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PACLITAXEL AND ITS MANAGEMENT IN CANCER THERAPY

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ABSTRACT
Paclitaxel is a broad-spectrum anticancer chemical obtained mostly from medicinal plants, specifically the bark of the yew tree Taxus brevifolia Nutt. It belongs to the diterpene taxanes class, which is today the most often used chemotherapeutic drug against many types of cancer.It has been shown in studies to have anticancer action against ovarian, lung, and breast malignancies. Paclitaxel, a taxane with microtubule stabilising properties, has remained the standard of treatment for primary ovarian cancer management. Taxanes with improved safety profiles and increased intra-tumor cytotoxicity have yet to outperform the original molecule inclinical trials. The mechanisms of PTX action illustrate the various ways in which PTX influences cellular functions, ultimately leading to programmed cell death. In addition, PTX is commonly utilised as a first-line therapy medicine for breast cancer (BC). Factors contributing to PTX resistance, such as ABC transporters, micro-RNAs (miRNAs), or mutations in specific genes, as well as PTX side effects such as peripheral neuropathy or hypersensitivity associated with the vehicle used to overcome its poor solubility, are driving extensive research into PTX use in preclinical and clinical studies.

KEYWORDS: Ovarian cancer, breast cancer, anti-cancer therapy, Paclitaxel, nanomedicine, phytochemicals.

INTRODUCTION
Cancer is becoming a prominent and life-threatening disease all over the world as a result of a lack of proper treatment. According to recent research, the number of cancer deaths worldwide has surpassed the rate of heart disease mortality.[1] With an expected increase in newly diagnosed cases in the near future and a dramatic influence at any level of sociosanitary care, it represents one of the largest concerns in medicine today.[2] Cancer's complicated structure and mutability have called into doubt general activities in prevention, early detection, screening, and therapy.[3] Several lifestyle and environmental variables, including as radiation, infections, lack of physical activity, usage of immunosuppressants, smoking, obesity, food quality, and alcohol intake, may contribute to the incidence of various tumour forms. Various cancer medicines have been developed in recent years. Surgery and radiation therapy are the foundational therapies for cancer, followed by a variety of specialised treatments such as chemotherapy, immunotherapy, hormone therapy, radiotherapy, and targeted therapy. Although treatments such as radiation and the use of traditional chemotherapeutics have great tumoricidal potential, they frequently destroy normal cells in addition to cancer cells, causing serious hematologic toxicity and tissue damage in patients.[4] Furthermore, chemotherapy has limited therapeutic advantages due to the presence of innate or acquired multiple drug resistance.[5] Targeted treatments with a multi-beneficial strategy are far preferable than conventional therapy.[6] They particularly prevent cancer cell proliferation and expansion.[7]

Nanomedicines now employed in clinical practise have been relatively effective in addressing medication development issues such as poor solubility and insufficient circulation time.[8] Paclitaxel is a broad-spectrum anticancer medication that belongs to the class of chemotherapeutic medicines that are most typically used to treat different solid tumours.[9] However, its applicability is severely limited due to its low solubility, re-crystallization upon dilution, and cosolvent-induced toxicity.[10] The use of appropriate pharmacological carriers may be able to overcome these constraints.[11]

One of the primary causes of cancer mortality is epithelial

ovarian carcinoma. One in every 70 women may get ovarian cancer throughout her lifetime, and the majority of these women willdie as a result of the disease. Despite the fact that the prognosis for women with ovarian cancer is very bad due to its late presentation and a lack of scientifically proven screening measures, the 5-year survival rate rose dramatically from 33% in 1982-1987 to 40% in 2000-2006.[12]

In advanced epithelial ovarian cancer, the standard of treatment includes surgical staging and resection, followed by paclitaxel-platinum chemotherapy. Maximal effort cytoreductive surgery, either initial or interval, with the goal of debulking to the point of no visible residual disease is related with better patient outcomes, with every 10% improvement in optimum cytoreduction rate contributing to a 5.5 percent increase in median survival.[13,14]

The Gynecologic Oncology Group (GOG), for example, has studied a significant variety of medicines over the last two decades, and only ifosfamide and paclitaxel (Taxol) have shown modest efficacy following such platinum-based chemotherapy.[15] Responses were documented in both platinum-refractory and platinum-sensitive individuals[16] who had only had one previous treatment in the landmark GOG phase II trial of Taxol.

The fast growth in the prevalence of numerous civilization illnesses, including cancer, is a critical feature of the modern period.[17] Breast cancer (BC) is the most frequent malignant illness in women and the primary cause of cancer mortality among them, and it is still a global public health concern.[18] Modern oncology techniques directed against BC, including advances in diagnosis, therapy, and prevention, play an important role in cancer care. Better understanding of the biologic heterogeneity of BC contributes to the creation of more effective therapeutic strategies in personalised medicine.[19]

Chemo-therapeuticals are currently classified into many types based on antimetabolites, alkylating agents, immunological elements, hormonal components, or mitotic deprivation.[20] Recently, two classes of chemotherapeutic medicines (anthracyclines and taxanes) have seen widespread usage in the adjuvant and neoadjuvant treatment of breast cancer.[21] Paclitaxel (PTX), a taxanoid antineoplastic medication having an effect on microtubule stability, is a commonly used chemotherapeutic treatment in a variety of malignancies. PTX's antimitotic action has been shown in a vast number of investigations.[22-24]

In these investigations, PTX triggered a chain reaction of signalling pathways that resulted in programmed cell death.[25,26] The modification of epigenetic markers is a novel aspect of cancer research, and PTX may also alter the production of particular microRNAs (miRNAs) linked to cancer growth. Furthermore, PTX can have a number of beneficial effects on immune response modulation via regulating chemokines, cytokines, or immune cells.[27,28] The poor clinical prognosis for patients with BC is due to resistance to PTX and other chemotherapeutics caused by disequilibrium in numerous signalling pathways, mutations in specific genes, and epigeneticderegulations.[29-31]

The global challenge in the use of PTX as a leading anticancer chemotherapeutic agent is to reduce adverse effects while boosting medication efficiency. Albumin-bound PTX (nab-PTX) is an excellent example of advancement in the oncology-related domain focused on the cross- connection of nanotechnology and cancer therapy.[32]

THE EVOLUTION OF PACLITAXEL

Paclitaxel was discovered not by coincidence, but as a consequence of a joint effort between the National Cancer Institute (NCI) and the United States Department of Agriculture (USDA) utilising a plant-screening programme to find novel and potent anticancer drugs.[33] The history of paclitaxel development is summarised in **"Figure – 1"** .

Between 1960 and 1981, the NCI Plant Programme, led by natural product chemist Jonathan Hartwell, collaborated with USDA botanist Robert Perdue to analyse over 15,000 wild plants worldwide and evaluate 115,000 extracts for anticancer potential. Paclitaxel was the only chemical accepted into clinical studies when the NCI screening programme finished in 1981.[34]

Paclitaxel was isolated from the bark of the Pacific yew tree Taxus brevifolia Nutt. (Taxaceae) hauled in from Gifford Pinchot National Forest to USDA headquarters in Maryland in August 1962 by Arthur S. Barclay, a 32-year-old USDA botanist.[35,36] Although the cytotoxic activityof the samples' bark was discovered to be able to inhibit in vitro growth in 9KB cell cultures containing human oral epidermoid carcinoma by September 1964,[37, 38] it took Mansukh Wani and Monroe Wall, working under contract with the NCI at the Research Triangle Institute (Research Triangle Park, NC), until 1967 to isolate and identify the extract's most active ingredient, which they named paclitaxel.

Despite the fact that clinical trials to explore the effect of paclitaxel on various tumours proliferated, few were able to begin as anticipated due to a lack of supply, with the only source being the extremely slow-growing Pacific yew. Hart-well quickly recognised that he was only generating half a gramme of refined paclitaxel extract for every 13 kilos of dry bark. A petition in 1990 to add the critically endangered T. brevifolia on the list of endangered species resulted in the passage of the Pacific Yew Act in 1992 to conserve the tree.[39]

Despite its scarcity, 22 years after its discovery in 1984, paclitaxel entered clinical trials. In 1987, Wiernik and

colleagues published the results of a phase - 1 study.[40] Paclitaxel was discovered to have clinically significant cytotoxic effect when an ovarian cancer research indicated that 30% of patients with platinum-resistant ovarian cancer responded to paclitaxel treatment, either totally or partially.[41] Another concern was the insolubility of paclitaxel in water, however these issues were later solved using an ethanol and Cremophor EL formulation. Cremophor EL is a polyethoxylated castor oil that was used to solubilize hydrophobic drugs such as paclitaxel.[42]

Paclitaxel was approved as a chemotherapeutic agent for the treatment of ovarian cancer in December 1992. Robert Holton and colleagues created a commercially viable semisynthetic to fulfil rising demand. Paclitaxel was also examined for its efficacy as a therapy for advanced breast cancer by the researchers. Following clinical trials, the medicine was proven to be effective against this illness, and the FDA authorised paclitaxel for treatment against breast cancer in 1994. Paclitaxel is currently used to treat ovarian cancer,[43] breast cancer, and non-small-cell lung cancer[44] as a single agent or in combination with other medications such as cisplatin or carboplatin.

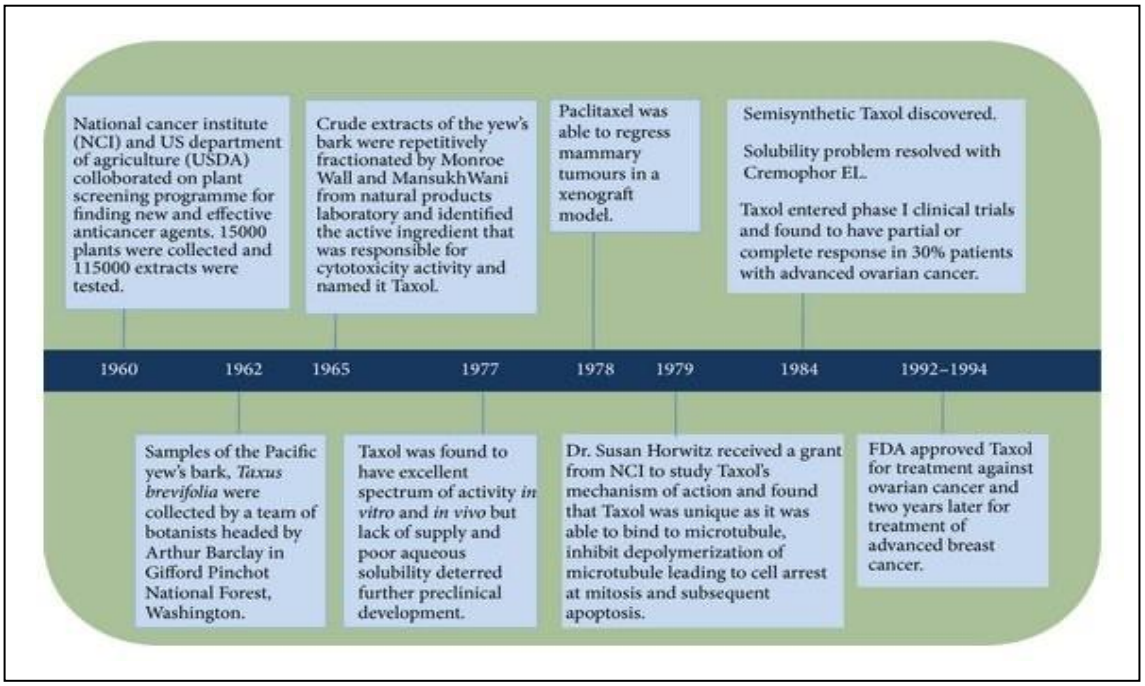

Figure 1: History of Paclitaxel Developmentthe Origin of Paclitaxel.

Bristol-Myers Squibb (BMS) trademarked PTX as Taxol™ in 1992,[45] and it is an antimitotic, anticancer medicine that was authorised by the FDA (Food and Drug Administration) in 1994 for treatment in breast cancer (BC).[46] PTX is utilised in the treatment of solid malignancies such ovarian cancer, hormone-refractory prostate cancer, and non-small cell lung cancer.[47] Mansukh Wani and Monroe Wall[48] were the first to isolate the active substance from the Pacific Yew tree (Taxus brevifolia). Before it was licenced by the FDA for ovarian cancer in 1992, the medication underwent additional clinical trials and testing on animal tumour models. Due to the huge demand for the medicine, the slow-growing T. brevifolia tree was unable to meet market and research demands; hence, the National Cancer Institute (NCI) decided that producing PTX from T. brevifolia was impracticable, non-environmentally aware, and financially burdening.[49,50] A fungus isolated from the phloem of T. brevifolia was related with a new way of mass-producing PTX in 1993.[51] In 1994, the FDA authorised a successful semi- synthetic process of manufacturing PTX, which is being used today.

CHEMICAL STRUCTURE

Paclitaxel, a taxane medication, is a diterpenoid pseudoalkaloid with the empirical formula : $C_{47}H_{51}NO_{14}$ **("Figure - 2")** with a molecular weight of 853.9 g/mol. Paclitaxel is made up of two molecules: a taxane ring with a four-membered oxetane side ring at places C_4 and C_5, and a homochiral ester side chain at position C_{13}. The side chain at C_{13} is critical because it is the active part that binds to microtubules, stabilises tubulin bundles, and induces microtubule disintegration in a GTP-independent way. As a result, cell growth is prevented by stopping the cell cycle at the metaphase/anaphase border and forming an incomplete metaphase plate of chromosomes, which is triggered by the stability of microtubule dynamics. Extensive study has revealed that cytotoxic action requires an intact taxane ring and an ester side chain.[52, 53]

- **Empirical formula :** $C_{47}H_{51}NO_{14}$
- **Molecular weight :** 853.9 g/mol Average mass: 853.9 Da

- **Systemic name:** (2α,5β,7β,10β,13α)-4,10-Diacetoxy-13-{[(2R, 3S)-3- (benzoylamino)- 2-hydroxy-3-phenylpropanoyl]oxy}-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate

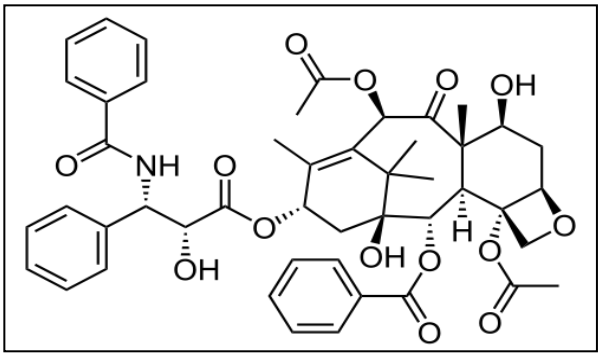

Figure 2: Chemical Structure of Paclitaxel.

Paclitaxel consist of taxane ring with a four-membered oxetane side ring at positions c4 and c5 and an active homochiral ester side chain at c13 that binds to microtubules in a guanosine triphosphate (gtp) independent manner to induce cytotoxicity activity.

MECHANISM OF ACTION

Paclitaxel is an anticancer medication that targets microtubules. Microtubules are cylindrical hollow structures with a diameter of around 25-30 nm that are made of tubulin polymers in dynamic equilibrium with tubulin heterodimers (containing of alpha and beta protein subunits).[54,55] Microtubules are responsible for the development of the mitotic spindle during cell division. They are also essential for the preservation of cell structure, motility, and cytoplasmic movement inside the cell. Tubulin production and microtubule assembly occur during the G2 and prophases of mitosis. Microtubules are in dynamic equilibrium with their component tubulins and, which are organised head to tail, with favoured quicker growth (plus ends) at one end and slower growth (minus ends) at the other. The length of the microtubule remains constant under steady-state conditions because the net tubulin assembly rate equals the net disassembly rate. Microtubule minus ends are often anchored mostly in the centrosome,[56] whereas plus ends explore the cytoplasm and interact with cellular structures.[57,58]

Dr. Horwitz discovered that paclitaxel, unlike vinca alkaloids, prevents cell division by promoting the assembly of stable microtubules, particularly from -tubulin heterodimers, and inhibiting their depolymerisation; as a result, exposed cells are arrested in the G2/M-phase of the cell cycle[59] and eventually undergo apoptosis, thereby inhibiting cell replication. Paclitaxel attaches to the N-terminal 31 amino acids of the beta-tubulin subunit in microtubules in a reversible way rather than tubulin dimers. Paclitaxel is also remarkable in its capacity to induce microtubule formation in vitro, even at low temperatures (4℃) and in the absence of GTP.[60]

Further study into the molecular principles of microtubule production has revealed[61] that paclitaxel may have another mechanism that permits cells to avoid drug toxicity, which leads to resistance and failure in chemotherapy. Ganguly and colleagues discovered that suppressing microtubule dynamics was unrelated to cell division. Treatment of mutant cell lines, Tax 11-6 (α-tubulin mutation) and Tax 18 (β-tubulin mutation), at concentrations ranging from 50 to 100 nmol/L, which should theoretically increase microtubule assembly to more normal levels and allow the cells to proliferate normally, instead suppressed microtubule dynamics rather than restoring normal behaviour. Paclitaxel at low concentrations reduced dynamics and so had no effect on the rate of microtubule detachment; however, higher drug doses that permitted normal cell division dramatically prevented detachment in mutant cell lines and recovered the rate to near normal levels. This action appears to be related to paclitaxel's ability to inhibit microtubule fragmentation[62] rather than its ability to suppress microtubule dynamics, as confirmed by live cell imaging, which revealed that microtubule detachment from centrosomes may be responsible for the generation of microtubule fragments, a process that paclitaxel reversed. Recent studies have also discovered that paclitaxel inhibits microtubule depolymerisation at low concentrations (less than nanomolar concentrations), whereas at high concentrations, paclitaxel increases the number and mass of microtubules, thus increasing microtubule stability, and also renders them non-functional by blocking the detachment of microtubule minus ends from centrosomes rather than plus ends.[63]

The apoptotic effects of weekly paclitaxel treatment may be the postulated mechanism of action. Paclitaxel appears to be independent of microtubule stability in the expression of apoptotic modulator genes. It might be due to changes in the transcription of various genes, such as DNA-damage response proteins, cytokines, or proteins involved in the regulation of cellular proliferation, apoptosis, and inflammation. Paclitaxel's apoptotic impact is determined by the concentration and length of exposure. Apoptosis in the S phase may be triggered with concentrations of at least 10 nm and exposure times of at least 12 hours. Depending on the dosage concentration of paclitaxel, two distinct apoptotic pathways have been postulated. Paclitaxel activates Raf-1, which is important for apoptotic regulation, at a concentration of 9≥ nm. At 9 ≥ nm, Raf-1 kinase is not involved, although apoptosis induction occurs under the impact of p53 and p21.[64,65] Paclitaxel causes irreversible mitotic arrest at the same dose after a 24-hour treatment, in addition to apoptotic arrest.[66] p53 is a crucial tumour suppressor that regulates proliferation and apoptosis, and its mutation occurs in more than half of all human malignancies. In normal cells, DNA damage boosts p53 levels, which subsequently initiates a G1 cell-cycle arrest mediated by p21, promoting either DNA damage repair processes or death and thus restricting the proliferation of genetically modified cell clones. To minimise chemo

resistance, cancer cells must be sensitised to DNA-damaging chemotherapeutic drugs via a functioning p53 signalling pathway. Paclitaxel action is now thought to be independent of p53 status, which is significant since the existence of silent or mutant p53 does not alter cancer cell susceptibility to taxanes, hence lowering chemoresistance.[67-70]

Paclitaxel also works by activating several signal-transduction pathways, some of which are involved with proapoptotic signalling. TLR-4 dependent pathway (either via MyD88 dependent or independent pathway), c-Jun N-terminal kinase (JNK), P38 Mitogen activated protein (MAP) Kinase, nuclear factor kappa B (NF-κB), Janus kinase- (JAK-) signal transducer and activator of transcription factor (STAT) pathway are the pathways associated with paclitaxel. One of the mechanisms for apoptosis induction is the mitogen-activated protein kinase (MAPK) pathway, which results in dephosphorylation of the proapoptotic proteins Bad and Bax, phosphorylation of Bcl2, and apoptosis induction. Bad and Bax (which enhance apoptosis) and Bcl2 (which suppresses apoptosis) are Bcl2 family regulatory proteins involved in programmed cell death. Induction of cytokines and pro-inflammatory proteins results in immunomodulatory effects of paclitaxel at low doses and cell death at larger doses. Changes in these pathways are also responsible for the development of paclitaxel resistance.[71-74] Weekly paclitaxel also has potent anti-angiogenic action.[75] Paclitaxel was able to inhibit new vascular development in mice at low, noncytotoxic dosages (0.3 and 6mg/kg per day) by reducing VEGF expression.[76,77] Low-dose, weekly paclitaxel has been studied in patients with advanced ovarian cancer, metastatic melanoma, and advanced head and neck cancer, and the results have been promising.[78-80] This alternative method of action of paclitaxel, which involves changing the period of delivery, may be beneficial in malignancies that have developed resistance to the same medication when given on a 3-weekly traditional schedule.

Paclitaxel has also been shown to increase hydroperoxide production and induce reactive oxygen species (ROS) generation by increasing the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which contributes to oxidative stress and may play a role in the potency of paclitaxel's anticancer activity.[81,82] Paclitaxel in combination with glucose (i.e., 2-deoxy-D-glucose, 2DG) and hydroperoxide (i.e., L-buthionine-S, R- sulfoximine, BSO) metabolism inhibitors has been found to selectively enhance breast cancer cell killing via hydrogen peroxide-induced metabolic oxidative stress, which may be effectively used to treat breast cancers.[83] However, the role of oxidative stress in the total cytotoxicity mechanism of paclitaxel remains unknown. **"Figure - 3"** summarises the mechanism of action of paclitaxel.

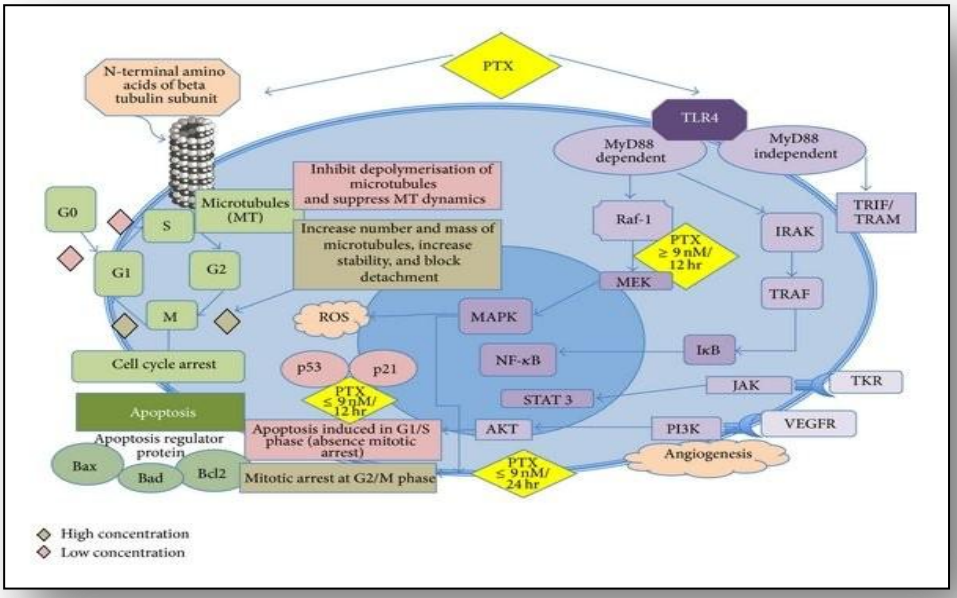

Figure 3: Mechanism of Action of Paclitaxel.

Paclitaxel targets microtubules. At high concentration, PTX causes mitotic arrest at G2/M phase whereas at low concentration, apoptosis is induced at G0 and G1/S phase either via Raf-1 kinase activation or p53/p21 depending on the dose concentration. Even at lower dose but with exposure beyond 24 hours, paclitaxel can cause mitotic arrest. Paclitaxel also activates multiple signaling pathway to exert proapoptotic activity as well as

immunomodulatory effect. Paclitaxel also develops resistance via these signaling pathways. PTX: Paclitaxel, TLR4: Toll-like receptor 4, G0: resting phase, G1; cells enlarge and make new protein, S phase: DNA replication, G2: preparation for division, M phase: cell division/mitosis, Raf-1: Raf kinase family, MEK/MAPK: mitogen activated protein kinase, IRAK: IL-1 receptor associated kinase, TRAF: TNFR associated factor, NF-κB: nuclear factor kappa B, TRIF/TRAM: TIR-domain-containing adapter- inducing interferon-β, TKR: tyrosine kinase receptor, VEGFR: vascular endothelial growth receptor, PI3K: phosphoinositide 3-kinase, JAK: janus kinase, STAT: signal transducer and activator of transcription factor.

PHARMACOKINETICS

Paclitaxel is a white to off-white crystalline powder that is extremely lipophilic and insoluble in water, making formulation problematic. It has a melting point of 216-217 degrees Celsius.[84,85] More than 90% of the medication binds swiftly and widely to plasma proteins, whereas only around 50% attaches to red blood cells. The inclusion of pre-medication medicines (before to chemotherapy) such as ranitidine, dexamethasone, or diphenhydramine had no effect on paclitaxel protein binding. Paclitaxel has a huge volume of dispersion of approximately 55 L/m2, which is lowered in females.

Paclitaxel disappearance from plasma has generally been thought to be biphasic. The first quick drop is due to drug diffusion to the peripheral compartment and elimination. The slower outflow of paclitaxel from the peripheral compartment contributes to the later phase.[86] A three-compartment model appears to be more accurate in the presence of more sensitive test techniques and later sample durations.[87] Paclitaxel has been proven to exhibit a nonlinear pharmacokinetic pattern **("Figure – 4").**

The pharmacokinetics were typically linear for 6- or 24-hour infusions, but nonlinear for shorter duration infusions because elimination clearance varied with dosage. There is a disproportionately higher rise in Cmax (highest plasma concentration) and AUC (area under plasma concentration) with increasing paclitaxel plasma concentration, coupled by a reduction in drug clearance from body tissues. The therapeutic significance of this nonlinear pattern is that increasing the dosage may result in an increase in toxicity, whilst decreasing the dose may change its effectiveness.[88]

Paclitaxel pharmacokinetics have been studied at various dosages up to 300mg/m^2 and with infusion regimens ranging from 3 to 24 hours. The maximum plasma concentrations are dose-dependent. The mean steady state volume of distribution in individuals treated with single dose infusions of 135 and 175mg/m^2 administered as 3- and 24-hour infusions varied from 198 to 688 L/m^2, demonstrating significant extravascular distribution and/or tissue binding. The terminal half-life has been reported to range from 1.3 to 8.6 hours (mean 5 hours), while total body clearance has been reported to range from 11.6 to 24.0 L/hr/m^2. Preclinical animal studies revealed high levels in nearly all organs. Paclitaxel is strongly protein-bound and has a high propensity for distribution in certain organs such as the kidney, lung, spleen, and extracellularfluids such as ascites and pleural fluids,[89] although its absorption in the brain is low.[90,91]

Paclitaxel exposure is particularly high in tumour tissue as compared to other tissues, and in addition to sluggish clearance from tumour tissue, the AUC in tumour tissue is approximatelyfive-fold greater than in plasma.

There is no indication of paclitaxel accumulation with many treatment sessions since the variability in systemic paclitaxel exposure for subsequent treatment cycles is small, as evaluated by AUC (0-∞) (area under plasma concentration-time curve from time 0 to infinity).[92] Paclitaxel clearance, on the other hand, is sequence dependent. Individuals who get a platinum-based drug before paclitaxel had lesser clearance and worse clinical toxicity than patients who receive paclitaxel before cisplatin.

When given intravenously, the drug undergoes extensive P-450-mediated hepatic metabolism by cytochrome enzymes (CYP3A and CYP2C8), with 70–80 % excreted into bile by adenosine triphosphate- (ATP-) binding cassette multidrug transporters such as P-glycoprotein (P-gp) and multidrug resistance protein - 2 (MRP-2) as metabolites or as the parent drug. Variation in MRP-2 activity has been observed to have a direct influence on effective paclitaxel exposure.[93] Because of enterocyte P-gp expression and first-pass metabolism in the liver, the bioavailability after oral administration is minimal. The majority of the medication is excreted in the faeces. Less than 10% of the medication is eliminated in the urine in its unaltered form,indicating substantial nonrenal clearance. Combinations of CYP3A and P-gp inhibitors may increase the oral bioavailability of taxanes.[94]

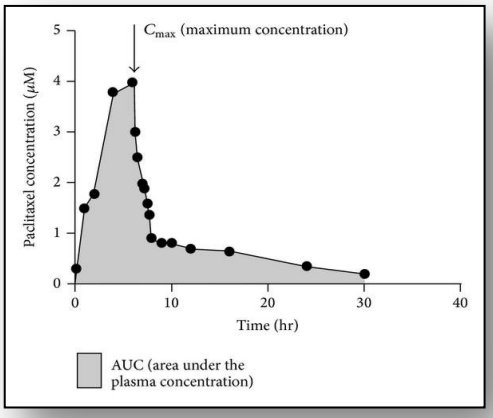

Figure 4: Plasma Pharmacokinetics of Paclitaxel.

Breast Cancer From The View of Prevalence and IntrinsicSubtypes

BC is the most common kind of cancer in women, accounting for 24% of all female cancers. BC affects approximately two million females globally and is responsible for over 620,000 fatalities each year. Age, number of births, genetic predisposition, ethnic origin, and use of oralcontraceptives all contribute to an elevated risk of BC in women.[95] Despite significant advancements in screening methods and programmes, the incidence and death rates continue to rise.[96]

Importantly, breast cancer is a heterogeneous disease with considerable diversity in phenotypes and genotypes, which means that no two individuals have the same clinical symptoms.[97] These distinctions complicate the process of identifying and targeting BC. BC is classified into three primary kinds and five subtypes based on changes in gene expression and the presence or absence of surface receptors, which result in different prognoses and treatment methods forpatients.[98] These subtypes are divided as HER2 positive (HER2+), luminal types, and triple- negative BC (TNBC) based on markers such as immunohistochemical characterization of receptors, the expression profile of human epidermal growth factor receptor 2 (HER2), and the KI67 proliferative index.[99] HER2+ BC is caused by the overexpression of the HER2 (ERBB2) gene, which codes for the transmembrane glycoprotein receptor p185HER2.[100] HER2 amplification was seen in 15-30% of invasive BC patients. Furthermore, a greater incidence of the HER2 mutation resulting to enhanced protein expression has been seen in gastric, esophageal, and other kinds of cancer.[101]

TNBC as the most aggressive type has a frequency of 10-20%, with a greater incidence in the cohort of young women. This genetic subtype is linked to an advanced stage, a higher tumour grade, and overall worse survival rates in individuals with cancer recurrence and metastasis.[102] TNBC is immunohistochemically distinguished by the absence of three receptors: oestrogen receptor (ER), progesterone receptor (PR), and HER2. This kind of BC is resistant to existing therapies due to a lack of receptors to target.[103,104] TNBC may also be characterised as claudin-low, basal-like, or molecular apocrine based on changes in gene signatures and histological characteristics **(as shown in "Table – 1").**[105] In addition, inherited mutations in the tumour suppressor genes BRCA1/2 were found in 15% of individuals with TNBC.[106] Furthermore, recent research suggests a link between genes such as BARD1, PALB2, and RAD51D and anincreased risk of TNBC.[107]

Luminal BC is distinguished by the presence of ER as well as the likelihood of PR. Luminal BC is divided into two subtypes based on the HER2 profile and the presence of proliferation genes such as CCNB1, MKI67, and MYBL2, which are commonly expressed in the luminal B subtype. Furthermore, luminal B is distinguished by increased expression of genes involved in growth receptor signalling.[108-110] When compared to luminal B, luminal A indicates molecular subtypes with a better prognosis, lower recurrence rate, and greater overall survival rate based on clinical prediction and patient prognosis.[111]

Importantly, because they include particular genetic changes from the tumours from which they were produced, human cancer-derived cell lines that are specific for each molecular subtype constitute useful tools for studying biological processes in cancer research.[112] "**Table– 1"** lists the BC subtypes linked with particular immunohistochemical signatures, as well as the cell line employed in in vitro investigations.

Table 1: Intrinsic Types of Bc With Corresponding Cell Lines.

Sl. No.	BC Type	Bc Subtype	Immunohistochemical Profile	Cancer Cell line
1.	**Luminal**	Luminal A	ER+, PR+, HER2−, Ki67 low expression	BT483, CAMA1, HCC712, EFM19, HCC1428, HCC712, IBEP2, KPL1, LY2, MCF7, MDAMB134, MDAMB134VI, MDAMB175, MDAMB175VII, MDAMB415, T47D, ZR751, ZR75B
		Luminal B (Luminal-HER2+)	ER+, HER2+, PR−, or Ki67 high expression	BSMZ, BT474, EFM192A, MDAMB330, MDAMB361,UACC812, ZR7527, ZR7530
2.	**TNBC**	Basal-like	ER−, PR−, HER2−	BT20, CAL148, DU4475, EMG3, HCC1143, HCC1187, HCC1599, HCC1806, HCC1937, HCC2157, HCC3153, HCC70, HMT3522, KPL-3C, MA11, MDAMB435, MDAMB436, MDAMB468, MFM223, SUM185PE, SUM229PE

		Claudin-low	ER−, PR−, HER2−, claudin 3−, claudin 4−, claudin 7− and E-cadherin	BT549, CAL120, CAL51, CAL851, HCC1395, HCC1739, HCC38, HDQ-P1, Hs578T, MDAMB157, MDAMB231, SKBR7, SUM102PT, SUM1315M02, SUM149PT, SUM159PT
3.	**Non- hormonal related HER2+**	HER2	ER−, PR−, HER2+ over-expression	AU565, HCC1008, HCC1569, HCC1954, HCC202, HCC2218,HH315, HH375, KPL-4, MDAMB453, OCUB-F, SKBR3, SKBR5, SUM190PT, SUM225CWN, UACC893

ABBREVIATIONS : BC, breast cancer; ER, estrogen receptor; HER2+, human epidermal growth factor receptor 2 positive; HER2−, human epidermal growth factor receptor 2 negative; PR, progesterone receptor, TNBC, triple-negative breast cancer.

CHEMOTHERAPY FOR BREAST CANCER

As previously said, BC is a diverse illness with distinct characteristics. It is critical to identify BC subtypes in order to select effective chemotherapeutic treatments. Chemotherapeutic medications are classified according to their method of action, which includes antimetabolites, endocrine treatment, immunologic therapy, alkylating agents of DNA, and antimitotic pharmaceuticals. During the synthesis phase, antimetabolites are responsible for inducing apoptosis. The structure of antimetabolites is similar to that of folate, purine, or pyrimidine and causes replication errors. Furthermore, many medications are analogues of natural chemicals that are essential for proper cellular activities. Antimetabolites that inhibit enzymes are classed as inhibitors of dehydrogenases, topoisomerases, nucleosides, and kinases.[113,114]

Methotrexate is a dehydrogenase inhibitor that works as a competitive inhibitor of DHFR (dihydrofolate reductase), causing folate buildup and subsequent suppression of synthesis.[115] Doxorubicin belongs to the topoisomerase II inhibitor family, and it plays an important role in the inhibition of topoisomerase II, the production of DNA adducts, and the development of oxidative stress.[116] Side effects of doxorubicin and other chemotherapy medicines are common issues during treatment. The invention of liposomal anthracyclines enabled the reduction of unpleasant symptoms and increased treatment efficacy.[117] Epirubicin, like other anthracyclines, acts as an intercalating agent with DNA, interfering with transcription and suppressing RNA synthesis.[118,119] Inhibitors of kinase Palbociclib and Ribociclib are both cyclin-dependent inhibitors that decrease proliferation by decreasing cyclin-dependent kinase (CDK) 4/6 activity.[120] The nucleoside inhibitors 5-fluorouracil, Capecitabine, and Gemcitabine have been linked to the silencing of transcription and translation in BC.[121] Immunological treatment focuses on molecular subtypes with HER2 receptors that are overexpressed.[122] Herceptin and Ado-trastuzumab are the two most widely used immunotherapy drugs. Herceptin, specifically, inhibits the extracellular domains of the HER2 receptor tyrosine kinase. Ado-trastuzumab, on the other hand, distributes the microtubule- inhibitory agent DM1 medication into cells with elevated HER2 levels. Endocrine therapy is an option for patients with hormone-positive receptors, and it includes treatment with a synthetic analogue of anti-gonadotropin releasing hormone (Goserelin), antiprogestines (Megestrol acetate), and anti-estrogens, which are further subdivided into ER antagonists (Tamoxifen) and aromatase inhibitors (Trozole).[123] DNA alkylating agents are chemicals that interact with DNA and prevent it from replicating. They are divided into three families depending on their basic mechanism of action: platinum-based drugs (cisplatin, carboplatin, oxaliplatin), nitrogen mustards (cyclophosphamide, chlorambucil), and organophosphorus compounds (Thiotepa). The antimitotic chemotherapeutical idea is a well-established therapy approach that inhibits cancer cell proliferation and invasion by modulating cellular division via changes in microtubule activity.

As a result, microtubule alteration results in cell cycle arrest and the apoptotic pathway. There are two types of microtubule inhibitors: synthetic and natural. Ixabepilone, a semi-synthetic analogue of epothilone B, is a synthetic chemo medication having antimitotic effects that has been approved for the treatment of metastatic breast cancer. Epothilones are microtubule inhibitors with a strong anti-PTX action.[124] The fact that Ixabepilone is more effective than PTX against resistant cells is due to the drug's distinct binding sites on microtubules. Antimitotic medications obtained naturally include marine and plant compounds that interact with tubulin. Eribulin mesylate is a halichondrin antineoplastic medication that interacts with microtubules, causing anaphase/metaphase arrest.[125]

Taxanes and alkaloids are plant-derived chemotherapeutic medicines. Taxanes (PTX, Cabazitaxel, and Docetaxel) are the most often used chemotherapeutic methods, and they, together with anthracyclines, constitute the first line of treatment for patients with metastatic and early-stage BC.[126] Importantly, certain dominant-negative mutations in genes involved in mitotic control are responsible for the establishment of resistance in cancer cells, reducing the efficiency of taxane therapy.[127] The second class of natural plant-derived chemo-drugs are alkaloids like

Vinblastine, which function as microtubule-disrupting agents, blocking tubulin polymerization.[128] To summarise, there are various chemotherapeutics available against BC, each with a unique mode of action. The selection of suitable medication is crucial for patients, and only a clear assessment of the tumour intrinsic type and stage of illness may reduce the development of recurrence or metastasis.

PACLITAXEL AND THE IMMUNE SYSTEM

The immune system is made up of two distinct but interconnected systems: innate and adaptive mechanisms. The innate immune system is the initial line of defence and comprises mostly of macrophages, dendritic cells (DCs), and natural killer (NK) cells, whereas the adaptive immunological mechanism is represented by T-lymphocytes. Antitumor immunity involves all components of the innate and adaptive mechanisms, including tumour identification, control, and eradication. Cancer cells, on the other hand, may avoid immune recognition and actively decrease antitumor immunity.

Paclitaxel exhibits a variety of dose-dependent immunomodulatory effects, as seen in **"Figure– 5"**. Paclitaxel is generally immunosuppressive at conventional doses because it suppresses a variety of cell types implicated in tumour rejection, including macrophages, effector T cells, and NK cells.[129] Paclitaxel, on the other hand, has a major immunogenic impact in boosting antitumor immunity at lower dosages than are generally employed for chemotherapy. Understanding the immunological foundation of paclitaxel may thus aid in optimising the manipulation of paclitaxel's immunomodulatory effects in the development of improved treatment alternatives in the management of advanced ovarian cancer.

Paclitaxel is a toll-like receptor 4 (TLR4) ligand that is expressed on innate immune cells such as macrophages. Paclitaxel binding to TLR4 on macrophages activates the MyD88, mitogen- activated protein kinase (MAPK), and transcription of nuclear factor NF-kappa B (NF-B) pathways (Figure 3), resulting in the activation and release of immunostimulatory cytokines such as tumour necrosis factor- (TNF-), interleukin-1 (IL-1) (IL-8). Activated macrophages can either induce direct tumour cell lysis by releasing lysosomal enzymes and nitric oxide (NO), or they can cause indirect tumour cell lysis by activating NK cells, DCs, and tumor- specific cytotoxic T-lymphocytes (CTLs).

NK cells are also innate immune cells capable of destroying tumour cells, particularly those with low class I MHC expression and so immune to CTLs. Paclitaxel can improve NK cell activity by increasing perforin mRNA and protein synthesis, an effector molecule implicated in NK cell-mediated cytotoxicity. The effect of low-dose paclitaxel on NK cells, on the other hand, remains debatable. Another research discovered that paclitaxel administration of human NK cells significantly reduces NK cell-mediated killing of K562 (human erythroleukemia) target cells in vitro without affecting NK cell survival.[130] However, weekly paclitaxel treatment for non-small cell lung cancer patients reduced NK cell activity only until the end of the first cycle, after which it progressively recovered.

Paclitaxel can directly activate dendritic cells, which also express TLR4. Paclitaxel binding to TLR on immature DCs enhances DC maturation by upregulating gene components of the antigen-processing machinery, costimulatory molecules, and IL-12p70. This improves DCs' capacity to stimulate T cells, which aids in antitumor immunity. Paclitaxel can also boost cytotoxic T-cell activity by increasing mannose-6-phosphate, which improves granzyme B permeability, and by inducing cytokine production patterns typical of the T helper type 1 phenotype via IL-2 (CD4 T cell) and IFN- (CD8 T cell) secretion. Activated CD8+ T cells can develop into CTL type 1 (Tcl) cells, which predominantly produce IFN-, and CTL type 2 (Tc2) cells, which predominantly produce IL-4, IL-5, and IL-10. Tc1 cells are powerful CTL implicated in cancer defence. Tc1 cells can recognise tumour antigens and cause tumour cell lysis in the presence of MHC class I. Tc2 cells' significance in the immune response is unclear, however their existence has been linked to disease development.

CD4+ CD25+ regulatory T-cells (Tregs), which account for roughly 5-10% of peripheral CD4+ T cells, play a crucial role in tumour immune evasion. There is mounting evidence that tumours include an excess of Tregs, which may inhibit immunological responses of other CD4+ and CD8+ cells[131] and promote tumour growth. Paclitaxel has been shown in animal experiments to lower the number and size of Treg cells, hence improving antitumor immunity. Similar results were seen with a selective decrease in the size and quantity of Treg populations in non- small cell lung cancer (NSCLC) patients' peripheral blood samples.

Paclitaxel also lowered the expression of the anti-apoptotic molecule Bcl-2 in Treg cells while boosting the expression of the equivalent proapoptotic component Bax, contributing to Treg apoptosis sensitivity to paclitaxel. This was demonstrated in a study using the 3LL Lewis tumour model, which demonstrated that Treg cells exposed to paclitaxel had downregulation of Bcl-2 and upregulation of Bax, and that blocking the Bcl-2 pathway impaired paclitaxel's ability to ablate Treg cells compared to T effectors, and that both Treg and T effectors were affected. These findings might imply that paclitaxel targets Bcl-2 rather than tubulin, which could explain why it has such a unique effect on Treg cells. Paclitaxel has recently been proven in vitro to target Bcl-2 and cause apoptosis. By inhibiting apoptosis, Bcl-2 family proteins play a significant role in tumorigenesis and multi-drug resistance.[132]

A few studies have also shown that paclitaxel has an effect on myeloid-derived suppressor cells(MDSCs), which are a heterogeneous population of immature myeloid cells that are immunosuppressive in nature and are recruited by cancer cells and found in higher numbers in advanced epithelial ovarian cancer. Paclitaxel at an ultralow dosage alters MDSC differentiation into DCs in a TLR4 independent way in a mouse investigation utilising C57BL/6 mice. As a result, paclitaxel in ultralow, noncytotoxic dosages, together with its angiogenesis-blocking capacity, may possibly improve immunotherapy efficacy by eliminating immunosuppressive populations like Tregs and MDSCs in tumor-bearing hosts. Immunosuppression is reversed in immunocompromised patients with advanced ovarian cancer who have increased Tregs and decreased levels of CD4+ T cell, CD8+ T cell, and NK subsets after a single course of combined carboplatin and paclitaxel chemotherapy, but not before one week or after three to four weeks. Tregs are reduced, but so are the proportions of IFN-secreting CD8+ T cells, T helper-1, Tc1, and NKT cells. The ratio of Tc1 to Tc2 cells risesdramatically.[133]

Following chemotherapy, both CD4+CD45RO+ and CD8+CD45RO+ memory T cells grew considerably and peaked about 2 weeks. The increase in memory T cells in ovarian cancer patients after chemotherapy likely opens the door to long-term immunological memory, which might prevent recurrence and metastasis. When compared to typical 3-week therapy, weekly administration of dose-dense therapy may be immunologically advantageous in mounting a sufficient immune response. Furthermore, administration of immunotherapy medicines may be perfect during the 2 weeks following chemotherapy, when temporary immune system reconstitution occurs.

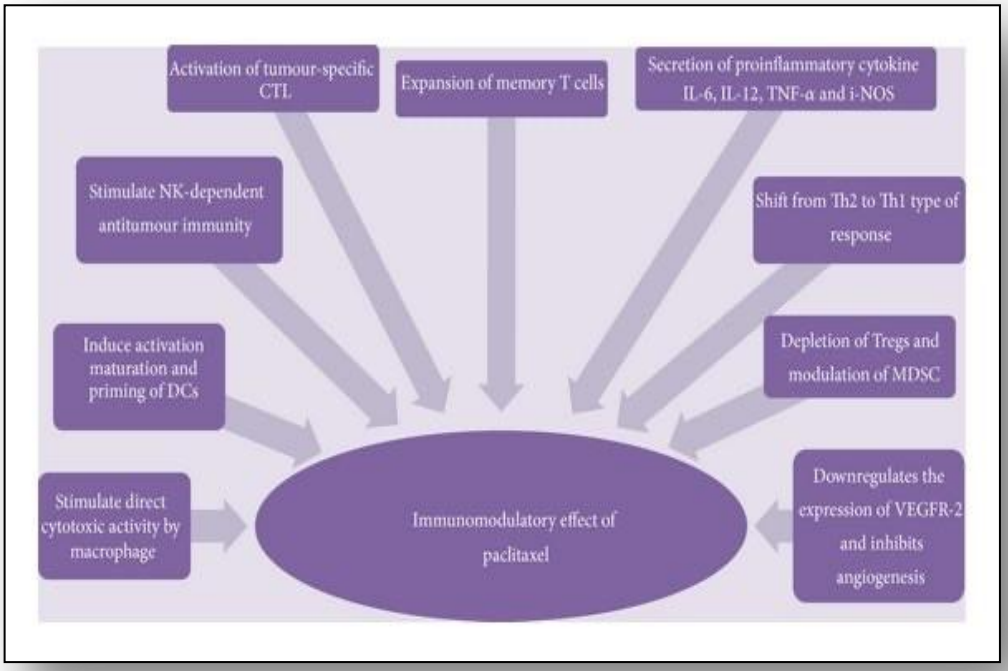

Figure 5: Immunomodulatory Effect of Paclitaxel.

PACLITAXEL: FUNDAMENTAL DRUG IN CHEMOTHERAPY AND NOVEL ADVANCES IN ITS APPLICATION

As previously stated, antimitotic chemotherapeutics inhibit the polymerization dynamic of microtubules, resulting in the production of mitotic arrests as a result of the activation of the mitotic checkpoint.

As a result, PTX, a taxane, is one of the most significant antineoplastic medications used in the treatment of a variety of malignancies, including BC.

1. The origin of Paclitaxel

PTX, which was marketed as Taxol™ by Bristol-Myers Squibb (BMS) in 1992, is an antimitotic, anticancer medicine that was authorised for use in BC by the FDA (Food and Drug Administration) in 1994. PTX is used to treat solid tumours such as ovarian cancer, hormone-refractory prostate cancer, and non-small cell lung cancer in clinical trials. Mansukh Wani and Monroe Wall were the first to isolate the active substance from the Pacific Yew tree (Taxus brevifolia). Before being licenced by the FDA for ovarian cancer in 1992, the medication underwent additional clinical trials and testing on animal

tumour models. Because of the huge demand for the medicine, the slow-growing T. brevifolia tree was unable to meet market and research demands; hence, the National Cancer Institute decided that producing PTX from T. brevifolia was impracticable, unsustainable, and financially burdensome (NCI). In 1993, a fungus isolated from the phloem of T. brevifolia was linked to a new way of mass-producing PTX. A successful semi-synthetic strategy of synthesising PTX was developed and authorised by the FDA in 1994, and it is still used today.[134]

2. Paclitaxel's mechanism of action

(I) Paclitaxel as a Polymerization Factor

PTX attaches to microtubules rather than tubulin dimers and promotes the assembly of alpha and beta tubulin subunits, the building blocks of microtubules. The medication decreases the critical concentration of tubulin necessary for assembly, facilitating tubulin polymer lengthening. The dynamics of microtubules are hampered by their stability. As a result of the inadequate needs of the mitotic checkpoint, the cell's capacity to divide is compromised, and cell division halts during the G2 or M phase. Even frigid temperatures and calcium have little effect on the polymerized and stable microtubules. Because the presence of calcium diminishes PTX's affinity for tubulin, the balance of polymerization/depolymerization swings towards polymerization to compensate. Furthermore, PTX promotes cytoskeletal anomalies in chondrocytes, causing microtubules to become stubby and straight in the cytoplasm, with roughendoplasmic reticulum as opposed to fine, sinous filaments in the control group. These alterations last for 48 hours after PTX is removed. The modified microtubules dislodge ribosomes from the rough endoplasmic reticulum and connect neighbouring endoplasmic reticulum complexes. PTX exclusively polymerizes free microtubules that are not connected to or pre-exist in microtubule organising centres (MTOC). When PTX is present, attached microtubules vanish. PTX disrupts the dynamics of microtubules and polymerization, as well as delaying mitotic advancement by inducing failure in chromosomal segregation, all of which finally leads to the induction of apoptosis and mitotic arrest.[135]

(II) Paclitaxel's Effect Depends on Concentration

In vitro investigations have shown that the mechanism of PTX cytotoxicity is greatly dependent on the drug concentration in the cell. Giannakakou et al. demonstrated that treatment with PTX at doses over 12 nm resulted in G2/M arrest of the lung cancer cell line A549 as well as breastMCF-7 cells. Lower doses of PTX (3-6 nm) have a comparable ability to limit cancer cell growth, resulting in programmed cell death. A research focused on drug concentration looked at the effect of modest dosages of PTX (10 nm) on cancer cell invasiveness. Researchers examined the influence of a non-anti-mitotic dose of PTX on transwell invasion of MDA-MB- 231 as a result of voltage-dependent sodium channel expression regulation in this in vitro investigation. Furthermore, modest doses of PTX (20 nm) in combination with a Wnt signalling inhibitor controlled molecular processes such as E-cadherin overexpression and -catenin decrease, resulting to inhibition of tumour growth, metastasis, and angiogenesis in BC.[136]

(III) Paclitaxel Affects Phosphorylation of Bcl-2

Although many researchers concur that PTX's cytotoxicity is due to its capacity to produce Bcl-2 hyperphosphorylation, numerous other studies show that Bcl-2 dephosphorylation occurs during apoptosis. However, because apoptosis does not start immediately after PTX treatment, the drug's cytotoxicity is influenced by the length of exposure and persistent Bcl-2 phosphorylation. However, other investigations have shown that phosphorylated Bcl-2 does not dimerize with BAX; hence, it is hypothesised that un-associated BAX promotes apoptosis.[137] The subsequent research, on the other hand, are older and likely less up to date than the earlier studies, and their results are based on prostate and leukaemia cell lines.

(IV) Paclitaxel Affects Calcium Signaling

Through the mitochondrial permeability transition pore, PTX causes the depletion of calcium ions from the mitochondrial reserve (PTP). The removal of calcium causes PTP to release the apoptogenic factor cytochrome C (cyto-C) from the mitochondria into the cytosol, so initiating apoptosis. The involvement of antimitotic medicines in the calcium signal cascade is thought to be connected to their negative effects. Changes in mitochondrial calcium uptake in various cells are responsible for the intensity and variability of these adverse effects. Using extremely high dosages of PTX causes mitochondrial rupture, the release of cyto-C, and the beginning of apoptosis without the outflow of calcium.[138] Even though most cells include mitochondria, it is unknown why peripheral neurons are the most damaged by PTX. When delivered at large dosages, PTX, on the other hand, promotes apoptosis in the presence of an extracellular calcium reservoir via calcium influx. Low dosages of PTX, on the other hand, showed apoptotic patterns irrespective of extracellular calcium concentration.

(V) The impact of Paclitaxel on micro-RNA Expression Profiles

MiRNA, a short non-coding RNA with a regulatory function in gene expression, can be alteredby a variety of antineoplastic medicines, including PTX. Several research on miRNA expression found a link between drug use and changes in miRNA expression patterns. The expression levels of let-7a and miR-205, both of which have tumour suppressor potential and target K-Ras and HER3, were altered in the BC cell line BT-474 following PTX treatment. Interestingly, PTX LDM therapy lowered the level of let-7f while increasing the expression of thrombospondin-1 (TSP-1) linked with anti-angiogenic potential.[139] In summary, preclinical experiments

indicated that PTX has modulatory potential in the control of miRNA expression, although further study is needed to determine the drug's role in BC treatment.

(VI)The Immunomodulatory Effects of Paclitaxel

The involvement of PTX in immunomodulation has also been shown, with both immune cell activation and repression related with tumour development. On the other hand, immune cell suppression may have a deleterious influence on the host immunological response to cancer growth. PTX appears to have a role in the control of host immunity by stimulating macrophages, resulting in the production of cytokines such as TNF- or IL-12, which activate natural killers (NK), dendric cells (DC), and cytotoxic T lymphocytes, culminating in the elimination of tumour cells. Furthermore, direct-acting PTX was tested in DC by binding to Toll-like receptors on the DC surface, boosting antigen-presenting cell maturation.Furthermore, the dose-dependent injection of PTX resulted in an increase in MHC class II levels.[140] PTX had an effect on immunomodulation in NK cells as well. A higher degree of cytotoxicity was associated with a larger amount of perforin, the critical effector protein of NK activity, leading to the hypothesis that PTX boosted NK cytotoxicity in a dose-dependent way.

2. Paclitaxel's effect on HER2 + breast cancer

In comparison to other subsets, the HER2+ subset of BC is actively biochemically researched.The effectiveness of PTX in HER2 + BC patients was uneven and contradictory. In 1998, HER2 + BC was discovered to be biochemically resistant to PTX. Overexpression of HER2 upregulates p21cip1, which suppresses p34cdc2, which is typically triggered by PTX to cause apoptosis of malignant cells in the G2/M phase, and therefore the cytotoxic impact of PTX was inhibited. More recent research on 3121 node-positive post-operative patients found that adding PTX to doxorubicin plus cyclophosphamide significantly reduced the risk of recurrenceand death after a 10-year follow-up.

In contrast, 65.2% of patients responding to taxanes had HER2+ tumours, whereas 35.5% had HER2 tumours. According to the author, PTX operates on a signalling transduction route particular to HER2+ malignancy. PTX causes the tumour suppressor protein p35 and the CDK inhibitor p21WAF1 to be activated. p21WAF1, on the other hand, is not activated as a result of p35 activation since cancer cells lack this tumour suppressor. Nonetheless, it is believed that p21WAF1 activation is c-raf-1 reliant since PTX activates c-raf-1 and p21WAF1 accumulation would be impossible in the absence of c-raf-1.

3. Dose ranges administered

A lot of research looked at different PTX dosages. Patients who were pre-treated withanthracyclines did not have a statistically significant response rate as compared to those who were not. Combining taxanes and anthracyclines reduces the likelihood of illness recurrence and relapse. Although Table 2 provides the clinical dosage ranges, depending on the clinical evaluation, a healthcare professional may administer various doses on a different schedule. **"Table – 2"** also shows how effective PTX is when used with other medicines. As previously stated, the medical literature does not disclose the immunohistochemical or histological profile of the BC, leading to the notion that the varying response in the trials might be attributable to the diverse patient body.

Table 2: Efficacy of Ptx As An Adjuvant Therapy.

Sl. No.	Neoadjuvantdrug combination	Patient eligibility	ConcentrationRange	Efficacy
1.	PTX after Doxorubicin + Cyclophosphamide	Node-positive BCwith resected adenocarcinoma	60 mg/m^2 doxorubicin + 600 mg/m^2 cyclophosphamide (IV infusion for 30 min to 2 h every 21 days, −4 cycles +4cycles of 225 mg/m^2 PTX (day 1 of each cycle)	PTX + doxorubicin + cyclophosphamide: ↑DFS by 17% Acceptable toxicity
2.	PTX + Bevacizumab	MBC patients with/without previous hormonal therapy or adjuvantchemotherapy	90 mg/m^2 PTX (day 1, 8, 15 every 4 weeks) + 10 mg/kg (day 1 and 15)	↑ progression-free survival (in comparisonto PTX alone) ↑ frequency of hypertension, proteinuria, headache, cerebrospinal ischemia
3.	PTX + Ttrastuzumab	Breast adenocarcinoma patients (tumor nolarger than 3 cm, node-negative, min. LVEF of 50%, adequate hematopoietic and liver function)	80 mg/m^2 PTX for 12 weeks + 4 mg/kg trastuzumab (day 1) → 2 mg/kg weekly (12 doses)	98.7% disease-freesurvival 99.2% 3-year rateof recurrence-freesurvival (95%CI)2.92% of patients reported adverse effects
4.	PTX + Trastuzumab then post-operative Doxorubicin +	Stage II or III BCpatients	Dexamethasone pretreatment (20 mg) + diphenhydramine (12 and 6 h before treatment) and H2-blocker (50 mg) Trastuzumab (one-time loading	75% clinical response with 18% complete pathologic response Stage 3 tumors responded more than

	Cyclophosphamide		dose 4 mg/kg) → weekly2 mg/kg IV infusion for11 weeks + 175 mg/m^2 of IV PTX over 3 h (every 3weeks, 4 cycles) 2–5 weeks post-op: doxorubicin + cyclophosphamide	stage 2 tumors

Explanatory notes: + plus/and; → followed by; ↑ increase. Abbreviations: BC, breast cancer; CR, complete response; DFS, disease-free survival; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; PR, partial response; PTX, Paclitaxel; rhG-CSF, recombinant human granulocyte colony-stimulating factor; h, hours; max., maximum; min., minimum.

4. Breast tumor resistance to Paclitaxel

Chemoresistance is a key issue in cancer treatment, as it is linked to poor response, tumour recurrence, and metastases. It is also the top cause of death among BC patients. Resistance that occurs before treatment is referred to as primary chemoresistance. Acquired resistance, on the other hand, might develop over time after chemotherapeutic exposure. As a result, PTX treatment may worsen acquired resistance, leading to chemotherapeutic failure. Notably, the processes behind the difficult and complicated nature of chemoresistance remain unknown.

For starters, overexpression of efflux drug proteins has been linked to resistance to many classes of chemotherapeutic drugs. P-glycoprotein (P-gp), commonly known as ABCB1 or MDR-1, is a member of the ATP-binding cassette (ABC) superfamily of drug efflux proteins. The ABCB gene is implicated in PTX resistance mediated by over-expression of P-gp, which is related with drug efflux outside of cells. Importantly, inhibiting ABCB1 boosted PTX sensitivity in PTX-resistant sublines of SK-BR-3 and MCF-7 cells considerably but not entirely. As a result, different pathways for PTX resistance in BC cells are proposed.

Furthermore, because of the relevance of the checkpoint function in PTX sensitivity, PTX resistance is connected with spindle assembly checkpoint (SAC). As a result, SAC proteins like as Mad2, BubR1, and Aurora A might be key indicators of PTX resistance. However, in PTX-treated cells, inhibition of Mad2 and BubR1 removed the checkpoint function, resulting in PTX resistance associated with a drop in cyclin-dependent kinase-1 activity. Furthermore, over-expression of Aurora kinase A (Aur-A) and FOXM1 was found in PTX-resistant TNBC cells, indicating that Aur-A plays a role in tumour cell resistance to PTX. Similarly, in MCF-7 cells, abnormally regulated expression of FOXM1 and KIF20A was linked to PTX resistance.

Furthermore, changes in the expression of microtubule-associated proteins (MAPs) such as Tau or MAP4 are crucial indicators of PTX sensitivity. Tau, a microtubule-associated protein, may be utilised to screen individuals for PTX therapy since its low expression rendersmicrotubules more susceptible and BC cells more sensitive to PTX.

5. Paclitaxel's side effects

Importantly, PTX is a commonly used chemotherapeutic drug that inhibits mitosis via microtubule stabilisation and, as a result, induces apoptosis. PTX's efficacy, however, is restricted by a variety of negative effects associated with its administration.

The most common PTX side effects include hypersensitivity and neuropathies. PTX must be prepared in a lipid-based solvent polyoxyl castor oil, commonly known as Cremophor^{TM}, anddehydrated ethanol because of its low solubility. However, this vehicle has been linked to histamine-mediated hypersensitivity responses, sensory neuropathy, or drug deliveryimpairment, as well as a limitation in its efficacy. PTX hypersensitivity, which can manifest as dyspnea, bronchospasm, urticaria, flushing, erythematous rash, hypotension, angioedema, chest discomfort, stomach pain, fever, or rigours, is frequently evident within the first 10 minutes of drug administration. Furthermore, PTX hypersensitivity generally results in the medication being stopped immediately. Pre-treatment with dexamethasone, diphenhydramine, or cimetidine, on the other hand, can minimise hypersensitivity responses. Importantly, lowering the PTX dosage by 20% or using Amitriptyline may help to reduce some of the neuropathic adverse effects. As previously stated, large dosages of various chemotherapeutic medicines, including PTX, are associated with peripheral neuropathy. In this context, Vahdat et al. investigated the decrease of neuropathy following high-dose PTX with oral administration of 10 g glutamine 3 times a day for 4 days (beginning 24 hours after PTX completion). When compared to the placebo control group, their clinical data indicated that individuals treated with glutamine had considerably lower levels of severity associated with peripheral neuropathy.

INTRAPERITONEAL (IP) CHEMOTHERAPY

Aside from dosage and schedule, the route of administration of chemotherapeutic drugs has a significant impact on result. Because intraperitoneal spread is prevalent and likely an early occurrence in epithelial ovarian cancer, delivering chemotherapy intraperitoneally would theoretically expose the tumour microcirculation to larger amounts of medication than systemic treatment while reducing systemic damage. A medicine that is systemically effective, penetrates deep into the inner core of tumour tissue, and stays within the peritoneal cavity for an extended length of time is

excellent for IP chemotherapy. The median time to recurrence was 25 months, although overall survival did not change substantially when compared to the control group that was subjected to observation alone. Treatment-related toxicity was minimal, and 11% of patients experienced technical issues.

NEWER FORMS OF PACLITAXEL

Over the last 40 years, next-generation taxanes have been developed with the goal of removing toxicity while boosting efficacy and convenience of administration. Abraxane is a new drug that combines paclitaxel into an albumin nanoparticle that is soluble in saline, hence removing the requirement for Cremophor EL, which is responsible for hypersensitivity responses during paclitaxel infusion. The nanoparticle albumin in nab-paclitaxel can bind to the glycoprotein gp60 receptor, an albumin receptor, and activate caveolin-1, a protein encoded by the CAV-1 gene in humans, leading to the formation of caveoli and allowing nab-paclitaxel to migrate across the endothelial cell membrane into the interstitial space, resulting in higher intra-tumor drug concentration. Furthermore, because Abraxane has linear pharmacokinetics, it may be administered at a greater dose than normal intravenous paclitaxel, resulting in a higher therapeutic ratio and increased effectiveness in solid tumours, particularly metastatic breast cancer. In 2005, the FDA approved Nab-paclitaxel for the treatment of breast cancer.

Paclitaxel poliglumex (PPX), commonly known as Xyotax, is another prodrug that accumulates in tumour tissue due to increased permeability of tumour arteries and a lack of lymphatic outflow. Paclitaxel poliglumex improves paclitaxel solubility, enables direct distribution to the intratumoral microenvironment, and allows for sustained active drug exposure while minimising systemic toxicity.

DHA-paclitaxel, also known as Taxoprexin, is a prodrug in which paclitaxel is covalently conjugated with the naturally occurring omega-3 fatty acid docosahexaenoic acid (DHA), a fatty acid that is easily taken up by tumour cells, increasing intra-tumoral concentration of paclitaxel and causing tumour cell apoptosis. When compared to traditional paclitaxel, DHA- paclitaxel has linear pharmacokinetics, lesser toxicity, and ease of administration, and it has showed antineoplastic effectiveness in animal models of cancer as well as in a phase III study including metastatic melanoma. In a recent investigation on human ovarian cancer cells, DHA was shown to reverse paclitaxel resistance by decreasing P-gp, downregulating the expression of multidrug resistance related proteins (MRP), and lowering the activity of the NF-B and p38MAPK signalling pathways.

CONCLUSION

In conclusion, in the era of contemporary radiation therapy procedures, the use of adjuvant radiation therapy for older women with right- or left-sided early-stage ER + breast cancer is not linked with an elevated risk of cardiac death within 10 years after treatment. Radiation treatment can be administered to elderly people with early-stage breast cancer as needed to assure cancer control without causing cardiac-related mortality in the short term. These findings would be strengthened by another study with a longer follow-up interval and more complete radiation therapy information, including the heart dosage. Prospective study should be conducted in the future to assess the potential value of adjuvant radiotherapy without hormone treatment in an aged population. PTX is a key medication in the treatment of BC. However, due to inconsistencies in its clinical usage, it is critical to enhance its qualities in relation to the decrease of cancer cell resistance to PTX, raise its effectiveness in cancer therapy, and reduce the adverse effects associated with the use of standard PTX. The usage of novel PTX alternatives is based on the regulation of molecular pathways and epigenetic processes, which are now a hot area of scientific study in the management of BC patients.

The review focused on the chemical structure of paclitaxel, its challenges in use, and different nanoparticles containing paclitaxel—their effectiveness and potential hazardous effect. It has been verified that the relevance of nanomedicine in cancer therapy is growing due to the reduced toxicity and enhanced safety and efficacy of drugs such as paclitaxel through excellent delivery to carcinoma cells and tissues.

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