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PHYTOCHEMICALS: A MULTITARGETED APPROACH TO PREVENT CERVICAL CANCER

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ABSTRACT

Cancer escapes the body's own immune system and establishes itself in any target organ. Despite initial success in classical therapy e.g. surgery, radiation and chemoprevention, cancer always relapse after some time. Targeted therapy to some extent showed better responses with lesser toxicity. However, the mutation in the target protein leads to drug resistance. Therefore, it seems logical & great need to boost body's own immune system and sensitize them against the tumor cells to achieve complete remission and disease-free survival. In Ayurveda, properties of some important plants namely *Tinospora cordifolia* (Giloy), *Berberis aristata* (Daru haldi) and *Boerhaavia diffusa* (Punarnava) have been already cited. According to Ayurveda, these plants are rich in antioxidants and therefore have

anti-inflammatory, anti-carcinogenesis, anti-angiogenic and immunomodulatory capabilities. In this review, we looked at how these herbs can aid in the prevention of cervical cancer. In medical research, simulation digestion is also a rising requirement that should be addressed.

Keywords: Cervical cancer, Phytochemicals, Chemoprevention, *Tinospora cordifolia*, *Berberis aristata*, *Boerhavia diffusa*

ABBREVIATION

HPV - Human papillomavirus

IL-2 - Interleukin-2

IL-10 - Interleukin-10

TNF- α - Tumor necrosis factor alpha

NF- κ B - Nuclear factor kappa B

NO - Nitric oxide

MHC-II - Major histocompatibility complex II

ERK1/2 - Extracellular signal-regulated kinases 1/2

SAAPK/JNK - Stress-activated protein kinase/c-Jun NH(2)-terminal kinase

MAPK - Mitogen-activated protein kinase

VEGF - Vascular endothelial growth factor

MMP - Matrix metalloproteinase

ROS - Reactive oxygen species

GSH - Glutathione

IR - Ionizing radiation

Rb - Retinoblastoma

COX-2/PGE2-JAK2/STAT 3 - Cyclooxygenase-2/ Prostaglandin E₂/ Janus kinase 2/ Signal transducer and activator of transcription 3

GM-CSF - Granulocyte-macrophage colony-stimulating factor

HIF-1 - Hypoxia-inducible factor 1

AP-1 - Activated protein-1

INTRODUCTION

According to GLOBOCAN 2020 data, 19.03 million new cases of cancer and 10.0 million deaths from cancer, were recorded worldwide. Among them, cervical cancer accounts for 3.1 percent and 3.4 percent of new cases and deaths respectively [1]. Cervical cancer death rates are higher in low- and middle-income countries than in high-income nations [2]. In India, cervical cancer is more common in rural areas than in urban areas due to a lack of awareness

about genital cleanliness, frequent cytological screening, medical facilities, socioeconomic position, and other variables [3]. Cervical cancer is caused by a variety of factors such as tobacco smoke [4], poor genital hygiene [3], but the HPV (Human Papilloma Virus) plays a crucial role in the infection of cervical cancer [5]. In addition, the majority of genital HPV infections are asymptomatic and unapparent. Oftentimes, the women having HPV infection, are self-

curable and do not result in precancerous cell changes, only chronic infection with specific HPV strains (mainly HPV 16 and 18) might result in cervical cell abnormalities or precancerous cell changes. If these abnormalities (pre-cancerous or high-grade lesions) are not treated promptly, eventually, they can progress to cervical cancer lesions [6]. By screening tests, cervical cancer can be identified in the precancerous stage and also can be treated. Hence, cervical cancer can be easily prevented from progression by early detection and treatment of precancerous lesions with regular screening programs [3, 7].

For prevention, there are two approaches, primary and secondary. In primary approaches, risk reduction and the development of HPV vaccines are included to prevent HPV infection [7]. Risk reduction comprises abstaining from sexual activity, mutual monogamy of virgins, use of condoms (not 100% reliable), regular screening, awareness, hygiene, taking immunity boosters or modulators in form of medicinal herbs, etc. However, effective primary cervical cancer prevention relies on HPV vaccination [8], even though HPV vaccines provide less protection against cervical cancer in HPV-positive women and those infected with HPV16 or HPV 18 or both oncogenic HPV genotypes [3]. Although, the price and accessibility of

vaccinations are a big challenge for a mass immunization program in developing nations such as India, due to the high cost of current vaccinations. Developing countries require a low-cost second-generation HPV vaccine [9]. The secondary approach includes screening and testing through prevention programs. The cervical screening can be done by two tests, the Papanicolaou smear (Pap test) and the HPV-based test. However, when compared to cytology, for detecting cervical pre-cancer or cancer, the HPV-based test was more effective as it provided greater protection against cervical cancer [4].

Although HPV has a critical role in the transformation of cervical epithelial cells to precancerous and then cancerous, apart from HPV, there are other factors that can cause cancer too. Many risk factors and molecular events including exposure to cigarette smoke and chronic inflammation as they increase oxidative stress [10], influence the process of transformation of cervical epithelial cells [7] (**Figure 1**). Regular screening is the most effective way to prevent cervical cancer as it eliminates the chances of developing cancer. Many chemotherapeutic or anti-viral drugs have been used to abolish HPV infection but their side effects limit their utilization. On the other hand, many plants and herbs play a vital role as therapeutics due to their lesser or no side effects. Besides, according

to researchers, chemotherapy treatments can be swayed by dietary phytochemicals and aid to cure patients. Surgery, radiation, and hormone treatments are the most commonly used treatments in cervical cancer, but they have severe side effects. Medicinal plants have the potential to be a promising source of novel therapeutic agents, particularly for cancer. Plants play an indispensable role in both medicine and economics. So, in numerous developing countries across the world, due to affordability, accessibility, and cultural beliefs, as a primary source of health medical treatment, traditional medicine is still used [11].

CHEMOPREVENTION BY MEDICINAL PLANTS

Chemopreventive compounds of either drug or plant should interfere in the process of carcinogenesis by inhibiting the transformation of normal cells to premalignant cells or the premalignant cells to malignant cells [12]. Synthetic drugs have been developed as chemotherapeutics but they are repeatedly showing adverse side effects and due to the development of chemoresistance, [13] bioactive phytochemicals are preferred as they act differentially on cancer cells only, without altering normal cells [14]. Ayurvedic anticancer therapy includes recommendations for lifestyle and use of specific foods and herbs which are very

helpful not only in preventing the progression of the disease but also make the patients feel better and comfortable overcoming the symptoms [15].

Almost all Phenolic compounds (Polyphenols and Phenolic acids), Terpenoids, and Alkaloids having antioxidant, antiproliferative, anticancer properties [16]. By infecting cell signaling pathways, polyphenols activate cell death signals and induce apoptosis in premalignant cells resulting in the inhibition of cancer development or progression. Regulation of cell signaling pathways by dietary polyphenols can also lead to the expression of several genes of inflammatory responses [17]. Many natural compounds are known to activate or deactivate many transcription factors that modulate tumor signalling pathways [18]. The high intake of foods and beverages which are rich in flavonoids has been associated with decreased risk of neoplasm [19] (Figure 2).

In a nutshell, therapeutic plants, or more precisely, the phytochemicals found in medicinal plants, interfere with the cell signaling pathways of cells that can proceed from premalignant to malignant. If the infection is detected early (while screening), it can be treated with immunomodulators to raise immunity and eliminate the infection, or with antivirals to eradicate the virus. So, in this review, we've

chosen three plants from the literature to analyze more in the prevention of cervical cancer.

- *Tinospora cordifolia*

Tinospora cordifolia is found all across India and also in Sri Lanka, Myanmar, and China. It is native to India and China's tropical regions, where it grows at altitudes of 300 to 500 meters in temperatures ranging from 25° to 45° C [20]. The chemical investigations of the plant have revealed the presence of a different class of compounds such as alkaloids, diterpenoids lactones, glycosides, steroids, phenol, aliphatic compounds, and polysaccharides in the plant [21]. Although the active components of *T. cordifolia*, which are responsible for therapeutic effects, have not been well defined yet, however, it may be possible that the synergistic effects of multiple constituents exhibited its high pharmacological values [21].

T. cordifolia is having immunostimulating properties which can be used in the prevention of tumor mediated immunosuppression as it boosts the immune system by increasing immunoglobulin and blood leukocyte levels and also increases the proliferation of stem cells [15]. Many alkaloids isolated from *T. cordifolia* showed diverse pharmacological activities including immunomodulatory, anti-viral, anticancer [22]. And also, these

alkaloids may play a vital role in the prevention task of cancer, including HPV-mediated cervical cancer. Among the alkaloids, berberine and palmatine are the most active components present in *T. cordifolia* stem [23]. *T. cordifolia* also shows antiproliferative activity. So, *T. cordifolia* can be established as a chemopreventive option for cervical cancer [24]. It has been reported that the presence of berberine in *T. cordifolia* extract significantly contributes to its anti-proliferative activity. In the study of Palmieri, the effects of *T. cordifolia* treatment have well resembled with the activity of pure berberine. It may be possible that the main effects of *T. cordifolia* were mediated by berberine [25]. The other study says *T. cordifolia* modulated the immunity by increasing cytotoxic T cells and B cells differentiation, antibody, level of cytokines like IL-2, IL-10, and TNF- α [26]. After giving the treatment of *T. cordifolia*, LPS-(lipopolysaccharide) induced TNF- α and NF- κ B translocation into the nucleus were remarkably reduced in THP-1 cells (human monocytic cell line) [27]. According to Nair and team, (1,4)-alpha-D-glucan from *T. cordifolia* activated the immune system through the activation of TNF- α and NF-kappa B and also macrophages [28]. One of the compounds of *T. cordifolia*, G1-4A (Polysaccharide), and its treatment increased the production of NO, expression

of MHC-II in murine macrophages and activated p38, ERK1/2, SAAPK/JNK, MAPK in RAW 264.7 cells (macrophage cell line) [29]. G1-4A treatment led to an increase in the CD69 expression in lymphocytes [30]. *T. cordifolia* stem extracts have considerable antioxidant properties so that consumption of this plant may prevent various diseases including cervical cancer [24]. Octacosanol, a compound of *T. cordifolia* inhibited angiogenesis, VEGF, MMP in mice [31]. According to Sharma and colleagues, the components N-Formylannonain, 11-hydroxymustakone, and yangabin are most abundant in *T. cordifolia* stems hosted by *Mangifera indica*. On the SiHa cervical cancer cell line, these chemicals have an IC₅₀ value of >100 µM [21]. The administration of hexane fraction of *T. cordifolia* induced Bax, reduced Bcl-2 expression, and stimulated constitutive expression of caspase-activated DNase in nucleus and cytoplasm [31]. *T. cordifolia* dry leaf extracts reduced Arachidonic Acid-induced ROS generation via enhancing catalase enzyme activity in THP-1 cells (Human monocytic Cells) [27].

- *Berberis aristata*

Berberis aristata is commonly known as “Daru Haldi” is a spinous shrub native to the northern Himalaya region. The plant is widely distributed in India (Western

Himalayas, Himachal Pradesh, and Nilgiri in the south), Srilanka, Bhutan, and hilly areas of Nepal in the Himalaya region [32]. In India, 55 species of the genus *Berberis* are there, of which 24 species (44 %) are reported from Uttarakhand [33]. It grows on an altitude range between 2200 to 3200 m [20, 32]. *B. aristata* has many activities, among them, 11% is contributed by anticancer activity [34]. Many alkaloids like berbamine, berberine, palmatine, jatrorrhizine, etc. are present in the roots of *B. aristata*. Berberine, the major alkaloid found in *B. aristata* has been reported as the major active constituent present in *B. aristata*. Moreover, maximum berberine content is accumulated in the root part (1.6–4.3 %) in most of the *Berberis* species [35]. Pai suggested that certain compounds present in *B. aristata* may enhance the potential of active compound berberine synergistically. Apart from berberine many other compounds are also present which may act in a composite manner [36]. Jagetia *et al.* reported that berberine in combination with *Alstonia scholaris*, enhanced the anticancer activity by increasing the apoptosis and lipid peroxidation while decreasing the enzymes GSH resulting in causing tumor remission and elimination [37]. Berberine and cisplatin combination followed by IR was proved better to increase apoptosis in SiHa and HeLa cells (cervical cancer cell

lines), in comparison to cisplatin alone based radiotherapy [38]. The LD₅₀ value of *B. aristata* is 5000mg/kg of body weight. So, the plant extract is safe to be used at any dose which is less than 5000 mg/Kg body weight [39]. According to Wang and colleagues, berberine prevents Rb mRNA degradation by acting directly on the poly (A) tail, allowing for stable Rb expression. Berberine inhibits Rb phosphorylation, preventing the dissociation of E2F from Rb and thereby inhibiting the transition from G1 to S phase. Berberine increases the phosphorylation of p53 via activating JNK/p38, which facilitates the entry of the apoptic proteins Bax and Bim into mitochondria. Berberine suppresses MMP2 and MMP9 expression by inhibiting the COX-2/PGE2-JAK2/STAT 3 signalling pathway [40]. Berberine effectively reduced the number of tumor-directed capillaries and serum nitrite levels, according to Hmasa and colleagues. In general, serum cytokines such as IL-1, IL-6, TNF- α , and GM-CSF are elevated in tumour cells, however their levels were lowered after berberine treatment. Antitumor and antiangiogenic factors like IL-2 and TIMP-1 are often low in tumours, but berberine treatment was shown to boost their levels. Berberine has the potential to drastically reduce HIF-1 expression [41]. Berberine inhibits constitutively active transcription factor, AP-1, and

downregulates HPV oncogenes expression in HPV16-positive cervical cancer cell line, SiHa, and HPV18-positive cervical cancer cell line, HeLa, in a dose- and time-dependent manner. In both types of cervical cancer cell lines, berberine decreased E6 and E7 levels of viral oncoprotein and increased p53 and Rb. By activating caspase-3, a higher dose of berberine reduces cell viability and induces apoptosis [42].

- *Boerhaavia diffusa*

Boerhaavia diffusa flourishes as weeds in India, Brazil, Africa, Australia, China, Egypt, Pakistan, Sudan, Sri Lanka, the United States, and Iran's tropical and subtropical climates. In India, six species of *Boerhaavia* have been identified, including *B. diffusa*. It is used to cure or treat a range of diseases in India, including cancer. There are many different types of classes in it, like alkaloid, rotenoids, glycosides, lignans, lipids, phenolic compounds [43]. Punarnavine is a plant extract that contains an alkaloid that is assumed to be the active component of Punarnava (*B. diffusa*) [44]. Rotenoids, flavonoids, glycosides, xanthenes, purine nucleosides, lignans, ecdysteroids, and steroids are all iso flavonoids found in the roots of *B. diffusa*. According to certain studies, *B. diffusa* exhibits qualities such as immunomodulation, hepatoprotection, anticancer

activity, antidiabetic activity, and anti-inflammation [45].

B. diffusa also has anti-cancer properties, according to Srivastava and co-workers, they demonstrated a dose-dependent cytotoxic effect of the BD (*B.diffusa*) root and leaf extracts on HeLa and U-87 carcinoma cell lines. The root (200g/mL) and leaf (300g/mL) crude ethanolic extracts showed 30 % and 40% cell death, respectively, while the alkaloidal fraction (300g/mL) with methotrexate (200 nM) indicated 40% cell death [46]. By suppressing DNA synthesis, reducing cell proliferation, and causing cancer cell apoptosis, *B. diffusa* slows the growth of the HeLa-human cervical cancer cell line.

B. diffusa showed an antiproliferative effect by inhibiting the S phase. The activation of caspase-9 and caspase-3 in *B. diffusa* culminated in apoptosis [47]. Punarnavine, a secondary metabolite identified in *B. diffusa*, inhibits MMP-2, MMP-9, VEGF, ERK-1, and ERK-2 production in the lung tissue of metastasis-induced animals [44]. It also triggers apoptosis by upregulating p53 and caspase-3 while suppressing Bcl-2 and NFκB signalling [48]. Many attributes of *B. diffusa* encompass anticancer, immunomodulatory, and immuno-suppressive activities. As a result, it can be employed as part of a multi-pronged approach to cancer therapy and treatment.

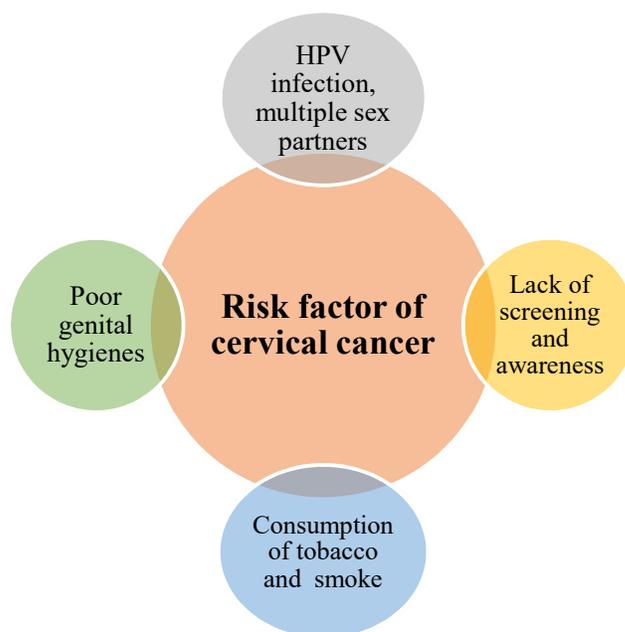


Figure 1: Risk factors for occurrence of cervical cancer

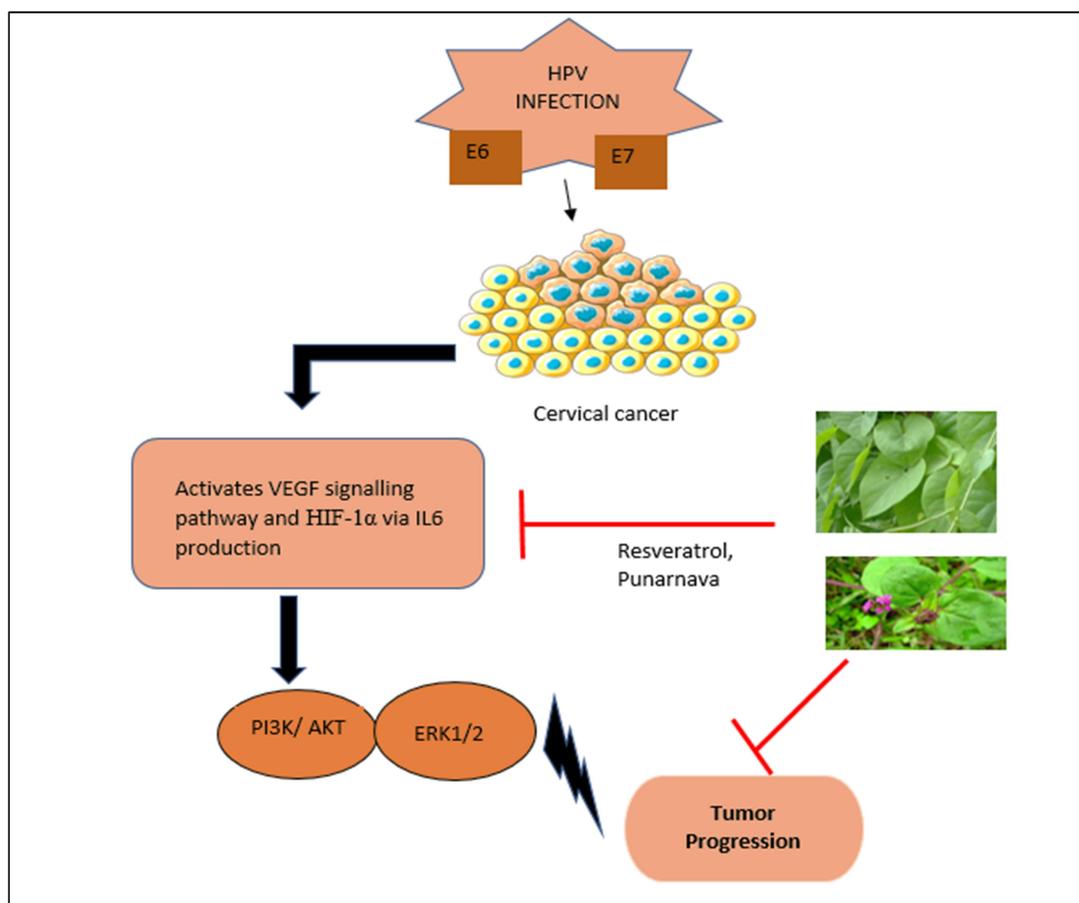


Figure 2: Schematic representation of natural herbs on signaling pathway in cervical cancer

FUTURE PROSPECTS AND CONCLUSION

Despite the availability of screening technologies for early diagnosis and treatment, cervical cancer remains a major public health concern, particularly in developing nations. Naturally occurring dietary phytochemicals produced from *Tinospora cordifolia*, *Berberis aristata*, and *Boerhavia diffusa* would lead to a better therapeutic regimen in cervical cancer prevention and treatment, because of their numerous roles in avoiding carcinogenesis. They target a variety of signaling pathways.

As a result, they can perform numerous tasks at once. In comparison to pharmaceuticals, they are safe and have no or low toxicity. They can be used alone or in combination with other conventional medications (such as cisplatin) or therapies (such as chemotherapy and radiotherapy) to improve their ability to target molecules in cancer. We should also concentrate on increasing its bioavailability, which is the only disadvantage of natural compounds. Apart from that, phytochemicals are a superior option for effectively preventing/

treating precancer/cancer without causing harm to patients.

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