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Comparison of Reported Adverse Events for Two Plant-Derived Anti-Cancer Therapeutics: Paclitaxel and Docetaxel

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Abstract **-** The purpose of this research is to compare trends in reported adverse events for two plant-derived taxane drugs, paclitaxel versus docetaxel, and examine the types of adverse events associated with paclitaxel and docetaxel in clinical use. This research is novel, because it is the first to examine reported adverse events post-market for two anti-cancer therapeutics, paclitaxel and docetaxel, using a public regulatory database that contains reports from manufacturers, clinicians, and patients. The research reveals that the frequency of adverse events for paclitaxel has grown exponentially from 1991 to 2023. The number of adverse events reported for paclitaxel grew 14.6 times from the 530 reported adverse events in 1993 to the 8,294 reported adverse events in 2023. The reported adverse events from docetaxel sharply increased and peaked in 2018 as it grew 305%, from 3,697 reported adverse events in 2017 to 14,988 reported adverse events in 2018. Paclitaxel's most frequent reaction type is dyspnoea (shortness of breath) with 6,694 reported adverse events resulting in dyspnoea. The most frequent reaction type reported for docetaxel was alopecia (loss of hair), with 29,536 reported adverse events resulting in alopecia. Additionally, docetaxel is associated with psychological and hair-related adverse events, and it is significant to note that the most frequent reaction types reported for paclitaxel did not include either hair or psychological effects. It is also noteworthy that death is one of the top reported adverse events associated with paclitaxel, but not docetaxel. The results of this study are significant because they reveal that paclitaxel and docetaxel, despite being members of the same class of drugs, induce distinct adverse event types and patterns in patients. These findings may help physicians and patients select the best taxane drug, as well as anticipate and monitor potential side effects, especially life-threatening reactions.

Keywords**:** paclitaxel, docetaxel, taxane, cancer, plant-derived medicines

1. Introduction

Paclitaxel and docetaxel are both members of the taxane class of drugs, renowned for their significant antiproliferative effects on cells and their roles in treating various cancers. Paclitaxel originated from the bark of the tree Taxus brevifolia [1] and docetaxel originated from a compound that was found in the European yew tree Taxus baccata [2] through discovery of further taxanes. Paclitaxel works through stabilizing the microtubules in the cell, which help form the mitotic spindle during cell division; paclitaxel binds to the beta-tubulin subunit, which encourages microtubules to remain stable and intact, rather than breaking down as they normally would during cell division. This ultimately inhibits cell division and disrupts the equilibrium of microtubules, causing cell cycle arrest (a process where cells stop progressing through the stages of the cell cycle) to occur at the G2/Mitosis phase and cause apoptosis (cell death). Additionally, paclitaxel activates several signal transduction pathways that are associated with apoptosis. Through these pathways, paclitaxel affects regulatory proteins such as Bad and Bax, which promote apoptosis, and Bcl-2, which prevents apoptosis. When paclitaxel may be administered weekly and in low doses, it may result in resistance of cancer cells. Paclitaxel may potentially improve its effectiveness when administered every three weeks in treating cancers that have developed resistance to the drug [3]. Docetaxel also prevents the breaking down of microtubules, thus arresting cells in the G2/Mitosis phase and causing apoptosis through Bcl-2 phosphorylation (a process where phosphate groups are added to the Bcl-2 protein which affects the function of the protein). Compared to paclitaxel, docetaxel binds more strongly to tubulin and more effectively improves Bcl-2 phosphorylation [4]. Paclitaxel became the first drug in the taxane class to receive approval from the Food and Drug Administration (FDA) in 1992 to treat ovarian cancer. Later on, this drug was approved for the following uses: non-small cell lung carcinoma, bladder cancer, metastatic breast cancer, and AIDS-related Kaposi sarcoma. Docetaxel was first approved by the FDA in 1996 to

treat metastatic breast cancer and presently, this drug is used to treat head and neck cancer, gastric cancer, non-small cell lung cancer, prostate cancer, and ovarian cancer [5].

The cytotoxic activity of taxane drugs depends on the presence of a taxane ring and an ester side chain in the chemical structure. Paclitaxel and docetaxel have similar chemical structures (Fig. 1). However, paclitaxel contains a benzene ring connected to its amide group, whereas docetaxel contains a tertbutoxy group connected to its amide group. In addition, paclitaxel contains an ester group on its taxane ring, while docetaxel contains an alcohol group at the same position.

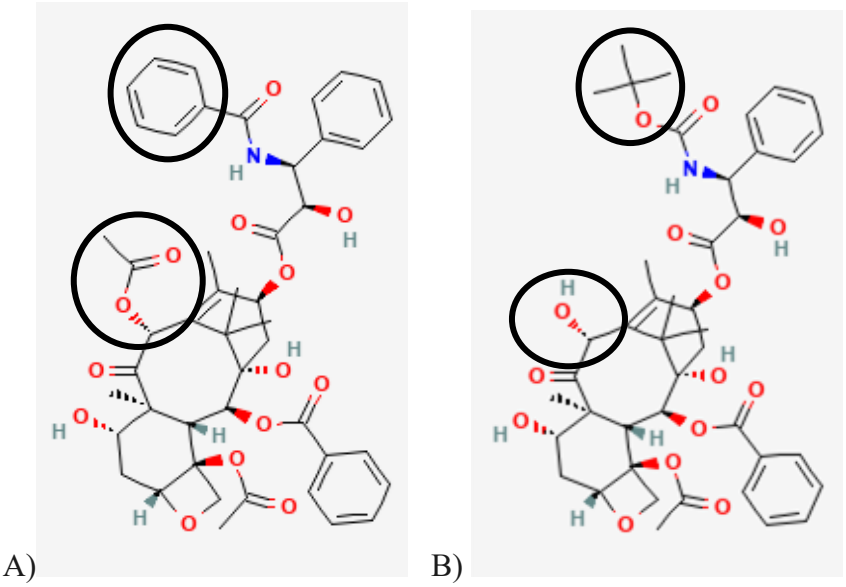

Fig. 1: Chemical structures of (A) paclitaxel and (B) docetaxel.

The taxane class of drugs has known side effects; these adverse effects are largely due to the antiproliferative action of the drugs. Taxanes are known to cause gastrointestinal bleeding. In addition, known side effects for the drug paclitaxel include the following: neuropathy, cardiac conduction abnormalities, bradycardia (abnormally slow heart rate), and rarely hepatitis and pneumonitis. Known side effects for the drug docetaxel include fluid retention, skin toxicities, and stomatitis. The purpose of this research is to compare trends in reported adverse events for paclitaxel versus docetaxel and examine the types of adverse events associated with paclitaxel and docetaxel in clinical use. This research is novel because it is the first to examine reported adverse events for paclitaxel and docetaxel using a regulatory database.

2. Methods

In this paper, the data analyzed originates from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) [7]. This post-marketing surveillance database includes all reports submitted to FDA regarding medication errors, adverse events, and product quality concerns for pharmaceuticals approved in the United States. This comprehensive database is known to be a valuable tool for assessing manufacturers' adherence to reporting regulations, as well as identifying safety concerns related to products. It is also significant to note the structure of the FAERS database follows the international safety reporting guidelines established by the International Conference on Harmonisation. Healthcare professionals, such as pharmacists, physicians, and nurses, and consumers have the option to report adverse events to FAERS or to the products' manufacturers. Manufacturers of pharmaceuticals are required to report adverse events when they receive a report from consumers for healthcare professionals [8]. The FAERS database was searched using the search terms "paclitaxel" and "docetaxel" to identify all reported adverse events for both generic and brand-name versions of these therapeutics. The reaction types and number of adverse events reported after the administration of paclitaxel and docetaxel were recorded between the years 1991 and 2023.

3. Results

Figure 2 shows the number of adverse events reported from the administration of paclitaxel each year from 1991 to 2023. The trendline present indicates that the frequency of adverse events has grown exponentially over time. The number of adverse events reported for paclitaxel grew 14.6 times from the 530 reported adverse events in 1993 to the 8,294 reported adverse events in 2023. Within the course of 20 years (2003-2023), the number of reported adverse events grew by more than 5 times. Additionally, the high r-squared value indicates that an exponential model fits the data well. Over the entire period under investigation, paclitaxel demonstrated more total adverse events than docetaxel. In terms of yearly adverse events, paclitaxel demonstrated a higher number of adverse events than docetaxel in every year since 1991, with the exception of the three-year period from 2018 to 2020.

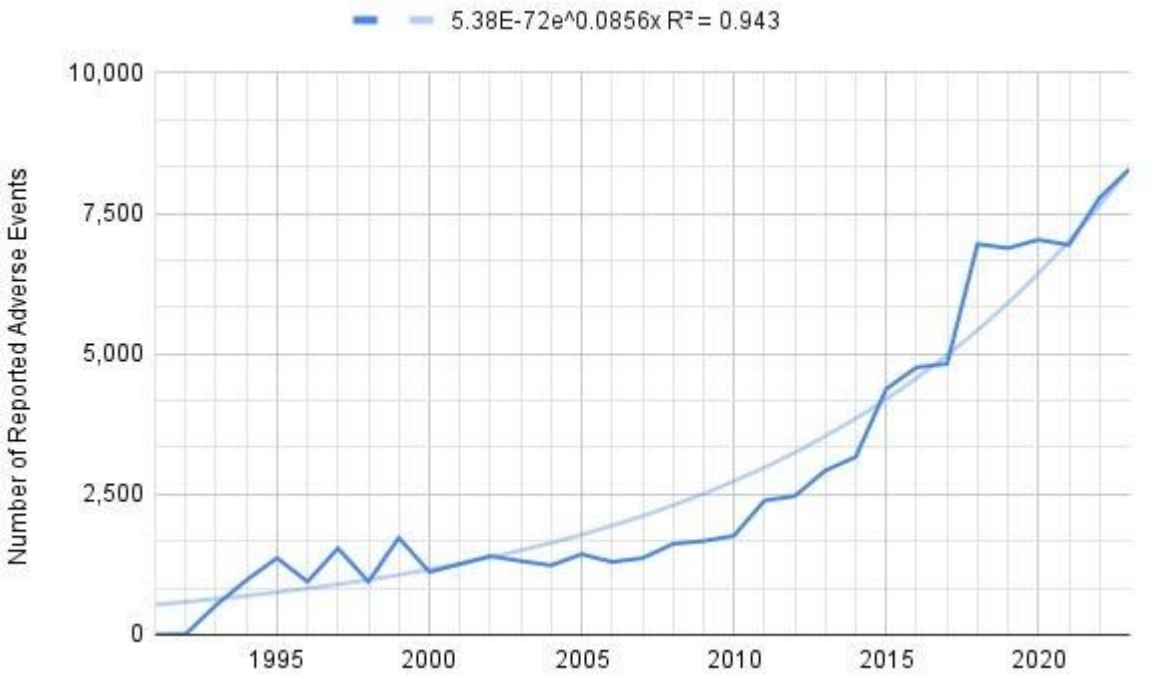

Fig. 2: Annual trends of adverse events reported from paclitaxel.

Figure 3 shows the number of adverse events reported from the administration of docetaxel each year from 1991 to 2023. In contrast to paclitaxel which demonstrated an exponential increase in reported adverse events, the number of reported adverse events from docetaxel grew much more gradually from 1993 to 2017. The reported adverse events from docetaxel sharply increased and peaked in 2018 as it grew 305%, from 3,697 reported adverse events in 2017 to 14,988 reported adverse events in 2018. The number of adverse events remained elevated in 2019, then declined to 4,585 reported adverse events by 2023.

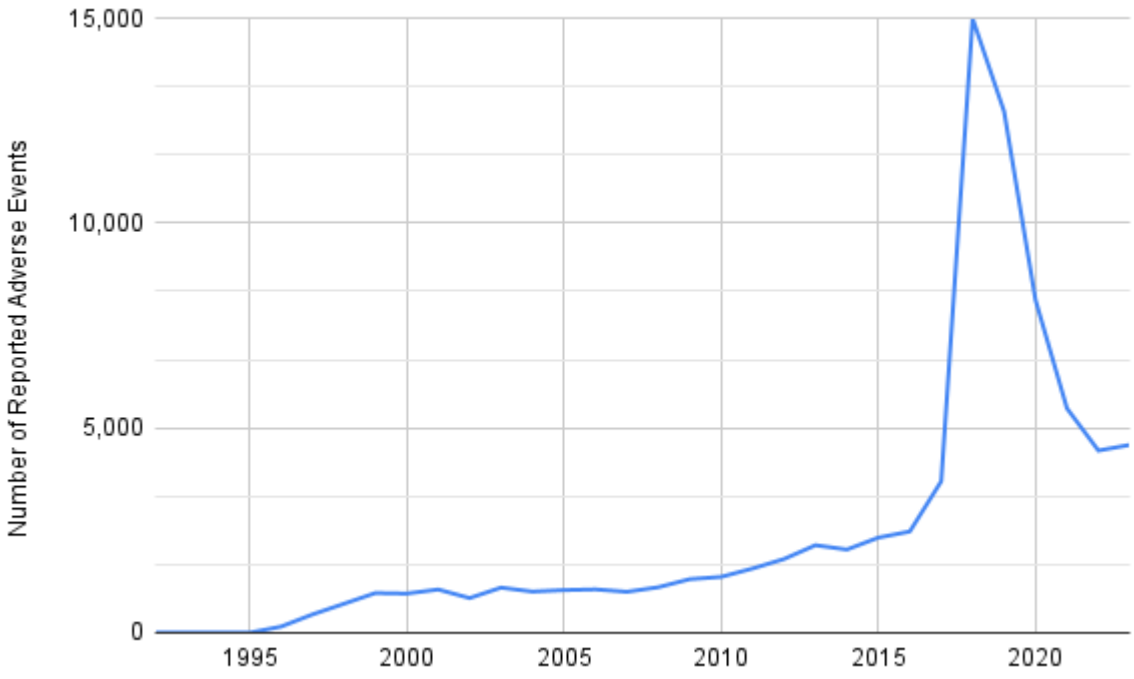

Fig. 3: Annual trend of adverse events from docetaxel.

Figure 4 shows the distribution of various types of reactions associated with the administration of the drug paclitaxel. Paclitaxel's most frequent reaction type is dyspnoea (shortness of breath) with 6,694 reported adverse events resulting in dyspnoea. The other most frequently reported reaction types are gastrointestinal (which include vomiting, nausea, and diarrhea) and hematologic (which include neutropenia, anemia, and thrombocytopenia). Notably, there were 3,584 reported adverse events for which death was noted as a reaction.

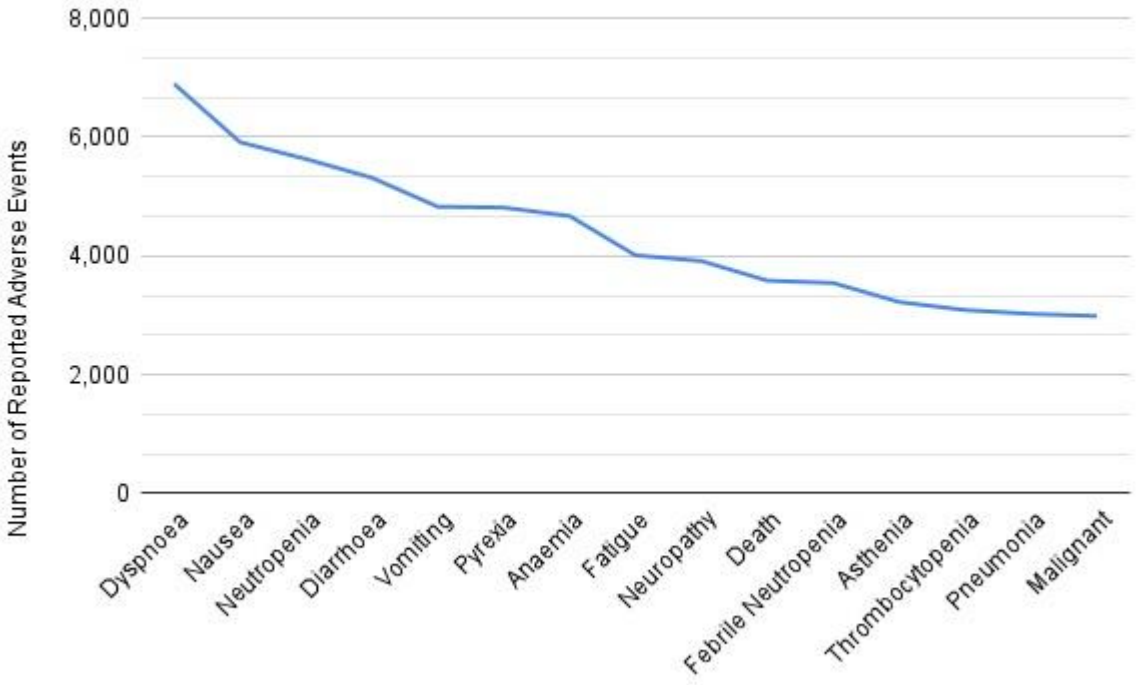

Fig. 4: Reaction types from paclitaxel.

Figure 5 shows the distribution of various types of reactions associated with the administration of the drug docetaxel. The most frequent reaction type reported for docetaxel was alopecia (loss of hair), with 29,536 reported adverse events resulting in alopecia. Docetaxel's adverse events are also dominated by other effects on the hair such as madarosis (loss of eyebrows and eyelashes), abnormal hair texture, and changes in hair color. Additionally, docetaxel is associated with psychological adverse events, such as emotional distress, anxiety, psychological trauma, and impaired quality of life. It is significant to note that the most frequent reaction types reported for paclitaxel did not include either hair or psychological effects. It is also important to note that death was not a frequently reported reaction type for docetaxel, in contrast to paclitaxel.

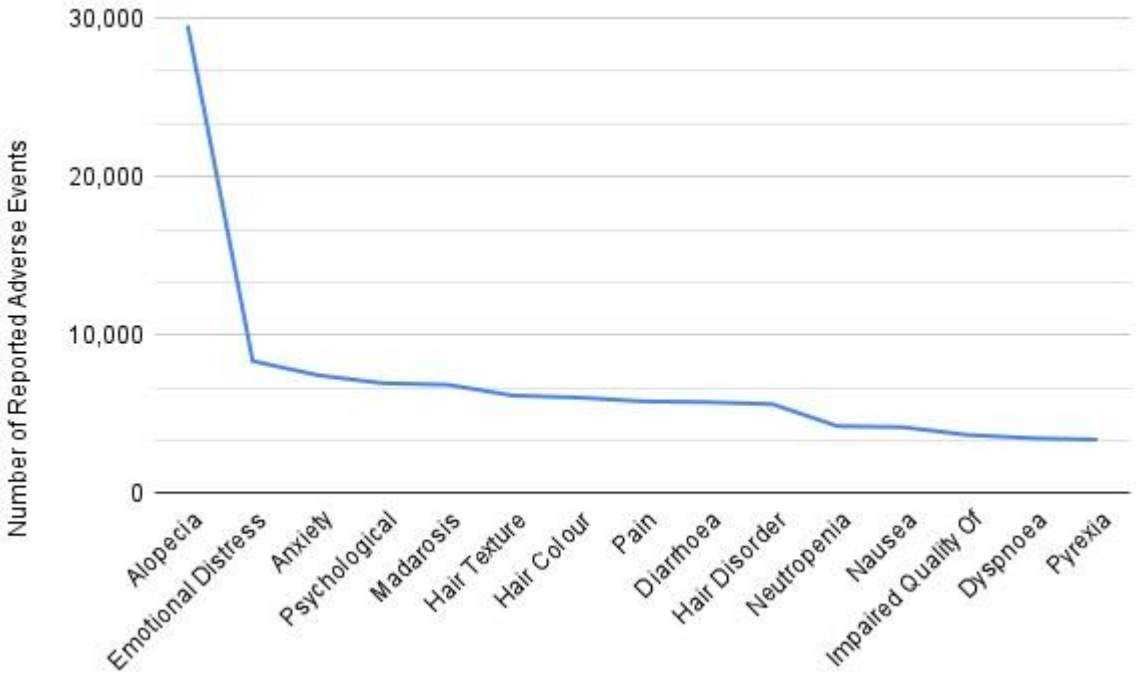

Fig. 5: Reaction types from docetaxel.

4. Discussion

The exponential increase in the number of adverse events from paclitaxel suggests that ongoing monitoring and further research into paclitaxel is crucial for patient safety. Docetaxel's peak in adverse events in 2018 followed by a decline could indicate a change in awareness of docetaxel. Understanding the reasons behind this peak and subsequent decline could provide valuable insights into the drug's dynamic side effect profile. Further research will be required to examine changes in usage patterns for paclitaxel and docetaxel over time, as well as changes in regulatory approval. The differences in adverse events and reaction types between paclitaxel and docetaxel demonstrate the importance of customized treatments for patients. For instance, patients taking paclitaxel may need more focused monitoring for respiratory and hematologic issues, while those taking docetaxel might require support for their hair loss and their mental health.

An analysis of the reaction types for paclitaxel in the FAERS database revealed that the most frequently reported side effects were dyspnoea (shortness of breath), nausea, and neutropenia (abnormally low count of neutrophils). According to the FAERS data, dyspnoea is more frequently reported than any other side effects reported for paclitaxel. In contrast, the most frequently reported side effects for docetaxel in the FAERS database were alopecia, emotional distress, psychological trauma, and madarosis (loss of eyebrows and eyelashes). Additionally, docetaxel is associated with either hair effects and psychological effects while paclitaxel is not associated with those effects. It is also noteworthy to mention that death is one of the top reported adverse events associated with paclitaxel. The results of this study are significant because they reveal that paclitaxel and docetaxel, despite being members of the same class of drugs, induce distinct adverse event types and patterns in patients. These findings may help physicians and patients select the best taxane drug, as well as anticipate and monitor potential side effects, especially life-threatening reactions such as dyspnoea. These results may also reveal the influence of drug structure on adverse reactions, as well as opportunities for improving upon the taxane drugs.

Although the FAERS is a valuable database for monitoring adverse events associated with pharmaceuticals and therapeutics, it presents several significant limitations that should be acknowledged. The FAERS database encourages public involvement in reporting adverse events, however, there is a potential for the introduction of inaccurate information. Such

inaccuracies may appear in the form of incomplete submissions, duplicates, or various other errors and not every adverse event may be reported. It is imperative to acknowledge that the presence of an adverse event report does not definitively establish a causal relationship between the drug and the adverse event. It is important to be aware that the information shown in the adverse events reports has not been confirmed by medical professionals and cannot be used to determine the frequency or incidence rate of the reported events.

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