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

Mochamad Rizki Budiman1,4*, Hesti Lina Wiraswati1,4*, Andri Rezano1,4*

1Graduate School of Biomedical Sciences Master Program, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia; 2Department of Cellular and Molecular Biology, Faculty of Medicine, Universitas Pasundan, Bandung, Indonesia; 3Department of Biomedical Sciences, Division of Parasitology, Faculty of Medicine, Universitas Padjadjaran, Jatnangor, Indonesia; 4Department of Biomedical Sciences, Division of Cell Biology, Faculty of Medicine, Universitas Padjadjaran, Jatnangor, Indonesia

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 May 2020.

RESULTS: The search yielded 72 articles relevant to this topic. Of note, PSP phytochemicals such as 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 acts 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 (PI3K/AKT) pathway as a Chemo-preventive mechanism. Furthermore, PSP can promote apoptosis, cell cycle arrest, inhibit proliferation, cell growth inhibition, and inhibit cancer progression that acts 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 (PI3K/AKT) 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].

| Cancer          | Mechanism               | Cell/animal models       | Reference |
|-----------------|-------------------------|--------------------------|-----------|
| Breast cancer   | Antiproliferative       | Nude mice bearing MCF-7-induced tumors | Xu et al. (2018) |
|                 | activity                | MCF-7                    | Vishnu et al. (2019) |
|                 | Antiproliferative       | MCF-7, MDA-MB-231        | Xu et al. (2018), Han et al. (2018), Xu et al. (2018), Sugata et al. (2015), Han et al. (2018) |
|                 | activity                | HCT-116 cell line        | Lim et al. (2013) |
|                 | Induce apoptosis        | BC 5637, T24 cell lines  | Li et al. (2018) |
|                 | HCT-116 cell line       | BC 5637, T24 cell lines  | Lim et al. (2013) |
|                 | Induce apoptosis        | HCT-116 cell line        | Lim et al. (2013) |
|                 | Induce apoptosis        | CF-1 mice with colon aberrant crypt foci | Lim et al. (2013) |
|                 | Induce apoptosis        | CF-1 mice with colon aberrant crypt foci | Lim et al. (2013) |
|                 | Antioxidant             | HepG2 cell line          | Lee et al. (2019), Chen et al. (2013) |
|                 | Induce apoptosis        | HepG2 cell line          | Chen et al. (2013), Sun et al. (2019), [81] |
|                 | Antioxidant             | HepG2 cell line          | Chen et al. (2013), Sun et al. (2019), [81] |
|                 | Induce apoptosis        | HeLa cell line           | Vishnu et al. (2019) |
|                 | Induce apoptosis        | HeLa cell line           | Vishnu et al. (2019) |
|                 | Induce apoptosis        | SGC7901 cell line        | Wu et al. (2015) |
|                 | Induce apoptosis        | SGC7901 cell line        | Wu et al. (2015) |
|                 | Induce apoptosis        | 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].

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 polyphenolic 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 Chemopreventive 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](https://oamjms.eu/index.php/mjms/index)
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 derivative 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. Dauosterol 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 4T1 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 colon 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\textsuperscript{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\textsuperscript{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.

**Acknowledgments**

We would like to thank all people involved in this study, especially to Faculty of Medicine Universitas Pasundan for their supports.

**References**

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(1):209-49. https://doi.org/10.3322/caac.21660

2. Bray F, Ferlay J, Soerjomataram I. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492

3. Forouzanfar MH, Afshin A, Alexander LT, Anderson HS, Bachman VF, Biryukov S, et al. Global, regional, and national comparative risk assessment of 79 behavioral, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: A systematic analysis for the global burden of disease study 2015. Lancet. 2016;388(10053):1659. https://doi.org/10.1016/S0140-6736(15)00192-1

4. Xiang Y, Guo Z, Zhu P, Chen J, Huang Y. Traditional Chinese medicine as a cancer treatment: Modern perspectives of ancient but advanced science. Cancer Med. 2019;8(5):1958-5. https://doi.org/10.1002/cam4.2108

5. Yin SY, Wei WC, Jian FY, Yang NS. Therapeutic applications of herbal medicines for cancer patients. Evid Based Complement Alternat Med. 2013;2013:302426. https://doi.org/10.1155/2013/302426

6. Kapinova A, Kubatka P, Golubnitschaja O, Kello M, Zubor P, Solar P, et al. Dietary phytochemicals in breast cancer research: Anticancer effects and potential utility for effective chemoprevention. Environ Health Prev Med. 2018;23(1):36. https://doi.org/10.1186/s12199-018-0724-1

7. Dako E, Retta N, Desse G. Comparison of three sweet potatoes (Ipomoea batatas (L.) Lam) varieties of nutritional

---

https://oamjms.eu/index.php/mjms/index
22. Kusano S, Tamasu S, Nakatsugawa S. Effects of the white-skinned sweet potato (Ipomoea batata L.) on the expression of adipocytokine in adipose tissue of genetic type 2 diabetic mice. Food Sci Technol Res. 2005;11:369-2. https://doi.org/10.3136/fstr.11.369

23. Ludvik B, Hanefeld M, Pacini G. Improved metabolic control by Ipomoea batata (Caiapo) is associated with increased adiponectin and decreased fibrinogen levels in type 2 diabetic subjects. Diabetes Obes Metab. 2008;10(7):586-2. https://doi.org/10.1111/j.1463-1326.2007.00752.x

PMid:17645559

24. Arogundade LA, Mu TH. Influence of oxidative browning inhibitors and isolation techniques on sweet potato protein recovery and composition. Food Chem. 2012;134(3):1374-4. https://doi.org/10.1016/j.foodchem.2012.03.035

25. Deng F, Mu T, Zhang M, Abegunde OK. Composition, structure, and physicochemical properties of sweet potato starches isolated by sour liquid processing and centrifugation. Starch Stärke. 2013;65(1-2):162-1. https://doi.org/10.1002/star.201200106

26. La Bonte DR, Picha DH, Johnson HA. Carbohydrate-related changes in sweet potato storage roots during development. J Am Soc Hortic Sci. 2000;125:200-4. https://doi.org/10.21273/jashs.125.2.200

27. Li H, Wang X, Li Y, Li P, Wang H. Polyphenolic compounds and antioxidant properties of selected China wines. Food Chem. 2009;112:454. https://doi.org/10.1016/j.foodchem.2008.05.111

28. Zhao JG, Yan QQ, Xue RY, Zhang J, Zhang YQ. Isolation and identification of colorless caffeoyl compounds in purple sweet potato by HPLC-DAD-ESI/MS and their antioxidant activities. Food Chem. 2014;161:22-6. https://doi.org/10.1016/j.foodchem.2014.03.079

PMid:24837917

29. Harrison HF, Mitchell TR, Peterson JK, Wechter WP, Majetic GF, Snook ME, et al. Contents of caffeoylquinic acid compounds in the storage roots of sixteen sweet potato genotypes and their potential biological activity. J Am Soc Hortic Sci. 2008;133:492. https://doi.org/10.21273/jashs.133.4.492

30. Robbins R.J. Phenolic acids in foods: An overview of analytical methodology. J Agric Food Chem. 2003;51(10):2866-7. https://doi.org/10.1021/jf026182t

PMid:12720366

31. Oki T, Masuda M, Furuta S, Nishiba Y, Terahara N, Suda I. Involvement of anthocyanins and other phenolic compounds in radical-scavenging activity of purple-fleshed sweet potato cultivars. J Food Sci. 2002;67(5):1752-6. https://doi.org/10.1111/j.1365-2621.2002.tb08718.x

32. Rumbaoa RG, Cornago DF, Geronimo IM. Phenolic content and antioxidant capacity of Philippine sweet potato (Ipomoea batatas subsp. L.) on the expression of inflammatory status, pro-inflammatory factor levels, and anti-nutritional factors. Global J Sci Front Research. 2016;16(4):1-16.

33. Islam S. Sweet potato (Ipomoea batatas L.) leaf: Its potential effect on human health and nutrition. J. Food Sci. 2006;71:13-1. https://doi.org/10.1111/j.1365-2621.2006.tb06912.x

34. Bovelli-Benjamin AC. Sweet potato: A review of its past, present, and future role in human nutrition. Adv Food Nutr Res. 2007;52:1-59. https://doi.org/10.1016/s1043-4526(06)52001-7

PMid:17425843

35. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: An overview. ScientificWorldJournal. 2013;2013:162750.
36. Harborne JB, Grayer RJ. The anthocyanins. In: The Flavonoids. Berlin, Germany: Springer; 1988. p. 1-20.
37. Hou DX, Fuji M, Terahara N, Yoshimoto M. Molecular mechanisms behind the chemopreventive effects of anthocyanidins. Biomed Res Int. 2004;2004(5):321-5. https://doi.org/10.1155/s1110724304003040
PMid:15577196
38. Wang H, Fan W, Li H, Yang J, Huang J, Zhang P, et al. Functional characterization of dihydroflavonol-4-reductase in anthocyanin biosynthesis of purple sweet potato underlies the direct evidence of anthocyanins functions against abiotic stresses. PLoS One. 2013;8:78484. https://doi.org/10.1371/journal.pone.0078484
PMid:24223813
39. Lee SL, Chin TY, Tu SC, Wang YJ, Hsu YT, Kao MC, et al. Purple sweet potato leaf extract induces apoptosis and reduces inflammatory adipokine expression in 3T3-L1 differentiated adipocytes. Evid Based Complement Alternat Med. 2015. https://doi.org/10.1155/2015/126302
PMid:26170870
40. Sayuti K, Yenrina R. Natural and Synthetic Antioxidants. PMid:26170870
41. Lin B, Gong C, Song H, Cui Y. Effects of anthocyanins on adipocyte differentiation. Food Chem. 2007;55(23):9427-5. https://doi.org/10.1021/acs.jafc.8b01387
PMid:17335944
42. Rezano A, Sarwiyanti RY, Nurzafirah LR, Edwinanto L, Istiqomah AA, Gunawan T, et al. Evaluation of cell viability suppression of purple sweet potato extract against MCF-7 cell line. Res J Environ. 2020;24(3):74-9.
43. Lee JH, Lee JY, Park JH, Jung HS, Kim JS, Kang SS, et al. Immunoregulatory activity by daucosterol, a β-sitosterol glycoside, induces protective Th1 immune response against disseminated candidiasis in mice. Vaccine. 2007;25(19):3834. https://doi.org/10.1016/j.vaccine.2007.01.108
PMid:17680049
44. Wang QG, Gu JF, Gao YC, Dai YJ. Daucosterol inhibits colon cancer growth by inducing apoptosis, inhibiting cell migration and invasion and, targeting caspase signaling pathway. Bangladesh J Pharmacol. 2016;11(3-4). https://doi.org/10.3329/bjp.v11i2.25754
PMid:30589398
45. Shih PH, Yeh CT, Yen GC. Anthocyanins induce the activation of phase II enzymes through the antioxidant response element pathway against oxidative stress-induced apoptosis. J Agric Food Chem. 2007;55(23):9427-5. https://doi.org/10.1021/jf071933i
PMid:17935293
46. Thoppil RJ, Bhatia D, Barnes KF, Haznagy-Radnai E, Hohmann J, Darvesh AS, et al. Black currant anthocyanins abrogate oxidative stress through Nrf2-mediated antioxidant mechanisms in a rat model of hepatocellular carcinoma. Curr Cancer Drug Targets. 2021;12(9):1244-7. https://doi.org/10.2174/156800912803987968
PMid:22873220
47. Yoshimoto M, Okuno S, Yoshinaga M, Ishiguro K, Yamakawa O. Antimutagenticity of mono-, di-, and tricaffeoylquinic acid derivatives isolated from sweetpotato (Ipomoea batatas L.) Leaf. Biosci Biotechnol Biochem. 2002;66(11):2336-1. https://doi.org/10.1271/bbb.66.2336
PMid:12506969
48. Islam I, Shaikh AU, Shahidul IM. Oxidative stress and chemopreventive potentials of phytochemicals from Ipomoea batatas (L.) Lam. Int J Cancer Res. 2009;5(3):83-4. https://doi.org/10.3923/ijc.2009.83.94
49. Zhao Y, Xue Y, Oberley TD, Kinningham KK, Lin SM, Yen HC, et al. Overexpression of manganese superoxide dismutase suppresses tumor formation by modulation of activator protein-1 signaling in a multistage skin carcinogenesis model. Cancer Res. 2001;61(16):6082-8.
statistics, 2008. CA Cancer J Clin. 2008;58(2):71-96. PMid:18287387
63. Umbas R, Safrafi F, Muchtar CA, Djatiasoesanto W, Hamid AR. Urologic cancer in Indonesia. Jpn J Clin Oncol. 2015;45(8):708-2. https://doi.org/10.1093/jjco/hvy066 PMid:26085688
64. Li WL, Yu HY, Zhang XJ, Ke M, Hong T. Purple sweet potato anthocyanin exerts antitumor effect in bladder cancer. Oncol Rep. 2018;40(1):73-2. https://doi.org/10.3892/or.2018.6421 PMid:29749527
65. Luo J, Manning BD, Cantley LC. Targeting the PI3K-Akt pathway in human cancer: Rationale and promise. Cancer Cell. 2003;4(4):257-2. https://doi.org/10.1016/s1535-6108(03)00248-4 PMid:14585353
66. Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signaling control tumor cell growth. Nature. 2006;441(7092):424-30. PMid:16724053
67. Liu P, Cheng H, Roberts TM, Zhao JJ. Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov. 2009;8(8):627-4. https://doi.org/10.1038/nrd2926 PMid:19644743
68. Li WL, Ji GH, Zhang XZ, Yu HY. The influence and mechanisms of purple sweet potato anthocyanins on the growth of bladder cancer BUI87 cell. Zhonghua Yi Xue Za Zhi. 2018;98(6):457-9. PMid:29429260
69. Ryan-Harshman M, Aldoori W. Diet and colorectal cancer: Review for Reconstruction and Development, The World Bank; 2015. PMid:20075718
70. Lim S, Xu J, Kim J, Chen TY, Su X, Standard J. Anti-Tumor activity of components isolated from purple sweet potato polysaccharides. Carbohydr Polym. 2015;132:31-40. https://doi.org/10.1016/j.carbpol.2015.06.045 PMid:26085688
71. Asadi K, Ferguson LR, Philpott M, Karunasinghe N. Cancer-preventive properties of an anthocyanin-enriched sweet potato in the APC(MIN) mouse model. J Cancer Prev. 2017;22(3):135-6. https://doi.org/10.15430/jcp.2017.22.3.135 PMid:29018778
72. Hagware A, Yoshino H, Ichihara T, Kawabe M, Tamaso S, Aoki H, et al. Prevention by natural food anthocyanins, purple sweet potato color and, red cabbage color, of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-associated colorectal carcinogenesis in rats initiated with 1,2-dimethylhydrazine. J Toxicol Sci. 2002;27(1):57-8. https://doi.org/10.2131/jts.27.57 PMid:11915369
73. Wu Q, Qu H, Jia J, Kuang C, Wen Y, Yan H, et al. Characterization, antioxidant and antitumor activities of polysaccharides from purple sweet potato. Carbohydr Polym. 2015;132:31-40. https://doi.org/10.1016/j.carbpol.2015.06.045 PMid:26256216
74. Gelband H, Chen CJ, Chen W. Liver cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Cancer: Disease Statistics, 2016. Geneva: World Health Organization; 2007. p. 90. https://doi.org/10.1136/jcp.51.2.96 PMid:9602680
75. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1-17. PMid:12525422
76. Miller D, Puricelli MD, Stack MS. Virology and molecular pathogenesis of HPV (human papillomavirus) associated oropharyngeal squamous cell carcinoma. Biochem J. 2012;443(2):339-3. https://doi.org/10.1042/bj20112017 PMid:22452816
77. Tang A, Hallouch O, Chernyak V, Kamaya A, Sirlin CB. Epidemiology of hepatocellular carcinoma: Target population for surveillance and diagnosis. Abdom Radiol. 2018;43(1):13-5. https://doi.org/10.1007/s00261-017-1209-1 PMid:28647765
78. Lee JH, Woo KS, Lee HU, Nam SS, Lee BW, Lee YY, et al. Intracuticular reactive oxygen species (ROS) removal and cytotoxicity effects of sweet potatoes of various flesh colors and their polyphenols, including anthocyanin. Prev Nutr Food Sci. 2019;24(3):293-8. https://doi.org/10.3746/pnfs.2019.24.3.293 PMid:31608254
79. Lazze MC, Pizzala R, Savio M, Stivala LA, Prosperi E, Bianchi L. Anthocyanins protect against DNA damage induced by tert-butyl-hydroperoxide in rat smooth muscle and hepatoma cells. Mutat Res Toxicol Environ Mutagen. 2003;535(1):103-5. https://doi.org/10.1016/s1383-5718(02)00285-1 PMid:12547288
80. Sun Y, Pan Z, Yang C, Jia Z, Guo X. Comparative assessment of phenolic profiles, cellular antioxidant and antiproliferative activities in ten varieties of sweet potato (Ipomoea Batatas) storage roots. Molecules. 2019;24(24):4476. https://doi.org/10.3390/molecules24244476 PMid:31817653
81. Zhao J, Ruan H, Gao QP, Li MY, Tao YQ, Zheng Y. Anti-tumor activity of components isolated from purple sweet potato polysaccharides. J Zhejiang Univ Med Sci. 2011;40(4):365-3. PMid:21845748
82. Huang G, Huang H. The derivatization and antitumor mechanisms of polysaccharides. Future Med Chem. 2017;9(16):1931-8. PMid:29076350
83. Chen Y, Liu J, Cao C, Bian G, Jiang J. Anti-Tumor activity of purple sweet potato juice and its apoptosis-inducing mechanism in HepG2 cells. Food Sci. 2013;1:237.
84. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-9. https://doi.org/10.1002/(sici)1096-9896(199909)189:1<12:aid-path431>3.0.co;2-f PMid:10451482
85. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Meeting, World Health Organization and International Agency for Research on Cancer. Human Papillomaviruses. Geneva: World Health Organization; 2007. p. 90. https://doi.org/10.1002/food.19890331018
86. Arends, M J, Buckley CH, Wells M. Aetiology, pathogenesis, and their polyphenols, including anthocyanin. Prev Nutr Food Sci. 2015;20:1632-4. https://doi.org/10.1080/14755361.2015.10020378
87. Miller D, Puricelli MD, Stack MS. Virology and molecular pathogenesis of HPV (human papillomavirus) associated oropharyngeal squamous cell carcinoma. Biochem J. 2012;443(2):339-3. https://doi.org/10.1042/bj20112017 PMid:22452816
88. Tobing MD, Sahiratmadja E, Dinda M, Hernowo BS, Susanto H. Anthocyanin exerts antitumor effect in bladder cancer. Oncol Rep. 2012;27(1):57-8. https://doi.org/10.2131/jts.27.57 PMid:13503788
89. Bhutta ZA, Farzadfar K, Cousens S, Yirona B, Darmstadt GL, et al. Human papillomavirus genotypes profile in cervical cancer and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. JAMA Oncol. 2019;5(12):1749-8. https://doi.org/10.1001/jco.2018.36.15_suppl.1568 PMid:31580378
90. Tang A, Hallouch O, Chernyak V, Kamaya A, Sirlin CB. Epidemiology of hepatocellular carcinoma: Target population for surveillance and diagnosis. Abdom Radiol. 2018;43(1):13-5. https://doi.org/10.1007/s00261-017-1209-1 PMid:28647765
91. Bud EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1-17. PMid:12525422
92. Miller D, Puricelli MD, Stack MS. Virology and molecular pathogenesis of HPV (human papillomavirus) associated oropharyngeal squamous cell carcinoma. Biochem J. 2012;443(2):339-3. https://doi.org/10.1042/bj20112017 PMid:22452816
90. De B, Rhome R, Jairam V, Özbek U, Holcombe RF, Buckstein M, et al. Gastric adenocarcinoma in young adult patients: Patterns of care and survival in the united states. Gastric Cancer. 2018;21(6):889-9. https://doi.org/10.1007/s10120-018-0826-x

PMid:29691758

91. Merchant SJ, Kim J, Choi AH. A rising trend in the incidence of advanced gastric cancer in young Hispanic men. Gastric Cancer. 2017;20(2):226-4. https://doi.org/10.1007/s10120-016-0603-7

PMid:26924751