent which improves the therapeutic efficacy and it is used in metastatic breast cancer treatment [38–41]. The clinical trial data on metastatic breast cancer treatment, MT monotherapy had shown average positive response in approx. 33 % of patients with no prior chemotherapy exposure [42]. The toxic effects related to MT such as cardiotoxicity and gastrointestinal effect like nausea, vomiting, fatigue were comparatively lower than other anthraquinone derivatives.

MT is used effectively in disease-modifying therapy (DMT), which can also be employed in the therapy of acute non-lymphocytic prostate cancer and leukemia. MT is a novel photosensitizer for photodynamic therapy for breast cancer and reported to cause MCF-7 cell death *in vitro* [43]. Recent advancements in Nano drug delivery technology and photodynamic therapy have the potential to become an effective alternative to surgery for advanced breast cancer, which reduce the total exposure of the drug to healthy tissues and organs [44, 45]. This review aims to summarize MT as a therapeutic molecule for breast cancer in case of both benign and malignant tumor, including its source, structural modification, physicochemical properties, mechanism, pharmacological action, its multiple drug resistance, pharmacokinetics and metabolism. A comprehensive survey of relevant various Nano formulations is provided, with innovations made in recent years to improve drug resistance and therapeutic effectiveness [46, 47].

Mitoxantrone-source, structural modification, physicochemical properties

MT (1, 4-bis-[[2-(dimethylamino) ethyl-amino]-9,10-anthracenedione) is being developed by the American Cyanamid Company and the Midwest Research Institute as a possible chemotherapeutic agent. Murdock *et al.* performed structural modifications of MT that included 5,8-dihydroxylation of the anthracenedione nucleus and replacement of both terminal dimethylamino groups with hydroxyethyl functions [48]**.** The MT compound was primarily developed from ballpoint pen ink ingredient, although it was discovered to have antitumor activity after a routine screening by the National Cancer Institute (NCI) [49–51]. Mitoxantrone (fig. 2) is a hydroxyquinone with amino functionalities attached to aliphatic side groups, but it lacks an amino sugar moiety at the C9 position [50–52]. The basis for the mitoxantrone structure was drew on discovery of ant leukemic agents had a distinct N–O–O triangular pharmacophore (fig. 3) which is previously there in anthracyclines and the amino group is removed, which was considered to have involved in anthracycline cardio toxic [51–53]. The physicochemical properties of MT are given in table 1 [54–60]**.**

Fig. 2: Structure of mitoxantrone

Table 1: Physicochemical properties of mitoxantrone

Characteristics	Physical properties
Occurrence	The synthetic compound belongs to the class of organic compounds.
Chemical class	Anthracenes
IUPAC	1,4-dihydroxy-5,8-bis[2-(2-hydroxyethylamino) ethyl amino] anthracene-9,10-dione and 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl) amino]ethyl]amino]-9,10anthracenedione dihydrochloride
Molecular formula	C_{22}-H_{28}-N_4-O_6 and $C_{22}H_{28}N_4O_6 \bullet 2HCl$
Molecular weight	Mitoxantrone: 444.5g/mol, Mitoxantrone hydrochloride: 517.41g/mol
Melting point	203-205 °C
Purity	>98.0%
Appearance	Blue-black solid
Solubility	Slightly soluble in methanol; sparingly soluble in water, practically insoluble in acetonitrile, acetone and chloroform.
Stability	15 ° to 25 °C (59 ° to 77 °F) under refrigeration.
Route of administration	Intravenous, Intraperitoneal, Continuous and Intermittent infusion.

Fig. 3: Structure of mitoxantrone with N-O-O triangular pharmacophore

Anticancer effects of mitoxantrone and possible pathways

Mitoxantrone exhibits its anticancer activity by acting as an intercalating agent. It inhibits both RNA and DNA synthesis. It is six to seven times more potent than anthracycline derivatives in inhibiting the incorporation of 3H-thymidine and 3H-uridine into DNA and RNA thus disrupting their replication respectively. It also binds to an enzyme called topoisomerase II, which tends to breakage of the DNA strands and stops the synthesis of DNA, resulting in cell death via apoptosis as shown (fig. 4) [61–63]. In addition, mitoxantrone has been reported to exhibit anticancer activity by various mechanisms like autophagy [64–66], paraptosis [67], radiosensitization [68, 69], aberrant cell metabolism [70–72].

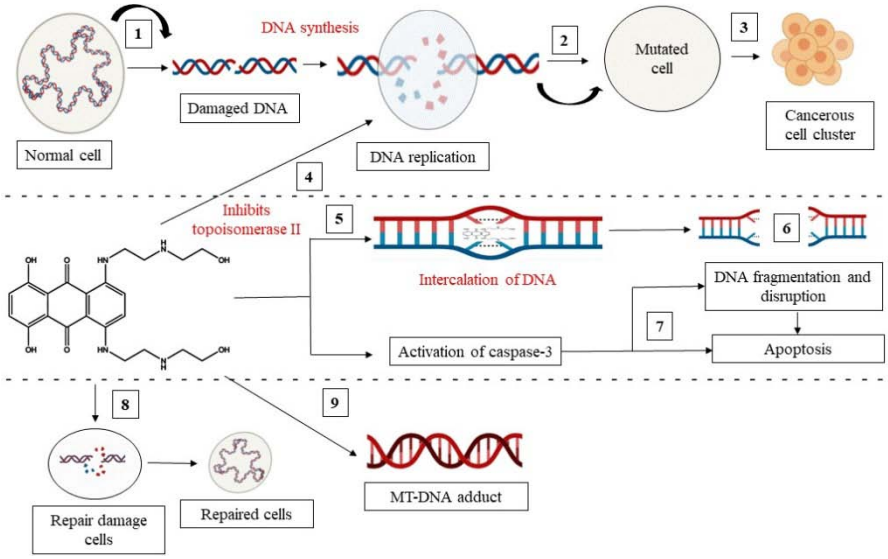

Fig. 4: Mechanism of action of mitoxantrone on cytotoxicity activity

There are multiple mechanisms by which MT shows its anticancer activity which is identified by several scientists through their research findings. Lown *et al.* [73] have demonstrated that, on increasing the concentration of MT progressively to already relaxed PM2-DNA, it shows an intercalative binding with isolated DNA plasmid, MT could also possibly show extensive inter DNA cross-linking with side arms of DNA, making a network of linked molecules. Similarly, Foye *et al.* [74] discuss that MT binds to isolated DNA at two sites, i.e. (1) Intercalation is seen between base pairs which are successive to each other and (2) Electrostatic interaction with DNA, occurring between amine side chains present in MT and phosphate groups present in DNA. The another study on the basis of *in vivo* study of interactions between MT and tumor cellular DNA demonstrated that, a) MT does not cause any changes in DNA supercoiling like other classical drugs with intercalating properties. b) It induces protein-related double and single strands DNA fragment and c) MT potentially disrupts single strands of non-protein-based DNA [75].

Mitoxantrone–targeting topoisomerase II inhibitor for cancer therapy

Topoisomerase inhibitors (TI), inhibits cancer cell proliferation by avoiding DNA replication, arousing DNA damage, and thus provoking cell cycle arrest. The DNA topoisomerase enzyme is divided into two types: type I and type II [74]. The DNA topology is altered by Type I topoisomerases by passing a single DNA strand by breaking in the opposing single strand and cleaving it with an active site that is tyrosine residue, producing a phosphodiester link with the enzyme [76]. Type II A topoisomerases, which include eukaryotic topoisomerase II and II, have a three-domain structure that spans the A and B subunits that form the homodimer (or heterotetramer in prokaryotes) as shown in (fig. 5). The N-terminal domain consists an ATP-binding region (ATPase domain), a core domain containing a TOPRIM fold and a DNA-binding region, and a C-terminal domain of unknown function [76, 77]. Eukaryotic TOP IIA has three sections known as the N-gate, DNA gate, C-gate, and the catalytic Tyr805, which is responsible for cleavage present in the DNA-gate. Topoisomerase II alters the structure of DNA strands by breaking and reconnecting the phosphodiester backbone of DNA using identical active site tyrosine residues [78]. This is accomplished through the production of temporary, enzyme-bridged double-strand breaks. This enzyme is commonly utilized as a marker of cancer cells due to its function in cell proliferation [77]. TOP II plays a critical part throughout the replication of DNA and its main activities are chromosomal segregation. Topoisomerase I, IIα, and IIβ are the targets for commercialized anti-cancer agents [78]. Topoisomerase IIα (Topo IIα) is the target of multiple chemotherapeutics such as anthracyclines and other intercalators, such as mitoxantrones [79]. It plays a vital role in DNA replication and has been associated in breast cancer with the proliferation of cellular and HER2/new protein overexpression [80]. Mitoxantrone may act as the topoisomerase IIα catalytic cycle. But, most likely by interfering with the activities of the enzyme, all of it stimulates the creation of protein-linked DNA strand breaks[81]. The cleavable complex is hypothesized to damage the DNA, to cause toxicity, and causes apoptosis in tumor cells. The sensitivity of cells to mitoxantrone depends on cell topoisomerase II α protein and lowered topoisomerase II resistance in breast cancer line cell lines to topoisomerase IIα inhibitors [82].

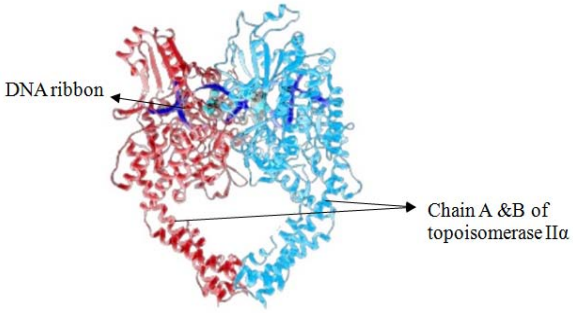

Fig. V: Structure of topoisomerase IIα

(Topoisomerase IIα enzymes with bound DNA and Two sub-family kind domains (The DNA ribbon is dark blue; the chain A of topoisomerase IIα is red; the chain B is light blue)) [83].

Mechanism of topoisomerase II inhibitor for cancer therapy

Prevention of the enzyme-DNA topoisomerase takes place by some of the generally accepted mechanisms at molecular level that are mentioned below [84, 85].

Substrate competitive inhibition

To the topoisomerase active site, an inhibitor molecule is attached which blocks the DNA substrate from binding. There are no known inhibitors that are topoisomerase-specific which function in this way, however present research on DNA-competitive inhibitors of other DNA-binding proteins imply that this mechanism might potentially function in DNA topoisomerases II [86].

Topoisomerase poisons mechanism

The DNA re-ligation is blocked by the protein-DNA-drug complex which is ternary. It prevents the enzyme from forming a "cleavage complex." This drug inhibits enzyme turnover and accumulation of cytotoxic cleavage complex within the cell in excessive quantities [87].

Potent inhibition of the ATP

The ATP binding site has one competitive inhibition of the type II topoisomerases that prevent enzymatic activation by ATP-hydrolysis. Type II topoisomerase is necessary for ATP synthesis as well as for the domain which binds ATP is distinct from the DNA binding domain. Further, the dependency or absence of DNA topoisomerases is distinguishable from the Mg 2+for catalytic activity. Mg2+ appears to be required for Type I A and Type II topoisomerases, however, catalytic action is required for Type IB topoisomerases if Mg 2+is not present. [87].

The stabilization of the cleavage complex

It is the topoisomerase II poisons mechanism which encompasses the production of a ternary complex that is locked of cleaved DNA, protein, and antineoplastic medication, which grows and produces cytotoxicity [85]. Anthracyclines, such as mitoxantrones, are anthracyclines that target type II A topoisomerases in the treatment of breast cancer. These agents are bound to cleaved DNA/protein complexes, blocking DNA binding and seal the enzyme to the cleavage complex [88]. This cleavage complex develops and causes a breakdown of the DNA strand and finally cell death. The most commonly known topoisomerase poisons work is the interplay between the-1 and+1 DNA base pairs of the protein-DNA cleavage complex. Additional hydrophobic and electrostatic interactions with both DNA and protein increase the poison's binding and prevent DNA from being relegated to topoisomerase II [89, 90].

The redox-dependent

The covalent and redox-dependent creation of a complex of drug-enzyme and the complex of DNA cleavage, which results in a same build-up and eventual cell death, is the mechanism of the second topoisomerase poison. The increased interfacial topoisomerase poison in the active site between two DNA base pairs is caused by the interactions of the DNA bases with the connected, four-ring pharmacological system. Hydrogen bonding to surrounding protein residues and local DNA bases has been discovered in the surrounding ring systems of antineoplastic medications [89, 91].

Catalytic inhibition

The third ideal topoisomerase inhibitory mechanism encompasses the competitive binding of small molecules to the ATP binding site present in the N-terminal region of type II topoisomerases by catalytic inhibition [85, 92]. The torsional strain of the supercoiled DNA provides the energy required for the activity of type I topoisomerases, whereas ATP hydrolysis provides the energy required for the action of type II topoisomerases [84]. The passage of the DNA T segment is blocked by the competitive hydrolysis of ATP through smaller molecules from passing through the G-Gate to the C-terminal domain, which leads to catalytic topoisomerase inhibition, DNA transcript halting as well as cells apoptosis. This mechanism is not responsible for the DNA and cell damage induced by topoisomerase poisons. Despite the fact that no anticancer drugs with this mechanism of inhibition are currently on the market [93].

Nano formulation development strategy of mitoxantrone

With its beneficial safety profile, MT has recently gained more attention as the therapeutic compound in the treatment of cancer therapy [84]. Even though, MT is classified as a Class III drug according to the Biopharmaceutical Drug Deposition and Classification System (BDDCS), owing to its low permeability, low metabolism and bioavailability. MT has limited therapeutic responses because of its drug resistance in tumor cells which is a most concern in malignancy [96, 97]. To address the low permeability of the drug across the cell membrane, incorporation of the hydrophilic drug (MT) into lipophilic carrier system, like liposomes, polymeric mixed micelles, nanoparticles such as NLCs, SLNs, Nano-diamond NPs, gold NPs, Albumin NPs, graphene oxide NPs, iron NPs etc. have been extensively reported [98–101].

The incorporation of MT in lipophilic carrier system is employed to overcome many challenges such as modulation sustained drug release, reverse multidrug resistance (MDR), and improve its bioavailability [102, 103]. Several research studies shows that nanotechnology imparts stable formulation of MT, improve its bioavailability and therapeutic efficacy [104–107]. Nano drug delivery methods are advanced techniques for delivering drugs to tumor cells with minimal drug leakage to healthy cells [108, 109]. The development of MT's Nano formulations can resolve the drug resistance in cancer cells and minimize drug efflux and enhance the retention of MT in malignant cells [33, 110]. Lu *et al.* have developed the solid lipid nanoparticles (SLNs) of MT, which improved the drug resistance in breast cancer and its lymph node metastases in mice. These MT-loaded SLNs depicted sustained release of the drug which have effectively inhibited the breast cancer and lymph node cancer in nude mice model with no toxicity in normal tissues and have reduced the lymph node cancer size up to 1.85±27.42 mm^3 compared to MT alone (119.32±57.30 mm^3) [111].

To improve the therapeutic targeting of MT, Though *et al.* developed Nanodiamonds (NDs) for the promising delivery of MT. NDs with diameters of about 5 nm and demonstrated their ability to enhance drug resistance while slowing tumor growth development, they evaluated the MT Nanodiamond complex, on the MDA-MB-231-Luc-D3H2LN in TNBC cell line that was virally transduced for resistance to MT, the comprehensive complex enhanced drug retention and efficacy. The results of the *in vitro* analysis suggested that MT Nano diamond could be a better drug delivery system for drug-resistant cancers [121]. Furthermore, ling *et al.* synthesized carrageenan hybrid nanostructured lipid carriers (NLCs) to improve the sustained drug release, bioavailability and anticancer efficacy for MT through the oral route. Results of the study depicted that the oral bioavailability of drug-loaded Nanocarriers was increased 3.5 times than free drug. The cytotoxicity investigation depicted that the MT Nanocarriers significantly enhances the anticancer efficacy compared to pure MT against MCF-7/MX cells and diminished the BCRP associated drug resistance [122].

Likewise, MT was utilized to reduce the MDR effect with photosensitive properties to improve anticancer efficacy. The MT was mixed with poly(ε-caprolactone)-pluronic F68 to prepare micelles. When it was subjected to close-infrared light and induced irritation, MDR's influence on MCF-7/ADR cells was reversed by photochemical interactions. This resulted in cytotoxicity of cancer cells. Usually, MT causes apoptosis in MCF-7/ADR cells by producing ROS and decreasing P-glycoprotein activity. These mixed micelles effectively reversed the MDR effect via photodynamic therapy [112]. MT possesses broad range of therapeutic effects to against advanced breast cancer [123]. It is found to be highly effective in ovarian cancer [124], colon cancer, non-Hodgkin's lymphoma, acute myeloid leukemia [125–127], bladder cancer [128], prostate cancer [129], and glioblastomas [113, 130]. The various Nano formulations loaded with MT for effective treatment in breast cancer therapy and various cancer treatment are compiled in (table 2).

Table II: Formulation development and strategies based on nanotechnology of mitoxantrone

Nano formulation	Method of preparation	Major component of the delivery system	Purpose	Key findings/conclusion
Multifunctional lipid-sodium glycocholate Nano carriers	Emulsification ultra-sonication method	Compritol 888, Cremophor RH40, Miglyol 812, lecithin	Combination therapy by combining the "BCRP bypassing effect."	Co-encapsulation of the hydrophilic anticancer drug, BCRP inhibitor, into TMLGNs is an effective platform for MDR reversal [39].
Hydrophobically Modified Pullulan Nanoparticles	Nano Precipitation method	Pullulan, cholesterol	Prevent the growth of cancer cells in the bladder and the migration of MB49 cells with nanoparticles	The release of Cholesterol-substituted pullulan polymer NPs is proportional to acidity. Also, larger NPs have shown better inhibition of cancer cells in the bladder due to migration than smaller NP [49].
Novel nanostructured lipid-dextran sulfate hybrid carriers (NLDCs)	Emulsification-ultra sonication Method.	Lipid-based drug delivery system.	Delivers water-soluble cytotoxic drug in cancer chemotherapy for MDR.	NLDCs of small size show high efficacy of drug encapsulation, long-term release characteristics, desired pharmacokinetics, and cytotoxicity [98].
MT-PFP/PPP mixed micelles	Solvent Evaporation method.	Poly(ε-caprolactone), poly (d, l-lactide-co-glycoside), poly (ethylene glycol) pluronic F68.	To examine the photosensitizing properties of MT clinically used as a PDT.	MT-PFP/PPP micelles were able to decrease P-gp activity, increase ROS levels and cell uptake, which reversed the MDR effect after irradiation and triggered cell apoptosis [112].
Plant virus-based Nanoparticles	Ultracentrifugation method.	Plant virus-based nanoparticles drug delivery system.	Delivery of MT prevents poor penetration of the blood-brain barrier	Uptake of CPMV–MT in U87-MG glioblastoma cells and this encapsulated MT maintain its therapeutic potential [113].
Solid lipid nanoparticles	Film dispersion–ultrasonication	Lecithin and Compritol®888	A novel approach to active delivery of antitumor drugs against breast cancer and lymph node metastases, with a therapeutic effect that is both inspiring and low in side effects.	P388 cell lymph node tumor model was effectively developed, and the suppression of MTO-SLN against the metastases was promising. The MTO-SLN was promising in the per cent inhibition of the tumor growth [114].
Nano diamond	-	Nano diamonds	To improve drug tolerance	Improved efficacy and drug retention in an MDA-MB-231-Luc-D3H2LN [115].
Nanostructured lipid-carrageenan hybrid carriers	Emulsification-ultra sonication	Compritol 888 ATO, miglyol 812, cremophor RH40 and lecithin	To enhance oral bioavailability, encapsulation efficiency, and reduce cytotoxicity	Enhance the encapsulation of breast cancer cells, increased oral bioavailability, and anti-tumor activity [116].
Folate-conjugated Albumin Nanoparticles	Chemical cross-linking with glutaraldehyde (Coacervation method)	Folate, Bovine serum albumin	BSANP targets to SKOV3 cells and enhance therapeutic potential for cancer chemotherapy	MT-BSANP-folate NPs increased the intracellular uptake of trapped MT in SKOV3 cell to enhance anticancer activity by passive accumulation [117].
Hyaluronic acid/ polyethylene glycol nanoparticles	Nano precipitation and lyophilisation	Hyaluronic acid, polyethylene glycol	To exhibit significant Cytotoxic effects on CD44-positive cell line.	NPs attached effectively to the receptor binding site demonstrate considerable cytotoxic effects in CD44-positive cell lines on cell viability [118].
Phospholipid-amorphous calcium carbonate hybrid nanoparticles	Facile solvent-diffusion method	Ammonium carbonate, anhydrous calcium, Chloride, PL (S100), DSPE-PEG2000, DSPE-PEG-FA	Enforce the delivery of active agents within cancer cells with increased drug penetration	NPs with enhanced performance, site targeting, controlled drug release, and increased drug penetration [119].
PEGylated Gold Nano complexes	Chemical reduction	Gold chloride trihydrate, Methoxy polyethylene glycol thiol	*In vivo* via passive targeting for cancer therapy, enhanced retention and permeability effect.	AuNPs-PEGs-MT enhanced stability, loading efficiency of Mitoxantrone (1.9-fold), and cytotoxicity [120].

Metabolism and its metabolites

The liver is the primary site of MT metabolism [131]. The metabolism of MT involves the microsomal pathway and/or peroxidase enzymes, including neutrophil myeloperoxidase are involved [132]. Its metabolites have been discovered in the bone marrow, kidney, heart, spleen, and lungs, in addition to the liver [127]. Inhibition of the functioning of cytochrome P450 combined oxidase function in a human hepatoma-derived cell line reduced the inhibitory effect of MT on cell proliferation. A rat hepatocyte model and human breast cancer cells both produced similar results [128–131]. Furthermore, phase II metabolism, namely conjugation with glucuronic acid and reduced glutathione (GSH), plays an important part in the MT detoxification process[133, 134]. Numerous pre-clinical studies have been carried out in rats, rabbits and anaesthetized pigs to identify different metabolites. Smyth *et al.* reported the oxidative metabolism of terminal hydroxyl groups of parent molecule (MT), causing the formation of the metabolites A and B. They have identified metabolites of mitoxantrone in plasma and urine. The metabolism in humans and animals indicated that MT might conjugate with glucuronic acid and glutathione [135]. Richard *et al.* separated several metabolites of MT in rabbits were identified as the mono and dicarboxylic acid derivatives [136].

They also evaluated the excretion of mitoxantrone in bile and urine. Mitoxantrone is mostly eliminated by the bile route, with minor levels excreted through the urine. The metabolite naphtoquinoxaline brings cellular damage to newborn cardiomyocytes that are isolated from rats [135]. This metabolite has already been discovered to be an *in vivo* MT product of biotransformation in humans, rats and pigs.

When examining the variability among interspecies, the metabolic distinction allying humans and rats is that the mono as well as dicarboxylic acid derivatives of MT were substantial bioproducts from human metabolism, whereas they are negligible in rats [136]. Except for the results reported by Shipp *et al.* in that no studies have been conducted that relate MT bioproducts to its most extreme undesirable impact i.e. late irreversible cardiotoxicity [137–139]**.**

Pharmacokinetics

According to Biopharmaceutical Drug Disposition and Classification System, MT is a class III drug that is poorly absorbed when given orally [96, 140]. The pharmacokinetics properties of MT are being studied in cancer patients as well as in animals through different routes of administration (intravenous, intrapleural, intraperitoneal, and intra-arterial) and were examined by HPLC and total radioactivity method [141]. After intravenous injection, MT has a rapid dispersion followed by a longer clearance process distinguished by extensive accumulation in highly perfused organs, according to pharmacokinetic experiments in humans and laboratory animals. Intravenous administration of MT follows a three-phase method for elimination from the blood plasma, a fast initial (α) distribution phase with a half-life (0.1 h), an intermediate (β) half-life distribution phase (1.1 h), and a terminal gamma elimination phase (γ) (42.6 h.) with a half-life of 12 d [75, 95]. After five days of the urinary sample collection, Albert *et al.*, in their study, stated that about the whole MT dose was retrieved in an unaltered form at a rate of 6.5 percent (range: 5.2-7.9 %) [75]. Despite the persistence of MT in the tissues, the pharmacokinetics of the drug did not appear to be affected by repeated daily administration for five days or at 3-week intervals for up to 12 courses, with no significant changes in the terminal half-life, urinary excretion, and volume of distribution [75, 142]. A steep dose-response curve, dose-limiting myelosuppression, and extensive tissue binding have been reported by systemic administration of MT. However, since MT is non-vesicant, regional drug administration can effectively solve these problems. Mitoxantrone is often delivered into a deep tissue compartment from which it is slowly retrieved, as illustrated by its prolonged plasma terminal phase half-life, extraordinarily large volume of distribution (Vd), and a relatively substantial quantity of mitoxantrone (>15 % of the administered dose) was found in necropsy tissues 35 d after dosing [82, 117]. These outcomes back up a pharmacologic justification for using mitoxantrone in an irregular dosage regimen.

Multiple drug resistance of mitoxantrone

Drug resistance tumor cells are considered to be a major concern of cancer chemotherapy. The principal aspect of clinical failure and death in cancer patients is due to resistance to chemotherapy. Patients who acquire resistance to cytotoxic treatment often develop resistance to several ant leukemic drugs, leading to multidrug resistance (MDR) phenotype in cancerous tissue. MT is a cell cycle non-specific anti-cancer drug and P-glycoprotein substrate used in the treatment of breast cancer [143]. Mitoxantrone transporter is identified as ABC-transporter in a breast cancer-derived cell line and is designated as “breast cancer resistance protein” (BCRP) and also as “mitoxantrone resistance-associated protein [144, 145]. The resistance occurs by possible mechanisms like decreased accumulation of intracellular drugs, often with over-expression of P-glycoprotein (MDR1) mediating increased drug efflux, enzymatic modifications that minimize susceptibility to DNA damage or improve DNA repair, altered drug metabolism, distribution, and binding site [146–149]. The inhibition of downstream death signaling pathways are all forms of drug resistance mechanisms generally observed with mitoxantrone [150–152]. In clinical studies, it is observed that efflux transport is carried out by ATP-binding cassette (ABC) transporters, which transport substrate drugs from the cell in an energy-dependent manner against a concentration gradient [150]. P glycoproteins (P-gp) and multidrug resistance proteins (MRPs) are two transmembrane xenobiotic transporter proteins that imparts a significant role in clinical drug resistance in drug-sensitive human breast cancer cells [152–156]. BCRP overexpresses several chemotherapeutic drugs, including mitoxantrone, adriamycin, and doxorubicin, out of the cell to several cancer cell lines [157–159].

Table 3: Toxicity of mitoxantrone

S. No.	Toxicities	Treatment	Dose	Drug delivery system	Main findings
1	Cardiovascular toxicity, Congestive heart failure and AML.	Advanced breast cancer	12 mg/m^{2}every 3 mo (140 mg/m^{2*})	MT intravenous infusion	Cardiac disease has been found in cancer patients who received cumulative dosages either alone or in conjunction with other cytotoxic agents. Elevated risk of Leukaemia in 0.25% of patients (n=802) has been observed [168].
2	Hematological Effects	ANLL	12 mg/m^{2}for 5 d or 14 mg/m^{2}for 3 d	MT intravenous infusion	Granulocyte recovery times for refractory ANLL have been recorded to be 26 to 32 d, but this refers to a count of at least 1000/l. MT is efficacious in previously untreated ANLL in conjunction with cytosine arabinoside. CR after 240 d of induction obtained 89% of patients treated with mitoxantrone [170].
3	Neutropenia	Prostate cancer	2–5 mg/m^2	MT intravenous infusion	The maximum dose of MT that could be tolerated was 4 mg/m2. Patients receiving 2–4 mg/m2 had no dose-limiting toxicities, while those receiving 5 mg/m2 had none [171].
4	Gastrointestinal toxicity.	Breast cancer	12 mg/m^2	MT intravenous infusion	43% (n=100) of patients treated had nausea, vomiting, or both, but these effects were severe in less than 1% of patients [107,172].
5	Hematologic toxicities and Non-hematologic toxicities.	Malignant lymphoma and Advanced solid tumor.	6-18 mg/m^2	PEGylated liposomal mitoxantrone-loaded into small unilamellar vesicles 60 nm plm60-s	Extreme leukopenia was found in only one patient (16 mg/m2). Some hematological toxicity symptoms include thrombocytopenia, erythropenia, and a drop-in hemoglobin level. Dyspnea, nausea, skin rash, vomit, pruritus, and an increase in ALT were among the non-hematologic toxicities, but they were all treated [173].
6	Alopecia	Breast cancer	12 mg/m^2	MT intravenous infusion	Dyspnea, nausea, skin rash, vomit, pruritus, and an increase in ALT were among the non-hematologic side effects, but they were all treated. No clinical cardiotoxicity was seen with dosages of 24-144 mg/m^2(mean 78 mg/m^2) [174].

*= maximum cumulative lifetime dose; *1= MT in combination with methylprednisolone; MS: Multiple sclerosis; LVEF: Left ventricular ejection fraction; n=Number of patients; AML: Acute myelogenous leukemia; ANLL: Acute Non-Lymphoblastic Leukemia; CR: complete remission ALT: Alanine aminotransferase.

Sri K *et al.* investigated in key role of multidrug resistance protein (MRP1) and ATP binding cassette Subfamily C Member 1 (ABCC1) in MT cross-resistance in the MCF7 cell line. The MCF7/VP resistant cell line exhibits elevated levels of MRP1 compared to the MCF7/WT parental cell line. MCF7/VP cells are 6–10 times relatively more resistant to MT than MCF7/WT cells. MT efflux is ATP-dependent and inhibited by cyclosporine A and sulfinpyrazone. With these agents, inhibition of MT efflux sensitizes cells to MT cytotoxicity and partially reverses MT resistance in MCF7/VP cells. It concluded that overexpression of MRP1 in MCF7/VP cells is expected to be enhance the MT efflux and resistance [160]

Potent inhibition of BCRP to minimize drug efflux is a promising approach to overcome drug resistance limitations [161–163]. However, because MT is a substrate of the BCRP efflux transporter, tumor cells are extremely resistant to it [156]. To improve MT efficacy, Nano carriers drug delivery that can minimize efflux, prolong drug retention in drug-resistant cancer cells, and induce complexity in tissues can be developed.

Toxicity of mitoxantrone

MT is a synthetic derivative with an antitumor activity similar to that of anthracyclines but with less toxicity [164]. The toxicity profile of MT is associated with the total dose administered. It is usually well-tolerated at standard doses [165]. Anaemia, cardiotoxicity, neutropenia, and liver toxicity were some of the most commonly reported unexpected side effects in Phase II/III clinical trials [166, 167]. Liver injury linked to MT is possibly due to hypersensitivity reaction [168]. The published data also indicate many other toxic effects (table 3)**.** Most of these side effects were intermediate or mild, such as nausea, abdominal pain, vomiting, fever, or bone marrow suppression. The major long-term toxicity is dose-dependent and is a strict limiting factor for the duration of treatment [169]. To reduce the risk of cardiac events, the drug should be administered slowly and carefully through an intravenous route (over 30 min, as it may cause severe local tissue damage) and administration of MT has shown good tolerance at an acceptable level [109]. Analogues of MT with much lower cardiotoxicity are currently being investigated in experimental animal models [58, 138].

Patents on mitoxantrone and related formulations

The records were found using a variety of databases, including Google Patents, Espacenet, WIPO, and the USPTO search engines. Terminologies like mitoxantrone, mitoxantrone formulations for cancer, use of mitoxantrone in breast cancer, etc., were used to perform a search in different databases. Considering patents written in English, we concentrated on the relevant material, title, abstract, and study status. There are some patents on the MT-based drug delivery system that were considered for this review and are listed in (table 4)**.**

Table 4: Patents on mitoxantrone based drug delivery systems

Nano-carrier system	Therapeutic agent	Therapeutic indication	Patent application number	Patent proprietor	Outcome
Liposome	Mitoxantrone	Non-Hodgkin's lymphoma, myeloma, advanced breast cancer, bladder, ovarian and hepatocellular carcinomas	US5858397A·1999	Univ British Columbia [CA]	Liposomal formulations of mitoxantrone [175]
Sustained-release implant	Mitoxantrone	Entity tumor/Solid tumors	CN101176710A·2008	Jinan Shuihua Medical Science [CN]	Mitoxantrone sustained-release agent for curing tumors [176]
Nanoparticles	Mitoxantrone	Prolongs the survival time of S180 mice, improves the efficacy, and reduces systemic toxicity	CN107684627A·2018	Univ Capital Medical Sciences	Mesoporous silicon dioxide-methotrexate-mitoxantrone nanoparticles [177]
Liposome	Mitoxantrone	High entrapment rate, strong stability and short half-life	CN103622909A·2014	Univ Jilin	Cardiolipin-liposome preparation and its application in antitumor drugs [178]
TRACER	Mitoxantrone	Pharmaceutical preparations and application of MT as a lymph tracer.	CN102397561A·2012	Univ Shenyang Pharmaceutical	Application of mitoxantrone as lymph tracer [179]

CONCLUSION

MT is an antibiotic with an antineoplastic activity that interferes with the growth and spread of cancer cells in the body. In spite of being potential anticancer drug, Mitoxantrone's utility is limited due to low permeability, low metabolism, bioavailability, drug resistance, cardiotoxicity, and gastrointestinal disorders. Mitoxantrone targeting topoisomerase II inhibitor for cancer therapy. To address these drawbacks, MT is now being formulated as Nanocarrier systems to enhance permeability, bioavailability, efficient tumor targeting, controlled drug release and drug resistance. The reviewed literature in this article emphasis on the recent advances of MT-containing Nano-drug delivery systems, such as Nano-diamond, PEGylated Gold Nano-complexes, lipid-based nanoparticles such as SLNs, NLCCs, micelles, and other lipid-based nanoparticles, transdermal cubic phases, and photodynamic therapy, as a better option for increasing the effectiveness of DDS in tumor treatment. However, till date, these Nano formulations containing MT are used only in *in vitro* and *in vivo* cell line studies.

FUTURE DIRECTION

In the future, Nanotechnology-based approaches such as SEDDS, Quantum dots, Carbon nanotubes, can be used as a promising therapeutic solution for targeting drug resistance and its low permeability. MT appears to be metabolized in the liver and hence further studies must be carried out to determine the effect of liver dysfunction on the disposition and toxicity of MT. Hence it is concluded that this literature serves as a valuable resource for a comprehensive review of MT as the potential target moiety for developing Nano strategies for clinical use. To overcome the drug resistance and toxicity issues which are currently research progress needs to be focused and improved on nanotechnology-based approaches.

ABBREVIATIONS

BC: Breast cancer, TNBC: Triple-negative breast cancer, MT: Mitoxantrone, DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid, ABC transporter: ATP-binding cassette transporter, BCRP: Breast cancer resistance protein, FDA: Food and Drug Administration, DMT: Disease-modifying therapy, TOP2A: Topoisomerase inhibitor type II, NCI: National Cancer Institute, PM2: Plaque morphology mutant, BDDCS: Biopharmaceutical Drug Deposition and Classification System, NPs: Nanoparticles, NLCs: Nano structured lipid carriers, SLNs: Solid lipid nanoparticles, MDR: Multidrug resistance, NDs: Nano diamonds, BSANPs: Bovine serum albumin nano particles, PFP: poly(ε-caprolactone)–pluronic F68–poly(ε-caprolactone), PLGA: Poly D, L-lactic-co-glycolic acid, PEG: Polyethylene glycol, NLCCs: Nanostructured lipid-carrageenan hybrid carriers, NLDCs: Novel nanostructured lipid-dextran sulfate hybrid carriers, PL/ACC:

Phospholipid/amorphous calcium carbonate, CHP: Cholesterol-substituted pullulan polymers, TMLGNs: Three-in-one multifunctional lipid sodium glycocholate nanoparticles, PDT: Photodynamic therapy, HPLC: High performance liquid chromatography, Vd: volume of distribution, MRP: Multidrug resistance protein, MS: Multiple sclerosis, LVEF: Left ventricular ejection fraction, AML: Acute myelogenous leukemia, ANLL: Acute Non-lymphoblastic Leukemia, CR: complete remission, ALT: Alanine aminotransferase, SEDDS: Self-emulsifying drug delivery systems.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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