Chapter 3

Photodyanamic Therapy in the Cervical Cancer

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Abstract

Cancer is one of the most common and feared illnesses in modern society. Its prevalence has been gradually rising in recent years. The fourth most common malignancy in women worldwide is cervical cancer (CC). Surgery, chemotherapy, and radiotherapy are examples of conventional treatments, but they are invasive and have negative side effects. In addition, metastasis is observed in roughly 70% of individuals with late-stage CC due to limits and treatment resistance. In addition to treating primary CC, photodynamic therapy (PDT) is an alternate CC treatment strategy that has been clinically shown to reduce subsequent metastasis. Because PDT is a non-invasive focused treatment with less adverse effects and reduced resistance to dose repetitions, it is believed to be much more beneficial. This review study's objective is to examine the studies on PDT's efficacy in treating cervical cancer.

INTRODUCTION

An international health issue is cervical cancer (CC). Cervical cancer (CC) is one of the most prevalent oncological conditions nowadays and a significant public health issue. In most countries, this sickness is the main reason why women die [1].

The International Organization for Research on Cancer estimates that there were 603,863 new cases of cervical cancer worldwide in 2020, of which 341,680 were fatal [2]. The 5-year survival rate for cervical cancer patients in various nations varies from 37% to 77% in 2020 [3]. The disease's stage, the occurrence of relapses, and the development of tumor metastases all play a significant role in the suggested treatment modalities [4]. Epidemiology research on cervical cancer has revealed a 12.66% increase in cases over

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the past ten years [5]. With specific goals for the years 2020–2030, the World Health Organization (WHO) developed a draft worldwide strategy to hasten the elimination of the CC in 2019. 90, 70, and 90 key points make up the overview, according to the WHO worldwide plan. HPV is the primary factor in the emergence of CC [6]. By the age of 15, 90% of girls should have had the HPV vaccine in its entirety. Around 35 and 45 years old, 70% of women should have another high performance test screening. For disorders characterized by cervical malignant diseases, 90% of women should obtain treatment. Conventional CC treatments such radiation, chemotherapy, and surgical excision are intrusive and have negative side effects [7]. Despite increasing developments, metastasis affects 70% of patients with late-stage CC because of the limitations of all surgical excision procedures and the resistance of cervical cancer stem cell (CCSC) to repeated therapies [8, 9]. As a result, the research is needed to develop alternate treatment combinations. PDT is an alternate therapeutic approach that has the potential to both prevent secondary metastasis of CCSC and provides clinical evidence for the initial eradication of CC [10]. Furthermore, PDT is known to be a highly targeted, non-invasive, localized treatment with less side effects, quicker recovery times, and lower resistance to repeated dosage treatments when compared to traditional treatments [11]. Recent clinical trials [12,13] have shown that PDT therapy utilizing 5-aminolevulinic acid (ALA) is an effective and well-tolerated therapeutic option for CC. These clinical trials still need to be improved in order to investigate the use of cutting-edge PDT therapy to trigger particular immune responses and entirely stop CC secondary migration [14].

Cervical cancer

Human papillomavirus (HPV) infection is frequently linked to cervical carcinoma (CC) (HPV). The HPV family which includes more than 200 distinct DNA viruses, can be split into subgroups with low and high infection risk [15]. 99% of occurrences of cervical cancer are caused by high-risk HPV, the most common of which being HPV-16 [16].

The results revealed that HPV is the primary cause of cervical cancer; thus, while other risk factors may raise the likelihood of developing cervical cancer, this particular type of cancer cannot arise in the absence of HPV [17]. The three kinds of possible cofactors in the pathogenesis of cervical cancer include host risk factors, viral risk factors, and environmental risk factors. Hormonal birth control, smoking, and sexual activity are all environmental risk factors [18-20]. A history of HPV infection with several strains, viral load, and integration of various viruses are all viral risk

factors [21]. Endogenous hormones, genetically associated variables and essentially any element that may influence the immune system response are all considered hosts risk factors [22].

CC is a cancerous type of tumor that develops in the cervix. Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the two subtypes recognized histologically (SCC) [23]. The formation rate of SCC is almost 70% higher than that of AC [23]. Women are frequently diagnosed with CC all over the world, but mainly in low- and middle-income nations like South Africa, India, China, and Brazil. In 2020, a total of 604,127 new cases of CC were reported worldwide, of which 341 831 resulted in death [24].

Re-infection with cervical cancer is conceivable as a result of the existence of HPV in the vaginal mucosa, which is necessary for the virus' resistant persistence [25]. Thus, the discovery of therapeutic approaches that enable the eradication of the virus from all genital tract mucosal surfaces where HPV is found represents the primary challenge. It is not possible to simultaneously destroy and/or ablate relatively large areas on the surface of the cervix, vagina, and vulva due to the risk of infection at these anatomical locations. The benefit of PDT is the ability to eradicate HPV in all localizations. A non-invasive alternative approach for treating cancer is photodynamic therapy (PDT). PDT is effective in getting rid of HPV. Squamous intraepithelial lesions and cervical cancer recurrence are primarily caused by HPV persistence. According to studies, HPV persistence accounts for 40% of recurrences following surgery [26]. There was no discernible change in the incidence of recurrence following surgery in the 5-year follow-up trial. It has been demonstrated that surgical methods cannot completely eradicate HPV [26, 27].

Lack of access to medical care for successful treatment plans, public awareness, smoking, oral contraceptive use, and HIV co-infections are additional variables that may affect the overall incidence rate of CC. Atypical vaginal discharge, vaginal bleeding (especially after intercourse), pelvic discharge, and pain following intercourse are typical signs and symptoms of CC [23]. It is expected that 11 million women would be diagnosed with CC in the next 10 to 20 years, necessitating greater study into early diagnosis and therapies [23].

Cervical Cancer Stages and Treatments

There are four stages of CC: stage I, where the cancer is limited to the cervix; stage II, where the cancer has spread to the upper two-thirds of the vagina or to the tissue surrounding the uterus; and stage IV, where the

cancer has extended to the lower two-thirds of the vagina. Stage III cancers have spread to the lower third of the vaginal or pelvic wall, as well as to the kidneys, lymph nodes, or both; Stage IV refers to cancer that has spread outside of the pelvis or to the lining of the bladder, rectum, or other bodily areas [28].

Surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy are the currently available 5 standard kinds of conventional treatment for CC.

The stage of the CC at the time of diagnosis determines the type of treatment used alone or in combination [29]. Conization or internal radiation therapy, as well as a total or partial hysterectomy, are surgical procedures used to treat stage 1 CC. [29]. Following a combination radical hysterectomy and excision of the pelvic lymph nodes in stage II CC, radiation and chemotherapy are frequently taken into consideration. Treatments for stage III CC include low-level chemotherapy with fol excision of the pelvic lymph nodes and combination radiation and chemotherapy. The tumor is then reduced with internal radiation therapy before a complete surgical hysterectomy [29]. Chemotherapy and radiation therapy may be used as palliative care in stage IV colorectal cancer to relieve discomfort and recurrent cancer symptoms [29]. Nonetheless, concentrated immunotherapies or clinical trials of severe surgical pelvic exenteration may be additional viable treatment options for stage IV CC.

The long- and short-term adverse effects of these conventional therapy techniques are significant, notwithstanding their promise. Surgery is extremely invasive and uncomfortable at any stage of CC [28]. It is well recognized that radiation therapy damages normal, healthy cells' DNA unintentionally, impairing their ability to repair and causing irreversible harm. Similar to how chemotherapy is poisonous to healthy tissues, it has immediate adverse effects include hair loss, nausea, vomiting, diarrhea, coughing, swollen legs, and weight loss [30]. Radiation or chemotherapy can have long-term adverse effects, such as persistent leg, back, or stomach pain, trouble urinating, and fatigue [30]. Also, new therapeutic options like targeted immunotherapies are still being tested in clinical settings, so it is unclear how effective they will be in the long run.

The early diagnosis of CC is still very poor, and CC in women frequently goes misdiagnosed until the late stages due to a lack of health and education facilities (particularly in developing nations), asymptomatic patients, and poor diagnostic pap test accuracy [31]. 38% of CC patients are diagnosed at stage III or IV, compared to 44% of those that are detected at stage II [31].

As a result, one of the top main examples is Advanced CC. Inadequate early detection, a lack of effective treatment regimens brought on by treatment resistance, and recurrence are the main contributors to cancer-related mortality in low- and middle-income countries.

Alternative Photodynamic Therapy for the Treatment of Cervical Cancer

Surgery, radiation therapy, and chemotherapy are all part of the standard anticancer treatment for colorectal cancer (CC), yet they all have drawbacks [32].

Damage to normal tissues, structural deformations, scarring, hyperpigmentation, and systemic adverse effects are all possible complications following surgery or radiation therapy. Moreover, the use of traditional medicines may result in multidrug resistance, which could result in treatment failure and illness recurrence. Many therapy strategies have been proposed to lessen toxicity and reduce side effects. The systematic exploration has recently begun to focus on non-traditional therapies that can effectively cure CC while reducing the invasiveness, unpleasant side effects, recurrence rate and metastasis of conventional therapies.

Photodynamic therapy (PDT) is a tried-and-true alternative treatment method for curing primary CC and eliminating CCSC to halt secondary metastases [10]. Since PDT is a highly targeted, non-invasive, localized treatment with few side effects, a speedy recovery, and no aftereffects, it has numerous advantages over conventional therapies. Due to the fact that PDT enables women to keep their fertility, it can also be viewed as an alternate kind of treatment for patients. Because patients' infertility is frequently brought on by surgery, chemotherapy, and radiation therapy [10]. A light-sensitive substance (photosensitizer, PS) is systemically applied as part of the treatment, and after that, the patient is exposed to a light source with a specific wavelength. Targeted cell death results from the oxidative damage caused by this [33]. Three essential elements—PS (topically or systemically viable), light (often generated by laser sources), and molecular oxygen—are necessary for PDT activity. PS preferentially accumulates in malignant tissue. It is triggered by local illumination of the lesion with visible light calibrated to activate the PS; this results in cell death [34]. In tumor tissues, PS has minimal accumulations. They are promptly expelled from the body or the target tissue after a brief time in the bloodstream. Penetration and retention into tissues significantly increase when administered in precisely designed nanoparticle compositions [35,36]. This is as a result of better

photosensitizer targeting and defense [37,38]. A therapeutic strategy utilizing photosensitizers with nanoparticles and light activation could potentially go beyond the restrictions of photodynamic therapy for the treatment of carcinomas in light of these processes [39].

Mechanism of Action of PDT for the Treatment of Cervical Cancer

In PDT procedures, a patient is given a light-stimulating photosensitizer (PS), also called a photosensitizer [40]. We give the patient's body enough time for the PS to disperse. A PS can passively and specifically accumulate in tumor cells due to the enhanced permeability and retention effect (EPR) that cancer cells have [12]. A laser source is used to apply irradiation of a specific wavelength to the localized tumor in the patient's cervical region during hysteroscopy when selective accumulation of PS develops. Red laser stimulation causes localized tumor PS to transition from its single baseline state to an induced triple state [40]. Reactive oxygen species (ROS) and other free radicals are produced in the type I reaction when PS in the excited ternary state combines with biomolecules, molecular oxygen, and water in the vicinity of tumor cells [40]. In type II reactions, excited triple state PS and excited triple state oxygen ($^3O_2$) combine to form reactive single oxygen ($^1O_2$).

Oxidative stress caused by the production of cytotoxic ROS and $^1O_2$ free radical species causes cell death by necrosis or apoptosis in primary and secondary CC tumor cells [40]. These types of cell death, which are triggered by oxidative stress in tumor cells, kill a primary CC tumor by destroying a variety of internal biomolecules, such as DNA, proteins, and ligands.

PDT causes DNA damage and oxidative stress in cancer cells by inducing apoptosis and autophagy [41]. A type of programmed cell death known as apoptosis is brought on by excessive or insufficient stimulation for cell growth, proliferation, and even cell damage [42]. An intracellular catabolic degradative process is called autophagy. As a result of oxidative stress, protein recycling occurs and aids in cancer cell survival as well as programmed cell death [43]. Recent research has revealed that apoptosis and autophagy frequently take place in the same cell. Both types of cell death can be brought on simultaneously by the ROS produced by PDT [44,45]. This particular PDT treatment may also cause other anticancer immune reactions, which could damage the vascular system of the tumor. CCSC removal should be increased to prevent secondary spread [10].

PDT produces hemostasis, artery narrowing and breakdown when it targets a tumor's vascular nature. This reduces the amount of oxygen and

nutrients that a tumor receives, assisting in the main and secondary CCSC breakdown [10]. As a result, CC PDT treatment can force the destruction of localized tumor tissue as well as crucial anti-tumor responses and an acute inflammatory process. Both of that assist eradicate primary CC and stop its secondary spread.

Recent PDT Clinical Studies for the Treatment of Cervical Cancer

The PS deposition in the afflicted tissue and singlet oxygen quantum yield are the two main factors that determine PDT's effectiveness. Moreover, PS has a significant impact on the drug's pharmacodynamics and pharmaceutical cokinetics [46]. For usage in PDT, porphyrins, chlorines, bacteriochlorolines and phthalocyanins have all been thoroughly investigated. Clinical approval has been granted to a number of substances [47, 48]. Bacteriochlorophyll derivatives with strong absorption in the long wavelength portion of the spectrum have lately been investigated for the treatment of big or deep-seated cancers [49]. Many experimental research has been carried out to investigate the tissues and cellular targets of PS as well as its methods of action [50, 51].

During PDT, targeted and microencapsulated delivery of cytotoxic and antibacterial drugs enhances cancer therapy outcomes. Poor encapsulation and insufficient medication dose frequently thwart the success of this technology. Thus, it is crucial to create novel, trustworthy microencapsulated dosage forms that have a high level of therapeutic efficacy. 168 randomized clinical studies for the treatment of PDT in CC were conducted in 2018, according to a comprehensive review by Zhang et al. [52].

The remission rate of patients was reported to have increased greatly by PDT by 82%, although it was emphasized that additional clinical research is required to identify the PS that is the most efficient and least hazardous. One of the important studies referenced in this review said that PS (Photofrin®) PDT successfully treated 50 early-stage CC patients with a 95% improvement, however the patients also suffered unfavorable photosensitivity and inflammation. In clinical situations where CC metastasizes, researchers have also proposed that combination chemo-PDT is required [52,53]. In contrast, the researchers looked into PDT treatment using the strong FDA-approved prodrug hexaminolevulinate (HAL) in 56 CC patients. They found that 90% of the patients had a full response to treatment with no recurrence, progression and/or lesions 2 years after treatment [54]. Most recently, researchers reported 45 patients had effective PDT for CC using Photoditazine® and PhotolonTM, and 86% of those patients did not experience a relapse 5 years following treatment [11].

However, when using FDA-approved ALA as PS in the treatment of PDT in the most notable and final preclinical CC patient, researchers found that there was minimal morbidity, a low incidence of side effects, and a 94.81% remission rate after a year of treatment [55,56]. Scientists also observed that PDT utilizing ALA in clinical phase trials has emerged as the most efficient and risk-free therapy option for the current control of CC. Prior to this medication being made available to the public health system, more research is required due to the constraints of reducing secondary spread [12,13].

Limitations and Future of PDT for Cervical Cancer Treatment

Low-dose PDT regimens may allow CC tumor survival and may also produce anti-tumor immunity, but medium-dose PDT therapy may induce positive apoptotic tumor cell death and cause necrotic tumor ablation of high-dose PDT, according to clinical and preclinical CC PDT studies [55, 56].

Consequently, to control the local main tumor and achieve immunosuppression of secondary spread to CCSC, moderate-to-high-dose PDT is typically needed in the treatment of CC. Overall, mounting data point to CC PDT's success being based on its ability to affect tumor-host interactions while tipping the scales in favor of the activation of specific immune responses and vascular closure to halt cancer dissemination. Therefore, additional research is needed to determine how to achieve controlled high dosing, immune responses that can completely stop secondary spread and clinical trial phases with improved light sources to induce deep tissue phototoxicity and limited skin photosensitivity in comparison to CC PDT [14]. There is still space for improvement, according to additional preclinical investigations despite the fact that the most recent clinical trials have shown the huge potential of CC PDT [57]. In a more recent study, combined PDT therapy suggested methods that need further study to be fully effective in CC [57]. According to some recent combination studies, PDT for colorectal and breast cancer has been shown to be effective when combined with cannabidiol (CBD) which also inhibits migration for the main cell cancer development ablation and secondary spread [58-60].

Conclusion

CC is one of the most successfully treatable types of cancer when the disease is detected at an early stage. Thus, it is crucial to create efficient substitute therapies that may cure HPV-related squamous intraepithelial lesions of cervical cancer and preinvasive cervical cancer without endangering the patient's fertility. The major conclusions from this analysis

are that conventional CC treatments such surgical excision, chemotherapy, and radiotherapy are invasive and have adverse side effects [7]. Due to the constraints of surgical excision and CCSC resistance to recurrent radiation and chemotherapy, over 70% of late-stage patients still experience recurrence or metastasis despite advancements in standard CC treatments [8, 9]. As a result, there is a critical need to investigate alternate therapeutic pairings.

PDT is a complementary cancer therapy that has been shown to treat primary CC while also removing CCSC to stop secondary metastases [10]. PDT is a far more beneficial treatment for CC since it is highly targeted, non-invasive, localized, has few side effects, heals quickly without leaving scars, and is also acceptable for repeated dosing with little to no resistance [11]. According to certain studies, PDT, which is employed as PS and is reported by ALA (5-aminolevulinic acid), has emerged as the most efficient and risk-free therapy method for the current control of CC. However, additional research must be conducted before this drug may be offered [12,13]. Moreover, the most recent CC PDT clinical trials have demonstrated remarkable promise, suggesting that additional preclinical trials can still be developed [57]. The investigation of controlled high dosing, light source transmission to induce deep tissue phototoxicity with limited skin photosensitivity and advanced studies aimed at inducing particular immune responses to completely eradicate secondary propagation are just a few examples of these CC PDT clinical trials improvements [14].

This awareness has pushed research on CC PDT and conventional medicines to the fore to examine these synergistic therapies that enable the targeting of numerous cell death pathways. In order to stop primary tumor growth and fight secondary metastasis, this synergistic treatment will stimulate host immune responses. The application of PDT aids in the successful treatment of pathological foci on the mucous membrane of the cervix; the method's efficacy and safety are guaranteed by its selective action on the tissues [61,62]. PDT provides for the preservation of the normal anatomical and functional aspects of the cervix because normal surrounding tissues are not destroyed during treatment, there are no obvious scars, and there is no cervical canal stenosis. PDT enables the preservation of the normal anatomical and functional aspects of the cervix while using the procedure without causing any harm to the surrounding healthy tissues.

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Chapter 4

Complementary And Alternative Therapies in the Brain Tumors

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Abstract

The brain tumor remains mostly fatal, highlighting the need for innovative treatments despite improvements in the surgery, radiation, and chemotherapy. The blood-brain barrier, redundant molecular pathways, and genetic heterogeneity have all hampered the utility of molecularly targeted drugs. As an therapeutic option and to reduce the symptoms, the frequency of Complementary and alternative medicine (CAM) has been increasing in brain tumors. CAM is operationally defined as any practice that aims at cure or at obtaining similar effects as evidence-based medicine, but without scientific evidence and without clinical trial data to support efficacy and safety. Mostly used type of CAM was biological base therapies including the herbal, diet supplementary, vitamin and minerals. The factors affecting use of CAM are the duration/situation of disease, educational level and history of CAM usage in society. In this chapter, a summary of CAM used as a targeted therapy for patients with glioblastoma is presented along with information on in vivo and in vitro studies and potential future therapeutic approaches.

HISTORY OF COMPLEMENTARY AND ALTERNATIVE THERAPIES

The first step in traditional and complementary therapy started in 1977 with the decision under the title of "Development of Research and Education in the Field of Traditional Medicine" (Şen 2022). Afterwards "Medical Plants" was published in 1978, "Traditional Medicine" in 1987, "Traditional Medicine and Modern Health Services" between 1981-1991, "Traditional Medicine Research and Evaluation Methodologies Guide" in 2000, and "The Legal Status of Traditional Medicine/Alternative and Complementary

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Medicine in the World" in 2001. Afterwards, "Traditional Medicine Strategy 2002-2005" was published by WHO and the "Beijing Declaration" in 2009 to promote the safe and effective use of traditional medicine (Muslumanoglu & Tayfun, 2019). The WHO Directorate-General requested that the "WHO Traditional Medicine Strategy 2002-2005", to be updated as "WHO Traditional Medicine Strategy 2014-2023", based on the assessment of the developments of countries and the current challenges. Through this strategy, it is aimed an appropriate integration of complementary and alternative therapies into health services, to regulate and control these therapies in a way that can be applied globally (WHO, 2013).

By the establishment of traditional and complementary practices in the health care system since the 20th century, the National Center for Complementary and Alternative Medicine (CAM) was established in 1998, affiliated to the United States National Institute of Health, in order to ensure their controlled use in the field of modern medicine. The first step in Turkey was taken by issuing the Acupuncture Treatment Regulation in 1991, and it was aimed to perform acupuncture with scientific methods (Lafçı & Kaşıkçı, 2014). Traditional, alternative and complementary medicine practices were first legally entered into our law with the Decree Law No. 663. The authority to execute, supervise and regulate traditional, alternative and complementary practices has been given to the General Directorate of Health Services (Talhaoğlu, 2021). The perception of the term alternative medicine as an alternative to modern medicine has caused the practices to not be included in a scientific platform. By making a regulation in the "Regulation on Traditional and Complementary Treatment Practices" published in the Official Gazette dated October 27, 2014 and numbered 29158, the phrase "Alternative medicine" was removed and the phrase "Traditional and complementary therapy Practices" became acceptable (Resmi Gazete, 2014).

DEFINITION OF COMPLEMENTARY AND ALTERNATIVE THERAPIES

Alternative medicine has been accepted by the public as a health service that replaces the medical treatment but is not accepted by the modern medicine. This treatment approach has been defined as all treatment practices that are not accepted by modern medicine (Tabish, 2008). The complementary medicine, on the other hand, includes the applications to support and strengthen the treatment, alleviate symptoms and improve the patient's quality of life in addition to medical treatment (Gilmour et al. 2011).

TYPES OF COMPLEMENTARY AND ALTERNATIVE TREATMENT PRACTICES

The types of CAM can be summarized under three broad titles according to the researches of The National Center for Complementary and Integrative Health (NCCIH):

1. Natural substances (medicinal plants, probiotics, etc.)
2. Mental and physical medicine (meditation, acupuncture, etc.)
3. Practices based on physical manipulation (massage, osteopathy, etc.)

Complementary and alternative treatment methods are handled in three main groups as cognitive-behavioral therapies and manipulative approaches, nutritional approaches and herbal approaches. Nutritional and herbal approaches have been mainly used in cancer patients (Le Rhun et al. 2019).

COMPLEMENTARY AND ALTERNATIVE THERAPIES IN CANCER PATIENTS

Cancer patients are frequently searching for CAM therapies in an effort to extend life and reduce negative effects of the disease or chemo- or radiotherapies (Lerner and Kennedy, 1992). CAM use in cancer patients has been reported between 9% and 83%, highlighting the variability in use among patients with cancer (Eisenberg et al. 1993; Bennett and Lengacher, 1999). Heterogeneity of cancer may be partially attributed to the variations in CAM use. The estimated percentage of CAM users showed a definite upward trend over time, rising from 25% in the 1970s and 1980s to more than 32% in the 1990s to 49% after 2000 (Horneber et al. 2012). 1471 cancer survivors reported using CAM at a rate of 66.5% in 2007 (Mao et al. 2011). In a different study, 29% of people was reported using CAM in Germany between 2014 and 2016 (Firkins et al. 2018).

Phytotherapy is used in the sense of treatment with plants today. Evidences for the safety and efficacy of plants in cancer treatment is limited. Since the doses used in cancer treatment are not standardized, care should be taken in terms of the side effects and interactions with cytotoxic drugs. Patients should use this treatment in accordance with the recommendations of their physicians. Herbal products that are frequently used in cancer treatment are turmeric (curcumin), green tea, ginger, pomegranate and garlic (Gullett et al. 2010). Naturally-occurring agents from these herbal products have received considerable attention for the prevention and treatment of cancers. These natural agents are safe and cost efficient in contrast to expensive chemotherapeutic agents, which may induce significant side effects. One of

these products, the pomegranate (Punica granatum L.) fruit exhibits strong antioxidant activity and is a rich source of anthocyanins, ellagitannins, and hydrolysable tannins. Studies have shown that the pomegranate fruit as well as its juice, extract, and oil exert anti-inflammatory, anti-proliferative, and anti-tumorigenic properties by modulating multiple signaling pathways, which suggest its use as a promising chemopreventive/chemotherapeutic agent (Sharma et al. 2017).

COMPLEMENTARY AND ALTERNATIVE THERAPIES IN BRAIN TUMORS

Primary brain tumors (PBTs) are frequently accompanied by neurologic complications and a poor prognosis, hence CAM use may be widespread in this population and all three CAM categories mentioned before were evaluated for their efficacy with an improvement in their quality of life. However, the exact risks and side effects have not been properly investigated in patients with PBTs (Armstrong et al. 2006).

The prognosis of PBTs varies according to the general and neurological conditions of the patients, WHO grade and molecular subtype, and the available treatments. Meningiomas and gliomas represent the most common PBTs in adults. 56.6% of all gliomas are glioblastomas, the most malignant type of glioma (WHO grade IV) (Ostrom et al. 2018). The median survival for glioblastoma patients ranges from 4 to 16 months in clinical investigations (Stupp et al. 2017; Weller et al. 2017), whereas at 12 months for the general population (Gramatzki et al. 2016). WHO grade II and grade III gliomas have a better prognosis with median survival times changing 5-13 years. Therefore, the cancer patients and family members may apply for CAM more frequently in this prognosis of severe disease and limited effectiveness of evidence-based medicine. It is likely that patients with glioblastoma feel more pressure to combat their cancer than those with less malignant tumors, as seen by the association between a diagnosis of glioblastoma and higher CAM use compared to patients with lower WHO grade gliomas (Le Rhun et al. 2019).

Several studies have shown that CAMs including the phytochemical compounds, such as phenolic acids extracted from fruits and vegetables, exhibit various cytotoxic and anti-proliferative effects as those of chemotherapeutics (Zhao et al. 2017; Lee et al. 2014; Yang et al. 2015). One of these compounds, a dietary polyphenol called ellagic acid (EA, 2,3,7,8-tetrahydroxy-chromeno; C14H6O8) is found in nuts and fruits including pomegranates and berries. In various mammalian tissues, EA

promotes anti-inflammatory activities and demonstrates antioxidant capacity, anti-fibrotic and chemopreventative effects (Seeram et al. 2005). EA has been identified as a potential neuroprotective agent, but there are not enough reports to determine whether and how EA acts to protect neurons in humans (de Oliveira 2016). EA exhibits anti-tumour pharmacological properties, such as inhibition of tumour formation and growth via cell cycle arrest, induction of apoptosis (Edderkaoui et al. 2008), and suppression of angiogenesis (Narayanan et al. 1999). EA was also shown to have successful in vitro therapeutic efficacy when combined with chemotherapeutics in glioma cell lines via inhibiting cadherin switch, angiogenesis, inhibition of O6-methylguanine DNA methyltransferase expression, time-dependent inhibition of P-glycoprotein (MDR1), activating apoptotic protein, p53 and caspase-3, expression (Çetin and Biltekin, 2019; Çetin et al. 2019; Cetin and Biltekin, 2020; Cetin et al. 2022). Clinical research is needed to prove the short-term and long-term efficacy and safety of ellagic acid in brain tumors.

Another herbal product, turmeric has an antiapoptotic effect in the treatment of cancer patients. The turmeric also shows an antioxidant effect via the phenolic acid compounds it contains, and a cytostatic effect via its oxygenated aromatic structures. A major polyphenolic compound of turmeric, named curcumin or diferuloylmethane, was shown to eliminate cancer cells derived from a variety of peripheral tissues. Oral delivery of this food component has been less effective because of its low solubility in water. A soluble formulation of curcumin crosses the blood–brain barrier but does not suppress normal brain cell viability. In vitro and in vivo studies indicated that solubilized curcumin effectively blocks brain tumor formation and also eliminates brain tumor cells by activating proapoptotic enzymes caspase 3/7, by suppressing Cyclin D1, P-NF-kB, BclXL, P-Akt, and VEGF, all of which blocks proliferation, survival and invasion of cancer cells (Purkauastha et al. 2009). Turmeric is recommended to be used with caution as it may cause bleeding disorders (Toptaş, Ateş, & Alagöz, 2017).

Green tea produced from the leaves of the *Camellia sinensis* plant contains several phenolic compounds including phenolic acid, catechin, etc. (İpek et al, 2021). In studies, the protective effect of catechins against cancer is explained by mechanisms such as inhibiting cell proliferation, ceasing the cell cycle, suppressing active receptors, reducing the release of cytokines, suppressing mitotic stimuli, preventing mutagenicity and genotoxicity, activating detoxification enzymes and accelerating apoptosis of cancer cells (Hazafa et al. 2020). In case of overdose, symptoms such as nausea, insomnia, diarrhea, confusion can be observed. It increases cognitive performance, provides mental alertness, shows weight loss and diuretic effect. It reduces

the effect of warfarin with the effect of vitamin K it contains (Cheng, 2007). Green tea is rich in non-oxidized catechins among which epigallocatechin-3-gallate (EGCG) stands out as the most abundant and active ingredients (Yang et al. 2011). Chemotherapeutic drug combined with EGCG was shown to sensitize the glioblastoma cells to temozolomide by increasing the apoptosis, reducing tumor growth and decreasing the expression of GRP78, which is over-expressed in chemoresistant cancer cells (Chen et al. 2011).

Ginger is a tuberous plant that grows 15-25 cm under the soil and reaches 1.5 meters in height. It is widely used in the traditional treatment of nausea-vomiting and colds. Studies have proven that gingerol and chagoal in its content inhibit the growth of cancer cells, sensitize cancerous cells by halting the cell cycle, and have antimetastatic and anti-invasive activities by targeting the signaling pathways of different cells. In addition, nausea-vomiting, which is one of the most common symptoms of cancer treatments, has been shown to have an antiemetic effect in the use of ginger. In excessive consumption, it can lead to bleeding disorders by reducing the platelet value in the blood (Bayraktar, 2021). A natural product Zerumbone, which is a ginger sesquiterpenoid phytochemical have antimetastatic effects on glioblastoma by reducing matrix metalloproteinase (MMP)-2/-9 expression, downregulating the mRNA experission level of IL-1β and MCP-1, two genes contributing to MMPs expression, inhibiting expression of Akt and total p44/42 MAPK (Erk1/Erk2), all of which have roles in repression of migration, invasion, and metastasis (Jalili-Nik et al. 2021).

CONCLUSION

CAMs are frequently used by the patients with brain tumors. Underlying needs and expectations, as well as potential interactions with tumor-specific treatments, and financial and quality of life burden, should be discussed with patients and caregivers. More research into the possible therapeutic and/or toxicological effects of CAMs on brain tumors would be necessary to fully comprehend the circumstances under which these CAMS may be safely used by people as a neuroprotective drug.

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