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A REVIEW ON TAXANES: AN IMPORTANT GROUP OF ANTICANCER COMPOUND OBTAINED FROM *TAXUS SP*

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ABSTRACT: Taxol is an important drug used for the treatment of various types of cancer. It is primarily obtained from *Taxus brevifolia* bark and has a long history of the developmental program of 50 years. It functions as a microtubule-stabilizing compound and inhibits mitosis of cancer cells, thereby providing a protective role in the treatment of cancers. In addition to it, taxol also interferes with a number of biochemical pathways and protein to bring about apoptosis and cell death. Since its inception, taxol has undergone various levels of modifications and formulations with a motive of making its action more effective. This has led to the development of Paclitaxel by Bristol-Myers Squibb for large scale commercialization. Consequently other semi-synthetic variants such as Docetaxel and Cabazitaxel were also developed for better actions. All these compounds are collectively called as Taxanes and contain a common ringed baccatin III structure in its molecule. This review is an attempt to illustrate the gradual development of anticancer taxanes from its precursor Taxol and its various pharmacological activities against the treatment of cancer. An extensive literature survey has been made to compile all the relevant information in relation to its development and pharmacological activity. Taxanes can be very well utilized in the treatment of various types of cancers. More clinical trials are a requirement of time for effective refinement of taxanes for the benefit of cancer patients.

INTRODUCTION:

From Nature to Laboratory: Taxol (generic name paclitaxel) is a microtubule-stabilizing drug used for the treatment of breast, ovarian, and lung cancer and is approved by food and drug administration, United States of America in the year 1992 [1].

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Chemically, taxol is a diterpenoid of natural product origin [2]. Its history dates back to six decades when an extensive search for an anticancer drug was done by the National Cancer Institute (NCI) and the United States Department of Agriculture (USDA) between the year 1960 and 1981 through a screening program involving collection and testing of 115000 extracts from 15000 plants [3].

It was in the year 1962, USDA botanist Arthur S. Barclay and 3 other college student field assistants collected 650 plant samples from California, Washington, and Oregon, including bark, twigs,

leaves, and fruit of *Taxus brevifolia* from Washington [4]. In 1964, the samples, in the form of crude extracts having cytotoxicity, were then transferred to Monroe Wall at the Research Triangle Institute, and crystalline substances were first isolated in the Wall's laboratory in 1966 with a proposed molecular formula containing carbon, hydrogen, oxygen. The name Taxol was first proposed to the crystals isolated from active extracts of *Taxus brevifolia* bark by Monroe Wall [5].

The accomplishment of the program was brought about through the decipherence of the chemical structure of taxol from *Taxus brevifolia* by the research group of Wani, Wall and coworkers in the year 1970 under a contract of Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, United States of America [6]. Taxol was then passed to NCI for further analysis and development of the drug. A further investigation of the pharma-cological activity of Paclitaxel was done by various groups of researchers. Fuchs and Johnson, 1978, reported taxol as an antineoplastic agent acting as mitotic spindle poison [7]. Later, Drs Schiff, Horwitz, and coworkers in 1979 investigated and verified the potent cytotoxic properties of Paclitaxel on the growth of human cervical cancer cells (HeLa) and also its ability to block cell division in late G2 or M phase of cell cycle [8, 9].

By the year 1984, further investigation on the biological activity of taxol and taxol acetates was performed [10, 11]. The phase I clinical trial of taxol was first performed in the year 1984, while the phase II trial was initiated in 1985 [12,] and in the year 1987, Wienrik reported a phase I trial and pharmacokinetic study of taxol [13]. Taxol was found to possess the cytotoxic potential of clinical significance when a study on ovarian cancer reported that 30% of the patients suffering from platinum-resistant ovarian cancer responded partially or completely [14]. The report on the phase II trial of taxol on metastatic breast cancer was done by Holmes and coworkers in the year 1991 [15]. The high demand for taxol resulted in severe depletion of the population of *Taxus brevifolia* as removal of barks resulted in the death of the trees. Thus, in 1992, the Pacific Yew act was passed to safeguard the tree from further population depletion. The act ensured that federal lands would be managed for sustainable harvesting and long term conservation of pacific yew [16]. Consequently, in order to obtain large quantities of taxol, NCI decided to transfer taxol to Bristol-Myers Squibb (BMS) for commercialization, which then trademarked the name 'taxol' and proposed a new generic name 'Paclitaxel' in the year 1992 [17].

Paclitaxel, originally extracted as taxol from the pacific yew, *Taxus brevifolia* barks, exhibited a low yield through a destructive method of extraction and complicated way of purification [18]. In addition to it, further development of drugs faced an initial hiccup due to its insolubility in water. The compound was slightly soluble in octanol, propylene glycol, butanol, and freely soluble in dimethyl acrylamide. The final formulation was achieved by Bristol-Myres Squibb using 50% Cremophor EL™ (CrEL) and 50% dehydrated ethanol as solvent. The final formulation contained 30 mg of Paclitaxel in 5 ml of 1:1 (v/v) of the mixture [19]. CrEL is a surfactant-containing formulation vehicle used for a number of drugs having poor water solubility including Paclitaxel [20].

In order to overcome the low yield issue, in the year 1995, Sanofi-Aventis, Bridgewater, NJ developed Docetaxel (Taxotere®), a semi-synthetic analog of Paclitaxel whose active ingredient is docetaxel, a lipophilic compound also having low water solubility but solubilized by micelle formation using polysorbate 80 [21]. Docetaxel differs from paclitaxel at two positions in its molecular structure, which enhances its solubility in water [22]. In June 2010, Food and Drug Administration, United States approved a new taxane by the name Cabazitaxel (Jevtana ®) as an alternative drug to the patients suffering from castration-resistant prostate cancer (CRPC) [23]. It is a semi-synthetic microtubule inhibitor and induces cell death by stabilization of microtubules [24]. Since its affinity towards P-glycoprotein is poor, the chances of resistance are also minimized, making it more effective [25].

Since its inception, a number of other semi-synthetic variants of taxol have been produced by pharmaceutical companies. These diterpenoids, including paclitaxel, docetaxel, and cabazitaxel, extensively used as chemotherapeutic agents for the treatment of cancer, are collectively called taxane

[26]. In this article, the term taxane would henceforth be used to designate taxol and associated compounds having anticancer activity. The important events associated with the development of Taxol in tabulated in **Fig. 1**.

Year	Event
1962	National Cancer Institute and United States Department of Agriculture inititated a screening programme to find new effective anticancer agent from plant sources.
1962	Samples of *Taxus brevifolia* was collected by Arthur Barclay from different regions of United States.
1964	Crude extracts were transferred to Monroe Wall at Research Triangle Institute for further investigations.
1966	Crystalline substances were first isolated through chemical techniques and an empirical formula containing carbon, hydrogen and oxygen was proposed.
1970	Decipherence of chemical structure by Wall, Mani and coworkers and consequently transferred to NCI for further drug development programme.
1978	Fusch and Johnson repoted taxol as a motitic poison and antineoplastic agent.
1979	Dr Schiff and Horwitz reported the cytotoxicity of human cervical cancer cells (HeLa).
1985	Phase I clinical trial of Taxol.
1985	Phase II clinical trial of Taxol.
1992	Pacific Yew act to protect *Taxus brevifolia* .
1992	Transferred to BMS for largescale production and commercialization.Taxol was consequently named as Paclitaxel.
1995	Introduction of Docetaxel (Taxotere®).
2010	Introduction of Cabazitaxel (Jevtana ®).

FIG. 1: IMPORTANT EVENTS ASSOCIATED WITH THE DEVELOPMENT OF TAXOL

***Taxus* as Source of Taxanes:** Investigation and isolation of taxanes and related compounds have always been a matter of curiosity since the last 6 decades. Structural elaboration of taxine, taxinine and O-cinnamoyl taxicin-I occurring in *Taxus baccata* L. were done way back in 1963 [27, 28]. Consequently taxol (Generic name paclitaxel) was first isolated from *Taxus brevifolia* in the early 1970s [29]. Taxol is produced by all species of *Taxus* though the taxoid content may vary from species to species and also between tissues of same species though the taxane biosynthetic pathway is the same for all the species [30]. An important breakthrough was the discovery of 10-deacetylbaccatin III, which later provided the precursor for semi-synthetic production of taxol [31, 32].

The environmental factors controlling the production of taxol have also been explored by various groups of researchers. It was found that there was a seasonal variation in taxol content in shoots and barks of *Taxus brevifolia* with variations more marked in barks in comparison to shoots [33]. It was also reported that the taxol content was higher in barks as compared to foliage through its content increases with age in both the plant parts [34]. The monthly variations of taxol content were also noted in *Taxus baccata* var. *fastigata*. It was observed that the highest taxol content was in the month of April.

The plants with green leaves contained more taxol in comparison to the plants with golden leaves [35]. Nine compounds, namely paclitaxel, pentaacetoxy-taxadiene, 1β-hydroxybaccatin I, baccatin IV, baccatin III, taxusin, C-14 oxygenated taxoid, rearranged taxoid and 7-xyloxyl-10-deacetyltaxol C was isolated from the roots of *Taxus wallichiana* [36]. In *Taxus brevifolia*, it was found that the concentration of taxanes decreased from the base of the stem to the tip of the plant which is due to the presence of higher taxane concentration in the phloem tissues and thickness of the inner bark from base of the stem to tip of the branch. The seasonal variation in taxane concentration was also observed, which had an increasing trend from late spring to early summer, indicating the ideal time to harvest these natural products and metabolites [37].

The regional variation of taxane concentration was also observed in the barks and needles of *Taxus cuspidata*, also indicating the renewable scope of harvesting raw material for mass production of drugs [38]. The variation in taxol content in the seeds of *Taxus cuspidata* reveals that the content is highest in testa followed by endosperm and embryo respectively. The taxol content of the fresh seed reached its maximum in the middle stage of seed maturation and declined with further maturity [39].

Chemical Nature of Taxanes: Taxanes are a group of structurally similar compounds that possess a common core ring structure called baccatin III. The taxanes are composed of a four-member oxetan ring attached at C4-C5 position and an ester side chain attached at C13. The configuration of the ester chain is important for the antitumor property of taxanes. The configuration differs from that of Paclitaxel in two ways, namely (i) in the mode of attachment to the C59 carbonyl in the C-13 side chain and (ii) absence of acetyl group esterified to the C-10 hydroxyl of the baccatin ring [40]. The third generation semi-synthetic analog of docetaxel is cabazitaxel. The molecular structure of docetaxel and cabazitaxel are almost similar and varies only in the presence of 2-methoxy side chains in cabazitaxel that substitute hydroxyl groups in docetaxel [41]. The structures of Baccatin III, paclitaxel, docetaxel, and cabazitaxel molecules are depicted in **Fig. 2, 3, 4,** and **5,** respectively.

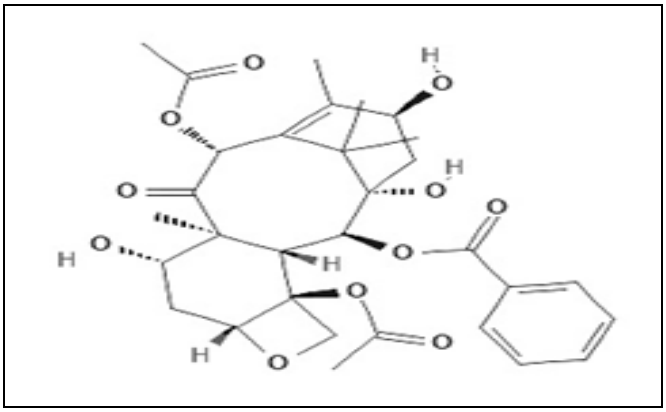

FIG. 2: MOLECULAR STRUCTURE OF BACCATIN III

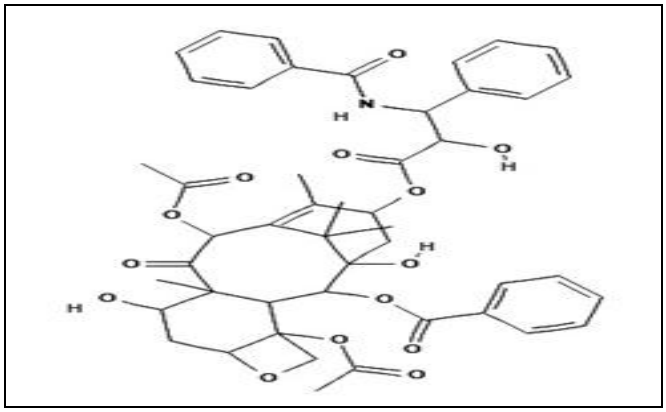

FIG. 3: MOLECULAR STRUCTURE OF PACLITAXEL

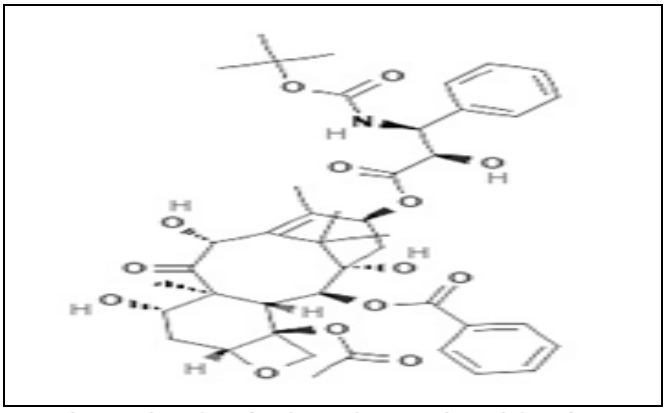

FIG. 4: MOLECULAR STRUCTURE OF DOCETAXEL

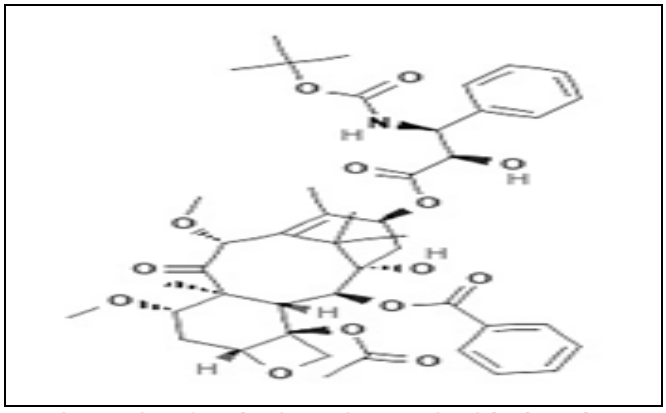

FIG. 5: MOLECULAR STRUCTURE OF CABAZITAXEL

Anticancer Activity and Mode of Action of Taxanes:

Anticancer Activity: Taxanes are being used in the cure of a number of cancers. At present, they are also used in conjugation with some other drugs in order to increase their activity and effectiveness.

Various formulations of taxanes, including micelles and nanoparticles, are also used to enhance the activity of the drug. The pharmacological activities of taxanes against selected cancers illustrated as follows.

Liver Cancer: Hepatocellular carcinoma or liver cancer is the 6th commonly diagnosed cancer and 4th leading cause of death in the year 2018, with 80% of the case reported from sub-Saharan Africa and eastern Asia [42].

It has been reported that nearly 692000 cases of hepatocellular carcinoma are reported per year, which amounts to 7% of all cancer deaths worldwide [43]. Hepatitis B virus (HBV) or hepatitis C virus (HCV), alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) are the most common risk factors of hepatocellular carcinoma [44]. The pharmacological activities of taxanes in counteracting liver cancer is presented in **Table 1**.

TABLE 1: PHARMACOLOGICAL ACTIVITY OF TAXANES AGAINST LIVER CANCER

Taxane type	Study system	Important outcome of study
Paclitaxel loaded in nanostructured lipidic carriers	*In-vitro*: HepG2 liver carcinoma cells *In-vivo*: Wistar rats	*In-vitro*: Dose-dependent decrease in cell viability and enhancement of ROS generation. Initiation of chromatin condensation, presence of condensed and fragmented nuclei indicative of apoptosis. *In-vivo*: Enhanced absorption of Paclitaxel [45].
Docetaxel in Gold nanoparticles encapsulated Apatite carrier	*In-vitro*: HepG2 liver carcinoma cells *In-vivo*: Mice	*In-vitro*: Concentration-dependent decrease in cell viability by Docetaxel .nanoparticles. Conglomeration of cells, development of blebs and bulge indicating the onset of apoptosis. *In-vivo*: Restoration of normal liver architecture in mice treated with docetaxel nanoparticles [46].
Docetaxel carboxymethyl cellulose nanoparticles	*In-vitro*: Hepatic stellate cells, Hep3B,HLF Human carcinoma cells *In-vivo*: Male C3H/HeNCrNarl mice	*In-vitro*: Dose-dependent decrease in the percentage of cell viability of hepatic stellate cells, HCA-1, Hep3B, and HLF cells. Molecular level: Dose-dependent downregulation of α- smooth muscle actin (α-SMA). and collagen I in hepatic satellite cells (HSCs) at both protein and mRNA levels *In-vivo*: Inhibition of tumour growth [47].
Cabazitaxel	*In-vitro*: SK-hep-1, SM-MC7721, Huh-7, HCC-LM3, Huh-TS-48, and SK- sora-5	*In-vitro*: A time and dose-dependent inhibition of Sk-hep-1, Huh-7, SMMc-7721, Huh-7, and HCC-Lm3 cell lines. Cell cycle arrest: Significant increase in cells at G2-M phase upon treatment with cabazitaxel in SK-hep-1 and Huh-7 cell lines. Molecular-level: Decrease in expression of Cdc25c, Cdc2, pCdc2 and cyclin B1 protein levels. Induction of apoptosis: Increase in the ration of apoptotic cells in case of SK-hep-1 and Huh- 7 cells along with a decline in anti-apoptotic protein Bcl2 and a stronger cleavage of poly ADP-ribose polymerase (PARP) [48].

Lung Cancer: Lung cancer is the most common malignancy and cause of cancer deaths worldwide in past few decades[49].The deaths due to lung cancer is expected to reach 3 million by the year 2035, with the incidence rate likely to double in both men (from 1.1 million in 2012 to 2.1 million in 2035) and women (from 0.5 million in 2012 to 0.9 million in 2035) [50]. The occurrence of lung cancer is higher in developed countries than in less developed countries and is related to tobacco smoking [51]. The pharmacological activities of taxanes in counter-acting liver cancer are presented in **Table 2**.

TABLE 2: PHARMACOLOGICAL ACTIVITY OF TAXANES AGAINST LUNG CANCER

Taxane type	Study system	Important outcome of study
Paclitaxel and survinin siRNA encapsulated into polyethyleneimine-block-polylactic acid	*In-vitro*: A549, A549^{Luc} lung cancer cells. Animal Model: BALB/c nude mice	*In-vitro*: Increase in cytotoxicity, nuclear fragmentation, chromosome abnormality and induction of G2/M cell cycle arrest in A549 cells. *In-vivo*: Effective tumor inhibition [52].
Caffeic acid with Paclitaxel	*In-vitro*: Non-small cell lung cancer (NSCLC) H1299 cells and normal Bease-2b cells	Antiproliferative action: Decrease in proliferation of NSCLC H1299. Arrest of H1299 cells is sub G1 phase of cell cycle and induction of apoptosis. Molecular level: activation of Bax, Bid, and downstream cleaved PARP, and phosphorylation of extracellular signal regulated kinase1/2 and c-Jun NH2-terminal protein kinase1/2. Activation of MAPK pathway involved in apoptosis[53].
Paclitaxel (PTX) loaded micelle delivery system (TP-M) with vitamin E-TPGS (TPGS) and PlasdoneS-630 Copovidone (PVPS630) as carriers	*In-vitro*:Caco-2, A549 and Lewis lung cancer cells *In-vivo*: Male Sprague-Dawley rats and male C57BL/6 mice	*In-vitro*: PTX-TP-M exhibited higher toxicity to A549 and Lewis cells than PTX alone due to improved cellular uptake. *In-vivo*: The tumour growth inhibition was higher upon treatment with PTX-TP-M. Reduction in tumour cell volume and mitotic cells [54].
Docetaxel loaded PEGylated liposomes with telimisartan	*In-vitro*: A549 lung cancer cell. *In-vivo*: Sprague–Dawley rats, athymic Nu/nu mice	*In-vivo*: Significant inhibition of tumour growth and mostly intact lung integrity in mice co-treated with docetaxel and telmisartan. Molecular level: Decrease in expression of antiapoptotic marker survinin and down regulation in expression of metastasis marker MMP9 and MMP2 in docetaxel and telmisartan cotreated groups [55].

Prostate Cancer: Prostate cancer stands second with respect to frequency of occurrence (after lung cancer) among men accounting 1276106 new cases and 358989 (3.8% of all deaths caused by cancer in men) deaths in 2018 [56]. The incidence of prostate cancer is highest in Oceania, followed by Northern America, Western Europe, Northern Europe, and the Caribbean, while African countries have lower incidence rates and mortality than developed countries [57]. The major risk factors associated with prostate cancer are high Body Mass Index (BMI), smoking habit, consumption of processed red meat, animal fat/saturated fat [58]. **Table 3** illustrates the pharmacological activity of taxanes in counteracting prostate cancers.

TABLE 3: PHARMACOLOGICAL ACTIVITY OF TAXANES AGAINST PROSTATE CANCER

Taxane type	Study system	Important outcome of study
Noscapine and Paclitaxel	*In-vitro*: LNCaP and PC-3 prostate cancer cell	*In-vitro*: Decrease in percentage of cell viability and increase in apoptosis in cancer cell lines Molecular-level: Significant decrease in the mRNA expression of Bcl-2 and increase in the mRNA expression of Bcl-2-associated X protein Bax, and Bax/Bcl-2 ratio in LNCaP and PC-3 cells. Decrease in expression of androgen receptor and prostate specific antigen [59].
Docetaxel with Desmopress in	*In-vitro*: PC3 prostate cancer cell *In-vivo*: Mice	*In-vivo*: Significant reduction in tumour volume in mice [60].
Docetaxel in combination with Impressic Acid and Acankoreanogenin	*In-vitro*: VCaP prostate cancer cell	*In-vitro*: Promotion of apoptosis in VCaP cells when treated with a combination of Docetaxel and Impressic Acid or Acankoreanogenin suggesting strong antiproliferative activity. Molecular level: Reduced activity of Nuclear factor-κB (NF-κB). Decreased expression of Bcl-2, NF-κB, p-Akt, and phosphorylated signal transducer and activator of transcription 3(p-Stat 3) and increased expression of phosphorylated c-Jun N-terminal kinase (p-JNK) [61].
Docetaxel-loaded nanoparticles	*In-vitro*: LnCaP and PC3 prostate cancer cells	*In-vitro*: A concentration dependent increase in cell death upon treatment with docetaxel loaded nanoparticles as evident from increase in lactate dehydrogenase release in the culture medium of in LnCaP , PC3 prostate cancer cells [62].
Cabazitaxel	*In-vitro*: Human prostate cancer LNCaP and PC-3 cells	*In-vitro*: Significant attenuation of proliferation of both the cancer cell lines. Molecular Level: Reduction in levels of androgen receptor and androgen receptor-associated factors HSP90α, HSP40, and HSP70/HSP90 organizing protein.Suppression of activity of anti-apoptotic factor HSP60 [63].
Cabazitaxel and Silbinin co-encapsulated cationic liposomes	*In-vitro*: PC-3 and DU-145 prostate cancer cells	*In-vitro*: Dose-dependent inhibition of cell growth, inhibition of cell migration and induction of apoptosis upon treatment with cabazitaxel and silbinin loaded nanoparticles. Cell cycle arrest: Colony formation and G2/M cell cycle arrest upon treatment with nanoparticles. Nucleus morphology: Onset of apoptosis as evident from cell membrane shrinkage, membrane blebbing, nuclear granulation *etc.* [64]
Bone targeted cabazitaxel nanoparticles.	*In-vitro*: PC-3 and C4-2B-luciferase prostate cancer cells	*In-vitro*: A dose and concentration-dependent inhibition on percentage survival of PC-3 and C4-2B prostate cancer cells along with high affinity to bind with bones. *In-vivo*: Significant reduction in tumor weight along with protection from bone lesion [65].

Pancreatic Cancer: Pancreatic cancer is the 11th most common cancer in the world, with 458,918 new cases resulting in 432,242 deaths (4.5% of all deaths caused by cancer) in 2018 [66] with a five-year relative survival rate of 8% only [67]. Pancreatic cancer is more common in males than in females and among black than among white [68]. Hereditary unmodifiable factors are major risks of pancreatic cancer. **Table 4** illustrates the pharmacological activity of taxanes in counteracting pancreatic cancers.

TABLE 4: PHARMACOLOGICAL ACTIVITY OF TAXANES AGAINST PANCREATIC CANCER

Taxane type	Study system	Important outcome of study
Albumin bound Paclitaxel nanoparticles (nab-PTX) and S-nitrosated human serum albumin dimer (SNO-HSA Dimer)	Human Pancreatic cancer cell (SUIT2-GLuc)	Antitumour activity in SUIT2 cancer model: Effective suppression of ascites and distant metastasis along with best survival rate by combination therapy [69].
Docetaxel nanoparticles in combination with radiotherapy	*In-vitro*: AsPC-1, BxPC-3 pancreatic cancer cells *In-vivo*: Mice	*In-vitro*: Decrease in number of cell colonies, increase in apoptosis and degree of tubulin polymerization upon treatment with docetaxel in combination with radiotherapy. Molecular-level: Increase in expression of caspase 3 *In-vivo*: Inhibition of growth in AsPC-1, BxPC-3 derived tumours[70].

Breast Cancer: Breast cancer forms the most common cancer in women and ranks the second most common cancer across the world, with a projected 1.7 million new cases by the year 2020. [71] Inherited mutations in Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) genes accounts to

about 5-10% of breast cancers [72]. It is reported that menopausal women are more prone to breast cancers than younger women under 45 years of age [73]. Taxanes find extensive use in the treatment of breast cancers. The pharmacological activity of three taxane representative, namely Paclitaxel, Docetaxel, and Cabazitaxel in counteracting breast cancers, are illustrated in **Table 5, 6,** and **7,** respectively.

TABLE 5: PHARMACOLOGICAL ACTIVITY OF PACLITAXEL AGAINST BREAST CANCER

Taxane type	Study system	Important outcome of study
Paclitaxel in combination with sorafenib and radiation therapy	*In-vitro*: MDA-MB-231 breast cancer cells *In-vivo*: BALB/c nude mice	*In-vitro*: Dose-dependent Suppression in the proliferation of breast cancer cells with increased sub-G0-G1 phase. Molecular-level: Increased expression of p21, CHOP, BAX, Apaf-1, and cleaved-caspase 3 and reduction in (B-Cell lymphoma) Bcl-2 levels suggesting induction of cell cycle arrest via caspase cleavage and inhibition of the Bcl-2 pathway. Cellular level: Increase in levels of cytochrome C in the cytosol indicating apoptosis through a cytochrome c–dependent pathway. *In-vivo*: Suppression of Caki1 and MB-231 cell xenograft tumors [74]
Cell-penetrating peptide producing nanoliposomes containing Paclitaxel	*In-vitro*: Human breast cancer cell MCF7. *In-vivo*: BALB/c nude mice	*In-vitro* cytotoxic effect: Inhibition of cell proliferation in concentration-dependent manner. *In-vivo* antitumor efficacy: Significant tumor inhibition in MCF7 tumor bearing mouse model as evident from the reduction in tumor weight [75].
Anti-EGFR anchored immunonanoparticle bearing Paclitaxel	*In-vitro*: MDA-MB-468 breast cancer cell. *In-vivo*: Athymic mice	*In-vitro* cytotoxic effect: Reduction in cancer cell viability *In-vivo* antitumor efficacy: Tumour reduction and higher Paclitaxel accumulation in tumor plasma[76].
Nab-Paclitaxel with Azetolizumab.	Phase III trial: Human females	Results: Nab-Paclitaxel with Atezolizumab prolonged the progression-free survival in patients suffering from triple-negative breast cancer [77].
Paclitaxel and Gebcitabine through methoxy poly (ethylene glycol)–poly (lactide-coglycolide)-polypeptide nanoparticles.	*In-vitro*: 4T1, MCF-7and MDA MB-231 breast cancer cells	*In-vitro*: Inhibition of proliferation of 4T1, MCF-7, and MDAMB-231 in a dose-dependent manner by Paclitaxel. A combination of Paclitaxel with Gebcitabine resulted in a significant reduction in viability of 4T1, MCF-7, and MDAMB-231 below 50%, indicating a synergistic effect. Reversal of drug resistance of human breast cancer cell [78].
Paclitaxel loaded with keratin nanoparticles	*In-vitro*: MCF7, MDA MB 231 breast cancer cells	Cell Death: Significant increase in the percentage of late apoptotic cells in MCF-7 and early apoptotic cell MDA MB 231 after 48 and 24 hours of treatment respectively. Molecular Level: Increase in expression of proapoptotic BAX gene and of cleaved caspase 3 (CC3) protein[79].

TABLE 6: PHARMACOLOGICAL ACTIVITY OF DOCETAXEL AGAINST BREAST CANCER

Taxane type	Study system	Important outcome of study
Docetaxel loaded in folic acid- and thiol-decorated chitosan nanoparticles	*In-vitro*: MDA-MBB-231 breast cancer cell	*In-vitro*: Improved cytotoxicity of docetaxel loaded in nanoparticles as compared to docetaxel. *Ex-vivo*: Successful transportation and improved oral bioavailability [80].
Dehydroartemisinin and docetaxel in pH sensitive nanoparticles	*In-vitro*: 4T1 mammary carcinoma cell	*In-vitro*: Reduction in cell viability along with G2/M cell cycle arrest Molecular-level: Increase in expression of E-Cadherin and decrease in expression of p-AKT, NF-κB, p65 and Matrix metalloproteinase-2 (MMP-2) arrest [81].
Docetaxel with ionizing radiation	*In-vitro*: MCF-7 breast cancer cell	*In-vitro*: A concentration and time-dependent decrease in viability of cancer cells upon co-treatment of docetaxel and ionizing radiation suggesting a synergistic effect[82].
Docetaxel with SC-43	*In-vitro*: MDA-MB-231, MDA-MB-468, and HCC-1937 breast cancer cells *In-vivo*: NCr athymic nude mice	*In-vitro*: Dose-dependent increase in anti-proliferative activity and apoptotic activity upon treatment with docetaxel and SC-43. Molecular level: Decrease in expression levels of p-stat 3 and stat 3 downstream effector cyclin D1. Increased in an expression of SHP1 with a sequential combination of docetaxel and SC-43. *In-vivo*: Suppression of tumor growth and tumor weight by combination treatment as compared to control [83].
Noscapine and Docetaxel	*In-vitro*: MDA-MBA231 and MDA-MB-468 breast cancer cells *In-vivo*: Mice	*In-vitro*: Increased cytotoxicity and decrease in cell viability upon treatment with a combination of Noscapine and Docetaxel Molecular-level: Downregulation in the expression of bcl-2, survivin, α-tubulin and pAKT. *In-vivo*: Reduction in tumor collage levels and higher intratumoral

		.uptake of liposomes loaded with drugs [84].
Ritonavir and Docetaxel	*In-vivo*: Cyp3a knockout mice ($Cyp3a^{-/-}$) Tumour model: K14cre; $Brca1F^{/F}$; $p53F^{/F}$ mouse model	*In-vivo*: Docetaxel and retanovir cotreatment resulted in a reduction of to one-third of its initial volume. Histological observation: Significant pleomorphism along with expanded stroma, fibrotic changes and abundance of apoptotic cell and absence of necrosis in mammary tumor cells [85].

TABLE 7: PHARMACOLOGICAL ACTIVITY OF DOCETAXEL AGAINST BREAST CANCER

Taxane type	Study system	Important outcome of study
Cabazitaxel-loaded Poly (2-ethylbutyl cyanoacrylate) nanoparticles	*In-vitro*: MDA-MB-231, MDA-MB-468, MCF-7 breast cancer cells. *In-vivo*: Mice	*In-vitro*: Toxicity of cabazitaxel to MDA-MB-231, MDA-MB-468, and MCF-7 breast cancer cell lines. Inhibition of tumor growth: Inhibition of tumor growth and complete remission of tumors in mice upon treatment with cabazitaxel nanoparticles. Inhibition of expression of CD206, a marker of M2 macrophages (protumorigenic and anti-inflammatory activity) [86].
Cabazitaxel and thymoquinone co-loaded lipospheres	*In-vitro*: MCF-7, MDA-MB-231 breast cancer cells	*In-vitro*: A dose-dependent reduction in cell viability of MCF-7 and MDA-MB-231 breast cancer cell lines upon treatment with Cabazitaxel-thumoquinone loaded nanoparticles. Cell cycle analysis: Concentration-dependent percent increase in sub G1 population upon treatment with lipospheres loaded with combination drug. Apoptosis: Increase in percentage of early apoptotic cells upon treatment with combination drugs [87].
Hyaluronic acid-coated cabazitaxel loaded solid lipid nanoparticles	*In-vitro*: MCF-7 breast cancer cells	*In-vitro*: Concentration-dependent decrease in cell viability upon treatment with cabazitaxel nanoparticles with enhanced cellular uptake as compared to controls [88].
Cabazitaxel loaded polymeric micelles	*In-vitro*: 4T1 metastatic breast cancer cells	*In-vitro*: Inhibition of 4T1 cell migration upon treatment with cabazitaxel loaded polymeric micelles. *In-vivo*: Inhibition of tumor growth upon treatment with Cabazitaxel loaded polymeric micelles [89].

Mode of Action of Taxanes: The mode of action of taxanes on cells can broadly divide into two types depending on its action pattern namely (a) Mitotic action and (b) Apoptotic action.

(a) Mitotic Action: This type of action is centered on mitotis where taxanes interact with the microtubules associated with the mitotic process. Taxanes, namely Docetaxel and Paclitaxel have similar mechanisms of action. Both of drugs have a stabilizing effect on microtubules on cells which counteract their depolymerization. This results in inhibition of correct separation of two identical sets of chromosomes and their consequent transfer during cell division. Docetaxel and Paclitaxel thus result in blockage of cell mitosis, ultimately leading to cell death [90]. It is reported that Paclitaxel promotes microtubule polymerization and arrest mitosis through activation of spindle assembly checkpoint and keeping a small number of unattached kinetochores to the microtubules finally delaying mitotic metaphase progression and inhibiting anaphase prompting complex [91].

Moreover, at higher concentrations, Paclitaxel is reported to suppress microtubule minus-end detachment from the centrosomes [92]. On a molecular level, taxol is reportedly to bind to a pocket in β-tubulin that faces microtubule lumen and is near the lateral interface between protofilaments, thereby affecting normal function and cellular processes [93] **Fig. 6**. The binding of Paclitaxel to the β-tubulin subunit results in the stabilization of microtubules through induction of conformational changes of the M-loop of β-tubulin, which results in more stable lateral interaction between adjacent protofilaments thereby changing microtubule dynamics and inducing mitotic block [94]. Cabazitaxel also possess a similar mode of action. The molecule binds to tubulin thereby promoting its assembly microtubule assembly and simultaneously inhibiting dis-assembly. This results in the stabilization of microtubules, interference of mitotic and interphase cellular functions, halting of cell cycle progression at metaphase, thereby triggering apoptosis of cancer cells [95].

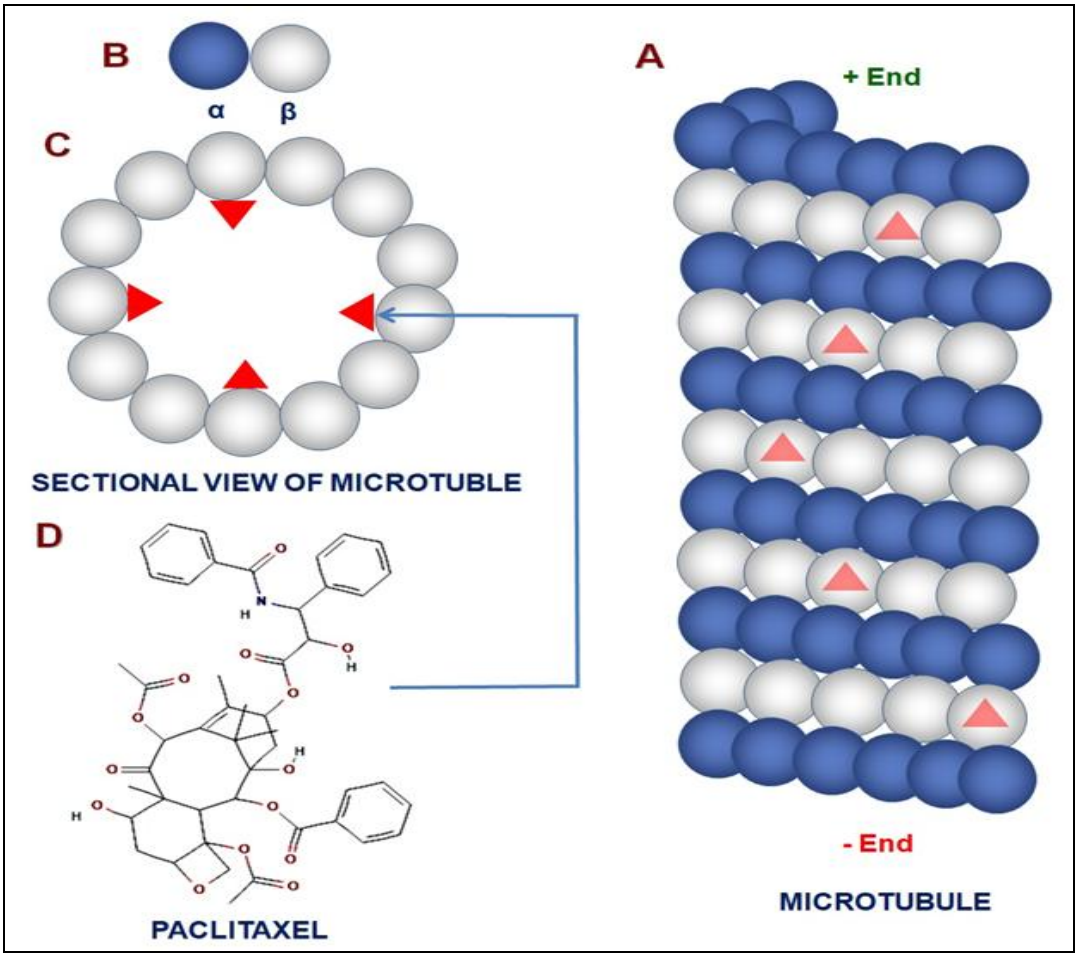

FIG. 6: REPRESENTATION OF SITE OF ACTION OF PACLITAXEL IN THE MICROTUBULE. (A) MICROTUBULE CONSISTING OF ALPHA AND BETA SUBUNIT OF TUBULIN WITH PACLITAXEL (IN RED TRIANGLE) ATTACHED TO INNER FACE OF BETA SUBUNIT. (B) A TUBULIN HETERODIMER SHOWING ALPHA AND BETA SUBUNIT. (C) A SECTIONAL VIEW OF MICROTUBULE SHOWING THE ATTACHMENT PATTERN PACLITAXEL ALONG THE WALL OF INNER LUMEN. (D) MOLECULAR STRUCTURE OF PACLITAXEL

(b) Apoptotic Action: Apoptotic action is quite diverse and includes the interaction of taxanes with various proteins and enzymes which are involved in the cell cycle, apoptosis, and cell death. Increased reactive oxygen species (ROS) is one of the earliest events of apoptosis and is brought about by Paclitaxel [96]. Taxanes are also reported to initiate a decrease in mitochondrial membrane potential ($\Delta\Psi_m$). It is reported from a study that Paclitaxel induces the opening of mitochondrial membrane permeability pore resulting in release of calcium from mitochondria [97]. In addition to it, Paclitaxel also results in the release of cytochrome c from mitochondria [98]. Caspases are the family of endoproteases that play an important role in cell inflammation and cell death [99]. Taxanes also activate caspases, thus initiating cell death and apoptosis [100]. B-cell lymphoma (Bcl-2) is the key protein that regulates programmed cell death and apoptosis [101]. They may be divided into two major groups, namely (a) antiapoptotic protein (BCL-2, BCL-XL, MCL-1, BFL-1, BCL-W), and (b) proapoptotic proteins (BAK, BAX) [102]. During apoptosis or cell death, oligomerization of pro-apoptotic effector proteins on the outer wall of the mitochondrial membrane results in mitochondrial membrane leakage and release of cytochrome c [103]. The apoptosis in cancer cells is further induced by phosphorylation and inactivation of antiapoptotic Bcl-2 by Paclitaxel [104]. Along with Bcl-2, p53 also plays a major role in the apoptotic process. The TP53 is the most frequently mutated gene associated to human cancers, which result in the production of mutant p53 proteins with loss in tumour suppression properties and concomitant gain of new oncogenic properties along with deregulated cell proliferation increased chemoresistance and altered tissue architecture [105].

It is an important tumor suppressor gene that regulates downstream expression of other genes involved in DNA repair, cell cycle arrest, and apoptosis [106]. It is reported that Paclitaxel act as a p53 inducers, thereby enhancing the apoptotic process [107]. A universal cell cycle inhibitor controlled by p53 is p21 [108]. It is regarded as a universal cyclin-dependent kinase (CDK) inhibitor and physically interacts and inhibits cyclin-CDK2, cyclin-CDK1, cyclin-CDK4/6 complexes thus regulate progression of the cell cycle during G1 and S phases [109]. It is reported that Paclitaxel results in an increase of expression p21 through up-regulation of p53 [110]. **Fig. 7** illustrates the various mechanism of action of taxanes leading to cell cycle arrest, cell death, and apoptosis.

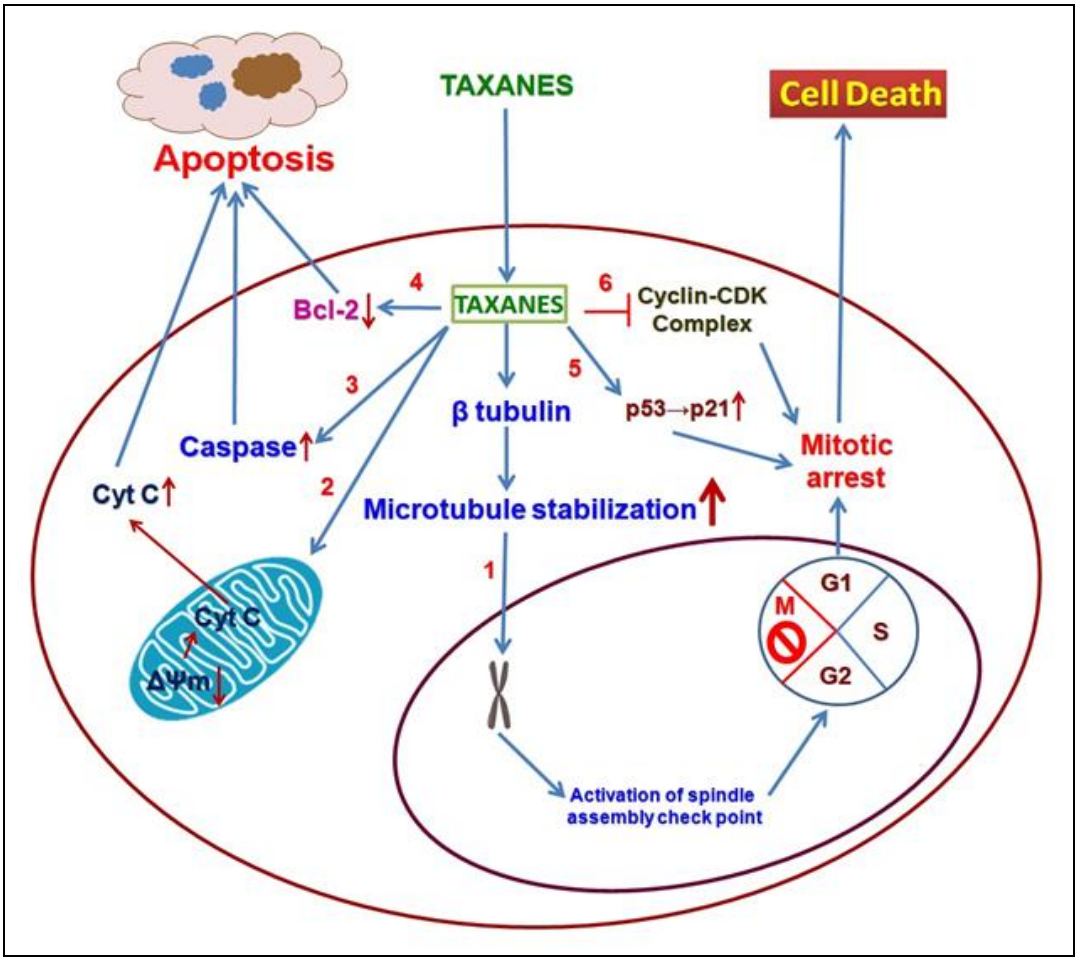

FIG. 7: SCHEMATIC REPRESENTATION OF MODE OF ACTION OF TAXANES ON A CANCER CELL. (1) TAXANES DIRECTLY INTERACT WITH MICROTUBULE RESULTING IN THEIR STABILIZATION AND INHIBITING DEPOLYMERIZATION. THIS ULTIMATELY RESULTS IN MITOTIC ARREST AND EVENTUALLY CELL DEATH. (2) TAXANES RESULTS IN DECREASE IN MITOCHONDRIAL MEMBRANE POTENTIAL ($\Delta\Psi_m$) RESULTING IN LEAKAGE OF CYTOCHROME C IN THE CYTOSOL WHICH PARTICIPATES IN APOPTOTIC PROCESS. UPREGULATION OF CASPASE (3) AND DOWN REGULATION OF ANTIAPOPTOTIC Bcl-2 (4) IS ALSO BROUGHT ABOUT BY TAXANES ALL OF WHICH ADDS UP TO THE APOPTOTIC PROCESS. TAXANES ALSO INDUCE THE EXPRESSION OF p53, p21 (5) AND INHIBITS CYCLIN CDK COMPLEXES (6) THUS INHIBITING THE CELL DIVISION

Metabolism of Taxanes: Taxanes are primarily metabolized in the liver and primarily eliminated through biliary excretion *via* faeces [111]. Taxanes are metabolized by hepatic cytochrome P450 (CYP450) enzyme systems [112]. The major metabolites of Paclitaxel are 3'-p-hydroxy-paclitaxel, and 6α-hydroxypaclitaxel which are produced by CYP3A4 and CYP2C8, respectively [113]. The oxidation of the tertiary butyl group on the synthetic side chain of docetaxel forms the main metabolic pathway in which CYP3A (3A4 and 3A5) family of cytochrome P450 enzymes plays the key role in the biotransformation [114]. Cabazitaxel is also metabolized in the liver by the same family of cytochrome P450 enzyme system [115]. Seven plasma metabolites of cabazitaxel are

detected [116]. Cabazitaxel is mainly excreted through faeces and a minor percentage through kidney [117].

Evolution in Formulation: Taxanes have been widely used as drugs for combating cancers. They act as potent mitosis inhibitors by interacting with the tubulin. The characteristic of the taxane skeleton is 10-baccatin III or 10-deacetyl baccatin III, which are bulky with poor aqueous solubility [118]. Thus excipients such as Cremophor EL and ethanol for Paclitaxel [119], polysorbate 80 (Tween 80) for docetaxel [120], polysorbate, ethanol and citric acid for Cabazitaxel [121] are used. Cremophor EL and polysorbate 80 have the capacity to entrap and solubilize taxane in water, forming micelles while citric acid acts as a pH stabilizing compound [122]. The adverse effects of these excipients, such as hypersensitivity, hemolysis, and cholestasis have also been reported [123]. Additionally, Paclitaxel forms the substrate of P-glycoprotein (P-gp), which actively pumps Paclitaxel out of the cells inducing drug resistance [124]. To overcome this problem, P-gp inhibitors such as verapamil and PSC833 were co-administered with taxanes, often resulting in toxicity and/or alteration in pharmacokinetics [125].

Nano based delivery systems act as a promising component in drug delivery as they improve the solubility of hydrophobic drugs and have reduced toxicity [126]. Abraxane ®, a paclitaxel albumin-bound nanoparticle formulations having particle size around 130nm, was approved in 2005 for treatment of metastatic breast cancer [127]. The formulations are advantageous as the solubility of hydrophobic taxanes are enhanced through encapsulation by albumin nanoparticles. Additionally, albumin-bound paclitaxel are also easier to infuse in higher doses than the standard doses of Paclitaxel with the higher response, lower toxicities, and less infusion time [128]. The reduced side effects of nanoparticles based Paclitaxel are largely due to the fact that they can escape the recognition of the reticuloendothelial system in the healthy tissues [129]. Nab-Paclitaxel is also a cremophor free water-soluble albumin-based Paclitaxel formulation and consists of 130 nm albumin-paclitaxel nano-particles. Treatment with nab-paclitaxel results in improved tolerability and higher response rates as compared to solvent-based formulations in patients with advanced metastatic breast cancer and non-small lung cancer [130]. Poly (lactic-co-glycolic acid) (PLGA) is a widely used biodegradable copolymer used for the development of paclitaxel delivery system [131]. They are homopolymers based on poly (lactic acid) (PLA) and poly (glycolic acid) PGA and has been approved by the US Food and Drug Administration (USFDA) for medical applications [132]. PLGA has very low toxicity because it undergoes hydrolysis into its monomers of glycolic acid and lactic acid, which in turn are endogenously metabolized by the human body through the Krebs cycle and finally eliminated as carbon dioxide and water [133]. Presently, PLGA nanoparticles are modified by Chitosan for sustained drug release and enhanced drug toxicity [134].

Liposomal formulations of taxanes have also been formulated, developed, and well described [135]. They are spherical lipid vesicles with a mean diameter of 100 nm and comprises of a hydrophobic phospholipid bilayer with or without cholesterol having an aqueous core [136]. Liposomal drugs have a low immunogenicity, limited toxicity, ability to carry larger molecules to the target site and capacity to accumulate in target tissue with enhanced bio-distribution [137]. Thus, the bulky hydrophobic paclitaxel molecule could be entrapped in liposomal phospholipid bilayer, and it's positioning representing a more metastable stage tending towards crystalline form [138]. LEP-LEU is a liposomal formulation, developed by NeoPharm Labs, consisting of Paclitaxel and is composed of dioleoylphosphatidylcholine (DOPC), cholesterol and cardiolipin in a molar ratio of 90:5:5 with final total lipid to drug molar ratio of 33:1 and achieving an 85% percent entrapment efficiency of Paclitaxel [139].

EndoTAG-1 is another formulation in which Paclitaxel is embedded in cationic liposomal membrane [140]. It is composed of cationic lipid dioleoyloxypropyltrimethylammonium (DOTAP), neutral lipid DOPC, Paclitaxel in molar ratio 50:47:3 and is the first formulation of cationic carrying paclitaxel to be used in clinical trial [141]. 1, 2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and cholesterol is also used as a constituent of liposome for delivery of paclitaxel [142]. In addition to it, dipalmitoylphosphatidylcholine (DPPC), and distearoyl phosphatidylcholine (DSPC) are also used for liposome assembly [143]. Stealth technology

is also used for the delivery of taxane molecules. In This technology, flexible hydrophilic polymers such as polyethylene glycol (PEG) is used as a protective hydrophilic layer on the surface of the liposomes and results in a reduction of clearance from the reticuloendothelial system [144]. Such stealth liposomes have a prolonged circulation time [145] and improved pharmacokinetic profile in comparison to the normal drug [146]. The attachment of hydrophilic polymers chains on the liposomes can be either through physical adsorption or covalent bonding using lipid molecules chemically functionalized at the head group, such as dipalmitoyl-Sn-glycero-3-phosphoethanolamine-N-[mPEG-5000] (DPPE-PEG) [147]. The stealth technology also enables the liposome to get undetected by mononuclear phagocyte system [148].

PEGylated liposomes have some side effects, including hand-foot syndrome, fatigue [149,] and skin toxicity [150]. Thus non-PEGylated liposomes were developed to avoid the side effects and, at the same time delivering the same benefits of PEGylated liposomes. Non-PEGylated Doxorubicin is now widely used for the delivery of Paclitaxel in the treatment of breast cancers [151].

CONCLUSION: It seems to be quite evident that the taxanes are constantly in upgradation mode both in terms of mechanistic aspects and clinical aspects. The avenues of up-gradation and improvisation of taxanes are wide open for further studies. Moreover, combination treatments (taxanes along with some other drugs) also require to be stressed upon to improve the efficacy and anticancer activity. This further opens the way for the exploration of new drugs from nature and natural resources plants being the only resort in this case.

From a botanical point of view, cultivation of *Taxus* sp requires more attention, and biotechnological approaches for mass production of taxanes through tissue culture techniques needs a primary focus. Treatment of cancer would be more accomplished if the affordability of the drugs is taken into consideration by the pharmaceutical industry and governmental policy. Reducing the prices of the drugs will not only make it more accessible to the people but also at the same time will play a distinct role as a popular anticancer medicine amongst the wide array of drugs. Thus, cost calculation of treatment should also form an important parameter along with drug development for the overall benefit of mankind, specifically with respect to the population of third world countries where the occurrence of cancers is going to an alarming level mainly triggered by pollution and haphazard lifestyle. Thus, taxanes form a group of a versatile compound that has acquired a place in the pharmaceutical world for the treatment of a wide array of cancer. However, opportunities for its further development both in terms of pharmacology and cost efficiency remain wide open for over benefit of patients and mankind.

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REFERENCES:

1. Khanna C, Rosenberg M and Vail DM: A review of paclitaxel and novel formulations including those suitable for use in dogs. Journal of Veterinary Internal Medicine 2015; 29(4): 1006-12.
2. Yang CH and Horwitz SB: Taxol®: The First Microtubule Stabilizing Agent. International Journal of Molecular Sciences 2017; 18(8): 1733.
3. Kampan NC, Madondo MT, McNally OM, Quinn M and Plebanski M: Paclitaxel and Its Evolving Role in the Management of Ovarian Cancer. BioMed Research International 2015; 2015: 413076.
4. Wall ME and Wani MC: Camptothecin and taxol: discovery to clinic-thirteenth Bruce F. Cain Memorial Award Lecture. Cancer Research 1995; 55(4): 753-60.
5. Walsh V and Goodman J: From taxol to taxol: the changing identities and ownership of an anti-cancer drug. Medical Anthropology 2002; 21(3-4): 307-36.
6. Wani MC, Taylor HL, Wall ME, Coggon P and McPhail AT: Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. Journal of American Chemical Society 1971; 93(9): 2325-27.
7. Fuchs DA and Johnson RK: Cytologic evidence that taxol, an antineoplastic agent from *Taxus brevifolia*, acts as a mitotic spindle poison. Cancer Treatment Reports 1978; 62(8): 1219-22.
8. Schiff PB, Fant J and Horwitz SB: Promotion of microtubule assembly *in-vitro* by taxol. Nature 1979; 277(5698): 665-67.
9. Horwitz SB, Lothstein L, Manfredi JJ, Mellado W, Parness J, Roy SN, Schiff PB, Sorbara L and Zeheb R: Taxol: mechanisms of action and resistance. Annals of New York Academy of Sciences 1986; 466: 733-44.

10. Manfredi JJ and Horwitz SB: Taxol: an antimitotic agent with a new mechanism of action. Pharmacology & Therapeutics 1984; 25(1): 83-125.
11. Mellado W, Magri NF, Kingston DG, Garcia-Arenas R, Orr GA and Horwitz SB: Preparation and biological activity of taxol acetates. Biochemical and Biophysical Research Communication 1984; 124(2): 329-36.
12. Kingston DG: The shape of things to come: structural and synthetic studies of taxol and related compounds. Phytochemistry 2007; 68(14): 1844-54.
13. Wiernik PH, Schwartz EL, Strauman JJ, Dutcher JP, Lipton RB and Paietta E: Phase I clinical and pharmaco-kinetic study of taxol. Cancer Res 1987; 47(9): 2486-93.
14. McGuire WP, Rowinsky EK, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK and Donehower RC: Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Annals of Internal Medicine 1989; 111(4): 273-79.
15. Holmes FA, Walters RS, Theriault RL, Forman AD, Newton LK, Raber MN, Buzdar AU, Frye DK and Hortobagyi GN: Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. Journal of the National Cancer Institute 1991; 83(24): 1797-05.
16. Campbell SJ and SA Whitney: The pacific yew environmental impact statement. In Georg GI, Chen TT, Ojima I, Vyas DM editors. Taxane Anticancer Agents: basic science and current status. ACS Symposium Series 583, Washington D.C.; 1994: 58-71.
17. Zhang D, Yang R, Wang S and Dong Z: Paclitaxel: new uses for an old drug. Drug Design Development and Therapy 2014; 8: 279-84.
18. Croteau R, Ketchum RE, Long RM, Kaspera R and Wildung MR: Taxol biosynthesis and molecular genetics. Phytochemistry Reviews 2006; 5(1): 75-97.
19. Gelderblom H, Verweij J, Nooter K and Sparreboom A: Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. European Journal of Cancer 2001; 37(13): 1590-98.
20. Shin YS, Min KJ, Choi SY and Lee NW: Non-convulsive seizure related to Cremophor EL™-free, polymeric micelle formulation of paclitaxel: a case report. Obstetrics & Gynecology Science 2018; 61(3): 421-24.
21. Hart M and Acott S: Physical and chemical stability of Taxotere (docetaxel) one-vial (20 mg/ml) infusion solution following refrigerated storage. Ecancer Medical Science 2010; 4: 202.
22. Yared JA and Tkaczuk KH: Update on taxane development: new analogs and new formulations. Drug Design,Development and Therapy 2012; 6: 371-84.
23. Paller CJ and Antonarakis ES: Cabazitaxel: a novel second-line treatment for metastatic castration-resistant prostate cancer. Drug Des Dev and Ther 2011; 5: 117-24.
24. Nightingale G and Ryu J. Cabazitaxel (jevtana): a novel agent for metastatic castration-resistant prostate cancer. Pharmacy & Therapeutics 2012; 37(8): 440-48.
25. Abidi A: Cabazitaxel: A novel taxane for metastatic castration-resistant prostate cancer-current implications and future prospects. Journal of Pharmacology and Pharmacotherapeutics 2013; 4(4): 230-37.
26. Yassine F, Salibi E and Gali-Muhtasib H: Overview of the Formulations and Analogs in the Taxanes' Story. Current Medicinal Chemistry 2016; 23(40): 4540-58.
27. Kurono M, Nakadaira Y, Onuma S,Sasaki K and Nakanlsh K: Taxinine. Tetrahedron Letters 1963; 2153-60.
28. Ueda K, Uyeo S and Yamamoto Y: The structure of Taxinine, a nitrogen free compound occurring in *Taxus caspidata*. Tetrahedron letters 1963; 2167-71.
29. Hao J, Guo H, Shi X, Wang Y, Wan Q, Song YB, Zhang L, Dong M and Shen C: Comparative proteomic analyses of two Taxus species (*Taxus media* and *Taxus mairei*) reveals variations in the metabolisms associated with paclitaxel and other metabolites. Plant and Cell Physiology 2017; 58(11): 1878-90.
30. Isah T: Natural sources of Taxol. British Journal of Pharmaceutical Research 2015; 6(4): 214-27.
31. Li BJ, Wang H, Gong T, Chen JJ, Chen TJ, Yang JL and Zhu P: Improving 10-deacetylbaccatin III-10-β-O-acetyltransferase catalytic fitness for Taxol production. Nature Communications 2017; 8: 15544.
32. Lin SL, Wei T, Lin JF, Guo LQ, Wu GP, Wei JB, Huang JJ and Ouyang PL: Bio-production of Baccatin III, an Important Precursor of Paclitaxel by a cost-effective approach. Molecular Biotechnology 2018; 60(7): 492-05.
33. Wheeler NC, Jech K, Masters S, Brobst SW, Alvarado AB, Hoover AJ and Snader KM: Effects of genetic, epigenetic, and environmental factors on taxol content in *Taxus brevifolia* and related species. Journal of Natural Products 1992; 55(4): 432-40.
34. Németh-Kiss V, Forgács E, Cserháti T and Schmidt G: Taxol content of various *Taxus* species in Hungary. Journal of Pharmaceutical and Biomedical Analysis 1996; 14(8-10): 997-01.
35. Griffin J and Hook I: Taxol content of Irish yews. Planta Medica 1996; 62(4): 370-72.
36. Chattopadhyay SK, Saha GC, Kulshrestha M, Tripathi V, Sharma RP and Mehta VK: The taxoid constituents of the roots of *Taxus wallichiana*. Planta Medica 1998; 64: 287-88.
37. Vance NC, Kelsey RG and Sabin TE: Seasonal and tissue variation in taxane concentrations of *Taxus brevifolia*. Phytochemistry 1994; 36(5): 1241-44.
38. Choi MS, Kwak SS, Liu JR, Park YG, Lee MK and An NH: Taxol and related compounds in Korean native yews (*Taxus cuspidata*). Planta Medica 1995; 61(3): 264-66.
39. Kwak SS, Choi MS, Park YG, Yoo JS and Liu JR: Taxol content in the seeds of *Taxus sp*. Phytochemistry1995; 40(1): 29-32.
40. Vaishampayan U, Parchment RE, Jasti BR and Hussain M: Taxanes: an overview of the pharmacokinetics and pharmacodynamics. Urology 1999; 54(6A Suppl): 22-29.
41. Azarenko O, Smiyun G, Mah J, Wilson L and Jordan MA: Antiproliferative mechanism of action of the novel taxane cabazitaxel as compared with the parent compound docetaxel in MCF7 breast cancer cells. Molecular Cancer Therapeutics 2014; 13(8): 2092-03.
42. Rawla P, Sunkara T, Muralidharan P and Raj JP: Update in global trends and aetiology of hepatocellular carcinoma. Contemporary Oncology (Pozn) 2018; 22(3): 141-50.
43. Aggarwal M, Arain A and Jin Z: Systemic treatment for hepatocellular carcinoma. Chronic Disease and Translational Medicine 2018; 4(3): 148-55.
44. Sayiner M, Golabi P and Younossi ZM: Disease burden of hepatocellular carcinoma: A global perspective. Digestive Diseases and Sciences 2019; 64(4): 910-17.
45. Harshita, Barkat MA, Rizwanullah M, Beg S, Pottoo FH, Siddiqui S and Ahmad FJ: Paclitaxel-loaded nanolipidic carriers with improved oral bioavailability and anticancer activity against human liver carcinoma. AAPS Pharm Sci Tech 2019; 20(2): 87.
46. Wan J, Ma X, Xu D, Yang B, Yang S and Han S: Docetaxel-decorated anticancer drug and gold nanoparticles encapsulated apatite carrier for the treatment of liver cancer. Journal of Photochemistry and Photobiology B 2018; 185: 73-79.

47. Chang CC, Yang Y, Gao DY, Cheng HT, Hoang B, Chao PH, Chen LH, Bteich J, Chiang T, Liu JY, Li SD and Chen Y: Docetaxel-carboxymethyl cellulose nanoparticles ameliorate CCl_4-induced hepatic fibrosis in mice. Journal of Drug Targetting 2018; 26(5-6): 516-24.
48. Chen R, Cheng Q, Owusu-Ansah KG, Chen J, Song G, Xie H, Zhou L, Xu X, Jiang D and Zheng S: Cabazitaxel, a novel chemotherapeutic alternative for drug-resistant hepatocellular carcinoma. American Journal of Cancer Research 2018; 8(7): 1297-06.
49. Wong MCS, Lao XQ, Ho KF, Goggins WB and Tse SLA: Incidence and mortality of lung cancer: global trends and association with socioeconomic status. Scientific Reports 2017; 7(1): 14300.
50. Didkowska J, Wojciechowska U, Mańczuk M and Łobaszewski J: Lung cancer epidemiology: contemporary and future challenges worldwide. Annals of Translational Medicine 2016; 4(8): 150.
51. de Groot PM, Wu CC, Carter BW and Munden RF: The epidemiology of lung cancer. Translational Lung Cancer Research 2018; 7(3): 220-33.
52. Jin M, Jin G, Kang L, Chen L, Gao Z and Huang W: Smart polymeric nanoparticles with pH-responsive and PEG-detachable properties for co-delivering paclitaxel and survivin siRNA to enhance antitumor outcomes. International Journal of Nanomedicine 2018; 13: 2405-26.
53. Min J, Shen H, Xi W, Wang Q, Yin L, Zhang Y, Yu Y, Yang Q and Wang ZN: Synergistic anticancer activity of combined use of caffeic acid with paclitaxel enhances apoptosis of non-small-cell lung cancer h1299 cells *in-vivo* and *in-vitro*. Cellular Physiology and Biochemistry 2018; 48(4): 1433-42.
54. Hou J, Sun E, Zhang ZH, Wang J, Yang L, Cui L, Ke ZC, Tan XB, Jia XB and Lv H: Improved oral absorption and anti-lung cancer activity of paclitaxel-loaded mixed micelles. Drug Delivery 2017; 24(1): 261-69.
55. Patel K, Doddapaneni R, Chowdhury N, Boakye CH, Behl G and Singh M: Tumor stromal disrupting agent enhances the anticancer efficacy of docetaxel loaded PEGylated liposomes in lung cancer. Nanomedicine (Lond) 2016; 11(11): 1377-92.
56. Rawla: Epidemiology of Prostate Cancer. World Journal of Oncology 2019; 10(2): 63-89.
57. Taitt HE: Global trends and prostate cancer: a review of incidence, detection, and mortality as influenced by race, ethnicity, and geographic location. American Journal of Mens Health 2018; 12(6): 1807-23.
58. Peisch SF, Van Blarigan EL, Chan JM, Stampfer MJ and Kenfield SA: Prostate cancer progression and mortality: a review of diet and lifestyle factors. World Journal of Urology 2017; 35(6): 867-74.
59. Rabzia A, Khazaei M, Rashidi Z and Khazaei MR: Synergistic anticancer effect of paclitaxel and noscapine on human prostate cancer cell lines. Iran Journal of Pharmaceutical Research 2017; 16(4): 1432-42.
60. Bass R, Roberto D, Wang DZ, Cantu FP, Mohamadi RM, Kelley SO, Klotz L and Venkateswaran V: Combining desmopressin and docetaxel for the treatment of castration-resistant prostate cancer in an orthotopic model. Anticancer Research 2019; 39(1): 113-18.
61. Jiang S, Zhang K, He Y, Xu X, Li D, Cheng S and Zheng X: Synergistic effects and mechanisms of impressic acid or acankoreanogein in combination with docetaxel on prostate cancer. RSC Advances 2018; 8: 2768-76.
62. Gallego-Yerga L, Posadas I, de la Torre C, Ruiz-Almansa J, Sansone F, Ortiz Mellet C, Casnati A, García Fernández JM and Ceña V: Docetaxel-Loaded Nanoparticles assembled from β-Cyclodextrin/Calixarene giant surfactants: physicochemical properties and cytotoxic effect in prostate cancer and glioblastoma cells. Frontiers in Pharmacology 2017; 8: 249.
63. Rottach AM, Ahrend H, Martin B, Walther R, Zimmermann U, Burchardt M and Stope MB: Cabazitaxel inhibits prostate cancer cell growth by inhibition of androgen receptor and heat shock protein expression. World J Urol 2019. doi: 10.1007/s00345-018-2615-x.
64. Mahira S, Kommineni N, Husain GM and Khan W: Cabazitaxel and silibinin co-encapsulated cationic liposomes for CD44 targeted delivery: A new insight into nanomedicine based combinational chemotherapy for prostate cancer. Biomedicine & Pharmacotherapy 2019; 110: 803-17.
65. Gdowski AS, Ranjan A, Sarker MR and Vishwanatha JK: Bone-targeted cabazitaxel nanoparticles for metastatic prostate cancer skeletal lesions and pain. Nanomedicine (Lond) 2017; 12(17): 2083-95.
66. Rawla P, Sunkara T and Gaduputi V: Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World Journal of Oncology 2019; 10(1):10-27.
67. Saad AM, Turk T, Al-Husseini MJ and Abdel-Rahman O: Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. BMC Cancer 2018; 18(1): 688.
68. Gordon-Dseagu VL, Devesa SS, Goggins M and Stolzenberg-Solomon R: Pancreatic cancer incidence trends: evidence from the Surveillance, Epidemiology and End Results (SEER) population-based data. International Journal of Epidemiology 2018; 47(2): 427-39.
69. Park J, Park SS, Lee KJ, Ju JE, Shin SH, Ko EJ, Lee Saa-Won, Seo MH, Lee JS, Song SY, Jeong SY and Choi EK: Docetaxel-polymeric nanoparticle enhances radio-therapeutic efficacy in human pancreatic cancer. Translational Cancer Research 2018; 7(1): 60-67.
70. Kinoshita R, Ishima Y, Chuang VTG, Nakamura H, Fang J, Watanabe H, Shimizu T, Okuhira K, Ishida T, Maeda H, Otagiri M and Maruyama T: Improved anticancer effects of albumin-bound paclitaxel nanoparticle *via* augmentation of EPR effect and albumin-protein interactions using S-nitrosated human serum albumin dimer. Biomaterials 2017; 140: 162-69.
71. Rivera-Franco MM and Leon-Rodriguez E: Delays in breast cancer detection and treatment in developing countries. Breast Cancer (Auckl) 2018; 12: 1178223417752677.
72. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, Ji X, Liu W, Huang B, Luo W, Liu B, Lei Y, Du S, Vuppalapati A, Luu HH, Haydon RC, He TC and Ren G: Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes and Diseases 2018; 5(2): 77-106.
73. Kamińska M, Ciszewski T, Łopacka-Szatan K, Miotła P and Starosławska E: Breast cancer risk factors. Prz Menopauzalny 2015; 14(3): 196-02.
74. Foglietta F, Spagnoli GC, Muraro MG, Ballestri M, Guerrini A, Ferroni C, Aluigi A, Sotgiu G and Varchi G: Anticancer activity of paclitaxel-loaded keratin nanoparticles in two-dimensional and perfused three-dimensional breast cancer models. International Journal Nanomedicine 2018; 13: 4847-67.
75. Choi KH, Jeon JY, Lee YE, Kim SW, Kim SY, Yun YJ and Park KC: Synergistic activity of paclitaxel, sorafenib, and radiation therapy in advanced renal cell carcinoma and

breast cancer. Translational Oncology 2019; 12(2): 381-88.
76. Zhang Y, Ge Y, Ping X, Yu M, Lou D and Shi W: Synergistic apoptotic effects of silibinin in enhancing paclitaxel toxicity in human gastric cancer cell lines. Molecular Medicine Reports 2018; 18(2): 1835-41.
77. Venugopal V, Krishnan S, Palanimuthu VR, Sankarankutty S, Kalaimani JK, Karupiah S, Kit NS and Hock TT: Anti-EGFR anchored paclitaxel loaded PLGA nanoparticles for the treatment of triple negative breast cancer. *In-vitro* and *in-vivo* anticancer activities. PLoS One 2018; 13(11): e0206109.
78. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Hegg R, Im SA, Wright GS, Henschel V, Molinero L, Chui SY, Funke R, Husain A, Winer EP, Loi S and Emens LA: Impassion 130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine 2018; 379(22): 2108-21.
79. Dong S, Guo Y, Duan Y, Li Z, Wang C, Niu L, Wang N, Ma M, Shi Y and Zhang M: Co-delivery of paclitaxel and gemcitabine by methoxy poly (ethylene glycol)-poly (lactide-coglycolide)-polypeptide nanoparticles for effective breast cancer therapy. Anti-Cancer Drugs 2018; 29(7): 637-45.
80. Sajjad M, Khan MI, Naveed S, Ijaz S, Qureshi OS, Raza SA, Shahnaz G and Sohail MF: Folate-functionalized thiomeric nanoparticles for enhanced docetaxel cytotoxicity and improved oral bioavailability. AAPS PharmSciTech 2019; 20(2): 81.
81. Tao J, Tan Z, Diao L, Ji Z, Zhu J, Chden W and Hu Y: Co-delivery of dihydroartemisinin and docetaxel in pH sensitive nanoparticles for treating metastatic breast cancer *via* the NF-κB/MMP-2 signal pathway. RSc Advances 2018; 8: 21735-44.
82. Doddapaneni R, Patel K, Chowdhury N and Singh M: Noscapine chemosensitization enhances docetaxel anticancer activity and nanocarrier uptake in triple negative breast cancer. Experimental Cell Research 2016; 346(1): 65-73.
83. Hendrikx JJMA, Lagas JS, Song JY, Rosing H, Schellens JHM, Beijnen JH, Rottenberg S and Schinkel AH: Ritonavir inhibits intratumoral docetaxel metabolism and enhances docetaxel antitumor activity in an immunocompetent mouse breast cancer model. International Journal of Cancer 2016; 138: 758-69.
84. Liu CY, Chen KF, Chao TI, Chu PY, Huang CT, Huang TT, Yang HP, Wang WL, Lee CH, Lau KY, Tsai WC, Su JC, Wu CY, Chen MH, Shiau CW and Tseng LM: Sequential combination of docetaxel with a SHP-1 agonist enhanced suppression of p-STAT3 signaling and apoptosis in triple negative breast cancer cells. Journal of Molecular Medicine (Berl) 2017; 95(9): 965-75.
85. Fard AE, Tavakoli MB, Salehi H and Emami H: Synergetic effects of Docetaxel and ionizing radiation reduced cell viability on MCF-7 breast cancer cell. Applied Cancer Research 2017; 37: 29.
86. Fusser M, Øverbye A, Pandya AD, Mørch Ý, Borgos SE, Kildal W, Snipstad S, Sulheim E, Fleten KG, Askautrud HA, Engebraaten O, Flatmark K, Iversen TG, Sandvig K, Skotland T and Mælandsmo GM: Cabazitaxel-loaded Poly (2-ethylbutyl cyanoacrylate) nanoparticles improve treatment efficacy in a patient derived breast cancer xenograft. Journal of Controlled Release 2019; 293: 183-92.
87. Kommineni N, Saka R, Bulbake U and Khan W: Cabazitaxel and thymoquinone co-loaded lipospheres as a synergistic combination for breast cancer. Chemistry and Physics of Lipids 2018; pii: S0009-3084.
88. Zhu CJ and An CG: Enhanced antitumor activity of cabazitaxel targeting CD44+ receptor in breast cancer cell line via surface functionalized lipid nanocarriers. Tropical Journal of Pharmaceutical Research 2017; 16(6): 1383-90.
89. Zhong T, He B, Cao HQ, Tan T, Hu HY, Li YP and Zhang ZW: Treating breast cancer metastasis with cabazitaxel-loaded polymeric micelles. Acta Pharmacologica Sinca 2017; 38(6): 924-930.
90. Zwawiak J and Zaprutko L: A brief history of taxol. Journal of Medical Sciences 2014; 1(83): 47-52.
91. Weaver BA: How Taxol/paclitaxel kills cancer cells. Molecular Biology of the Cell 2014; 25(18): 2677-81.
92. Priyadarshini K and Aparajita UK: Paclitaxel Against Cancer: A Short Review. Medicinal Chemistry 2012; 2: 139-41.
93. Kellogg EH, Hejab NMA, Howes S, Northcote P, Miller JH, Fernando Diaz J, Downing KH and Nogales E: Insights into the distinct mechanisms of action of taxane and non-taxane microtubule stabilizers from cryo-EM structures. Journal of Molecular Biology 2017; 429(5): 633-46.
94. Mukhtar E, Adhami VM and Mukhtar H: Targeting microtubules by natural agents for cancer therapy. Molecular Cancer Therapeutics 2014; 13(2): 275-84.
95. Yanamadala G, Praveen srikumar P, Rushyendra GV, Gupta VRM and Srinivasarao S: Development and validation of a novel RP-HPLC method for the determination of cabazitaxel in bulk and formulations. Indo American Journal of Pharmaceutical Research 2013; 3(10): 8266-72.
96. Bidkar AP, Sanpui P and Ghosh SS: Efficient induction of apoptosis in cancer cells by paclitaxel-loaded selenium nanoparticles. Nanomedicine (Lond) 2017; 12(21): 2641-51.
97. Brewer JR, Morrison G, Dolan ME and Fleming GF: Chemotherapy-induced peripheral neuropathy: Current status and progress. Gynecologic Oncology 2016; 140(1): 176-83.
98. Sun J, Jiang L, Lin Y, Gerhard EM, Jiang X, Li L, Yang J and Gu Z: Enhanced anticancer efficacy of paclitaxel through multistage tumor-targeting liposomes modified with RGD and KLA peptides. International Journal of Nanomedicine 2017; 12: 1517-37.
99. McIlwain DR, Berger T and Mak TW: Caspase functions in cell death and disease. Cold Spring Harbor Perspectives in Biology 2013; 5(4): a008656.
100. Jelínek M, Balušíková K, Schmiedlová M, Němcová-Fürstová V, Šrámek J, Stančíková J, Zanardi I, Ojima I and Kovář J: The role of individual caspases in cell death induction by taxanes in breast cancer cells. Cancer Cell International 2015; 15(1): 8.
101. Yao Y and Marassi FM: Reconstitution and characterization of BCL-2 family proteins in lipid bilayer nanodiscs. Methods in Molecular Biology 2019; 1877: 233-46.
102. Tessoulin B, Papin A, Gomez-Bougie P, Bellanger C, Amiot M, Pellat-Deceunynck C, Chiron D: Bcl2-family dysregulation in b-cell malignancies: from gene expression regulation to a targeted therapy biomarker. Frontiers in Oncology 2019; 8: 645.
103. Opferman JT and Kothari A: Anti-apoptotic BCL-2 family members in development. Cell Death & Differentiation 2018; 25(1): 37-45.
104. Correia C, Lee SH, Meng XW, Vincelette ND, Knorr KL, Ding H, Nowakowski GS, Dai H and Kaufmann SH:

Emerging understanding of Bcl-2 biology: Implications for neoplastic progression and treatment. Biochimica et Biophysica Acta 2015; 1853(7): 1658-71.
105. Blandino G and Di Agostino S: New therapeutic strategies to treat human cancers expressing mutant p53 proteins. Journal of Experimental & Clinical Cancer Research 2018; 37(1): 30.
106. Hientz K, Mohr A, Bhakta-Guha D and Efferth T: The role of p53 in cancer drug resistance and targeted chemotherapy. Oncotarget 2016; 8(5): 8921-46.
107. Simabuco FM, Morale MG, Pavan ICB, Morelli AP, Silva FR and Tamura RE: p53 and metabolism: from mechanism to therapeutics. Oncotarget 2018; 9(34): 23780-823.
108. El-Deiry WS. p21 (WAF1) Mediates Cell-Cycle Inhibition, Relevant to Cancer Suppression and Therapy. Cancer Research 2016: 76(18): 5189-91.
109. Georgakilas AG, Martin OA and Bonner WM. p21: A two-faced genome guardian. Trends in Molecular Medicine 2017; 23(4): 310-19.
110. Lv C, Qu H, Zhu W, Xu K, Xu A, Jia B, Qing Y, Li H, Wei HJ and Zhao HY: Low-dose paclitaxel inhibits tumor cell growth by regulating glutaminolysis in colorectal carcinoma cells. Frontiers in Pharmacology 2017; 8: 244.
111. Oshiro C, Marsh S, McLeod H, Carrillo MW, Klein T and Altman R: Taxane pathway. Pharmacogenetics and Genomics 2009; 19(12): 979-83.
112. Paolini M, Poul L, Berjaud C, Germain M, Darmon A, Bergère M, Pottier A, Levy L and Vibert E: Nano-sized cytochrome P450 3A4 inhibitors to block hepatic metabolism of docetaxel. International Journal of Nanomedicine 2017; 12: 5537-56.
113. Cardonick E, Broadrup R, Xu P, Doan MT, Jiang H and Snyder NW: Preliminary results of identification and quantification of paclitaxel and its metabolites in human meconium from newborns with gestational chemotherapeutic exposure. PLoS One 2019; 14(2): e0211821.
114. Czejka M, Greil R, Ulsperger E, Schnait H, Kienesberger K, Brumnik T, Farkouh A and Schierholz J: Evidence for the conversion of docetaxel into 7-epidocetaxel in patients receiving conventional Taxotere® based chemotherapy. Journal of Analytical Oncology 2014; 3: 37-78.
115. Tsao CK, Cutting E, Martin J and Oh WK: The role of cabazitaxel in the treatment of metastatic castration-resistant prostate cancer. Therapeutic Advances in Urology 2014; 6(3): 97-104.
116. Ferron GM, Dai Y and Semiond D: Population pharmacokinetics of cabazitaxel in patients with advanced solid tumors. Cancer Chemotherapy and Pharmacology 2013; 71(3): 681-92.
117. Malalagama GN, Chryssidis S and Parnis FX: CT findings in patients with Cabazitaxel induced pelvic pain and haematuria: a case series. Cancer Imaging 2017; 17(1): 17.
118. Narvekar M, Xue HY, Eoh JY and Wong HL: Nanocarrier for poorly water-soluble anticancer drugs--barriers of translation and solutions. AAPS Pharm Sci Tech 2014; 15(4): 822-33.
119. Huang ST, Wang YP, Chen YH, Lin CT, Li WS and Wu HC: Liposomal paclitaxel induces fewer hematopoietic and cardiovascular complications than bioequivalent doses of Taxol. International Journal of Oncology 2018; 53(3): 1105-17.
120. Schwartzberg LS and Navari RM: Safety of Polysorbate 80 in the Oncology Setting. Advances in Therapy 2018; 35(6): 754-67.
121. Lê L, Berge M, Tfayli A, Prognon P and Caudron E: Discriminative and Quantitative Analysis of Antineoplastic Taxane Drugs Using a Handheld Raman Spectrometer. BioMed Research International 2018; 8746729.
122. Ojima I, Lichtenthal B, Lee S, Wang C and Wang X: Taxane anticancer agents: a patent perspective. Expert Opinion in Therapeutic Patents 2016; 26(1): 1-20.
123. Feng L and Mumper RJ: A critical review of lipid-based nanoparticles for taxane delivery. Cancer Letters 2013; 334(2): 157-75.
124. Nanayakkara AK, Follit CA, Chen G, Williams NS, Vogel PD and Wise JG: Targeted inhibitors of P-glycoprotein increase chemotherapeutic-induced mortality of multidrug resistant tumor cells. Science Reports 2018; 8(1): 967.
125. Amin ML: P-glycoprotein Inhibition for Optimal Drug Delivery. Drug Target Insights 2013; 7: 27-34.
126. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-TorresLS, Diaz-Torres LA, Grillo R, Swamy MK, Sharma S, Habtemariam S and Shin HS: Nano based drug delivery systems: recent developments and future prospects. Journal of Nanobiotechnology 2018; 16(1): 71.
127. Ventola CL: Progress in nanomedicine: approved and investigational nanodrugs. Physical Therapy 2017; 42(12): 742-55.
128. Ajabnoor GMA: Classical taxane versus the new generation, nab-paclitaxel chemotherapy in the treatment of breast cancer. MOJ Cell Science & Report 2017; 4(3): 66-71.
129. Ma P and Mumper RJ: Paclitaxel nano-delivery systems: a comprehensive review. Journal of Nanomedicine & Nanotechnology 2013; 4(2): 1000164.
130. Rajeshkumar NV, Yabuuchi S, Pai SG, Tong Z, Hou S, Bateman S, Pierce DW, Heise C, Von Hoff DD, Maitra A and Hidalgo M: Superior therapeutic efficacy of nab-paclitaxel over cremophor-based paclitaxel in locally advanced and metastatic models of human pancreatic cancer. British Journal of Cancer 2016; 115(4): 442-53.
131. Cho H, Gao J and Kwon GS: PEG-b-PLA micelles and PLGA-b-PEG-b-PLGA sol-gels for drug delivery. Journal of Controlled Release 2015; 240: 191-01.
132. Rezvantalab S, Drude NI, Moraveji MK, Güvener N, Koons EK, Shi Y, Lammers T and Kiessling F: PLGA-Based Nanoparticles in Cancer Treatment. Frontiers in Pharmacology 2018; 9: 1260.
133. Gossmann R, Langer K and Mulac D: New Perspective in the Formulation and Characterization of Didodecyl-dimethylammonium Bromide (DMAB) Stabilized Poly (Lactic-co-Glycolic Acid) (PLGA) Nanoparticles. PLoS One 2015; 10(7): e0127532.
134. Lu B, Lv X and Le Y: Chitosan-Modified PLGA nanoparticles for control-released drug delivery. Polymers 2019; 11: 304.
135. Allen TM and Cullis PR: Liposomal drug delivery systems: from concept to clinical applications. Advanced Drug Delivery Reviews 2013; 65(1): 36-48.
136. Gilabert-Oriol R, Ryan GM, Leung AWY, Firmino NS, Bennewith KL and Bally MB: Liposomal formulations to modulate the tumour microenvironment and antitumour immune response. International Journal of Molecular Sciences 2018; 19(10). pii: E2922.
137. Lamichhane N, Udayakumar TS, D'Souza WD, Simone CB 2nd, Raghavan SR, Polf J and Mahmood J: Liposomes: clinical applications and potential for image-guided drug delivery. Molecules 2018; 23(2): pii: E288.
138. Koudelka S and Turánek J: Liposomal paclitaxel formulations. Journal of Controlled Release 2012; 163(3): 322-34.

139. Bulbake U, Doppalapudi S, Kommineni N and Khan W: Liposomal formulations in clinical use: An Updated Review. Pharmaceutics 2017; 9(2). pii: E12.
140. Hsueh CT, Selim JH, Tsai JY and Hsueh CT: Nanovectors for anti-cancer drug delivery in the treatment of advanced pancreatic adenocarcinoma. World Journal of Gastroenterology 2016; 22(31): 7080-90.
141. Chang HI and Yeh MK: Clinical development of liposome-based drugs: formulation, characterization and therapeutic efficacy. International Journal of Nano-medicine 2012; 7: 49-60.
142. Hong SS, Choi JY, Kim JO, Lee MK, Kim SH and Lim SJ: Development of paclitaxel-loaded liposomal nano-carrier stabilized by triglyceride incorporation. Inter-national Journal of Nanomedicine 2016; 11: 4465-77.
143. Olusanya TOB, Haj Ahmad RR, Ibegbu DM, Smith JR and Elkordy AA: Liposomal Drug Delivery Systems and Anticancer Drugs Molecules 2018; 23(4): 907.
144. Lamichhane N, Udayakumar TS, D'Souza WD, Simone CB 2nd, Raghavan SR, Polf J and Mahmood J: Liposomes: Clinical Applications and Potential for Image-Guided Drug Delivery. Molecule 2018; 23(2): pii: E288.
145. Zylberberg C and Matosevic S: Pharmaceutical liposomal drug delivery: a review of new delivery systems and a look at the regulatory landscape. Dr Del 2016; 23(9): 3319-29.
146. Ross C, Taylor M, Fullwood N and Allsop D: Liposome delivery systems for the treatment of Alzheimer's disease. International Journal of Nanomedicine 2018; 13: 8507-22.
147. Mineart KP, Venkataraman S, Yang YY, Hedrick JL and Prabhu VM: Fabrication and Characterization of Hybrid Stealth Liposomes. Macromolecules 2018; 51(8): 3184-92.
148. Samuelsson E, Shen H, Blanco E, Ferrari M and Wolfram J: Contribution of Kupffer cells to liposome accumulation in the liver. Colloids and Surfaces B: Biointerfaces 2017; 158: 356-62.
149. Savani M, Murugan P and Skubitz KM: Long-term cure of soft tissue sarcoma with pegylated-liposomal doxorubicin after doxorubicin and ifosfamide failure. Clinical Sarcoma Research 2019; 9: 1.
150. Kubicka-Wołkowska J, Kędzierska M, Lisik-Habib M and Potemski P: Skin toxicity ina patient with ovarian cancer treated with pegylated liposomal doxorubicin: A case report and review of the literature. Oncology Letters 2016; 12(6): 5332-34.
151. Uriarte-Pinto M, Escolano-Pueyo Á, Gimeno-Ballester V, Pascual-Martínez O, Abad-Sazatornil MR and Agustín-Ferrández MJ: Trastuzumab, non-pegylated Liposomal-encapsulated doxorubicin and paclitaxel in the neoadjuvant setting of HER-2 positive breast cancer. International Journal of Clinical Pharmacy 2016; 38(2): 446-53.

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