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The Potential of *Taxus sumatrana* as a Candidate for Cancer Therapy

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A B S T R A C T

This article aims to review the literature on studies supporting using *Taxus sumatrana* (Miq.) de Laub (*Cemara Sumatra*) as a cancer treatment. The method involved a literature review using the keywords "*Taxus sumatrana*" and chemical compound or pharmacological activity. There are no reports of pharmacological activity related to cancer from extracts or parts of the *T. sumatrana* plant. Despite a lack of scientific evidence supporting its anticancer activity, *T. sumatrana* is widely used to treat cancer traditionally. So, further research is needed to validate using *T. sumatrana* as a cancer treatment. Pharmacodynamic studies are necessary to demonstrate its mechanism of action. Additionally, toxicity studies are needed to determine the safety, ensuring no toxic effects on normal cells. Further research is also required to evaluate the effectiveness of *T. sumatrana* in clinical cancer treatment. In conclusion, *T. sumatrana* promises to be a natural medicine for cancer treatment. However, its validated use as a cancer treatment requires adequate supporting data scientifically.

INTRODUCTION

Taxus sumatrana is believed to have potential as a cancer treatment because it contains compounds like paclitaxel, which has been proven effective in treating several types of cancer. Despite long-standing traditional use for cancer treatment, no scientific research validates these claims. The popularity of Taxus began when paclitaxel was isolated from the Yew tree (*Taxus brevifolia*) from the Pacific Northwest in 1971 by the NCI (National Cancer Institute) (Wani & Horwitz, 2014). It is important to note that paclitaxel is a pure compound isolated from the bark of *T. brevifolia* rather than other parts of the plant, such as the bark, leaves, or twigs of *T. sumatrana,* as commonly used.

The bark, leaves, or twigs are used traditionally and massively for several diseases, making this plant increasingly rare. In Indonesia, *T. sumatrana* is currently listed as a protected plant based on the Regulation of the Minister of Environment and Forestry (MENLHK, 2018). A qualitative study provided insights into using *T. sumatrana* as an anticancer agent. The study concluded that the traditional use of this plant for anticancer purposes was based on assumptions, as it contains paclitaxel, a compound known for its anticancer properties (Sudarmin et al., 2020).

Based on the above, it is necessary to conduct a literature review to determine the capacity of scientific research that is available to date to support the use of this plant as a cancer drug. If the supporting data is considered insufficient, then it can be recommended what research should be carried out in the future.

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METHODS

A literature review used the keyword "*Taxus sumatrana*" and chemical content or pharmacological activity. As only a few articles focused on *T. sumatrana*'s pharmacological activity, various search engines were used to find research journals. After screening over 100 journals, books, and proceedings, 19 resources (listed in Annex 1) related to the research objectives were selected.

RESULTS AND DISCUSSION

Botanical Review of T. sumatrana

Cemara Sumatra, known by the scientific name *Taxus sumatrana* (Miq.) de Laub, belongs to the Taxaceae family (Spjut, 2007). *T. sumatrana* is a species of large tree that can grow up to 45 meters tall with a diameter exceeding 1 meter. The shape and size of the leaves vary depending on the tree's age. Young leaves are linear-lanceolate and often falcate, while older leaves are nearly linear and straight. The pollen cones are globular, and the mature seeds measure approximately six by five mm (De Laubenfels, 1988), as shown in Figure 1.

Figure 1. *Taxus sumatrana* Tree (Hidayat et al., 2014).

T. sumatrana is found in the Eastern Himalayas, North Myanmar, Southeast China, Taiwan, South Vietnam, and the Philippines, as well as in Sumatra (Indonesia) (De Laubenfels, 1988). This species is found growing naturally at Sumatera Island: Mt. Kerinci in Jambi, Mt. Tujuh in Jambi, Dolok Sibuaton Conservation Forest Area in North Sumatera, Mt. Dempo in South Sumatera, and Mt. Singgalang in West Sumatera (Frianto, 2016; Frianto & Novriyanti, 2017). Its local name varies, known as "*Cemara Sumatra*" in West Sumatera, "*Tampinur Batu*" in Karo, or "*Kayu Taji*" in Mt. Dempo (Muhaimin, 2017).

T. sumatrana thrives in moist subtropical forests, tropical highland ridges, and forests at 1400-2300 m. The tree is valued because it is not widely cultivated due to its slow growth and limited distribution. In addition, over-exploitation of Taxus species has led to their progressive extinction, causing all Taxus species to be included in CITES Appendix II (as *Taxus* spp.) and included in the endangered category on the IUCN Red List. Specific policies and immediate action on Taxus conservation plans and measures must be implemented in many areas.

Chemical Compounds and Pharmacological Activities of T. sumatrana

Various chemical compounds have been isolated from *T. sumatrana*'s bark, leaves, and twigs. Bark yielded paclitaxel, baccatin III, cephalomannine, 19-hydroxybaccatin III, 19-hydroxy-13-oxobaccatin III, 7-epi-10-deacetyltaxol, 1-epi-10-deacetylcephalomannine, and 10-deacetyl-13-oxobaccatin III (Kitagawa et al., 1995). Wallifoliol, taxuspine F, 13-O-acetyl wallifoliol, and taxumairol Q were obtained from leaves and twigs (Shen et al., 2002). Leaves and twigs also yielded Tasumatrol A-Z (Shen et al., 2003; Shen et al., 2005; Shen et al., 2005; Shen et al., 2005; Shen et al., 2007; Shen et al., 2008), Taiwantaxins A-D (Wang et al., 2009), and other chemical compounds (Kuo et al., 2015; Luh et al., 2009).

Several of these compounds have been found to have cytotoxic effects against various cancer cell lines in vitro study, including paclitaxel (Liebmann et al., 1993); wallifoliol, taxuspine F, and 3, 6, 7,10-deacetylbaccatin III (Shen et al., 2002); tasumatrol F (Shen et al., 2005); tasumatrols I and K (Shen et al., 2005); tasumatrol (Shen et al., 2007); tasumatrol Z (Shen et al., 2008); and Taiwantaxin B (Wang et al., 2009).

The discovery of paclitaxel can be traced back to 1971 when it was first isolated from *T. brevifolia* Nutt., a different species of Taxus (Wani & Horwitz, 2014). However, the amount of paclitaxel obtained from each plant part is relatively low and varies significantly. For example, the bark of *T. brevifolia* yields approximately 0.015%, which means that roughly 7,000 kg of raw materials from 2,000 to 2,500 yew trees are needed to produce just 1 kg of paclitaxel (Vidensek et al., 1990). Similarly, the yields from other species are also relatively low, ranging from 0.001% to 0.1% of the dry weight of leaves or bark (Witherup et al., 1990). Paclitaxel has been authorized for use as a chemotherapy agent for various cancers based on the comprehensive supporting data, including breast cancer (Perez, 1998; Sato et al., 2003), ovarian cancer (Kumar et al., 2010), non-small cell lung cancer (NSCLC) (Ramalingam & Belani, 2004), pancreatic

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adenocarcinoma (Saif et al., 2010), and Kaposi's sarcoma (Régnier-Rosencher et al., 2013).

What is the Supporting Data for Using T. sumatrana as a Cancer Medicine?

Unfortunately, all the reports of pharmacological activity provided are in vitro cytotoxic activity of isolated pure chemical compounds. No information was found on the activity of bark, leaves, twigs, or their extracts used as natural medicines.

Numerous chemical compounds have been isolated from the *T. sumatrana*. Some of these compounds have been tested for cytotoxic activity against cancer cell lines in an in vitro study, and the results vary from none, weak to strong activity. Except for paclitaxel, it is not yet clear whether cell death is caused by apoptosis or necrosis. Drugs with potential cancer-fighting properties are expected to induce cell death through apoptosis, not necrosis mechanisms. Death cell fragments, known as apoptotic bodies, can be excreted by phagocytes such as macrophages to prevent tissue damage.

It is important to note that paclitaxel is the compound from *T. sumatrana* that has been comprehensively studied in non-clinical and clinical trials. Although *T. sumatrana* contains paclitaxel, it cannot be assumed that the bark, leaves, or twigs provide the same effect as paclitaxel. It is important to determine whether the paclitaxel in the bark, leaves, or twigs of *T. sumatrana* is present in sufficient amounts to be effective as a cancer medicine. Dose-ranging studies are needed to determine the dose and what doses are equivalent to the optimal dose of paclitaxel. Pharmacodynamic studies are necessary to demonstrate that herbs or crude extracts can inhibit the cell cycle or induce cell death, similar to paclitaxel's mechanism of action.

It is also required to conduct toxicity studies on bark, leaves, or twigs to ensure that they do not harm normal cells or other cell components, which could ultimately lead to adverse effects. Additionally, they may be more effective in killing cancer cells than paclitaxel, as they contain not only paclitaxel but also other chemical compounds. Several unanswered questions require scientific studies to clarify assumptions and uncertainties.

CONCLUSIONS

After conducting a literature review, it can be concluded that using *T. sumatrana* as an anticancer is based on assumptions. It is because it contains paclitaxel, known for its anticancer properties. However, there is no scientific evidence to support the use of bark, stems, twigs, or extracts from the plant. Therefore, it is important to validate this use through a scientific approach.

By conducting further research, we hope to contribute to scientific knowledge and an inventory of the pharmacological activity of *T. sumatrana* as a medicinal plant. It is also crucial to scientifically confirm the practice of using *T. sumatrana* as a cancer medicine, which has been in use for a long time. These studies will provide scientific justification for using *T. sumatrana* as a cancer drug and determine whether it is appropriate and scientifically justified.

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APPENDICES

List of reviewed journals, books, proceedings

Annex 1. List of reviewed journals, books, proceedings

No	Author (s)	Title	Year	Published in
1	De Laubenfels	Coniferales: Taxaceae	1988	Flora Malesiana, 10(1), 347–351.
2	Frianto, D.	The distribution pattern and the density potential of *Taxus sumatrana* in Mount Tujuh, Kerinci District, Jambi.	2016	Proceeding *Seminar Nasional Masyarakat Biodiversity Indones*
3	Frianto, D., & Novriyanti, E.	Eksplorasi potensi *Taxus sumatrana* di Gunung Kerinci, Sumatera.	2017	Proceeding *Seminar Nasional Masyarakat Biodiversity Indonesia*
4	Kitagawa, I., Mahmud, T., Kobayashi, M., Roemantyo, H., & Shibuya, H.	Taxol and its Related Taxoids from the Needles of *Taxus Sumatrana*	1995	*Chemical and Pharmaceutical Bulletin*, *43*(2). https://doi.org/10.1248/cpb.43.365
5	Kuo, W. L., Chen, F. C., Chen, K. J., & Chen, J. J.	Taxusumatrin, a new taxoid from the stem bark of *Taxus sumatrana*	2015	*Chemistry of Natural Compounds*, *51*(3). https://doi.org/10.1007/s10600-015-1308-6
6	Luh, L. J., Abd El-Razek, M. H., Liaw, C. C., Chen, T. A., Lin, Y. S., Kuo, Y. H., Chien, C. Te, & Shen, Y. C	Tri- and bicyclic taxoids from the Taiwanese Yew *Taxus sumatrana*	2009	*Helvetica Chimica Acta*, *92*(7), 1349–1358. https://doi.org/10.1002/hlca.200900022
7	Shen, Y. C., Cheng, K. C., Lin, Y. C., Cheng, Y. Bin, Khalil, A. T., Guh, J. H., Chien, C. Te, Teng, C. M., & Chang, Y. T.	Three new taxane diterpenoids from *Taxus sumatrana*	2005	*Journal of Natural Products*, *68*(1). https://doi.org/10.1021/np040132w
8	Shen, Y. C., Hsu, S. M., Lin, Y. S., Cheng, K. C., Chien, C. Te, Chou, C. H., & Cheng, Y. Bin.	New bicyclic taxane diterpenoids from *Taxus sumatrana*	2005	*Chemical and Pharmaceutical Bulletin*, *53*(7). https://doi.org/10.1248/cpb.53.808
9	Shen, Y. C., Lin, Y. S., Cheng, Y. Bin, Cheng, K. C., Khalil, A. T., Kuo, Y. H., Chien, C. Te, & Lin, Y. C	Novel taxane diterpenes from *Taxus sumatrana* with the first C-21 taxane ester	2005	*Tetrahedron*, *61*(5). https://doi.org/10.1016/j.tet.2004.10.110
10	Shen, Y. C., Lin, Y. S., Hsu, S. M., Khalil, A. T., Wang, S. S., Chien, C. Te, Kuo, Y. H., & Chou, C. H.	Tasumatrols P-T, five new taxoids from *Taxus sumatrana*	2007	*Helvetica Chimica Acta*, *90*(7). https://doi.org/10.1002/hlca.200790133

No	Author (s)	Title	Year	Published in
11	Shen, Y. C., Pan, Y. L., Lo, K. L., Wang, S. S., Chang, Y. T., Wang, L. T., & Lin, Y. C.	New taxane diterpenoids from Taiwanese *Taxus sumatrana*	2003	*Chemical and Pharmaceutical Bulletin*, *51*(7). https://doi.org/10.1248/cpb.51.867
12	Shen, Y. C., Wang, S. S., Chien, C. Te, Kuo, Y. H., & Khalil, A. T.	Tasumatrols U-Z, taxane diterpene esters from *Taxus sumatrana*	2008	*Journal of Natural Products*, *71*(4). https://doi.org/10.1021/np078016r
13	Shen, Y. C., Wang, S. S., Pan, Y. L., Lo, K. L., Chakraborty, R., Chien, C. Te, Kuo, Y. H., & Lin, Y. C.	New taxane diterpenoids from the leaves and twigs of *Taxus sumatrana*	2002	*Journal of Natural Products*, *65*(12). https://doi.org/10.1021/np0202273
14	Spjut, R. W.	Taxonomy and nomenclature of Taxus (Taxaceae)	2007	*Journal of the Botanical Research Institute of Texas*, *1*(1)
15	Sudarmin, S., Diliarosta, S., Pujiastuti, R. S. E., Jumini, S., & Tri Prasetya, A.	The instructional design of ethnoscience-based inquiry learning for scientific explanation about *Taxus sumatrana* as cancer medication	2020	*Journal for the Education of Gifted Young Scientists*, *8*(4). https://doi.org/10.17478/jegys.792830
16	Vidensek, N., Lim, P., Campbell, A., & Carlson, C.	Taxol Content in Bark, Wood, Root, Leaf, Twig, and Seedling from Several Taxus Species	1990	*J. Nat. Prod.*, *53*(6), 1609–1610. https://doi.org/10.1021/np50072a039
17	Wang, S. S., Abd El-Razek, M. H., Chen, Y. G., Chien, C. Te, Guh, J. H., Kuo, Y. H., & Shen, Y. C.	abeo-taxane diterpenoids from the Taiwanese yew *Taxus sumatrana*	2009	*Chemistry and Biodiversity*, *6*(12). https://doi.org/10.1002/cbdv.200900003
18	Wani, M. C., & Horwitz, S. B.	Nature as a Remarkable Chemist: A Personal Story of the Discovery and Development of Taxol®	2014	*Anticancer Drugs*, *25*(5), 482–487. https://doi.org/doi:10.1097/CAD.0000000000000063
19	Witherup, K. M., Look, S. A., Stasko, M. W., Ghiorzi, T. J., & Muschik, G. M.	Taxus spp. needles containing amounts of taxol comparable to the bark of *Taxus brevifolia*: analysis and isolation	1990	*Journal of Natural Products*, *53*(5), 1249–1255.