Cancer Insight

Homepage: https://www.anserpress.org/journal/CI

Therapeutic Effects of Natural Products Isolated from Different Microorganisms in Treating Cervical Cancer: A Review

Dipro Mukherjee [a], Dibyajit Lahiri [a*], Moupriya Nag [b*]

[a] *Department of Biotechnology, University of Engineering & Management, Kolkata 700160, West Bengal, India*

ABSTRACT

Cervical cancer is defined as a cancer arising in the cells of cervix that causes unusual vaginal bleeding, discharges, pain in the pelvic region, or pain during sexual activity. Cervical cancer is currently reported to be the fourth most prevalent malignancy among women globally. Surgery includes pelvic lymphadenectomy as well as radical hysterectomy, radiotherapy, as well as chemotherapy are the most common therapies for treating cervical cancer. Another approach includes targeted medication which affects the epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2) for the curing cervical cancer. However, these therapies have the potential for risks and complications: surgery can result in bleeding and may cause organ damage surrounding the surgery, and clots may also start to form in the deep veins of the legs; radiotherapy can result in menopause, infertility, discomfort, or pain during intercourse; and chemotherapy can actually impact rapidly dividing cells along with cancer cells in the human body system. In this review, we will discuss about the use of several Randomised controlled trials (RCTs) for treating malnutrition in various oncology patients.

*Corresponding authors: Dibyajit Lahiri, Moupriya Nag.

E-mail addresses: moupriya.nag@uem.edu.in; dibyajit2011@gmail.com

ISSN 2972-3388

doi: 10.58567/ci01020003

Received 4 December, 2022; Accepted 17 December, 2022; Available online 20 December, 2022

In this review, we will discuss about the various therapeutic effects of natural products isolated from different microorganisms in treating cervical cancer.

KEYWORDS: Cyclooxygenase-2 (COX-2); Epidermal growth factor receptor (EGFR); Pelvic lymphadenectomy; Radical hysterectomy; Radiotherapy; Chemotherapy

1 Introduction

These medications commonly recommended for treating cervical cancer revealed a range of side effects as well as causing treatment resistance [1-10]. Cisplatin, which is one of the most efficient anticancer medications, includes a self-defense mechanism that enables it to develop resistance [11-13]. When patients suffering from cervical cancer are considered, 5-fluorouracil (5-FU) has also showed resistance and adverse effects [12-14].

Natural compounds derived from living species, such as plants and animals, contain a number of active components that have been claimed to be interesting alternatives to chemotherapy medications or to be effective for application in combination with chemotherapeutic treatments [15-17]. For instance, purified f laxseed hydrolysate (PFH), isolated from Lignan, causes apoptosis in HeLa cells and prevents angiogenesis as well as metastasis [18]. In SiHa as well as CaSki cells, thymoquinone obtained from Nigella sativa had an apoptotic as well as anti-proliferative property. Some of the examples of natural compounds recognized so far are ethanolic extracts of Bauhinia variegate candida known as Praeruptorin-B and a quite famous tea. MicroRNA that includes miRNA as well as miR also play an important role in pathological growth of cancer as well as in cancer metastasis [19-23]. Numerous natural compounds have been shown to have anti-cancer properties by modulating cancer-related miRNAs. An experiment demonstrated that extracts of Spatholobus suberectus Dunn can be employed to promote apoptosis when miR-657 or activating transcription factor 2 (ATF2) was regulated in the cells of U266, U937 [24]. Another recognized natural substance, Salvia miltiorrhiza has the ability to inhibit cancer growth through regulating miR-216b [25-27]. Another natural compound, 10S-10-acetoxychavicol acetate (ACA) obtained from Alpinia conchigera was found to be inducing apoptosis on the cells of SiHa and CaSki. The technique of targeting miRNAs employing natural products have a promising future for treating cervical cancer [28]. Numerous publications in the last 5 years showed no studies that primarily focuses on the principles, effectiveness as well as the concentration of natural compounds responsible for treating cervical cancer.

Relevant experimental data reported during the last few years were gathered using Google Scholar database and PUBMED (containing Medline). These studies explained the anticancer properties of natural products

when used for treating cervical cancer. The NCBI PubChem website was referred to identify the chemical structures of substances obtained from natural compounds [29-32].

2 Apoptosis

Apoptosis is defined as a distinct type of cell death and also considered as an essential process responsible for regulating the cell survival homeostasis [33]. It can also be defined as a process that destroys potential cancerous cells and is triggered by cell atrophy, novel protein production, and cell suicide genes; it also has a significant impact on the malignant phenotype [34-37]. As a result, apoptosis is utilized in cancer research in the form of an anticancer mechanism. In Hela as well as in SiHa cells, several researches were conducted to understand the anti-cancer mechanism of natural compounds that are mediated by apoptosis.

3 Various Natural Compounds

A group of researchers surprisingly found 4w to be more effective when compared to its parent compounds and thus can be utilized for triggering anti-cancer potential in Hela cells [38]. A study also reported that purple root tubers as well as Ipomoea batatas leaves contain anthocyanins that can induce CFP or YFP activity in HeLa cells [39-41]. The therapy caused apoptosis, cell cycle arrest, and modification in cell architecture. Furthermore, the leaf anthocyanins had a much stronger anti-cervical cancer cell potential. Glycosmis parva contain Arborinine which possess the ability to downregulate Bcl2-L1 when incubated for 24 hours in HeLa cells [42]. Arborinine also has the ability to trigger apoptosis and to inhibit the migration of cancer and thus it acts as an effective anti-cancer compound. It can also inhibit the growth of tumor spheroid more efficiently when compared to several other chemotherapeutic drugs that include bleomycin, gemcitabine, and cisplatin.

β-elemene, a sesquiterpene compound isolated from the herb Curcuma zedoaria when introduced in SiHa cells were found to increase the expression of p53, p15 and Bax while on the other hand it decreased the expression of cyclin D1, MMP-2, Bcl-2, β-catenin, TCF7, and c-Myc [43-45]. The result also stated that the compound exhibits the potential to stop cell cycle along with that I can also inhibit migration. Along with that, I can also inhibit cell proliferation as well as cell invasion and can trigger apoptosis by blocking the Wnt/-catenin signalling cascade in cervical cancer calls. Nanoparticles of copper oxide that are usually produced from Azadirachta indica, Murraya koenigii, Tamarindus indica, Hibiscus rosasinensis and Moringa oleifera. These

nanoparticles when introduced in HeLa cells showed various anti-cancer properties that include triggering apoptosis and inhibiting oxidant [46-48]. When HeLa cells are treated with a cocktail of polymeric micelles and TPGS/F127/P123 coupled with curcumin extracted from Curcuma longa [49]. Apoptosis, apoptosis mediated apoptosis, and stopping cell cycle were all produced as a result of the processes. Emodin, a chemical compound when introduced in SiHa and C33A cells was found to be able to reduce the activity of HOCl/OCl- as well as p-Akt and was also able to inhibit NO- and O2- [51]. Studies also stated that emodin was able to induce cytotoxicity in cells, DNA damage and also oxidative stress. Epifriedelinol that can be obtained easily from Aster tataricus as well as from Vitex peduncularis when introduced to HeLa cells showed increment of level of caspase-3, -8, and -9 level while on the other hand the level of Bcl-2, -xL, survivin, as well as of actin was reduced [52]. Using the methods, it lowered cell viability and promoted apoptosis when anti-apoptotic protein expression is inhibited, while pro-apoptotic protein expression is increased. Furthermore, the ratio of pro-apoptotic to anti-apoptotic proteins was adjusted. When Eugenol isolated from Syzygium aromaticum was introduced into HeLa as well as SiHa cells, it was able to upregulate caspase-3, Bax, PARP, and ROS and also downregulate XIAP as well as Bcl-2 [53]. The compound was also able to change the cell viability depending on time or dose with a steady morphological variation and thus exhibit an effective inhibitory potential. Another study also stated about introducing icaritin isolated from Epimedium into both HeLa as well as SiHa cells upregulated ROS, c-caspase-3, Bax and c-caspase-9 while it downregulated both Bcl-2 as well as XIAP [54-57]. Icaritin when administered in the cells of SiHa and HeLa showed increased cell death when severe oxidative DNA damage was induced, resulting in breaking of significant amount of DNA strand and activating the intrinsic apoptotic pathway. A group of researchers also studied the efficiency of juncusol isolated from Juncus inflexu by introducing them in the cells of HeLa, CaSki as well as SiHa cells and found that the compound exhibited the potential of inducing apoptosis and inhibiting cell proliferation [33]. By analysing the cell cycle it was also concluded that G2/M as well as sub G1 cell populations were increased when treated with juncusol [58-65]. Moreover, this compound when added to HeLa cells was able to increase the activity of caspase-3, -8, as well as -9 which further suggest that it can also induce apoptosis. Additionally, this compound was able to inhibit tubulin polymerization as well as cause activation of EGFR which further propose that the compound can effectively stop G2/M-phase cell cycle and inhibit the migration of cells. Methyl protodioscin derived from Polygonatum sibiricum was studied for its anti-cancer efficiency. It was found to cause apoptosis of cells when

added to HeLa cells since it increases ROS and well as G2/M phase [66-69]. An experiment using methyl protodioscin showed that the compound can be effectively used to alter cell morphology, to stop cell cycle and also to inhibit cell proliferation. A study also revealed that when mitomycin C (MMC) present in ginger (Gi) was co administered with frankincense (Fr) oil and introduced to HeLa cells, both cytotoxicity as well as apoptosis was increased [70-73]. In HeLa cells, Fr-MMC miraculously survived nuclear apoptosis when administered at lower dosage compared to Gi-MMC. A cocktail of MMC with Gi-NE and Fr-NE tested on HeLa cells, significantly increase the cytotoxicity of MMC. Researchers also studied the antitumor properties of both naringenin oxime as well as oxime ether derivatives [74-77]. Furthermore, analysing cell cycle also proposed that compound 6 was able to extend the subG1 phase and also to induce apoptosis when administered to HeLa as well as SiHa cells. Nitensidine B, a guanidine alkaloid derived from Pterogyne nitens Tul leaves when introduced in HPV16 as well as SiHa cells were observed to induce caspase-3 and -7 and to inhibit aldolase A, pyruvate kinase, alpha-enolase and also glyceraldehyde 3-p-dehydrogenase [78-81]. An experiment was conducted using nitensidine B that further established the fact that this compound can effectively be used to induce apoptosis as well as to inhibit glycolysis. Notoginsenoside R7, a triterpenoid saponin derived from Panax notoginseng was observe to possess the ability to upregulate Bax, p-PTEN, and Akt and to downregulate Bcl-2, -XL, caspase-3, -9, and raptor when added to HeLa cells [82-84]. This compound was even found to reduce the tumour weight. Finally, notoginsenoside R7 may be employed for treating cervical cancer as well as numerous tumours associated with PI3K/PTEN/Akt/mTOR signalling pathway.

HeLa, SiHa, C-33A, and CaSki cells when experimented with osthole produced from Cnidiummonnieri (L.) Cusson, significantly elevated the amounts of Bax, H2AX, E-cadherin, and c-caspase-3, -9 proteins. [85-87]. On the other hand, osthole was responsible for downregulating Bcl-2, β-catenin, N-cadherin, p-IKKα, p-p65, NF-κB, MMP-2, -9, vimentin, IKKα, p65 and p50. Studies also stated that osthole can efficiently induce apoptosis and inhibit cell viability, cell invasion, cell proliferation and cell migration. The research revealed that physcion was linked to cell cytotoxicity, oxidative stress, apoptosis and inducing DNA damage. In HeLa cells, when silver nanoparticles (AgNPs) derived from garlic, turmeric and green tea undergo the process of phyto-synthesis can lower cell viability, trigger apoptosis and inhibit oxidizing agent [88]. The two compounds, paclitaxel and piperine isolated from the plant Piper nigrum when combined together can be used to increase the level of Bax, c-PARP, Bcl-2 and caspase-3 on the other hand the level of both p-Akt and Mcl-1 is decreased when

experimented with both HeLa as well as PTX cells. The combination was also able to induce cell apoptosis [89-91]. When HeLa cells are treated with the two compounds prenylflavonoid C1 as well as C5, obtained from Mallotus conspurcatus have the potential to upregulate EGFP, Bcl-2, Apaf-1, cytochrome c, ROS, caspase-3, and -9 while on the other hand they downregulate c-Myc and hTERT [92]. The compounds also induce mitochondrial dysfunction, apoptosis as well as cytotoxicity and inhibit the activity of telomerase. Another compound obtained from Dioscoreae rhizome when treated with both HeLa as well as C33A cells are able to upregulate JNK, PERK, Bax, PARP, p38, ATF4, caspase-3, -8, -9 while it downregulates the level of Bcl-2 [93-95]. It also initiates induction of ROS and the ER stress pathway. The two polyphenols, resveratrol present in red grapes and red wines and pterostilbene found in blueberries and grapes when experimented with HeLa cells showed upregulation of caspase-3 and downregulation of both PCNA and VEGF [96]. Experimenting these compounds with both PC1 as well as HPV E6 cells stated that are also able to supress the growth of tumour especially in the cervical cancer cell lines and can also induce cell cycle arrest. Tf-CT-ME isolated from Tripterygium wilfordii, exhibit the potential to elevate the level of c-caspase-3, downregulate Bcl-2/Bax, trigger cell cycle arrest and also possesses anti-proliferative property when tested against HeLa cells [97]. Thymoquinone, a phytochemical compound obtained from Nigella sativa when added to both SiHa as well as CaSki cells showed upregulation of Bax and E-cadherin while downregulation of Bcl-2, Twist1, and vimentin [98-99]. The fruity parts of Terminalia bellerica Roxb., Terminalia chebula Retz., and Phyllanthus emblica Linn. when combined together resulted in the formation of Triphala, an efficient polyherbal Ayurvedic drug. This drug when tested against HeLa cells showed inhibition of cell proliferation and induction of apoptosis [100]. Thus, triphala showed remarkable potential in the treatment of cervical cancer. Alpinia conchigera produces 1 0S'-10 -acetoxychavicol acetate (ACA) that can upregulate the level of both RSU1 and GAPDH and downregulate miR-629 when treated against CaSki and SiHa cells [101]. It can also induce apoptosis and reduce cell viability. Thus, ACA emerged to be a potential anti-cancer agent. 3,5,40-trimethoxystilbene with 5,6,7-trimethoxyflavone constitute 4f that further exhibit the ability to activate cytotoxic as well as the apoptotic potential when experimented with HeLa cells [102]. It not only modifies the nuclei existing in HeLa cells morphologically but also can induce cell death via inducing apoptosis. 5 0 -epi-SPA-6952A isolated from Streptomyces diastatochromogenes can upregulate the level of Bax/Bcl-2, caspase-3, -9, p53, cytochrome c and c-PARP, downregulate MMP, induce apoptosis, stop cell cycle, alter cellular morphology and inhibit

cellular migration as well as proliferation. All these includes all the natural extracts derived so far that were able to trigger cell death in cervical cancer [103].

4 Conclusions

Thus, the review focused on the naturally derived compounds exhibiting anti-tumor potential against cervical cancer. They also modulated multi-drug resistance as well as miRNAs, possess antiangiogenesis, and anti-metastasis properties and can induce apoptosis. Naturally derived compounds like emodin, Penicillium sclerotiorum and curcumin were found to be the best inducers of apoptosis. Lignan and Pistacia vera L., exhibited the most anti-angiogenic. Besides EGCG there are 5 other natural compounds that can inhibit metastasis of cervical cancer. In cervical cancer pine rosin along with numerous natural compounds were found to sensitise drug resistance. Few researchers also revealed that naturally derived compounds can efficiently regulate miRNA The non-clinical outcomes of this study are expected to pave the way for the development of new cervical cancer therapies having significantly fewer adverse consequences that can be utilised in clinic.

References

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.;
6. 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]

7. 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]

8. 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]

9. 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.

10. 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]

11. 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]

12. 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]

13. 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]

14. 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]

15. 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]

16. 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]

17. [PubMed]

18. 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]

19. Escuin, D.; López-Vilaró, L.; Bell, O.; Mora, J.; Moral, A.; Pérez, J.I.; Arqueros, C.; Cajal, T.R.Y.; Lerma, E.; Barnadas, A. MicroRNA1291 Is Associated With Locoregional Metastases in Patients With Early-Stage Breast Cancer. Front. Genet. 2020, 11, 562114. [CrossRef]

20. 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]

21. 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]
22. 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]
23. 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]
24. Lowe, S.W.; Lin, A.W. Apoptosis in cancer. Carcinog. 2000, 21, 485–495. [CrossRef]
25. 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]
26. 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]
27. 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]
28. 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]
29. 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]
30. 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.
31. J. Biomed. Nanotechnol. 2017, 13, 1631–1646. [CrossRef]
32. 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,
33. 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]
34. 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]

35. 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.

36. 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]

37. 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]

38. 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]

39. 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]

40. 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]

41. 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]

42. 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]

43. 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]

44. 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]

45. 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]

46. 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]

47. [PubMed]

48. 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]

49. 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]

50. 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]

51. 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]

52. 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]

53. Phuah, N.H.; Azmi, M.N.; Awang, K.; Nagoor, N.H. Suppression of microRNA-629 enhances sensitivity of cervical cancer cells to 1^{0}S-1^{0}-acetoxychavicol acetate via regulating RSU1. OncoTargets Ther. 2017, 10, 1695–1705. [CrossRef] [PubMed]

54. 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]

55. 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]

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

57. 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]

58. 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]

59. 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]

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

61. 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]

62. 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]

63. 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]

64. 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]

65. 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]

66. 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]

67. 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]

68. 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]

69. 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]

70. 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]

71. 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]

72. 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]

73. 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]

74. 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]

75. Sul'ain, M.D.; Fashihah Zakaria, M.F.J. Anti-Proliferative Effects of Methanol and Water Extracts of Pyrrosia piloselloides on the Hela Human Cervical Carcinoma Cell Line. APJCP 2019, 20, 185.

76. Panicker, N.G.; Balhamar, S.O.M.S.; Akhlaq, S.; Qureshi, M.M.; Rizvi, T.S.; Al-Harrasi, A.; Hussain, J.; Mustafa, F. Identification and Characterization of the Caspase-Mediated Apoptotic Activity of Teucrium mascatense and an Isolated Compound in Human Cancer Cells. Molecules 2019, 24, 977. [CrossRef] [PubMed]

77. Lord, C.J.; Ashworth, A. Targeted therapy for cancer using PARP inhibitors. Curr. Opin. Pharmacol. 2008, 8, 363–369. [CrossRef] [PubMed]

78. Ma, J.; Waxman, D.J. Combination of antiangiogenesis with chemotherapy for more effective cancer treatment. Mol. Cancer Ther. 2008, 7, 3670–3684. [CrossRef]

79. Rajabi, M.; Mousa, S.A. The Role of Angiogenesis in Cancer Treatment. Biomediences 2017, 5, 34. [CrossRef] [PubMed]

80. Tomao, S.; Tomao, F.; Rossi, L.; Zaccarelli, E.; Caruso, D.; Zoratto, F.; Panici, P.B.; Papa, A. Angiogenesis and antiangiogenic agents in cervical cancer. OncoTargets Ther. 2014, 7, 2237–2248. [CrossRef] [PubMed]

81. Shivamadhu, M.C.; Srinivas, B.K.; Jayarama, S.; Chandrashekaraiah, S.A. Anti-cancer and anti-angiogenic effects of partially purified lectin from Praecitrullus fistulosus fruit on in vitro and in vivo model. Biomed. Pharmacother. 2017, 96, 1299–1309. [CrossRef]

82. Seifaddinipour, M.; Farghadani, R.; Namvar, F.; Bin Mohamad, J.; Kadir, H.A. Cytotoxic Effects and Anti-Angiogenesis Potential of Pistachio (Pistacia vera L.. Hulls against MCF-7 Human Breast Cancer Cells. Molecules 2018, 23, 110. [CrossRef]

83. Foda, H.D.; Zucker, S. Matrix metalloproteinases in cancer invasion, metastasis and angiogenesis. Drug Discov. Today 2001, 6, 478–482. [CrossRef]

84. Weber, G.F. Why does cancer therapy lack effective anti-metastasis drugs? Cancer Lett. 2013, 328, 207–211. [CrossRef]

85. Chanvorachote, P.; Chamni, S.; Ninsontia, C.; Phiboonchaiyanan, P.P. Potential Anti-metastasis Natural Compounds for Lung Cancer. Anticancer Res. 2016, 36, 5707–5718. [CrossRef]

86. Zhang, L.; Zhou, J.; Qin, X.; Huang, H.; Nie, C. Astragaloside IV inhibits the invasion and metastasis of SiHa cervical cancer cells via the TGF-β1-mediated PI3K and MAPK pathways. Oncol. Rep. 2019, 41, 2975–2986. [CrossRef] [PubMed]

87. Wang, Y.-Q.; Lu, J.-L.; Liang, Y.-R.; Li, Q.-S. Suppressive Effects of EGCG on Cervical Cancer. Molecules 2018, 23, 2334. [CrossRef] [PubMed]

88. Hung, C.-Y.; Lee, C.-H.; Chiou, H.-L.; Lin, C.-L.; Chen, P.-N.; Lin, M.-T.; Hsieh, Y.-H.; Chou, M.-C. Praeruptorin-b inhibits 12-otetradecanoylphorbol-13-acetate-induced cell invasion by targeting akt/nf-kappab via matrix metalloproteinase-2/-9 expression in human cervical cancer cells. Cell Physiol. Biochem. 2019, 52, 1255–1266. [PubMed]

89. Lee, C.-Y.; Yang, S.-F.; Wang, P.-H.; Su, C.-W.; Hsu, H.-F.; Tsai, H.-T.; Hsiao, Y.-H. Antimetastatic effects of Terminalia catappa leaf extracts on cervical cancer through the inhibition of matrix metalloprotein-9 and MAPK pathway. Environ. Toxicol. 2019, 34, 60–66. [CrossRef]

90. Onder, T.T.; Gupta, P.B.; Mani, S.A.; Yang, J.; Lander, E.S.; Weinberg, R.A. Loss of E-Cadherin Promotes Metastasis via Multiple Downstream Transcriptional Pathways. Cancer Res. 2008, 68, 3645–3654. [CrossRef]

91. Vasan, N.; Baselga, J.; Hyman, D.M. A view on drug resistance in cancer. Nat. Cell Biol. 2019, 575, 299–309. [CrossRef]

92. Gillet, J.-P.; Gottesman, M.M. Mechanisms of Multidrug Resistance in Cancer. In cryoEM; Springer Science and Business Media LLC: Berlin, Germany, 2010; Volume 596, pp. 47–76.

93. Faustino, C.; Neto, Í.; Fonte, P.; Macedo, A. Cytotoxicity and Chemotherapeutic Potential of Natural Rosin Abietane Diterpenoids and their Synthetic Derivatives. Curr. Pharm. Des. 2018, 24, 4362–4375. [CrossRef]

94. Levrier, C.; Rockstroh, A.; Gabrielli, B.; Kavallaris, M.; Lehman, M.; Davis, R.A.; Sadowski, M.C.; Nelson, C. Discovery of thalicthuberine as a novel antimitotic agent from nature that disrupts microtubule dynamics and induces apoptosis in prostate cancer cells. Cell Cycle 2018, 17, 652–668. [CrossRef]

95. Levrier, C.; Sadowski, M.C.; Rockstroh, A.; Gabrielli, B.; Kavallaris, M.; Lehman, M.; Davis, R.A.; Nelson, C. 6α-Acetoxyanopterine: A Novel Structure Class of Mitotic Inhibitor Disrupting Microtubule Dynamics in Prostate Cancer Cells. Mol. Cancer Ther. 2016, 16, 3–15. [CrossRef]

96. Ho, C.S.; Yap, S.H.; Phuah, N.H.; In, L.L.; Nagoor, N.H. MicroRNAs associated with tumour migration, invasion and angiogenic properties in A549 and SK-Lu1 human lung adenocarcinoma cells. Lung Cancer 2014, 83, 154–162. [CrossRef]

97. Di Leva, G.; Croce, C.M. miRNA profiling of cancer. Curr. Opin. Genet. Dev. 2013, 23, 3–11. [CrossRef] [PubMed]

98. Wu, S.; Huang, S.; Ding, J.; Zhao, Y.; Liang, L.; Liu, T.; Zhan, R.; He, X. Multiple microRNAs modulate p21Cip1/Waf1 expression by directly targeting its 3^0 untranslated region. Oncogene 2010, 29, 2302–2308. [CrossRef] [PubMed]

99. Reddy, K.B. MicroRNA (miRNA. in cancer. Cancer Cell Int. 2015, 15, 1–6. [CrossRef] [PubMed]

100. de Moura, M.D.; de Se Silva, J.; de Oliveira, R.A.G.; de Diniz, M.; Barbosa-Filho, J.M. Natural products reported as potential inhibitors of uterine cervical neoplasia. Acta Farm. Bonaer. 2002, 21, 67–74.

101. AL, A.O. Dietary supplements as a treatment for cervical cancer: A systematic review. Nutr. Hosp. 2013, 28, 1770–1780.

102. Wang, S.; Zheng, C.; Peng, C.; Zhang, H.; Jiang, Y.-P.; Han, T.; Qin, L.-P. Plants and cervical cancer: An overview. Expert Opin. Investig. Drugs 2013, 22, 1133–1156. [CrossRef]

103. Roy, M.; Mukherjee, A.; Sarkar, R.; Mukherjee, S.; Biswas, J. In Search of Natural Remediation for Cervical Cancer. Anti-Cancer Agents Med. Chem. 2014, 15, 57–65. [CrossRef]