A Comprehensive Study on Tubulin Binding Agents and Their Impact on Cancer Cell Dynamics

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Abstract - Mitosis, the cell division process, plays a crucial role in the growth and development of living organisms. During this, the tubulin proteins (α- and β-tubulin) play a critical role in chromosome segregation, which contributes to tumor progression. It is, therefore, a primary concern to stop the activity of tubulin with Tubulin-Binding Agents (TBAs). They are a group of drugs that selectively target microtubules, dynamic protein structures essential for the formation of the mitotic spindle, and the segregation of chromosomes during the division of tumor cells. This review aims to present a summary of TBAs, including taxanes (Paclitaxel, Docetaxel) and vinca alkaloids (Vincristine, Vinblastine, Vinorelbine), extensively researched and commonly employed as anticancer medications, the combination of TBAs and well-known chemotherapy drugs like carboplatin, cisplatin and to explain their mechanism of action in impeding mitosis by interfering with the dynamic behavior of microtubules.

IndexTerms - Tubulin, Microtubules, Cytoskeleton, Cancer, Tubulin Binding Agents (TBAs), Microtubule-Associated Proteins (MAPs).

I. INTRODUCTION

Microtubules are integral components of the cytoskeleton that play a vital role in cell divisions. Besides maintaining cellular structure and organization, they are associated with mitosis, cell motility, and molecule transport [1,2]. The microtubules are constructed by a protein called tubulin, whose variable expression is essential for cell division [1,3]. The hollow cylindrical structure of microtubules, with a circumference of 24 to 25 nm, is made of α- and β-tubulin in an alternate pattern as shown in Figure-1 [1]. These globular proteins have a molecular weight of 100,000 daltons (50k daltons each) [2,4]. γ-tubulins, δ-tubulins, and var epsilon-tubulins, another class of tubulins, are rare proteins located in the centrosomes and assist in the folding and assembly of α- and β-tubulins, leading to the formation of microtubules [2,5].

Microtubules are polar molecules with a GTP-bound state at the positive terminal. There are a total of 8α- and 7β-tubulin isotopes in the human body with conserved amino acid sequences at the N-terminal and diverged sequences at the C-terminal, which provide sites for protein interactions and modifications [3,4]. The length of microtubules undergoes constant rescue (addition of tubulin heterodimers) and catastrophe (removal of tubulin heterodimers) during cell division, enabling proper segregation of chromosomes by the mitotic spindles [3]. This continuous polymerization and de-polymerization of Microtubules are carried out by a family of Microtubule-Associated Proteins (MAPs) including MAP2, MAP4, mip-90, tau, and MAP6 (STOP Proteins) [5].

In cancer cells, tubulin isotopes exhibit variable expression levels, leading to increased cyclin-B1 expression and uncontrolled cell division. Most cancer studies focus on β-tubulin proteins, with fewer studies on α-tubulins. Different types of cancer show varying levels of β-tubulin isotope expression. For example, breast cancer cell lines exhibit high βI- and βIII-tubulin expression and low βII-tubulin expression. Ovarian cancer shows increased βIII- and βIVa-tubulin action and low βII-tubulin expression, while Non-Small Cell Lung Cancer (NSCLC) exhibits high βV- and low βII-tubulin expression. Gastric and prostate cancers are associated with high βIII-tubulin expression [3].

Thus, the utmost concern is in blocking tubulin proteins in cancer using tubulin binding agents (TBAs) such as Taxanes and Vinca alkaloids are crucial for inhibiting mitosis and inducing cell apoptosis [3,4]. However, in many cases, cancer cells are resistant to TBAs due to factors such as the cell line, catastrophe frequency, and drug concentration. For example, βIII-tubulin continues to support cell dynamics even when TBAs are administered, hindering their action on tumor cells [3,4]. Therefore, further studies on βIII-tubulin and its properties are being proposed by the researchers. This review focuses on understanding the mechanisms of action and exploring innovative strategies for TBA-based therapies, which can lead to novel cancer treatments and impact aberrant cell division.
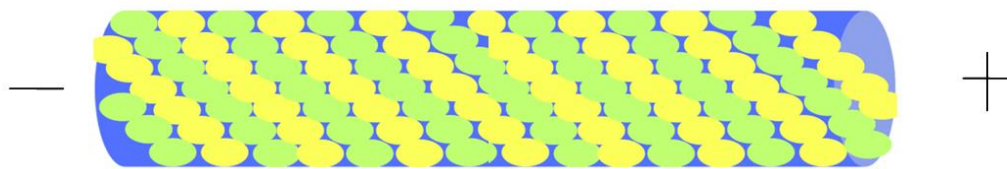
Figure-1: Basic structure of Microtubule with an alternate pattern of α- and β-tubulin proteins

α-tubulin   β-tubulin

II. THE ROLE OF TUBULIN BINDING AGENTS (TBAS) IN MITOSIS OF A CANCER CELL

Anti-mitotic drugs, known as Tubulin Binding Agents (TBAs), can be classified into two categories: microtubule stabilizers and destabilizers. Taxanes and Epothilones are microtubule stabilizers, whereas Vinca alkaloids act as microtubule destabilizers, arresting tumor cell mitosis [3,4,6]. The proper function of the mitotic spindle is essential for successful mitosis. Microtubules play a critical role in activating the Spindle Assembly Checkpoint (SAC), ensuring both the metaphase-to-anaphase transition and proper chromosome segregation during mitotic phases. Researchers have explored ways to block the SAC using specific anti-microtubule agents to induce mitotic arrest, as depicted in Figure-2. Upon drug administration, it binds to the C-terminal of tubulin proteins, interfering with microtubule activity, either stabilizing or destabilizing it. Consequently, SAC activation is inhibited, leading to the failure of tumor cells to progress from metaphase to anaphase. This results in the formation of multinucleated tetraploid cells without proper chromosome segregation, ultimately leading to cell death, G1 phase arrest, evasion of the apoptotic pathway, genetic instability, and eventual degradation by ubiquitin ligases [4,6,7]. Studies are also been conducted on the administration of low-concentration TBAs that affect Angiogenesis, the hedgehog signaling pathway, and invadopodia as shown in Figure-3. The microtubule-targeting molecules like vinca alkaloids are directly involved in reducing the blood flow through the tumors [8]. The effect of TBAs at low concentrations like paclitaxel, docetaxel, and vinblastine disrupts the microtubules of endothelial cells resulting in perforated blood vessels. This leads to the accumulation of tumor cells inside the new blood vessels followed by the blockage of blood flow and oxygen supply to the cancer cells [9,10].

The hedgehog signaling pathway is one of the mechanisms which are required for the developmental process of a few organs and tissues like lungs, muscle cells, and neural patterns and also to regulate the polarity of the Central Nervous System. The pathway gets activated when a Shh molecule binds to the Ptch protein leading to further activation of the Smo protein which switches on the Gli protein to reach its target in the nucleus and to perform the proliferation and other regulatory processes [11]. Any aberrations in the mechanism might lead to serious issues like birth defects, tissue regeneration, and sometimes to the growth of cancer cells; glioblastoma, melanoma, and carcinomas in the ovary, breast, and lungs [12]. This pathway increases the Epithelilal-Mesenchymal Transition (EMT) by surging the expression of enzymes that degrades ECM; for example Matrix MetalloProteinases (MMPs). However, the TBAs work upon binding to the Hh molecule and blocking the activation of the Gli protein to inhibit the ECM dissolving enzymes [13,14].
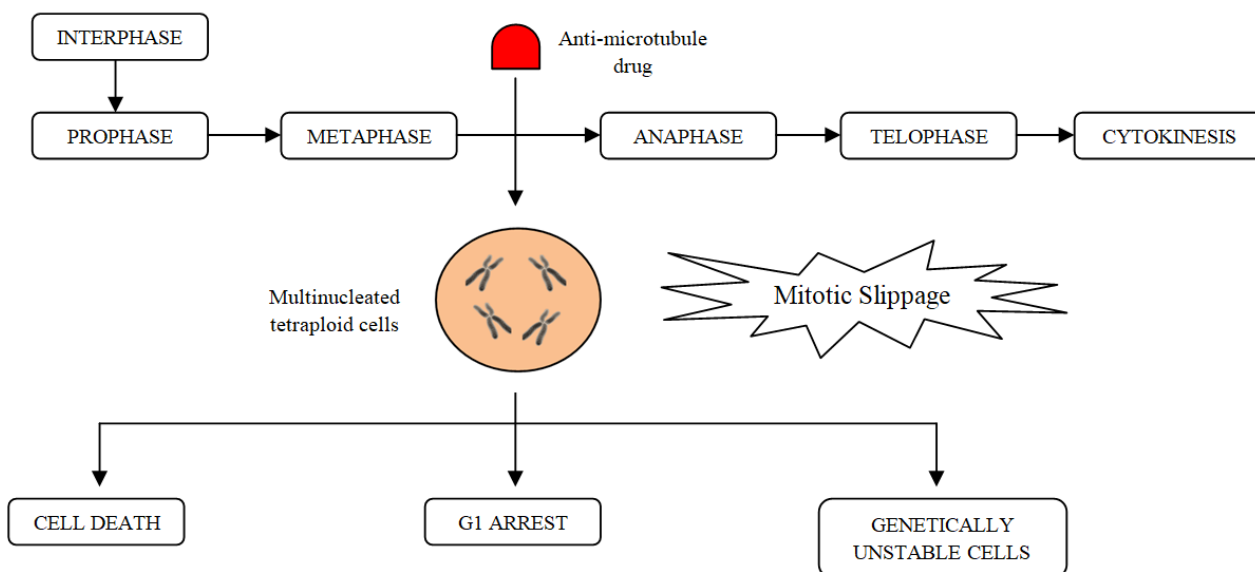

Figure-2: Mechanism of action of Tubulin Binding Agents (TBAs) in mitosis of tumor cells

There are a few actin-rich structures called Invadopodia, which help in the invasion of tumor cells from the primary region. They are similar to MMPs that cleave the ECM proteins, by puncturing the basement membrane and making a way for the cell to reach the stromal region [15,16]. Apart from TBAs, anti-microtubule drugs like Diosgenin, and Cortactin are specific towards actin and stop the motility of the cytoskeleton of Invadopodia thus preventing the invasion [17]. However, the effectiveness of TBAs varies highly depending on the specific cancer cell line, the required drug concentration, and the duration. Ongoing research involves live imaging of different cell lines to better understand the intricate consequences of TBAs on mitotic slippage and apoptosis [4,18,19].

III. RESISTANCE TO APOPTOSIS INDUCED BY ANTI-MICROTUBULE DRUGS

Studying Tubulin Binding Agents (TBAs) and their specificity presents significant challenges due to variations in the tubulin binding site between different organisms, ranging from yeast to humans [5]. Despite these challenges, researchers have extensively investigated TBA's potential mechanism of action against microtubules, and multiple mechanisms have been proposed to explain drug resistance.
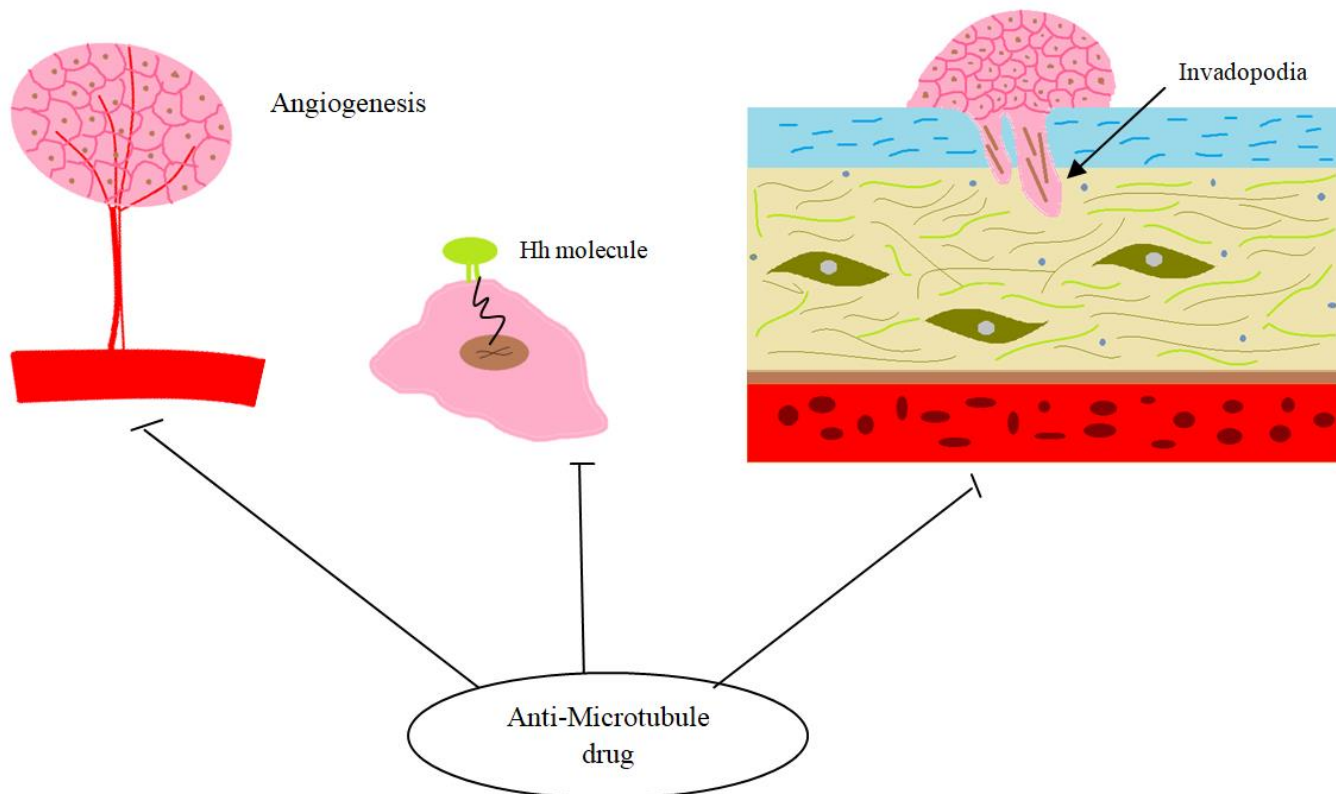

Figure-3: Effect of Anti-Microtubule drug on i) Angiogenesis; it blocks the formation of new blood vessels by disruption of tumor cells leading to necrosis ii) Blocking the Hedgehog pathway; it targets the hedgehog molecule which is involved in over expression of ECM degrading enzymes iii) Action on Invadopodia; it targets the actin-binding site thereby inhibiting the movement of cancer cell through invadopodia which highly requires actin for its motility.

In tumor cells, initial mutations occur in the binding sites of Microtubule-Associated Proteins (MAPs) and tubulins through post-translational modifications, resulting in alterations to the microtubule structure. When TBA is administered, these mutations and structural alterations prevent effective interference with the mitosis process, allowing tumor cells to continue forming the mitotic spindle and undergo cell division. Furthermore, cancer cells activate various anti-apoptotic mechanisms, including the activation of the PI3K/AKT pathway and mutations in critical genes such as p53 and BCL2. They upregulate anti-regulatory proteins as well to enhance cell growth, proliferation, and resistance to drug-induced apoptosis. Notably, the expression of efflux transporters like P-glycoproteins is increased in cancer cells, promoting drug export from the cell membrane. Consequently, this reduces the intracellular drug concentration, impairing the cell's ability to undergo apoptosis [5,6,20].

Apart from all these mechanisms, cancer cells also can activate autophagy as a protective mechanism against anti-microtubule drugs, allowing them to bypass apoptosis and continue proliferating. Overcoming resistance to apoptosis induced by anti-microtubule drugs remains an active area of research. Combining anti-microtubule drugs with other targeted therapies or agents that modulate the resistance mechanisms may enhance their effectiveness and improve patient outcomes.

IV. COMBINATION OF TBA DRUGS

Cancer cells can develop resistance to single drugs over time, making the treatment less effective. By using a combination of drugs, it becomes more challenging for cancer cells to simultaneously develop resistance to all the drugs involved. Tumors are often composed of a heterogeneous population of cancer cells, with different genetic and molecular characteristics. Some cells may be more susceptible to one type of drug, while others are not affected. This approach, combination therapy or multi-target therapy can help overcome or delay the development of drug resistance, extending the effectiveness of the treatment. Integration of tubulin-binding agents (TBAs) with other chemotherapy drugs is a common strategy in cancer treatment, particularly for various types of solid tumors. The first clinically implemented microtubule-targeting drug was paclitaxel in the year 1992 against ovarian cancer. It is a type of taxane chemotherapy drug derived from the Pacific yew tree. It is classified as a mitotic inhibitor, meaning it interferes with cell division or mitosis by stabilizing microtubules in the cell [21,22]. The latest studies have proposed that combining drugs with different mechanisms of action can lead to synergistic effects; the combined treatment is more effective in killing cancer cells than each drug used alone. For example, TBAs disrupt cell division, while other drugs like RTK inhibitors may target different growth factors like Epidermal growth factor (EGF), Vascular endothelial growth factor (VEGF), and Herceptin-2 EGF, thus increasing the overall efficacy of the treatment [22]. Here is the most common combination (Platinum- and taxane-based drugs) that are used to treat various types of cancer.

V. PLATINUM- AND TAXANE-BASED DRUGS

Platinum-based drugs (such as carboplatin and cisplatin) and taxane-based drugs (such as paclitaxel and docetaxel) are used in the treatment of various types of cancers, either as single agents or in combination with other drugs implemented in Chemotherapies or Targeted therapies. Some of the common types of cancers include Ovarian cancer, Breast cancer, NSCLC, Pancreatic cancer, etc.

Individual mechanisms of action of taxanes [4,23] and platinum-based drugs are illustrated in Figure-4 [24,25]. When the taxane-based drug is administered, it shutdowns three different mechanisms; i) Suppression of the Bcl-2 gene ii) Attachment to β-tubulin iii) Increased expression of Cytochrome-C protein (Figure-4a) [23]. Bcl-2 is a regulatory protein that regulates the apoptotic pathways (mainly associated with Breast Cancer). But in tumor cells, the overexpression of the Bcl-2 gene with the presence of RAF1 proteins highly promotes cell growth and proliferation. When platinum-based drugs are made to act upon, it activates the mitochondrial apoptotic pathway by increasing the expression of Bcl-2 Interacting Mediator (BIM) in the microtubule resulting in the movement of BIM proteins to mitochondria and activating mitochondrial-mediated apoptosis [26]. Simultaneously, taxanes increase the expression of Cytochrome-c (Cyt-c) which is a mitochondrial protein involved in the formation of apoptosome complex and initiates a series of biochemical events leading to cell death. Due to its microtubule-targeting property, taxane attaches to the C-terminal binding site of β-tubulin and stabilizes the microtubule by preventing the activation of various transcription factors involved in cell differentiation. In addition, microtubule stabilization also guides the kinetochore to strongly attach the chromosomes and spindle fibers thus resulting delay in the chromosome segregation [23]. All these actions finally lead to tumor cell apoptosis.

The mechanism of action of platinum-based drugs varies depending upon the drug-delivery system which can be through liposomes or nanoparticles as shown in Figure-4b in which the main reason to is to increase the bioavailability and decrease the toxic side effects (neurotoxicity, hypersensitivity, etc). Taking the Liposomal drug-delivery system into account, drugs are loaded into the core of the liposome [24] whereas in nanoparticle dependent drug-delivery system, the drugs are made to bind to the tumor-targeting ligand of the Pt nanoparticles as shown [25]. As soon as the drug enters the tumor cell, it penetrates the nucleus and forms a covalent bond with the Adenine or Guanine region of the DNA leading to its cross-linkage of it. This leads to the suppression of all the genes produced by the tumor cells, makes them weak, and finally results in cell death [24,25].

Among these, the combination of Paclitaxel and Carboplatin is frequently used in the treatment of ovarian cancer. Paclitaxel stabilizes microtubules, preventing their disassembly, while carboplatin is a platinum-based chemotherapy drug that damages DNA by the formation of cross-links (platinum-based drugs) and inhibits cell division [27]. This combination is referred to as TC or CT regimen and is usually given in cycles, with each cycle typically lasting three weeks (21 days) [28]. Recent trials are working on nanoparticle drug delivery systems to increase the bioavailability, reduce the toxicological effects and increase the pharmacodynamic and pharmacokinetic profile [27]. It's important to note that ovarian cancer treatment is highly individualized, and the choice of chemotherapy regimen may vary based on factors such as the patient's overall health, the stage of ovarian cancer, and other individual considerations. Docetaxel and Cisplatin; This combination is commonly used in the treatment of non-small cell lung cancer (NSCLC). Docetaxel inhibits microtubule disassembly by stabilizing it similar to paclitaxel, while cisplatin damages DNA and disrupts cell division similar to carboplatin. The combination helps to target cancer cells more effectively and improves treatment outcomes [29].
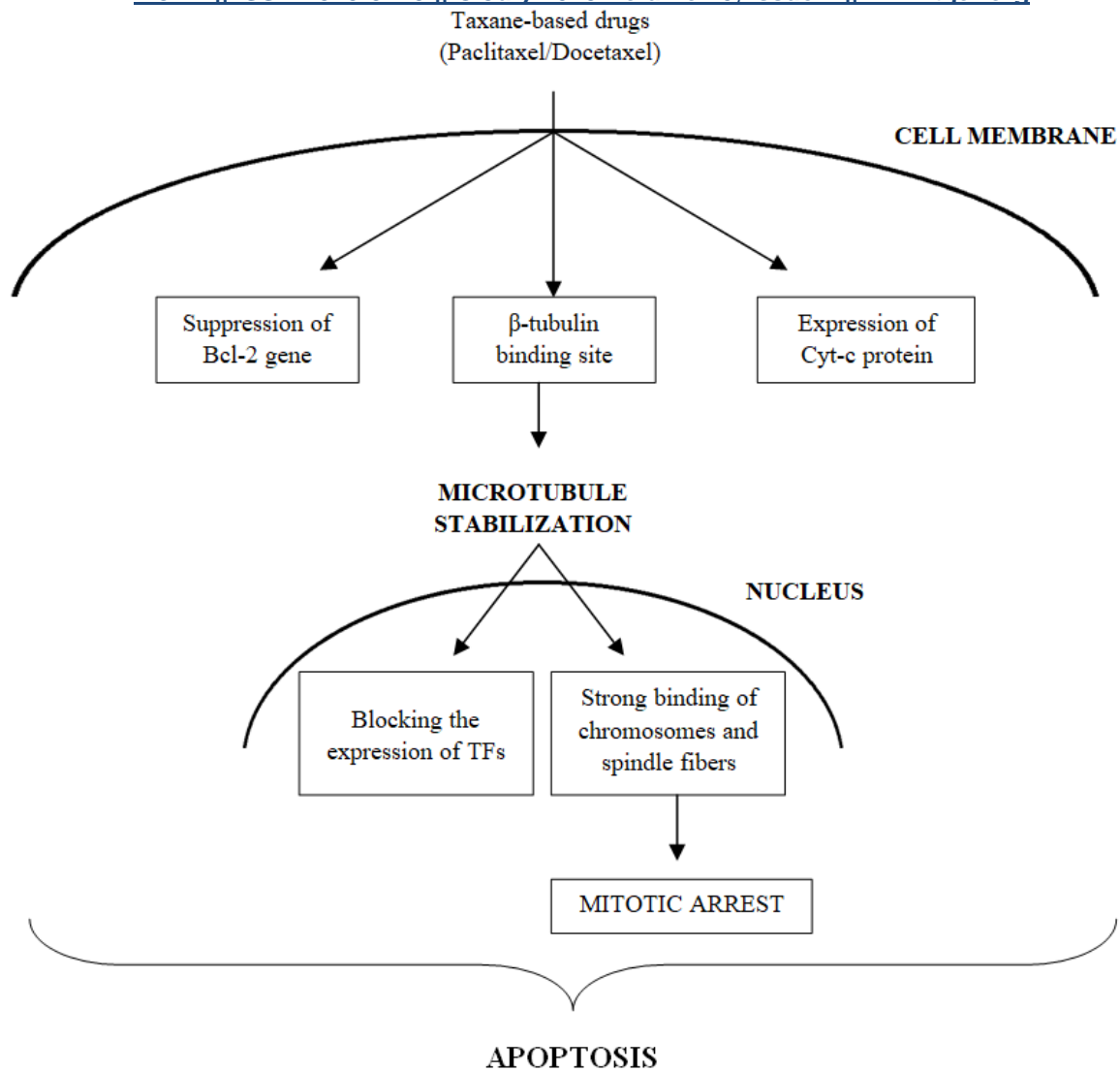
Taxane-based drugs
(Paclitaxel/Docetaxel)

CELL MEMBRANE

| Suppression of Bcl-2 gene | β-tubulin binding site | Expression of Cyt-c protein |

MICROTUBULE STABILIZATION

NUCLEUS

| Blocking the expression of TFs | Strong binding of chromosomes and spindle fibers |

MITOTIC ARREST

APOPTOSIS

Figure-4(a): Effect of taxane-based drugs (Paclitaxel/Docetaxel)

VI. MECHANISM OF ACTION OF VINCA ALKALOIDS

Vinca alkaloids are a class of chemotherapeutic agents derived from the Madagascar periwinkle plant (*Catharanthus roseus*). In contrast to taxanes, Vinca alkaloids act against microtubules by destabilizing them as shown in Figure-5. These alkaloids have a direct effect on microtubules by binding with the tubulin subunits. This prevents the polymerization of tubulin dimers leading to the curvature of protofilaments (actin-like structures in microtubules) which in turn holds the chromosome strongly and prevents the mitosis. Moreover, it increases the expression of the Stathmin protein that isolates the tubulin dimers and promotes catastrophe; tubulin polymerization gets blocked and the microtubule loses its stability. There is a calcium-modulated protein called Calmodulin (CaM) which is involved in the synthesis of microtubule-associated proteins; mainly MAP6. MAP6 binds to the lattice of the microtubule and promotes polymerization. But the alkaloids suppress the activity of CaM proteins followed prevent the formation of MAPs [30].
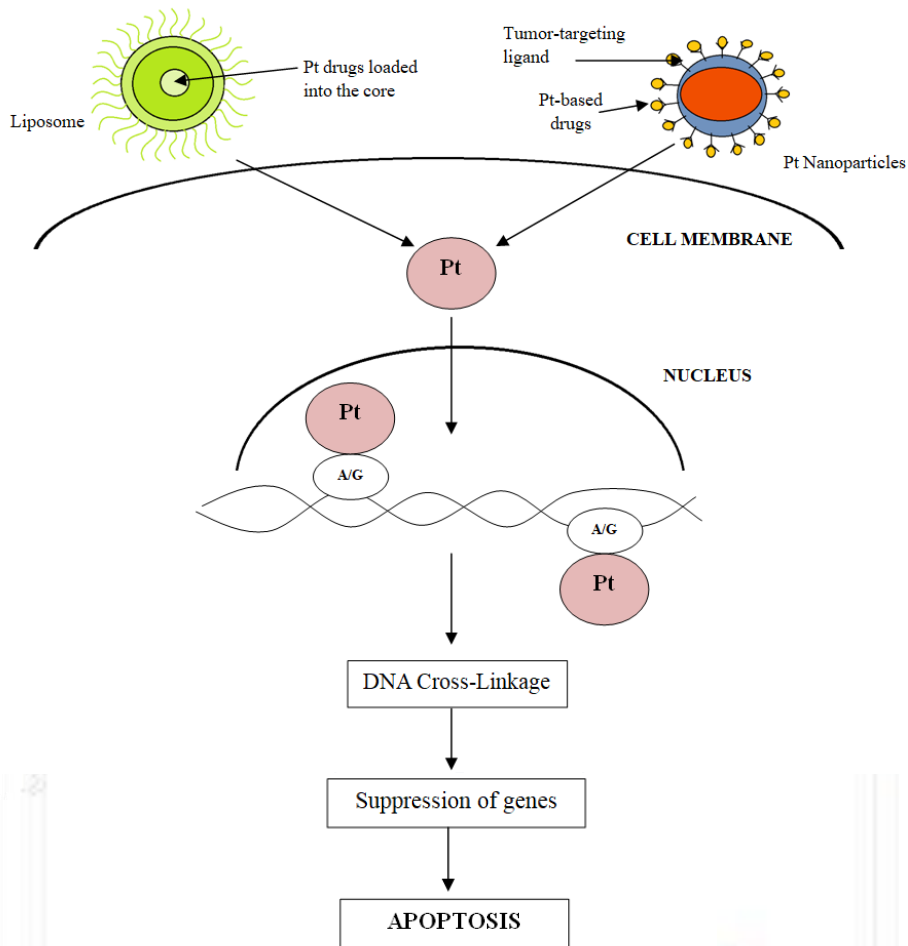
Figure-4(b): Mechanism of action of Platinum-based drugs on tumor cells

A combination of Vinca alkaloids (Vincristine, Vinblastine, Vinorelbine) and other chemotherapy drugs are widely used in the treatment of cancer. For example, the most common combination, Vinorelbine and Platinum-based drugs (cisplatin or carboplatin) work efficiently in the treatment of Non-small cell lung cancer (NSCLC). These alkaloids in combination are also involved in curing various cancer types like Ovarian cancer, Breast cancer, Hodkin's, and Non-hodkin's lymphoma [31].
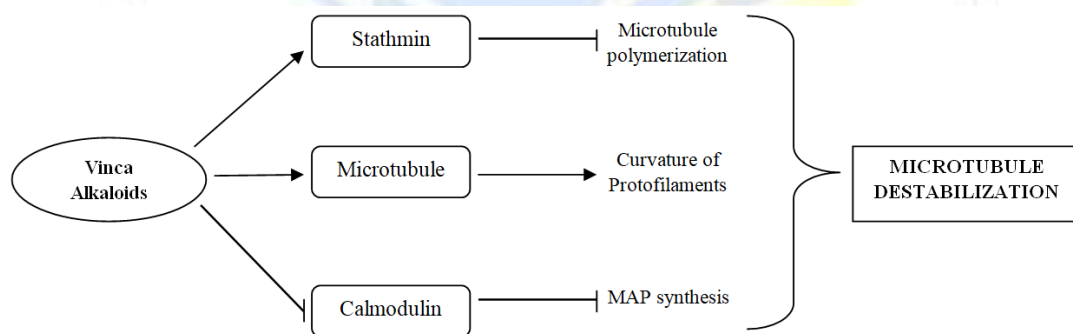

Figure-5: Mechanism of action of Vinca alkaloids on tumor cells

VII. CONCLUSION

Mitosis, a critical process in cell division, heavily relies on tubulin proteins, making them attractive targets for cancer treatment. TBAs, including Taxanes and Vinca alkaloids, have been extensively researched as promising anticancer medications due to their selective microtubule-targeting properties. The review has provided insights into the mechanisms of action of these agents, revealing their ability to disrupt microtubule dynamics and hinder mitosis in tumor cells, ultimately leading to apoptosis. Despite the challenges posed by drug resistance, ongoing research seeks to overcome these obstacles, side-effects and explore innovative TBA-based therapies by using various drug-delivery systems. Moreover, the combination of TBAs with other chemotherapy drugs has shown promising results, offering a multi-target approach to improve treatment efficacy and combat resistance. As the understanding of TBAs' complex interactions with cancer cells advances, the potential for novel cancer treatments and their impact on aberrant cell division becomes increasingly evident, bringing hope for better outcomes in cancer patients.

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