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Purple Sweet Potato Phytochemicals: Potential Chemo-preventive and Anticancer Activities

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Abstract

BACKGROUND: Purple sweet potato (PSP; Ipomoea batatas (L.) lam.) is a perennial plant from the morning glory family Convolvulaceae. This plant contains many functional compounds and a high concentration of anthocyanins and phenols, in contrast to other sweet potato plants of different colors. Both in vitro and in vivo studies have shown that parts of PSP have interesting functions in the setting of cancer.

AIM: This article is a collective review of the potential properties of PSP in cancer, with an emphasis on its effects in breast, bladder, colorectal, liver, gastric, and cervical cancers.METHODS: Major English research databases, including PubMed, Web of Science, Scopus, and Google Scholar, were searched for studies evaluating the activity of PSP against cancer published ended in Mei 2020.

RESULTS: The search yielded 72 articles relevant to this topic. Of note, PSP phytochemicals such anthocyanins and caffeoylquinic acid derivatives act as an antioxidant that scavenges free radicals and regulates the Keap1-Nrf2 signaling pathway, acts as an antimutagenic agent, and has anti-inflammatory activity by inhibiting activation of mitogen-activated protein kinases and the NF-κB pathway as a Chemo-preventive mechanism. Furthermore, PSP can promote apoptosis, cell cycle arrest, inhibit proliferation, cell growth inhibition, and inhibit cancer progression that actions collectively sum as anticancer activity in many cancer cells. The primary target-signaling pathway that is interfered by PSP is the phosphatidylinositol-3-kinase/protein kinase B pathway, which is a very common mutated pathway in cancer cells that regulates many physiologic processes inside the cells.

CONCLUSION: As a promising medicinal plant that may serve as a Chemo-preventive and anticancer agent, further research on PSP is required to determine its clinical uses and potential as a food supplement.

Introduction

Cancer is the second leading cause of mortality worldwide, with 19.3 million new diagnoses and 10 million cancer-related deaths in 2020, for which 70% of the mortality occurred in low- and middle-income countries [1]. The most commonly diagnosed type of cancer is lung cancer, followed by female breast, prostate, and colorectal cancers [2]. Furthermore, lung cancer has become the leading cause of cancer-related mortality, followed by colorectal, stomach, and liver cancers [2]. Behavioral and dietary risks can increase the risk of cancer mortality, and the top five behavioral and dietary risks are low consumption of fruits and vegetables, high body mass index, physical inactivity, alcohol consumption, and use of tobacco [3]. Conventional treatment modalities for cancer remain widely used today while various novel cancer treatments are under investigation [4]. Nevertheless, researchers continue searching for the best treatment to cure cancer. In this context, medicinal herbs with active phytochemicals have already been recognized as a complementary approach in cancer treatment, showing effects for survival, modulation of the immune response, and quality of life improvement of cancer patients [5]. Abundant evidence has mounted showing that bioactive phytochemicals affect cancer-related pathways, including cell signaling, regulation of the cell cycle, response to oxidative stress, inflammation, and inhibition of cancer cell growth. Several candidates for the phytochemical compounds that have beneficial effects are flavonoids, carotenoids, and phenolic acids [6].

Materials and Methods

This article aims to review the collective literature on the purple sweet potato (PSP) plant in terms of its

Chemo-preventive and anticancer activities. A literature search strategy was performed using PubMed, Web of Science, Scopus, and Google Scholar to find articles published in the English language that ended in May 2020. The keywords used were the following: "purple sweet potato," "cancer," "Chemo-preventive," and "antitumor." All retrieved articles were sorted based on the subtheme classifications in this article into PSP constituents, chemoprevention, and anticancer activity. The objective of this review is to present studies that were published about PSP in terms of its potential Chemo-preventive and anticancer activities as a supplement, health product, and adjuvant therapy, and to further the knowledge base for the medical community.

Results

Overall, this article search strategy found 72 articles. Twenty-five articles were attributed to PSP constituents and the other 22 articles records were about chemoprevention and 25 articles, respectively, were about the anticancer activity of PSP.

PSP

PSP is a perennial plant that is part of the morning glory family (*Convolvulaceae*). The tuber part of PSP is the primary organ that is most harvested because its main functions are storing nutrients and reproduction. The plant ranges in size and colors of skin and flesh, and the skin and flesh colors indicate differences in the concentrations of active substances in the plant [7]. The leafy greens from PSP, which have a high content of bioactive phytochemicals such as anthocyanins and phenolic acids, are consumed mostly in African and Asian countries and are very popular because of the belief in their beneficial health effects [8]. Many nutrient- and anthocyanin-rich plants have a purple to dark purple flesh color [9].

In particular, PSP has a primary role as an energy supplier and a source of nutrients due to its richness in carbohydrates, fiber, β-carotene, minerals, and other nutrients [10]. The plant is cultivated in the tropics and subtropics and some regions in developing countries [11]. Because PSP has many beneficial health properties [12], the plant has been used in the health sector because of its function as an antioxidant, anti-inflammatory, and anticancer activity in various cancer treatments (Table 1) [13].

Constituents

As a sweet potato, PSP is a healthy food because of its various metabolites, primarily antioxidants. The different flesh color of the sweet potato has been observed and measured by its metabolites, particularly flavonoids. A liquid chromatography/electrospray ionization-mass spectrometry study determined the metabolic profiles of different types and colors of sweet potato plants and identified a total of 213 metabolites [14]. Similar to these sweet potato metabolic profiles, other studies reported the same constituents in the PSP metabolite profile, consisting of primary and secondary metabolites [15], [16]. PSP has nutritional characteristics as a bioactive compound divided into primary metabolites consisting of certain carbohydrate compounds, proteins, and lipids. In addition, secondary metabolites such as carotenoids, flavonoids, anthocyanins, and phenolic acids derivatives have great potential for human health. However, bioactivities of PSP vary according to the PSP varieties, plant parts, extraction method, solvent type used, storage, and processing [13].

Table 1: Mechanism of anticancer activity of purple sweet potato extracts in cancers

Cancer	Mechanism	Cell/animal models	Reference
Breast cancer	Antiproliferative activity	Nude mice bearing MCF-7-induced tumors	Xu *et al*. (2018)
	Antiproliferative activity	MCF-7	Vishnu *et al*. (2019)
	Induce apoptosis	MCF-7, MDA-MB-231	Xu *et al*. (2018), Han *et al*. (2018)
	Inhibit cell cancer growth	MCF-7, MDA-MB-231	Xu *et al*. (2018), Sugata *et al*. (2015), Han *et al*. (2018)
	Anticancer progression	4TI mice with metastasis	Han *et al*. (2008)
Bladder cancer	Antiproliferative activity	BIU87 cell line	Li *et al*. (2018)
	Induce apoptosis	BC 5637, T24 cell lines	Li *et al*. (2018)
Colorectal cancer	Cell cycle arrest	SW480 cell line	Lim *et al*. (2013)
	Antiproliferative activity	CF-1 mice with colon aberrant crypt foci	Lim *et al*. (2013)
	Antiproliferative activity	HCT-116 cell line	Vishnu *et al*. (2019)
	Induce apoptosis	CF-1 mice with colon aberrant crypt foci	Lim *et al*. (2013)
Liver cancer	Antioxidant	HepG2 cell line	Lee *et al*. (2019), Chen *et al*. (2013)
	Induce apoptosis	HepG2 cell line	Chen *et al*. (2013)
	Antiproliferative activity	HepG2 cell line	Sun *et al*. (2019), [81]
Cervical cancer	Antiproliferative activity	HeLa cell line	Vishnu *et al*. (2019)
	Induce apoptosis	HeLa cell line	Vishnu *et al*. (2019)
	Cell cycle arrest	HeLa cell line	Vishnu *et al*. (2019)
Gastric cancer	Inhibit cell cancer growth	SGC7901 cell line	Wu *et al*. (2015)
	Induce apoptosis	SGC7901 cell line	Wu *et al*. (2015)
	Inhibit cell cancer growth	SNU-1 cell line	Sugata *et al*. (2015)
	Induce apoptosis	SNU-1 cell line	Sugata *et al*. (2015)

Carbohydrates from PSP, such as starch, are the dominant compounds, followed by monosaccharides and oligosaccharides such as sucrose, maltose, and glucose [17], [18], [19]. The fiber content of PSP includes polysaccharides such as pectin, lignin, cellulose, and hemicellulose. Monosaccharides such as rhamnose, arabinose, galactose, and mannose are also found in PSP [20]. The PSP protein component is dominated by sporamin [21]. Other proteins from PSP are acidic glycoproteins and arabinogalactan [22], [23]. Isoleucine, valine, methionine, cysteine, phenylalanine, and tyrosine represent the primary amino acids from PSP [24]. Small amounts of lipids are also found in sweet potatoes [25].

The polyphenolic compounds found in PSP are mainly phenolic acids, flavonoids, stilbene, and lignans [26]. Several studies have been published on the antioxidant activity of polyphenolic compounds. The periderm region, cortex, and stele of the tuber tissue are the organs that contain the highest amount of polyphenolic compounds in PSP [27].

Total phenolic compounds in PSP consist of phenolic acids including caffeoylquinic acid and caffeoyl diglucoside. The root part of the PSP contains the primary type of polyphenols, represented by caffeoylquinic acid derivatives [28]. The following flavonoids are part of phenolic compounds consisting of anthocyanins, quercetin, myricetin, luteolin, and kaempferol that were found in the orange-flesh- and purple-flesh-colored sweet potato [16].

The types of phenolic acids in sweet potatoes are typically hydroxybenzoic acid and hydroxycinnamic acid [29]. Chlorogenic acid has been known as the major compound as a free radical scavenger in sweet potatoes [30]. The phenolic compounds found in sweet potatoes serve to contribute to free radical scavenging [31].

Flavonoids are important secondary metabolites produced in plants and have many derivatives, such as anthocyanins, flavans, flavones, flavanone, flavonols, and chalcone [32]. Anthocyanin derivative examples are delphinidin, cyanidin, pelargonidin, malvidin, and peonidin [33]. These phytochemical compounds are found in many fruits and flowers that are colored, and they offer health benefits such as free radical scavengers, anticancer agents, and anti-inflammatory agents, and chemoprevention providers [34], [35]. Furthermore, some metabolites, including flavonoids and phenolic acids, were identified as existing in higher concentrations in PSP than other sweet potatoes. Anthocyanins, quinic acid, and ferulic acid are predominant in PSP. Flavonoids such as quercetin, chrysoeriol, and O-hexoside were found in higher concentrations in PSP than in sweet potatoes with other flesh colors [15], [16].

Chemoprevention

PSP anthocyanins, a flavonoid class, are water-soluble pigments with the reported possible role as an antioxidant, anti-inflammatory agent, and antimutagenicity as a component of chemoprevention in cancer. Anthocyanins also have an anticancer activity such as inhibiting proliferation, promoting cell cycle arrest, and inducing apoptosis (Figure 1) [36], [37], [38], [39], [40]. In the process of carcinogenesis, inflammatory cells release reactive nitrogen species and reactive oxygen species (ROS) that may damage DNA and lead to mutations [41]. Anthocyanins are antioxidant compounds that can capture free radicals, thereby reducing the damage from oxidative stress to the genome, and also prevent transformation to the malignant cell type by gene mutation and ultimately the occurrence of tumors [42].

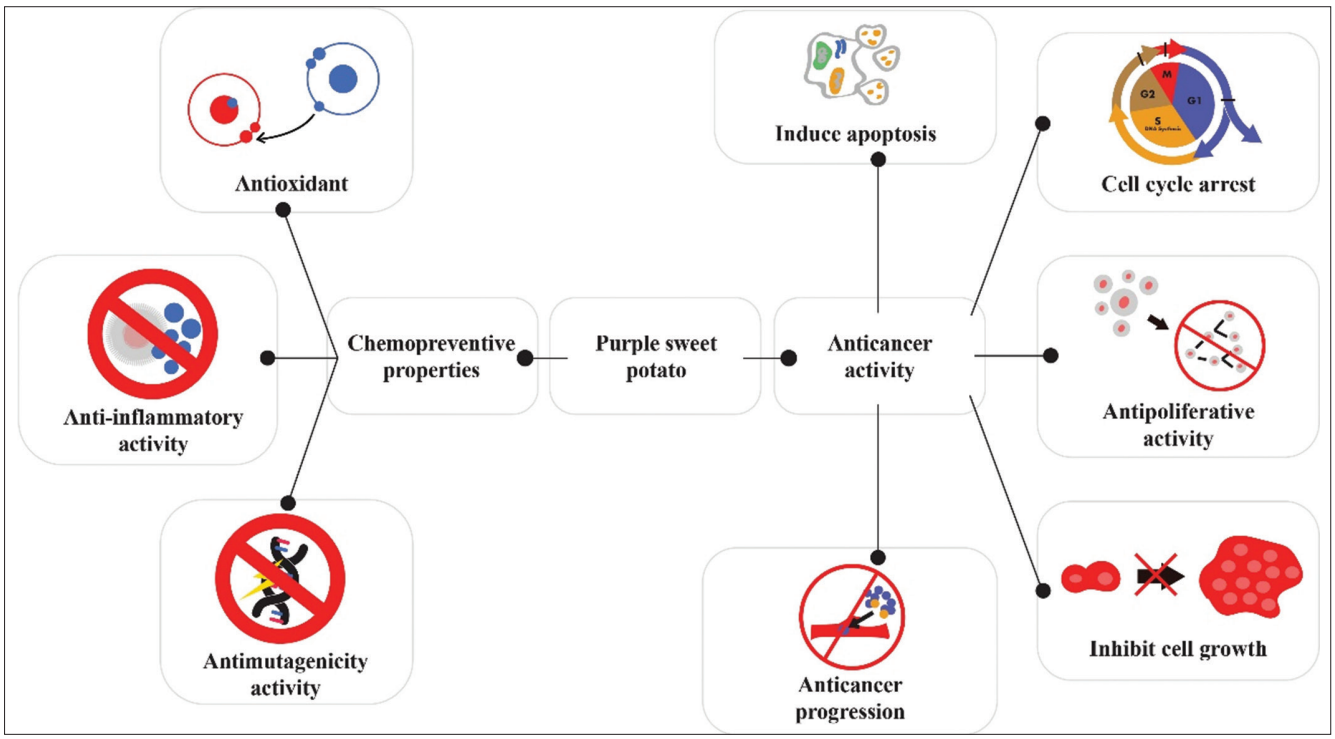

Figure 1: Schematic of the properties of purple sweet potato (PSP). This plant offers beneficial medicinal effects due to its Chemo-preventive properties, such as antioxidant, anti-inflammatory, and antimutagenicity activities, thereby protecting normal cells from tumorigenesis. In addition, PSP has an anticancer activity that consists of inducing apoptosis, arresting the cell cycle, contributing to antiproliferation, and inhibiting cell growth, and cancer progression

Glycosides of polyhydroxy or polymethoxy derivatives of 2-phenyl benzopyrylium compose the structure of anthocyanins flavonoids, which have two aromatic rings and a heterocyclic ring [41]. These chemical frameworks allow anthocyanins to have a strong potential to donate electrons, which is an essential antioxidant property [41]. Specifically, the 3', 4', and 5' hydroxyl positions on the B ring and the 3' hydroxyl positions on the C ring are the part of anthocyanins that provide the properties to create an antioxidant effect. Research has found that the elemental activity of the antioxidant response is affected by anthocyanins through the Keap1-Nrf2 protein signaling pathway, which is an important protein in the antioxidant protective response [42], [43], [44].

As reported by Yoshimoto *et al*. [45], PSP caffeoylquinic acid derivatives were used to observe antimutagenic effects in *Salmonella typhimurium* TA98 undergoing treatment targeting the Trp-P-1 mutagen. Results showed that caffeoyl groups bound to quinic acid could inhibit mutagenic activity by protecting them from DNA damage. Moreover, previous data from Konczak-Islam *et al*. [46] reported a positive effect of anthocyanin-rich extract of PSP to inhibit reverse mutation of S. typhimurium by direct reaction with activated mutagen in a dose-dependent manner. Furthermore, research from [47] reported the positive effect of antimutagenicity from the extract of PSP leaves through inhibiting mutation induction by Trp-P-1 on *S. typhimurium* TA98 because of the caffeoylquinic acid derivatives that were identified in the plant leaves.

During the abnormal cellular transformation that occurs in the process of becoming a cancer cell, multiple mutations in the somatic cell can lead to cumulative genetic defects and thus promote cancer [42]. Anthocyanins protect human cells with an antioxidant ability from a severe mutation from the high level of oxidative stress by preventing point mutation. Thereby, the antimutagenicity effect is part of anthocyanin's ability to act in human somatic cells [42].

Other research reported that anthocyanins may inhibit mitogen-activated protein kinase (MAPK) and activator protein 1, which play a role in promoting cancer formation. Inhibition of transcriptional activity and transformation of the cell from activator protein 1 by anthocyanins, such as delphinidin, petunidin, and cyanidin, has been demonstrated in JB6 cells. Delphinidin is an anthocyanin derivate that can block MAPK/extracellular signal-regulated kinase (ERK) protein kinase, stress-activated protein kinase/ERK protein kinase, and c-Jun phosphorylation, and thus plays a critical role in the signaling pathway that can prevent cancer promotion [48], [49]. The chronic inflammation process that occurs in this setting is often the vanguard for tumors. Chronic inflammation plays an important role in the tumorigenesis process that involves the release of inflammatory factors from abnormal overexpression of these factors. Research suggests that the expression and release of inflammatory factors may be regulated by anthocyanins acting to block nuclear factor κ light chain enhancer of activated B-cells (NF-κB) as a transcription factor and function to provide anti-inflammatory action through multiple signaling pathways [42]. For example, inhibition of NF-κB activation stimulated by an external trigger, such as lipopolysaccharide or interferon-γ, may result from cyanidin, delphinidin, and petunidin directly acting on the phosphoinositide-3-kinase/protein kinase B and MAPK pathways [42]. Another study found that anthocyanins may inhibit the activation of the signal transducer and activator of transcription 3, and downregulate the expression of NF-κB [42]. In the case of tumor growth and metastasis, regulating the inflammatory response has a significant contribution to preventing cancer development, and the antioxidant and anti-inflammatory activities of anthocyanins may create a positive impact on this condition of tumor development [41]. The mechanism to control the regulation of cancer proliferation is to inhibit the G0/G1 interphase from the cell cycle by upregulating two cyclin-dependent kinase inhibitors, p21 and p27, and by suppressing cyclins D1 and E [41].

Anticancer activity

Breast cancer

Breast cancer is the most common cancer among women and the leading cause of cancer-related mortality in women, with an estimated 2.1 million annual cases. In 2018, approximately 627,000 women died of breast cancer. Breast cancer more commonly affects women in developing countries, and the global incidence is increased [2]. Breast cancer-associated gene 1 (*BRCA1*) and *BRCA2* are the two main genes correlated with susceptibility to breast cancer. The lifetime risk because of mutation in these genes for progression to breast cancer is 60–85%, and this mutation is found in 2–3% of all breast cancers [50]. A current area of significant research focus is breast cancer and dietary factors. Studies showed that various breast cancer cell lines treated with PSP tuber and leaves show significant effects for cancer antiproliferation. The MCF-7 breast cancer cell line treated with anthocyanins extracted from PSP leaves and tubers underwent apoptosis through the caspase cascade pathway and exhibited the effect of cell cycle arrest that concluded antiproliferative activity. Based on these study results, PSP tubers showed great effects in breast cancer cell lines [51], [52].

β-Sitosterol-D-glucoside (β-SDG) is a newly isolated phytosterol from sweet potato and has been reported to have effects on various cancer cell lines due to its Chemo-preventive and antiproliferative activities [53], [54], [55]. Treatment with β-SDG in an animal model showed a notable reduction in tumor size and weight. Furthermore, the animal study reported a reduced level of serum cancer antigens CA125 and CA153 in b-SDG-treated mice compared to the control group. In the *in vitro* experiments, β-SDG demonstrated

apoptotic cell induction in MCF-7 and MDA-MB-231 cell lines and suppressed breast cancer growth [56].

The phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) signaling pathway prevents apoptosis and promotes cell survival in human cancer. Dysregulation of the PI3K/Akt pathway is closely related to tumor promotion and cancer development [57]. In addition, PI3K triggers the retention of cytoplasmic Bax and Akt inhibition on the outer membrane of mitochondria to translocate of Bad protein. This signal also facilitates Bad and Bcl-xl interaction to maintain the integrity of the mitochondrial membrane and block cytochrome *c* from being released to the cytoplasm [58].

In another study, β-SDG was shown to induce the mitochondrial apoptotic pathway by an increase of the miR-10a-5p significantly in the MCF-7 breast cancer cell line. This result and other findings for this cell line investigation suggested that the mechanisms for apoptosis were via both the caspase-dependent and caspase-independent pathways. Thus, the breast cancer cells treated with β-SDG significantly led to cell apoptosis [56].

Regarding the effects of PSP in different components of the plant, Sugata *et al*. [59] reported a comparison between peeled and unpeeled PSP in terms of their effects in cancer cell lines to investigate the function of anti-inflammatory properties and anticancer activity. The MCF-7 breast cancer cell lines that were subjected to the treatment showed anticancer activity in a concentration- and time-dependent fashion that inhibited cell line growth but showed obvious differences between the extracts.

Research findings were reported by Han *et al*. [60] on the use of daucosterol isolated from PSP. An *in vitro* study showed that daucosterol induced apoptosis through Pi3k/Akt/NF-κB in MCF-7 cell lines, whereas an animal study showed that daucosterol linoleates inhibited tumor growth and weight in MCF-7 xenograft nude mice. Daucosterol downregulated expression of Bcl-xl, Bcl-2, and X-linked inhibitor of apoptosis protein and otherwise caused an increase in Bax with bad protein, with activation of apoptosis by the caspase-dependent cascade in tumor tissue. In the 4TI mouse model of spontaneous metastasis, daucosterol linoleates inhibited the progression of metastasis, decreased the number of metastasis foci in the lung, and inhibited the size of the metastatic tumor and the distribution of metastatic foci in lung tissue. An *in vitro* study confirmed these results with suppressed expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in both tumor and lung tissue [60].

Bladder cancer

Globally, the most common cancer affecting older adult patients is bladder cancer, with an estimated 549,000 diagnoses and 200,000 cases of mortality annually. This cancer more commonly affects male versus female patients and predominantly occurs in Western Europe and North America [2], [61], [62]. Bladder cancer is the second most common urologic cancer in Indonesia after prostate cancer and is almost always correlated with previous bladder stones [63].

An *in vitro* study revealed that PSP contributed to the antitumor effect in BC 5637 and T24 cells by suppressing cell viability, augmenting the MMP collapse, and promoting apoptosis by upregulating proapoptotic proteins and downregulating anti-apoptotic proteins, and inducing cell cycle arrest, suggesting suppression of the PI3K/Akt signaling [64].

The unregulated activation in the PI3K pathway has been detected in many cancer diseases [65], [66]. In human cancer, the most common activated protein signaling pathway is the PI3K signaling pathway, which works to regulate and link oncogenes and various receptor classes to perform essential cellular functions [67]. Finally, other findings showed that anthocyanins from PSP can inhibit cell growth, and antiproliferation activity of bladder cancer BIU87 cell lines by promoting apoptosis in a time- and dose-dependent manner. Refer to this study that needs more information PSP to the molecular mechanism on bladder cancer cell from *in vitro* level to *in vivo* experiment [68].

Colorectal cancer

The incidence of colorectal cancer remains more than 1.8 million cases in 2018 [2]. Colorectal cancer is cancer in colonic crypt cells that have expressed tumor suppressor genes and oncogenes and thereby triggered mutation. Polyp formation resulting from the sum of mutations in somatic cells in the colon can lead to unregulated mitotic division in colonic mucosal cells. The presence of aberrant crypt foci is characteristic in colorectal mucosa that can be detected in early changes of the mucosal colon [69]. In one study, the HCT-116 cell line of colon cancer was treated with anthocyanins purified from sweet potato leaves and tubers and showed apoptosis activity and cell cycle arrest that was concluded as antiproliferative activity. This study showed that PSP leaves showed greater effects in colon cancer cell lines [51].

The study by Lim *et al*. [70] reported that anthocyanins in PSP extracts induced cell cycle arrest and possibly decreased the number of cells by stopping the cell cycle at the G1 interphase, by inhibiting cell proliferation, and by inducing apoptosis in the SW480 colonic cancer cell line. In CF-1 mice with colon aberrant crypt foci induced by azoxymethane and treated with dietary PSP, results were preponderant apoptotic caspase-3 expressions and decreased proliferating cell nuclear antigen, thus providing positive protection in colorectal cancer.

An *in vivo* study reported four types of dietary supplements using the AIN-76A formula, PSP flesh,

PSP skin, and anthocyanin-rich extract for APC^{MIN} mice to assess the effects of these components/formulations in preventing colorectal cancer. Results showed that a diet rich in anthocyanins – PSP flesh, skin, and anthocyanin-rich extract – could reduce the adenoma number in APC^{MIN} mice, suggesting a Chemo-preventive and protective effect in colorectal cancer [71]. In another study by Hagiwara *et al*. [72] showed that PSP can protect against 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP) promotion of cancer growth. Furthermore, PSP showed efficacy against the development of PhIP in colon tissue in an *in vivo* study on male rats type F344/DuCrj treated with a diet containing 1,2-dimethylhydrazine an initiator carcinogen, for which dietary treatment was continued with PhIP as the second carcinogen for carcinogenesis in colon cancer.

A study on the activity of polysaccharides isolated from PSP, consisting of glucose, galactose, xylose, and rhamnose, reported a positive effect on antioxidant and antitumor activity in SW620 colon cancer cell lines under treatment. The analytic method using Annexin V-EGFP/PI and flow cytometry showed strongly inhibited cell growth. The apoptotic process happened in late apoptotic SW620 colon cancer cells. It can be assumed that the PSP polysaccharides are part of the apoptosis-inducing process in tumor cells [73]. In addition, a study reported that WiDr colon adenocarcinoma cell lines treated by PSP extracts from the peeled and unpeeled plants exhibited anticancer activity in a concentration- and time-dependent fashion, in which cell growth was inhibited and no significant difference was observed between peeled and unpeeled extracts [59].

Liver cancer

Liver cancer commonly causes mortality in many regions globally, particularly in East Asia and the Pacific, South Asia, and parts of Sub-Saharan Africa, where the disease is primarily caused by a long-term history of liver infection and fatty liver disease [74]. Hepatocellular carcinoma is the primary liver cancer and accounts for 80% of the liver cancer cases worldwide [75]. Liver cancer is a leading cause of cancer-related mortality in several regions globally, with 953,000 diagnoses and 819,000 cases of mortality in 2017 [76]. Hepatocellular carcinoma is a major contributor to mortality in many countries with low- or mid-level resources as a significant burden disease [77].

A study by Lee *et al*. [78] reported that polyphenols improved antioxidant action *in vitro*. Primarily, anthocyanins may protect from DNA mutations caused by *t*-BHP in rat liver cells and normalized ROS in cell damage by resulting from oxidative stress [79]. However, the antioxidant functions of PSP concerning *tert*-butyl hydroperoxide-stimulated HepG2 cells showed a strong antioxidant effect and suppressed oxidative damage by removing ROS. This study documented that PSP has the highest number of polyphenols and anthocyanins compared with other sweet potatoes. Pretreatment of HepG2 cells with an extract of a PSP cultivar impacted the eradication of ROS, which may preserve cell function and prevent oxidative cellular damage [78]. Moreover, a study comparing ten varieties of sweet potato conducted by Sun *et al*. [80] showed that the PSP flesh has more highly phenolic content than other sweet potato varieties and had antioxidant and antiproliferative activities against the human hepatic carcinoma cell lines HepG2.

Other research reported that polysaccharides from PSP, such as β-D-glucose chitosan pyranose and glycoprotein, had a potential antitumor effect through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay in HepG2 cells [81]. Polysaccharide derivatives induced cell apoptosis in HepG2 cell lines because of the increased expression of Bax and Bad proteins that initiated apoptosis in cancer. In addition, these PSP polysaccharides inhibited angiogenesis and affected the cancer cell cycle [82].

Another study to explore antitumor activity from PSP by inducing apoptosis in HepG2 showed that PSP induces apoptosis in HepG2 with marked upregulation of Fas, FADD, caspase-3, caspase-8, and p53 mRNA and protein expression levels. Moreover, active fragments of extrinsic pathway caspase-8, and intrinsic pathway caspase-9, and common pathway caspase-3 of apoptosis cascade showed a significant increase, especially caspase-3. These findings may indicate that PSP may stimulate inhibition of cell proliferation and promote cell apoptosis in HepG2 cell lines by entering the extrinsic pathway and also that p53 plays an important protein in this pathway [83].

Cervical cancer

Cervical cancer was estimated to have 570,000 diagnoses and 311,000 cases of mortality globally in 2018. This disease took fourth place as the most frequently clinically diagnosed cancer, and it is the leading cause of cancer-related mortality among women [2]. The cause of cervical cancer is a group of carcinogens that comprise the 12 oncogenic types of human papillomavirus (HPV), based on an IARC monograph. Other factors that contribute to cervical cancer are immunosuppressive conditions, parity, smoking, and oral contraceptive use [84], [85]. Mucosal HPV cervical carcinoma is divided into low- and high-risk HPV [86]. High-risk HPV tends to lead to cervical cancer with the following oncogenic types of HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 [87], [88]. A study in Indonesia showed that the most common HPV types are 16, 18, 45, and 52 [89]. The E7 protein in high-risk HPV induces inactivation of the Rb protein, whereas the E6 protein promotes the degradation of the tumor protein P53 to modulate carcinogenesis in cervical cancer [86], [88].

An *in vitro* study found that the effect of PSP tubers and leaves in HeLa cells showed a positive result. The cervical cancer HeLa cell line treated with anthocyanins that were purified from PSP leaves and tubers showed progression to apoptosis, cell cycle arrest, and antiproliferative activity. Extracts of PSP leaves had greater effects on cervical cancer cell lines than the tubers [51].

Another study reported that PSP polysaccharides – glucose, galactose, β-D-glucose chitosan pyranose, and glycoprotein – had antitumor activity in HeLa cells. Results on MTT assay showed a potential antitumor effect with these purified polysaccharides. This study called for more investigation on the molecular mechanisms of the antitumor effects of PSP in cervical cancer cell lines [81].

Gastric cancer

Gastric cancer is still important cancer worldwide as the fifth most often diagnosed cancer and the third leading cause of cancer-related mortality, with an estimated incidence of more than 1 million cases and mortality in 783,000 cases in 2018 [2]. In the United States, more than 95% of all cases of gastric cancers are diagnosed in patients older than 40 years; the average age of onset is 68 years [90]. New cases of gastric cancer have dramatically declined; however, the rate of decline has recently slowed and stabilized and has even reversed with a trend toward a slight increase in young adults [91].

A report by Wu *et al*. [73] found that polysaccharides from PSP positively correlated with cell growth inhibition and apoptotic induction in SGC7901 gastric cancer cells. The constituents of PSP polysaccharides investigated were glucose, galactose, xylose, and rhamnose. The authors concluded that PSP polysaccharides play an important role in chemoprevention and anticancer activity for this cell line [73].

Other research used a comparison between the effects of peeled and unpeeled PSP extracts on cancer cell lines to investigate the function of anti-inflammatory properties and anticancer activity. Positive effects were reported for SNU-1 gastric cancer cells through growth inhibition of cell lines with no significant difference observed between peeled and unpeeled PSP. Nevertheless, apoptosis induction in the SNU-1 cell line only occurred with treatment using peeled PSP crude extract, but these observations need further elucidation [59].

Conclusions

Multiple such compounds have been discovered in PSP and present positive and significant results. The main compounds that have been investigated are the PSP polysaccharides, flavonoids, phenolic acids, and sterol derivatives. For a better understanding of the PSP on Chemo-preventive and anticancer effects, more *in vitro* research and clinical trials are needed to explore the potential of the plant's many bioactive compounds. Future research should focus on these components to more fully explore the properties of PSP considering as promising herbs as food products and pharmaceutical products, ranging from supplements, causative drugs, and adjuvant drugs, for all health sectors and primarily for cancer disease.

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