World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

Cannabis sativa: Cervical cancer treatment- Role of phytocannabinoids-A story of concern

Ravindra B. Malabadi [1,*], Sadiya MR [2], Prathima TC [2], Kiran P. Kolkar [3], Simuzar S. Mammadova [4] and Raju K. Chalannavar [1]

[1] *Department of Applied Botany, Mangalore University, Mangalagangotri-574199, Mangalore, Karnataka State, India.*
[2] *Department of Biochemistry, JSS Medical College, Mysore- 570015, Karnataka State, India.*
[3] *Department of Botany, Karnatak Science College, Dharwad-580003, Karnataka State, India.*
[4] *Department of Business Management, Azerbaijan State Economy University (ASEU), 6 Istiglaliyyat Street, AZ 1001 Baku, AZERBAIJAN*

World Journal of Biology Pharmacy and Health Sciences, 2024, 17(02), 253–296

Publication history: Received on 05 January 2024; revised on 31 January 2024; accepted on 03 February 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.17.2.0076

Abstract

This litrature review paper highlights the role of phytocannabinoids in controlling cervical cancer. Cervical cancer is one of the leading causes of cancer death among females worldwide. Cervical cancer (CC) is a malignant form of tumor which originates in the cervix. Cervical cancer, which develops in a woman's cervix, is the second-most common cancer among women in India The causative agent of cervical cancer is persistent infection with high-risk subtypes of the Human Papillomavirus (HPV) and the E5, E6 and E7 viral onco-proteins cooperate with host factors to induce and maintain the malignant phenotype. Human papillomavirus (HPV) is responsible for subclinical/clinical lesions in cervical cancer. HPV types 16 and 18 are the most common HPV types identified in invasive cervical cancer. Currently, the recommended therapeutic regimens include chemotherapy, radiation therapy either alone or in combination and surgical interventions. However, they present several limitations including side effects or ineffectiveness. Medicinal plants including Cannabis sativa have been used for decades for health benefits and to treat several different diseases including cervical cancer. Cannabis has been used for thousands of years for recreational, medicinal, or religious purposes. Phytocannabinoids are cannabinoids that occur naturally in the cannabis plant. The two phytocannabinoids the most well known for their therapeutic properties are, Δ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). Cannabis and cannabinoids hold big promise for cancer therapy. However, there is a need to understand more about the role of Endocannabinoid system (ECS) in normal human physiology and malignant transformations. Molecular mechanisms of Endocannabinoid system (ECS) regulation and anticancer properties of cannabis also need to be clarified. The treatment durations in the existing trials are also of concern. Future epidemiological and clinical studies are required to further assess the benefits of herbal medicines for the prevention of cervical cancer. In addition, preclinical and human clinical trial evaluations of cannabis for cervical cancer treatment have not specifically been conducted, so further investigations related to this are warranted. Therefore, HPV immunization programme is the best ideal solution for the eradication of cervical cancer.

Keywords: Cannabidiol (CBD); Cervical cancer; Endocannabinoid system (ECS); India; Human Papillomavirus (HPV); Cannabidiol (CBD); Risk factors

1 Introduction

Cervical cancer is one of the leading causes of cancer death among females worldwide [1- 11]. Cervical cancer (CC) is the fourth most commonly diagnosed cancer in women worldwide [1- 11, 146]. It remains a public health related issue

* Corresponding author: Ravindra B. Malabadi

among females of Africa, Middle East, South America, and Asia particularly India with over half a million new cases reported each year [1- 20, 146-160]. Cervical cancer, which develops in a woman's cervix, is the second-most common cancer among women in India [12- 27, 44-92, 146]. It is caused by persistent infection by the Human Papillomavirus (HPV) [1- 90]. India accounts for nearly a quarter of all cervical cancer deaths in the world [1- 30, 44-104, 146]. India recorded the highest number of cervical cancer cases in Asia, followed by China, according to a latest Lancet study on the disease [1- 30, 44-92, 146]. This research study revealed that out of the 40% of the total deaths from cervical cancer, 23% occurred in India, and 17% in China [1- 30, 44-95, 146]. Globally, there were around 6,04,127 new cases of cervical cancer and 3,41,831 deaths occurred in 2020 [1- 30, 44-92, 146]. Of these, India reported around 23% of the total cervical cancer cases, as per the data. More than 58% of all cases of cervical cancer globally were estimated in Asia followed by Africa (20%), Europe (10%) and Latin America (10%) and more than half of deaths were estimated in Asia (58%) followed by Africa (22%), and Latin America (9%) [1- 30, 44-92-104, 146]. Around 39% of all cases occurred in China (18%) and India (23%) and 40% of total deaths from cervical cancer (17% in China; 23% in India) was reported [1- 30, 44-92, 146]. This study is based on The Global Cancer Observatory (GLOBOCAN) 2020 estimates, including geographical and socioeconomic development, and temporal aspects [1- 30, 44-92-104, 146]. Human Papillomaviruses (HPV) are ubiquitous and have been detected in a wide variety of animals as well as in humans and are specific for their respective hosts [1- 30, 44-92-104, 146]. More than 200 types of HPV have been recognized on the basis of DNA sequence data showing genomic differences [1-30, 44-92-104,146-200]. Eighty-five HPV genotypes are well characterized [1-30, 44-92-104, 146]. An additional 120 isolates are partially characterized potential new genotypes [1- 104, 143-160-200]. Pap and HPV tests are used to detect potentially precancerous and cancerous processes in the cervix or colon, allowing for earlier treatment [1- 104, 143-160].

Cervical cancer treatment options include surgical interventions, chemotherapy and/or radiotherapy either alone or in combination, stem cell therapy, gene therapy, immunotherapy, targeted therapy, ablation therapy, nanoparticles, natural antioxidants, radionics, chemodynamic therapy, sonodynamic therapy, and ferroptosis-based therapy and vaccination [1-104, 143- 160]. However, they present several limitations including side effects or ineffectiveness. Even though these conventional treatment modalities have shown promise, the unwanted short and long terms side effects are vast [1-104, 143-160]. Ablation therapy has emerged as a minimally invasive procedure that burns or freezes cancers without the need for open surgery. Chemotherapy, the primary choice for treatment of cancer, is often ineffective or/and presents itself with many debilitating side effects, including loss of appetite, nausea, insomnia, and anxiety [1- 104, 143-160]. Surgery at any stage of cervical cancer is highly invasive and painful. Radiation therapy is known to induce unwanted DNA damage in normal healthy cells, leading to loss in cellular recovery, cell cycle arrest, loss of fertility and un-repairable damage [1- 104, 143-160]. Furthermore whereas chemotherapy is toxic to healthy tissues and so brings about short-term side effects such as hair loss, vomiting, diarrhea, coughing, swelling of the legs and weight loss [1-104]. The long term side effects from either radiation or chemotherapy include permanent abdomen, back or leg pain, trouble urinating, and feeling tired [1- 104, 143-160]. Moreover, additional treatment options such as targeted immunotherapies are novel and so remain in clinical stage trials, whereby their overall effectiveness remains unknown [1-104, 143-160]. However, all these have toxic side effects, poor pharmacodynamics properties, resistance to metastasis, poor bioavailability and non-specificity limiting their clinical utility to a large extent. Therefore, it is important to search for new novel therapeutic agents that are naturally synthesized and cheaper, but still remain effective. Drugs are used to treat cancer. Most drugs available in the market are chemosynthetic drugs and have side effects on the patient during and after the treatment, in addition to cancer itself. For instance, hair loss, loss of skin color and texture, loss of energy, nausea, infertility, etc. To overcome these side effects, naturally obtained drugs from medicinal plants are preferred. Medicinal plants have been used for decades for health benefits and to treat several different diseases including cervical cancer [105-142, 361-363]. Tribal people in the Himalayan region used Cannabis as a home made herbal medicine for many diseases including cervical cancer [257-293]. Researchers at the Indian Institutes of Technology Madras, Tamilnadu, India and Mandi have metabolically engineered plant cells to increase production of anti-cancer drug camptothecin (CPT) [361-363]. Herbal medicine has become a very safe, non-toxic, and easily available source of cancer-treating compounds. Components of cannabis extracts, including cannabinoids and terpenes, may present an alternative for controlling side effects and may be used for tumour shrinkage together with chemodrugs [257-293]. Cannabinoids act on so called Endocannabinoid system (ECS) that operates in our body to maintain homeostasis [290-293]. ECS promotes healthy development of tissues and regulates many processes in our organism and when disbalanced may lead to disease, including cervical cancer [257-293].

In a traditional Indian *Ayurvedic* system of medicine, plants and plant-based constituents have been extensively used for the treatment and management of different types of viral and other diseases including cervical cancer [105-142]. *Ayurveda* is a holistic approach to health and wellness that emphasizes balance between body, mind, and spirit [105-142]. It is one of the oldest and the most respected Indian herbal medicinal traditions in the world [105-142]. *Ayurveda* means 'Science of life'. It provides a complete system to have a long and healthy life [105-142]. India has the exclusive distinction of its own recognized traditional medicine; Ayurveda, Yoga, Unani, Siddha, and Homoeopathy

(AYUSH) [105-142]. Many safe traditional formulations of AYUSH, which are well known immunity modulators, have been used for centuries to control the viral disease, cervical cancer, respiratory disorders and in allergic conditions [105-142]. The use of plant-based traditional medicine is experiencing a revival, as it is seen as safer and healthier than synthetic drugs [105-142]. Indeed, one advantage of traditional remedies over modern drugs is that their effects and margin of safety have been known for long [105-142]. The rich secondary metabolism that characterizes plants make them a source of compounds that may have a yet unknown therapeutic potential, only limited by the availability of resources to perform clinical trials [105-142]. It is claimed that natural products (mostly from plant origin) will be the most important source of new drugs in the future for cervical cancer [105-142]. There is a rich and efficient herbal medicine beings exist in the villages of India which form integral part of the family and plays an important social, religious and economic role [105-142]. Rich and efficient herbal medicine traditions still exist in the villages of India comprised of belief knowledge, practices and skills pertaining to health care and management of diseases [105-142]. Medicinal plants have a long history of use in the treatment of several viral disease including cervical cancer [105-142]. Today, the cost of health care is constantly rising, and affecting people's ability to afford health coverage [105-142]. Drug-based medicines are being unaffordable for economically poor countries like India and problematic in the Western countries due to numerous side effects [105-142]. The drug should be the last rather than first mean of treatment, beginning with the natural healing method like *Ayurveda* [105-142].

Figure 1 The wild growth of Cannabis sativa in Indian Himalaya region

Cannabis sativa L. belongs to the family *Cannabaceae* was used as a medicine before the Christian era in Asia**,** mainly in India**,** China, Bhutan, Nepal, Azerbaijan, Afghanistan, Morocco, Pakistan, Egypt, Iran, and Persians [257-293]. Cannabis has been used for thousands of years for recreational, medicinal, or religious purposes [257-293]. Cannabis has a long history in India, recorded in legends and religion (Figure-1, 2) [257-293]. It was found in various habitats ranging from sea level to the temperate and alpine foothills of the Indian Himalaya Region (**Figure**-1, 2) from where it was probably spread over the last 10,000 years [257-293]. Many historians believed that Indian Himalayan Region was the centre of origin of *Cannabis sativa* L. and *Cannabis indica* L. [257-293]. Cannabis oil (CBD oil) was used as dengue mosquito repellent for controlling dengue viral fever, monkeypox, cervical cancer treatment, bacterial infections and fungal diseases [257-293]. *Cannabis sativa* L., is classified into two types as Industrial *Cannabis sativa*, hemp or Medical *Cannabis sativa* L.(drug or marijuana) based on its THC (Λ9-tetrahydrocannabinol) content [257-293, 372]. Medical *Cannabis sativa* (drug or marijuana) contains very high levels of THC (Λ9-tetrahydrocannabinol) (above 0.3 to 38% of dry weight) [257-293]. On the other hand Industrial *Cannabis sativa* L. (Hemp) contains very low levels of THC (0 to 0.3% of dry weight) [257-293, 372]. However, due to the presence of psychoactive molecules, Λ9-tetrahydrocannabinol (Λ9-THC) and Λ8-tetrahydrocannabinol (Λ8-THC), Cannabis cultivation and its use is restricted/regulated in many countries [257-293, 372].

There are many growing Indian companies (Bombay Hemp Company, BOHECO, Satliva, Clean Green Biosystems or Clean Green Bio Research Foundation, Hemp Fabric Lab, Vedi, Happy Hemp, SUI, Its Hemp, Bhu:Sattva's, Health Horizons, Hemis, Hemp Republic, Hempsters, B.E. Hemp, India Hemp Co., Inc, India Hemp Organics, Its Hemp, The Trost, and Gin Gin) involved in promoting the Indian hemp products, marketing, R & D research, cultivation, harvesting, processing, manufacturing, trading, wholesaling, retailing, innovating, advocating and motivating customers across India and around the world [257-293]. This will help to boost the Indian economy and increase the productivity of the Indian hemp (fiber type) [257-293, 372].

Figure 2 Cannabis sativa with female inflourescence

2 Cannabis sativa: Phytocannabinoids

Phytocannabinoids are cannabinoids that occur naturally in the cannabis plant [257-293, 372]. The classical cannabinoids are formed through decarboxylation of their respective 2-carboxylic acids (2-COOH), a process which is catalyzed by heat, light or alkaline conditions [257-293, 372]. These cannabinoids are abundant in the viscous resin that is produced by glandular structures in the cannabis plant called trichomes [257-293]. This resin is also rich in terpenes, which are responsible for the characteristic smell of the cannabis plant [257-293, 372]. The phytocannabinoids are mostly insoluble in water but are soluble in alcohol, fat and other non-polar organic solvents. In alkaline conditions, they can form water-soluble phenolate salts, being essentially phenols [257-293]. Of over 480 different compounds present in the cannabis plant, only around 66 have been identified as cannabinoids. The most well known of these compounds is the Δ9-tetrahydrocannabinol (Δ9-THC), the main psychoactive ingredient in the plant. Other common cannabinoids include cannabidiol (CBD) and Cannabinol (CBN). The cannabinoids are separated into subclasses that include: Cannabigerols (CBG), Cannabichromenes (CBC), Cannabidiols (CBD), Tetrahydrocannabinols (THC), Cannabinol (CBN), Cannabinodiol (CBDL), Cannabicyclol (CBL), Cannabielsoin (CBE), Cannabitriol (CBT), Cannabivarin (CBV), Tetrahydrocannabivarin (THCV), Cannabidivarin (CBDV), Cannabichromevarin (CBCV), Cannabigerovarin (CBGV), and Cannabigerol Monoethyl Ether (CBGM). Of these, THC is the main psychoactive component in the plant [257-293, 372]. This compound reduces pain perception in the brain and is also neuroprotective. THC has a similar affinity for the CB1 and CB2 receptors. Cannabidiol (CBD), on the other hand, is not psychoactive and has been found to act as a CB1 receptor antagonist [257-293]. CBN is effective at relieving convulsions or seizures, anxiety, nausea and inflammatory changes. Cannabigerol is also not psychoactive and acts as a CB1 receptor antagonist [257-293, 372].

The two cannabinoids, the most well known for their therapeutic properties are, Δ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). THC and CBD are the neutral homologs of tetrahydrocannabinolic acid (THCA) and Cannabidiol acid (CBDA) respectively [257-293, 372]. A conventional classification model of Cannabinoids is due to their chemical contents dividing them to eleven subclasses including Cannabigerol (CBG), Δ9-tetrahydrocannabinol (Δ9-THC),

Cannabidiol (CBD), Cannabichromene (CBC), Cannabinol (CBN), (−)-Δ8-transtetrahydrocannabinol (Δ8-THC), Cannabicyclol (CBL), Cannabinodiol (CBND), Cannabielsoin (CBE), and Cannabitriol (CBT) [257-293]. The official discovery of Δ9-tetrahydrocannabinol (THC) is commonly attributed to Dr. Raphael Mechoulam affectionately referred to as the Godfather of Cannabis Science. Δ9-tetrahydrocannabinol (THC) was discovered in 1964 by Dr. Raphael Mechoulam and his colleagues at Israel's Weizmann Institute of Science. The credit of the discovery of Cannabidiol (CBD) in 1963 and Δ9-tetrahydrocannabinol (THC) in 1964 isolated from *Cannabis sativa* attributed to Dr. Raphael Mechoulam and his team [257-293, 372, 372].

3 Cervical cancer in India: Major Challenges

In India, cancer is not a nationally notifiable disease. The prevalence of cervical cancer screening is very low (2%) in India. Cervical cancer screening is substantially higher among women with education and Government Health insurance coverage. Wealth-based inequality exists in the prevalence of cervical cancer screening and the prevalence is concentrated among the women from wealthier quintiles [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. According to the Indian Council of Medical Research's National Cancer Registry Programme (ICMR-NCRP), the estimated number of cervical cancer cases in the country in 2023 was more than 3.4 lakh [15, 16]. According to data from the Government of India, there were 8,534 estimated cases of cervical cancer (incidence) in Tamil Nadu state, India in 2023. Cancer survival data from Population Based Cancer Registries (PBCR) reflect the average outcome of patients in the population, which is critical for cancer control efforts [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Despite decreasing incidence rates, cervical cancer is the second most common female cancer in India, accounting for 10% of all female cancers [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. The disparity in survival between the populations could explain the overall effectiveness of the health care system. This informs the policymakers to identify and address inequities in the health system. The population-based survival study should be expanded and continued to assess cancer survival trends as well as the impact of cancer control activities such as screening programme in India [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Under the initiative, persons aged over 30 are targeted for screening for three common cancers, cervical, breast and oral. Screening for these cancers was an integral part of service delivery under the Ayushman Arogya Mandir (formerly Ayushman Bharat-Health and Wellness Centres) [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Cervical cancer accounted for 6-29% of all cancers among women in India. Papumpare district in the state of Arunachal Pradesh, India had the highest incidence rate of cervical cancer (27.7) in Asia. The first population based survival study from Bangalore, Karnataka, India reported a 5-year cervical cancer survival rate of 38.3%. A recent SurvCan-3 study reported a 5- year cervical cancer survival rate in India, ranging between 38.6% and 63.9%. Thus, the data collection from ICMR-Population-Based Cancer Registries (PBCRs) involves active retrospective data abstraction, laborious and a complex process of analysis and reporting [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Trained registry staff typically go to different resource centers (hospitals, vital statistics departments and diagnostic laboratories) for collecting data on a standardized core form. This delays the process of real-time reporting and bringing out the most recent cancer statistics. The incidence and mortality of cervical cancer declined over past three decades but it is still a major public health problem in India [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Information, education and communication activities for girls, boys, parents and community for the prevention and control of cervical cancer should be provided throughout the country [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220].

In India, in spite of alarmingly high cervical cancer figures, there is no nationwide Government-sponsored screening program. In India, majority of cervical cancer disease go unreported, unrecognized or un-investigated and may only be noticed after major health or death has occurred [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Several factors contribute to these low screening rates. Cervical cancer, which is often contracted via sexual activity, is subject to cultural stigma in India, as it is in many places. A study of ethnic minority women in India reports several barriers to screening, including lack of awareness, fear of loss of fertility, embarrassment, shame, and low perceived. Another study reviewing the barriers for Indian women revealed socioeconomic barriers, language barriers, and a limited understanding of health and disease in the rural area [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Screening rates are lower in low socioeconomic and low-resource areas with racial, ethnic, and age variations. Studies showed that women with obesity and chronic disease may have lower cervical and breast cancer screening rates. Unfortunately, after most treatment for cervical cancer, patient will not be able to get pregnant. This is because surgery to remove patient womb (a radical hysterectomy) radiotherapy as part of treatment that affects the womb. Losing fertility can be very difficult to cope with if someone hope to become pregnant in the future. Even if women were not planning to have any children, the loss of fertility can be quite a shock and emotional. It is the end of a particular phase of life. Women have all the feelings that come with a natural change of life (menopause). On top of that, patient have to cope with a diagnosis of cervical cancer.

The established fertility-sparing approaches for the management of early-stage cervical cancer for women who plan pregnancy are associated with a decline in fertility and an increased risk of pregnancy complications. Fertility-preserving procedures such as loop electrosurgical excision procedure (LEEP), cold-knife conization, and trachelectomy in women diagnosed with cervical cancer can be considered as safe and effective treatments that preserve reproductive potential [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Current fertility-preserving procedures, based on the balance of the oncological characteristics of patients as well as their desire for reproduction, allow one to obtain acceptable reproductive and obstetric outcomes in women treated for cervical cancer. Cervical cancer treatment can cause issues with fertility, leaving women unable to become pregnant or carry a child through pregnancy. When cervical cancer is diagnosed early and treatment is provided successfully, infertility issues can usually be avoided. If cervical cancer is diagnosed at advanced stages, more extensive treatment is required, which will likely result in infertility.

Another reason is that most of the women in rural area in India are depending on local traditional herbal healers for medical treatment which is cost effective, and easily available[104-142]. Cervical cancer is one of the sex related disease and women feel shy and afraid to talk about it. Tribal people in the Himalayan region used Cannabis as a home made herbal medicine for many diseases including cervical cancer [257-293]. The situation is compounded by the country's limited resources, which include few trained health-care personnel to conduct the tests and scarce equipment and lab facilities. As a result, screening strategies used in developed countries may not be feasible in India [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Of the six hundred thousand new cases of cervical cancer worldwide in 2020, one in five occurred in India, where it is the second-leading cause of death after breast cancer. This grievous toll is largely because only few women undergo screening. According to one of the study in India, only 2 percent of Indian women have ever undergone screening, relative to 85 percent women in high-income developed countries [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. The rates of screening were particularly low in hard-to-reach tribal populations in rural part of India. Therefore, experimental study should be conducted to assess the burden of cervical cancer in India. This will help to review the performance characteristics of available cervical cancer screening tools, so as to provide evidence-based recommendations for application of most practically suited screening test to be used in resource-poor field settings [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220].

A common screening test is the Pap smear, in which trained personnel collect cervical cells from the patient to check for changes that may turn into cervical cancer if left untreated [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Alternatively, clinicians may conduct a visual inspection with acetic acid (VIA) test, in which they swab vinegar on the cervix and look for color change that could indicate precancerous or cancerous cells. This is inexpensive and fairly straightforward test is used for primary screening in India but is not free of problems. Health care workers in India and inter-professional team members must educate young female patients (ideally, prior to initiating sexual activity) and their families about this highly effective vaccine. This activity details primary prevention strategies, screening guidelines, diagnostic evaluations, current staging, and specific treatment modalities for invasive cervical cancer [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220].

Since the early detection of cervical cancer remains very poor due to lack of education and health care (especially in developing countries) [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Further patients being asymptomatic and lack of accuracy in diagnostic pap smears, cervical cancer in women often goes by undiagnosed until its late stages, when patients start experiencing symptoms such as abdominal pain or unexplained vaginal bleeding. Generally, 44% of cervical cancer cases are diagnosed in stage II and 38% in either stage III or IV. Thus, advanced cervical cancer is one of the major leading cancer related mortalities in low- and medium-income countries mostly due to poor early screening, as well as lack of effective treatment regimens caused by therapy resistance and recurrence [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220].

Administering the screening test is only a component of cervical cancer screening that involves community mobilization to motivate large number of women to participate, training of all levels of service providers, ensuring further assessment of screen positive women and ensuring appropriate treatment, and follow-up of the screen detected abnormalities. It is extremely important to ensure appropriate investigations of the screen positive women to establish the disease and treatment of the screen detected cases of cervical cancer [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. Traditionally, colposcopy followed by directed biopsies have been used to confirm diagnosis in the screen positive women and subsequent treatment decisions were made on the basis of histology report. However, this multiple visit approach (at least three) is very inconvenient for the women and the compliance is often poor. Several alternate strategies have been recommended and adopted to reduce the number of visits and improve compliance of the women. Over-treatment is acceptable as the treatment methods are simple and safe and the treated women with negative histology will require less intensive follow-up. In more basic settings where organizing

colposcopy and histopathology is challenging, a more simpler approach like direct treatment of the screen positive women ("screen and treat") is also recommended [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220].

The inter-professional team can provide public health education and multidisciplinary care to improve cervical cancer awareness, prevention, screening, and management. Primary care clinicians performing cervical cancer screening, colposcopies, and LEEP procedures, must have ongoing dialogues with gynecologists about findings of suspicious cervical lesions, management, and treatment. Appropriate protocols and guidelines across healthcare systems can improve outcomes by optimizing treatment and follow-up. Developing a culturally sensitive system directed at increasing patient-centered education will require the input of diverse healthcare professionals and staff with multilingual skills and cross-cultural competency. A second screening test is sometimes recommended for the women positive on the primary screening test. The second test is called triaging test and the women positive on both the tests are only referred for colposcopy. Such triaging strategy is used if the primary screening test is less specific and/or if the colposcopy services are insufficient and expensive.

The National Cancer Registry Programme (NCRP) was established in 1981 by the Indian Council of Medical Research (ICMR) for the systematic collection of data on cancer through the population based cancer registries (PBCRs) and hospital-based cancer registries (HBCRs) in various parts of the country [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. To collect data on a standardised core form, trained registry staff visits various sources such as hospitals, diagnostic labs, vital registration to register cancer cases. Unlike incidence, the mortality data collection is incomplete in cancer registries due to incomplete or incorrect certification of cause of death. Despite the systematic collection of incidence data, there is inadequate follow-up information on outcome of cancer patients registered by the PBCR. Obtaining follow-up of cancer patients in India poses numerous challenges due to cancer not being a notified disease, lack of complete nationwide cause of death registration and its linkages with the registry. The Government of India has implemented screening for oral, breast, and cervical cancers throughout the country[1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220]. India is committed to meeting the WHO's target of eliminating cervical cancer. Very recently on 2nd Feb 2024, cervical cancer was in big news (NDTV) because of the fake news of the death of Indian model and an erotic actress Poonam Pandey as a part of cervical cancer awareness programme. In spite of global falling trends, cervical cancer remains a major healthcare challenge for India, South Asia Association for Regional Cooperation region, and other low- and middle-income countries [1, 2, 12-21, 29, 44-47, 51-55, 59-64, 78-95, 146-154, 158-208, 215, 220].

On 1st of February, 2024, Finance minister Nirmala Sitharaman (2024 Budget), confirmed that the government of India will focus on cervical cancer vaccination, opening new medical colleges and extending Ayushman Bharat cover to ASHA (Accredited Social Health Activist) and Anganawadi workers [19-21]. The government of India, New Delhi is planning to include the Human Papillomavirus (HPV) vaccine in the country's immunisation program, potentially making vaccines to prevent cervical cancer more affordable [19-21]. Finance Minister Nirmala Sitharaman also stated that the Indian government aims to encourage vaccination for girls aged 9 to 14 to prevent cervical cancer [19-21]. Currently, the HPV vaccine is available in private hospitals at a cost of up to ₹4,000 per dose [19-21]. Additionally, the Government of India plans to establish more medical colleges [19-21]. In June 2022, based on fresh evidence on disease burden in India, evidence on effectiveness of single dose of HPV vaccine, clinical trial data and experience of the Sikkim Government, India on the introduction of the vaccine, the National Technical Advisory Group on Immunization recommended the introduction of HPV vaccine in the universal immunization with "a one-time catch-up for 9-14 year-old adolescent girls followed with routine introduction at nine years" [19-21]. Presently, the Serum Institute's (Cyrus Poonawalla, Pune, Maharashtra) made-in-India vaccine against cervical cancer, CERVAVAC, is available in the private market for about Rs 2,000 per dose [19-21]. MSD Pharmaceuticals Pvt Ltd, a wholly-owned subsidiary of Merck Sharp and Dohme (known as Merck and Co, Inc in the US and Canada) continues to sell its HPV vaccine Gardasil 4 (quadrivalent vaccine) in India which is currently priced at Rs 3,927 per dose [19-21]. Gardasil 4 (made by Merck) offered protection against four types of HPV — 6, 11, 16, and 18 — and targeted over 70% of cervical cancer cases [19-21].

One of the recent survey conducted by Kaur et al. 2023 in India mentioned that the real-world challenges that still exist in India [195]. A total of 316 eligible and complete responses to the 21 questions were analyzed [195]. Screening of mothers and vaccinating their daughters was considered as the most important strategy to prevent cervical cancer by 65.8% (208/316) [195]. Screening was offered to all asymptomatic eligible females by 79% (250/316) [195]. Improvement in screening rates requires promoting the national program (67.7%; 214/316), strengthening existing infrastructure (62%; 196/316), regular training of primary healthcare workers (57.6%; 182/316), and increasing awareness among schools and colleges (57.9%; 183/316) [195]. Almost all responders (93%; 294/316) wanted to have human papillomavirus (HPV) vaccination included in the national immunization schedule [195]. Cost of vaccine was considered a major roadblock. If it became available at INR 250 per dose, 96.8% (306/316) respondents

would recommend it for all eligible patients [195]. With the impending availability of this indigenous tetravalent HPV vaccine jointly produced by Department of Biotechnology, Government of India and Serum Institute of India Pvt Ltd, Cyrus Poonawalla, Pune, Maharashtra, India the war against cervical cancer just got easier [195].

4 Cervical cancer in Azerbaijan

Cervical cancer is the second most common malignant tumor among Azerbaijan women [366-371]. In spite of widespread early diagnostics, the vast majority of patients applied to the clinics at late, locally advanced stages of cervical cancer (about 46% of patients have stage IIB-IIIB stage disease at diagnostics) [370]. According to the latest data from WHO published in 2020, the cervical cancer death in Azerbaijan reached 278 or 0.35% of total deaths [371]. Better understanding of the molecular basis of cervical cancer in Azerbaijan region is essential for further improvement of treatment results. [370]. Taking into account that mutations in the proto-oncogene PIK3CA pathway is common event in several human cancers [370]. Therefore, one of the study performed genomic analysis and investigated the types and frequency of PIK3CA mutations among cervical cancer patients in Azerbaijan [366-370]. Cervical cancer ranks as the 5th most frequent cancer among women in Azerbaijan and the 3rd most frequent cancer among women between 15 and 44 years of age in Azerbaijan [366-371]. Current estimates indicated that every year 425 women are diagnosed with cervical cancer and 256 die from the disease. However, in Western Asia, the region Azerbaijan belongs to, about 2.5% of women in the general population are estimated to harbor cervical HPV-16/18 infection at a given time, and 72.4% of invasive cervical cancers are attributed to HPVs 16 or 18 [366-371]. Cervical cancer is the third most common female cancer in Azerbaijan and the vast majority of these patients apply to the clinic at late stages [366-369]. Today cisplatin-based concurrent chemoradiotherapy is the standard treatment for locally advanced cervical cancer. But in general the treatment results remains poor and response to treatment varies in a wide range [366-371].

Last year in 2023, more than 3,000 women were registered with cervical cancer in Azerbaijan. "According to the worldwide statistics of 2020, cervical cancer ranks first among all malignant gynecological tumors in terms of frequency of occurrence [366-371]. According to the World Health Organization, about 300 thousand women die from cervical cancer every year. Some of them are at a much younger age [366-371]. According to official statistics, cervical cancer is the second most common malignant tumor in women after breast cancer in Azerbaijan: "In 2022, 3 thousand 16 women were registered with this disease in Azerbaijan. Therefore, cervical screening programs and vaccination against Human papilloma virus, in the next 20 years has protected women in Azerbaijan population and other parts of world [366-371]. Cervical cancer is expected to be reduced to a minimum in developed countries during this period. It goes without saying that serious steps should be taken in this direction in Azerbaijan as well [366-371]. It was agreed to train medical specialists in order to conduct screening examinations with the latest technology, to examine nearly 2,000 women in Lankaran, the southern zone of Azerbaijan, and as a result of these examinations to determine whether they are at risk of cervical cancer, to educate communities and young people about these diseases [366-371].

To define the probability of PIK3CA as an individual prognostic factor, one of the study evaluated the frequency of PIK3CA gene mutation and it's impact on post chemoradiotherapy tumor response rate [366-370]. One of the study investigated examination and treatment results of 148 locally advanced cervical cancer patients treated at Azerbaijan National Center of Oncology from 2015 to 2017. According to this study reported, nineteen patients (12,8%) had adenocarcinoma while 129 (87,2%) had squamous cell carcinoma [366-369]. Distribution by stages was as following: IIA - 20,3%, IIB - 44,1%, IIIB - 32,2%, IVA - 3,4% patients [366-369]. Patients received concurrent chemoradiotherapy: external beam radiotherapy (IMRT) by 1,8 Gy fraction to 45, weekly cisplatin (40 mg/m2) and 4 fractions 7 Gy 3D image guided high dose rate brachytherapy [368]. This study investigated tumor samples to identify somatic hotspot mutations within the helical or the catalytic domains of PIK3CA gene [368-370]. Analysis was conducted by RT-PCR method. Response rate was assessed by comparison of the highest tumor size in any direction on pretreatment and after 5 weeks EBRT pre-brachytherapy MRI images [368]. This study revealed activation of PIK3CA gene in 43 (29,1%) patients totally. PIK3CA mutations were found in four cases (21,1%) of adenocarcinomas and in 39 (30,2%) patients with squamous cell cervical cancer [368]. The predominant mutation sites were E542K and E545K in the helical domain of the PIK3CA gene [368]. This study showed that locally advanced cervical cancer patients with hotspot mutations of PIK3CA had higher tumor response rate (non-significantly) after concurrent chemoradiotherapy than patients without these mutations [368]. Further investigation with a larger dataset is required to validate these findings and to explore probability of PIK3CA signaling pathway inhibitors use in patients with cervical cancer [368-370].

Furthermore, cancer morbidity of the female genitalia in Azerbaijan within a ten-year period (1957-1966), cervical cancer occupies the first place-86.6% [366-369]. It is observed more frequently among Russian female population (46.4 per 100 000 wives) and more rarely among aboriginal female population (7.1 per 100 000 wives) [366-369]. Of 2488 patients with cervical cancer, 24.5% showed previous lesions against which background cancer would arise [366-

370]. Patients with cervical ruptures, advanced erosions, polyps should be identified as high-risk groups of cervical cancer [366-369]. Therefore, overall the number of cases of cervical cancer is very high and increased in Azerbaijan population [366-370].

5 Etiological agent of Cervical cancer

The single most important etiological agent of cervical cancer is infection by high-risk Human Papillomavirus (HPV) [1-104, 143-220]. All HPV are non-enveloped double stranded DNA viruses. Their genomes are circular and approximately 8 kilobase pairs in size. Most encode eight major proteins, 6 located in the "early" region, 2 in the "late" region [1-104, 143-220]. The primary cause of pre-cancerous and cancerous cervical lesions is infection with a high-risk or oncogenic HPV types. Most cases of cervical cancer occur as a result of infection with HPV16 and 18 [1-104, 143-220]. The link between HPV and cervical cancer was established in the last 30 years based on the detection of HPV type 16 in cervical cancer tissue by Harald zur Hausen [1-104, 143-220]. Cervical cancer is the fourth most common female cancer worldwide and results in over 300, 000 deaths globally. The causative agent of cervical cancer is persistent infection with high-risk subtypes of the human papillomavirus and the E5, E6 and E7 viral oncoproteins cooperate with host factors to induce and maintain the malignant phenotype [1-104, 143-220]. Cervical cancer is a largely preventable disease and early-stage detection is associated with significantly improved survival rates [1-104, 143-220]. Indeed, in high-income(developed) countries with established vaccination and screening programs, it is a rare disease. However, the disease is a killer for women in low- and middle-income countries who, due to limited resources, often present with advanced and untreatable disease [1-104, 143-220]. Treatment options include surgical interventions, chemotherapy and/or radiotherapy either alone or in combination. HPV types 16 and 18 are the most common HPV types identified in invasive cervical cancer [1-104, 143-220]. High-risk types, especially HPV16, are found to be highly prevalent in human populations. The infection is usually transmitted by sexual contact, causing squamous intraepithelial lesions [1-104, 143-220]. Most lesions disappear after 6–12 months due to immunological intervention. However, a small percentage of these lesions remain and can cause cancer [1-104, 143-220]. The results of a meta-analysis showed that the highest prevalence of HPV occurs at the age of 25 years, which could be related to changes in sexual behavior [1-104, 143-220]. HPVs can infect basal epithelial cells of the skin or inner lining of tissues and are categorized as cutaneous types or mucosal types [1-104, 143-220]. Cutaneous types of HPV are epidermitrophic and target the skin of the hands and feet. Mucosal types infect the lining of the mouth, throat, respiratory tract, or anogenital epithelium [1-104, 143-220]. Based on their association with cervical cancer and precursor lesions, HPVs types also be grouped to high-risk and low-risk HPV types. Low-risk HPV types include types 6, 11, 42, 43, and 44. High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70 [1-104, 143-220]. Included in the high-risk group are some HPV types that are less frequently found in cancers but are often found in squamous intraepithelial lesions (SILs) [1-104, 143-220].

Papillomaviruses (HPV) are members of the Papovaviridae family, which also includes polyomavirus and simian vacuolating virus [1-104, 143-220]. The HPV genome consists of a single molecule of double-stranded, circular DNA containing approximately 7,900 bp associated with histones [1-104, 143-220]. HPV is a relatively small, non-enveloped virus, 55 nm in diameter. It has an icosahedral capsid composed of 72 capsomers, which contain at least two capsid proteins, L1 and L2 [1-104, 143-220]. The virus is said to somewhat resemble a golf ball when viewed by electron microscopy [1-104, 143-220]. Transmission of HPV occurs primarily by skin-to-skin contact. Epidemiologic studies clearly indicated that the risk of contracting genital HPV infection and cervical cancer is influenced by sexual activity [1-104, 143-220]. HPV is very resistant to heat and desiccation, and nonsexual transmission via fomites can also occur, such as by prolonged exposure to shared contaminated clothing [1-104, 143-220]. An individual is at greater risk of becoming infected with HPV, if he or she has had multiple sexual partners at any time or is the partner of someone who has had multiple sexual partners [1-104, 143-220]. Sexual activity at an early age also places an individual at increased risk, as does a history of other sexually transmitted diseases, genital warts, abnormal Pap smears, or cervical or penile cancer in an individual or sexual partner [1-104, 143-220]. Condom usage may not adequately protect individuals from exposure to HPV since HPV can be transmitted by contact with infected labial, scrotal, or anal tissues that are not protected by a condom [1-104, 143-220]. In addition to sexual activity, age is an important determinant of risk of HPV infection[1-104, 143-220]. The greatest risk of HPV infection coincides with greatest metaplastic activity. Greatest metaplastic activity occurs at puberty and first pregnancy and declines after menopause [1-104, 143-220]. HPV infection is most common in sexually active young women, 18 to 30 years of age. There is a sharp decrease in prevalence after 30 years of age [1-104, 143-220]. However, cervical cancer is more common in women older than 35 years, suggesting infection at a younger age and slow progression to cancer[1-104, 143-220]. Persistence of infection is more common with the high-risk oncogenic HPV types and is an important determinant in the development of cervical cancer[1-104, 143-220].

Human papillomavirus (HPV) is an etiologic agent of cervical cancer and is the most common sexually transmitted disease in women [1-104, 143-220]. HPV-infected cervical epithelial cells that undergo transformation, change from

being well organized to highly dysplastic and the degree of dysplasia is graded based on severity [1-104, 143-220]. PCR amplification of HPV genomes is the most sensitive method for the detection of cervicovaginal HPV [1-104, 143-220]. The two most commonly used PCR primer sets, MY09/MY11 (MY-PCR) and GP5+/GP6+ (GP+-PCR), for the detection of HPV DNA in cervicovaginal lavage samples from women [1-104, 143-220]. Cervical cancer is a largely preventable disease and early-stage detection is associated with significantly improved survival rates. Indeed, in high-income countries with established vaccination and screening programs it is a rare disease [1-104, 143-220]. However, the disease is a killer for women in low- and middle-income countries who, due to limited resources, often present with advanced and untreatable disease [1-104, 143-220]. Cervical cancer is a major cause of cancer mortality in women and more than a quarter of its global burden is contributed by developing countries [1-104, 143-220]. Factors relating to sexual behavior have also been linked to cervical cancer [1-104, 143-220]. One study found that an increased risk of cervical cancer is observed in people with multiple sexual partners [1-104, 143-220]. Moreover, many studies have also suggested that women with multiple sexual partners are at high risk for HPV acquisition and cervical cancer. Furthermore, Oral contraceptive (OC) pills are known to be a risk factor for cervical cancer. It has been reported that the use of OC for 5 years or more can double the risk of cancer[1-104, 143-220].

In 1991, Scientists developed the first HPV vaccine. In the early years, Dr. Jian Zhou and Dr. Ian Frazer created "virus-like particles" that mimicked HPV [1-104, 143-220]. The vaccine is composed of these particles, which do not contain any of the DNA, and can not cause an HPV infection or a cancer [1-104, 143-220]. The body produces the antibodies needed to fight the particles to generate immunity within the body. This then prepares the body to remove infection if it is ever exposed in the future[1-104, 143-220]. Using this technology, Dr. Dough Lowy and Dr. John Schiller eventually developed the HPV vaccine after finding that multiple HPV proteins could regroup and form these non-infectious virus-like particles that helped humans to develop antibodies and fight future HPV infections [1-104, 143-220]. The researchers Doug Lowy, and John Schiller, known in the 1990s that their studies of two cancer-causing genes would lead to the first commercially available vaccine against the two deadliest forms of the cancer-causing Human Papillomavirus (HPV) [1-104, 143-220].

In 2014, Gardasil 9 (HPV 9) approved by US Food and Drug Administration. The second iteration of Gardasil offered protection from several low-risk, wart-causing HPV strains in addition to the high-risk cancer-causing HPV strains that were protected with HPV4 [1-104, 143-220]. Gardasil 9, the only HPV vaccine currently used in the United States, prevents infection from 9 HPV types: HPV 16 and 18, two high-risk types of HPV that cause ~70% of cervical cancers and other HPV cancers; HPV 31, 33, 45, 52, and 58, high-risk types of HPV that account for another 10% to 20% of cervical cancers [1-104, 143-220]. Further HPV 6 and 11, which cause 90% of genital warts. The trials that led to its approval found it to be nearly 100% effective in preventing the 6 HPV cancers caused by all 7 cancer-causing HPV types [1-104, 143-220]. Following extensive clinical trials through seven years of design and testing, which found that the vaccine offered nearly 100% protection against HPV 16 and 18, it was approved for use in girls ages 9-26 in the US [1-104, 143-220]. Gardasil (HPV4) licensed and approved for girls by US Food and Drug Administration. In 2018, US Food and Drug Administration approved expanded use of Gardasil **9** [1-104, 143-220]. The FDA expanded the vaccine's approval to include females and males 27-45 years old. By October 2019, 100 countries worldwide incorporated HPV vaccination into their regular vaccine schedule [1-104, 143-220]. US Food and Drug Administration approves expanded use of Gardasil 9. The FDA originally only approved the vaccine for cervical cancer prevention, but based on additional research in 2020, they expanded it to include cervical, vaginal, vulvar, anal, oropharyngeal, and other head and neck cancers [1-104, 143-220]. Therefore, World Health Organization (WHO) hopes to eradicate vaccine-preventable cervical cancer within the next century. 90% of girls fully vaccinated with the HPV vaccine by age 15 [1-104, 143-220]. Furthermore, 70% of women initially screened with high-performance testing by age 35 and a secondary test at age 45; and 90% of pre-cancers treated and 90% of invasive cancers managed [1-104, 143-220].

Cervical cancer is treated by a combination of chemotherapy, radiotherapy, targeted therapy, immunotherapy, and sometimes surgery [1-104, 143-220]. Pap tests are used to detect potentially precancerous and cancerous processes in the cervix or colon, allowing for earlier treatment. According to the recent study, the age-standardized incidence of cervical cancer in 2020 was higher than the threshold set by WHO's Cervical Cancer Elimination Initiative in 173 of 185 countries [1-104, 143-220]. However, the steep decrease in incidence observed in some countries, such as India, Thailand, Brazil, and Poland, could be attributed to multiple factors, including declines in fertility rates and lower parity, which are declining across successive generations of women, or improvement in the coverage of screening programs [1-104, 143-220]. This will increase the access to treatment services especially in the urban population of the registry catchment areas. It is to be noted that, all over the world, cervical cancer is the fourth most common cancer among women, with an estimated 6,04,000 new cases and 3,42,000 deaths in 2020, of which the Region accounted for 32% and 34%, respectively [1-104, 143-220]. Further, the World Health Organization (WHO) had confirmed that India is soon going to receive Human Papillomavirus (HPV) vaccination to eliminate cervical cancer as a public health problem [1-104, 143-220]. So far, Bhutan, Maldives, Myanmar, Sri Lanka and Thailand have introduced nationwide HPV vaccination

to treat cervical cancer. Meanwhile, National Technical Advisory Group on Immunisation (NTAGI) chief also confirmed that cervical cancer is manageable if the disease is diagnosed early[1-104, 143-220]. He added that screening to detect cervical cancer is important after the age of 35 and it needs to be taken as a mission as "India has the largest burden of deaths due to cervical cancer [1-104, 143-220].

6 Human papillomavirus (HPV) Vaccine

There are currently 3 HPV vaccines approved by the U.S. Food and Drug Administration (FDA) to prevent HPV infection: Gardasil, Gardasil 9, and Cervarix[1-104, 143-220]. Each of these vaccines protects against HPV genotypes 16 and 18, which collectively cause about 70% of cervical cancers. Both Gardasil vaccines also protect against HPV genotypes 6 and 11, which cause 90% of genital warts [1-104, 143-220]. Gardasil 9 also protects against HPV genotypes 31, 33, 45, 52, and 58 [1-104, 143-220]. As of 2017, Gardasil 9 is the only HPV vaccine available for use in the United States, although Gardasil and Cervarix continue to be used worldwide [1-104, 143-220]. The Centers for Disease Control (CDC), USA currently recommends vaccination for male and female people ages 9 through 26, although the FDA has recently approved vaccination up through age 45 [1-104, 143-220]. Those who have undergone vaccination must still be screened for HPV [1-104, 143-220]. Additionally, even if an individual has been exposed to HPV, vaccination is still recommended as they can benefit from protection against other HPV types in the vaccine to which they are naïve [1-104, 143-220]. Trials leading to the approval of Gardasil and Cervarix demonstrated that the vaccines are nearly 100% effective in providing protection against both persistent cervical infections and dysplasia caused by HPV types 16 and 18 [1-104, 143-220]. The trials that led to the approval of Gardasil 9 found it to be nearly 100% effective in preventing cervical, vulvar, and vaginal disease caused by the 5 additional HPV types that it targets [1-104, 143-220]. Recent data demonstrated that protection against the targeted HPV genotypes persists for at least 10 years with Gardasil, at least 9 years with Cervarix, and at least 6 years with Gardasil 9[1-104, 143-220].

7 HPV Infection and Transmission

Nearly all cases of cervical cancer can be attributed to infection with human papillomavirus (HPV). HPV types are categorized as low-risk or high-risk strains depending on their oncogenic potential[1-104, 143-220]. Low-risk strains of HPV may be asymptomatic or may cause anogenital warts, whereas high-risk strains are oncogenic. Over 99% of precancerous lesions (cervical dysplasia) and cervical carcinomas are caused by high-risk HPV infection [1-104, 143-220]. More than 200 strains of HPV have been identified, of which approximately 40 infect the anogenital region [1-104, 143-220]. The 15 and 18 of these HPV strains have been classified as high-risk genotypes [1-104, 143-220]. Sexual contact is necessary for HPV transmission, and HPV remains the most common sexually transmitted infection in the world. It is most prevalent in teen-aged women and women aged 20 to 30 years, concordant with timing of first sexual contact [1-104, 143-220]. Early age of first sexual intercourse and multiple sexual partners are known risk factors for high-risk HPV infection. Most young women are capable of mounting an effective immune response that clears the HPV infection or decreases the viral load to undetectable levels within 8- 24 months [1-104, 143-220]. Additional known factors that increase the likelihood of HPV persistence include tobacco use, immunosuppression, low socioeconomic status, and long-term use of oral contraceptives [1-104, 143-220]. Although the vast majority of women with high-risk HPV infection do not develop cancer, persistent infection (>2 years) with high-risk HPV types is widely recognized as the primary causative factor for development of cervical cancer [1-104, 143-220]. In an immunocompetent woman, progression to invasive cervical carcinoma typically occurs 10-20 years after primary infection[1-104, 143-220]. Virtually all cervical neoplasias and cancers are attributable to high-risk HPV genotypes, and approximately 70% of all cervical cancer cases are attributable to types 16 and 18 [1-104, 143-220]. Type 16 is responsible for 50% of squamous cell carcinomas and 55-60% of all cervical cancers, whereas type 18 causes about 20% of cervical adenocarcinomas. Other oncogenic strains of HPV include types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, which combined cause 25% of cervical carcinomas. Infection with certain HPV types causes a proportion of cancers of the anus, vulva, vagina, penis, and oropharynx as well[1-104, 143-220]. Almost all cervical cancers are either squamous cell carcinoma or adenocarcinoma[1-104, 143-220]. The major steps known to be necessary in cervical carcinogenesis include HPV infection, HPV persistence, progression to dysplasia, and invasion [1-104, 143-220].

8 Cervical cancer

Cervical cancer, the fourth most common cancer among women worldwide, is caused almost entirely by Human Papillomavirus (HPV) [1-104, 143-220]. High-risk types of HPV can lead to cervical intraepithelial lesions which, over time, can progress to cervical cancer [1-104, 143-220]. Cervical cancer is a largely preventable disease. Primary prevention and screening are the most effective modalities for decreasing the healthcare burden and mortality attributable to cervical cancer. Cervical cancer continues to rank among the top gynecologic cancers worldwide [1-104,

143-220]. According to current data, it is ranked 14th among all cancers and is the 4th most common cancer among women worldwide. Cervical cancer intervention focuses on primary and secondary prevention [1-104, 143-220]. Primary prevention and screening are the best methods to decrease the burden of cervical cancer and mortality. In Canada, the United States and other developed countries, most screening and diagnostic efforts are directed toward the early identification of high-risk Human papillomavirus (HPV) lesions through HPV testing and Papanicolaou (Pap) smears [1-104, 143-220]. HPV testing identifies exposure to both low- and high-risk types of HPV, whereas Pap smears identify abnormal cytology. Since 2006, HPV vaccination has been available to prevent cervical cancer [1-104, 143-220]. Although HPV testing is not recommended in women younger than 30 years, low-risk younger women should begin screening with Pap tests at age 21 and continue until age 65, as per the United States Preventive Services Task Force (USPSTF) recommendations [1-104, 143-220]. Newer recommendations offer 3- to 5-year intervals between screenings based on a patient's prior results and the use of Pap and HPV co-testing. As cervical cancer is a sexually transmitted infection (STI), it is preventable, and the global incidence can be reduced through targeted education, screening, and intervention [1-104, 143-220].

Since 2006, vaccination has been available for the prevention of cervical cancer. Vaccination can improve cancer death rates in populations with higher mortality rates and in developing countries where resources may not be available for routine screening [1-104, 143-220]. Decades of studies have confirmed that cervical infection by high-risk HPV types is a precursor event to cervical cancer. The natural history of cervical cancer as a continuous single disease process progressing gradually from mild cervical cervical intraepithelial neoplasia (CIN1) to more severe degrees of neoplasia and microinvasive lesions (CIN2 or CIN3) and finally to invasive disease has been the basis for diagnosis, therapeutic measures, and secondary preventive strategies [1-104, 143-220]. It is plausible that high-risk HPV infection occurs early in life, may persist, and, in association with other factors promoting cell transformation, may lead to a gradual progression to more severe disease [1-104, 143-220]. HPV cannot be cultured in the laboratory from clinical specimens and immunologic assays are not adequate for detection of HPV infections. The primary diagnostic tools have been cytology and histology. Recently, molecular methods to detect HPV DNA sequences in clinical specimens have been introduced [1-104, 143-220].

Current literature reported that HPV is found in most sexually active people at some point during their lifetime [1-104, 143-220]. There are more than 200 types of known HPV, with 20 HPV types identified as cancer-related. HPV exposure rates are only known in women since men are not screened outside of research protocols[1-104, 143-220]. HPV types 16 and 18 are the most common HPV types identified in invasive cervical cancer. Population-based HPV prevalence studies showed the greatest prevalence of high-risk HPV occurs in adults younger than 25 years, and cervical cancer deaths peak in middle-aged women between 40 and 50 years [1-104, 143-220]. Studies have shown that HPV-related cervical disease in women younger than 25 years is largely self-limiting. However, those with co-infection of multiple HPV types may be less likely to have spontaneous clearance and, thus, progress to cancer [1-104, 143-220]. HPV is transmitted by skin-to-skin contact, including during sexual intercourse, hand-to-genital contact, and oral sex [1-104, 143-220]. Risk factors for HPV and cervical cancer include young age at sexual initiation, multiple sexual partners, high parity, smoking, herpes simplex, HIV, co-infection with other genital infections, and oral contraceptive use [1-104, 143-220].

Worldwide, cervical cancer is commonly diagnosed in women especially within low- and middle-income countries such as South Africa, India, China, and Brazil [1-104, 143-220]. In 2020, a worldwide total of 604 127 new cases of CC was reported with 341 831 of these cases resulting in death. The vast majority of new cases (84%) and 90% of CC deaths occur in low- and middle-income countries, due to the high incidence rates of women being infected with the sexually transmitted Human papilloma virus (HPV) [1-104, 143-220]. HPV persistent infection in women over the age of 35 years old is responsible for approximately 70% of all diagnosed cervical cancer cases in low- and middle-income countries worldwide [1-104, 143-220]. Other factors which may also contribute to the overall incidence rate of CC include lack of health care access in relation to early diagnosis and efficient treatment regimes, public awareness, smoking, the use of oral contraceptives and HIV co-infections [1-104, 143-220].

Cervical cancer poses a significant global burden and remains a serious therapeutic challenge especially in LMICs where resources are limited and current therapeutic options are often unaffordable and inaccessible [1-104, 143-220]. It is therefore, essential for all countries to endorse the resolution passed by the World Health Assembly in 2020 calling for the “Elimination of Cervical Cancer” by 2030 through achieving the following 3 targets: (1) HPV vaccination of 90% of girls by the age of 15 years, (2) screening of 70% of women at 35 years and then 45 years with high-performance tests, and (3) treatment of 90% precancerous lesions and management of 90% invasive cancer cases [1-104, 143-220].

Furthermore, current therapeutic options for cervical cancer are associated with debilitating side effects and tumor drug resistance, and despite considerable advancement with the use of combination therapies to improve the efficacy

of single-agent treatments, new and improved therapies to treat cervical cancer are still urgently needed [1-104, 143-220]. Some examples of alternative therapies that have been explored in cervical cancer include immunotherapy, targeted therapy, and genetic approaches such as CRISPR/Cas9 and RNAi [1-104, 143-220]. While these therapies showed increasing promise in treatment outcomes, many of them remain investigational and are expensive alternatives [1-104, 143-220]. An approach that may lead to rapid and cost-effective drugs is to identify commercially available non-cancer drugs that target the host factors that co-operate with the HPV oncoproteins, particularly E6 and E7, that drive cervical cancer progression [1-104, 143-220]. This strategy which combines a targeted approach with drug repurposing is attractive as, compared to conventional anti-cancer therapies, it should identify more efficacious drugs with significantly reduced side effects and because their safety profiles are known they are expected to be rapidly advanced into clinical trials[1-104, 143-220].

9 Types of Cervical cancer (CC)

Cervical cancer (CC) is a malignant form of tumor which originates in the cervix [1-104, 143-220]. Cervical cancer is divided into 2 histological types, namely Adenocarcinoma (AC) and Squamous cell carcinoma (SCC) [1-104, 143-220]. SCC originates from the squamous cell outer lining of the cervix, whereas AC originates from inner glandular cervical cells. SCC has a higher occurrence rate of about 70% when compared to AC [1-104, 143-220]. Squamous cell carcinoma and adenocarcinoma are the most common histological subtypes of cervical cancer, with squamous cell carcinoma being vastly more frequent [1-104, 143-220]. Adenocarcinoma constitutes approximately 5% of invasive cervical cancers worldwide, although this percentage is increasing in some countries. Both subtypes resulted from precursor lesions, cervical intraepithelial neoplasia (CIN), or carcinoma in situ (CIS) [1-104, 143-220]. Squamous CIS and adenocarcinoma in situ (AIS) are the most immediate precursors to invasive cervical cancer [1-104, 143-220]. Adenocarcinoma of the cervix should be carefully distinguished from endometrial adenocarcinoma with immunohistochemistry and HPV in situ hybridization [1-104, 143-220]. Most malignancies arise from the sqamocolumnar junction of the cervix. Microscopically, anastomosing irregular nests or single tumor cells with stromal inflammation or desmoplasia are present[1-104, 143-220]. Lymphovascular invasion (LVI) may also be present. Grading is predicated on nuclear pleomorphism, nucleoli size, mitotic activity, and necrosis, and does not correlate with prognosis [1-104, 143-220].

10 Cervical cancer stages

There are 4 stages of cervical cancer: in stage I the cancer is isolated to the cervix region only [1-104, 143-220]. In stage II the cancer has spread to the upper two-thirds of the vagina or into the tissue surrounding the uterus. In stage III the cancer has spread to the lower third of the vagina and/or pelvic wall, and/or has caused kidney problems, and/or has shown lymphatic spread [1-104, 143-220]. In stage IV the cancer has spread beyond the pelvis, or has spread to the bladder lining, or rectum or other parts of the body[1-104, 143-220].

11 Cervical cancer: Symptoms and Risk Factors

Early-stage cervical cancer is often asymptomatic and may be diagnosed during a routine screening or pelvic examination [1-104, 143-220]. Cervical cancer originates in the cervix which is the narrow opening into the uterus and is connected to the vagina through the endocervical canal [1-104, 143-220]. The cervix is divided into the ectocervix and endocervix. The ectocervix is covered with stratified squamous epithelial cells, the endocervix consists of simple columnar epithelial cells. Stratified squamous and columnar epithelium form the squamocolumnar junction in the endocervical canal [1-104, 143-220]. The area where these regions meet is called the “transformation zone”, which consists of metaplastic epithelium that replaces the columnar lined epithelium of the endocervix [1-104, 143-220]. This zone is the most likely site for the development of cervical cancer because it is a major site of premalignant transformation via persistent HPV infection [1-104, 143-220]. The viral E5, E6 and E7 proteins contribute to the induction and maintenance of the cervical cancer phenotype by exploiting host cell machinery. Early-stage cervical cancer is often asymptomatic and may be diagnosed during a routine screening or pelvic examination [1-104, 143-220]. The most common symptoms include heavy or abnormal vaginal bleeding, in particular following intercourse [1-104, 143-220]. Some women may present with a vaginal discharge that may be watery, mucoid, or purulent and malodorous. However it is rarely seen in isolation of other symptoms [1-104, 143-220]. In advanced disease, patients may experience lower limb oedema, flank pain, as well as pelvic or lower back pain [1-104, 143-220]. Additionally, bowel and/or bladder related complaints such as changes in pressure or the passage of urine and/or faeces through the vagina indicated invasion of the bladder and rectum respectively [1-104, 143-220]. A pelvic examination is administered in patients with any symptoms of cervical cancer and involves visualization of the cervix and vaginal mucosa and biopsy if an abnormality is seen [1-104, 143-220]. The cervix might appear normal when the disease is

micro-invasive or in the endocervical canal. Large tumors on the other hand may appear to completely replace the cervix and metastatic lesions may be identified through enlarged palpable lymph nodes [1-104, 143-220].

Cervical cancer may not cause any signs or symptoms in its early stages. Symptoms often appear once the tumor grows into surrounding tissues and organs. Other health conditions can cause the same symptoms as cervical cancer [1-104, 143-220]. The signs or symptoms of cervical cancer include: abnormal vaginal bleeding including between periods, after menopause and after sexual intercourse, abnormal or increased amount of vaginal discharge, foul-smelling vaginal discharge, unusually long or heavy periods, bleeding after a pelvic exam or vaginal douching, pain during sexual intercourse. difficulty urinating, difficulty having a bowel movement, leaking of urine or feces from the vagina, pin in the pelvic area or lower back that may go down one or both legs, leg swelling, often in one leg, loss of appetite, weight loss, shortness of breath, coughing up blood, chest or bone pain and fatigue [1-104, 143-220]. When cancer develops in the cervix of a female, it is termed as cervical cancer (CC). Cervical cancer usually develops slowly over time with initial appearance of abnormal cells in the cervical tissue [1-104, 143-220]. Later, cancer cells start to grow and spread more deeply into the cervix and to surrounding areas.

The risk factors of cervical cancer are Human Papilloma Virus (HPV) infection, early marriage, sexually active at younger age, having multiple sexual partners, poor genital hygiene, smoking, multiple pregnancies, weakened immune system, malnutrition, and prolonged use of oral contraceptive pills (OCPs) [1-104, 143-220]. The organs in the female reproductive system include the uterus, ovaries, fallopian tubes, cervix, and vagina. The uterus is hollow, pear-shaped organ where a fetus grows [1-104, 143-220]. The cervix is the lower, narrow end of the uterus connecting the body of the uterus to the vagina (birth canal). The lower part of the cervix (ectocervix) lies within the vagina and the upper two-thirds of the cervix (endocervix) lies above the vagina [1-104, 143-220]. Most cervical cancers originate in the area where the endocervix and ectocervix join. Women with pre-cancers and early cervical cancers usually have no signs and symptoms. Signs and symptoms of cervical cancers appear only after the cancer has reached an advanced stage[1-104, 143-220]. More severe symptoms may develop at advanced stages of cervical cancers and are- Irregular, inter-menstrual (between periods) bleeding, abnormal vaginal bleeding after sexual intercourse and a pelvic examination or bleeding after menopause, vaginal discomfort or odorous discharge from vagina, the discharge may contain some blood and may occur between periods or after menopause, pain during sex, back, leg or pelvic pain, fatigue, weight loss, loss of appetite, and swelling in one leg [1-104, 143-220]. Persistent HPV infection causes more than 99% of all cervical cancers. Every year, there are more than 500,000 new cases of cervical cancer and approximately 250,000 deaths due to cervical cancer worldwide [1-104, 143-220]. Eighty percent of cases occur in developing countries. In the United States, about 4000 women die yearly from cervical cancer [1-104, 143-220]. Mortality is higher among women not screened in the past 5 years and those without consistent follow-up after identifying a precancerous cervical lesion. Trends showed that women with the highest-mortality risk may be less likely to receive HPV vaccination. More than 75% of cervical cancer cases are due to high-risk HPV types 16 and 18 [1-104, 143-220]. Other HPV types also can cause malignancy. Some low-risk HPV types, specifically types 6 and 11, cause condylomata acuminate, commonly referred to as anogenital warts [1-104, 143-220]. Although, there are more than half a million cases of HPV identified annually, most are low-grade infections and will spontaneously resolve within 2 years. The progression of high-grade lesions and cancer is seen in the presence of other carcinogenic risk factors [1-104, 143-220].

According to the Federation of Gynaecology and Obstetrics (FIGO) stage II cervical cancer has a 46% chance and stage III to IV has a 70% chance of recurrence, so patients' full recovery rates from cervical cancer remain very low [1-104, 143-220]. Furthermore, recurring cervical cancer treatment remains a constant challenge and a patient's prognosis is often poor with an overall survival rate of less than 5% despite following intensive chemo- and radiotherapy treatment regimens [1-104, 143-220]. This poor prognosis of recurrent cervical cancer is usually attributed to numerous factors including cervical cancer tumor stem cell biological behavior, limitations of surgical complete excision, as well as resistance to repeated radio- and chemotherapy [1-104, 143-220]. Thus, due to the complex characteristics and high risk of cervical cancer recurrence, conventional treatment selections often have to consider the staging of prognosis, as well as the advantages/limitations of each therapy [1-104, 143-220].

Primary prevention of cervical cancer involves HPV vaccination to prevent cervical cancer. The estimated effectiveness of HPV vaccination is 90%. A quadrivalent vaccine that prevents cervical cancer and genital warts caused by low-risk HPV types is widely available in the United States [1-104, 143-220]. The recommended and approved age for vaccination is 9 to 45 years for both females and males. Vaccination can significantly impact cervical cancer mortality in women in low-resource areas and those in high-risk racial and ethnic groups [1-104, 143-220].

12 Cervical cancer: Early Screening, Treatment and Evaluation

Cervical cancer screening tests such as conventional cytology (PAP smear), liquid based cytology (LBC), Human Papillomavirus (HPV) testing, and visual inspection on acetic acid (VIA) can detect cervical precancerous lesions in healthy, and asymptomatic women [1-104, 143-230]. The most important screening methods are traditional Pap smear, visual inspection with acetic acid and Lugol's iodine (VIA/VILI), liquid-based cytology (LBC) and HPV testing. The disease burden of cervical cancer has been significantly reduced in developed countries by Pap smear, mainly in the United States, since 1950s [1-104, 143-230].

Patients with cervical cancer are usually asymptomatic during the early stages. A complete medical history must include a sexual history, including the patient's age at first sexual encounter. Sexual history also includes questions about post-coital bleeding and pain during intercourse [1-104, 143-225]. The physical exam must include a complete evaluation of the external and internal genitalia. Positive exam findings in women with cervical cancer might include a friable cervix, visible cervical lesions, erosions, masses, bleeding with the examination, and fixed adnexa [1-104, 143-220]. Many patients will have no positive findings on physical examination. Screening by Pap and/or HPV testing is essential in the workup and diagnosis of patients with cervical cancer and its precursor lesions [1-104, 143-220]. According to the United States Preventative Services Task Force (USPTF), Pap screening is recommended beginning at age 21. At age 30, HPV testing starts in conjunction with Pap smear and HPV testing at age 65[1-104, 143-220].

The most widely used cervical screening test is cytology. High-income countries have integrated cytology screening services in medical and public health services and have achieved high coverage through better program organization [1-104, 143-220]. This has resulted in substantial declines in cervical cancer incidence and mortality over time. Some of the middle-income countries in South and Central America and in Asia also implemented population-based cervical cancer screening using cytology for a few decades [1-104, 143-220]. However, these programs were largely ineffective in reducing cervical cancer burden due to poor coverage with screening, treatment and follow-up care and lack of quality assurance. Majority of the low middle income countries (LMICs) have neither initiated nor have the capacity to initiate and sustain quality assured cytology screening programs in their underdeveloped and fragmented health services with several competing priorities, lack of resources, and trained manpower [1-104, 143-220]. Cytology needs good quality laboratory infrastructure, rigorous monitoring and supervision, highly skilled technicians or pathologists and a good system of recalling the screen positives. All these are very challenging to implement in the low resourced countries [1-104, 143-220]. Cytology results are the most widely reported using The Bethesda system (TBS). The threshold for positive cytology for referral for triaging/diagnostic investigations such as colposcopy may be at atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL) in various settings [1-104, 143-220]. All women with atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion (ASC-H), LSIL or high-grade squamous intraepithelial lesion (HSIL) report on cytology must have further evaluation with colposcopy. The management options for ASCUS smears are either repeat smear after 6 months or HPV test (triaging) or direct colposcopy[1-104, 143-220].

Cytology smears are prepared by spreading the cervical cell specimen collected using a spatula and cervical brush on to a glass slide which is then fixed and stained using Papanicolaou (PAP) staining [1-104, 143-220]. Cytology is a highly subjective and provider dependent test with varying performance between laboratories and cytologists reading the smears. High frequency of cervical inflammation in developing countries contributes to significant amount of inflammatory debris in PAP smear, posing major challenges in interpretation and reporting [1-104, 143-220]. The high false negative rate (14–33%) is largely due to limitations of sampling and smear preparation. Quality assurance in preparing, fixing, staining, reading and reporting the smears is critical for accurate results. The sensitivity and specificity of a single, quality assured PAP smear to detect CIN 2+ lesions is around 60– 95%, respectively [1-104, 143-220].

Colposcopy is the diagnostic procedure of choice for evaluating abnormal cytology and/or persistent high-risk HPV infection [1-104, 143-220]. More recently, advanced imaging modalities such as MRI and PET scans have been utilized for staging. A pelvic MRI is excellent for detecting local tumour extension and can also be used for monitoring tumor response [1-104, 143-220]. PET scans are more sensitive than CT scans for detecting nodal and visceral metastases [1-104, 143-220]. This is critical as nodal disease can significantly influence prognosis. Precancerous lesions are managed conservatively for women younger than 25 years [1-104, 143-220]. Most positive findings in women younger than 25 years are low-risk cervical dysplasia and will resolve spontaneously. Colposcopy evaluates persistent, abnormal cytology or lesions suspected to be moderate or high risk [1-104, 143-220]. If invasive cancer is diagnosed, the next step in management is staging to determine further treatment.

Staging is based on findings and results from reported signs and symptoms, examination, tissue pathology, and imaging. Grading is based on the size and depth of the cancer and signs of spread to other organs [1-104, 143-220]. Treatment of

early-stage disease is typically surgical resection, ranging from a conization to a modified radical hysterectomy. However, women with high-risk pathology pos-tresection may require adjuvant treatment with chemotherapy and radiation [1-104, 143-220]. Conization or trachelectomy may be an option for women with early-stage disease who desire future fertility. For patients with more advanced disease, concurrent chemoradiation is the standard of care[1-104, 143-220].

Pap test (Pap smear): During a Pap test, a doctor uses a long swab to scrape a few cells from the inside of patient cervix. They send the swab to a lab, where it is checked for abnormal cells. A Pap test is the main screening test for cervical cancer in India[1-104, 143-220]. A Pap test (or what some used to call Pap smears) checks the cells of cervix, to make sure there are no abnormal cells. Abnormal cells can change over time and become cancerous without pain or symptoms [1-104, 143-220]. It is a quick test done in healthcare provider's office or at a women's health clinic [1-104, 143-220]. A sample of cells is taken from your cervix and sent to the lab. The lab checks the sample for any abnormal cells that may lead to cancer. A Pap test does not test for other cancers or sexually transmitted infections such as chlamydia, gonorrhea or human immunodeficiency virus (HIV) [1-104, 143-220]. Regular Pap tests check for cervical cell changes, which can be followed closely to make sure they clear up. 90% of cervical cancer can be prevented with early treatment [1-104, 143-220]. If abnormal cells are found, they can be treated early, which may mean less treatment and less time spent recovering. The earlier cervical cancer is found, the better your chance of survival[1-104, 143-220].

Ever since the introduction of the Papanicolaou (PAP) smear test was published in 1941 in American Journal of Obstetrics and Gynecology, PAP test linked with definitive treatment has prevented millions of women from cervical cancer in the developed countries [1-104, 143-220]. Due to limited availability of resources, a lack of infrastructure and difficulty in getting highly trained professionals, widespread implementation of PAP test dependent cervical cancer screening program has not been established in low and middle income countries such as India [1-104, 143-220]. Therefore, after availability of non-cytological tests such as visual inspection on acetic acid (VIA) and Human papillomavirus (HPV) DNA test, there is a paradigm shift in cervical cancer screening methods [1-104, 143-220].

However, the accuracy of traditional Pap smear could be easily affected by following factors: the level of cytological room, professional technicians, sampling method, slide quality, dyeing skills, and cytological personnel experience [1-104, 143-220]. In developed countries with high standard experimental conditions and technical level, the sensitivity of cytology is as high as 80%−90%. On the other hand, in resource-limited regions, it could be as low as 30%−40% [1-104, 143-220]. To overcome the limitations of traditional Pap smear in cervical cancer screening. LBC was developed and approved by Food and Drug Administration (FDA) in 1996 for clinical-use purpose. Compared with the traditional Pap smear, the sensitivity of LBC was significantly improved [1-104, 143-220]. Meanwhile, organized and practicable LBC screening program has also been established in developed countries which could ensure cervical cancer screening strategy is carried out continuously and effectively[1-104, 143-220].

Liquid based cytology (LBC) offers an improved test specimen collection with lower frequency of unsatisfactory smears, lower debris, and shorter time needed for interpretation compared to conventional cytology [1-104, 143-220]. It is the first technical advancement in cervical cytology in more than 50 years. For LBC, the cervical cell specimen is washed into a vial of liquid transport medium and filtered and a random sample is presented as a thin layer on a slide avoiding overlapping of cells [1-104, 143-220]. LBC samples may be used for reflex HPV and other molecular testing (for triaging in case of ASCUS report). However, LBC has more or less equivalent sensitivity and specificity as compared to cytology for the detection of CIN 2 or worse lesions [1-104, 143-230].

HPV test: A doctor takes a small sample of cervical cells and sends it to a lab, where they check for high-risk HPV strains. Doctors can do this test at the same time as a Pap test, or on its own. These tests can only show if patients are at higher risk for cervical cancer after exposure to HPV[1-104, 143-220]. Unlike other DNA viruses, conventional cell cultures cannot detect HPV. The MY09/MY11 primer set-mediated PCR (MY-PCR) (16, 28) and the GP51/GP61 primer set-mediated PCR (GP1-PCR) are the most frequently used amplification systems for the detection of HPV DNA in clinical samples [1-104, 143-220]. These gene specific primer set for the detection of HPV in clinical samples in India were synthesized and supplied by Eurofins Genomics India Pvt Ltd., Bengalore, Karnataka State, India. The MY09-MY11 primer set is synthesized with several degenerate nucleotides in each primer and is thus a mixture of 25 primers, including HMB01, capable of amplifying a wide spectrum of HPV types (16, 28) [1-104, 143-220]. The GP51-GP61 primer set consists of a fixed nucleotide sequence for each primer and detects a wide range of HPV types by using a lowered annealing temperature during PCR [1-104, 143-220]. The detection of high-risk HPV in cervical lesion biopsies and exfoliated cells has evolved from restriction endonuclease cleavage patterns and hybridization techniques to polymerase chain reaction (PCR)-based system, and most recently next-generation sequencing (NGS) assays [1-104, 143-220]. The most frequently used amplification systems for the detection of HPV DNA in clinical samples are based on MY09/MY11 and GP5+/GP6+ consensus primer sets mediated PCR, amplifying DNA fragments in the conserved L1

region of approximately 450bp and 150bp respectively [1-104, 143-220]. Currently, HPV genotyping is primarily based on the detection of individual types by various methods that utilizing the highly conserved *L1* gene and PCR-based methods. These PCR methods employed consensus primers that could target and amplify different sized fragments such as 455 bp with the MY09/11|PGMY system, 150 bp with the GP5+/6+ system, or <100 bp with SPF10 [1-104, 143-220]. Furthermore, another point that is worth noting is that all these techniques remained the most validated methodology to identify and characterize clinically relevant HPV. Additionally, the type-specific probes are always to be used to achieve HPV genotyping, besides DNA sequencing [1-104, 143-220]. Other types of assays may be type-specific with immediate discrimination and quantitation of specific HPV types in an "onetube" assay. These methods employ real time (RT)-PCR techniques, coupled with beta-globin detection for internal quality control utilizing specialized detection systems [1-104, 143-220]. Cervical cancer malignant pathways are tightly correlated to the viral E6 and E7 oncoprotein activities which could also contribute to the accumulation of cellular genomic mutations and viral integration [1-104, 143-220]. Therefore, identification of HPV E6/E7 mRNA has been shown to be promising in cervical cancer screening. And most of the assays utilized reverse transcriptase PCR or nucleic acid sequence-based amplification to identify E6/E7 genome fragments [1-104, 143-220].

In recent years, with the rapid development of science and technology, the application of artificial intelligence (AI) based products is booming [37, 39]. In cervical cancer prevention and control, AI also showed to be promising in cytologybased screening and colposcopy examination based on the image pattern recognition [37, 39]. These AI-based technology or system can intelligently identify lesions and assist medical staff in clinical examination and diagnosis which could alleviate difficulties in diagnosis in primary clinics [37, 39].

In past two decades, various research work has convincingly established the utility of VIA and HPV test in developing countries [1-104, 143-220]. The evidences were evaluated by the World Health Organization (WHO) and recommendations have been recently published for comprehensive cervical cancer control strategies for the low and middle income countries [1-104, 143-220]. For any successful screening program, achieving high coverage (>70%) of the target population rather than frequent screening is the most important determinant [1-104, 143-220].

Surgery: Surgical resection is offered to patients with early-stage disease confined to the cervix. It can range from relatively non-invasive procedures such as cervical conization to more extensive operations such as radical hysterectomy [1-104, 143-220]. Although surgery is the preferred treatment modality for early-stage cervical cancer, it is especially important in younger patients for whom preservation of ovarian function and/or fertility is desired. Surgery is also indicated in select patients with recurrent disease[1-104, 143-220].

Types of Surgery- Cervical conization-This surgery removes a cone-shaped section of tissue from the cervix. The surgeon may use a scalpel (cold-knife conization), a laser or an electrical current passed through a thin wire (loop electrosurgical excision procedure), Radical trachelectomy, Extrafascial hysterectomy, Radical hysterectomy, Laparoscopic radical hysterectomy, Lymph node evaluation [1-104, 143-220]. Detecting lymph node involvement is essential, as it yields important prognostic information and guides therapeutic decision-making [1-104, 143-220]. Hysterectomy: This surgical procedure removes the uterus and cervix. Surgery is the most common treatment for cervical cancer, and could include: Pelvic lymph node dissection: Lymph nodes are removed from the pelvic area for examination. Para-aortic lymphadenectomy: Lymph nodes are removed from around the aorta, the main artery that leads to the heart. Sentinel lymph node mapping: This technique causes the lymph nodes closest to the cervix to glow with a fluorescent light [1-104, 143-220]. Doctors use this to figure out where cancer cells from the cervix might spread, and they take a biopsy [1-104, 143-220].

Treatment for cervical cancer depends on the cancer stage, overall health and tolerance for certain medications or therapies. Other treatment options for cervical cancer might include: Chemotherapy: Drugs that target and kill cancer cells in patient body. Radiation: A high-energy X-ray beam that destroys cancer cells so they cannot spread. Doctors often use a combination of external and internal radiation [1-104, 143-220]. External radiation beams target the pelvic area. Internal radiation places small, hollow tubes filled with radioactive isotopes directly into the tumor to destroy it [1-104, 143-220]. Immunotherapy: Drugs that boost patients body's natural ability to detect and kill cancer cells. Visual screening tests :VIA involves naked eye visualization of the cervix 1 min after the application of 3–5% dilute acetic acid under bright light [1-104, 143-220]. Test results are reported as negative, positive or suspicious of invasive cancer and their criteria are given in the VIA screening was followed by a 31% reduction in cervical cancer mortality in a randomized trial in Mumbai, India[1-104, 143-220]. In a randomized trial in South India, VIA screening was associated with 25% decline in cervical cancer incidence and 35% reduction in mortality [1-104, 143-220]. This evidence culminated in the launching of a population based VIA screening program in the state of Tamil Nadu in India. Large number of nurses have been trained in providing VIA throughout the primary health centers in the state and 55% of

targeted 15 million have been screened through the first round of a VIA screening program during 2012–2014 [1-104, 143-220].

If a patient has early-stage cervical cancer, it may be possible to have surgery to remove the cancer but leave all other reproductive organs in place so that she might be able to still become pregnant. Cone biopsy and radical trachelectomy are surgical options for early-stage cervical cancer that preserve fertility. A cone biopsy may be recommended for early-stage cervical cancer (stage 1a) which removes a cone-shaped piece of cervical tissue. It may be performed with or without surgical exploration of the pelvic lymph nodes. The scientific literature suggests that patients who had a cone biopsy tend to have shorter pregnancies (shorter by 3 weeks) but very rarely the earlier delivery is harmful to the newborn baby. A radical trachelectomy may be recommended for cervical cancer stages 1a or 1b and involves removal of the entire cervix and the tissue next to the cervix (parametria). Sometimes, a permanent stitch (cerclage bandage) can be placed around the internal opening of the cervix to hold it closed. This procedure is mostly done in combination with a removal of pelvic lymph nodes. This procedure preserves the uterus for fertility reasons. Cancer Research in UK reported babies have been born safely to women who have had this type of operation. However, there is a higher risk of miscarriage or having the baby born prematurely. In pregnant women who have had a radical trachelectomy, the baby must be born by caesarean section due to the permanent stitch.

A radical hysterectomy with or without removing a safety margin around the cervix is an option if fertility is not desired. Radical hysterectomy removes the uterus, cervix, and soft tissue around the cervix and the top of the vagina. The ovaries can be removed or preserved, depending on some factors, including the patient's age. The procedure is often offered along with a removal of pelvic lymph nodes [1-104, 143-220]. Treatment of cervical cancer stages 2 to 4 cannot rely on surgery alone because the tumor is too advanced and cannot be removed completely with a safety margin. In these patients, radiation treatment, chemotherapy or a combination of both play an important roles to achieve good patient outcomes. Radiotherapy treatment for cervical cancer may stop the ovaries from producing female hormones and cause menopause [1-104, 143-220]. If radiotherapy is required, but the ovaries do not need to be treated, it is possible for one or both of the ovaries to be temporarily moved higher into the abdomen, so they are not exposed to the radiation treatment. This is a surgical procedure called ovarian transposition, and it may help to keep the ovaries functioning. Depending on a women’s age and individual circumstances, losing fertility can be distressing, while for others it may not be as concerning. Even if the patient was not planning to have children, the loss of fertility can be emotional. Surgery that includes removal of the ovaries will induce surgical menopause, and all the symptoms that may come along with menopause.

Photodynamic therapy (PDT): Photodynamic therapy (PDT) [223] is an alternative treatment modality that has been proven to treat primary cervical cancer, as well as eradicate Cervical cancer stem cells (CCSCs) to prevent secondary metastasis [1-104, 143-220, 223]. PDT has numerous advantages over conventional therapies, since it is a very specific non-invasive localized treatment, with very few side effects [223]. It has a short healing time with no scarring, and it is highly tolerant to repeated doses with little to no resistance[1-104, 143-220, 223]. Furthermore, PDT may be considered for patients as an alternative treatment, as it allows them to preserve their fertility, whereas surgery, chemo- and radiotherapy often induce sterility in patients [1-104, 143-220, 223]. The current ongoing clinical trials have reported that PDT therapy with 5-aminolevulinic acid (ALA) has emerged as an effective and tolerable treatment strategy for the control of cervical cancer [223]. PDT treatments utilize a light-excitable dye known as a photosensitizer (PS) which is administered to a patient [1-104, 143-220, 223]. The photosensitizer (PS) is given time to distribute throughout the patient’s body [223]. Due to the enhanced permeability and retention effect (EPR) which cancer cells possess, a photosensitizer (PS) is able to accumulate in tumor cells passively and selectively [1-104, 143-220, 223]. Once photosensitizer (PS) selective accumulation has occurred an external light source at particular wavelength of irradiation is applied to the localized tumor in the patient’s cervical area via hysteroscopy [223]. The application of red laser light excites the localized tumor photosensitizer (PS) from its single ground state to an excited triplet state [1-104, 143-220, 223].

Although cervical cancer is one of the most common malignancies diagnosed in pregnancy, it poses unique staging and treatment challenges in pregnant patients [1-104, 143-220]. A maternal-fetal medicine specialist should evaluate patients to discuss fetal risks and potential pregnancy loss. Women must weigh the risk of delaying treatment until after delivery versus proceeding immediately with treatment [1-104, 143-220]. Radiotherapy remains a crucial component in the treatment of cervical cancer. Randomized evidence from the 1990s and early 2000s has established radiotherapy in almost every facet of treatment; it may be utilized as a definitive or adjuvant treatment with or without platinum-based chemotherapy [1-104, 143-220]. Radiation-induced cancers tend to appear several decades after treatment. Vaginal stenosis and vaginal canal shortening can develop over months to years after treatment. Stenosis can make it difficult for intercourse and gynecological exams [1-104, 143-220]. Consistent use of a vaginal dilator is typically recommended. However, compliance is highly variable. Sexual dysfunction is quite common, ranging from a lack of

desire for sexual activity to a lack of adequate vaginal lubrication [1-104, 143-220]. Compared with radiotherapy alone, there are consistent overall survival, disease-free survival, and local control advantages. It is postulated that chemotherapy acts as a radiosensitizer [1-104, 143-220]. Adjuvant therapy chemoradiotherapy may be added after surgical resection should the patient have high-risk features. Overall survival and progression-free survival benefits have been demonstrated with the addition of chemotherapy to radiotherapy in certain high-risk postoperative patients [1-104, 143-220].

The most commonly used platinum-based drugs are cisplatin and carboplatin. Common adverse effects include neutropenia, thrombocytopenia, anemia, febrile neutropenia, nephrotoxicity, neurotoxicity, and infection [1-104, 143-220]. Although cisplatin is the drug of choice, carboplatin can be used in patients who may not tolerate cisplatin, particularly if they already have underlying renal disease [1-104, 143-220]. Carboplatin is thought to have lower efficacy than cisplatin. However, prospective data suggested non-inferiority in effectiveness and a statistically significant lower incidence of febrile and non-febrile neutropenia and creatinine elevation [1-104, 143-220]. Bevacizumab carries the risk of hypertension, hemorrhage, thromboembolic events, renal injury, and ovarian failure in premenopausal women. Pembrolizumab is known for precipitating autoimmune phenomena such as pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies[1-104, 143-220].

Traditional and innovative patient education methods can increase overall awareness of cervical cancer and the need for prevention and early screening [1-104, 143-220]. Literature showed that healthcare professionals may not consistently recommend or discuss HPV vaccination with all target patients. Some women and parents of young daughters may also have reservations about vaccinations that prevent them from being vaccinated[1-104, 143-220]. Additional medical education for clinicians serving high-risk populations may increase awareness, prevention, and screening of those patients at risk for the highest mortality[1-104, 143-220]. Although a patient may prefer counseling directly from the healthcare professional, additional community outreach efforts are necessary. Culturally sensitive information, appropriate language to reach lower health literacy populations, and targeted efforts to reach women not yet sexually active are needed to expand patient awareness and education and to initiate screening beyond the clinical setting [1-104, 143-220].

Cervical cancer develops when abnormal cells grow in a person's cervix. The cervix is the lower part of the uterus, a pear-shaped organ where a fetus grows during pregnancy [1-104, 143-220]. It connects the uterus to the vagina. Cervical cancer begins when healthy cells in the cervix change and become cancerous (malignant) [1-104, 143-220]. These cells multiply and grow out of control, forming tumors [1-104, 143-220]. Cervical cancer can also spread to other nearby organs, such as the uterus and vagina, or to distant parts of the body. Things that can put patient at higher risk of cancer caused by HPV infections include: Becoming sexually active at a younger age, having multiple sexual partners, having unprotected sex (without condoms), having a weakened immune system as a result of HIV (the virus that causes AIDS), or from medications that suppress the immune system, Not getting the HPV vaccine, smoking cigarettes: Women who smoke are about twice as likely to develop cervical cancer compared with women who do not smoke [1-104, 143-220]. Exposure to diethylstilbestrol (DES) before birth: This medication was prescribed to pregnant women between 1940 and 1971 to prevent miscarriage. Studies later found it was not effective [1-104, 143-220]. Daughters exposed to DES in their mother's womb are at higher risk of developing certain cancers including cervical cancer not related to HPV [1-104, 143-220]. Long-term use of oral birth control: The risk of cervical cancer increases for women who take oral contraceptives over several years. However, research showed that after several years off of oral contraceptives, patient risk level returns to normal [1-104, 143-220].

Cancer screening aims to detect preclinical disease in an apparently healthy population through systematic administration of a simple and safe test to all men/women belonging to a specified target age group [1-104, 143-220]. Since the primary objective of cervical cancer screening is to detect the premalignant lesions (known as cervical intraepithelial neoplasia [CIN]), World Health Organization (WHO) recommended screening of women between 30 and 49 years of age [1-104, 143-220]. At this age, the women have the highest possibility of harboring the CIN 2 and CIN 3 lesions that are considered as true cervical cancer precursors or high grade lesions. Screening at younger age detects large number of low grade lesions that regress of their own and the women are subjected to unnecessary biopsies and treatment [1-104, 143-220]. However, screening of HIV positive women should be initiated whenever they are sexually active. The upper age range can be extended to 55–60 years age if resources permit [1-104, 143-220]. The frequency of screening in the screen negative women depends on the screening test being used and the resources available within the program. Too frequent screening should be avoided and the minimum interval between two rounds of screening should be 5 years [1-104, 143-220]. Programs with limited resources can extend the interval to 10 years, if a highly sensitive screening test (such as HPV DNA test) with very low possibility of missing cases can be used [1-104, 143-220]. Even once a lifetime screening around the age of 40 years can reduce cervical cancer incidence by 30%. Achieving

high coverage (>70%) of the target population rather than frequent screening is the most important determinant of success of the screening program [1-104, 143-220].

Accumulated evidence on all cervical screening tools available showed that HPV testing is an acceptable, safe and highly efficacious procedure for detecting cervical cancer precursors [1-104, 143-220]. Sampling dependency and quality control is also favorable for HPV testing as compared to cytology. In middle income countries like India with lack of infrastructure and non availability of trained professionals, non cytological screening tests like VIA and HPV test are a viable alternative to cytological screening [1-104, 143-220]. From the perspective of health policy, though at present HPV test as the primary screening test may have high upfront cost but because of its high sensitivity, specificity and negative predictive value, there is net cost saving in HPV detection based screening program due to high and prolonged protection that allows screening interval to be increased [1-104, 143-220]. HPV testing will be most suitable in the post vaccination era in view of low prevalence of HPV infection and neoplasia, when subjective tests like cytology and VIA will be more challenging with poor accuracy [1-104, 143-220]. Along with awareness and education change from a cellular to viral test will be more effective in controlling the huge burden of cervical cancer [1-104, 143-220]. Cervical cancer stem cells (CCSCs) have been identified as the underlying cause of relapse and resistance to repeated chemo- and radiotherapy after successful primary conventional treatments have been applied [1-104, 143-220].

13 Role of Cannabis sativa in Controlling Cervical cancer

Currently, the recommended therapeutic regimens include chemotherapy, radiation therapy, and surgery. However, they present several limitations including side effects or ineffectiveness. Therefore, it is important to search for new novel therapeutic agents that are naturally synthesized and cheaper, but still remain effective [221-223, 236, 246, 372*]. Medicinal plants have been used for decades for health benefits and to treat several different diseases [105-142]. The therapeutic potential of medicinal Cannabis was demonstrated in various medical conditions such as sleep disorders, nausea, anorexia, emesis, pain, inflammation, neurodegenerative diseases, epilepsy, and cancer [257-295, 372]. Both Medical Cannabis (Marijuana or drug type) and Industrial *Cannabis sativa* hemp is used for controlling numerous diseases, such as cervical cancer, chronic pain, asthma, rheumatoid arthritis (RA), wound healing, constipation, multiple sclerosis (MS), cancer, inflammation, glaucome, neurodegenerative disorders (Epilepsy-seizure disorder, Alzheimer's disease, Parkinson's disease), dengue viral disease, Huntington's disease, Tourette's syndrome, dystonia, Lennox-Gastaut Syndrome (LGS), Dravet Syndrome (DS), obesity, weight loss, anorexia, emesis, osteoporosis, schizophrenia, cardiovascular disorders, sleep disorders, traumatic brain injury (TBI), post traumatic stress injury, drug addiction (Marijuana), AIDS, Wasting syndrome, amyotrophic lateral sclerosis (ALS), depression and anxiety, diabetes, migraine (headache disorder), covid-19 (SARS-CoV-2), leishmaniasis (Kala-Azar), and metabolic syndrome related disorders, to name just a few, are being treated or have the potential to be treated by Cannabinoid agonists/ antagonists/cannabinoid-related compounds [257-360, 372].

According to recent studies, cannabis inflorescences are rich in secondary metabolites, comprised mainly of two major groups, namely cannabinoids and terpenes [257-295]. Cannabis-based products are widely used for various medicinal conditions [257-300]. Currently, the most common method to identify and quantify cannabinoids are liquid chromatographic methods coupled to UV-VIS or mass spectrometric detectors [257-295, 372]. In a research study reported, it was found that CBD inhibited cell proliferation and induces apoptosis in a series of human breast cancer cell lines including MCF-10A, MDA-MB- 231, MCF-7, SK-BR- 3, and ZR-7-1 and further studies found it to possess similar characteristics in PC-3 prostate cancer cell line [257-350]. In the one of the study reported by Lukhele and Motadi, (2016) [221] cervical cancer cell lines (SiHa, HeLa, and ME-180) were exposed to different concentrations of Cannabis sativa extracts and that of its compound, cannabidiol, for the investigation of their anti-proliferative activity [221-223, 236, 246]. This study confirmed that Cannabis sativa extracts and Cannabidiol possess anti-proliferative effects using MTT assay [221-223]. MTT assay determines IC50, which represents the half maximal concentration that induces 50 % cell death [221-223, 236, 246]. Cannabis sativa extracts were able to reduce cell viability and increase cell death in SiHa, HeLa, and ME-180 cells [221-223, 236, 246]. These results correlated with the earlier findings , whereby they reported reduced cell proliferation in colorectal cancer cell lines following treatment with Cannabis sativa [221-223, 236, 246]. Another study reported that Cannabis sativa extracts rich in cannabidiol were able to induce cell death in prostate cancer cell lines LNCaP, DU145, and PC3 at low doses (20–70 µg/ml) [221-223, 236, 246-300]. It was suggested that cannabidiol might be responsible for the reported activities. Therefore, cannabidiol was included as a reference standard in order to determine whether the reported pharmacological activities displayed by Cannabis sativa extracts might have been due to the presence of this compound [221-223, 236, 246-300].

Therefore the study of Lukhele and Motadi, (2016) [221] showed that the activity of one of the extracts might have been due to the presence of cannabidiol. It further demonstrated the ability of Cannabis sativa to induce apoptosis with or

without cell cycle arrest and via mitochondrial pathway [221-223]. More research needs to be done elucidating the mechanism between the active ingredients and molecular targets involved in the regulation of the cell cycle [221-223, 236, 246-300]. Results obtained indicated that both cannabidiol and Cannabis sativa extracts were able to halt cell proliferation in all cell lines at varying concentrations [221-223, 236, 246-300]. They further revealed that apoptosis was induced by cannabidiol as shown by increased subG0/G1 and apoptosis. Apoptosis was confirmed by overexpression of p53, caspase 3 and bax. Apoptosis induction was further confirmed by morphological changes, an increase in Caspase 3/7 and a decrease in the ATP levels [221-223, 236, 246-300]. Therefore, these data suggested that cannabidiol rather than Cannabis sativa crude extracts prevent cell growth and induced cell death in cervical cancer cell lines [221-223, 236, 246-300]. However, further studies should also take into consideration and examine how HPV expression is altered by *Cannabis sativa* or its individual components (CBD and THC) in different tissues to produce stronger data to determine if CBD or *Cannabis sativa* crude extracts (which contain THC) are helpful or harmful in terms of aggravating other cancer types [221-223, 236, 246-360].

The first pilot clinical trial of cannabinoids as cancer treatment in 9 glioblastoma patients was published in 2006 and found that intracranially administered THC was safe. Recently, the results of a randomised, placebo-controlled phase 1b study with nabiximols oromucosal spray (standardised extract of Cannabis sativa L. with an approximate 1:1 ratio of THC and CBD) in combination with doseintense temozolomide in patients with recurrent glioblastoma multiforme were published [221-223, 236, 246-300]. Of the 21 patients in this study, survival at one year was 83% in the 12 patients treated with nabiximols, while it was significantly lower at 44% in the 9 patients treated with placebo, leading the authors to recommend further exploration in an adequately powered randomised controlled trial [221-223, 236, 246-360]. So far, however, randomized, placebo-controlled studies with a larger number of cancer patients are lacking at all.

CBD may be particularly useful for gynecological cancers [221-223, 236, 246-360]. Tetrahydrocannabinol (THC) may inhibit endometrial cancer proliferation and migration. Tetrahydrocannabivarin (THCV) may be useful as well as it may enhance anandamide's anticancer effect [221-223, 236, 246-300].

Flavonoids in cannabis, like kaempferol and luteolin, possessed antitumor activity. Terpenes like myrcene, beta-caryophyllene, humulene, limonene, and pinene have anticancer properties [221-223, 236, 246-350]. Studies showed that medical cannabis could be useful in the treatment of cervical cancer [221-223, 236, 246-360]. One study showed that, out of 31 women with cervical cancer, 83% reported that medical cannabis provided relief for their cancer or treatment-related symptoms [221-223, 236, 246-360]. Medical cannabis helped with the following: Lab studies using cell lines suggest that cannabidiol (CBD) in particular may be helpful for cervical cancer treatment [221-223, 236, 246-300].

A systematic review of medical cannabis for gynecological pain in general (including cancer, endometriosis, interstitial cystitis, pelvic pain, and many more), published in 2022 showed that doses of up to 70 mg THC and 2000 mg CBD per week helped to relieve pain in between 61% to 95.5% of the women studied [221-223, 236, 246-300]. There have been concerns over cannabis usage, its immunomodulatory effects, and a positive cross-sectional association with human papillomavirus (HPV)-related head and neck cancer [221-223, 236, 246-300]. There is no data suggesting that cannabis increases cervical HPV burden [221-223, 236, 246-300]. However, even though the results look positive, similar problems showed up in these studies as they do with many others regarding medical cannabis [221-223, 236, 246-300]. These issues include: low sample sizes, and rarely discernment between different types of cannabis [221-223, 236, 246-300]. Related to the above, rarely any differentiation between different doses and concentrations of particular cannabinoids, terpenes, and flavonoids [221-223, 236, 246-300]. Lack of randomized controlled trials (RCTs), and lab studies do not always reflect real life, and particularly high doses of cannabinoids may be needed doses exceeding that of average non-medical adult use [221-223, 236, 246-300]. In several lab studies, cannabinoids have been shown to induce apoptosis (programmed cell death) of human cervical carcinoma cells [221-223, 236, 246-300]. Cannabidiol (CBD) may be of particular use, but in some cases, a chemically similar version (an analog) of anandamide, methanandamide, was used [221-223, 236, 246-360]. It seems that increasing anandamide concentration in the body may be of particular help. Inhibiting COX-2 enzymes, which are common in sites of inflammation, could be key to treating cervical (and other) types of cancer [221-223, 236, 246-350]. Inhibition of COX-2 enzymes may also helped to treat cancer pain and increase the efficacy of chemotherapy [221-223, 236, 246-360].

Cervical cancer (CC) is the fourth most diagnosed cancer in women worldwide. Conventional treatments include surgery, chemo- and radiotherapy, however these are invasive and may cause severe side effects[1-105, 143-221-223, 236, 246-360]. Furthermore, approximately 70% of late-stage cervical cancer patients experience metastasis, due to treatment resistance and limitations [1-105, 143-221-223, 236, 246]. Thus, there is a dire need to investigate alternative therapeutic combination therapies. According to the study conducted by Razlog et al. (2022), photodynamic therapy (PDT) is an alternative cervical cancer treatment modality that has been clinically proven to treat primary Cervical

cancer, as well as to limit secondary metastasis [1-105, 143-221-223, 236, 246]. Since PDT is a non-invasive localized treatment, with fewer side effects and lessened resistance to dose repeats, it is considered far more advantageous[1-105, 143-221-223, 236, 246]. However, more clinical trials are required to refine its delivery and dosing, as well as to improve its ability to activate specific immune responses to eradicate secondary cervical cancer spread [1-105, 143-221-223, 236, 246]. Cannabidiol (CBD) isolates have been shown to exert *in vitro* cervical cancer anticancer effects, causing apoptosis post treatment, as well as inducing specific immune responses, which obstruct tumor invasion and angiogenesis, and so hinder CC metastatic spread [1-105, 143-221-223, 236, 246]. It has a particular focus on the combinative administration of CBD with these treatments in order to prevent cervical cancer secondary migration and so possibly encourage future research studies to focus on this synergistic effect to eradicate cervical cancer [1-105, 143-221-223, 236, 246]. PDT is an alternative cervical cancer treatment modality that has been proven to treat primary cervical cancer, as well as eradicate cervical cancer stem cells (CCSCs) to prevent secondary metastasis [1-105, 143-221-223, 236, 246]. Since PDT is a very specific non-invasive localized treatment, with very few side effects and it has a short healing time with no scarring, as well as being suitable for repeated dosing, with little to no resistance being found, it seems to be a far more advantageous treatment for cervical cancer[1-105, 143-221-223, 236, 246].

An extensive review by Seltzer et al. (2020) [233] discussed the most recent findings that strongly support CBD as a promising cytotoxic cancer drug [1-105, 143-221-223, 233, 236, 246-360]. However, the antitumor effects appear to be largely dependent on cancer type and drug dose/concentration. *In vitro* and *in vivo* cancer research has shown that CBD can effectively control tumor growth[1-105, 143-221-223, 236, 246-360]. Numerous cell culture and animal studies have demonstrated the antitumor effects of CBD in various cancer types, noting that it can prevent proliferation, metastasis, angiogenesis, as well as exert pro-apoptotic cell death effects [1-105, 143-221-223,233, 236, 246-360, 372]. Furthermore, PDT treatment of colorectal and breast cancer was combined with cannabidiol (CBD), complete cancer primary cell cancer growth ablation and migratory suppression for secondary spread was possible [1-105, 143-221-223, 236, 246-360]. Furthermore, another parallel studies have reported that CBD has the ability to stimulate various immune system responses which result in the signaling of anti-tumor signaling pathways, which are capable of controlling/ limiting metastatic tumor growth [1-105, 143-221-223, 233, 236, 246-360].

Luschnig and Schicho (2019), on the abilities of CBD to treat various gynecological diseases, they noted that CBD drastically reduced cervical cancer *in vitro* cells growth via apoptotic cell death mechanisms, while successfully generating anti-tumor immune responses post treatment, aiding in the control of cervical cancer stem cells (CCSCs) metastatic tumor proliferation and secondary spread [1-105, 143-221-223, 233, 236, 246-360]. Moreover, within *in vitro* cervical cancer treatment studies performed by Ramer et al. (2010 and 2008) and Lukhele and Motadi (2016), it was noted that CBD is able to activate specific immune responses, which can aid in the treatment the primary, as well as secondary treatment of cervical cancer [1-105, 143-221-223, 233, 236, 246-360]. Drugs that target the endocannabinoid system are of interest as pharmacological options to combat cancer and to improve the life quality of cancer patients[1-105, 143- 360]. From this perspective, cannabinoid compounds have been successfully tested as a systemic therapeutic option in a number of preclinical models over the past decades [1-105, 143- 360]. As a result of these efforts, a large body of data suggests that the anticancer effects of cannabinoids are exerted at multiple levels of tumour progression via different signal transduction mechanisms [1-105, 143-221-223, 233, 236, 246-360]. Accordingly, there is considerable evidence for cannabinoid-mediated inhibition of tumor cell proliferation, tumor invasion and metastasis, angiogenesis and chemoresistance, as well as induction of apoptosis and autophagy [1-105, 143- 360]. Further studies showed that cannabinoids could be potential combination partners for established chemotherapeutic agents or other therapeutic interventions in cancer treatment [221- 360]. Research in recent years has yielded several compounds that exert promising effects on tumor cells and tissues in addition to the psychoactive Δ9-tetrahydrocannabinol, such as the non-psychoactive phytocannabinoid cannabidiol and inhibitors of endocannabinoid degradation [221- 360]. The property of cannabinoids, in particular, to induce inhibition of tumor growth and spread at multiple levels of tumor progression argues for the use of these substances as an add-on option in tumor treatment [221-360]. However, it should also be noted that research into the efficacy, dosage and drug safety of cannabinoids in tumor therapy still has a long way to go, especially with regard to clinical trials to be conducted, through which alone the benefits and advantages for cancer patients but also possible risks can be defined [221- 360].

14 Endocannabinoid system (ECS)

Endocannabinoid system (ECS) (Figure-3) is an ancient, evolutionary stable homeostasis system in human and animals [221- 360]. It consists of three components—ligands, including 2-arachidonoylglycerol (2-AG) and arachidonoyl ethanolamide (AEA or anandamide), receptors, such as cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), and the metabolizing enzymes—fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [221- 360]. The endocannabinoid system (ECS) is a complex cell-signaling system that helps to regulate our body functions, including sleep, mood, digestion, memory, reproduction, fertility, appetite and digestion, metabolism, chronic pain,

inflammation and other immune system responses, motor control, cardiovascular system function, muscle formation, bone remodeling and growth, liver function, reproductive system function, stress, skin and nerve function [221- 360]. These functions all contribute to homeostasis, which refers to stability of our internal environment. For example, if an outside force, such as pain from an injury or a fever, throws off our body's homeostasis, then our endocannabinoid system (ECS) kicks in to help our body return to its ideal operation [221-360]. The structure of the main psychoactive phytocannabinoid, tetrahydrocannabinol (Δ9-THC), was determined in Israel by Mechoulam and Gaoni in 1964. This discovery opened the gate for many of the subsequent developments in the field of endocannabinoid system (ECS) research [221- 360, 372]. Mechoulam's milestone discovery that Δ9 -THC (tetrahydrocannabinol) is the primary psychoactive principle, and the ensuing elucidation of the ECS, opened the gate for a new era in cannabis history [221-360]. Both plant-derived Δ9-THC (tetrahydrocannabinol) and the first endocannabinoids were discovered in Israel by the laboratory led by Professor Raphael Mechoulam, clearly stood out as a giant of modern Cannabis science [221- 360].

The entry of the endocannabinoid (EC) system into modern research as a potential target of pharmacotherapeutic intervention began with the discovery and cloning of specific Gi/o protein-coupled cannabinoid receptors, termed as CB1 and CB2 [221- 360]. While CB1 receptors are primarily localized in the central nervous system, CB2 receptors are mostly expressed on cells of the immune system (Figure-3) [221- 360]. Around the turn of the millennium, the non-selective cation channel transient receptor potential vanilloid 1 (TRPV1) was described as an additional receptor target for several cannabinoids such as AEA and the non-psychoactive phytocannabinoid CBD [221- 360]. Recently, further substances from Cannabis sativa L., which are also found in other plants, have been investigated for their anticancer effects [221- 360]. This concerns, for example, the sesquiterpene β- caryophyllene, a potent CB2 agonist. In the hitherto performed studies, β-caryophyllene showed antiproliferative and pro-apoptotic properties on various cancer cell lines and enhanced the cytostatic effects of classical chemotherapeutic agents such as doxorubicin and sorafenib [221- 360, 372].

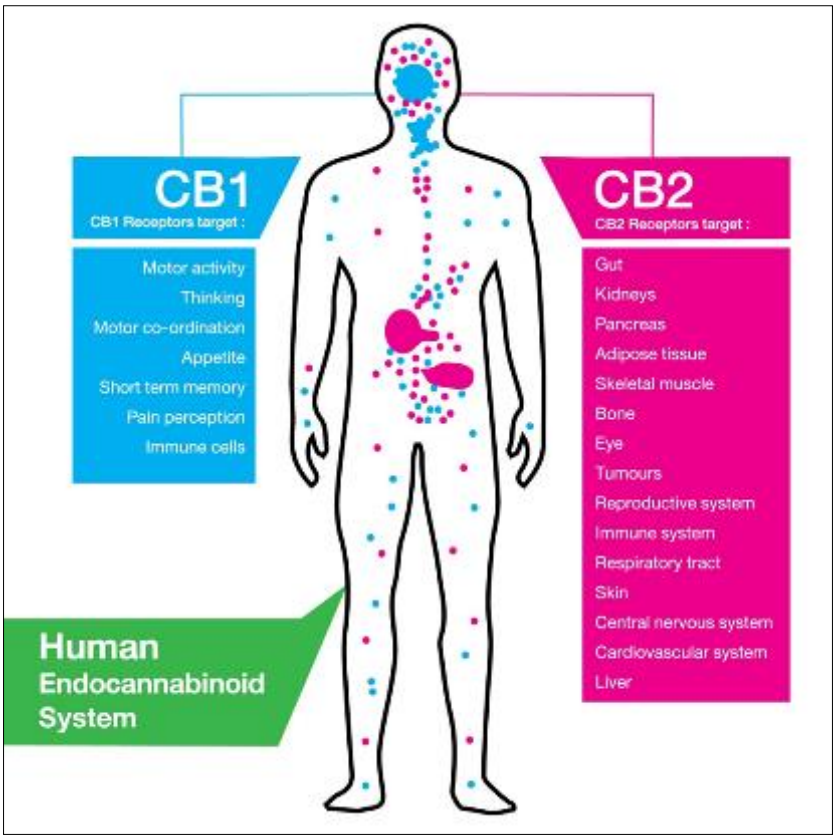

Figure 3 Human Endocannabinoid System (ECS) with CB1 and CB2 receptors Target

As a regulator of homeostasis, ECS regulates the activity of brain, endocrine, and immune systems [221- 360]. One such regulatory mechanism is the regulation of energy metabolism (Figure-3). ECS increases the energy intake, facilitates its storage, and decreases the expenditure [221- 360]. The Endocannabinoid system (ECS) represented a critical part of understanding Δ9-tetrahydrocannabinol (THC) and its potent effects on the human body [221- 360]. Humans and other mammals contain an Endocannabinoid system (ECS) within their bodies, which plays a significant role in maintaining

homeostasis, or balance, in the body [221- 360]. This unique Endocannabinoid system (ECS) also influences regulatory processes as diverse as appetite, sleep, mood, stress, energy levels, and reproduction (Figure-3). The Endocannabinoid system (ECS) produces endogenous Cannabinoids (produced internally) and responds to exogenous Cannabinoids (produced externally), like the ones found in Cannabis, which are called Phytocannabinoids [221- 360]. Endogenous Cannabinoids are now generally referred to as 'endocannabinoids' and, together with cannabinoid receptors, constitute the 'Endocannabinoid system [221- 360].

Cancer is a disease of dysregulated and uncontrolled cell division and cell proliferation. Successful malignization requires mutations in multiple genes [221- 360]. Cannabinoids as endogenous regulators of homeostasis are the molecules that can potentially be used for cancer therapy [221- 360]. They may be particularly useful in palliative care. Endocannabinoid system (ECS) is active in virtually all cells of our organism [221- 360]. During human adult life, it regulates homeostasis of many tissues, playing critical role in proper brain function by regulating neuronal synaptic communications affecting critical organismal functions, including general metabolism, growth and development, reproduction, learning and memory formation, mood, and behavior, among others [221- 360]. In the cells, endocannabinoids acting in CB-receptor-dependent and independent manner exhibit anti-oxidative properties, are involved in clearance of damaged molecules and regulate mitochondrial activity [221- 360]. Similarly, in cancer cells, such as gliomas and leukemia, cannabinoids promote oxidative stress. Cannabinoids contribute to recycling of damaged molecules and are likely involved in autophagy of healthy tissues [221- 360]. Classical cannabinoid receptors include CB1 and CB2 [221- 360]. CB1 is expressed at a higher level in central and peripheral nervous systems, while CB2 is expressed in many different tissues, including the immune system, internal organs, skin, bone, muscle, and glia in the brain [221- 360].

Phytocannabinoids, Λ9-tetrahydrocannabinol (THC), cannabidiol (CBD), and D9- tetrahydrocannabivarin (THCV) showed to activate cannabinoid receptors CB1 and CB2 [221- 360]. Another interesting thing is that enndocannabinoids, and phytocannabinoids interact with other receptors CB1 and CB2 throughout the body [221- 360]. THC and CBD also can affect the levels of anandamide in the brain [221- 360]. Moreover, THC can increase AEA and adenosine levels. It appears that ECS controls the fate of many cells in the organism, regulating the cell division and proliferation, apoptosis, necrosis and autophagy in several organs and organ systems, including the brain, skin, and immune system [221- 360]. In the central nervous system (CNS), the ECS system functions as a neuroprotective system that controls glutamate excitotoxicity, calcium influx, inflammation, and autophagy [221- 360]. In skin, ECS activity maintains the cutaneous homeostasis through the regulation of skin cell proliferation, survival, and differentiation [221- 360]. In the immune system, the central role is played by CB2 receptors that are mainly expressed by cells (T and B lymphocytes) and peripheral tissues of the immune system (spleen and thymus) where it regulates immune suppression, apoptosis, and cell migration [221- 360].

Cancer can be considered an age-associated disease, due to the accumulation of cellular and DNA damage [221- 360]. In general, it is believed that the activity of ECS declines with age [221- 360]. The metabolic abnormality of lipids has been linked to cancer due to their crucial regulatory roles in signaling pathways involved in initiation and progression of malignancies [221- 360]. The ECS is a biological system comprised of lipid-derived endocannabinoids, cannabinoid receptors, and the enzymes responsible for endocannabinoid metabolism [221- 360]. The ECS is dysregulated in numerous diseases, including cancer. Cannabinoids exert their biological actions primarily through the activation of various receptors, and many of them are likely to be altered in cancer [221- 360]. To date, many studies using immunohistochemical staining, Western blotting, qRT-PCR, or a combined method have demonstrated overexpression or expression of CB1R and/or CB2R in human cancers, including cervical, glioma, lymphoma, leukemia, breast, lung, ovarian, pancreatic, prostate , skin and thyroid cancers, endometrial, esophageal, head and neck, hepatocellular, renal, and mobile tongue carcinomas [221- 360]. A large body of evidence has indicated that the overexpression of CB1R or CB2R is correlated with reduced survival, increased risk of metastasis and recurrence, and poor prognosis and clinical outcomes [221- 360].

These data suggest that cannabinoid receptors are potential prognostic indicators for cancer patients and should caution us that such indicators are very cancer specific [221- 360]. Another study has validated the involvement of DNA methylation in suppressing CNR1 transcription in the same cancer type [221- 360]. In addition to DNA methylation, miRNAs (miRs)—well-characterized small non-coding RNA molecules (20–22 nt) play pivotal roles in many biological and pathological processes, including cancer [221- 360]. Therefore, it is not surprising if these small RNA molecules also contribute to the dysregulation of cannabinoid receptors in cancer [221- 360]. Growing evidence has demonstrated that GPR55 is overexpressed in numerous malignancies, including breast and colorectal cancers, endometrial and squamous cell carcinomas [221- 360]. Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the two most bioactive endocannabinoids, which trigger activation of CB receptors and regulate downstream signaling pathways in a receptor-dependent or -independent manner [221- 360]. Growing evidence has indicated differential regulation of

endocannabinoids AEA and 2-AG in numerous cancers [221- 360]. The AEA and 2-AG were increased in many cancer cell lines and tissues, including glioblastoma, meningioma, pituitary adenoma, endometrial sarcoma, prostate, and colon carcinoma [221- 360]. Additionally, the concentrations of 2-AG and AEA were higher in cancer related cells (CRC) than in healthy neighboring tissues [221- 360]. Although 2-AG was elevated in various human malignancies, the functional evidence does not support an oncogenic role of 2-AG in tumour progression [221- 360]. Indeed, 2-AG exhibits an anticancer property in several model systems. 2-AG suppresses pancreatic cancer cell proliferation and tumour growth in vitro and in vivo [221- 360].

Furthermore, Lysophosphatidylinositol (LPI) is an endogenous agonist of GPR55 receptor. The levels of LPI have been shown to be elevated in two cancer types: breast and colorectal cancers[221- 360]. Numerous studies have shown an overexpression of MAGL in various human malignancies, including prostate adenocarcinomas, malignant melanoma, osteosarcoma, hepatocellular carcinoma, cervical, colorectal, and endometrial cancers [221- 360]. The overexpression of MAGL is correlated with larger tumor size, vascular invasion, poor differentiation, and clinicopathological stage of several cancers [221- 360]. Therefore, the elevated monoacylglycerol lipase (MAGL) may act as an indicator of poor prognosis in cancer patients [221- 360]. Consistently, in a mouse model, CBD also suppresses tumor growth and metastasis of breast cancer cells via attenuation of macrophage recruitment to xenograft tumor sites [221- 360]. Recently, a study conducted by Cherkasova et al. 2022 [222] using two neuroblastoma cell lines as a model system, revealed a suppressive role of cannabinol (CBN) on neuroblastoma cell proliferation, invasion, and angiogenesis through miR-34a-mediated targeting via inhibition of AKT pathway [221- 360]. These data indicated that cannabinoids can trigger programmed death of cancer cells via receptor-independent signalling [221- 360]. Various in vitro and in vivo experiments have shown that cannabinoids can target almost every hallmark of cancer [221- 360]. They inhibit proliferation, reduce inflammation, stimulate apoptosis, and inhibit tumor invasiveness, angiogenesis, and metastasis [221- 360]. One of the most important effects of cannabinoids, besides their antitumor ability, is that they are less likely to affect non-transformed normal cells surrounding tumors, and they may even have protective effects [221- 360]. Autophagy and apoptosis are two essential mechanisms of regulation of uncontrolled growth. Autophagic activity of cannabinoids observed in several major cancers [221- 360]. The well-established antineoplastic mechanisms of cannabinoids are alterations in ceramide de novo synthesis [221- 360]. In cancer cells, increased ceramide levels, a neutral lipid backbone of complex sphingolipids, can occur under chemotherapy, radiation, and stimulation of CB receptors [221- 360]. Activation of CB1 and CB2 receptors by synthetic cannabinoid agonists could stimulate apoptosis via ceramide synthesis and TNF-receptor activation [221- 360]. Inflammation is a large component of carcinogenesis. ECS plays a central in the regulation of function of immune system and control of inflammation [221- 360]. Similarly, many phytocannabinoids exert strong anti-inflammatory effects upon local or systemic application [221- 360]. CBD was shown to inhibit the invasiveness of lung cancer cell lines by inhibiting ICAM-1 [221- 360]. Cannabinoids may inhibit the invasion and metastasis of cancer cells through down-regulation of vascular endothelial growth factor (VEGF), matrix metalloproteinase 2, matrix metalloproteinase 9, E-cadherin, cyclooxygenase 2 (COX-2), and hypoxia-inducible factor α[221- 360].

Some preclinical studies have shown that Cannabis extracts may be more effective than cannabinoids alone for cancer treatment [221- 360]. For instance, high-CBD extract showed higher affinity for CB1 and CB2 receptors than CBD alone [221- 360]. As a result, a high-CBD extract was more potent in preventing intestinal polyps' formation in animal models [221- 360]. The cannabis plant is rich in terpenes and flavonoids, biologically active substances which can also be used in cancer treatment. There are more than 20,000 terpenes in nature, with around 200 found in Cannabis plants. The monoterpene myrcene, sesquiterpenes β-caryophyllene, and α-humulene are often present in Cannabis chemovars [221- 360]. However, the spectrum of terpenes can vary from plant to plant. Importantly, β -caryophyllene may sensitize different cancer cell lines to conventional chemotherapy drug doxorubicin [221- 360]. Thus, combining different cannabinoids with β -caryophyllene may become advantageous in cancer therapy, which needs further investigation [221- 360]. Another terpene, limonene, is a cyclic monoterpene mainly present in citrus plants and is also present in cannabis. In the bladder cancer cell line, limonene caused G2/M cell cycle arrest, decreased migration, and metastasis, and increased Bax and caspase 3, thus inducing apoptosis [221- 360]. In in vivo models, limonene decreased tumor growth, induced apoptosis, and reduced c-Jun and c-myc expression [221- 360]. Pinene is present in pine resins, rosemary, basil, and parsley. As multiple preclinical data showed that pinene was able to reduce the cell viability, stimulate apoptosis, and induce cell cycle arrest in numerous cancer cell lines [221- 360]. Soursop (*Annona muricata)* is a fruit found mainly in the rainforest of Southeast Asia, South America, and Africa. It is green with a prickly outer texture and a soft and creamy internal texture. The taste is commonly compared to a strawberry or pineapple. Research also showed that soursop has natural cytotoxicity effects. For cancer patients, chemotherapy and radiation therapy are cytotoxic therapies (meaning they kill cancer cells). The fruit also has an ability to reduce the cell growth on a number of cancer cell lines, including breast, lung, pancreatic, prostate, ovarian, and colorectal [364]. **Ramphal** (*Annona reticulata* L.) is one of the traditionally important plants used for the treatment of various ailments. including cancer. Ramphal may connote other types of fruits in the *Annona* family, such as custard apple and sweetsop. Annonaceous

acetogenins are a group of constituents obtained from plants belonging to Annonaceae, having potentials of anti-neoplastic agents [365].

The number of clinical studies related to the role of cannabis and cannabinoids in cancer is critically low [221- 360]. Today, there are few human trials regarding the palliative effects of cannabinoids in cancer patients, and even fewer regarding their anti-cancer effects [221- 360]. Moreover, adding THC to temozolomide treatment increased the sensitivity of chemotherapy-resistant glioma cells to the treatment in mice models [221- 360]. Another study showed that the combination of THC with CBD enhanced radiation's effects on the murine glioma model. CBD may also overcome the oxaliplatin resistance of cancer cells via inhibition of superoxide dismutase 2 and activation of autophagic response [221- 360].The combination of CBD with a conventional chemotherapy agent, carmustine, caused inhibition of proliferation in glioblastoma multiforme cell line and overcame the carmustine resistance via activation of TRPV2 [221-360]. Additionally, the combination of CBD with THC showed higher anti-proliferative action on glioblastoma multiforme cell lines [221- 360]. Furthermore, CBD stimulated TRPV2 and increased uptake of cytotoxic drugs by glioma cancer cells without affecting normal astrocytic cells [221- 360]. The combination of THC with CBD also enhanced the action of temozolomide in mouse models.

Before cannabinoids can be prescribed as an actual treatment in cancer patients, their pharmacokinetics should be considered [221- 360]. In vitro studies showed that CBD can inhibit cytochrome P450, which is responsible for the metabolism of many medications, including conventional chemotherapeutics [221- 360]. As a result, a high concentration of CBD may increase the toxicity and decreased the potency of standard anti-cancer therapy [221- 360]. Thus, the interaction of cannabinoids with cytochrome P450 raised a valuable concern about combining it with conventional chemotherapeutics [221- 360]. A clinical study involving 24 patients receiving irinotecan or docetaxel that were using cannabis showed that the addition of cannabis tea did not significantly affect clearance and medication exposure [221- 360]. However, there is an obvious need for more data regarding cannabinoid pharmacokinetics and interaction with other medications, as many cancer patients are using cannabis for different purposes [221- 360]. Significant concern for using cannabis with anti-cancer treatment was raised in patients undergoing immunotherapy. These results may be related to the immunosuppressive effects of cannabinoids and cannabis use should be carefully considered in patients on immune checkpoint inhibitors[221- 360].

Cancer patients are accessing cannabis to alleviate various symptoms and improve their quality of life. Cancer poses a significant public health challenge in both developed and developing nations, with a rising global incidence of patients facing the threat of death due to abnormal cell proliferation. Cannabis medication may reduce the devastating symptoms experienced by cancer patients, such as pain, emesis, anxiety, loss of appetite, and poor sleep quality [221- 360]. The reasons for cannabis ingestion were to alleviate the physical symptoms such as pain, nausea, and loss of appetite (75%); neuropsychiatric symptoms (63%), recreational use (35%), and cancer treatment (26% [221- 360]. However, they can affect drug metabolism and affecting traditional cancer treatment and have a negative impact on immunotherapy [221-360]. Thus, there is a huge need for clinical trials regarding the specific anti-cancer therapy and cannabinoid use to uncover their anti-neoplastic benefits, as well as to ensure the safe conditions for their ingestion by cancer patients [221- 360]. However, some scientists reported that in immunocompetent animals, THC induced tumor growth, possibly due to its immunosuppressive effect [221- 360]. On the other hand, the anti-inflammatory effects of endo- and phytocannabinoids can be used to prevent and treat colorectal cancer [221- 360]. There are also controversial data regarding the cannabinoid's action on cancer cells [221- 360]. Such results are excellent proof that cannabinoids cannot be blindly taken as an anti-cancer agent in every case[221- 360]. Careful analysis of their various cellular effects, considering the molecular subtypes of cancer and possible drug interactions, must be done. Otherwise, they may cause more harm than benefit to struggling cancer patients [221- 360]. Overall, there is an extensive need for more well-designed, high-quality clinical trials regarding the anti-cancer and palliative properties of cannabinoids [221- 360]. However, as cannabis is classified as a Schedule I drug, it is difficult to conduct multicenter trials, regulatory hurdles delay such trials, and access to research-grade cannabis medications that match the products used by the cancer patients may be limited. All these factors affect cannabis research and data efficacy[221- 360].

Cannabis and cannabinoids hold big promise for cancer therapy [221- 360]. However, there is a need to understand more about the role of ECS in normal human physiology and malignant transformations [221- 360]. All three components of ECS are typically upregulated in cancers, but addition of cannabinoids, over-expression, or sometimes downregulation of CB1/CB2 receptors actually inhibits the cancer growth [221- 360]. Molecular mechanisms of ECS regulation and anti-cancer properties of cannabis also need to be clarified [221- 360]. However, we need more data on human consumption of cannabis, from case reports to clinical trials. Moreover, we need to know how cannabinoids interact with these drugs [221- 360].

15 Conclusions

Cervical cancer is one of the leading causes of cancer death among females worldwide and its behavior epidemiologically likes a venereal disease of low infectiousness. Early age at first intercourse and multiple sexual partners have been shown to exert strong effects on risk. The wide differences in the incidence among different countries also influenced by the introduction of screening. Therefore, society-based preventive and control measures, screening activities and HPV vaccination are recommended. Cervical cancer screening methods have evolved from cell morphology observation to molecular testing. High-risk HPV genotyping and liquid-based cytology are common methods which have been widely recommended and used worldwide. In future, accurate, cheap, fast and easy-to-use methods would be more popular. Artificial intelligence also shows to be promising in cervical cancer screening by integrating image recognition with big data technology. Therefore, HPV immunization programme is the best ideal solution for the eradication of cervical cancer.

The disease burden of cervical cancer has decreased significantly in developed countries and regions in last decades. However, it is still serious in less developed countries and regions, and effective preventive measures in these areas still face serious challenges. At present, there are various available prevention and control measures that are cost-effective and scientific evidence-based to meet the needs of areas with different economic levels. It is gratifying to note that the globe has achieved a strategic consensus on the elimination of cervical cancer and also has developed and released the global strategy to accelerate the elimination of cervical cancer. Although the global elimination of cervical cancer has a long way to go. It is believed that through large-scale continuous promotion and widely use of existing effective prevention and control measures, cervical cancer will become the first cancer eliminated by human beings.

However, these hypotheses required experimental validation of phytocannabinoids in controlling cervical cancer. In addition, subsequent *in vitro* and *in vivo* experiments are needed to elucidate their efficacy against cancer. However, much of the evidence comes from animal and *in vitro* studies and overall clinical Evidence-Based Complementary and Alternative Medicine evidence to support these herbal interventions remains weak and lacking. Furthermore, there are many experimental issues and data presented is not enough for the scientific validation. The treatment durations in the existing trials are also of concern. This uncertainty is mainly caused by methodological limitations such as poor study design, relatively small sample sizes, inappropriate outcome measures and primary and secondary end-point selection, and invalid statistical analysis. Future epidemiological and clinical studies are required to further assess the benefits of herbal medicines for the prevention of cancer. In addition, preclinical and human clinical trial evaluations of cannabis for cervical cancer treatment have not specifically been conducted. Therefore, further investigations of more human clinical trials data are warranted.

According to the recently published prospective observational study showed that cannabis use significantly shortens the time to tumor progression and overall survival of cancer patients. This study illustrated that cannabis use, in this case via modulation of the immune system, can lead to negative and thus life-threatening effects for cancer patients. In addition, a retrospective observational study showed a reduction in the response rate to nivolumab, although the addition of cannabis here had no effect on progression-free survival or overall survival. However, it is worth noting that the administration of cannabinoids in these studies conducted in relatively small patient groups was through the consumption of cannabis oil or smoked/inhaled cannabis, and in many cases the cannabis products were also changed during the course of the study. On the other hand, these data are counterbalanced by an overwhelming number of studies that clearly showed that activation of the EC system is an important factor in tumour defense and thus could serve as a promising target for pharmacological anticancer interventions. The property of cannabinoids, in particular, to induce inhibition of tumor growth and spread at multiple levels of tumor progression argues for the use of these substances as an add-on option in tumor treatment. However, it should also be noted that research into the efficacy, dosage and drug safety of cannabinoids in tumor therapy still has a long way to go, especially with regard to clinical trials to be conducted, through which alone the benefits and advantages for cancer patients but also possible risks can be defined.

There are also controversial data regarding the cannabinoid's action on cancer cells. Such results are excellent proof that cannabinoids cannot be blindly taken as an anti-cancer agent in every case. Careful analysis of their various cellular effects, considering the molecular subtypes of cancer and possible drug interactions, must be done. Otherwise, they may cause more harm than benefit to struggling cancer patients. Overall, there is an extensive need for more well-designed, high-quality clinical trials regarding the anti-cancer and palliative properties of cannabinoids. However, the use of cannabis can affect drug metabolism and traditional cancer treatment and have a negative impact on immunotherapy.

Finally, there is a deep gap between laboratory scale research, clinical scale and even commercialization. Most of the experiments were conducted on animal model. However, some of the animal model experiments results showed failure

in human clinical trials in case of cancer. This would be the biggest barrier for the commercialization of plant material for cancer treatment.

Compliance with ethical standards

Acknowledgments

We would like to thank and acknowledge, Karen Viviana Castaño Coronado, Chief Communication Officer (CCO) and CO-Founder of LAIHA (Latin American Industrial Hemp Association), and CEO- CANNACONS, Bogota, D.C., Capital District, Colombia for thoughtful discussions, critical comments, supporting, promoting, encouraging and appreciating this research work. We also thank all the members of LAIHA for supporting and encouraging this research work.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Bobdey S, Sathwara J, Jain A, Balasubramaniam G. Burden of cervical cancer and role of screening in India. Indian J. Med Paediatr Oncol. 2016, 37:278-85.

[2] Burmeister CA, Khan SF, Schafer G. et al. Cervical cancer therapies: Current challenges and future perspectives. Tumour Virus Research. 2022, 13: 200238.

[3] Burd EM. Human Papillomavirus and Cervical Cancer. CLINICAL MICROBIOLOGY REVIEWS. 2003, 16 (1):1–17.

[4] Kojalo U, Tisler A, Parna K. An overview of cervical cancer epidemiology and prevention in the Baltic States. BMC Public Health. 2023, 23:660. https://doi.org/10.1186/s12889-023-15524-y.

[5] Zur Hausen H, Papillomaviruses in the causation of human cancers - A brief historical account, Virology. 2009. https://doi.org/10.1016/j. virol.2008.11.046.

[6] Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC, Human papillomavirus and cervical cancer, Lancet. 2013, https://doi.org/10.1016/S0140-6736(13) 60022-7.

[7] Zhang S, Xu H, Zhang L, Qiao Y. Cervical cancer: Epidemiology, risk factors and screening. Chinese Journal of Cancer Research. 2020, 32 (6): 720-728.

[8] Frazer IH, Cox, J. Finding a vaccine for human papillomavirus. Lancet. 2006, 367:2058–2059.

[9] Terzic M, Makhadiyeva D, Bila J, Andjic M, Dotlic J, Aimagambetova G, Sarria-Santamera A, Laganà AS, Chiantera V, Vukovic I, Kocijancic Belovic D, Aksam S, Bapayeva G, Terzic S. Reproductive and Obstetric Outcomes after Fertility-Sparing Treatments for Cervical Cancer: Current Approach and Future Directions. J Clin Med. 2023, 30:12(7):2614.

[10] **Bedell SL**, Goldstein LS, Goldstein AR, et al. Cervical Cancer Screening: Past, Present, and Future. Sex Med Rev. 2020, 8:28e37.

[11] Can cervical cancer cause infertility? | Prof Andreas Obermair » Professor Andreas Obermair. 2024.

[12] Sathishkumar K, Sankarapillai J et al. Survival of patients with cervical cancer in India – findings from 11 population based cancer registries under National Cancer Registry Programme. The Lancet. 2023.

[13] Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. Indian J. Med Res. 2022, 156: 598-607.

[14] Ratner M, Ian Frazer. Nat Biotechnol. 2007, **25**: 1377.

[15] Cervical Cancer in India (prescriptec.org). 2023.

[16] NDTV Report: Over 3.4 Lakh Cervical Cancer Cases In India In 2023: Parliament Informed. 2nd Februarly 2024. News Press Trust of India. 2024.

[17] Frazer IH. The HPV Vaccine Story. ACS Pharmacol Transl Sci. 2019, 29:2(3):210-212.

[18] Tewari KS, Monk BJ. Evidence-based treatment paradigms for management of invasive cervical carcinoma. J. Clin Oncol. 2019, 37:2472-2489.

[19] All about cervical cancer vaccination that got special push in Budget 2024 - India Today.

[20] Budget 2024 | Government of India to focus on vaccination against cervical cancer - The Hindu

[21] Govt of India to focus on vaccination against cervical cancer, announces Finance Minister Nirmala Sitharaman Finance Minister Nirmala Sitharaman lays down government's plans for the health sector in the 2024 Interim Budget. February 01, 2024 12:08 pm | Updated February 02, 2024 06:05 pm IST.

[22] Get Screened - Screening For Life | Screening For Life. 2023.

[23] Cervical Cancer Symptoms - NCI. 2023.

[24] Cervical Cancer (indiancancersociety.org) 2023.

[25] Using Cannabis for Cervical Cancer: What the Current Research Says (leafwell.com). 2024.

[26] Cannabis in the Fight Against Cervical Cancer - MedWell Health and Wellness Centers. 2023.

[27] CBD for Cervical Cancer: Research, Dosage, Side Effects & More (mydosage.com) 2023.

[28] CBD for Cervical Cancer: Research, Dosage, Side Effects & More (mydosage.com) 2023.

[29] Easing the Cervical Cancer Disease Burden In India | Think Global Health. 2023.

[30] Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: Follow-up of four European randomised controlled trials. Lancet. 2014, 383:524–32.

[31] Mumba JM, Kasonka L, Owiti OB, et al. Cervical cancer diagnosis and treatment delays in the developing world: Evidence from a hospital-based study in Zambia. Gynecol Oncol Rep. 2021, 37:100784.

[32] Cohen PA, Jhingran A, Oaknin A, et al. Cervical cancer. Lancet. 2019, 393:169-82.

[33] Chen W, Zhang X, Molijn A, et al. Human papillomavirus type-distribution in cervical cancer in China: the importance of HPV 16 and 18. Cancer Causes Control. 2009, 20:1705-13.

[34] Harari A, Chen Z, Burk RD. Human papillomavirus genomics: past, present and future. Curr Probl Dermatol. 2014, 45:1-18.

[35] Castle PE, Porras C, Quint WG, et al. Comparison of two PCR-based human papillomavirus genotyping methods. J. Clin Microbiol. 2008, 46:3437-45.

[36] Arbyn M, Verdoodt F, Snijders PJ, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. Lancet Oncol 2014, 15:172-83.

[37] Bao H, Bi H, Zhang X, et al. Artificial intelligence assisted cytology for detection of cervical intraepithelial neoplasia or invasive cancer: A multicenter, clinical-based, observational study. Gynecol Oncol. 2020, 159:171-8.

[38] Poljak M, Oštrbenk Valenčak A, Gimpelj Domjanič G, et al. Commercially available molecular tests for human papillomaviruses: a global overview. Clin Microbiol Infect. 2020, 26:1144-50.

[39] Bao H, Sun X, Zhang Y, et al. The artificial intelligence-assisted cytology diagnostic system in large-scale cervical cancer screening: A population based cohort study of 0.7 million women. Cancer Med. 2020, 9:6896-906.

[40] Clarke MA, Wentzensen N, Mirabello L, et al. Human papillomavirus DNA methylation as a potential biomarker for cervical cancer. Cancer Epidemiol Biomarkers Prev. 2012, 21:2125-37.

[41] Zhao FH, Lin MJ, Chen F, et al. Performance of high-risk human papillomavirus DNA testing as a primary screen for cervical cancer: a pooled analysis of individual patient data from 17 population-based studies from China. Lancet Oncol. 2010, 11:1160-71.

[42] Bruni L, Diaz M, Castellsagué X, et al. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J. Infect Dis. 2010, 202:1789-99.

[43] Resnick RM, Cornelissen MT, Wright DK, et al. Detection and typing of human papillomavirus in archival cervical cancer specimens by DNA amplification with consensus primers. J. Natl Cancer Inst. 1990, 82:1477-84.

[44] Sankaranarayanan R, Wesley RS, editors. 2003. A Practical Manual on Visual Screening for Cervical Neoplasia IARC Technical Publication No. 41.

[45] **Sankaranarayanan** R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. HPV screening for cervical cancer in rural India. N. Engl J. Med. 2009, 360:1385–94.

[46] Remschmidt C, Kaufmann AM, Hagemann I, et al. Risk factors for cervical human papillomavirus infection and high-grade intraepithelial lesion in women aged 20 to 31 years in Germany. Int J. Gynecol Cancer. 2013, 23:519-26.

[47] Prabhu M, Eckert LO. Development of World Health Organization (WHO) recommendations for appropriate clinical trial endpoints for nextgeneration Human Papillomavirus (HPV) vaccines. Papillomavirus Res. 2016, 2:185-9.

[48] Small W Jr., Bacon MA, Bajaj A, et al Cervical cancer: A global health crisis. Cancer. 2017, 123:2404-12.

[49] Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J. Pathol. 1999, 189:12-9.

[50] Garland SM, Giuliano A, Brotherton J, et al. IPVS statement moving towards elimination of cervical cancer as a public health problem. Papillomavirus Res. 2018, 5:87-8.

[51] Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: A cluster-randomised trial. Lancet. 2007, 370:398–406.

[52] Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U. Screening of cervical neoplasia in HIV-infected women in India. AIDS. 2013, 27:607–15.

[53] Sankaranarayanan R, Nessa A, Esmy PO, Dangou JM. Visual inspection methods for cervical cancer prevention. Best Pract Res Clin Obstet Gynaecol. 2012, 26:221–32.

[54] Sankaranarayanan R, Rajkumar R, Esmy P, Fayette J, Shanthakumary S, Frappart L, et al. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. Br. J. Cancer. 2007, 96:738–43.

[55] Dolman L, Sauvaget C, Muwonge R, Sankaranarayanan R. Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: A systematic review. BJOG. 2014, 121:929–42.

[56] Sauvaget C, Fayette JM, Muwonge R, Wesley R, Sankaranarayanan R. Accuracy of visual inspection with acetic acid for cervical cancer screening. Int J. Gynaecol Obstet. 2011**,** 113:14–24.

[57] WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. 2017.

[58] Safaeian M, Kiddugavu M, Gravitt PE, Ssekasanvu J, Murokora D, Sklar M, et al. Comparability of self-collected vaginal swabs and physician-collected cervical swabs for detection of human papillomavirus infections in Rakai, Uganda. Sex Transm Dis. 2007, 34:429–36.

[59] Sahasrabuddhe VV, Bhosale RA, Kavatkar AN, Nagwanshi CA, Joshi SN, Jenkins CA, et al. Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV-infected women in India. Int J. Cancer. 2012, 130:234–40.

[60] **Banerjee D**, Mittal S, Mandal R, Basu P. Screening technologies for cervical cancer: Overview. Cytojournal. 2022, 29, 19:23.

[61] Shikova E, Todorova I, Ganchev G, Kouseva-Dragneva V. Detection and Typing of Human Papillomaviruses by PCR, Biotechnology & Biotechnological Equipment. 2009, 23(1): 877-880.

[62] Qu W, Jiang G, Cruz Y, Chang CJ, Ho GY, Klein RS, Burk RD. PCR detection of human papillomavirus: comparison between MY09/MY11 and GP5+/GP6+ primer systems. J Clin Microbiol. 1997 , 35(6):1304-10.

[63] Prakash P, Patne SC, Singh AK, Kumar M, Mishra MN, Gulati AK. PCR and genotyping for HPV in cervical cancer patients. J. Global Infect Dis. 2016, 8:100-7.

[64] Nayar R, Wilbur DC. The pap test and Bethesda 2014. Acta Cytol. 2015, 59:121–32.

[65] Burmeister CA, Khan SF, Schafer G, Mbatani N, Adams T, Moodley J, Prince S. Cervical cancer therapies: Current challenges and future perspectives. Tumour Virus Research. 2022, 13: 200238.

[66] Brisson M, Drolet M. Global elimination of cervical cancer as a public health problem. Lancet Oncol. 2019, 20(3):319-321.

[67] Symptoms of cervical cancer | Canadian Cancer Society.

[68] Whitlock EP, Vesco KK, Eder M, Lin JS, Senger CA, Burda BU. Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: A systematic review for the U.S. preventive services task force. Ann Intern Med. 2011, 155:687-97.

[69] Pimple SA, Mishra GA. Global strategies for cervical cancer prevention and screening. Minerva Ginecol. 2019, 71(4):313-320.

[70] Chizenga EP, Chandran R, Abrahamse H. Photodynamic therapy of cervical cancer by eradication of cervical cancer cells and cervical cancer stem cells. Oncotarget. 2019, 10: 4380-4396.

[71] Ivanova VA, Verenikina EV, Nikitina VP, et al. Photodynamic therapy for preinvasive cervical cancer. J Clin Oncol. 2020, 38:6035-6035.

[72] Hull R, Mbele M, Makhafola T, et al. Cervical cancer in low and middle-income countries. Oncol Lett. 2020, 20:2058-2074.

[73] McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: A retrospective cohort study. Lancet Oncol. 2008, 9:425–34.

[74] Chao X, Song X, Wu H, You Y, Wu M, Li L. Selection of treatment regimens for recurrent cervical cancer. Front Oncol. 2021, 11:618485.

[75] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J. Clin. 2021, 71:209-249.

[76] Cervical Cancer Screening Every 5 Years OK. Cancer Discov. 2018, 8(10):1204.

[77] Farghaly H, Bourgeois D, Houser PM, Padmanabhan V, Lage JM, Hoda RS. Routine vaginal Pap test is not useful in women status-post hysterectomy for benign disease. Diagn Cytopathol. 2006, 34(9):640-3.

[78] https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/india-has-the-most-cervical-cancer-patients-in-asia. 2023.

[79] Indian Budget 2024: Prescription for cervical cancer vaccine, new medical colleges - The Economic Times (indiatimes.com).

[80] Foran C, Brennan A. Prevention and early detection of cervical cancer in the UK. Br J. Nurs. 2015, 24(10):S22-4, S26, S28-9.

[81] Pierre-Victor D, Stephens DP, Omondi A, Clarke R, Jean-Baptiste N, Madhivanan P. Barriers to HPV Vaccination Among Unvaccinated, Haitian American College Women. Health Equity. 2018, 2(1):90-97.

[82] Manini I, Montomoli E. Epidemiology and prevention of Human Papillomavirus. Ann Ig. 2018, 30(4 Supple 1):28-32.

[83] Ghosh I, Mandal R, Kundu P, Biswas J. Association of Genital Infections Other Than Human Papillomavirus with Pre-Invasive and Invasive Cervical Neoplasia. J Clin Diagn Res. 2016, 10(2):XE01-XE06.

[84] Mendu S, Boukhechba M, Gordon JR, Datta D, Molina E, Arroyo G, Proctor SK, Wells KJ, Barnes LE. Design of a Culturally-Informed Virtual Human for Educating Hispanic Women about Cervical Cancer. Int Conf Pervasive Comput Technol Healthc. 2018 May, 2018:360-366.

[85] Zhang S, Xu H, Zhang L, Qiao Y. Cervical cancer: Epidemiology, risk factors and screening. Chin J Cancer Res. 2020 , 31, 32(6):720-728.

[86] Hutchcraft ML, Miller RW. Bleeding from Gynecologic Malignancies. Obstet Gynecol Clin North Am. 2022 , 49(3):607-622.

[87] Burness JV, Schroeder JM, Warren JB. Cervical Colposcopy: Indications and Risk Assessment. Am Fam Physician. 2020, 01, 102(1):39-48.

[88] Querleu D, Morrow CP. Classification of radical hysterectomy. Lancet Oncol. 2008 , 9(3):297-303.

[89] Why India Could Miss 2030 Target To Eliminate Cervical Cancer (indiaspend.com). 2023.

[90] Cervical Cancer in India (prescriptec.org).

[91] https://www.livemint.com/science/health/india-records-highest-number-of-cervical-cancer-cases-in-asia-study-116. 2023.

[92] India has the most cervical cancer patients in Asia: Lancet - The Economic Times (indiatimes.com). 2023.

[93] Pap Test | Johns Hopkins Medicine. 2024.

[94] Arbyn M, Ronco G, Anttila A, Meijer CJ, Poljak M, Ogilvie G, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine. 2012, 30(Suppl 5):F88–99.

[95] Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: A systematic review. Ann Intern Med. 2000, 132:810–9.

[96] Cuzick J, Myers O, Hunt WC, Robertson M, Joste NE, Castle PE, et al. A population-based evaluation of cervical screening in the United States: 2008-2011. Cancer Epidemiol Biomarkers Prev. 2014, **23**:765–73.

[97] Habtemariam LW, Zewde ET, Simegn GL. Cervix Type and Cervical Cancer Classification System Using Deep Learning Techniques. Med Devices (Auckl). 2022, 15:163-176.

[98] Kuhn L, Denny L. The time is now to implement HPV testing for primary screening in low resource settings. Prev Med. 2017, 98:42-44.

[99] Rauh-Hain JA, Melamed A, Schaps D, Bregar AJ, Spencer R, Schorge JO, Rice LW, Del Carmen MG. Racial and ethnic disparities over time in the treatment and mortality of women with gynecological malignancies. Gynecol Oncol. 2018 , 149(1):4-11.

[100] Wang X, Huang X, Zhang Y. Involvement of Human Papillomaviruses in cervical cancer. Front Microbiol. 2018, 9:2896.

[101] Salib MY, Russell JHB, Stewart VR, Sudderuddin SA, Barwick TD, Rockall AG, Bharwani N. 2018 FIGO Staging Classification for Cervical Cancer: Added Benefits of Imaging. Radiographics. 2020 ; 40(6):1807-1822.

[102] Castellano T, Ding K, Moore KN, Landrum LM. Simple Hysterectomy for Cervical Cancer: Risk Factors for Failed Screening and Deviation From Screening Guidelines. J Low Genit Tract Dis. 2019, 23(2):124-128.9.

[103] Chen HH, Meng WY, Li RZ, Wang QY, Wang YW, Pan HD, Yan PY, Wu QB, Liu L, Yao XJ, Kang M, Leung EL. Potential prognostic factors in progression-free survival for patients with cervical cancer. BMC Cancer. 2021, 10, 21(1):531.

[104] Quinn BA, Deng X, Colton A, Bandyopadhyay D, Carter JS, Fields EC. Increasing age predicts poor cervical cancer prognosis with subsequent effect on treatment and overall survival. Brachytherapy. 2019 , 18(1):29-37.

[105] Malabadi RB, Kolkar KP, Acharya M, Divakar MS, Chalannavar RK. Diabetes mellitus: Role of Botanical Pharmacy. International Journal of Innovation Scientific Research and Review. 2022, 4(3): 2536-2541.

[106] Malabadi RB, Kolkar KP, Acharya M, Chalannavar RK. METFORMIN: A novel Antidiabetic drug of Botanical origin. International Journal of Innovation Scientific Research and Review. 2022, 4(2): 2411-2415.

[107] Malabadi RB, Kolkar KP, Chalannavar RK. Natural plant gum exudates and mucilages: Pharmaceutical updates. International Journal of Innovation Scientific Research and Review. 2021, 3(10): 1897-1912.

[108] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Role of botanical essential oils as a therapy for controlling coronavirus (SARS-CoV-2) disease (Covid-19). International Journal of Research and Scientific Innovations. 2021, 8(4): 105-118 (DOI: dx.doi.org/10.51244/IJRSI.2021.8407).

[109] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Camphor tree, Cinnamomum camphora (L.), Ethnobotany, and pharmacological updates. Biomedicine. 2021, 41 (2): 181-184 (DOI: https://doi.org/10.51248/.v41i2.779).

[110] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. An age old Botanical weapon for Herbal therapy: Camphor tree, Cinnamomum camphora. International Journal of Innovation Scientific Research and Review. 2021, 3(7): 1518-1523.

[111] Malabadi RB. In vitro propagation of spiral ginger (Costus speciosus) (Koen.) Sm. Indian Journal of Genetics and Plant breeding. 2002, 62(3): 277-278.

[112] Malabadi RB, Nataraja K. In vitro plant regeneration in Clitoria ternatea. Journal of Medicinal and Aromatic Plant Sciences. 2002, 24: 733-737.

[113] Fridlender M, Kapulnik Y, Koltai H. Plant derived substances with anti-cancer activity: from folklore to practice. Front. Plant Sci. 2015, 6:799. doi: 10.3389/fpls.2015.00799.

[114] Malabadi RB, Vijayakumar S. Assessment of antidermatophytic activity of some medicinal plants. Journal of Phytological Research. 2005, 18 (1):103-106.

[115] Malabadi RB. Antibacterial activity in the rhizome extract of Costus speciosus (Koen.). Journal of Phytological Research. 2005, 18 (1): 83-85.

[116] Malabadi RB, Mulgund GS, Nataraja K. Screening of antibacterial activity in the extracts of Clitoria ternatea (Linn.). Journal of Medicinal and Aromatic Plant Sciences. 2005, 27: 26-29.

[117] Acharya M, Divakar MS, Malabadi RB, Chalannavar RK. Ethnobotanical survey of medicinal plants used by the "Nalike" community in the Bantwala taluk of Dakshina Kannada district, Karnataka, India. Plant Science Today. 2022, 9(2): 461-468. (Early Access). https://doi.org/10.14719/ pst.1470.

[118] Malabadi RB, Mulgund GS, Nataraja K. Ethanobotanical survey of medicinal plants of Belgaum district, Karnataka, India. Journal of Medicinal and Aromatic Plant Sciences. 2007, 29 (2):70-77.

[119] Malabadi RB, Vijayakumar S. Assessment of antifungal activity of some medicinal plants. International Journal of Pharmacology. 2007, 3 (6):499-504.

[120] Malabadi RB, Vijaykumar S. Evaluation of antifungal property of medicinal plants. Journal of Phytological Research. 2008, 21(1):139-142.

[121] Malabadi RB, Mulgund GS, Nataraja K. Evaluation of antifungal activity of selected medicinal plants. Journal of Medicinal and Aromatic Plant Sciences. 2010, 32(1):42-45.

[122] Malabadi RB, Meti NT, Chalannavar RK. Role of herbal medicine for controlling coronavirus (SARS-CoV-2) disease (COVID-19). International Journal of Research and Scientific Innovations. 2021a, 8(2): 135-165.

[123] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Traditional herbal folk medicine used for controlling coronavirus (SARS CoV-2) disease (Covid-19). International Journal of Innovation Scientific Research and Review. 2021b, 3 (7): 1507-1517.

[124] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Outbreak of Coronavirus (SARS-CoV-2) Delta variant (B.1.617.2) and Delta Plus (AY.1) with fungal infections, Mucormycosis: Herbal medicine treatment. International Journal of Research and Scientific Innovations. 2021c, 8(6): 59-70.

[125] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Vaccine development for coronavirus (SARS-CoV-2) disease (Covid 19): Lipid nanoparticles. International Journal of Research and Scientific Innovations. 2021d, 8(3): 189-195. 86.

[126] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Triphala: An Indian Ayurvedic herbal formulation for coronavirus (SARSCoV- 2) disease (Covid-19). Int. J. Curr. Res. Biosci. Plant Biol. 2021e, 8(8): 18-30. doi: https://doi.org/10.20546/ijcrbp.2021.808.003.

[127] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Role of plant based hand sanitizers during the recent outbreak of coronavirus (SARS-CoV-2) disease (Covid-19). Significances of Bioengineering & Biosciences. 2021f, 5(1): 458-46.

[128] Malabadi RB, Mulgund GS, Meti NT, Nataraja K, Vijayakumar S. Antibacterial activity of silver nanoparticles synthesized from whole plant extracts of Clitoria ternatea. Research in Pharmacy. 2012, 2(4):11-21.

[129] Malabadi RB, Meti NT, Mulgund GS, Nataraja K. Vijayakumar S. Recent advances in plant derived vaccine antigens against human infectious diseases. Research in Pharmacy. 2012, 2(2):08-19.

[130] Malabadi RB, Lokare Naik S, Meti NT, Mulgund GS, Nataraja K, Vijayakumar S. Synthesis of silver nanoparticles from in vitro derived plants and callus cultures of Clitoria ternatea, Evaluation of antimicrobial activity. Research in Biotechnology. 2012, 3(5): 26-38.

[131] Malabadi RB, Chalannavar RK, Meti NT, Mulgund GS, Nataraja K, Vijayakumar S. Synthesis of antimicrobial silver nanoparticles by callus cultures and in vitro derived plants of Catharanthus roseus. Research in Pharmacy. 2012, 2(6):18- 31.

[132] Malabadi RB, Meti NT, Mulgund GS, Nataraja K, Vijayakumar S. Synthesis of silver anoparticles from in vitro derived plants and callus cultures of Costus speciosus (Koen.): Assessment of antibacterial activity. Research in Plant Biology. 2012, 2(4): 32-42.

[133] Malabadi RB, Chalannavar RK, Meti NT, Gani RS, Vijayakumar S, Mulgund GS, Masti S, Chougale RB, Odhav B, Sowmyashree K, Supriya S, Nityasree BR, Divakar MS. Insulin Plant, Costus speciosus: Ethnobotany and Pharmacological Updates. International Journal of Current Research in Biosciences and Plant Biology. 2016, 3(7):151-161.

[134] Malabadi RB, Chalannavar RK, Meti NT, Vijayakumar S, Mulgund GS, Gani RS, Supriya S, Sowmyashree K, Nityasree BR, Chougale A, Divakar MS. Antidiabetic Plant, Gymnema sylvestre R. Br.,(Madhunashini): Ethnobotany, Phytochemistry and Pharmacological Updates. International Journal of Current Trends in Pharmacobiology and Medical Sciences. 2016, 1(4):1-17.

[135] Malabadi RB, Chalannavar RK, Supriya S, Nityasree BR, Sowmyashree K, Meti NT. Role of botanical drugs in controlling dengue virus disease. International Journal of Research and Scientific Innovations. 2018, 5(7): 134-159.

[136] Malabadi RB, Chalannavar RK. Safed musli (Chlorophytum borivilianum): Ethnobotany, phytochemistry and pharmacological updates. International Journal of Current Research in Biosciences and Plant Biology. 2020, 7(11): 25-31. (DOI: doi.org/10.20546/ijcrbp.2020.711.003).

[137] Malabadi RB, Meti NT, Chalannavar RK. Updates on herbal remedy for kidney stone chronic disease. International Journal of Research and Scientific Innovations. 2021, 8(2):122-134.

[138] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Recent updates on the role of herbal medicine for Alzheimer's disease (Dementia). International Journal of Current Research in Biosciences and Plant Biology. 2021, 8(1): 14-32. (doi: https://doi.org/10.20546/ijcrbp.2020.801.002).

[139] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Recent updates on Leishmaniasis: Kala-Azar outbreak, risk factors and herbal treatment. International Journal of Current Research in Biosciences and Plant Biology. 2021, 8(6): 1-22 (DOI: 10.20546/ijcrbp.2021.806.001).

[140] Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. The iconic Baobab (Adansonia digitata L.): Herbal medicine for controlling coronavirus (SARS-CoV-2) disease (Covid-19). International Journal of Innovation Scientific Research and Review. 2021, 3(8): 1635-1647.

[141] Malabadi RB, Kolkar KP, Acharya M, Chalannavar RK. Constipation-A major health disorder: Role of herbal medicine treatment. International Journal of Innovation Scientific Research and Review. 2022, 4(4): 2634-2645.

[142] Malabadi RB**,** Kolkar KP, Acharya M, Chalannavar RK. Tea (Camellia sinensis): Phytochemistry and Health Benefits- Tea Cup that Cheers has Tears. International Journal of Innovation Scientific Research and Review. 2022, 4(4): **2**620- 2633.

[143] Elbaz M, Ahirwar D, Xiaoli Z, Zhou X, Lustberg M, Nasser MW, et al. TRPV2 is a novel biomarker and therapeutic target in triple negative breast cancer. Oncotarget. 2016, 9:33459–70.

[144] Nabissi M, Morelli MB, Santoni M, Santoni G. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. Carcinogenesis. 2013, 34:48–57.

[145] Nabissi M, Morelli MB, Offidani M, Amantini C, Gentili S, Soriani A, et al. Cannabinoids synergize with carfilzomib, reducing multiple myeloma cells viability and migration. Oncotarget. 2016, 7:77543–57.

[146] Muthuramalingam MR, Muraleedharan VR. Patterns in the prevalence and wealth-based inequality of cervical cancer screening in India. BMC Women's Health. 2023, 23:337.

[147] Srivastava AN, Misra JS, Srivastava S, Das BC, Gupta S. Cervical cancer screening in rural India: status & current concepts. Indian J. Med Res. 2018, 148(6):687–96.

[148] Thulaseedharan JV, Frie KG, Sankaranarayanan R. Challenges of health promotion and education strategies to prevent cervical cancer in India: a systematic review. J Educ Health Promot. 2019, 29(8):216.

[149] Vora KS, Saiyed S. Cervical cancer screening in India: Need of the hour. Cancer Res Stat Treat 2020, 3:796-7.

[150] Singh M, Jha RP, Shri N, Bhattacharyya K, Patel P, Dhamnetiya D. Secular trends in incidence and mortality of cervical cancer in India and its states, 1990- 2019: data from the Global Burden of Disease 2019 Study. BMC Cancer. 2022, 22:149 https://doi.org/10.1186/s12885-022-09232-w

[151] Bobdey S, Sathwara J, Jain A, Balasubramaniam G. Burden of cervical cancer and role of screening in India. Indian J. Med Paediatr Oncol. 2016, 37:278-85.

[152] Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS, ICMR-NCDIR-NCRP Investigator Group. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Glob Oncol. 2020, 6:1063–75.

[153] Sreedevi A, Javed R, Dinesh A. Epidemiology of cervical cancer with special focus on India. Int J Womens Health. 2015, 16(7):405–14.

[154] Krishnamoorthy Y, Ganesh K, Sakthivel M. Prevalence and determinants of breast and cervical cancer screening among women aged between 30 and 49 years in India: Secondary data analysis of National Family Health Survey - 4. Indian J. Cancer. 2022, 59(1):54–64.

[155] Abreu et al.: A review of methods for detect human Papillomavirus infection. Virology Journal. 2012, 9:262.

[156] Morelli MB, Offidani M, Alesiani F, Discepoli G, Liberati S, Olivieri A, et al. The effects of cannabidiol and its synergism with bortezomib in multiple myeloma cell lines. A role for transient receptor potential vanilloid type-2. Int J. Cancer. 2014, 134:2534–46.

[157] QU W, JIANG G, CRUZ Y et al. PCR Detection of Human Papillomavirus: Comparison etween MY09/MY11 and GP51/GP61 Primer Systems. JOURNAL OF CLINICAL MICROBIOLOGY. 1997, 35(6): 1304–1310.

[158] Das BC, Sharma JK, Gopalkrishna V, Das DK, Singh V, Gissmann L, et al. A high frequency of human papillomavirus DNA sequences in cervical carcinomas of Indian women as revealed by Southern blot hybridization and polymerase chain reaction. J Med Virol. 1992a, 36(4):239–45.

[159] Srinivasan S, Johari V, Jesani A. Cervical cancer screening in India. Ethics dumping. Berlin: Springer, 2018. p. 33e48.

[160] Global Burden of Disease Collaborative Network. Global burden of disease study 2019 (GBD 2019) results. Seattle: Institute for Health Metrics and Evaluation (IHME), 2020.

[161] Dhillon PK, Mathur P, Nandakumar A, Fitzmaurice C, Kumar GA, Mehrotra R, et al. The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990–2016. Lancet Oncol. 2018, 19(10):1289–306.

[162] Murthy NS, Chaudhry K, Saxena S. Trends in cervical cancer incidence– Indian scenario. Eur J Cancer Prev. 2005, 14(6):513–8..

[163] Dhillon PK, Yeole BB, Dikshit R, Kurkure AP, Bray F. Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976–2005: an age–period–cohort analysis. Br J. Cancer. 2011, 105(5):723–30.

[164] Balasubramaniam G, Gaidhani RH, Khan A, Saoba S, Mahantshetty U, Maheshwari A. Survival rate of cervical cancer from a study conducted in India. Indian J Med Sci. 2021, 73(2):203-11.

[165] Nandakumar A, Ramnath T, Chaturvedi M. The magnitude of cancer cervix in India. Indian J Med Res. 2009, 130(3):219–21.

[166] Das BC, Gopalkrishna V, Sharma JK, Roy M, Luthra UK. Human papillomavirus DNA in urine of women with preneoplastic and neoplastic cervical lesions. Lancet. 1992b, 340(8832):1417–8.

[167] Sureshkumar BT, Shanmughapriya S, Das BC, Natarajaseenivasan K. A population-based study of the prevalence of HPV in three districts of Tamil Nadu, India. Int J Gynecol Obstet. 2015, 129(1):58–61.

[168] Patel KR, Vajaria BN, Begum R, Desai A, Patel JB, Shah FD, et al. Prevalence of high-risk human papillomavirus type 16 and 18 in oral and cervical cancers in population from Gujarat, West India. J Oral Pathol Med. 2014, 43(4):293–7.

[169] Shrestha IB et al. Awareness of Cervical Cancer, Risk Perception, and Practice of Pap Smear Test among Young Adult Women of Dhulikhel Municipality, Nepal. Hindawi Journal of Cancer Epidemiology. 2023. Volume 2023, Article ID 6859054, 9 pages.

[170] Sathishkumar K, Sankarapillai J et al. Survival of patients with cervical cancer in India – findings from 11 population based cancer registries under National Cancer Registry Programme. The Lancet. 2023. 1-10

[171] Ramamoorthy T, Sathishkumar K, Das P, Lakshminarayana SK, Mathur P. Epidemiology of human papillomavirus related cancers in India: findings from the National Cancer Registry Programme. cancer. 2022, 16:1444.

[172] Ministry of Health and Family Welfare, Government of India. National Programme for prevention & control of cancer, diabetes, cardiovascular diseases & stroke (NPCDCS): National Health Mission, 2022 [cited 2022 September 24].

[173] Jayant K, Sankaranarayanan R, Thorat RV, et al. Improved survival of cervical cancer patients in a screened population in rural India. Asian Pac J Cancer Prev. 2016, 17(11):4837–4844.

[174] Health technology assessment of strategies for cervical cancer screening in India. School of Public Health Postgraduate Institute of Medical Education and Research Chandigarh (India).

[175] Mehrotra R, Yadav K. Cervical cancer: formulation and implementation of Govt of India guidelines for screening and management. Indian J Gynecol Oncol. 2022, 20(1):4.

[176] Swaminathan R, Rama R, Shanta V. Lack of active follow-up of cancer patients in Chennai, India: implications for populationbased survival estimates. Bull World Health Organ. 2008, 86: 509–515.

[177] Kulothungan V, Sathishkumar K, Leburu S, et al. Burden of cancers in India: estimates of cancer crude incidence, YLLs, YLDs and DALYs for 2021 and 2025 based on National Cancer Registry Program. BMC Cancer. 2022, 22:527.

[178] ICMR-National Centre for Disease Informatics and Research (ICMR-NCDIR). Report of National Cancer Registry Programme 2020. Bengaluru (India). ICMR-NCDIR, 2020.

[179] Bagchi S. India launches a plan for the national cancer screening program. BMJ. 2016, 17(355): i5574

[180] Mehrotra R, Yadav K. Cervical Cancer: Formulation and Implementation of Govt of India Guidelines for Screening and Management. Indian Journal of Gynecologic Oncology. 2022, 20:4 https://doi.org/10.1007/s40944-021-00602-z.

[181] India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990–2016. Lancet Oncol. 2018, 19(10):1289–1306. https://doi.org/10.1016/S1470- 2045(18)30447-9. Epub 2018 Sep 12. Erratum in: Lancet Oncol. 2018 Oct 3.

[182] Kaur P, Mehrotra R, Rengaswamy S, Kaur T, Hariprasad R, Mehendale SM, Rajaraman P, Rath GK, Bhatla N, Krishnan S, Nayyar A, Swaminathan S. Human papillomavirus vaccine for cancer cervix prevention: Rationale and recommendations for implementation in India. Indian J. Med Res. 2017, 146:153–7.5

[183] Chatterjee P: Delhi first state to launch the HPV vaccine as public health program in schools. http://indianexpress.com/article/cities/ delhi/delhi-first-state-to-launch-hpv-vaccine-as-public-healthprogramme-in-schools/. Accessed 29 April 2021.6

[184] Maggi R. Assessing breast and cervical cancer in India: A literature review, 2018.789

[185] Hariprasad R, Babu R, Arora S, Mehrotra R. Capacity building in cancer screening using ECHO (extension for community healthcare outcomes): innovative and cost-effective model. J Glob Oncol. 2018, 4(Supplement 2):160s–160s.

[186] Dhanasekaran K, Verma C, Kumar V, Hariprasad R, Gupta R, Gupta S, Mehrotra R. Cervical cancer screening services at tertiary healthcare facility: an alternative approach. Asian Pac J Cancer Prev. 2019, 20(4):1265–9.

[187] Dhillon PK, Hallowell B, Agrawal S, Ghosh A, Yadav A, Van Dyne E, Senkomago V, Patel SA, Saraf D, Hariprasad R, Dumka N, Mehrotra R, Saraiya M. Is India's Public health care system prepared for cervical cancer screening: evaluating facility readiness from the fourth round of the district level household and facility survey (DLHS-4). Prev Med. 2020.

[188] Gupta R, Gupta S, Mehrotra R, Sodhani P. Cervical cancer screening in resource-constrained countries: current status and future directions. Asian Pac J. Cancer Prev. 2017.

[189] Kedar A, Kannan R, Mehrotra R, Hariprasad R. Implementation of population-based cancer screening program in a pilot study from India: views from health personnel. Indian J Community Med. 2019, 44(1):68–70.

[190] Mishra R. An epidemiological study of cervical and breast screening in India: district-level analysis. BMC Womens Health. 2020, 20:225.

[191] Hariprasad R, Tulsyan S, Babu R, Dhanasekaran K, Thakur N, Hussain S, Tripathi R, Sreenivas V, Sharma S, Sriram L, Singh S, Mehrotra R. Evaluation of a chip-based, point-of-care, portable, real-time micro PCR analyzer for the detection of high-risk human papillomavirus in uterine cervix in India. JCO J Glob Oncol. 2020.

[192] Nilima N, Mani K, Kaushik S, Rai SN. Cervical Cancer Screening and Associated Barriers amongWomen in India: A Generalized Structural Equation Modeling Approach. Cancers 2022, 14: 3076. https://doi.org/10.3390/cancers14133076.

[193] Devarapalli P, Labani S, Nagarjuna N, Panchal P, Asthana S. Barriers affecting uptake of cervical cancer screening in low and middle income countries: A systematic review. Indian J. Cancer. 2018, 55: 318.

[194] Nene B, Jayant K, Arrossi S, Shastri S, Budukh A, Hingmire S, Muwonge R, Malvi S, Dinshaw K, Sankaranarayanan R. Determinants of women's participation in cervical cancer screening trial, Maharashtra, India. Bull. Word Health Organ. 2007, 85: 264–272.

[195] Kaur S, Sharma LM, Mishra V, et al. Challenges in Cervical Cancer Prevention: Real-World Scenario in India. South Asian J. Cancer. 2023, 12(1):9–16.

[196] Bhatla N, Singhal S, Saraiya U, , et al, (on behalf of FOGSI Expert group). Screening and management of preinvasive lesions of the cervix: Good clinical practice recommendations from the Federation of Obstetrics and Gynaecologic Societies of India (FOGSI). J. Obstet Gynaecol Res. 2020, 46(02):201–214.

[197] Vidhubala E, Niraimathi K, Shewade HD, Mahadevan S. Cervical cancer care continuum in South India: evidence from a community- based screening program. J. Epidemiol Glob Health. 2020, 10 (01):28–35.

[198] Sankaranarayanan R, Nene BM, Dinshaw KA, et al, Osmanabad District Cervical Screening Study Group. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. Int J. Cancer. 2005, 116(04):617–623.

[199] Parikh PM, MaheshwariU, KrishnaVM, et al.Robust protective effect of COVID-19 vaccination in India-results of survey in the midst of pandemic's second wave. South Asian J. Cancer. 2021, 10(01):28–31.

[200] Patil KM, Sawant SS. Awareness of cervical cancer among women aged 18-25 years in rural areas. Int J. Community Med Public Health. 2023, 10:2784-9.

[201] Saha A, Chaudhury AN, Bhowmik P, Chatterjee R. Awareness of cervical cancer among female students of premier colleges in Kolkata, India. Asian Pac J. Cancer Prev. 2010, 11(4):1085-90.

[202] Chawla B, Taneja N, Awasthi AA, Kaur KN, Janardhanan R. Knowledge, attitude, and practice on screening toward cervical cancer among health professionals in India- a review. Women's Health. 2021, 17:17455065211017066.

[203] Roy B, Tang TS. Cervical cancer screening in Kolkata, India: beliefs and predictors of cervical cancer screening among women attending a women's health clinic in Kolkata, India. J. Cancer Educ. 2008, 23(4):253-9.

[204] Rashid S, Labani S, Das BC. Knowledge, awareness and attitude on HPV, HPV vaccine and cervical cancer among the college students in India. PloS One. 2016, 11(11):e0166713.

[205] Bobdey S, Sathwara J, Jain A, Balasubramaniam G. Burden of cervical cancer and role of screening in India. Indian J Med Paediatr Oncol. 2016, 37(4):278-85.

[206] Siddharthar J, Rajkumar B, Deivasigamani K. Knowledge, awareness and prevention of cervical cancer among women attending a tertiary care hospital in Puducherry, India. J Clin Diagn Res. 2014, 8(6):OC01-3.

[207] Aswathy S, Quereshi MA, Kurian B, Leelamoni K. Cervical cancer screening: Current knowledge and practice among women in a rural population of Kerala, India. Indian J. Med Res. 2012, 136(2):205-10.

[208] Prabhu M, Eckert LO. Development of World Health Organization (WHO) recommendations for appropriate clinical trial endpoints for next-generation Human Papillomavirus (HPV) vaccines. Papillomavirus Res. 2016, 2:185-9.

[209] Small W Jr., Bacon MA, Bajaj A, et al Cervical cancer: A global health crisis. Cancer. 2017, 123:2404-12.

[210] Zhao FH, Lewkowitz AK, Hu SY, et al. Prevalence of human papillomavirus and cervical intraepithelial neoplasia in China: A pooled analysis of 17 population-based studies. Int J. Cancer. 2012, 131:2929-38.

[211] Yuan Y, Cai X, Shen F, et al. HPV post-infection microenvironment and cervical cancer. Cancer Lett. 2021, 497:243-54.

[212] Prakash P, Patne SC, Singh AK, Kumar M, Mishra MN, Gulati AK. PCR and genotyping for HPV in cervical cancer patients. J. Global Infect Dis. 2016, 8:100-7.

[213] Bruggmann D, Quinkert-Schmolke K, Jaque JM, Quarcoo D, Bohlmann MK, Klingelho¨fer D, et al. Global cervical cancer research: A scientometric density equalizing mapping and socioeconomic analysis. PLoS ONE. 2022, 17(1): e0261503.

[214] Graham SV. Human papillomavirus: gene expression, regulation and prospects for novel diagnostic methods and antiviral therapies. Future Microbiol. 2010 , 5(10): 1493–1506.

[215] Singh D, Vignat J et. el., Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health. 2023, 11: e197–206.

[216] WHO. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Health Organization, 2020.

[217] Frazer I. NATURE BIOTECHNOLOGY. 2007, 25: 12.

[218] Frazer I. The HPV Vaccine Story. ACS Pharmacol. Transl. Sci. 2019, 2: 210−212.

[219] Simms KT, Adam Keane et al. Benefits, harms and cost-effectiveness of cervical screening, triage and treatment strategies for women in the general population. Nature Medicine. 2023. https://doi.org/10.1038/s41591-023-02600-4.

[220] Monica A, Mishra R. An epidemiological study of cervical and breast screening in India: district-level analysis. BMC Women's Health. 2020: 20:225.

[221] Lukhele ST, Motadi LR. Cannabidiol rather than Cannabis sativa extracts inhibit cell growth and induce apoptosis in cervical cancer cells. BMC Complement Altern Med. 2016, 16:335.

[222] Cherkasova V, Wang B, ., Gerasymchuk M, Fiselier A, Kovalchuk O, Kovalchuk I. Use of Cannabis and Cannabinoids for Treatment of Cancer. Cancers 2022, 14: 5142. https://doi.org/10.3390/ cancers14205142.

[223] Razlog R, Kruger CA, Abrahamse H. Enhancement of conventional and Photodynamic therapy for Treatment of Cervical Cancer with Cannabidiol. Integrative Cancer Therapies 2022, 21: 1–11.

[224] Hinz B, Ramer R. Cannabinoids as anticancer drugs: Current status of preclinical research. British Journal of Cancer. 2022, 127:1–13. https://doi.org/10.1038/s41416-022-01727-4.

[225] Ligresti A, Moriello AS, Matias I, et al. Anti-tumor activity of plant cannabinoids with the emphasis on the effect of cannabidiol on human breast cancer. J Pharmacol Exp Ther. 2006, 318(3):1375–87.

[226] Alexander A, Smith PF, Rosengren RJ. Cannabinoids in the treatment of cancer. Cancer Lett. 2009, 285:6–12.

[227] Shrivastava A, Kuzontkoski PM, Groopman JE, Prasad A. Cannabidiol induces programmed cell death by coordinating the cross-talk between apoptosis and autophagy. Mol Cancer Ther. 2011, 10(7):1161–72.

[228] Yamaori S, Kushihara M, Yamamoto I, Watanabe K. Characterization of major phytocannabinoids, cannabidiol and cannabinol, as isoform-selective and potent inhibitors of human CYP1 enzymes. Biochem Pharmacol. 2010, 79:1691–8.

[229] Safaraz S, Adhami VM, Syed DN, Afaq, Mukhtar H. Cannabinoids for cancer treatment: Progress and promise. Cancer Res. 2008, 68(2):339–44.

[230] Sharma M, Hudson JB, Adomat H, Guns E, Cox ME. In Vitro Anticancer Activity of Plant-Derived Cannabidiol on Prostate Cancer Cell Line. Pharmacol Pharm. 2014, 5:806–20.

[231] Caffarel MM, Andradas C, Perez-Gomez E, Guzman M, Sanchez C. Cannabinoids: A new hope for breast cancer therapy? Cancer Treat Rev. 2012, 38:911–8.

[232] Romano B, Borrelli F, Pagano E, Cascio MG, Pertwee RG, Izzo AA. Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. Phytomedicine. 2014, 21(5):631–9.

[233] Seltzer ES, Watters AK, MacKenzie D Jr, Granat LM, Zhang D. Cannabidiol (CBD) as a promising anti-cancer drug. Cancers. 2020, 12:3203.

[234] Zhelyazkova M, Kirilov B, Momekov G. The pharmacological basis for application of cannabidiol in cancer chemotherapy. Pharmaciana. 2020, 67:239-252

[235] Ayakannu T, Taylor AH, Willets JM, Konje JC. The evolving role of the endocannabinoid system in gynaecological cancer. Hum Reprod Update. 2015, 21:517-535.

[236] Luschnig P, Schicho R. Cannabinoids in gynecological diseases. Med Cannabis Cannabinoids. 2019, 2:14-21. Velasco G, Sánchez C, Guzmán M. Anticancer mechanisms of cannabinoids. Curr Oncol. 2016, 23:S23-S32.

[237] Dariš B, Tancer Verboten M, Knez Ž, Ferk P. Cannabinoids in cancer treatment: therapeutic potential and legislation. Bosn J. Basic Med Sci. 2019, 19:14-23.

[238] Go YY, Kim SR, Kim DY, Chae SW, Song JJ. Cannabidiol enhances cytotoxicity of anti-cancer drugs in human head and neck squamous cell carcinoma. Sci Rep. 2020, 10:20622.

[239] Taylor AH, Tortolani D, Ayakannu T, Konje JC, Maccarrone M. (endo) cannabinoids and gynaecological cancers. Cancers. 2020, 13:37.

[240] Afrin F, Chi M, Eamens AL, et al. Can hemp help? Low-thc cannabis and non-THC cannabinoids for the treatment of cancer. Cancers. 2020, 12:1033.

[241] Atalay S, Jarocka-Karpowicz I, Skrzydlewska E. Antioxidative and anti-inflammatory properties of Cannabidiol. Antioxidants. 2019, 9:21.

[242] Laezza C, Pagano C, Navarra G, et al. The endocannabinoid system: A target for cancer treatment. Int J. Mol Sci. 2020, 21:747.

[243] Das S, Kaul K, Mishra S, Charan M, Ganju RK. Cannabinoid signaling in cancer. Adv Exp Med Biol. 2019, 1162:51-61.

[244] Burstein S, Salmonsen R. Acylamido analogs of endocannabinoids selectively inhibit cancer cell proliferation. Bioorg Med Chem. 2008, 16:9644-9651.

[245] Hinz B, Ramer R. Anti-tumour actions of cannabinoids. Br. J. Pharmacol. 2019, 176:1384-1394.

[246] Afrin F, Chi M, Eamens AL, et al. Can hemp help? Low-thc cannabis and non-Liu C, Sadat SH, Ebisumoto K, et al. Cannabinoids promote progression of HPV-positive head and neck squamous cell carcinoma via p38 MAPK activation. Clin Cancer Res. 2020, 26:2693-2703.

[247] Stasiłowicz A, Tomala A, Podolak I, Cielecka-Piontek J., Cannabis sativa L. as a natural drug meeting the criteria of a multitarget approach to treatment. Int J. Mol Sci. 2021, 22:778.

[248] Nkune NW, Kruger CA, Abrahamse H. Synthesis of a novel nanobioconjugate for targeted photodynamic therapy of colon cancer enhanced with cannabidiol. Oncotarget. 2022, 13: 156-172.

[249] Mokoena D, P George B, Abrahamse H. Enhancing breast cancer treatment using a combination of cannabidiol and gold nanoparticles for photodynamic therapy. Int J. Mol Sci. 2019, 20:4771.

[250] Ramer R, Merkord J, Rohde H, Hinz B. Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1. Biochem Pharmacol. 2010, 79:955-966.

[251] Ramer R, Hinz B. Inhibition of cancer cell invasion by cannabinoids via increased expression of tissue inhibitor of matrix metalloproteinases-1. J. Natl. Cancer Inst. 2008, 100: 59-69.

[252] Hall W, Christie M, Currow D. Cannabinoids and cancer: causation, remediation, and palliation. Lancet Oncol. 2005, 6:35-42.

[253] Kogan NM. Cannabinoids and cancer. Mini Rev Med Chem. 2005, 5:941- 952.

[254] Bifulco M, Laezza C, Gazzerro P, Pentimalli F. Endocannabinoids as emerging suppressors of angiogenesis and tumor invasion (review). Oncol Rep. 2007, 17:813-816.

[255] Häuser W, Welsch P, Radbruch L, Fisher E, Bell RF, Moore RA. Cannabis-based medicines and medical cannabis for adults with cancer pain. Cochrane Database Syst Rev. 2023, 5: 6(6).

[256] Woerdenbag HJ, Olinga P, Kok EA, Brugman DAP, van Ark UF, Ramcharan AS, Lebbink PW, Hoogwater FJH, Knapen DG, de Groot DJA et al. Potential, Limitations and Risks of Cannabis-Derived Products in Cancer Treatment. Cancers. 2023, 15: 2119. https://doi.org/10.3390/ cancers15072119.

[257] Malabadi RB, Kolkar KP, Chalannavar RK. *Cannabis sativa*: Ethnobotany and phytochemistry. International Journal of Innovation Scientific Research and Review. 2023, 5(2): 3990-3998.

[258] Malabadi RB, Kolkar KP, Acharya M, Chalannavar RK. *Cannabis sativa*: Medicinal plant with 1000 molecules of pharmaceutical interest. International Journal of Innovation Scientific Research and Review. 2023, 5(2):3999-4005.

[259] Malabadi RB, Kolkar KP, Chalannavar RK. *Cannabis sativa*: Industrial hemp (fiber type)- An Ayurvedic traditional herbal medicine. International Journal of Innovation Scientific Research and Review. 2023, 5 (2): 4040-4046.

[260] Malabadi RB, Kolkar KP, Chalannavar RK. Medical *Cannabis sativa* (Marijuana or Drug type), The story of discovery of Δ9-Tetrahydrocannabinol (THC). International Journal of Innovation Scientific Research and Review. 2023, 5 (3):4134-4143.

[261] Malabadi RB, Kolkar KP, Chalannavar RK. Δ9-Tetrahydrocannabinol (THC): The major psychoactive component is of botanical origin. International Journal of Innovation Scientific Research and Review. 2023, 5(3): 4177-4184.

[262] Malabadi RB, Kolkar KP, Chalannavar RK. *Cannabis sativa*: Industrial Hemp (fibre-type)- An emerging opportunity for India. International Journal of Research and Scientific Innovations (IJRSI). 2023, X (3):01-9.

[263] Malabadi RB, Kolkar KP, Chalannavar RK. Industrial *Cannabis sativa* (Hemp fiber type):Hempcrete-A plant based eco-friendly building construction material. International Journal of Research and Innovations in Applied Sciences (IJRIAS). 2023, 8(3): 67-78.

[264] Malabadi RB, Kolkar KP, Chalannavar RK, Lavanya L, Abdi G. *Cannabis sativa*: The difference between Δ8-THC and Δ9-Tetrahydrocannabinol (THC). International Journal of Innovation Scientific Research and Review. 2023, 5(4): 4315-4318.

[265] Malabadi RB, Kolkar KP, Chalannavar RK, Lavanya L, Abdi G. Hemp Helps Human Health: Role of phytocannabinoids. International Journal of Innovation Scientific Research and Review. 2023, 5 (4): 4340-4349.

[266] Malabadi RB, Kolkar KP, Chalannavar RK, Lavanya L, Abdi G. *Cannabis sativa*: Botany, cross pollination and plant breeding problems. International Journal of Research and Innovations in Applied Science (IJRIAS). 2023, 8 (4): 174-190.

[267] Malabadi RB, Kolkar KP, Chalannavar RK, Lavanya L, Abdi G, Baijnath H. Cannabis products contamination problem: A major quality issue. International Journal of Innovation Scientific Research and Review. 2023, 5(4): 4402-4405.

[268] Malabadi RB, Kolkar KP, Chalannavar RK, Lavanya L, Abdi G. Medical *Cannabis sativa* (Marijuana or drug type): Psychoactive molecule, Δ9-Tetrahydrocannabinol (Δ9-THC). International Journal of Research and Innovations in Applied Science. 2023, 8(4): 236-249.

[269] Malabadi RB, Kolkar KP, Chalannavar RK, Mondal M, Lavanya L, Abdi G, Baijnath H. *Cannabis sativa*: Release of volatile organic compounds (VOCs) affecting air quality. International Journal of Research and Innovations in Applied Science (IJRIAS). 2023, 8(5): 23-35.

[270] Malabadi RB, Nethravathi TL, Kolkar KP, Chalannavar RK, Mudigoudra BS, Lavanya L, Abdi G, Baijnath H. *Cannabis sativa*: Applications of Artificial Intelligence and Plant Tissue Culture for Micropropagation. International Journal of Research and Innovations in Applied Science (IJRIAS). 2023, 8(6): 117-142.

[271] Malabadi RB, Nethravathi TL, Kolkar KP, Chalannavar RK, Mudigoudra BS, Abdi G, Baijnath H. *Cannabis sativa*: Applications of Artificial intelligence (AI) in Cannabis industries: In Vitro plant tissue culture. International Journal of Research and Innovations in Applied Science (IJRIAS). 2023, 8 (7): 21-40.

[272] Malabadi RB, Kolkar KP, Brindha C, Chalannavar RK, Abdi G, Baijnath H, Munhoz ANR, Mudigoudra BS. *Cannabis sativa*: Autoflowering and Hybrid Strains. International Journal of Innovation Scientific Research and Review. 2023, 5(7): 4874-4877.

[273] Malabadi RB, Kolkar KP, Chalannavar RK, Munhoz ANR, Abdi G, Baijnath H. *Cannabis sativa*: Dioecious into Monoecious Plants influencing Sex Determination. International Journal of Research and Innovations in Applied Science (IJRIAS). 2023, 8(7): 82-91.

[274] Malabadi RB, Kolkar KP, Chalannavar RK, Abdi G, Munhoz ANR, Baijnath H *Cannabis sativa*: Dengue viral disease-Vector control measures. International Journal of Innovation Scientific Research and Review. 2023, 5(8): 5013-5016.

[275] Malabadi RB, Nethravathi TL, Kolkar KP, Chalannavar RK, Mudigoudra BS, Abdi G, Munhoz ANR, Baijnath H. *Cannabis sativa*: One Plant-One-Medicine for many diseases-Therapeutic Applications. International Journal of Research and Innovations in Applied Science (IJRIAS). 2023, 8(8): 132-174.

[276] Malabadi RB, Nethravathi TL, Kolkar KP, Chalannavar RK, Mudigoudra BS, Abdi G, Munhoz ANR, Baijnath H. Fungal Infection Diseases- Nightmare for Cannabis Industries: Artificial Intelligence Applications International Journal of Research and Innovations in Applied Science (IJRIAS). 2023, 8(8):111-131.

[277] Malabadi RB, Kolkar KP, Chalannavar RK, Baijnath H. *Cannabis sativa*: Difference between Medical Cannabis (marijuana or drug) and Industrial hemp. GSC Biological and Pharmaceutical Sciences. 2023, 377-381.

[278] Malabadi RB, Kolkar KP,Chalannavar RK, Acharya M, Mudigoudra BS. *Cannabis sativa*: 2023-Outbreak and Re-emergence of Nipah virus (NiV) in India: Role of Hemp oil. GSC Biological and Pharmaceutical Sciences. 2023, 25(01):063–077.

[279] Malabadi RB, Kolkar KP, Chalannavar RK, Acharya M, Mudigoudra BS. Industrial *Cannabis sativa*: Hemp-Biochar-Applications and Disadvantages. World Journal of Advanced Research and Reviews. 2023, 20(01): 371–383.

[280] Malabadi RB, Kolkar KP, Chalannavar RK, Vassanthini R, Mudigoudra BS. Industrial *Cannabis sativa*: Hemp plastic-Updates. World Journal of Advanced Research and Reviews. 2023, 20 (01): 715-725.

[281] Malabadi RB, Kolkar KP, Chalannavar RK. Industrial *Cannabis sativa*: Hemp oil for biodiesel production. Magna Scientia Advanced Research and Reviews. 2023, 09(02): 022–035.

[282] Malabadi RB, **Sadiya MR**, Kolkar KP, Chalannavar RK. Biodiesel production via transesterification reaction. Open Access Research Journal of Science and Technology. 2023, 09(02): 010–021.

[283] Malabadi RB, **Sadiya MR**, Kolkar KP, Chalannavar RK. Biodiesel production: An updated review of evidence. International Journal of Biological and Pharmaceutical Sciences Archive. 2023, 06(02): 110–133.

[284] Malabadi RB, Kolkar KP, Chalannavar RK. Industrial *Cannabis sativa*: Hemp oil for biodiesel production. Magna Scientia Advanced Research and Reviews. 2023, 09(02): 022–035.

[285] Malabadi RB, **Sadiya MR**, Kolkar KP, Lavanya L, Chalannavar RK. Quantification of THC levels in different varieties of *Cannabis sativa*. International Journal of Science and Research Archive. 2023, 10(02): 860–873.

[286] Malabadi RB, **Sadiya MR**, Kolkar KP, Chalannavar RK. Pathogenic *Escherichia coli* (*E. coli*) food borne outbreak: Detection methods and controlling measures. Magna Scientia Advanced Research and Reviews, 2024, 10(01), 052–085.

[287] O'Shaughnessy, WB. On the preparations of the Indian hemp or Gunjah, Transactions of the Medical and Physical Society of Bengal 1838–1840, p. 421–61. Reprint in: Mikuriya, TH (Ed.): Marijuana Medical papers 1839–1972, Medi-Comp Press, Oakland, 1973.

[288] Mechoulam R, Shvo Y, Hashish I. The structure of cannabidiol. Tetrahedron. 1963, 19:2073–8.

[289] Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964, 86:1646–7.

[290] Mechoulam R, Gaoni Y. The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Lett. 1967, 12:1109–11.

[291] Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. Science. 1970, 169:611–2.

[292] Schwarz R, Ramer R, Hinz B. Targeting the endocannabinoid system as a potential anticancer approach. Drug Metab Rev. 2018, 50:26–53.

[293] Ligresti A, Bisogno T, Matias I, De Petrocellis L, Cascio MG, Cosenza V, et al. Possible endocannabinoid control of colorectal cancer growth. Gastroenterology. 2003, 125:677–87.

[294] Caffarel MM, Andradas C, Mira E, Pérez-Gómez E, Cerutti C, Moreno-Bueno G, et al. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. Mol Cancer. 2010, 9:196.

[295] Xian XS, Park H, Cho YK, Lee IS, Kim SW, Choi MG, et al. Effect of a synthetic cannabinoid agonist on the proliferation and invasion of gastric cancer cells. J Cell Biochem. 2010, 110:321–32.

[296] Caffarel MM, Sarrió D, Palacios J, Guzmán M, Sánchez C. Δ9-Tetrahydrocannabinol inhibits cell cycle progression in human breast cancer cells through Cdc2 regulation. Cancer Res. 2006, 66:6615–21.

[297] Laezza C, Pisanti S, Crescenzi E, Bifulco M. Anandamide inhibits Cdk2 and activates Chk1 leading to cell cycle arrest in human breast cancer cells. FEBS Lett. 2006, 580:6076–82.

[298] Roberto D, Klotz LH, Venkateswaran V. Cannabinoid WIN 55,212-2 induces cell cycle arrest and apoptosis, and inhibits proliferation, migration, invasion, and tumor growth in prostate cancer in a cannabinoid-receptor 2 dependent manner. Prostate. 2019, 79:151–9.

[299] Go YY, Kim SR, Kim DY, Chae SW, Song JJ. Cannabidiol enhances cytotoxicity of anti-cancer drugs in human head and neck squamous cell carcinoma. Sci Rep. 2020, 10:20622.

[300] Zhang X, Qin Y, Pan Z, Li M, Liu X, Chen X, et al. Cannabidiol induces cell cycle arrest and cell apoptosis in human gastric cancer SGC-7901 cells. Biomolecules. 2019, 9:302.

[301] Massi P, Valenti M, Vaccani A, Gasperi V, Perletti G, Marras E, et al. 5-Lipoxygenase and anandamide hydrolase (FAAH) mediate the antitumor activity of cannabidiol, a non-psychoactive cannabinoid. J Neurochem. 2008, 104:1091–1100.

[302] Hart S, Fischer OM, Ullrich A. Cannabinoids induce cancer cell proliferation via tumor necrosis factor alpha-converting enzyme (TACE/ADAM17)-mediated transactivation of the epidermal growth factor receptor. Cancer Res. 2004, 64:1943–50.

[303] Scott KA, Dalgleish AG, Liu WM. The combination of cannabidiol and Δ9-tetrahydrocannabinol enhances the 22anticancer effects of radiation in an orthotopic murine glioma model. Mol Cancer Ther. 2014, 13:2955–67.

[304] Liu C, Sadat SH, Ebisumoto K, Sakai A, Panuganti BA, Ren S, et al. Cannabinoids promote progression of HPV-positive head and neck squamous cell carcinoma via p38 MAPK activation. Clin Cancer Res. 2020, 26:2693–703.

[305] Fowler CJ. Delta9-tetrahydrocannabinol and cannabidiol as potential curative agents for cancer: a critical examination of the preclinical literature. Clin Pharmacol Ther. 2015, 97:587–96.

[306] Salazar M, Carracedo A, Salanueva IJ, Hernández-Tiedra S, Lorente M, Egia A, et al. Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. J.Clin Invest. 2009, 119:1359–72.

[307] Mechoulam R, Hanus LO, Pertwee R, Howlett AC, Early phytocannabinoid chemistry to endocannabinoids and beyond. Nat. Rev. Neurosci. 2014, 15: 757–764.

[308] Mechoulam R, Gaoni Y. The absolute configuration of D1- tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Lett. 1967, 8: 1109–1111.

[309] Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. Science. 1970, 169: 611–612.

[310] Mechoulam R. Marijuana: Chemistry, Pharmacology, Metabolism, and Clinical Effects, Academic Press: New York, NY, USA, 1973.

[311] Pertwee RG. Endocannabinoids and their pharmacological actions. In Endocannabinoids, Pertwee, R.G., Ed., Springer: Berlin, Germany, 2015, Volume 231, pp. 1–37. 2015.

[312] Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Grin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the Cannabinoid receptor. Science. 1992, 258: 1946–1949.

[313] Kaplan J. Marijuana. Report of the Indian Hemp Drugs Commission- 1893–1894. Thomas Jefferson Publishing Co., Silver Spring, MD. 1969.

[314] Cristino L, Becker T, Di Marzo V. Endocannabinoids and energy homeostasis: An update. BioFactors. 2014, 40: 389–397.

[315] Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat. Cancer. 2011, 11: 886–895.

[316] Skaper SD, di Marzo V. Endocannabinoids in nervous system health and disease: The big picture in a nutshell. Philos. Trans. R. Soc. B Biol. Sci. 2012, 367: 3193–3200

[317] Bifulco M, Laezza C, Pisanti S, Gazzerro P. Cannabinoids and cancer: Pros and cons of an antitumour strategy. J. Cereb. Blood Flow Metab. 2006, 148: 123–135.

[318] Velasco G, Sánchez C, Guzmán M. Towards the use of cannabinoids as antitumour agents. Nat. Rev. Cancer. 2012, 12, 436–444.

[319] Hinz B, Ramer R. Cannabinoids as anticancer drugs: Current status of preclinical Res. Br. J. Cancer. 2022, 127: 1–13.

[320] Romano B, Borrelli F, Pagano E, Cascio MG, Pertwee RG, Izzo AA. Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. Phytomedicine. 2013, 21: 631–639.

[321] Ramer R, Merkord J, Rohde H, Hinz B. Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1. Biochem. Pharmacol. 2010, 79: 955–966.

[322] Tomko AM, Whynot EG, Ellis LD, Dupré DJ. Anti-Cancer Potential of Cannabinoids, Terpenes, and Flavonoids Present in Cannabis. Cancers. 2020, 12: 1985.

[323] Russo EB, Taming THC. Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br. J. Pharmacol. 2011, 163: 1344–1364.

[324] Mangal N, Erridge S, Habib N, Sadanandam A, Reebye V, Sodergren MH. Cannabinoids in the landscape of cancer. J. Cancer Res. Clin. Oncol. 2021, 147: 2507–2534.

[325] Preet A, Ganju RK, Groopman JE. D9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo. Oncogene. 2008, 27: 339–346.

[326] Yamaori S, Okamoto Y, Yamamoto I, Watanabe K, Cannabidiol, a Major Phytocannabinoid, As a Potent Atypical Inhibitor for CYP2D6. Drug Metab. Dispos. 2011, 39: 2049–2056.

[327] Fowler DW, Dalgleish AG. Cannabis-Derived Substances in Cancer Therapy—An Emerging Anti-Inflammatory Role for the Cannabinoids. Curr. Clin. Pharmacol. 2010, 5, 281–287.

[328] Victorson D, McMahon M, Horowitz B, Glickson S, Parker B, Mendoza-Temple L. Exploring cancer survivors' attitudes, perceptions, and concerns about using medical cannabis for symptom and side effect management: A qualitative focus group study. Complement. Ther. Med. 2019, 47: 102204.

[329] Sarfaraz S, Adhami VM, Syed DN, Afaq F, Mukhtar H. Cannabinoids for Cancer Treatment: Progress and Promise. Cancer Res. 2008, 68: 339–342.

[330] Reid M. A qualitative review of cannabis stigmas at the twilight of prohibition. J. Cannabis Res. **2020**, 2: 46.

[331] Malach M, Kovalchuk I, Kovalchuk O. Medical Cannabis in Pediatric Oncology: Friend or Foe? Pharmaceuticals. 2022, 15: 359.

[332] Taha T, Meiri D, Talhamy S, Wollner M, Peer A, Bar-Sela G. Cannabis impacts tumour response rate to nivolumab in patients with advanced malignancies. Oncologist. 2019, 24:549–54.

[333] Kenyon J, Liu W, Dalgleish A. Report of objective clinical responses of cancer patients to pharmaceutical-grade synthetic cannabidiol. Anticancer Res. 2018, 38:5831–5.

[334] Bar-Sela G, Cohen I, Campisi-Pinto S, Lewitus GM, Oz-Ari L, Jehassi A, et al. Cannabis consumption used by cancer patients during immunotherapy correlates with poor clinical outcome. Cancers (Basel). 2020, 12:2447.

[335] Scott KA, Dennis JL, Dalgleish AG, Liu WM. Inhibiting heat shock proteins can potentiate the cytotoxic effect of cannabidiol in human glioma cells. Anticancer Res. 2015, 35:5827–37.

[336] Ivanov VN, Wu J, Wang TJC, Hei TK. Inhibition of ATM kinase upregulates levels of cell death induced by cannabidiol and γ-irradiation in human glioblastoma cells. Oncotarget. 2019, 10:825–46. Erratum in: Oncotarget. 2019, 10:7012–3.

[337] Ivanov VN, Wu J, Hei TK. Regulation of human glioblastoma cell death by combined treatment of cannabidiol, γ-radiation and small molecule inhibitors of cell signaling pathways. Oncotarget. 2017, 8:74068–95.

[338] Liu WM, Scott KA, Shamash J, Joel S, Powles TB. Enhancing the in vitro cytotoxic activity of Δ9-tetrahydrocannabinol in leukemic cells through a combinatorial approach. Leuk Lymphoma. 2008, 49:1800–9.

[339] Deng L, Ng L, Ozawa T, Stella N. Quantitative analyses of synergistic responses between cannabidiol and DNA-damaging agents on the proliferation and viability of glioblastoma and neural progenitor cells in culture. J Pharmacol Exp Ther. 2017, 360:215–24.

[340] Holland ML, Panetta JA, Hoskins JM, Bebawy M, Roufogalis BD, Allen JD, et al. The effects of cannabinoids on P-glycoprotein transport and expression in multidrug resistant cells. Biochem Pharmacol. 2006, 71:1146–54.

[341] Holland ML, Lau DT, Allen JD, Arnold JC. The multidrug transporter ABCG2 (BCRP) is inhibited by plant-derived cannabinoids. Br J. Pharmacol. 2007, 152:815–24.

[342] McKallip RJ, Nagarkatti M, Nagarkatti PS. Δ-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumour immune response. J. Immunol. 2005, 174:3281–9.

[343] Zhu LX, Sharma S, Stolina M, Gardner B, Roth MD, Tashkin DP, et al. Δ-9- tetrahydrocannabinol inhibits antitumour immunity by a CB2 receptor-mediated, cytokine-dependent pathway. J Immunol. 2000, 165:373–80.

[344] Glodde N, Jakobs M, Bald T, Tüting T, Gaffal E. Differential role of cannabinoids in the pathogenesis of skin cancer. Life Sci. 2015, 138:35–40.

[345] Haustein M, Ramer R, Linnebacher M, Manda K, Hinz B. Cannabinoids increase lung cancer cell lysis by lymphokine-activated killer cells via upregulation of ICAM-1. Biochem Pharmacol. 2014, 92:312–25.

[346] Lei X, Chen X, Quan Y, Tao Y, Li J. Targeting CYP2J2 to enhance the anti-glioma efficacy of cannabinoid receptor 2 stimulation by inhibiting the proangiogenesis function of M2 microglia. Front Oncol. 2020, 10:574277.

[347] Yang Y, Huynh N, Dumesny C, Wang K, He H, Nikfarjam M. Cannabinoids inhibited pancreatic cancer via P-21 activated kinase 1 mediated pathway. Int J. Mol Sci. 2020, 21:8035.

[348] Ramer R, Hinz B. Cannabinoids as anticancer drugs. Adv Pharmacol. 2017, 80:397–436.

[349] Ramer R, Hinz B. New insights into antimetastatic and antiangiogenic effects of cannabinoids. Int Rev Cell Mol Biol. 2015, 314:43–116.

[350] Casanova ML, Blázquez C, Martínez-Palacio J, Villanueva C, Fernández-Aceñero MJ, Huffman JW, et al. Inhibition of skin tumour growth and angiogenesis in vivo by activation of cannabinoid receptors. J Clin Invest. 2003, 111:43–50.

[351] Blázquez C, Casanova ML, Planas A, Gómez Del Pulgar T, Villanueva C, Fernández-Aceñero MJ, et al. Inhibition of tumour angiogenesis by cannabinoids. FASEB J. 2003, 17:529–31.

[352] Blázquez C, González-Feria L, Alvarez L, Haro A, Casanova ML, Guzmán M. Cannabinoids inhibit the vascular endothelial growth factor pathway in gliomas. Cancer Res. 2004, 64:5617–23.

[353] Solinas M, Massi P, Cantelmo AR, Cattaneo MG, Cammarota R, Bartolini D, et al. Cannabidiol inhibits angiogenesis by multiple mechanisms. Br J Pharmacol. 2012, 167:1218–31.

[354] Thapa D, Lee JS, Heo SW, Lee YR, Kang KW, Kwak MK, et al. Novel hexahydrocannabinol analogs as potential anti-cancer agents inhibit cell proliferation and tumour angiogenesis. Eur J Pharmacol. 2011, 650:64–71.

[355] Picardi P, Ciaglia E, Proto M, Pisanti S. Anandamide inhibits breast tumourinduced angiogenesis. Transl Med UniSa. 2014, 10:8–12.

[356] Ramer R, Fischer S, Haustein M, Manda K, Hinz B. Cannabinoids inhibit angiogenic capacities of endothelial cells via release of tissue inhibitor of matrix metalloproteinases-1 from lung cancer cells. Biochem Pharmacol. 2014, 91:202–16.

[357] Braile M, Cristinziano L, Marcella S, Varricchi G, Marone G, Modestino L, et al. LPS-mediated neutrophil VEGF-A release is modulated by cannabinoid receptor activation. J. Leukoc Biol. 2021, 109:621–31.

[358] McAllister SD, Murase R, Christian RT, Lau D, Zielinski AJ, Allison J, Almanza C, Pakdel A, Lee J, Limbad C. et al. Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. Breast Cancer Res. Treat. 2011, 129: 37–47.

[359] Zhu LX, Sharma S, Stolina M, Gardner B, Roth MD, Tashkin DP, Dubinett SM. Λ-9-Tetrahydrocannabinol Inhibits Antitumor Immunity by a CB2 Receptor-Mediated, Cytokine-Dependent Pathway. J. Immunol. 2000, 165: 373–380.

[360] McKallip RJ, Nagarkatti M, Nagarkatti PS. Λ-9-Tetrahydrocannabinol Enhances Breast Cancer Growth and Metastasis by Suppression of the Antitumor Immune Response. J. Immunol. 2005, 174: 3281–3289.

[361] Sharma AN, Dewangan HK, Upadhyay PK. Comprehensive Review on Herbal Medicine: Emphasis on Current Therapy and Role of Phytoconstituents for Cancer Treatment. Chem Biodivers. 2024 Jan 11:e202301468. doi: 10.1002/cbdv.202301468.

[362] Tata Memorial: Anti-cancer Plants Study By Tata Memorial To Start In Pen | Mumbai News - Times of India (indiatimes.com). 2023.

[363] IIT India- researchers engineer plant cells to produce drug for cancer https://www.thehindu.com/sci-tech/health/iit-researchers-engineer-plant-cells-to-produce-2024.

[364] Can Soursop (Graviola) Help Fight Cancer? (verywellhealth.com).

[365] Mishra ML, Shukla UN. RAMPHAL: AN ETHNO-MEDICINAL PLANT. Marumegh. 2018, 3(1): 20-24.

[366] Aliyev AJ, Melikova LA, Bagirova EE, Akbarov KS, Aliyeva AM et al. Prevalence of Human Papillomavirus in Laryngeal Squamous Cell Carcinoma in Azerbaijan population. Head Neck Cancer Res. 2018; 3 :1:03.

[367] Bakhshalieva FG. Nekotorye épidemiologicheskie faktory zabolevaemosti rakom zhenskikh polovykh organov v Azerbaĭdzhanskoĭ SSR [Some epidemiological factors in the incidence of female genital cancer in the Azerbaijan SSR]. Vopr Onkol. 1975;21(10):89-92.

[368] Isayev IH, Akbarov KS, Melikova LA, Quliyev EH, Aliyeva NS. National Center of Oncology, Baku, Azerbaija. Tumor response rate after concurrent chemoradiotherapy depending on PIK3CA mutation status in Azerbaijanian patients with locally advanced cervical cancer. 2015.

[369] Azerbaijan: Human Papillomavirus and Related Cancers, Fact Sheet 2023 (hpvcentre.net). Azerbaijan Human Papillomavirus and Related Cancers. Fact Sheet 2023.

[370] Akbarov K, Isayev I, Melikova L, Guliyev E, Aliyeva N. 312P - PIK3CA gene mutation frequency among cervical cancer patients in Azerbaijan. Annals of Oncology. 2017; 28: 10: 92.

[371] Cervical cancer in Azerbaijan (worldlifeexpectancy.com). 2023.

[372] Malabadi RB, **Mammadova SS**, Kolkar KP, Sadiya MR, Chalannavar RK, Castaño Coronado KV. *Cannabis sativa*: A therapeutic medicinal plant-global marketing updates. World Journal of Biology, Pharmacy and Health Sciences. 2024; 17(02): 170–183