Review

In-silico Molecular Docking and Bibliometric Analyses of Dyes Used in Photodynamic Therapy in Cervical Cancer

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Article

In-Silico Molecular Docking and Bibliometric Analyses of Dyes Used in Photodynamic Therapy in Cervical Cancer

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Abstract: Cervical cancer is a significant global health concern, with human papillomavirus (HPV) infection being a crucial risk factor. Photodynamic therapy (PDT) is an attractive, minimally invasive treatment for HPV-related cervical lesions, which uses photosensitizers and light to selectively destroy abnormal cells. We aim to provide an overview of the various sorts of dyes that are utilized in PDT for decreasing the incidence and mortality of cervical cancer. Besides, the article discusses ongoing clinical trials for PDT in low-grade squamous intraepithelial neoplasia (LSIL) and high-grade squamous intraepithelial lesions (HSIL), as well as preclinical approaches for PDT in cervical cancer using various dyes. Moreover, it highlights potential dyes for PDT, examine them in *in-silico* condition, their pros and cons and also the solutions for enhancing their anticancer compatibility. We also display that PDT is a promising therapeutic strategy for the diagnosis and treatment of HPV-associated cervical lesions. Moreover, it shows that using different classes of dyes improves the anticancer effects of PDT. Finally, among all dyes which are used in PDT, Fullerene demonstrated high tendency to over expressed receptors in cervical cancer cells and seems to be a proper candidate for be used in PDT more than before, but further research is necessary to assess its long-term efficacy and safety.

Keywords: cervical cancer; human papillomavirus (HPV); photodynamic therapy (PDT); squamous intraepithelial neoplasia; bibliometric analysis; molecular docking; fullerene

1. Introduction

Cervical cancer is a leading cause of cancer-related deaths in women worldwide [1]. Human papillomavirus (HPV) is a major risk factor for the development of cervical cancer [2]. Cervical lesions that precede cancer development are often difficult to diagnose and treat using conventional methods. CIN1, CIN2, CIN3, HSIL, and LSIL are all precancerous lesions that can develop in the cells

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lining the cervix (Table 1). LSIL is the mildest of these lesions, while CIN2 is intermediate and CIN3 is the most severe. HSIL includes both CIN2 and CIN3, and is considered a high-risk precursor to cervical cancer. Without treatment, HSIL has a higher risk of progressing to cancer than LSIL or CIN1.

To address this challenge, researchers have developed an innovative technology that uses photodynamic therapy (PDT) to increase the efficiency of diagnosis and treatment of background and precancerous lesions of the cervix associated with HPV [3]. PDT is a minimally invasive therapeutic approach that involves the use of photosensitizers and light to selectively destroy abnormal cells [3]. The new technology uses a combination of a fluorescent dye and a special imaging system that enables real-time visualization of cervical lesions [4,5]. During the procedure, the photosensitizer is applied to the cervix, and the area is illuminated with light of a specific wavelength [6]. The photosensitizer then produces reactive oxygen species that selectively destroy abnormal cells [7]. This targeted approach reduces the risk of damage to healthy cells and improves the effectiveness of treatment [8]. In addition, the imaging system used in this technology allows for accurate and efficient diagnosis of cervical lesions associated with HPV [9]. By detecting lesions in their early stages, this technology can lead to more effective treatment and improved patient outcomes [4,10].

Table 1. Different types of cervical cancer based on histology indices [11].

Abnormality	Description	Histology	Risk of Progression
LSIL	Low-grade squamous intraepithelial lesion	CIN1	Low
CIN1	Cervical intraepithelial neoplasia 1	Mild dysplasia	Low
CIN2	Cervical intraepithelial neoplasia 2	Moderate dysplasia	Moderate
CIN3	Cervical intraepithelial neoplasia 3	Severe dysplasia/carcinoma in situ	High
HSIL	High-grade squamous intraepithelial lesion	CIN2-CIN3	High
ASC-US	Atypical squamous cells of undetermined significance	-	-
ASC-H	Atypical squamous cells, cannot exclude HSIL	-	-

The development of this innovative technology represents a significant step forward in the diagnosis and treatment of HPV-associated cervical lesions. By improving the accuracy and effectiveness of diagnosis and treatment, this technology has the potential to reduce the incidence and mortality of cervical cancer worldwide.

One aspect of the development of PDT is choosing the best dye for this procedure. In other words, there are various dyes that have been used in this method during recent years but recognizing and evaluating them is important to develop brand-new photosensitizers with higher anticancer ability and more convenience of use [12].

In this article, we aim to provide an overview of the potential benefits of PDT in reducing the incidence and mortality of cervical cancer. We will summarize the safety and effectiveness of PDT for patients with high-risk low-grade squamous intraepithelial neoplasia (LSIL) of the cervix, cervical ectropion, high-risk HPV infection, postmenopausal women with persistent HPV infection and/or low-grade cervical neoplasia (CIN1).

For this purpose, we investigate the use of PDT for the treatment of cervical cancer based on bibliometric analysis. Number of studies explored the applications of PDT in this field, with photo chemotherapy, nanoparticles, and photosensitizing agents were evaluated. Additionally, we tried to

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find the highest binding affinity of those molecules to overexpressed receptors in cervical cancer cells, suggesting it could be a promising agent for use in PDT.

2. Results and Discussion

2.1. PubMed online data base analysis for PDT of cervical cancer

An analysis of the PubMed online database revealed 134 surveys were found from 2006 to 2023 that have examined the applications of PDT in the field of treating cervical cancer cells (Figure 1). The number of studies about the applications of PDT in the field of treating cervical cancer cells has decreased since 2019.

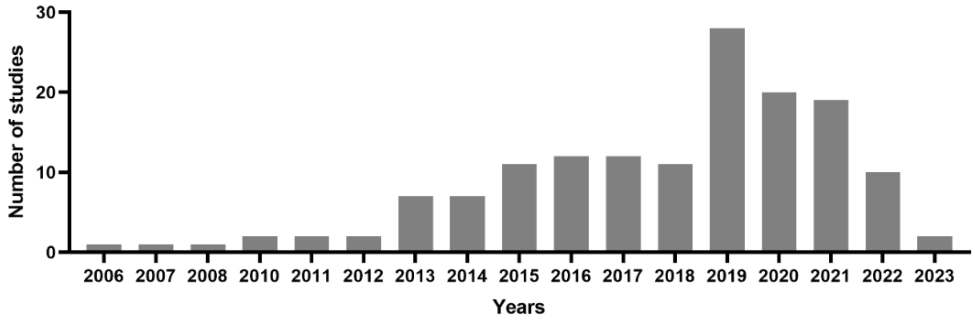

Figure 1. The number of studies about the usages of photodynamic therapy in the field of treating cervical cancer cells.

2.2. Photo chemotherapy, nanoparticles and photosensitizing agents were the most frequent MeSH keywords that have been used in the field of the usages of PDT in the field of treating cervical cancer cells

VOSviewer software analysis categorized all 134 studies into 36 items, 4 clusters, 542 links and total link strength of 3211. Moreover, according to analysis of VOSviewer software on all 134 surveys that have investigated the usages of PDT in the field of treating cervical cancer cells, it turned out that photo chemotherapy was the most frequent type of MeSH keyword till today (Figure 2 and Table 2). After photo chemotherapy, nanoparticles and photosensitizing agents were in the second and third place (Table 2).

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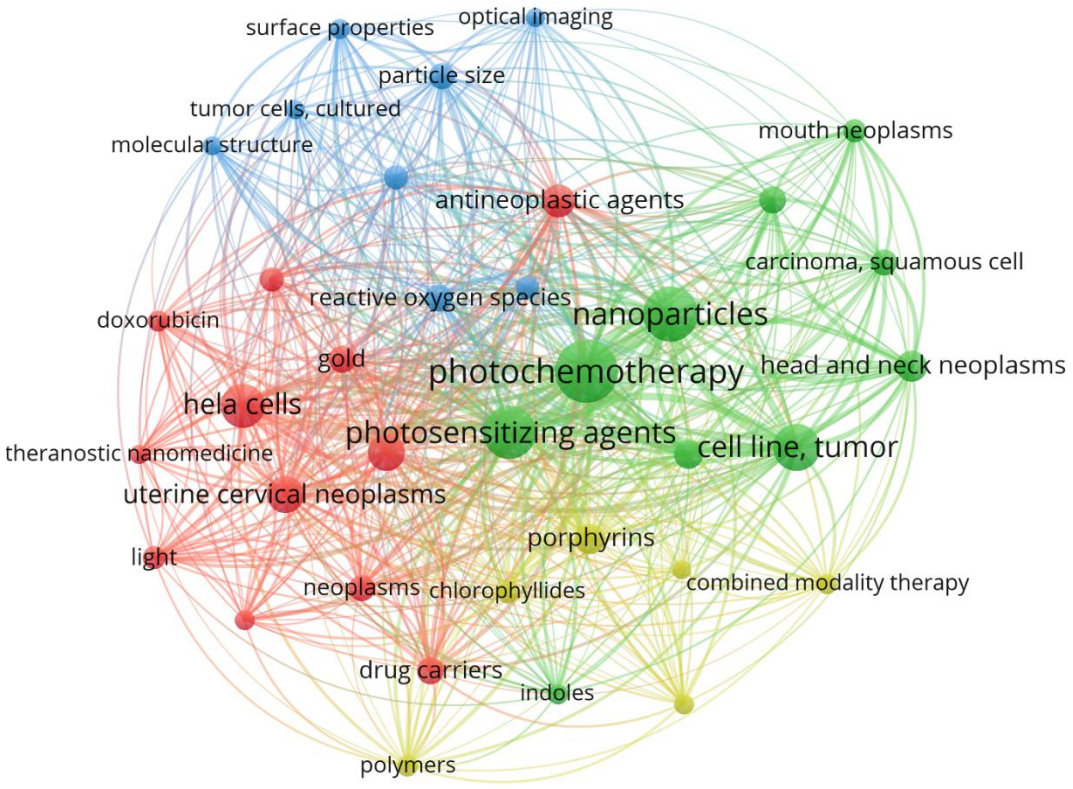

Figure 2. The most frequent MeSH keywords that have been used in the field of the usages of photo dynamic therapy in the field of treating cervical cancer cells. The size of square of each key-word represents the frequency of it.

Table 2. Three most frequent keywords in the studies that have investigated the usages of photodynamic therapy in the field of treating cervical cancer cells.

Keywords	Cluster	Link	Total link strength	Occurrence
Photo chemotherapy	2	35	692	110
Nanoparticles	2	35	525	84
Photosensitizing agents	2	35	523	78

2.3. Fullerene has the most binding affinity to overexpressed receptors in cervical cancer cells

Table 3 shows that Fullerene exhibited the highest binding affinity to receptors that are overexpressed in cervical cancer cells. Additionally, Figure 3 displays all participant molecules and interactions involved in the binding process of Fullerene with mentioned receptors. The 2D structures of Fullerene with the highest affinity to the mentioned receptors is shown in Figure 4.

Table 3. The affinity of dyes that have been used in photodynamic therapy to the of receptors that are overexpressed in cervical cancer cells (Kcal/mole).

	Receptor								
Dye	**FRα***	**TR1**	**EGFR**	**CD13**	**CD44**	**CD133**	**VCAM-1**	**VEGFR**	**BR**
5-aminolevulinic acid	-5.3	-5.0	-4.4	-5.3	-4.5	-3.2	-4.2	-3.2	-5.1
Protoporphyrin IX	-10.1	-9.9	-11.0	-11.5	-8.6	-5.5	-8.4	-6.6	-10.1
Hematoporphyrin	-8.4	-9.9	-10.7	-11.0	-8.5	-5.6	-8.7	-6.4	-9.5
Zinc phthalocyanine	-14.8	-13.9	-15.9	-15.7	-12.3	-8.4	-11.5	-9.7	-15.0
Chlorin e6	-11.5	-10.9	-9.9	-12.7	-9.5	-6.6	-9.3	-7.4	-11.8
Talaporfin Sodium	-13.1	-13.3	-13.5	-17.0	-12.3	-8.2	-12.4	-8.6	-13.3
Indocyanine Green (ICG)	-15.8	-10.7	-10.7	-12.7	-8.9	-7.5	-8.1	-6.6	-11.2
Rose Bengal	-11.9	-12.6	-9.9	-13.4	-11.4	-7.4	-10.2	-7.9	-9.6

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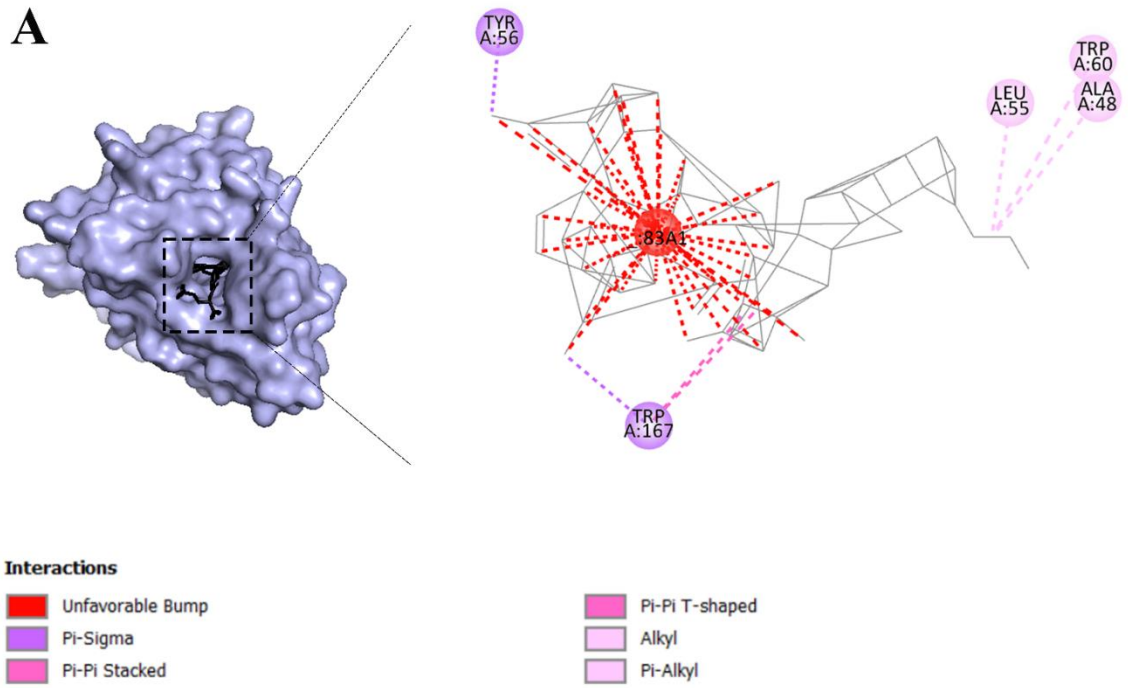
Photofrin	-9.8	-9.6	-10.8	-11.2	-8.5	-5.6	-8.5	-6.6	-9.7
Hypericin	-13.3	-13.8	-16.0	-15.3	-14.1	-7.8	-12.2	-10.0	-12.4
Methylene Blue	-10.5	-8.1	-8.1	-8.2	-6.8	-5.0	-6.6	-4.9	-8.6
Curcumin	-10.9	-8.8	-7.8	-8.2	-7.3	-5.6	-6.7	-5.5	-8.9
Texaphyrin	-10.9	-11.6	-11.8	-11.8	-10.7	-7.1	-8.6	-7.2	-10.7
Bacteriochlorin	-12.6	-10.3	-11.0	-10.8	-10.3	-6.5	-8.3	-7.2	-9.4
Fullerene	-39.1	-30.1	-22.7	-28.4	-26.8	-19.9	-22.3	-23.0	-29.3
Eosin	-13.0	-13.1	-14.0	-13.6	-12.1	-7.4	-10.2	-8.6	-11.5
Erythrosine	-10.7	-11.2	-10.7	-11.9	-10.2	-6.9	-8.6	-7.5	-9.8
Methyl Violet	-11.7	-8.4	-7.6	-8.4	-7.0	-5.5	-6.5	-5.7	-8.0
Aluminum phthalocyanine chloride	-15.3	-15.6	-15.0	-16.2	-12.9	-9.0	-11.5	-10.2	-15.1

*Folate receptor α (FRα), Transferrin receptor 1 (TR1), Epidermal growth factor receptor (EGFR), Prominin 1 (CD133), vascular endothelial growth factor receptor (VEGFR), vascular cell adhesion molecule 1 (VCAM-1), Aminopeptidase-N (CD13) and Biotin receptor (BR).



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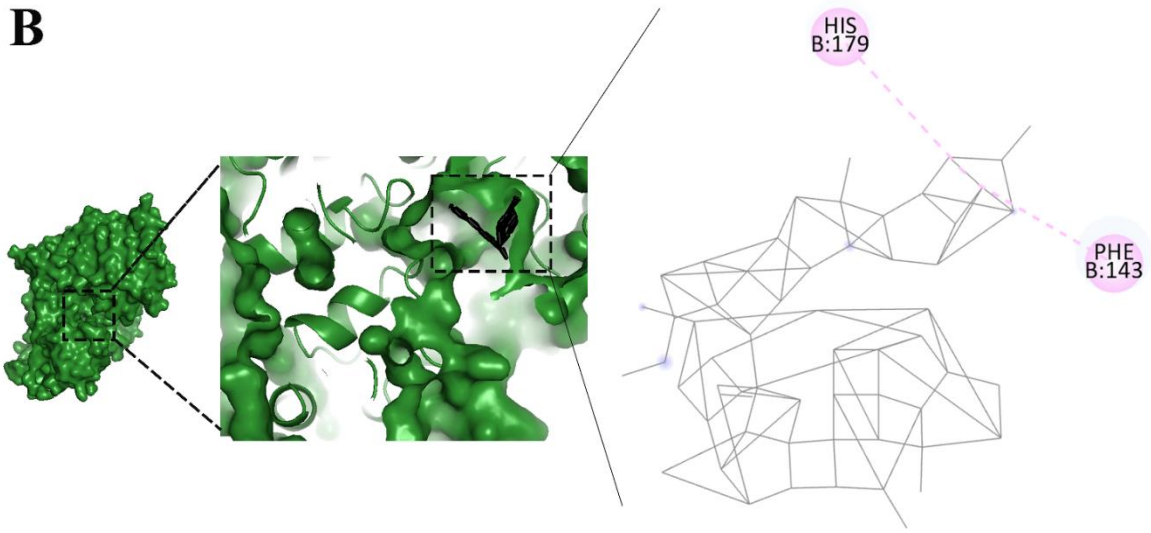
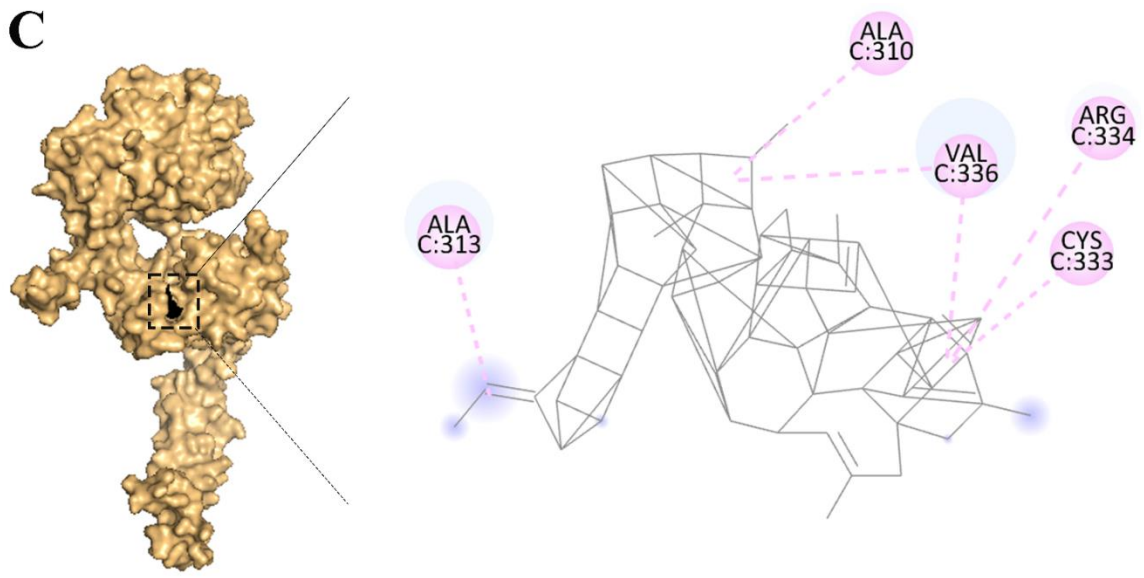


Interactions

Pi-Alkyl



Interactions

Alkyl

Pi-Alkyl

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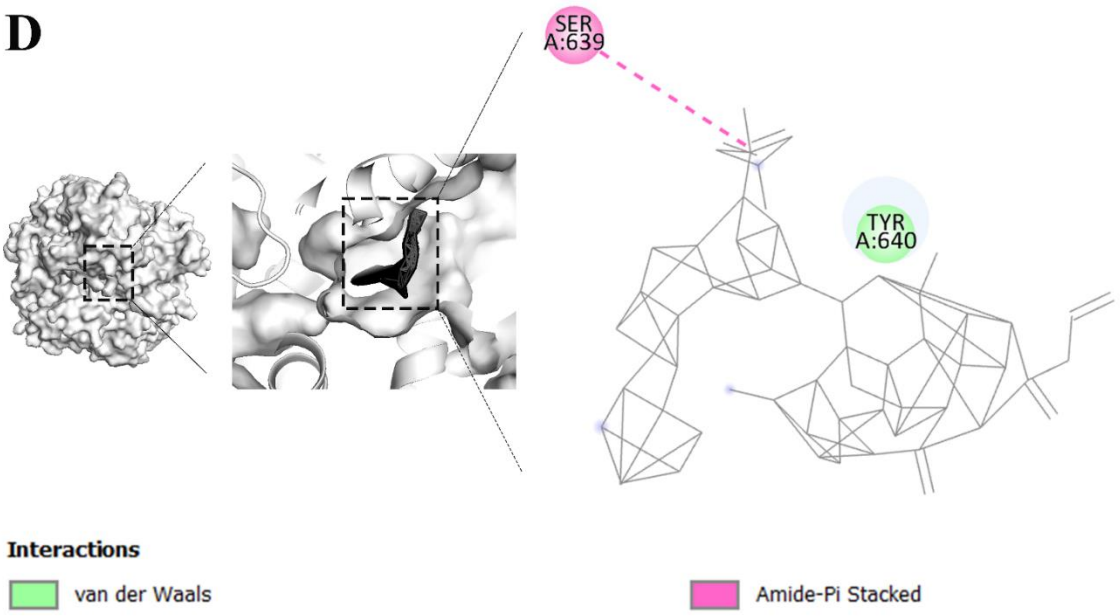

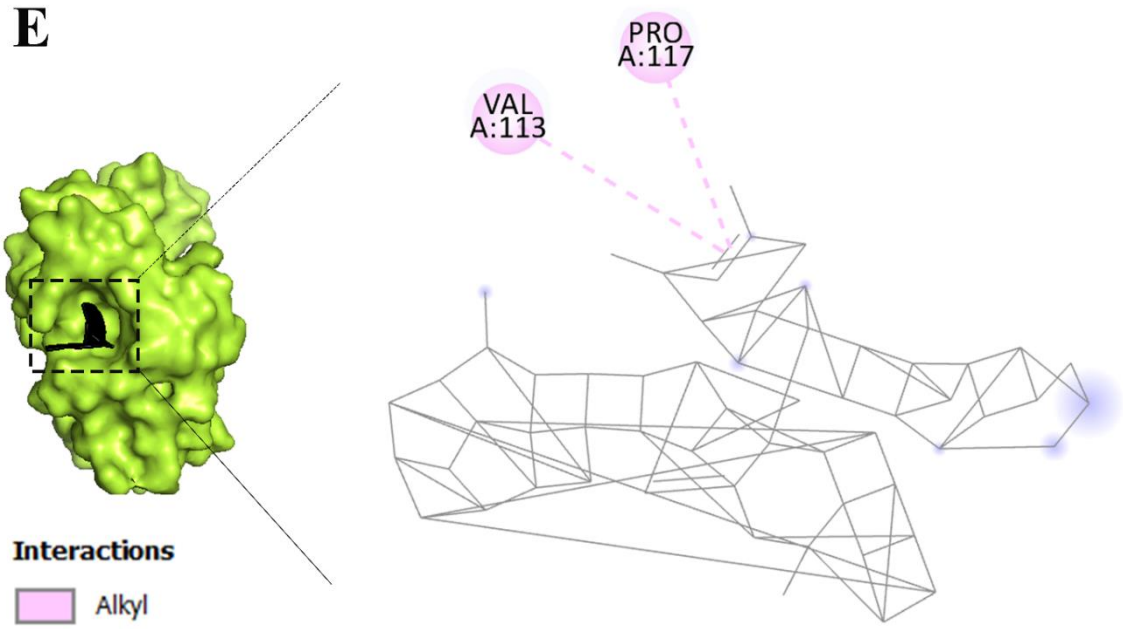

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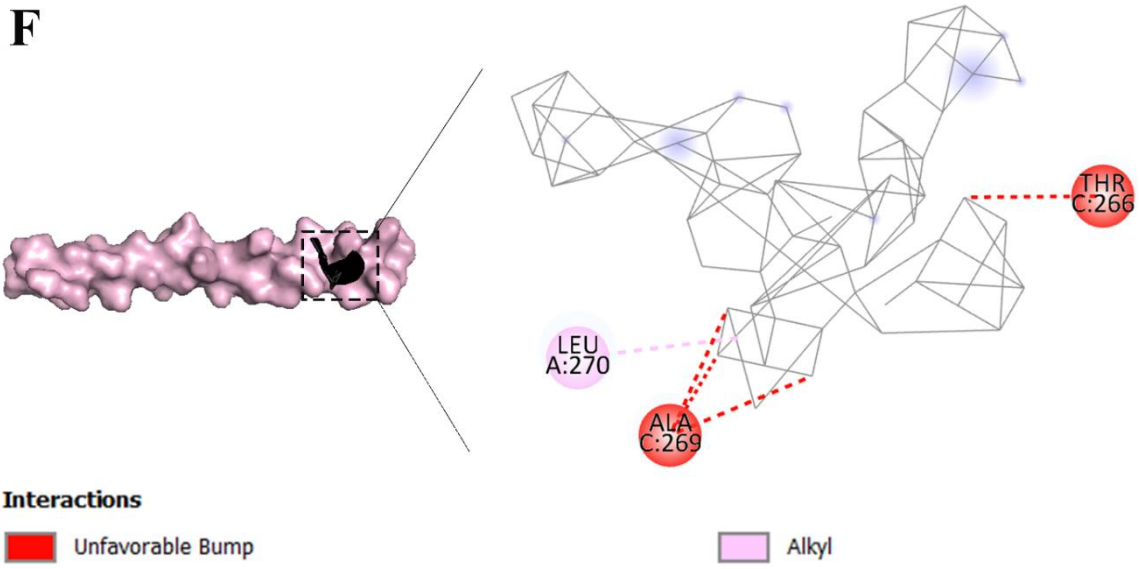

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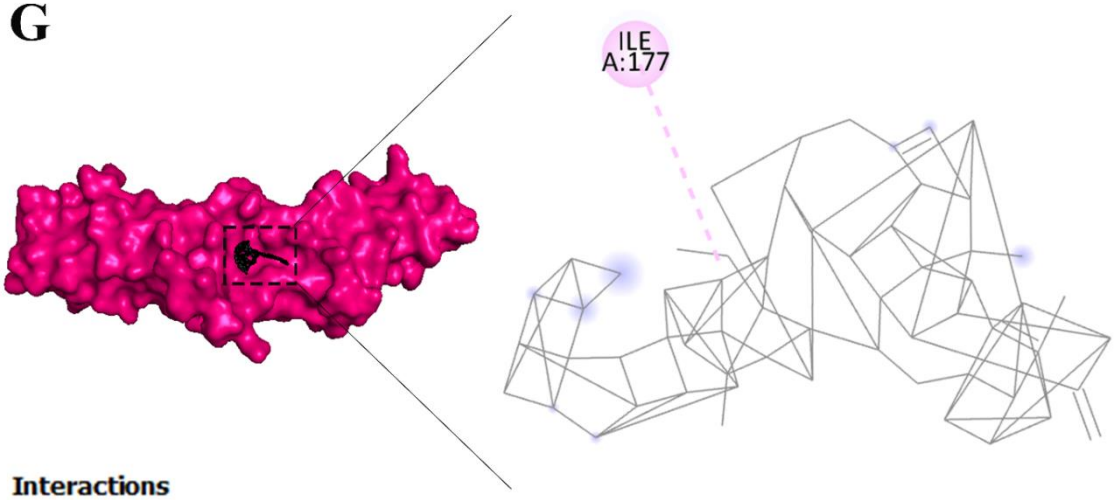

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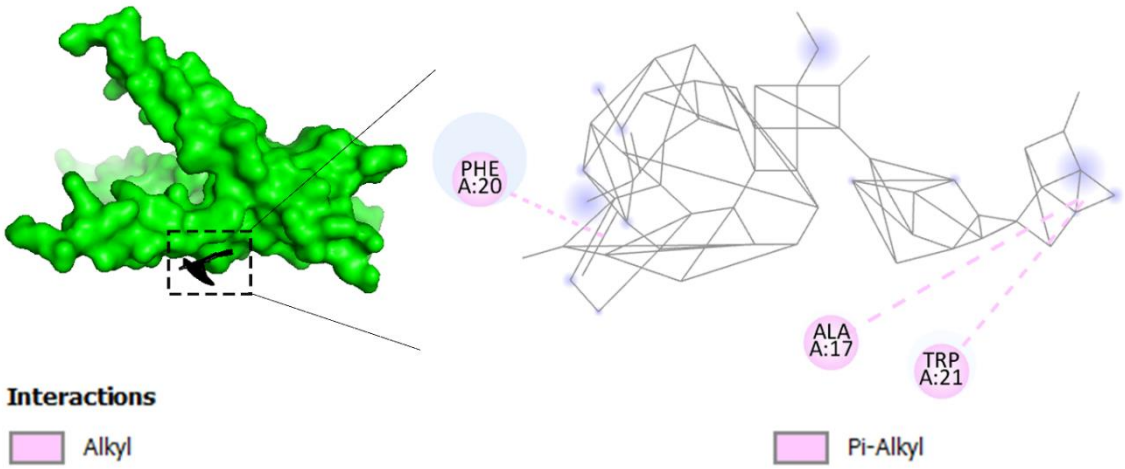

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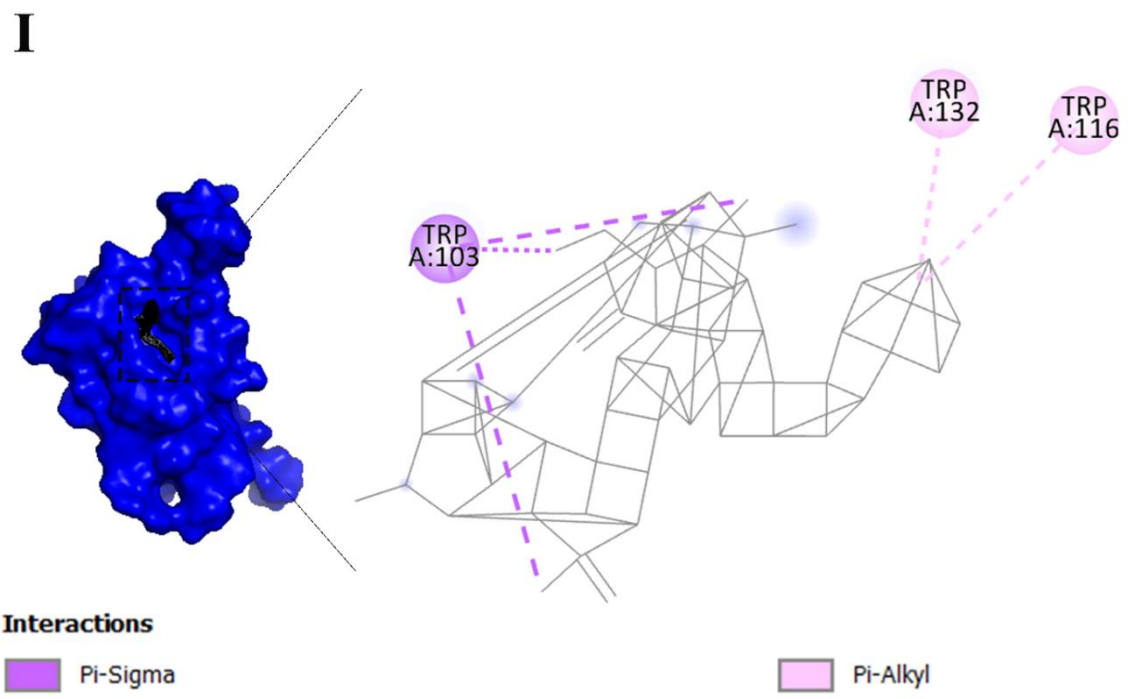

Figure 3. The molecules and interactions that are involved in the binding site of best binding conformation Fullerene and the overexpressed receptors in cervical cancer. The interactions between Fullerene and following receptors: Folate receptor α (FRα) (A), Transferrin receptor 1 (TR1) (B), Epidermal growth factor receptor (EGFR) (C), Aminopeptidase-N (CD13) (D), CD44 (E), Prominin 1 (CD133) (F), Vascular cell adhesion molecule 1 (VCAM-1) (G), Vascular endothelial growth factor receptor (VEGFR) (H), and Biotin receptor (BR) (I) are demonstrated in details.

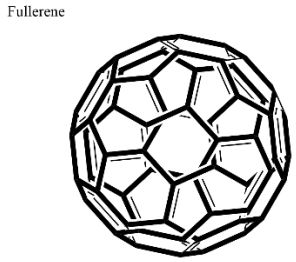

Figure 4. The 2D structure of Fullerene.

2.4. PDT as a novel approach for cervical cancer therapy

Although previous studies have mentioned the benefits of PDT in treatment of cervical cancer [25], our analysis demonstrated that the number of studies about the application of PDT in treatment of cervical cancer has decreased since 2019. This result is in contrast to the findings of prior researches.

2.5. Photo chemotherapy, nanoparticles and photosensitizing agents were the most frequent MeSH keywords that have been used in the field of the usages of PDT in the field of treating cervical cancer cells

This study showed that photo chemotherapy were the most frequent MeSH keywords that have been used in the field of the usages of PDT in the field of treating cervical cancer cells (Table 2, Figure 2). After that, nanoparticles and photosensitizing agents are in second and third place, respectively. In better words, in order to increase the efficacy of anticancer treatment in cervical cancer, scientists have tried to combine PDT with chemotherapy [26]. Our finding is confirmed by this result.

On the other side, researcher have tried to improve the delivery of photosensitizing agents in order to increase the efficacy of PDT. One of the strategies for this purpose is using nanoparticles [27].

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In better words, during recent years, studies are going forward to examine the application of nanoparticles in order to increase the delivery and efficacy of photosensitizers in PDT [27]. This fact validates our findings obtained from our analysis.

2.6. Fullerene with the best affinity to overexpressed receptors in cervical cancer

Previous studies have remarketed that scientists have been trying to increase the delivery of photosensitizers to cancer cells to improve the efficacy of PDT [27]. This studies have also remarked that receptors that are overexpressed on the surface of cancer cells can be a potential binding site for photosensitizers (Figure 5) [27]. Thus, it can be said that the photosensitizers with the most tendency to attach to overexpressed receptors on the surface of cancer cells can make the delivery of itself to cancer cell easier [27]. Thus, the photosensitizers that have the most tendency to mentioned receptor, can be considered as a proper candidate in order to be used in PDT. Our *in-silico* analysis demonstrated that Fullerene has the most affinity to overexpressed receptors I cervical cancer cells (Table 3). Therefore, it can be a photosensitizer with high potential for being used in PDT in order to treat cervical cancer but more *in-vitro* and *in-vivo* studies are needed to confirm this result.

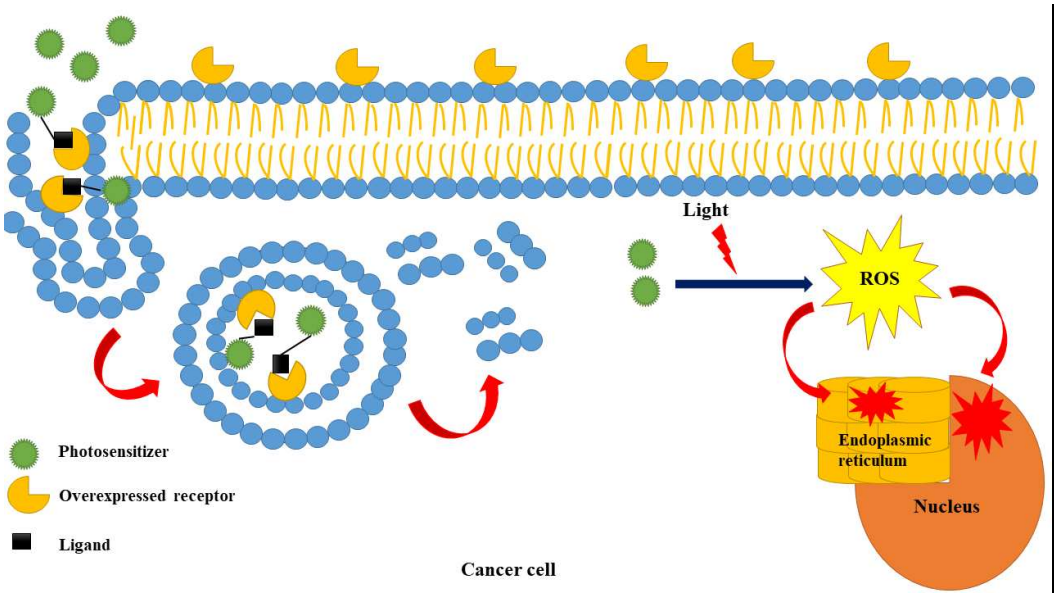

Figure 5. The role of overexpressed receptor in the process of death originated from photodynamic therapy in cervical cancer cells.

2.7. Approved dyes for clinical approaches of PDT of cervical cancer

There are different types of dyes which are used in PDT clinical studies of cervical cancers:

5-aminolevulinic acid (ALA): ALA is a photosensitizer that is used in PDT for cervical cancer [28]. A several clinical trials evaluated the safety and efficacy of ALA-PDT in patients with cervical intraepithelial neoplasia (CIN) (Tables 5 and 6). Further clinical studies are needed to evaluate the long-term efficacy of ALA-PDT in the treatment of cervical cancer.

Aluminum phthalocyanine chloride: Aluminum phthalocyanine chloride is a second-generation photosensitizer that is used in PDT for various cancers, including cervical cancer [29]. Further clinical studies are needed to evaluate the long-term efficacy of aluminum phthalocyanine chloride-mediated PDT in the treatment of cervical cancer.

Photofrin: Photofrin is a photosensitizer that has been approved for use in PDT for various cancers, including cervical cancer [28]. Further clinical studies are needed to evaluate the long-term efficacy of photofrin-mediated PDT in the treatment of cervical cancer.

Hexaminolevulinate: Hexaminolevulinate is a photosensitizer that is used in PDT for various cancers, including cervical cancer [28]. Further clinical studies are needed to evaluate the long-term efficacy of hexaminolevulinate-mediated PDT in the treatment of cervical cancer.

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Talaporfin sodium: Talaporfin sodium is a photosensitizer that has been approved for use in photodynamic therapy for various cancers, including cervical cancer [30]. Studies have shown that talaporfin-based PDT can be effective for treating cervical cancer [30].
Chlorin e6: Chlorin e6 is another photosensitizer that are used in PDT for cervical cancer [31]. It has a high absorption rate in the near-infrared region, which can penetrate deeper into tissue than other photosensitizers. It has also been shown to have high selectivity for cancer cells over healthy cells, making it a promising candidate for use in PDT [32].
Porphyrin derivatives: Porphyrin derivatives, such as protoporphyrin IX and hematoporphyrin derivatives, are natural photosensitizers that are used in PDT for cervical cancer [33]. These compounds are naturally occurring molecules in the body and have been shown to accumulate in cancer cells at higher rates than in healthy cells. When exposed to light at a specific wavelength, these photosensitizers generate reactive oxygen species that can destroy cancer cells [34].
Texaphyrins: Texaphyrins are a class of synthetic molecules that have been investigated for their potential use in PDT for various cancers, including cervical cancer [35]. Preclinical studies have shown that texaphyrin-based PDT can be effective for inducing cell death in cancer cells [36].

2.8. Clinical trials for PDT for LSIL

There have been several clinical trials, pilot, retrospective and prospective studies investigating the use of PDT for the treatment of LSIL using different photosensitizing dyes (Table 4). Clinical trials investigating the use of PDT for the treatment of LSIL have shown promising results using different photosensitizing dyes, including ALA, Aluminum phthalocyanine chloride, photofrin, hexaminolevulinate, talaporfin sodium and chlorin e6. Further studies are needed to confirm the efficacy and safety of these treatments and to determine the optimal treatment parameters.

Table 4. Treatment of low-grade squamous intraepithelial lesion with photodynamic therapy.

Dye	Patients	CR (%)	Type	Country	References
5-aminolevulinic acid	115	79.0	Phase 3	China Hungary Germany Slovakia	[37]
	48	88.6	Retrospective	China	[38]
	110	81.8	Prospective	China	[39]
	97	92.0	Prospective	China	[40]
	51	79.4	Prospective	Japan	[41]
	176	84.7	Pilot	China	[42]
	46	65.2	Retrospective	China	[43]
	30	73.3	Retrospective	China	[44]
	66	75.0	Retrospective	Brazil USA	[45]
	39	76.9	Prospective	China	[46]
	12	33.0	Prospective	UK	[47]
	22	63.6	Prospective	China	[48]
	79	90.7	Prospective	China	[49]
	44	88.6	Retrospective	China	[50]
	30	80.0	Prospective	Mexico	[51]
	55	90.0	Retrospective	China	[43]
Aluminum phthalocyanine chloride	11	91.7	Prospective	Brazil	[29]
Chlorin e6	18	88.9	Prospective	China	[31]

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	18	100	Prospective	Russia	[3]
Chlorin e6 + Photofrin	28	82.0	Retrospective	Russia	[52]
Hexaminolevulinate	262	95.0	Phase 2	Germany Norway	[53]
Photofrin	105	90.0	Prospective	Japan	[54]
Talaporfin sodium	9	88.9	Prospective	Japan	[30]

2.9. Clinical trials for PDT for HSIL

HSIL are more advanced precancerous lesions that have a higher risk of progressing to cervical cancer. Several dyes have been tested for photodynamic therapy (PDT) for HSIL in clinical trials (Table 5), including ALA, chlorin e6, porphyrin, and hexaminolevulinate. Although these dyes have shown promising results in terms of complete response rates, they have also been associated with higher recurrence rates compared to surgical treatments such as CKC. Further research is needed to optimize the effectiveness and safety of PDT for HSIL.

Table 5. Treatment of high-grade squamous intraepithelial lesion with photodynamic therapy.

Dye	Patients	CR (%)	Date	Type	Country	References
5-aminolevulinic	148	86.5	2022	Retrospective	China	[55]
acid	32	31.0	2002	Phase 1&2	United States	[56]
	7	42.0	1999	Prospective	Germany	[57]
	8	50.0	2021	Prospective	China	[48]
	5	80.0	2010	Prospective	China	[58]
	68	88.2	2022	Retrospective	China	[59]
	183	71.0	2022	Prospective	China	[60]
	96	89.5	2022	Retrospective	China	[61]
	99	88.9	2022	Retrospective	China	[62]
Porphyrin	20	91.0	2016	Retrospective	Korea	[63]
	88	53.4	2010	Prospective	Belarus	[64]
	46	87.0	2013	Retrospective	Korea	[65]
	34	97.1	2022	Retrospective	Korea	[66]
	49	90.4	2008	Prospective	Russia	[67]
	28	90.0	2003	Prospective	Japan	[33]
Chlorin e6	18	72.2	2022	Prospective	China	[31]
	24	70.0	2022	Prospective	Russia	[3]
Hexaminolevulinate	24	63.0	2008	Prospective	Germany	[68]

According to the information registered in the clinicaltrials.gov, among the 591 studies registered on photodynamic therapy of various types of cancer until the end of March 2023, only seven studies were related to cervical cancer, the information of which is shown in Table 6. Based on the information contained in the clinicaltrials.gov (Table 6) as well as the published clinical articles in Tables 5 and 6 and their analysis, Figures 6 and 7 were obtained. Figure 6 shows the frequency of applications of dyes in PDT of cervical cancer in which 5-aminolevulinic acid is ranked the first. In addition, the China is ranked the first in terms of clinical studies on PDT of cervical cancer (Figure 7).

Table 6. Clinical trials on of treatment of cervical cancer with photodynamic therapy during 1999-2023 (U. S. National Library of Medicine).

Dye	NCT number	Type of cancer	Status	Country	Start Date	Phase

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Lutetium texaphyrin	NCT00005808	CIN 2 &3	Terminated	United States	2000	1
Taporfin Sodium	NCT00028405	CIN	Completed	United States	2001	1
Aminolaevulinic acid	NCT00369018	CIN	Completed	Germany Norway	2006	1&2
	NCT00708942	CIN	Terminated	France Germany Norway	2009	2
	NCT01256424	CIN	Completed	Germany Norway	2011	2
	NCT02304770	Persistent High-Risk HPV Infection CIN	Completed	China	2015	2
	NCT02631863	CIN LSIL Papillomavirus Infections	Completed	China	2016	2
	NCT04484415	CIN 2 &3	Completed	China	2022	3

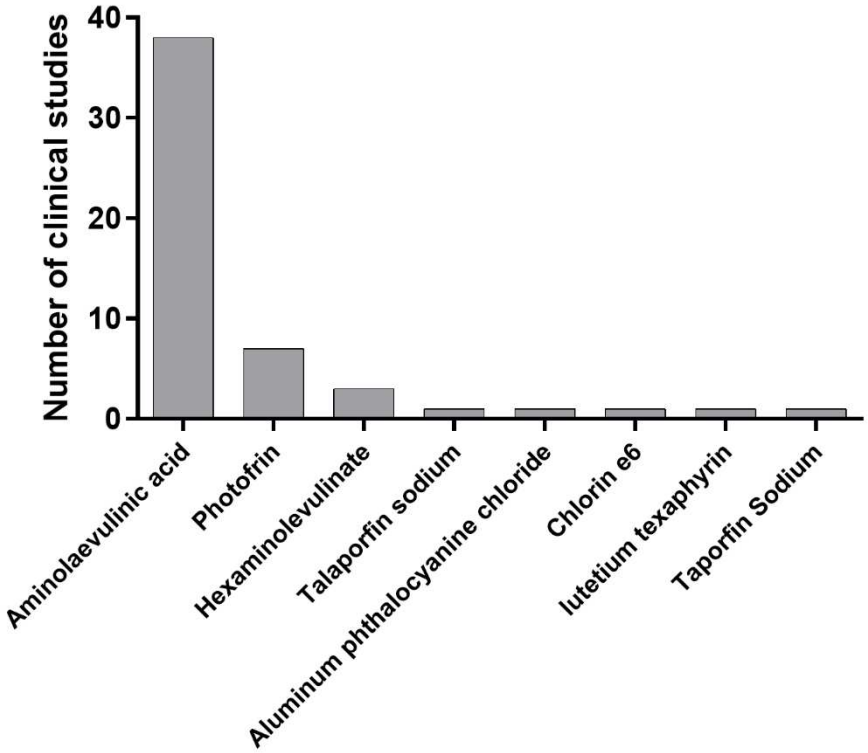

Figure 6. Frequency of application of dyes for photodynamic therapy of cervical cancer during 1999-2023 in clinical trials.

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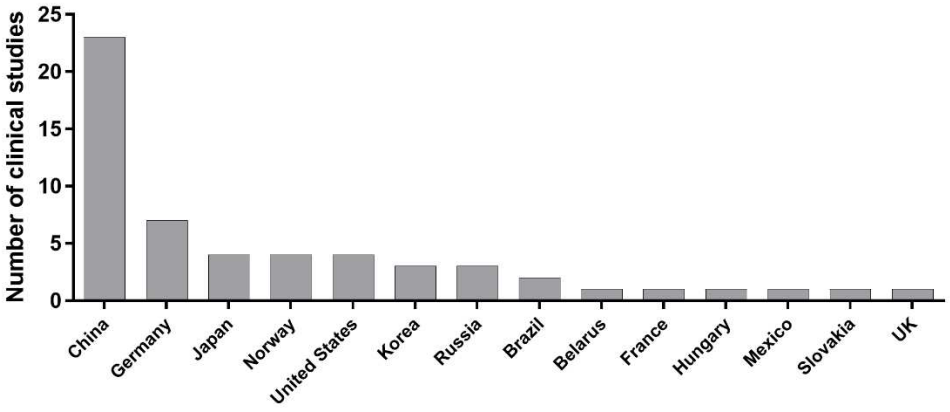

Figure 7. Frequency of country contributions in clinical trials on photodynamic therapy of cervical cancer during 1999-2023.

2.10. Preclinical approaches of PDT of cervical cancer

There are other kind of dyes are available for PDT of cervical cancer have shown promise in preclinical studies, further research is needed to determine their safety and efficacy in human trials (Table 7).

Curcumin: Curcumin is a natural polyphenol compound found in turmeric, and has been shown to have anti-cancer properties [69]. Studies have investigated the use of curcumin-based PDT for cervical cancer [70].

Hypericin: Hypericin is a compound found in St. John's wort. It has been found to have photosensitizing properties and has been used in PDT for cervical cancer [71]. When hypericin is activated by light, it produces reactive oxygen species that can damage cancer cells. Hypericin has been shown to be effective in killing cancer cells in vitro and in animal studies [72], but more research is needed to determine its effectiveness in humans.

Indocyanine green (ICG): ICG is a water-soluble near-infrared dye that has been used in PDT for various cancers, including cervical cancer [73]. Preclinical studies have shown that ICG can also be used for PDT of cervical cancer [74].

Methylene blue: Methylene blue is a blue dye that has been used in medicine for many years. It has been found to be effective in PDT for cervical cancer [75]. There are evidences showed that methylene blue-mediated PDT was effective in inducing cell death in cervical cancer cells [71,76].When methylene blue is activated by light, it produces reactive oxygen species that can damage cancer cells. Methylene blue has been shown to be effective in killing cancer cells in vitro and in animal studies, but more research is needed to determine its effectiveness in humans.

Rose Bengal: Rose Bengal is a red dye that has been used in medicine for many years. It has also been found to have photosensitizing properties and has been used in PDT for cervical cancer [72]. When Rose Bengal is activated by light, it produces reactive oxygen species that can damage cancer cells. Rose Bengal has been shown to be effective in killing cancer cells in vitro and in animal studies [72], but more research is needed to determine its effectiveness in humans.

Zinc phthalocyanine: This is a photosensitizer that can be used in PDT for cervical cancer [32]. It has a high absorption rate in the red-light region, which makes it effective for use in PDT. When exposed to light at a specific wavelength, the photosensitizer generates reactive oxygen species that can destroy cancer cells [32].

Table 7. Comparison of different dyes for photodynamic therapy (PDT) in cervical cancer with approve preclinical effects.

Dye	Pros	Cons
Curcumin	Natural compound with low toxicity	Limited water solubility Low bioavailability

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	Anti-inflammatory and antioxidant properties Has been shown to induce cell death in cancer cells Potential for tumor-selective accumulation	Requires activation by light
Hypericin	High tumor selectivity Good tissue penetration	Requires activation by light Potential skin photosensitivity
Methylene blue	FDA-approved Low toxicity	Low tumor selectivity Requires high concentrations
Indocyanine green	FDA-approved for clinical use High water solubility Can be activated by near-infrared light Allowing for deeper tissue penetration	Limited tumor selectivity Rapid clearance from the body May require high doses for therapeutic effect Potential for skin photosensitivity and allergic reactions.
Rose Bengal	Good tumor selectivity Low toxicity	Requires activation by light Potential skin photosensitivity
Zinc phthalocyanine	High absorbance in the red spectrum Good tumor selectivity	Low water solubility Potential toxicity

2.11. Potential dyes for PDT of cervical cancer

There are several dyes that have been investigated for their potential use in PDT for various cancer in preclinical studies, but have not yet been used in cervical cancer settings.

Other chlorophyll derivatives except chlorin e6: Chlorophyll and its derivatives (including chlorin e6) have been investigated for their potential use in PDT for various cancers, including cervical cancer [77]. Studies have shown that chlorophyll-based PDT can induce apoptosis in cancer cells [78].

Methyl violet: Methyl violet is a cationic dye that has been shown to have photodynamic activity [79]. Preclinical studies have investigated the use of methylene violet-based PDT for cancer [79].

Bacteriochlorins: Bacteriochlorins are a class of photosensitizers that have been investigated for their potential use in PDT for various cancers [80]. There is no study to show that bacteriochlorin-based PDT can be effective for treating cervical cancer.

Fullerenes: Fullerenes are a class of carbon molecules that have been investigated for their potential use in PDT for various cancers [81]. Preclinical studies have shown that fullerene-based PDT can be effective for inducing cell death in cancer cells [82].

Xanthene dyes: Xanthene dyes such as eosin and erythrosine are a class of fluorescent dyes that have been used in various applications, including as photosensitizers in PDT for various cancers [82].

2.12. Scoring of application of dyes for PDT of cervical cancer

The scores in Table 8 are calculated based on a weighted scoring system, where each parameter is given a score between 1 and 5, depending on its relative importance. For the clinical application section, the following parameters are considered.

FDA approval status: if a dye has been approved by the FDA for clinical use, it is given a score of 5. If it is in clinical trials, it is given a score of 4. If it has only been tested in preclinical studies, it is given a score of 3. If there is no data available, it is given a score of 1.

Efficacy: this refers to the effectiveness of the dye in treating cervical cancer. If there is strong evidence supporting its efficacy, it is given a score of 5. If there is some evidence, it is given a score of 3. If there is little or no evidence, it is given a score of 1.

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Safety: this refers to the safety profile of the dye, including its potential for side effects. If there is strong evidence supporting its safety, it is given a score of 5. If there is some evidence, it is given a score of 3. If there is little or no evidence, it is given a score of 1.

For the preclinical and potential dyes section, the following parameters are considered:

Preclinical efficacy: this refers to the effectiveness of the dye in preclinical studies. If there is strong evidence supporting its efficacy, it is given a score of 5. If there is some evidence, it is given a score of 3. If there is little or no evidence, it is given a score of 1.

Preclinical safety: this refers to the safety profile of the dye in preclinical studies. If there is strong evidence supporting its safety, it is given a score of 5. If there is some evidence, it is given a score of 3. If there is little or no evidence, it is given a score of 1.

Potential for clinical translation: this refers to the potential for the dye to be translated into clinical use. If there is strong evidence supporting its potential for clinical use, it is given a score of 5. If there is some evidence, it is given a score of 3. If there is little or no evidence, it is given a score of 1.

The final score for each dye is calculated by summing the scores for each parameter and dividing by the total possible score (out of 25 for clinical application, and out of 15 for preclinical and potential dyes). The higher the final score, the better the dye is considered to be for use in PDT for cervical cancer.

Table 8. Scoring system for evaluation of various dyes used in clinical, preclinical, and potential applications of photodynamic therapy (PDT) for cervical cancer.

Dye	Clinical Studies*	Preclinical Studies	Potential Use	Overall Score
5-aminolevulinic acid	5	5	5	15
Porphyrin derivatives	5	5	5	15
Zinc phthalocyanine	5	5	3	13
Chlorin e6	4	5	4	13
Talaporfin Sodium	4	4	4	12
Indocyanine Green (ICG)	3	5	4	12
Rose Bengal	4	4	3	11
Photofrin	5	4	2	11
Hypericin	2	5	4	11
Methylene Blue	3	4	3	10
Curcumin	2	4	4	10
Texaphyrins	3	3	3	9
Chlorophyll Derivatives	2	3	3	8
Bacteriochlorins	2	3	3	8
Fullerenes	1	3	2	6
Xanthene Dyes (Eosin, Erythrosine)	1	2	2	5
Methyl Violet	1	2	2	5

* The scoring system is based on a scale of 1 to 5 for each category (clinical studies, preclinical studies, potential use) with 5 being the highest score. The overall score is the sum of the scores in each category.

2.13. Challenges and solutions related to using dyes for PDT of cervical cancer

One of the major challenges in using these dyes for cancer treatment is their limited solubility in water, which can reduce their effectiveness and increase their toxicity. However, nanotechnology can help overcome this challenge by improving the solubility and stability of the dyes, as well as enhancing their selective delivery to cancer cells [83].

Nanoparticle-based delivery systems have been developed for a variety of photosensitizers, including porphyrins, chlorophylls, and phycobilins. These nanoparticles can be designed to target specific cancer cells, enhance the photosensitizer's solubility and stability, and improve its

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biodistribution and pharmacokinetics. Additionally, some nanoparticles themselves can exhibit intrinsic anticancer activity and can enhance the therapeutic effect of PDT.

Overall, the combination of photosensitizers and nanotechnology has great potential for developing effective and targeted PDT for cervical cancer and other types of cancer.

There are some challenges related to the use of dyes for PDT of cervical cancer, besides their solubility. Here are some of them:

Tumor targeting: It can be a challenge to specifically target the dye to the tumor cells, while minimizing the uptake by healthy tissues, which could lead to toxicity.
Depth of penetration: The depth of penetration of the light used to activate the dye can be limited, which means that tumors located deeper in the body may be difficult to treat.
Photobleaching: Dyes can undergo photobleaching, which means that they lose their ability to generate reactive oxygen species upon exposure to light. This can limit their efficacy in PDT.
Stability: Some dyes can be unstable in biological environments, which can affect their efficacy and safety.
Regulatory approval: The regulatory approval of dyes for clinical use can be a lengthy and expensive process, which can limit their availability for PDT of cervical cancer.
Solubility: One challenge related to the use of dyes for PDT of cervical cancer is their solubility in biological fluids, which can affect their effectiveness and potential toxicity.

Some potential solutions to the challenges related to the use of dyes for PDT of cervical cancer are listed below:

Solubility: One solution could be to use lipid-based or polymeric nanocarriers to encapsulate the dye and improve its solubility and stability.
Tissue penetration: To improve tissue penetration, different delivery methods such as intra-tumoral injection or topical application may be explored.
Specificity: Specificity can be improved by utilizing targeting strategies such as ligand conjugation to the dye or by using activatable dyes that are only activated in cancer cells.
Photobleaching: Photobleaching can be reduced by optimizing the dye concentration and light dose, as well as by using photostable dyes.
Toxicity: Toxicity can be minimized by using lower doses of the dye and light, as well as by optimizing the drug delivery method to minimize off-target effects.
Regulatory approval: It is important to follow established regulatory guidelines for drug development and clinical trials to ensure safety and efficacy before seeking regulatory approval for clinical use.
Tumor targeting: Tumor targeting can be achieved through the use of targeted delivery systems, such as nanoparticles, stem cell derived exosomes or liposomes [84–87], which can be conjugated with specific ligands or antibodies that recognize and bind to tumor cells. This can increase the accumulation of the photosensitizer in the tumor, while minimizing its uptake in healthy tissues, thereby improving the selectivity of PDT and reducing off-target effects. Another approach is to use light sources with a specific wavelength that can selectively activate the photosensitizer in the tumor, while minimizing activation in surrounding healthy tissues.

3. Materials and Methods

3.1. Data collection and extraction for bibliometric analysis

In March 2023, we assessed PubMed online database in order to identify the most frequent keywords that have been used in the field of the usages of photo dynamic therapy in the field of treating cervical cancer cells with the following strategy: ((Cervical Cancer*[Title/Abstract]) OR (Cervical Cancer*[MeSH Terms]) OR (Cervical neoplas*[MeSH Terms]) OR (Cervical neoplas*[Title/Abstract]) OR (Cervical tumor*[Title/Abstract]) OR (Cervical tumor*[MeSH Terms])) AND ((photodynamic therapy[MeSH Terms]) OR (photodynamic therapy[Title/Abstract]) OR (photodynamic[Title/Abstract]) OR (photodynamic[MeSH Terms])) AND ((Nanomaterial[MeSH Terms]) OR (Nanomaterial[Title/Abstract]))

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In the next step, we analyzed the publications that resulted from our search by VOSviewer software (v.1.6.8, 2018). Mentioned software has the capability of analyzing the semantic contents of the titles of publications, keywords, abstracts and relating them to the citation count data and visualize the findings by producing a bubble map. We selected the most frequent MeSH keywords that have at least 10 occurrences in mentioned studies in order to perform our analysis by this software. Besides, we excluded some MeSH keywords from our analysis including: "humans, animals, male, female, mice and xenograft model antitumor assay". Finally, this software gave us the most frequent MeSH keywords that have been used in the field of the usages of photo dynamic therapy in the field of treating cervical cancer cells.

3.2. Molecular interactions and docking studies of receptors that are overexpressed in cervical cancer cells and various dyes that are used in PDT

The nine receptors which have been overexpressed on the surface of cervical cancer cells were extracted from prior studies [13–21] (Table 9).

Table 9. The list of receptors that are overexpressed in cervical cancer cells.

Receptor	Reference
Folate receptor α	[13]
Transferrin receptor 1	[14]
Epidermal growth factor receptor	[15]
CD44	[16]
Prominin 1 (CD133)	[17]
Vascular endothelial growth factor receptor 2	[18]
Vascular cell adhesion molecule-1	[19]
Aminopeptidase-N (CD13)	[20]
Biotin receptor	[21]

We then utilized Auto dock vina [22] to examine the binding affinity of all mentioned receptors to various dyes that are used in PDT (Table 9). We obtained the 3D structures of the 19 dyes and nine receptors (Folate receptor α (FRα), Transferrin receptor 1 (TR1), Epidermal growth factor receptor (EGFR), CD44, Vascular endothelial growth factor receptor 2 (VEGFR 2), Vascular cell adhesion molecule-1 (VCAM-1), Aminopeptidase-N (CD13) and Biotin receptor (BR)) from the PUBCHEM [23] and Protein Data Bank (PDB) databases. The PDB codes for these receptors were 4km6, 2nsu, 7sye, 1poz, 2met, 1vsc, 4fyq and 5n7x, respectively. Prominin 1 (CD133) was downloaded from UniProt with UniRef ID of UniRef90_O43490 [16].

In the next step, remodeling of receptors with SWISS-MODEL Server [15] was performed. We then merged nonpolar hydrogens and ione pairs and assigned Gasteiger partial charges to each ligand atom. Grid boxes were generated using the Computed Atlas of Surface Topography of proteins (CASTp 3.0). Finally, we conducted docking and achieved nine conformations for each receptor and dye. All docking conformations were ranked according to the binding affinity, and the conformation with the lowest negative energy and RMSD ≤ 2 Å was selected as the best one.

3.3. Visualization of inter-molecular interaction

The visualization of the 3D structure of the best conformations was performed using PyMOL software (The PyMOL Molecular Graphics System, Version 1.2r3pre, Schrödinger, LLC.). In addition, the detailed data about intermolecular interactions between the ligand and receptor were visualized in 2D using Discovery Studio Visualizer [24].

We will also discuss the limitations and future directions of PDT for the treatment of cervical lesions. After evaluating the current clinical applications of PDT, we discussed preclinical studies that have used different dyes, potential dyes for future studies on the application of PDT for cervical cancer. After that, we evaluate compounds with the potential of being dye in PDT in *in-silico* situation.

Finally, we discussed the current challenges and potential solutions for the application of PDT for cervical cancer.

3.4. Data collection and extraction for systematic analysis of dyes for PDT of cervical cancer

Furthermore, a comprehensive literature search was conducted to identify relevant articles on the use of PDT for the treatment of HPV-associated cervical lesions. The search was performed using several electronic databases, including PubMed, Embase, Scopus, and Web of Science. The search was limited to articles published in English language and from the year 1999 to the present.

The following keywords were used for the search: "photodynamic therapy", "cervical cancer", "cervical lesions", "human papillomavirus", "HPV", "precancerous lesions", "dye", "photosensitizer", and "cervix". The search was conducted by combining these keywords using Boolean operators (AND, OR). The titles and abstracts of the retrieved articles were screened to identify potentially relevant studies. The full text of these articles was then reviewed to determine their eligibility for inclusion in the analysis. In addition to the electronic database search, the reference lists of relevant articles were manually searched to identify additional studies that met the inclusion criteria.

The selection of articles for inclusion in this evaluation was based on the following criteria: (a) studies that evaluated the safety and efficacy of PDT in the treatment of HPV-associated cervical lesions, (b) studies that included patients with high-risk LSIL of the cervix, cervical ectropion, high-risk HPV infection, postmenopausal women with persistent HPV infection and/or CIN, and (c) studies that were published in peer-reviewed journals. Two reviewers independently screened the articles and resolved any discrepancies by discussion.

4. Conclusions

In conclusion, these findings suggest that research in the field of PDT for cervical cancer has been ongoing for several years, but it may have slowed down in recent years. Photo chemotherapy, nanoparticles, and photosensitizing agents appear to be the most commonly used approaches in these studies. Moreover, Fullerene is a promising candidate among the dyes used in PDT due to its high binding affinity to overexpressed receptors in cervical cancer cells. However, more research is necessary to confirm the potential of Fullerene and to develop effective PDT treatments for cervical cancer.

PDT using a combination of a fluorescent dye and special imaging system represents a significant advancement in the diagnosis and treatment of cervical lesions associated with HPV. This minimally invasive approach offers a targeted therapy for abnormal cells while reducing the risk of damage to healthy tissue. Additionally, research has demonstrated that ALA-PDT is an effective and safe alternative for treating CIN and HSIL associated with HPV. By detecting and treating these lesions early, PDT and ALA-PDT have the potential to reduce the incidence and mortality of cervical cancer worldwide. Continued research and development in this area may lead to further advancements in the diagnosis and treatment of HPV-associated cervical lesions, ultimately improving patient outcomes and reducing the global burden of cervical cancer.

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