Project on

A Review of the Therapeutic Potential of Natural products for the Treatment of Cervical Cancer

[In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy]

Submitted To

The Department of Pharmacy,

Faculty of Allied Health Sciences,

Daffodil International University

Submitted By

Student ID:191-29-199

Section: 21th DSC-B

Department of Pharmacy,

Faculty of Allied Health Sciences,

Daffodil International University

……..

May 2023

APPROVAL

This project paper, **"A Review of the Therapeutic Potential of Natural products for the Treatment of Cervical Cancer"** submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

BOARD OF EXAMINERS

……

Dr. Muniruddin Ahmed

Professor and Head,

Department of Pharmacy,

Faculty of Allied Health Sciences,

Daffodil International University

…… Internal Examiner 1

……. Internal Examiner 2

…… External Examiner 3

DECLARATION

I hereby declare that this project report, **"A Review of the Therapeutic Potential of Natural products for the Treatment of Cervical Cancer".** I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

Supervised By

……..

Mr. Shadhan Kumar Mondal

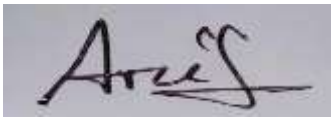
Lecturer

Department of Pharmacy

Faculty of Allied Health Sciences

Daffodil International University

Submitted By



……..

Md. Ariful Islam Bhuiyan

ID: 191-29-199

Department of Pharmacy

Faculty of Allied Health Sciences

Daffodil International University

ACKNOWLEDGEMENT

I might want to communicate my profound applause to the All-powerful Allah who has given me the capacity to finish my undertaking work and the chance to concentrate in this subject.

I'm a lot of thankful to my honorable project supervisor of Mr. Shadhan Kumar Mondal Lecturer, Department of Pharmacy, Daffodil International University for her brilliant direction and steady oversight just as for giving essential data in regards to the task and furthermore for her help in finishing the project.

I would like to express my humble regards to Dr. Muniruddin Ahmed, Professor and Head, Department of Pharmacy, Daffodil International University.

I also wish to offer my respect to all of the teachers of Pharmacy Department, Daffodil International University and thankful to other members for their excellent cooperation with us.

Finally, I would like to express my gratitude towards my parents and other family members for their kind cooperation and encouragement which helped me in completion of this project.

Dedicated…….

My Parents

The persons who always encourage me in every sphere of my life.

Abstract

Cervical cancer is the fourth most prevalent cancer among women worldwide. Regarding the fact that many natural products have been shown to be successful against cervical cancer, there hasn't been a comprehensive investigation that categorized them corresponding to their anti-cancer pathways. Investigators in the present research collected information on recent studies on natural treatments for cervical cancer published in Pubmed (which includes Medline) and Google Scholar. Apoptosis activation, angiogenesis suppression, metastatic suppression, resistance reduction, and miRNA regulation were the five groups into which their tactics fell. Cervical cancer was avoided by a total of 64 natural products. It has been demonstrated that several of these have numerous impacts against cervical cancer, including Penicillium sclerotiorum excerpts from Cassia Fistula L., ethanol extracts from Bauhinia variegate candida, thymoquinone obtained from Nigella sativa, lipid-soluble extracts of Pinellia pedatisecta Schott., and 1′S-1′-acetoxychavicol acquired from Alpinia in summary, ingredients might become desirable prospects for brand-new cancer medications.

Contents

List of figures

List of tables

Chapter I
Introduction

1. Introduction

Cervical cancer, or cervical cancer, is characterized by abnormal vaginal bleeding, vaginal discharge, pelvic pain, or pain during sexual action [1]. At present, cervical carcinoma is the fourth most prevalent cancer in women globally [2]. In accordance with Globocan 2018, cervical cancer accounts for 3.2% of all cancer occurrences. The primary therapies for cervical cancer are radiation, chemotherapy, and surgeries like radical hysterectomy and pelvic lymphadenectomy [3]. Specific treatment, which regulates the cyclooxygenase-2 (COX-2) and epidermal growth factor receptor (EGFR), is an alternative treatment for cervical cancer [4,5,6,7]. Yet these therapies did highlight possible dangers and negative effects: Menstruation, infertility, unpleasantness, or pain throughout sexual action are all possible side effects of radiotherapy. Surgery carries a danger of blood clots in the deep veins of the legs, bleeding, and harm to the nearby organs. Chemotherapy side effects in different body systems may impact both cancer cells and rapidly dividing cells [8, 9]. The commonly recommended therapies for cervical cancer were also associated with a number of side effects and resistance to drugs [10]. Cisplatin, one of the most potent anticancer drugs, has the capacity to fight off therapy by means of a defense mechanism [11]. 5-fluorouracil (5-FU) has also been connected to side effects and cases of tolerance in individuals with cervical cancer. [12]. Therefore, the main goal of our study has been to identify fresh, potent natural treatments for cervical cancer. Natural products produced from living things, including plants and animals, contain a number of active ingredients that are said to be suitable replacements for or additions to chemotherapeutic drugs [13,14]. For instance, refined flaxseed hydrolysate (PFH), which is separated from lignan, induces apoptosis in HeLa cells and inhibits angiogenesis and metastasis [15]. Thymoquinone from Nigella sativa also had an anti-proliferative and a lethal effect in SiHa and CaSki cells. Praeruptorin-B, Bauhinia variegate candida ethanol isolates, and renowned tea are among these natural components. MicroRNA regulates the pathological development and dissemination of cancer. (miRNA, miR) [16,17]. Many organic compounds have demonstrated anti-cancer effects by regulating miRNAs linked to cancer. Spatholobus suberectus Dunn extract induces apoptosis in U266, U937 cells by regulating miR-657/activating transcription factor 2 (ATF2), based to investigations conducted with our

group [18]. Another natural substance, Salvia miltiorrhiza, showed anti-cancer activity by regulating miR-216b [19]. It has been demonstrated that the 10S-10 -acetoxychavicol acetate (ACA) from Alpinia conchigera interacts with SMAD4 and miR-210 to induce apoptosis in SiHa and CaSki cells. Natural remedies for miRNA-targeted cervical cancer treatment have great potential. [20]. However, research over the past five years have not organized the causes, efficacy, and concentration of natural products for cervical cancer. The present study's goal is to evaluate nonclinical investigation into the anti-cancer properties of natural substances. The natural substances were organized according to their processes, including inhibiting angiogenesis, resistivity, and the regulation of microRNAs [19].

1.1 Epidemiology and risk factors of cervical cancer

Cervical cancer is the second most common cancer in women globally, and 80% of cases are found in less developed nations. In the USA, 13 000 women received a cervical cancer diagnosis in 2002, and 4100 of them would pass away as a result of the disease, based on the American Cancer Society. The typical age at identification is 47 in North America, where about half of cases are found before the age of 35. [21] Additionally, cervical cancer deaths are considerably more common in women over the age of 55, possibly as a result of the disease being more advanced at the time of their diagnosis. The primary cause promoting the growth of cervical cancer is the human papillomavirus. (HPV). More than 90% of squamous cervical tumors contain HPV DNA. Although several HPV types have been associated with anogenital neoplasia, HPV types are responsible for the majority of identified malignancies. (16, 18, 31, 35, 39, 45, 51, 52, and 58) [22]. E6 and E7, two regulatory units on HPV 16 and 18, encode the proteins required for viral construction. The E6 oncoprotein binds to the tumor suppressor gene TP53, preventing its proteolytic degradation and disabling an inherent cell-cycle barrier. 8–10 Retinoblastoma gene products (pRb) associate with and are rendered inactive by the E7 oncoprotein, allowing HPV 16 or 18-infected cells to pass unhindered by means of the cell cycle [23]. The ability of HPV 16 to attach to and annihilate TP53 in vitro varies according to its genomic changes. Both the distribution pattern and, most likely, the ability of these discrepancies to induce cancer vary. For example, the Asian-American subtype tends to impact younger women and has been associated with a more lethal malignant malignancy. More warning signs for

cervical cancer include the onset of sexual activity before the age of 16, having more than four sexual partners altogether, and a history of genital warts. HIV-positive people and people taking antiviral drugs have a higher risk of developing cervical cancer. smoking cigarettes (and perhaps having been exposed to tobacco in the surroundings) [24].

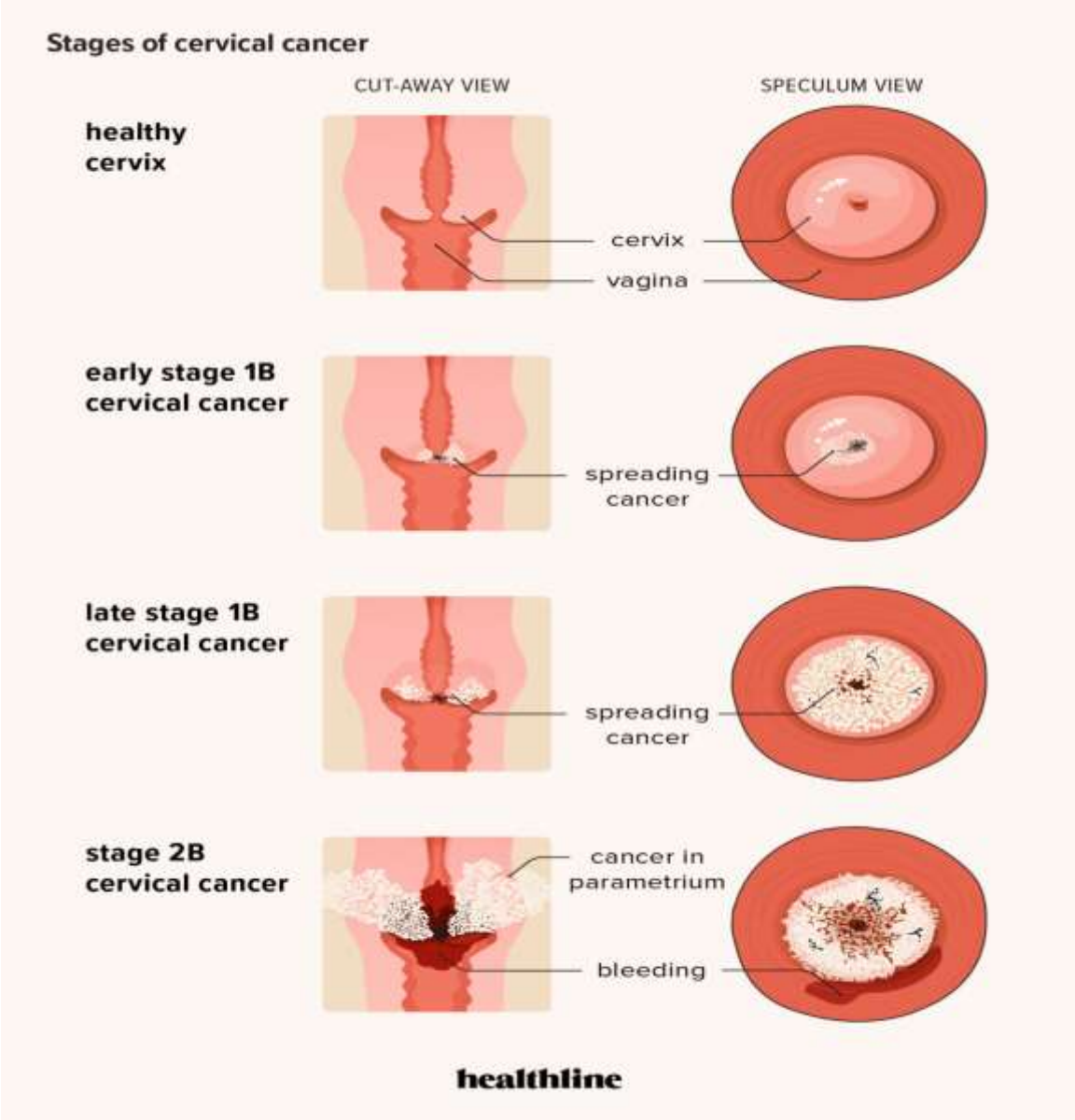


Figure 1: Stages of cervical cancer [25]

1.2 Diagnosis and pathology of cervical cancer

Cervical cancer may be suspected based on a Pap test examination or the sight of a cervix lesion. because so many Pap smear findings are non-diagnostic or erroneously negative when invasive malignancy occurs, any worrying lesion must be subjected to a biopsy. If a biopsy shows cells that suggest micro invasion and the patient lacks a visibly invasive malignancy, a cone biopsy should be carried out [26]. To properly stage functionally concealed lesions, sufficiently underneath stroma must always be recovered to allow for an accurate knowledge of the depth and width of invasion below the basal layer. In about 80% of instances, squamous dysplasia occurs before recurrent cervical cancer. Adenocarcinomas of the cervix make up about 20% of invasive cervical malignancies, and in more developed countries, they are more common than follicular carcinomas [27]. Regardless of the fact that oncogenic HPV DNA has been discovered in adenocarcinomas20,21, smoking does not seem to be a possible risk factor for this histopathological subgroup of adenocarcinomas. Although pre-malignant epidermal lesions are more frequently detected by Pap smear examinations than adenocarcinoma-in-situ, which is likely the underlying illness in the majority of cases [28]. Clear-cell carcinomas, a rare subtype of adenocarcinoma, make up less than 5% of all cases. Diethylstilbestrol use during pregnancy has previously been linked to a number of instances involving young women. Simply due to this chemical was declared illegal in 1971, the number of incidents related to its use during pregnancy has gone down [29]. The majority of postmenopausal females treated with diethylstilbestrol who acquire concise carcinomas do so. Two additional uncommon varieties include small-cell (neuroendocrine) carcinomas and ependymomas.

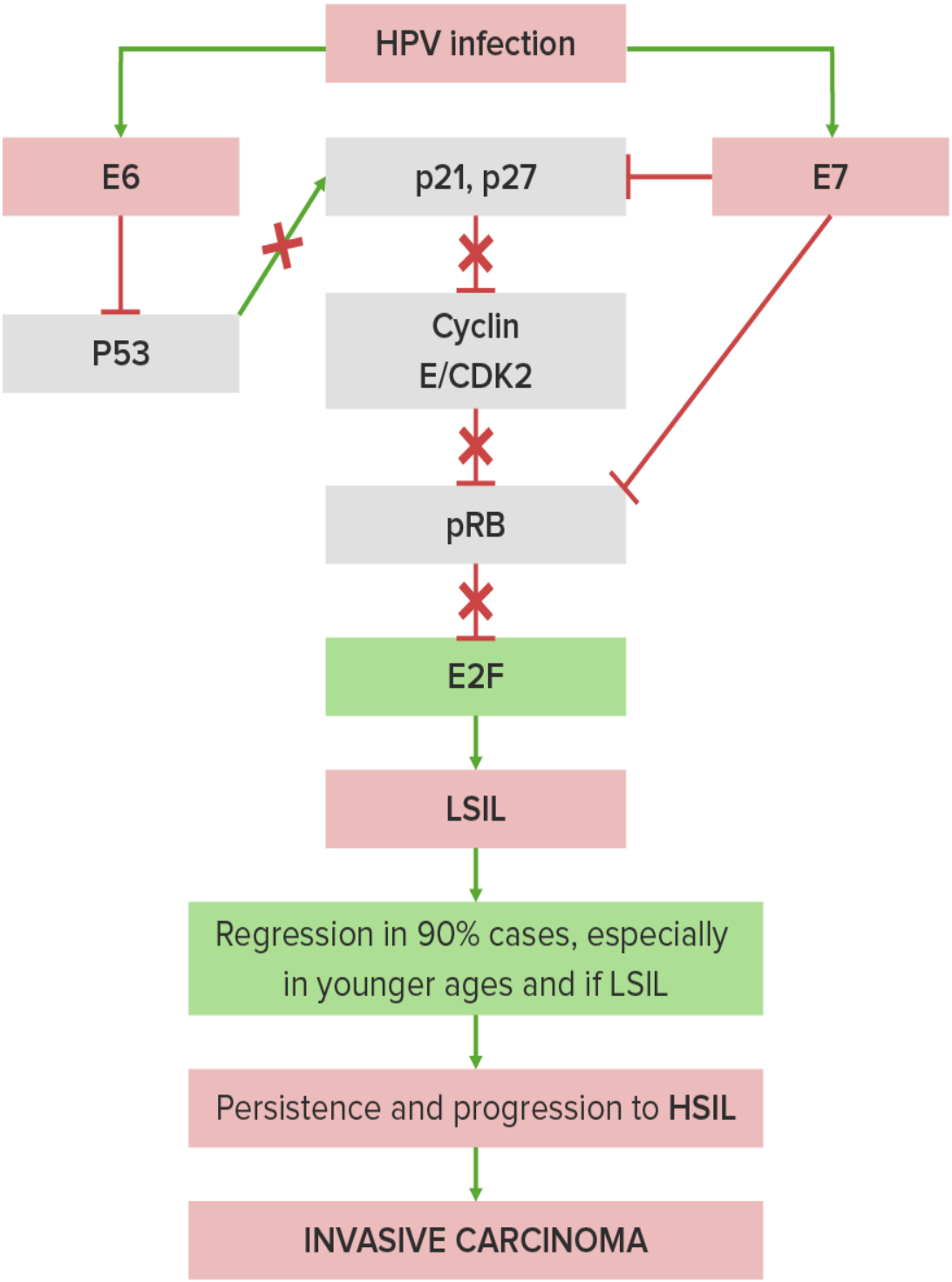


Figure 2: Pathology of cervical cancer [30]

1.3 Pathogenesis of cervical neoplasia

HIA type, immunosuppression, sex steroid hormones (based on connections between cervical cancers and elevated fertility and long-term oral contraceptive pill use), and smoking are just a few of the potential cofactors linked in progression discovered by observational research. 47"9 Additionally, the bulk of these cofactors appear to affect CIN 3 progression rather than CIN 3 malignancy. (from latent HPV infection or low grade CIN). [31] Numerous studies have been conducted on the effects of smoking, and an epidemiological link between smoking and cervical cancer has been found (odds ratio of about 2). The toxins found in tobacco smoke are great candidates for co-causes of cervical cancer accompanying HPVs. Smokers are more likely to develop cytologically abnormal cells and larger, more serious histological lesions. Elevated nicotine Dimer levels in the normal epithelium close to cervical intraepithelial and infiltrative neoplasia have been related to nicotine, indicating a direct effect on cervical epithelial tissue at the DNA region. [32] Cervical mucus contains cigarette smoke residue, including nitrosamines. 5" 52 The different cervical representation of cytochrome P450 enzymes, which stimulate cancer-causing nitrosamines, and glutathione S transferase, which denatures proteins, may have an impact on an individual's vulnerability to nicotine carcinogens. Once a diagnosis of distant metastatic tissue has been made, the patient is categorized. [33] However, in the case of a reappearance or if a more serious sickness is discovered after surgery, the stage that was determined at the time of the initial diagnoses shouldn't be changed. The stage is determined by assessment and is primarily determined by the size of the pelvic or cervix-localized tumor. In 1994, changes were made to the FIGO staging system to clarify the terminology used to characterize micro invasive cervical cancer (stages IA1 and IA2) and to divide stage IB into IB1 (4 cm) and IB2 (>4 cm) tumors [34].

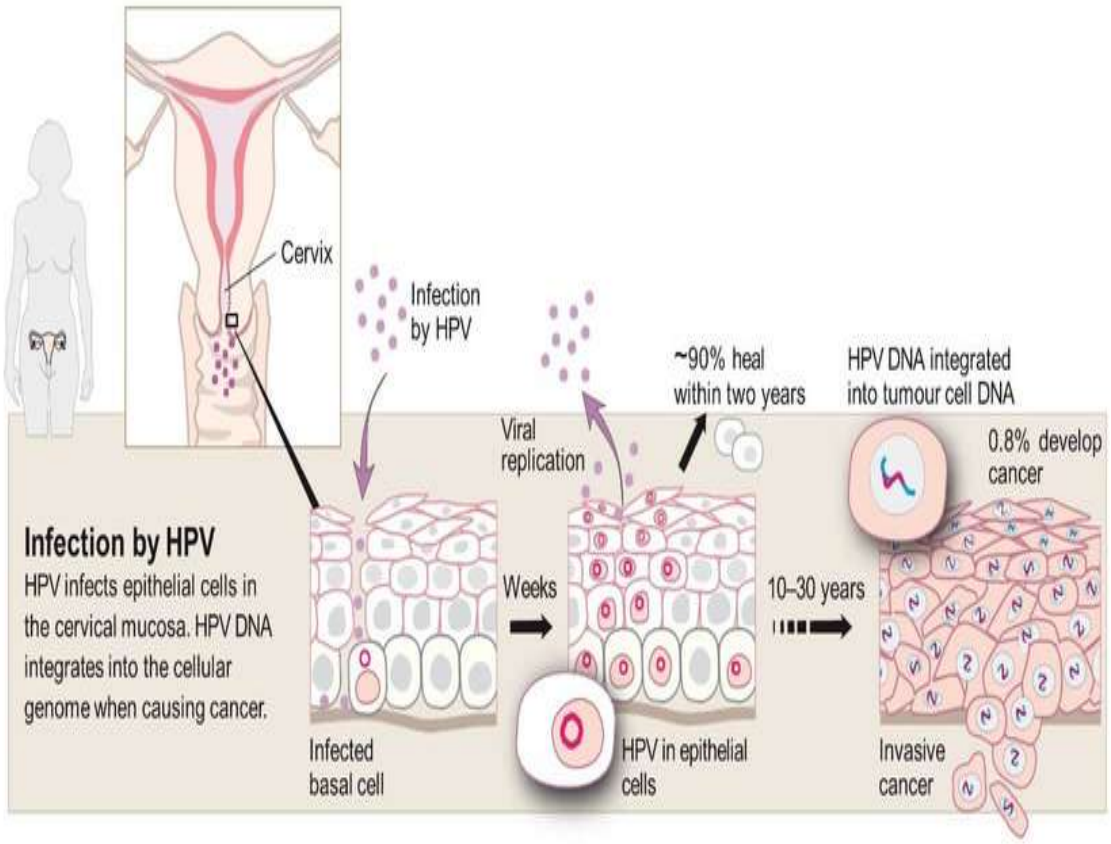


Figure 3: Pathogenesis and pathology of cervical neoplasia [35]

1.4 Chemotherapy

Once a diagnosis of remote metastatic tissue has been made, the patient is staged. despite the case of a recurrence or if a more severe sickness is discovered after surgery, the process set at the time of the initial diagnosis should not be changed. The stage is determined by assessment and is primarily determined by the extent of the pelvic or cervix-localized tumor. In 1994, changes were made to the FIGO classification system to clarify the terminology used to characterize micro invasive cervical cancer (stages IA1 and IA2) and to divide stage IB into IB1 (4 cm) and IB2 (>4 cm) tumors [36]. Cisplatin has been compared to the medication formulation of cisplatin and paclitaxel in a phase 3 uncontrolled study. The combined therapy beat single-agent cisplatin in terms of response time and survival, but at the cost of recurrent toxic effects on the bone marrow [37]. There have been no data on the quality-of-life assessments of the two therapeutic groups, and the benefit for survival is minimal (a few weeks). One factor that seems to have a detrimental effect on chemotherapy effectiveness is whether such a recurrence occurs within a formerly

irradiated zone. About 25% of patients whose renewal happens beyond the irradiated region respond to chemotherapy, as opposed to 5% of patients whose recurrent happens within the irradiation zone [38]. There is further work to be done in the areas of the best chemotherapy schedule to utilize in conjunction with early irradiation and whether combined chemotherapy can act as a long-term radiation advancement to boost remote control. (panel 2). The potential benefits of rigorous anemia restoration after radiation are being examined in a phase-3 experiment. [39] Phase 1 experimental vaccine protocols using HPV 16 E7 peptides as an antigenic determinant are being investigated for those with repeated or continuing cervical cancers. The effectiveness of a vaccine created to protect versus HPV 16 infection has since been established. Long-term immunity may be found in future studies, which might avoid an increasing amount of cervical cancers [40].

Chapter II
Purpose of the study

2.1 Purpose of the study

Cancer that begins in the cervix's cells is called cervical cancer. The cervix is the uterus' bottom, thin end. (womb). The uterus and vagina are connected via the cervix. (birth canal). Typically, cervical cancer progresses gradually over time. The objectives of this review mentioned below:

- The purpose of this study was to determine women's knowledge of cervical cancer, its monitoring, the responsibility of doctors, sources of information, and justifications for not going through screening if they had not already had the disease tested for.
- To know the different treatment option for the management of cervical cancer.
- To find out the different natural products which have therapeutic efficacy for the treatment of cervical cancer.
- To know the source & mechanism of those natural products.

Chapter III
Methodology

3.1 Methodology

Methods for assembling and evaluating data were gathered from a variety of linked reviews published between 1995 and 2022 utilizing search engines like PubMed, Research Gate, Google Scholar, and Medline, among others. The procedures employed in the investigation are covered in this chapter. Some basic terms, such as "Cervical cancer pathogenesis," " Cervical cancer treatment," " Cervical cancer diagnostic technique," and " Cervical cancer preventive measures," were used to search for me. I learned more by reading every collected review paper. The information acquired has been finally summarized.

3.2 Data analysis strategy

Data assembly, cleansing, and organization are mutual actions encompassed in data analysis techniques. The data must go through these events, which typically involve using data investigation software, in order to be prepared for business use. Data analytics, another name for data analysis, is well-defined as the science of inspecting raw data in order to make defensible extrapolations about the data.

Chapter IV
Literature Review

4.1 Plants and cervical cancer: an overview

Cervical cancer, which remains to be the main cause of cancer-related death for women in developing countries, is the second most common gynecological malignant tumor that is seriously harmful to women's health. Plants have been the subject of much scientific research as prospective all-natural cervical cancer treatment representatives; however, the results are now distributed throughout a number of studies. A comprehensive synthesis and comprehension of the career potential is needed in order to aid further plant research for anti-cervical cancer medications. This review goes over and assesses the existing knowledge concerning the processes and anti-cervical cancer properties of plants, as well as the possibilities for utilizing these plants in the future. The primary focus of this evaluation is on the plants that have been implicated in scientific in vitro and/or in vivo studies as cervical cancer therapies. Due to standard chemotherapy's incapacity to reduce mortality and serious side effects, natural items are good alternatives for demonstrating synergistic and attenuating impacts on anticancer drugs. The chemical composition and mechanisms of action of a few naturally occurring plants with the potential to prevent cervical cancer have been studied, but many more are still unknown. More study and clinical trials are needed in order to use these therapeutic herbs appropriately [41].

4.2 A Review of the Therapeutic Potential of Natural Drugs for the Treatment of Cervical Cancer

Cervical cancer is the fourth most common cancer in women worldwide. Considering the fact that numerous natural products have been studied for their efficacy against cervical cancer, there hasn't been a critical summary that categorized them according to their anti-cancer processes. Investigators in this study obtained data on natural treatments for cervical cancer that had been published within the previous three years through Pubmed (which includes Medline) and Google Scholar. Apoptosis activation, angiogenesis restriction, metastasis repression, resistant lowering, and miRNA manipulation were the five divisions into which their methods fell. A total of 64 chemical substances guarded against cervical cancer. It has been proven that some of these, such as Penicillium sclerotiorum extracts from Cassia fistula L., ethanol extracts from Bauhinia variegate candida, thymoquinone derived from Nigella sativa, lipid-soluble extracts from Pinellia pedatisecta Schott., and

1′S-1′-acetoxychavicol obtained from Alpinia, have numerous effects against cervical In conclusion, natural substances may provide ideal choices for cutting-edge cancer treatments [42].

4.3 Potential Mechanisms of Plant-Derived Natural Products in the Treatment of Cervical Cancer

Cervical cancer, the second-most common gynecological malignancy worldwide, gravely jeopardizes the health of women because of its high rates of morbidity and mortality. The dangers of conventional therapy include drug resistance, reinstatement, and spread. Consequently, the development of novel, very potent, and inconspicuous drugs for both the prevention and treatment of cervical cancer is urgently required. In recent years, natural compounds derived from plants have been studied as prospective anticancer therapies that selectively kill tumor cells while having negligible adverse effects. A growing body of research has shown that natural products can successfully treat cervical cancer using a number of different mechanisms, such as the reduction of telomerase activity, induction of apoptosis, inhibition of angiogenesis, enhancement of immunity, and recovery of multidrug resistance. The concepts and therapeutic advantages of plant-derived natural products on cervical cancer are discussed in this article, which also provides details on developing effective anti-cervical-cancer drugs with minimal side effects [43].

Chapter V
Results & Discussion

5.1 Results

5.1.1 Apoptosis

Apoptosis, a peculiar kind of cell death, is a critical process that regulates the balance of the survival of cells. Cell shrinkage, the production of new proteins, and genes that cause cell suicide all contribute to the process of apoptosis, which kills potentially dangerous cells. [44] Additionally, it significantly affects the phenotype of cancerous cells. Apoptosis is used in cancer research as an anticancer strategy, which explains why. A total of 47 studies have been done in Hela and SiHa cells to understand the apoptosis-mediated anti-cancer mechanism of natural substances. In total, 54 natural objects were investigated [45].

Compound Name	Plant name	Uses	Mechanism	Reference
Anthocyanins	Root tubers and leaves of Ipomoea batatas	Induction of apoptosis	↑CFP/YFP	[34]
Eugenol	Syzygium aromaticum	Induction of apoptosis	Bcl-2, XIAP	[54]
Physcion	Rhamnus	Inhibition of apoptosis	HOCl/OCl-, p-Akt	[55]
Nitensidine B	Leaves of Pterogyne nitens Tul.	Inhibition of apoptosis	caspase-3, -8, -9	[35]

Table 1: Apoptosis inhibition compound

5.1.2 Compounds that's have efficacy against cervical cancer

Numerous substances found in natural foods demonstrated an apoptotic action versus cervical cancer. The table below displays the compounds' chemical structures [46].

Classification	Compound	Source	Dose; Duration	Efficacy	Mechanism
Plant	Epifriedelinol	Aster tataricus	500, 1000 µg/mL; 72 h	Induction of apoptosis	caspase-3, -8, -9
Plant	Icaritin	Epimedium	25 µM; 24, 48, 72 h	Inhibition of proliferation	Bcl-2, XIAP
Plant	Juncusol	Juncus inflexu	24, 48, 72 h	Inhibition of proliferation	tubulin polymerization
Plant	Methyl protodioscin	Rhizoma of Polygonatum sibiricum	31, 40, 49 µM; 24 h	cell cycle arrest Inhibition of proliferation	ROS
Plant	Mitomycin C	Ginger, Frankincense	10 µg/mL; 24 Hax	cell cycle arrest Inhibition of proliferation	caspase-3, -7 ↓Bcl2-L1
Etc.	Naringenin oxime	Naringenin oxime ether	185 µg/mL;	cell cycle arrest Inhibition of proliferation	caspase-3
Plant	Notoginsenoside	Panax notoginseng	40 µM; 24, 36, 48 h	Inhibition of proliferation	Bax, p-PTEN
Plant	Osthole	Cnidiummonnieri (L.)	160, 200, 240µM; 24, 48 h	Inhibition of proliferation	Bax,c-caspase-3, -9 proteins
Plant	Piperine	Piper nigrum L.	4µM; 24, 48 h	mitochondrial dysfunction	PCNA, VEGF

Plant	Tf-CT-ME	Tripterygium wilfordii	0.5,1,2 µg/mL; 24 h	apoptosis Inhibition of proliferation	↑c-caspase-3 ↓Bcl-2/Bax
Etc.	Thymoquinone	Nigella sativa	10, 20, 40 µM;	Inhibition of migration and invasion	Bax,E-cadherin

Table 2: Substances effective against cervical cancer [60-65]

5.1.3 Anti-angiogenesis

A variety of tumor forms develop and spread primarily as a result of angiogenesis. Regional angiogenesis is essential for the development of metastatic disease because it provides the malignant tumor with oxygen and essential nutrients, promotes tumor growth, and allows the tumor to infiltrate nearby healthy tissue. Particularly, angiogenesis is crucial for the onset, spread, and progression of cervical cancer. It also has to do with blocking p53 and maintaining hypoxia-inducible factor-1, which induced amplification of VEGF [47]. Therefore, preventing angiogenesis may be crucial for treating the illness. This activity is seen in four natural products against HeLa cells and CaSki cells. (Table 2). MMP-2 and -9 were dramatically inhibited after HeLa cells received treatment with Praecitrullus fistulosus lectin protein (PfLP), which is grown and consumed in sub-tropical countries. This suppression resulted in the promotion of apoptosis and a decrease of angiogenesis. [48] With 24 hours and a dose of 50 g/mL, this approach proved effective. PfLP's anticancer and anti-angiogenic activities were seen in vivo at doses of 10 mg/kg on days 7, 9, and 11 following the implantation of tumor cells. There were no negative effects or increased issues in the trial. Purified flaxseed hydrolysate (PFH), obtained by lignan extraction, has been shown to promote apoptosis and prevent angiogenesis and metastasis in HeLa cells. This process was brought about by the upregulation of caspase-3 and the downregulation of MMP-2 and VEGF. In an effort to cover a 48-hour period, the effective dose was 17.4 g/mL. [49] These results suggest that PFH may be an effective cancer-fighting drug. Based on the findings of our study, Kuriakose et al. said that treatments with ethyl acetate aid in the extraction of Penicillium sclerotiorum from Cassia fistula L. by increasing activation of Bax, p53, and Apaf-1 and decreasing Bcl-2 in HeLa cells. The

main active ingredients in this therapy were benzoic acid, oleic acid, and hexadecanoic acid. At a concentration of 7.75 g/mL, it may induce cell cycle arrest and suppress angiogenesis through controlling activities. Seifaddinipour et al. reported that ethyl acetate extracts separated from Pistacia vera L. downregulated TNF, Bcl-2, IAP, and TRAF in CaSki cells [50].

Classification	Compound	Source	Dose; Duration	Efficacy	Mechanism
Fruit	PfLP	Praecitrullus fistulosus	In vitro: 50 µg/mL; 24 h	Induction of apoptosis	MMP-2, -9
Fruit	flaxseed hydrolysate	Lignan	17.4 µg/mL; 48 h	Inhibition of angiogenesis and metastasis	MMP-2, VEGF
Fungus	Ethyl acetate	Penicillium sclerotiorum	7.75 µg/mL; 24 h	Inhibition of angiogenesis	Bax, p53, Apaf-1
Plant	Ethyl acetate	Pistacia vera L.	µg/mL; 72 h	Inhibition of angiogenesis	IAP, TRAF

Table 3: Anti-angiogenesis [66-68]

Overall, four natural substances showed anti-angiogenesis, though the underlying mechanisms were very different in each case. [51] MMP, which has a sophisticated and important role in the development and spread of cancer, is suppressed by two medications. Bcl-2 was inhibited by two substances, and it also had an anti-angiogenesis effect by stopping VEGF, TNF, and IAP activity. Compared to earlier anti-angiogenesis examinations, the substance's concentration in the Penicillium sclerotiorum study (7.75 g/mL) was significantly lower. By raising the levels of the genes of Bax, p53, and Apaf-1 and inhibiting Bcl-2, it was shown to promote not only anti-angiogenesis but also cell cycle arrest and death at dosages of 5 g/mL, 25 g/mL, and 50 g/mL [52].

5.1.4 Anti-Metastasis

Both the repeated expansion of tumor colonies and the transfer of abnormal cells from the organ of origin to other parts of the body are manifestations of metastasis. [54] Instead of their primary tumors, metastases are usually what cause cancer patients to pass away. This process includes intricate processes such cancer cell migration, invasion, and extravasation into the bloodstream. EGCG was one of six chemical compounds that stopped metastasis. (Table 3). The chemical structures of molecules are shown in Figure 4 [53].

Classification	Compound	Source	Dose; Duration	Efficacy	Mechanism
Plant	Astragaloside IV	Radix	200 µg/mL	Inhibition of cell metastasis	E-cadherin ↓ p38, PI3K
Seed	Thymoquinone	Nigella sativa	5 µg/mL 24h	Induction of apoptosis	Twist1, Zeb1
Plant	Ethanol extract	variegata candida	25 µg/mL; 24 h	migration and invasion	MMP-2, -9
Plant	Ethanol extract	Terminalia	25,50, µg/mL; 24 h	Inhibition of cell metastasis	MMP-9, ERK1/2

Table 4: Anti-Metastasis [69]

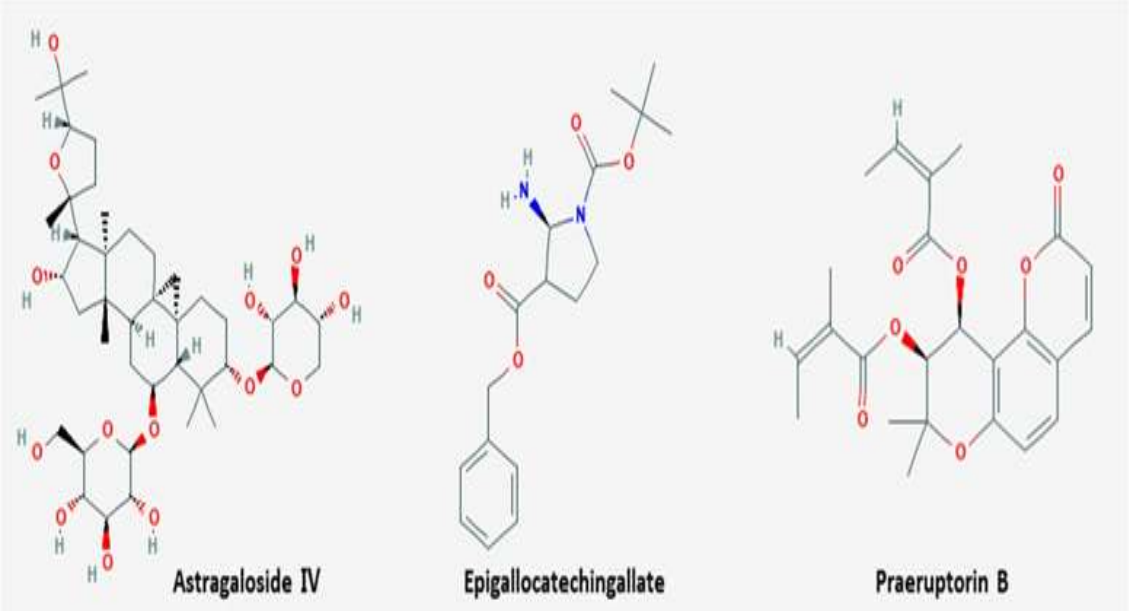


Figure 4: Chemical structures of compounds derived from natural products inhibiting metastasis [55]

5.1.5 Drug Resistance

Drug resistance is complicated because of the heterogeneity of tumors, the tumor microenvironment, and other aspects. Unfortunately, a sizable minority of patients have cancers that do not respond to treatment. [56] Any effective anticancer medication may cause this disease to develop, and it may do so in a number of different ways. From five investigations that looked at natural products that can regulate drug resistance, Figures 5 and 6 show the chemical compositions of compounds that reduce drug resistance [57].

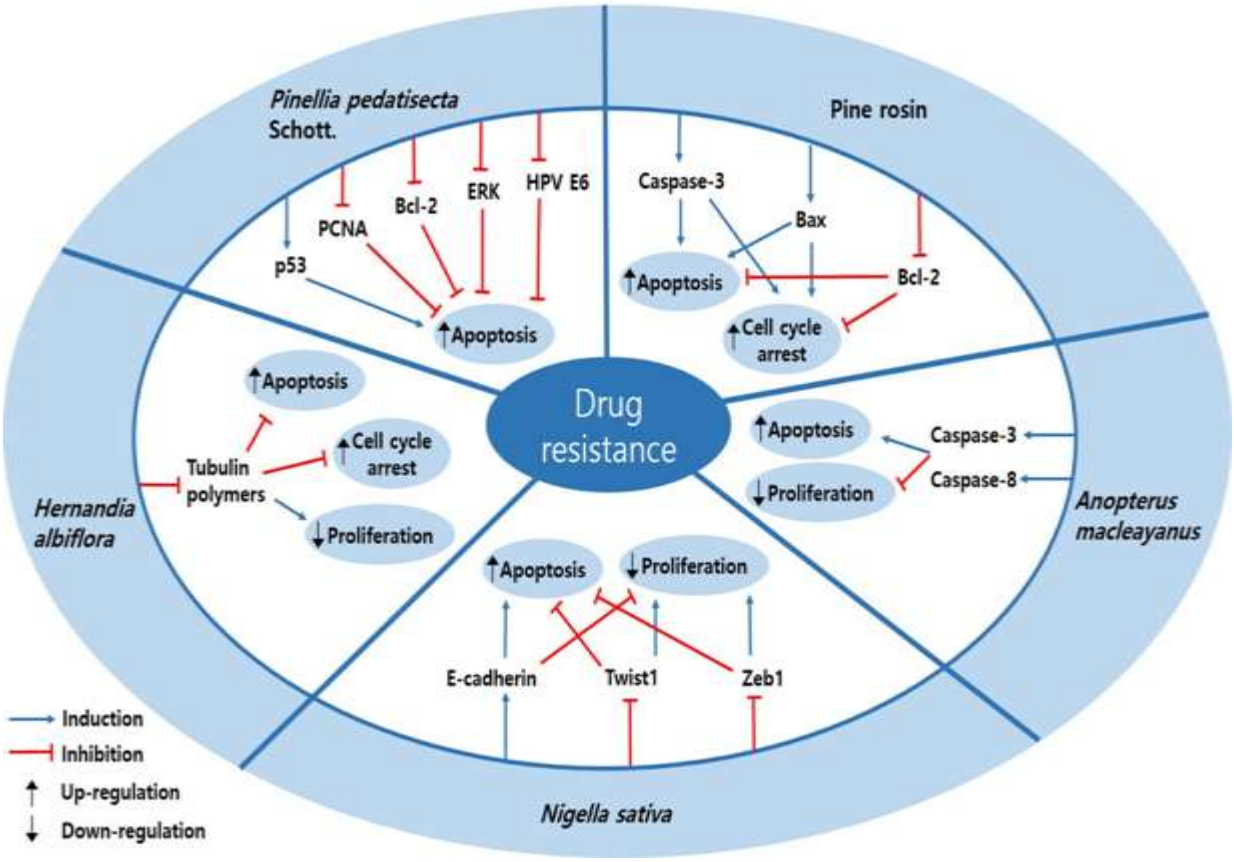


Figure 5: Schematic diagram of drugs resistance signal pathways regulated by natural products in cervical cancer [58].

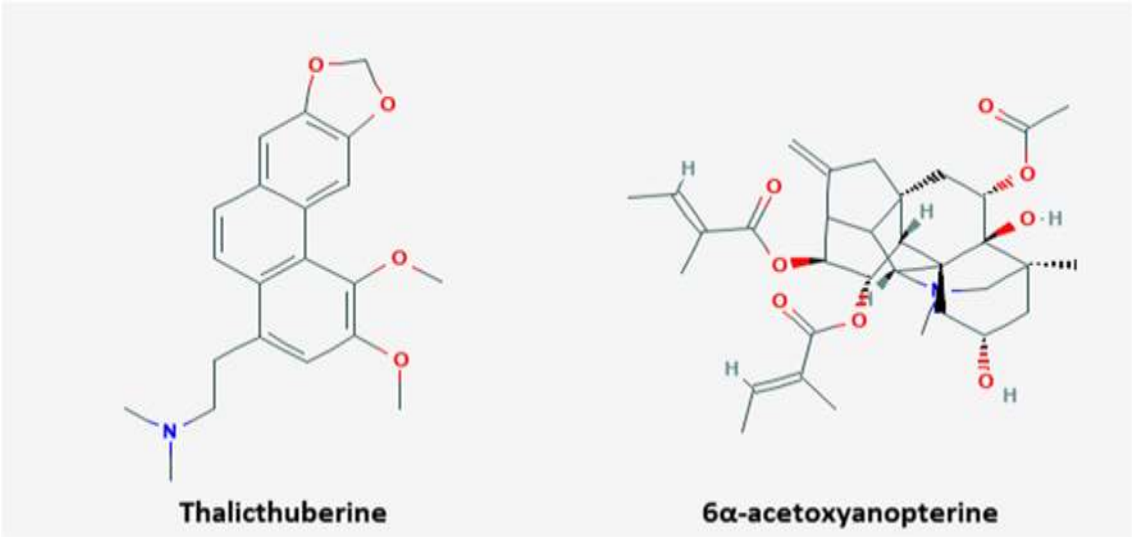


Figure 6: Chemical structures of compounds derived from natural products sensitizing drug resistance [59]

5.2 Discussion

With an IC50 value of 2.21 M, Li et al. showed that 4w of DHA-Based acylhydrazones induce anti-cancer effect for 48 hours in Hela cells. The fact that 4w was nearly 17 times more energetic than the parent molecules is remarkable. In an investigation by Vishnu et al., it was discovered that the anthocyanins from the purple Ipomoea batatas rhizomes and leaves increased CFP/YFP activity in HeLa cells. 100 and 200 g/mL of the treatment were given over the course of 48 hours. The results showed that the medication resulted in cell morphological alterations, cell cycle arrest, and apoptosis. The leaf anthocyanins also displayed a considerably enhanced action towards cervical cancer cells. Caspase-3 and -7 are increased in Glycosmis parva. Mechanisms like caspase, Bcl-2, Bax, ROS, PARP, and p-Akt have been backed by a large number of chemical apoptosis studies. The three routes that were most important were those regulating caspase, Bcl-2, and Bax. The loss or inactivation of caspase considerably slows down the onset of apoptosis, which causes a huge imbalance in economic growth and, as a result, the abnormal progression of human cancer. Out of the 30 chemicals that cause cervical cancer to apoptose, 19 caspase-inducing compounds were the most common, and 16 of them activated caspase-3. It has been found that the 19 natural extracts contribute to cervical cancer cell killing. Swanepoel et al. shown that Anemone nemorosa obtained from the roots causes a pause in the early mitotic phase of the cell cycle. Apoptosis was confirmed via fluorescence labeling with annexin V-FITC. The expression levels of PS translocation, c-caspase-3, -8, and ROS elevated as a consequence to the treatment within 24 hours at an IC50 value of 20.33 2.480 g/mL. After 48 hours, the MMP and ROS levels also decreased. The pathway was disrupted, causing apoptosis, autophagy, and the reduction of development, based on the research's results. Overall, four natural substances showed anti-angiogenesis, despite the underlying mechanisms were very different in each case. MMP, which has a complex and important role in the development and progression of cancer, is disrupted by two medications. Bcl-2 was inhibited by two substances, and it also had an anti-angiogenesis effect by stopping VEGF, TNF, and IAP activities. The amount of Penicillium sclerotiorum employed in the study (7.75 g/mL) was significantly less than that used in other anti-angiogenesis investigations.

In SiHa cells, astragaloside IV from Radix Astragali treatment led to increased E-cadherin production and decreased levels of p38 and PI3K [82]. Astragaloside IV also demonstrated that cell spreading was suppressed in SiHa cell lines. 200 g/mL was the optimum dose for a 24-hour period. HeLa cells were treated with green tea's epigallocatechin gallate (EGCG), which inhibited the production of VEGF, MMP-2, and -9. As a consequence of this, at a concentration of 50 g/mL, it induced apoptosis for 48 hours. Additionally, it stopped cervical cancer cells from multiplying and metastasizing by decreasing VEGF, CDK2, and ERK1/2. Praeruptorin-B, which has been isolated from Peucedanum praeruptorum Dunn, reduced the expression of NF-B, MMP-2, and -9 in HeLa and SiHa cells. After being exposed to the rosin abietane diterpenoid, which is derived from pine rosin, HeLa cells' levels of caspase-3, Bax, and Bcl-2 were increased whereas Bcl-2 levels were decreased [89]. In particular, TH1 cell numbers increased whereas TH2 and TH17 cell numbers decreased. These processes were successful when HeLa cells were exposed to a concentration of 1.08 0.12 M. Additionally, it resulted in apoptosis and cell cycle arrest in HeLa cells. In the opinion of Levrier, talicthuberine from Hernandia albiflora may have decreased the number of tubulin polymers on HeLa cells.

Chapter VI
Conclusion

6.1 Conclusion

In our study, we looked at herbal treatments for cervical cancer that also had anti-tumor capabilities. The impact of 64 natural substances on apoptosis, angiogenesis, metastasis, multi-drug resistance, and miRNAs have been shown in a number of ways. Most naturally occurring substances, including Penicillium sclerotiorum, emodin, and curcumin, trigger apoptosis. Four natural substances, including lignan and Pistacia vera L., have demonstrated anti-angiogenic activities in cervical cancer cells. Together with five other natural substances, EGCG inhibited the metastasis of cervical cancer. Five studies found that pine rosin and other natural substances boosted cervical cancer patients' resistance to therapy. Studies demonstrating the regulation of miRNA by natural substances are few and far between. The non-clinical results of this study should lay the groundwork for the development of innovative cervical chemotherapy medicines with fewer side effects, which can be used in clinics.

Chapter VII
Reference

Reference

1. Urasa, M.; Darj, E. Knowledge of cervical cancer and screening practices of nurses at a regional hospital in Tanzania. Afr. Health Sci. 2011, 11, 48–57. [PubMed]

2. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424. [CrossRef] [PubMed]

3. Kim, J.Y.; Byun, S.J.; Kim, Y.S.; Nam, J.-H. Disease courses in patients with residual tumor following concurrent chemoradiotherapy for locally advanced cervical cancer. Gynecol. Oncol. 2017, 144, 34–39. [CrossRef] [PubMed]

4. Hertlein, M.L.; Lenhard, M.; Kirschenhofer, A.; Kahlert, S.; Mayr, D.; Burges, A.; Friese, K. Cetuximab monotherapy in advanced cervical cancer: A retrospective study with five patients. Arch. Gynecol. Obstet. 2011, 283, 109–113. [CrossRef] [PubMed]

5. Kurtz, J.; Hardy-Bessard, A.-C.; Deslandres, M.; Lavau-Denes, S.; Largillier, R.; Roemer-Becuwe, C.; Weber, B.; Guillemet, C.; Paraiso, D.; Pujade-Lauraine, E. Cetuximab, topotecan and cisplatin for the treatment of advanced cervical cancer: A phase II GINECO trial. Gynecol. Oncol. 2009, 113, 16–20. [CrossRef]

6. Gaffney, D.K.; Winter, K.; Dicker, A.P.; Miller, B.; Eifel, P.J.; Ryu, J.; Avizonis, V.; Fromm, M.; Greven, K. A Phase II study of acute toxicity for Celebrex™ (celecoxib) and chemoradiation in patients with locally advanced cervical cancer: Primary endpoint analysis of RTOG. Int. J. Radiat. Oncol. 2007, 67, 104–109. [CrossRef] [PubMed]

7. Herrera, F.G.; Chan, P.; Doll, C.; Milosevic, M.; Oza, A.; Syed, A.; Pintilie, M.; Levin, W.; Manchul, L.; Fyles, A. A prospective phase I–II trial of the cyclooxygenase-2 inhibitor celecoxib in patients with carcinoma of the cervix with biomarker assessment of the tumor microenvironment. Int. J. Radiat. Oncol. 2007, 67, 97–103. [CrossRef] [PubMed]

8. Broutet, N.; Eckert, L.; Ullrich, A.; Bloem, P. Comprehensive Cervical Cancer Control: A Guide to Essential Practice; World Health Organization: Geneva, Switzerland, 2014; pp. 1–378.

9. Lee, J.; Jeong, M.I.; Kim, H.-R.; Park, H.; Moon, W.-K.; Kim, B. Plant Extracts as Possible Agents for Sequela of Cancer Therapies and Cachexia. Antioxidants 2020, 9, 836. [CrossRef]

10. Federico, C.; Sun, J.; Muz, B.; Alhallak, K.; Cosper, P.F.; Muhammad, N.; Jeske, A.; Hinger, A.; Markovina, S.; Grigsby, P.; et al. Localized Delivery of Cisplatin to Cervical Cancer Improves Its Therapeutic Efficacy and Minimizes Its Side-Effect Profile. Int. J. Radiat. Oncol. 2020. [CrossRef]

11. Shen, D.-W.; Pouliot, L.M.; Hall, M.D.; Gottesman, M.M. Cisplatin Resistance: A Cellular Self-Defense Mechanism Resulting from Multiple Epigenetic and Genetic Changes. Pharmacol. Rev. 2012, 64, 706–721. [CrossRef]

12. Sun, C.; Brown, A.J.; Jhingran, A.; Frumovitz, M.; Ramondetta, L.; Bodurka, D.C. Patient Preferences for Side Effects Associated With Cervical Cancer Treatment. Int. J. Gynecol. Cancer 2014, 24, 1077–1084. [CrossRef] [PubMed]

13. Momtazi-Borojeni, A.A.; Ghasemi, F.; Hesari, A.; Majeed, M.; Caraglia, M.; Sahebkar, A. Anti-Cancer and Radio-Sensitizing Effects of Curcumin in Nasopharyngeal Carcinoma. Curr. Pharm. Des. 2018, 24, 2121–2128. [CrossRef] [PubMed]

14. Nasreen, S.; Safeer, S.; Dar, K.K.; Andleeb, S.; Ejaz, M.; Khan, M.A.; Ali, S. Etiology of hepatocellular carcinoma and treatment through medicinal plants: A comprehensive review. Orient. Pharm. Exp. Med. 2018, 18, 187–197. [CrossRef]

15. Ezzat, S.M.; Shouman, S.A.; ElKhoely, A.; Attia, Y.M.; Elsesy, M.E.; El Senousy, A.S.; Choucry, M.A.; El Gayed, S.H.; El Sayed, A.A.; Sattar, E.A.; et al. Anticancer potentiality of lignan rich fraction of six Flaxseed cultivars. Sci. Rep. 2018, 8, 544. [CrossRef] [PubMed]

16. Hong, B.; Li, J.; Huang, C.; Huang, T.; Zhang, M.; Huang, L. miR-300/FA2H affects gastric cancer cell proliferation and apoptosis.

Open Med. 2020, 15, 882–889. [CrossRef]

17. Escuin, D.; López-Vilaró, L.; Bell, O.; Mora, J.; Moral, A.; Pérez, J.I.; Arqueros, C.; Cajal, T.R.Y.; Lerma, E.; Barnadas, A. MicroRNA- 1291 Is Associated With Locoregional

Metastases in Patients With Early-Stage Breast Cancer. Front. Genet. 2020, 11, 562114. [CrossRef]

18. Lim, H.J.; Park, M.N.; Kim, C.; Kang, B.; Song, H.-S.; Lee, H.; Kim, S.-H.; Shim, B.S.; Kim, B. MiR-657/ATF2 Signaling Pathway Has a Critical Role in Spatholobus suberectus Dunn Extract-Induced Apoptosis in U266 and U937 Cells. Cancers 2019, 11, 150. [CrossRef]

19. Kim, C.; Song, H.-S.; Park, H.; Kim, B. Activation of ER Stress-Dependent miR-216b Has a Critical Role in Salvia miltiorrhiza Ethanol-Extract-Induced Apoptosis in U266 and U937 Cells. Int. J. Mol. Sci. 2018, 19, 1240. [CrossRef]

20. Phuah, N.H.; Azmi, M.N.; Awang, K.; Nagoor, N.H. Down-Regulation of MicroRNA-210 Confers Sensitivity towards 1'S-1'- Acetoxychavicol Acetate (ACA) in Cervical Cancer Cells by Targeting SMAD. Mol. Cells 2017, 40, 291–298. [CrossRef]

21. Noh, S.; Choi, E.; Hwang, C.-H.; Jung, J.H.; Kim, S.-H.; Kim, B. Dietary Compounds for Targeting Prostate Cancer. Nutritients 2019, 11, 2401. [CrossRef]

22. Lowe, S.W.; Lin, A.W. Apoptosis in cancer. Carcinog. 2000, 21, 485–495. [CrossRef]

23. Li, F.-Y.; Wang, X.; Duan, W.-G.; Lin, G.-S. Synthesis and In Vitro Anticancer Activity of Novel Dehydroabietic Acid-Based Acylhydrazones. Molecules 2017, 22, 1087. [CrossRef] [PubMed]

24. Vishnu, V.R.; Renjith, R.S.; Mukherjee, A.; Anil, S.R.; Sreekumar, J.; Jyothi, A.N.; Alummoottil, J.N. Comparative Study on the Chemical Structure and In Vitro Antiproliferative Activity of Anthocyanins in Purple Root Tubers and Leaves of Sweet Potato (Ipomoea batatas). J. Agric. Food Chem. 2019, 67, 2467–2475. [CrossRef] [PubMed]

25. Piboonprai, K.; Khumkhrong, P.; Khongkow, M.; Yata, T.; Ruangrungsi, N.; Chansriniyom, C.; Iempridee, T. Anticancer activity of arborinine from Glycosmis parva leaf extract in human cervical cancer cells. Biochem. Biophys. Res. Commun. 2018, 500, 866–872. [CrossRef] [PubMed]

26. Wang, L.; Zhao, Y.; Wu, Q.; Guan, Y.; Wu, X. Therapeutic effects of β-elemene via attenuation of the Wnt/β-catenin signaling pathway in cervical cancer cells. Mol. Med. Rep. 2018, 17, 4299–4306. [CrossRef] [PubMed]

27. Rehana, D.; Mahendiran, D.; Kumar, R.S.; Rahiman, A.K. Evaluation of antioxidant and anticancer activity of copper oxide nanoparticles synthesized using medicinally important plant extracts. Biomed. Pharmacother. 2017, 89, 1067–1077. [CrossRef]

28. Wang, J.; Liu, Q.; Yang, L.; Xia, X.; Zhu, R.; Chen, S.; Wang, M.; Cheng, L.; Wu, X.; Wang, S. Curcumin-Loaded TPGS/F127/P123 Mixed Polymeric Micelles for Cervical Cancer Therapy: Formulation, Characterization, and In Vitro and In Vivo Evaluation.J. Biomed. Nanotechnol. 2017, 13, 1631–1646. [CrossRef]

29. Moreira, T.F.; Sorbo, J.M.; Souza, F.D.O.; Fernandes, B.C.; Ocampos, F.M.M.; De Oliveira, D.M.S.; Arcaro, C.A.; Assis, R.P.; Barison, A.; Miguel, O.G.; et al. Emodin, Physcion, and Crude Extract of Rhamnus sphaerosperma var. pubescens Induce Mixed Cell Death, Increase in Oxidative Stress, DNA Damage, and Inhibition of AKT in Cervical and Oral Squamous Carcinoma Cell Lines. Oxidative Med. Cell. Longev. 2018, 2018, 1–18. [CrossRef]

30. Yang, J.; Fa, J.; Li, B. Apoptosis induction of epifriedelinol on human cervical cancer cell line. Afr. J. Tradit. Complement. Altern. Med. 2017, 14, 80–86. [CrossRef]

31. Das, A.; Harshadha, K.; Dhinesh Kannan, S.; Hari Raj, K.; Jayaprakash, B. Evaluation of therapeutic potential of eugenol-a natural derivative of Syzygium aromaticum on cervical cancer. APJCP 2018, 19, 1977.

32. Chen, X.; Song, L.; Hou, Y.; Li, F. Reactive oxygen species induced by icaritin promote DNA strand breaks and apoptosis in human cervical cancer cells. Oncol. Rep. 2018, 41, 765–778. [CrossRef] [PubMed]

33. Kuo, C.-Y.; Schelz, Z.; Tóth, B.; Vasas, A.; Ocsovszki, I.; Chang, F.-R.; Hohmann, J.; Zupkó, I.; Wang, H.-C. Investigation of natural phenanthrenes and the antiproliferative potential of juncusol in cervical cancer cell lines. Phytomedicine 2018, 58, 152770. [CrossRef] [PubMed]

34. Ma, Y.-L.; Zhang, Y.-S.; Zhang, F.; Zhang, Y.-Y.; Thakur, K.; Zhang, J.-G.; Wei, Z.-J. Methyl protodioscin from Polygonatum sibiricum inhibits cervical cancer through cell cycle arrest and apoptosis induction. Food Chem. Toxicol. 2019, 132, 110655. [CrossRef]

35. Al-Otaibi, W.A.; Alkhatib, M.H.; Wali, A.N. Cytotoxicity and apoptosis enhancement in breast and cervical cancer cells upon coadministration of mitomycin C and essential oils in nanoemulsion formulations. Biomed. Pharmacother. 2018, 106, 946–955. [CrossRef]

36. Latif, A.D.; Gonda, T.; Vágvölgyi, M.; Kúsz, N.; Kulmány, Á.; Ocsovszki, I.; Zomborszki, Z.P.; Zupkó, I.; Hunyadi, A. Synthesis and In Vitro Antitumor Activity of Naringenin Oxime and Oxime Ether Derivatives. Int. J. Mol. Sci. 2019, 20, 2184. [CrossRef]

37. Souza, F.D.O.; Sorbo, J.M.; Regasini, L.O.; Rosa, J.C.; Czernys, É.D.S.; Valente, V.; Moreira, T.F.; Navegante, G.; Fernandes, B.C.; Soares, C.P. Nitensidine B affects proteins of the glycolytic pathway and induces apoptosis in cervical carcinoma cells immortalized by HPV. Phytomedicine 2018, 48, 179–186. [CrossRef] [PubMed]

38. Li, L.; Sun, J.-X.; Wang, X.-Q.; Liu, X.-K.; Chen, X.-X.; Zhang, B.; He, Z.-D.; Liu, D.-Z.; Chen, L.-X.; Wang, L.-W.; et al. Notoginsenoside R7 suppresses cervical cancer via PI3K/PTEN/Akt/mTOR signaling. Oncotarget 2017, 8, 109487–109496. [CrossRef]

39. Che, Y.; Li, J.; Li, Z.; Li, J.; Wang, S.; Yan, Y.; Zou, K.; Zou, L. Osthole enhances antitumor activity and irradiation sensitivity of cervical cancer cells by suppressing ATM/NF-κB signaling. Oncol. Rep. 2018, 40, 737–747. [CrossRef]

40. Selvan, D.A.; Mahendiran, D.; Kumar, R.S.; Rahiman, A.K. Garlic, green tea and turmeric extracts-mediated green synthesis of silver nanoparticles: Phytochemical, antioxidant and in vitro cytotoxicity studies. J. Photochem. Photobiol. B Biol. 2018, 180, 243–252. [CrossRef]

41. Xie, Z.; Wei, Y.; Xu, J.; Lei, J.; Yu, J. Alkaloids from Piper nigrum Synergistically Enhanced the Effect of Paclitaxel against Paclitaxel-Resistant Cervical Cancer Cells through the Downregulation of Mcl-1. J. Agric. Food Chem. 2019, 67, 5159–5168. [CrossRef]

42. Zhang, Y.; Zhou, D.; Liu, W.; Li, C.; Hao, L.; Zhang, G.; Deng, S.; Yang, R.; Qin, J.K.; Li, J.; et al. Cytotoxic Activity and Related Mechanisms of Prenylflavonoids Isolated from Mallotus conspurcatus Croizat. Chem. Biodivers. 2019, 16, e1800465. [CrossRef] [PubMed]

43. Lin, C.-L.; Lee, C.-H.; Chen, C.-M.; Cheng, C.-W.; Chen, P.-N.; Ying, T.-H.; Hsieh, Y.-H. Protodioscin induces apoptosis through ROS-mediated endoplasmic reticulum stress via the JNK/p38 activation pathways in human cervical cancer cells. Cell. Physiol. Biochem. 2018, 46, 322–334. [CrossRef] [PubMed]

44. Chatterjee, K.; Mukherjee, S.; Vanmanen, J.; Banerjee, P.; Fata, J.E. Dietary Polyphenols, Resveratrol and Pterostilbene Exhibit Antitumor Activity on an HPV E6-Positive Cervical Cancer Model: An in vitro and in vivo Analysis. Front. Oncol. 2019, 9, 352. [CrossRef] [PubMed]

45. Chen, Y.; Qu, D.; Fu, R.; Guo, M.; Qin, Y.; Guo, J.; Chen, Y. A Tf-modified tripterine-loaded coix seed oil microemulsion enhances anti-cervical cancer treatment. Int. J. Nanomed. 2018, 13, 7275–7287. [CrossRef] [PubMed]

46. Li, J.; Khan, A.; Wei, C.; Cheng, J.; Chen, H.; Yang, L.; Ijaz, I.; Fu, J. Thymoquinone Inhibits the Migration and Invasive Characteristics of Cervical Cancer Cells SiHa and CaSki In Vitro by Targeting Epithelial to Mesenchymal Transition Associated Transcription Factors Twist1 and Zeb1. Molecules 2017, 22, 2105. [CrossRef] [PubMed]

47. Zhao, Y.; Wang, M.; Tsering, J.; Li, H.; Li, S.; Li, Y.; Liu, Y.; Hu, X. An Integrated Study on the Antitumor Effect and Mechanism of Triphala Against Gynecological Cancers Based on Network Pharmacological Prediction and In Vitro Experimental Validation. Integr. Cancer Ther. 2018, 17, 894–901. [CrossRef] [PubMed]

48. Phuah, N.H.; Azmi, M.N.; Awang, K.; Nagoor, N.H. Suppression of microRNA-629 enhances sensitivity of cervical cancer cells to 1′S-1′-acetoxychavicol acetate via regulating RSU1. OncoTargets Ther. 2017, 10, 1695–1705. [CrossRef] [PubMed]

49. Wang, R.; Yang, W.; Fan, Y.; Dehaen, W.; Li, Y.; Li, H.-J.; Wang, W.; Zheng, Q.; Huai, Q.-Y. Design and synthesis of the novel oleanolic acid-cinnamic acid ester

derivatives and glycyrrhetinic acid-cinnamic acid ester derivatives with cytotoxic properties. Bioorganic Chem. 2019, 88, 102951. [CrossRef]

50. Hassan, A.H.; Choi, E.; Yoon, Y.M.; Lee, K.W.; Yoo, S.Y.; Cho, M.C.; Yang, J.S.; Kim, H.I.; Hong, J.Y.; Shin, J.-S.; et al. Natural products hybrids: 3,5,4'-Trimethoxystilbene-5,6,7-trimethoxyflavone chimeric analogs as potential cytotoxic agents against diverse human cancer cells. Eur. J. Med. Chem. 2018, 161, 559–580. [CrossRef]

51. Fan, Y.; Zhang, Y.; Liu, Y.; Xu, W.; Yang, Y.; Hao, Y.; Tao, L. A natural product enhances apoptosis via mitochondria/caspase- mediated pathway in HeLa cells. J. Cell. Biochem. 2019, 120, 16811–16823. [CrossRef]

52. Fiandalo, M.; Kyprianou, N. Caspase control: Protagonists of cancer cell apoptosis. Exp. Oncol. 2012, 34, 165–175. [PubMed]

53. Kang, M.H.; Reynolds, C.P. Bcl-2 Inhibitors: Targeting Mitochondrial Apoptotic Pathways in Cancer Therapy. Clin. Cancer Res.

2009, 15, 1126–1132. [CrossRef] [PubMed]

54. Huh, W.K.; Gomez-Navarro, J.; Arafat, W.O.; Xiang, J.; Mahasreshti, P.J.; Alvarez, R.D.; Barnes, M.N.; Curiel, D.T. Bax-Induced Apoptosis as a Novel Gene Therapy Approach for Carcinoma of the Cervix. Gynecol. Oncol. 2001, 83, 370–377. [CrossRef] [PubMed]

55. Swanepoel, B.; Venables, L.; Octavian-Tudorel, O.; Nitulescu, G.M.; Van De Venter, M. In Vitro Anti-proliferative Activity and Mechanism of Action of Anemone nemorosa. Int. J. Mol. Sci. 2019, 20, 1217. [CrossRef]

56. Dwarka, D.; Thaver, V.; Naidu, M.; Koorbanally, N.A.; Baijnath, A.H. In vitro chemopreventative activity of strelitzia nicolai aril extract containing bilirubin. Afr. J. Tradit. Complement. Altern. Med. 2017, 14, 147–156. [CrossRef]

57. Lee, K.M.; Lee, K.; Choi, Y.K.; Choi, Y.J.; Seo, H.S.; Ko, S.G. SH003-induced G1 phase cell cycle arrest induces apoptosis in HeLa cervical cancer cells. Mol. Med. Rep. 2017, 16, 8237–8244. [CrossRef]

58. Dos Santos, K.M.; Gomes, I.N.F.; Silva-Oliveira, R.J.; Pinto, F.E.; Oliveira, B.G.; Chagas, R.C.R.; Romão, W.; Reis, R.M.; Ribeiro,

R.I.M.D.A. Bauhinia variegata candida Fraction Induces Tumor Cell Death by Activation of Caspase-3, RIP, and TNF-R1 and Inhibits Cell Migration and Invasion In Vitro. BioMed Res. Int. 2018, 2018, 1–10. [CrossRef]

59. Suh, S.-S.; Kim, S.-M.; Kim, J.E.; Hong, J.-M.; Lee, S.G.; Youn, U.J.; Han, S.J.; Kim, I.C.; Kim, S. Anticancer activities of ethanol extract from the Antarctic freshwater microalga, Botryidiopsidaceae sp. BMC Complement. Altern. Med. 2017, 17, 509. [CrossRef]

60. Suh, S.-S.; Yang, E.J.; Lee, S.G.; Youn, U.J.; Han, S.J.; Kim, I.-C.; Kim, S. Bioactivities of ethanol extract from the Antarctic freshwater microalga, Chloromonas sp. Int. J. Med Sci. 2017, 14, 560–569. [CrossRef]

61. Prasad, R.; Rana, N.K.; Koch, B. Dendrobium chrysanthum ethanolic extract induces apoptosis via p53 up-regulation in HeLa cells and inhibits tumor progression in mice. J. Complement. Integr. Med. 2017, 14, 14. [CrossRef]

62. Ma, J.F.; Wei, P.F.; Guo, C.; Shi, Y.P.; Lv, Y.; Qiu, L.X.; Wen, L.P. The Ethyl Acetate Extract of Gynura formosana Kitam. Leaves Inhibited Cervical Cancer Cell Proliferation via Induction of Autophagy. BioMed Res. Int. 2018, 2018, 1–10. [CrossRef]

63. Kuriakose, G.C.; M, D.L.; Bp, A.; Rs, H.K.; Th, A.K.; Ananthaswamy, K.; Chelliah, J. Extract of Penicillium sclerotiorum an endophytic fungus isolated from Cassia fistula L. induces cell cycle arrest leading to apoptosis through mitochondrial membrane depolarization in human cervical cancer cells. Biomed. Pharmacother. 2018, 105, 1062–1071. [CrossRef] [PubMed]

64. Dan, V.M.; Muralikrishnan, B.; Sanawar, R.; S, V.J.; Burkul, B.B.; Srinivas, K.P.; Lekshmi, A.; Pradeep, N.S.; Dastager, S.G.; Santhakumari, B.; et al. Streptomyces sp. metabolite(s) promotes Bax mediated intrinsic apoptosis and autophagy involving inhibition of mTOR pathway in cervical cancer cell lines. Sci. Rep. 2018, 8, 2810. [CrossRef] [PubMed]

65. Davidson, K.T.; Zhu, Z.; Bai, Q.; Xiao, H.; Wakefield, M.R.; Fang, Y. Blueberry as a Potential Radiosensitizer for Treating Cervical Cancer. Pathol. Oncol. Res. 2019, 25, 81–88. [CrossRef] [PubMed]

66. Huang, H.; Zhang, M.; Yao, S.; Zhang, M.; Peng, J.; Guiling with the Pinellia Pedatisecta (PE) Advisory Group; Xu, C.-J.; Ye, Y.; Gui, S. Immune modulation of a lipid-soluble extract of Pinellia pedatisecta Schott in the tumor microenvironment of an HPV + tumor-burdened mouse model. J. Ethnopharmacol. 2018, 225, 103–115. [CrossRef] [PubMed]

67. Khazaei, S.; Ramachandran, V.; Hamid, R.A.; Esa, N.M.; Etemad, A.; Moradipoor, S.; Patimah, I. Flower extract of Allium atroviolaceum triggered apoptosis, activated caspase-3 and down-regulated antiapoptotic Bcl-2 gene in HeLa cancer cell line. Biomed. Pharmacother. 2017, 89, 1216–1226. [CrossRef] [PubMed]

68. Esposito, T.; Sansone, F.; Franceschelli, S.; Del Gaudio, P.; Picerno, P.; Aquino, R.P.; Mencherini, T. Hazelnut (Corylus avellana L.) Shells Extract: Phenolic Composition, Antioxidant Effect and Cytotoxic Activity on Human Cancer Cell Lines. Int. J. Mol. Sci. 2017, 18, 392. [CrossRef]

69. Mannarreddy, P.; Denis, M.; Munireddy, D.; Pandurangan, R.; Thangavelu, K.P.; Venkatesan, K. Cytotoxic effect of Cyperus rotundus rhizome extract on human cancer cell lines. Biomed. Pharmacother. 2017, 95, 1375–1387. [CrossRef]

70. Vijayarathna, S.; Chen, Y.; Kanwar, J.R.; Sasidharan, S. Standardized Polyalthia longifolia leaf extract (PLME) inhibits cell proliferation and promotes apoptosis: The anti-cancer study with various microscopy methods. Biomed. Pharmacother. 2017, 91, 366–377. [CrossRef]