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Cytotoxic Activity of Endophytic Fungus against HeLa Cells (Cervical Cancer Cells): A Article Review

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A B S T R A C T

Cancer is one of the leading causes of death in every country worldwide. It has been growing rapidly every year. One type of cancer is cervical cancer. Cervical cancer fourth rank suffered in women worldwide after endometrial, colorectal, and breast cancer. This review article aims to summarize and describe several research reports of endophytic fungi and their cytotoxic activity against HeLa cells (cervical cancer cells). This article review was made by conducting a literature study. Literature is collected from various sources such as official pharmaceutical scientific books, national and international journals published in the last twenty years. Endophytic fungi play an important role in providing a constant supply of anticancer with minimal side effects and high target specificity at an affordable cost.Therefore, it is necessary to explore and utilize the compounds contained in endophytic fungi. Further research on endophytic fungi needs to be done to find new drug candidates to fight deadly diseases in humans such as cervical cancer.

Keywords: Endophytic Fungus, Cytotoxic Activity, Cervical Cancer, He La Cells.

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INTRODUCTION

Cancer is one of the leading causes of death in every country worldwide. It has been growing rapidly every year. Cancer was characterized by the presence of abnormal cells in body tissues. Cancer grows uncontrollably, invade and moves between cells and tissues. One type of cancer is cervical cancer.Cervical cancer fourth rank suffered in women worldwide after endometrial, colorectal, and breast cancer[1]. Every year, about 500 thousand new cervical cancer cases were discovered worldwide and more than 250 thousand of them are deaths. Meanwhile, in Indonesia, there are around 40 thousand new cases found every year [2].Based on the results of research conducted by the International Agency for Research on Cancer (IARC) reported cervical cancer is caused by Human Papilloma Virus (HPV) infection [3].

In general, cervical cancer is treated with therapies such as surgery, radiotherapy, and chemotherapy. In addition, anti-cancer drugs or commonly called cytostatic drugs are also used to inhibit cancer cell proliferation mechanisms [4]. However, anticancer drugs have toxic effects during or after treatment. Toxic effects include nausea and vomiting, anorexia, anemia, hair loss, decreased immunity, etc [5].

Drugs with minimal side effects are alternative methods for the treatment of diseases (cancer) used conventionally. Anticancer drugs derived from natural ingredients are considered important because they have few side effects. Therefore, many studies showed that raw materials from natural ingredients as alternative medicines that are more effective with minimal side effects. Researchers have begun to focus their research on renewable sources, which have not yet been explored, including endophytic fungus. Since Taxol synthesized by the fungus *Taxomyces Andreana* isolated from the stems of *Taxus brevifolia* was discovered, endophytic fungi have become a natural ingredient as a natural biosynthetic producer[6,7]. This fungus has the potential to be used as a therapeutic agent against various diseases, especially antitumor/anticancer and antibacterial agents [8,9]. In the last two decades, research focusing on finding new drug sources from endophytic fungi has increased rapidly. Based on data obtained from a search of the PubMed site, from 1964-2021 there were approximately 8,201 articles published using the keyword "*Endophytic Fungi*". This review article aims to summarize and describe several research reports of endophytic fungi and their cytotoxic activity against HeLa cells (cervical cancer cells).

METHOD

This article review was made by conducting a literature study. Literature is collected from various sources such as official pharmaceutical scientific books, national and international journals published in the last twenty years (2000-2020). The literature was collected from trusted online journal sites such as ScienceDirect, NCBI, Researchgate, PubMed, Google Scholar/Google Scholar, and other electronic sources with the keywords “endophytic fungi”, “cytotoxic activity”, “cervical cancer”, “HeLa cells” and “ anti-cancer drugs”.

RESULT AND DISCUSSION

Research on the effect of endophytic fungi extract that was isolated from mangrove plants on cancer cells was carried out to determine the mechanism of its cytotoxic activity (10). In this study, the extract of endophytic fungi showed strong inhibition, cytotoxicity, and potential to produce natural antitumor compounds. Penicillium Citrinum was isolated from the mangrove Bruguiera sexangula var. Rhynchopetalids collected in the South China Sea also have antibacterial and cytotoxic activities [11].

Table 1: Cytotoxic activity of endophytic fungi against HeLa cells.

No	Endophytic Fungus	Plant Name	Compound	Type of cancer tested	Cytotoxic activity (IC_{50})	References
1.	*Penicillium citrinum*	*Tapiscia sinensis* Oliv.	penicillocitrin A	Hela	50 µg/mL	(12)
			2-(2-acetyl-hydrazinyl)		30 µg/mL	
			Benzamide		15 µg/mL	
			Secalonic acid A		20 µg/mL	
			3β, 5α, 9α- trihydroxy-(22E, 24R)-ergost-7,22-dien-6-one		60 µg/mL	
2.	*Pestalotiopsis fici*	*Camellia sinensis*	Pestaloficiols J Pestaloficiols K Pestaloficiols L	Hela	21.2 µg/mL 99.3 µg/mL 8.7 µg/mL	(13)
3.	*Talaromyces radicus*	*Catharanthus roseus*	Vincristine	Hela	4.2 µg/mL	(14)
4.	*Perenniporia tephropora*	*Taxus chinensis* var. *mairei*	Perenniporin A Ergosterol Rel-(+)-(2aR,5R,5aR,8S,8aS,8bR)-decahydro-2,2,5,8-tetramethyl-2H-naphtho[1,8-bc]furan-5-ol Albicanol	Hela	30.44 µg/mL 1.16 µg/mL 6.93 µg/mL 14.20 µg/mL	(15)
5.	*Penicillium chrysogenum*	*Laurencia sp.*	PenicisteroidsA	Hela	15 µg/mL	(16)
6.	*Pestalotiopsis fici*	*Camellia sinensis*	Chloropupukeanolides C Chloropupukeanolides D Chloropupukeanolides E	Hela	2.3 µM 1.2 µM 31.8 µM	(17)
7.	*Penicillium citrinum*	*Bruguiera sexangula* var. *rhynchopetala*	Asam asterrat	Hela	21.6 µg/mL	(18)
8.	*Pestalotiopsis fici*	*Camellia sinensis (Theaceae)*	Pestalofone F Pestalodiol C	Hela	14.4 µmol/L 16.7 µmol/L	(19)
9	*Pestalotiopsis fici*	*Camellia sinensis (Theaceae)*	Pestalofone J Pestalofone K	Hela	44.3 µmol/L 65.5 µmol/L	(20)
10	*Pestalotiopsis fici*	*Camellia sinensis (Theaceae)*	Siccayne	Hela	48.2 µM	(21)
11	*Pestalotiopsis foedan*	*Bruguiera sexangula*	(-)-(4S,8S)-Foedanolide (+)-(4R,8R)-Foedanolide	Hela	5.4 µg/mL 15.8 µg/mL	(22)
12	*Pestalotiopsis photiniae*	*Podocarpus macrophyllus*	MP [4-(3′,3′-dimethylallyloxy)-5-methyl-6-methoxyphthalide]	Hela	36.0 µg/mL	(23)
13	*Pestalotiopsis vaccinia*	*K. candel*	Pestalamine A	Hela	22.0 µg/mL	(24)
14	*Pestalotiopsis karstenii*	*Camellia sasanqua.*	Pestalrone B	Hela	12.6 µg/mL	(25)
15	*Pestalotiopsis sp.*	*Podocarpus macrophyllus*	Pestaloquinol A Pestaloquinol B	Hela	8.8 µM 8.8 µM	(26)

The endophytic fungal compound Penicillium citrinum was isolated from the medicinal plant Tapiscia sinensis Oliv. were collected from Shennongjia District. Tapiscia sinensis Oliv leaves are sterilized and cut into small sections. The cut segments were placed on potato dextrose agar (PDA) in a petri dish and incubated in an incubator with a constant temperature at 28 °C.The five compounds found were tested for cytotoxic activity against HeLa cells using the Tetrazolium Micro Microculture method. The results showed five compounds of the endophytic fungus P. citrinum (penicillocitrin A (1), 2- (2-acetyl-hydrazinyl) (2), benzamide (3), secalonic acid A (4), and 3β, 5α, 9α-trihydroxy - (22E, 24R) -ergost-7,22-dien-6-one (5)) evaluated its cytotoxicity activity against Hela cells with values 50 µg/mL, 30 µg/mL, 15 µg/mL, 20 µg/mL, dan 60 µg/mL respectively[12].

The endophytic fungus Pestalotiopsis fici isolated from the Camellia sinensis plant was obtained from the suburbs of Hangzhou, Zhejiang, China.Three isoprenylated chromone derivatives, namely Pestaloficiols J, Pestaloficiols K, and Pestaloficiols L, showed cytotoxicity activity against HeLa cells with IC_{50} values of 21.2 M, 99.3µM, and 8.7 M, respectively[13]. Talaromyces radicus isolated from C. roseus produced a 670 g/L vincristine compound. The vincristine compound resulted in the inhibition of HeLa cell growth with an IC_{50} value of 4.2 g/mL. However, it was not significantly affected against normal cells [14].

Endophytic fungus Perenniporia tephropora. isolated from the plant chinensis var. mairei. four compounds were identified, namely Perenniporin A, Ergosterol, Rel-(+)-(2aR,5R,5aR,8S,8aS,8bR)-decahydro-2,2,5,8-tetramethyl-2H-naphtho[1,8- bc]furan-5-ol and Albicanol. The reseach results showed the cytotoxic activity of the four compounds with IC_{50} values respectively 30.44 g/mL, 1.16 g/mL, 6.93 g/mL, 14.20 g/mL [15].

Cultures of extracts of Penicillium chrysogenum QEN-24S, an endophytic fungus that was isolated from marine red algae species of the genus Laurencia. A new was compound obtained, namely penicisteroids A.The results showed that penicisteroid A had selective cytotoxic activity against HeLa tumor cell lines with an IC_{50} value of 15 g/mL [16].

Endophytic fungus Pestalotiopsis fici isolated from Camellia sinensis. Three compounds were found, namely Chloropupukeanolides C, Chloropupukeanolides D, and Chloropupukeanolides E. Then, these compounds were tested on HeLa cells.The results showed that the compound had cytotoxic activity against HeLa cells with IC_{50} values of 2.3 M, 1.2 M, and 31.8 M, respectively [17].

Asteric acid compound obtained from the ethyl acetate extract of the endophytic fungus P. citrinum HL-5126 isolated from the plant mangrove Bruguiera sexangula var. rhynchopetala collected in the South China Sea. All compounds were tested for their cytotoxic activity against HeLa cells and evaluated by the MTT method. The results showed that asteric acid showed cytotoxic activity against Hela cells with an IC_{50} value of 21.6 g/mL [18].

The culture of Pestalotiopsis fici was extracted from the branches of Camellia sinensis in Hangzhou, China. Seven new compounds have been identified, namely: Pestalodiol F, Pestalodiol G, Pestalodiol H, Pestalodiol A, Pestalodiol B, Pestalodiol C, and Pestalodiol D. The results showed that Pestalofone F had cytotoxic activity against HeLa cells with an IC_{50} value of 14.4 mol/L and Pestalodiol C showed an IC_{50} value of 16.7 mol/L [19].

Pestalotiopsis fici isolated from the tea plant Camellia sinensis grown on different solid substrate fermentation cultures. Seven new compounds have been identified, namely (Pestalofones I– K (1-3)) meroterpenoid dimer dengan 2- (7-benzoyl-2,3-dihydrobenzofuran-2-yl) -1-phenylethan- 1-one (in 1) dan 2- (7-benzoyl-2,3-dihydrobenzofuran-2-yl) -1- (3,8-dioxatricyclo [5.1.0.02,4] oct-4-yl) ethan-1-one. The results showed that Pestalofones J and K compounds which have weak cytotoxic activity against human HeLa cells were tested, with IC_{50} values of 44.3 and 65.5 mol/L, respectively [20].

*Pestalotiopsis fici*was isolated from the branches of Camellia sinensis in Hangzhou, China. Six compounds have been identified, namely pestaloficiols Q-S, anofinic acid, siccayne and pyrenophorol. The results showed that only siccayne compound had cytotoxic activity against both HeLa cell lines, with an IC_{50} value of 48.2 M [21].

Endophytic fungus Pestalotiopsis foedan isolated from Bruguiera sexangula in Hainan, China. The fungal strain was cultured on slants of potato dextrose agar (PDA) at 28 °C for 7 days. compounds have been identified as (-) - (4S, 8S) -Foedanolide and (+) - (4R, 8R) –foedanolide. Both compounds were tested for their cytotoxicity activity against HeLa cell lines. The compound (+) - (4R, 8R) -foedanolide showed significant activity against HeLa tumor cells with an IC_{50} value of 5.4 g/mL, while the compound (-) - (4S, 8S)-Foedanolide with an IC_{50} value of 15.8 g/mL [22].

MP[4-(39,39-dimethylallyloxy)-5-methyl-6-methoxyphthalide] was obtained from liquid culture of Pestalotiopsis photiniae isolated from the Chinese Podocarpaceae plant Podocarpus macrophyllus. MP significantly inhibited the proliferation of HeLa tumor cell lines with an IC_{50} value of 36 g/mL (23).

The endophytic fungus Pestalotiopsis vacinii was isolated from Kandelia candel (L.) Druce (Rhizophoraceae), a viviparous mangrove species widely distributed in coastal and estuarine areas of southern China. The endophytic fungus Pestalotiopsis vacinii was grown in PDA media. The six compounds found in this study were Pestalamine A, cyclo (4-hydroxy-R-Pro-S-Leu), p-hydroxy benzaldehyde, benzocaine, ethyl p-hydrobenzoate, and ethyl p-anisate. Pestalamine A showed moderate cytotoxic activity against human cancer cell lines MCF-7, HeLa, and HepG2 with IC_{50} values of 40.3, 22.0, and 32.8 mM, respectively [24].

Endophytic fungus Pestalotiopsis karstenii isolated from Camellia sasanqua in Nanning, Guangxi Province, China. Two new compounds were identified, namely Pestalrone A and Pestalrone B. The fungal strains were then cultured on PDA agar medium at 28°C for 10 days. Pestalrone A and Pestalrone B were tested for their cytotoxic activity against five human tumor cell lines (HeLa, U-251, A549, HepG2, and MCF-7) with DDP as a positive control. As a result, Pestalrone A had no inhibitory effect, while Pestalrone B showed significant cytotoxic activity against HeLa, HepG2, and U-251, with IC_{50} values of 12.6, 31.7 and 5.4 g/mL, respectively [25].

Endophytic fungus Pestalotiopsis sp. isolated from Podocarpus macrophyllus (Thunb.) in Kunming, China. Two new compounds were found, namely Pestaloquinols A and Pestaloquinols B. These compounds were then tested for cytotoxicity against HeLa cells. The result is that both compounds have cytotoxicity activity with an IC_{50} value of 8.8 M [26].

CONCLUSION

Endophytic fungi are a natural source of cancer drugs in the future, especially their ability to inhibit the growth of various cancer cells, including cervical cancer (HeLa cells). Based on several research results indicate types of endophytic fungi such as Penicillium citrinum, Pestalotiopsis fici, Talaromyces radicus, Perenniporia tephropora, Penicillium chrysogenum, Pestalotiopsis foedan, Pestalotiopsis photiniae, Pestalotiopsis vaccinia, Pestalotiopsis karstenii and Pestalotiopsis sp. isolated from various types of plants have cytotoxic activity against HeLa cells by inhibiting the proliferation of HeLa tumor cells.

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