3 Biotech (2023) 13:246
https://doi.org/10.1007/s13205-023-03673-1

REVIEW ARTICLE

Anti-cancerous effect of corn silk: a critical review on its mechanism of action and safety evaluation

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Received: 24 February 2023 / Accepted: 13 June 2023 / Published online: 23 June 2023

Abstract
Cancer is a broad collection of diseases that can begin in almost any organ or tissue of the body. Corn silk is the hair-like stigmata of female maize flowers which is generally discarded as waste from maize cultivation. The current study targets the anti-cancer potential of corn silk and its bioactive compounds namely, polyphenols, flavonoids, and sterols. The polyphenols and flavonoids like quercetin, rutin, apigenin and beta-sitosterol are a range of compounds from corn silk which were investigated for their anticancer effect. Corn silk showed apoptotic and antiproliferative effects in cancer cells through different signalling pathways, essentially the serine/threonine kinases (Akt)/lipid kinases (PI3Ks) pathway. The study revealed that corn silk compounds target immune cell responses, induce cell cytotoxicity, and upregulate the expression of proapoptotic genes p53, p21, caspase 9, and caspase 3 in certain cancer cell lines including HeLa cervical cancer cells, MCF-7 breast cancer cells, PANC-02 pancreatic cancer cells and Caco-2 colon cancer cells. Flavonoids derived from corn silk enhance T cell mediated immune response and decrease inflammatory factors. Corn silk bioactive compounds were found to reduce the side effects of cancer therapy. Antioxidants of corn silk, quercetin and rutin help in reducing the nephrotoxicity of chemotherapeutic drugs. The study also suggests that corn silk has anti-cancerous potential as it targets tumour suppression and inhibits metastasis A dose of 500 mg/kg body weight of corn silk has been found safe for human consumption. Corn silk extract can be used as a preventive or therapeutic step to cure cancer. The anti-cancer property, mechanism and role of corn silk in controlling cancer-related side effects have been critically reviewed providing new scope for the use of corn silk in cancer therapy.

Keywords Anti-cancer · Corn silk · Phytochemicals · Apoptosis · Antiproliferative · Toxicity

Introduction

Cancer, also known as a neoplasm, is a group of diseases in which the cells grow abnormally, invade the adjacent cells or spread to other parts of the body (World Health Organisation 2019). According to the International Agency for Research on Cancer (IARC), about 19 million new cases of cancer were found in 2020 and 9 million cases were from Asia alone, with lung cancer having the maximum number of incidents (1,315,136). There were about 9.9 million deaths from cancer in 2020 and Eastern Asia reported the highest number of deaths from cancer (The International Agency for Research on Cancer 2020). Lung cancer (1.7 million deaths), colorectal cancer (9,35,173 deaths), liver cancer (8,30,180 deaths), stomach cancer (7,68,793 deaths), breast cancer (6,84,996 deaths), oesophageal cancer (5,44,076 deaths), pancreatic cancer (4,66,003 deaths) and prostate cancer (3,75,304 deaths) had the highest mortality rates. Approximately 1,958,310 (including 54,540 cases of oral cancer, 348,840 cases of digestive system cancer, 256,290 cases of respiratory system cancer, 104,930 cases of skin cancer, 300,590 cases of breast cancer, 414,350 cases of genital system cancer, 59,610 cases of leukaemia) new cancer cases are expected to emerge in 2023 in the United States (Siegel et al. 2023). The causative factors of cancer include ageing, tobacco consumption, faulty eating habits, obesity, excessive alcohol consumption, exposure to ionizing radiation, environmental pollutants, infections like

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hepatitis B, C and HIV and some inherited genetic defects (Saini et al. 2020). Different types of cancers are carcinoma, sarcoma, leukaemia, lymphoma, and multiple myeloma as shown in Fig. 1. Cancer will be the leading cause of death by 2060 surpassing ischemic heart disease, which is the current leading cause of death according to WHO estimates (Mattiuzzi and Lippi 2019).

Research for the treatment and prevention of cancer has always been crucial for researchers and medical professionals. With massive development in science and technology, several treatments, medicines and techniques have come into use. These include chemotherapy, immunotherapy, radiation therapy, surgical treatments etc. Phytonutrients from certain plant and herbal sources with potential anti-tumour properties have come to the light and can be a potential source for cancer treatment (Liu et al. 2021).

Corn silk (*Zea mays* L.) has been used as an ancient traditional medicine in countries like China, Turkey, the United States and France for treating ailments like oedema, cystitis, prostate disorders, kidney stones, urinary infections, and bedwetting. It is the stigmata of the female maize flower which are visible as yellowish, 10–20 cm long soft threads (Singh et al. 2022a, b, c). Corn silk is treated as a waste product and generally discarded after the maize cultivation.

Corn silk is a rich source of bioactive compounds, so far compounds like maysin, maysin derivatives, terpenoids, vanillic acid, caffeic acid, and epicatechin monogallate have been discovered with properties like anti-diabetic, anti-obesity and anti-microbial. Bioactive compounds like maysin, rutin, quercetin, apigenin, beta-sitosterol, ascorbic acid and chlorogenic acid found in corn silk have also been known to induce cancer cell apoptosis, upregulate the proapoptotic genes and downregulate the anti-apoptotic genes in cancer cells, hence generating an anti-cancer effect. Many studies have found corn silk to be effective in treating breast cancer, colon cancer, pancreatic cancer and cervical cancer cells. Maysin, a type of flavone present in corn is known to have antioxidant and anticancer properties (Al-Oqail et al. 2019). Corn silk polysaccharides also have inhibitory effects on the proliferation of human cervical cancer cells (Li et al. 2020). The antioxidative, anti-inflammatory and capability to improve immune responses are the proposed mechanisms behind the anti-cancer effects of corn silk (Mada et al. 2020).

Therefore, the current review aims to recognise the anti-tumour capacity of corn silk and recognise the major mechanisms and pathways involved in the anticancer effect. The study reveals that corn silk compounds trigger tumour suppression and inhibit its growth by signalling

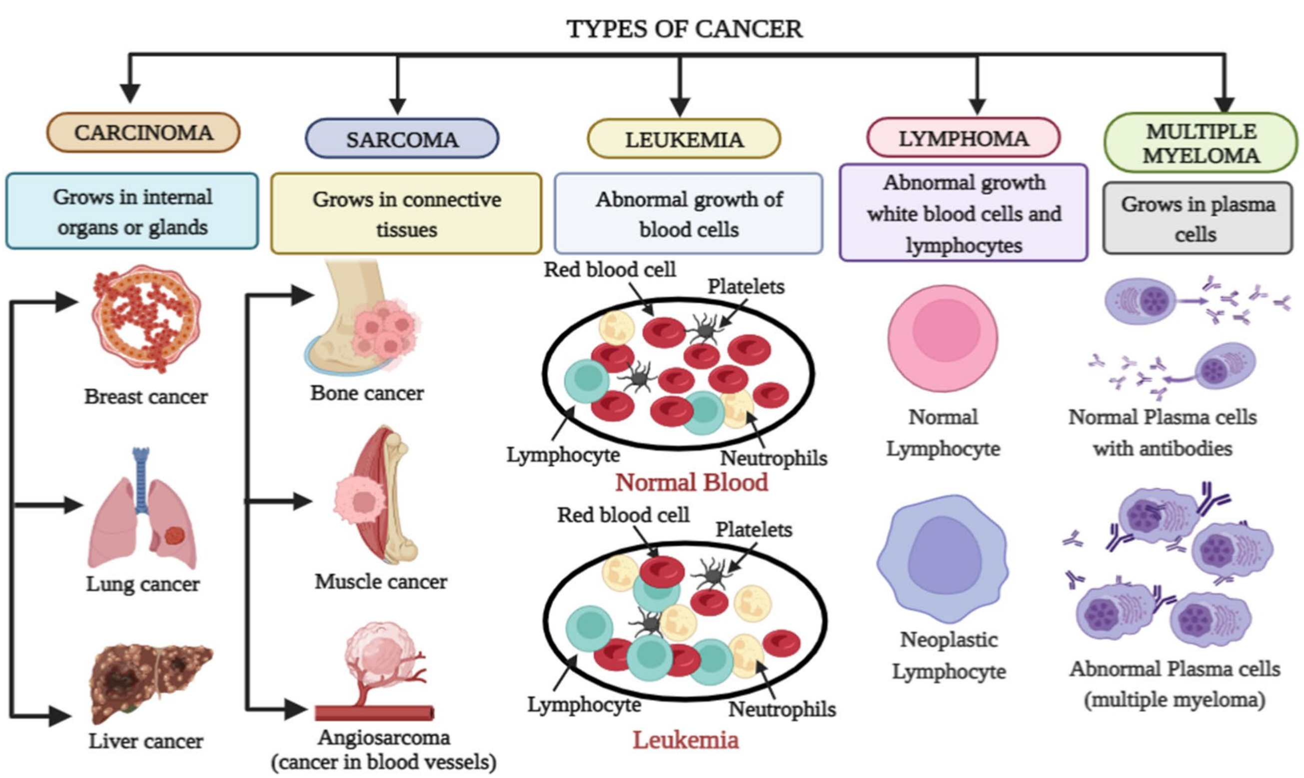

Fig. 1 Types of cancer. Five major types of cancer are represented in the figure. Carcinoma is the type of cancer that grows in internal organs, this includes breast cancer, lung cancer and liver cancer. Sarcoma is the cancer that grows in connective tissues like bone cancer, muscle cancer and angiosarcoma. Leukaemia is the tumour growth in blood cells. Lymphoma is the tumour of white blood cells and lymphocytes. Multiple myeloma is the cancer of plasma cells

the cell pathways Epidermal growth factor receptors (EFGR)/ lipid kinases (PI3K), restoring the T cell immune responses, inhibiting migration of tumour cells, increasing the reactive oxygen species (ROS) and lipid peroxidation levels and by inducing cytotoxicity in pancreatic, cervical, colon and breast cancer cells.

Methodology

The literature search and screening for the review article were done on ScienceDirect, SciELO, SpringerLink, Google Scholar and PubMed as the major database. The references of articles were explored to search for related articles for the study. Keywords used for the search were corn silk nutritional composition, cancer, cancer and phytonutrients and anti-cancer properties of corn silk. The search discovered 64 articles published between 2014 and 2023.

Nutritional composition of different varieties of corn silk

The nutritional composition of corn silk is shown in Table 1. Corn silk has a moisture content ranging from 3.5 to 89.3%, the protein content of 8.9–17.94%, fat content of 0.5–2.4%, ash content of 5–8%, fiber content of 14.8–61.08%, carbohydrate content of 13.2–70.9% and is a rich source of antioxidants.

The various Mexican varieties of corn silk were analyzed by Mendoza-López et al. (2018). The *Gordo* variety showed the highest fiber and carbohydrate content of 53.3% and 70.9%, respectively. *Conico* with pink–red silk had a fiber content of 44.9% and carbohydrate content of 68.9%, *Conico* with dark red silk had a fiber content of 39.5% and carbohydrate content of 69.3% while *Conico* with light brown silk had a fiber content of 39.4% and carbohydrate content of 68.1%. *Cristalino* with green–yellow silk had 43.9% of fiber and 65.1% of carbohydrates. *Conico* with light brown silk had the highest moisture and fat content of 88.3% and

Table 1 Nutritional composition of various corn silk varieties

Varieties	Moisture (%)	Total carbohydrate (%)	Protein (%)	Total fiber (%)	Fat (%)	Ash (%)	References
Gordo with brown silk	83.6	70.9	16.7	53.3	0.9	5.0	Mendoza-López et al. (2018)
Cónico with pink–red silk	82.3	68.9	16.6	44.9	1.1	5.9	
Cónico with dark red silk	85.5	69.3	14.3	39.5	0.9	5.7	
Cónico with light brown silk	88.3	68.1	14.1	39.4	1.8	5.8	
Cristalino with green yellow silk	85.9	65.1	19.1	43.9	1.6	6.1	
Baby corn (immature silks)	89.3	27.8	12.9	48.5	1.2	5.2	Rahman and Rosli (2014)
Sweet corn (Mature silks)	84.4	29.7	8.9	51.2	0.6	5.5	
G5417 (corn silk at silking stage)	7.8	56.1	15.29	14.8	0.5	5.29	Singh et al. (2022a, b, c)
Caloocan corn silk (micro-wave dried corn silk powder)	3.34	13.2	14.8	61.08	2.4	5.6	Logan-del Castillo et al. (2020)
Sweet corn (obtained from Thailand)	9.06 g/100 g	51.37 g/100 g	17.94 g/100 g	16.11 g/100 g	0.91 g/100 g	4.6 g/100 g	Aukkanit et al. (2015)
Red (immature corn silk)	3.5	49.98	16.55	25.51 g/100 g	1.75	6.2	Gebrail et al. (2018)
Yellow (immature corn silk)	4.1	53.03	14.87	23.79 g/100 g	1.5	6.8	
Red (mature corn silk)	5.9	36.24	14.3	40.22 g/100 g	1.3	8	
Yellow (mature corn silk)	6.6	40.7	13.3	36.61 g/100 g	1.37	8	

1.8% while *Conico* with pink–red silk had the lowest moisture content of 82.3%, *Gordo* and *Conico* with dark red silk had the lowest fat content of 0.9%. *Cristalino* had the highest protein and ash content of 19.1% and 6.1%. *Gordo* had 16.7% of protein content and 5% of ash content. *Conico* with pink–red silk had a protein content of 16.6% and an ash content of 5.9%. *Conico* with dark red silk had 14.3% protein and 5.7% of ash content and *Conico* with light brown silk had 14.1% of protein and 5.8% of ash content.

The immature corn silk from baby corn had higher moisture and protein content of 89.3% and 12.9% as compared to mature corn silk from sweet corn which had a moisture content of 84.4% and protein content of 8.9%. Mature silk from baby corn had higher fiber content of 51.2% in comparison to the fiber content (48.5%) of immature baby corn silk. Mature silk showed a higher percentage of ash (5.5%) as compared to immature silk (5.2%). Immature silk had 1.2% of fat content and 27.8% of carbohydrate content while mature silk had 0.6% of fat content and 29.7% of carbohydrate content (Rahman and Rosli 2014).

G5417, a hybrid variety of corn silk, had high carbohydrate (56.1%) and protein (15.29%) content but low moisture and lipid content of 7.8% and 0.5%. It showed a fiber content of 14.8% and 5.29% of ash content (Singh et al. 2022a, b, c). A local corn silk variety obtained from Juliana Market, Caloocan City used for incorporation of microwave-dried corn silk powder in beef patties had a low moisture content of 3.34% but a high fiber content of 61.08% and a high protein content of 14.8%. It had a carbohydrate content of 13.2%, a lipid content of 2.4% and an ash content of 5.6% (Logan-del Castillo et al. 2020). Sweet corn variety from Thailand was analyzed for incorporation of corn silk in low-fat meatballs by Aukkanit et al. (2015). The dried corn silk powder had a high carbohydrate content of 51.37 g/100 g, a protein content of 17.94 g/100 g, a low-fat content of 0.91 g/100 g, a moisture content of 9.06 g/100 g, a fiber content of 16.11 g/100 g and an ash content of 4.6 g/100 g.

White corn with red and yellow mature and immature corn silks from Oromia, Ethiopia was analyzed by Gebrail and Zewdu (2018) for its nutritional composition. Yellow mature silk had the highest moisture content of 6.6% while red mature silk, yellow immature silk and red immature silk had a moisture content of 5.9%, 4.1% and 3.5%. Red immature corn silk had the highest protein content of 16.5% as compared to other varieties which had a protein content of 14.87%, 14.3% and 13.3%. The highest fiber content (40.22 g/100 g) was found in red mature corn silk while the yellow immature corn silk had the lowest fiber content (23.79 g/100 g). Red immature silk had a fiber content of 25.51% and yellow mature silk had 36.61% of fiber. The fat content of red and yellow immature corn silk was 1.75% and 1.5% and that of red and yellow mature corn silk was 1.3% and 1.37%. Red immature silk and red mature silk had carbohydrate content of 49.98% and 36.24% while yellow immature and yellow mature silk had 53.03% and 40.7% of carbohydrate content. Both red and yellow mature corn silk had 8% of ash content while red immature and yellow immature corn silk had 6.2% and 6.8% of ash content.

From the above discussions, it can be concluded that the nutritional composition of corn silk varies with the variety. Based on protein content, the *Cristalino* (Mexican) variety of corn silk had the highest protein content (19.1%) and fiber content (61.08%) as compared to the other varieties of corn silk. Considering protein, fiber and ash content, the *Cristalino* variety is the best among the varieties discussed. Corn silk is a good source of protein, fiber, ash and carbohydrates although it has low fat content, it can be incorporated into food products to make protein and fiber-rich foods.

Phytonutrients in corn silk

Phytochemicals are certain natural compounds present in plants which help them to grow and protect them from injuries and pathogens (Montané et al. 2020). Recent research has shown the therapeutic role of these phytochemicals in various diseases like diabetes, cancer, hypertension, obesity and hyperlipidaemia. Corn silk is an abundant source of polyphenols, flavonoids and other bioactive compounds. The antioxidant activity, total phenolic content and flavonoid content of corn silk (G5417 variety) were studied at the silking stage by Singh et al. (2022a, b, c). Corn silk showed high antioxidant activity in terms of Trolox equivalent antioxidant capacity (TEAC) of 75.25 mg/g dry weight, free radical scavenging activity (FRSA) of 45.40% and ferric ion reducing power (FRAP) activity of 86.77%. Corn silk at the silking stage revealed a higher antioxidant activity using DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity with IC_{50} value of 0.059 mg (Žilić et al. 2016). The antioxidant activity and content of different fractional extracts of corn silk were studied by Nurraihana et al. (2018) and it was found that ethyl acetate fraction showed the highest DPPH activity of 83.89% while hexane fraction showed 12.86% and water fraction showed 70.99% of DPPH activity.

The different phytochemicals identified in different varieties of corn silk are shown in Table 2. The different phenolic compounds in baby corn Malaysian variety of corn silk were investigated by Nurraihana et al. (2018). Good amounts of flavones, flavanols, isoflavonoids, flavone C-glycosides and flavanol *O*-glycosides were found in the corn silk. Four hybrid corn silk varieties ZP Exp, ZP 555, ZP 341, and ZP 366 were collected from Serbia and analysed by Žilić et al. (2016) for the phytochemicals present in them. Compounds like maysin, maysin derivatives, methoxymaysin derivatives, chlorogenic acid, anthocyanins and proanthocyanidins were

Table 2 Bioactive compounds present in different varieties from various regions of corn silk

Origin of corn silk	Variety of corn silk	Phytochemicals identified	Compound class	References
Malaysia	Baby corn (vegetable variety)	Mirificin, 3′-*O*-methylmaysin, Irisolone, Gallocatechin 3-*O*-gallate, Epicatechin monogallate, Epigallocatechin 3-*O*-(3-*O*-methylgallate), Theaflavanin, Mirificin, Isoorientin 7-*O*-rhamnoside, Violanthin, Pectolinarin	Flavonoids	Nurraihana et al. (2018)
		Okanin 4-methyl ether 3′-glucoside	Chalcones	
		Theobromine, 1,3,7-Trimethyluric acid	Alkaloid	
Serbia	Hybrid varieties (ZP Exp, ZP 555, ZP 341, ZP 366)	5-*O*-Caffeoylquinic acid, 3-*O*-Caffeoylquinic acid, 4-*O*-Caffeoylquinic acid, *p*-Coumaroylquinic acid	Chlorogenic acid (Phenolic acids)	Žilić et al. (2016)
		Maysin, Maysin derivative, Methoxymaysin derivatives	Flavonoids	
		Anthocyanins and Proanthocyanidins	Polyphenols	
Iraq	Mature corn silks	Quercetin, Rutin, Kaempferol, Maysin derivatives, Methoxymaysin derivatives	Flavonoids	Ismael et al. (2017)
Thailand	Pacific 271 and Zeba SG 17 hybrids	Flavonoids, tannins, terpenoids, and steroids	Polyphenols	Limmatvapirat et al. (2020)
Indonesia	Bisma, Arjuna and Srikandi Putih	Beta-sitosterol and stigmasterol	Sterols	Haslina et al. (2017)
China	Dried corn silk	Vanillic acid, caffeic acid, ferulic acid, protocatechuic acid	Phenolic acids	Wang et al. (2019)
		Luteolin and apigenin	Flavone	

detected in cornsilk samples. Further, it was also concluded that corn silk at the silking stage showed better antioxidant activity. Mature corn silk from Iraq was analyzed for the detection of quercetin, rutin and kaempferol (Ismael et al. 2017). The study showed a better and higher concentration of the three flavonoids (quercetin, rutin and kaempferol) in the 80% ethanolic extract.

Pacific 271 and Zeba SG 17 hybrid varieties of corn silk from Thailand were studied by Limmatvapirat et al. (2020) for detecting their phytochemical composition. The qualitative analysis showed the presence of tannins, terpenoids, steroids and flavonoids in baby corn silk hybrids. High DPPH and FRAP EC_{50} values of ascorbic acid of 14.60 µg/ml and 25.12 µg/ml were found in corn silk samples. Bisma, Arjuna and Srikandi Putih (local Indonesian corn silk varieties) varieties were studied, Bisma variety showed the highest total phenolic content (TPC) of 8262.93 µg GAE/g, Arjuna showed a TPC of 6331.15 µg GAE/g and Srikandi Putih showed least TPC value of 3367.10 µg GAE/g. Total flavonoid content was also highest in the Bisma variety (236.03 µg GAE/g) as compared to Arjuna (178.33 µg GAE/g) and Srikandi Putih (136.36 µg GAE/g) varieties (Haslina et al. 2017). Beta-sitosterol content of the Bisma variety was also found to be high and was about 1343.93 ppm.

Corn silk aqueous extract was analyzed for the identification of different constituents of corn silk that migrate into the blood. A total of 76 compounds were detected, caffeic acid and 10 of its derivatives, (*E*)-p-coumaric acid and 2 of its derivatives, ferulic acid and 4 of its derivatives, 5 flavones and other constituents (Wang et al. 2019). Salicylic acid, (*E*)-p-coumaric acid, 4-(2-hydroxyethyl)benzoic acid, ferulic acid, citric acid, {(3R,5R)-5-[(1S)-1- hydroxypropyl]tetrahydro-3-furanyl}acetic acid, 2-furanacrylic acid, protocatechuic acid, vanillic aldehyde, vanillic acid, caffeic acid, luteolin and apigenin were among the compounds that migrated into the bloodstream.

Compounds like theaflavin, epicatechin and epigallocatechin-gallate identified in Malaysian corn silk by Nurraihana et al. (2018) have anti-cancer as well as antioxidant potential. Epicatechin causes apoptosis of breast cancer cells through DNA fragmentation, increased expression of pro-apoptotic protein and by increasing ROS (Ferdous and Yusof 2021). Chlorogenic acid (CGA) identified in corn silk (Žilić et al. 2016) possesses anticancer properties as it can induce ROS generation and inhibit cell cycle progression at S-phase in human colon cancer cells (Hayakawa et al. 2020). Maysin, maysin derivatives and methoxymaysin have antioxidant and anticancer effects (Žilić et al. 2016). Quercetin, rutin and kaempferol found in Iraqi corn silk (Ismael et al. 2017) have been identified as anti-carcinogenic agents. Quercetin induces apoptosis and has been beneficial in controlling cancer cell proliferation in different types of cancers such as liver cancer, breast cancer, colorectal cancer, gastric cancer, oral cancer, leukaemia and lung cancer (Vafadar et al. 2020). Rutin can also cause apoptosis of cancer cells by increasing reactive oxygen species (ROS) and by arresting the cell cycle (Ferdous and Yusof, 2021). Kaempferol induces apoptosis in different cancer cell types including leukaemia, lung cancer and prostate cancer (Ismael et al. 2017). Beta-sitosterol identified by Haslina et al. (2017) in Indonesian varieties of corn silk also has an anticancer effect by inhibiting proliferation, and metastasis and arresting the cell cycle in cancerous cells. Ferulic acid can cause tumour suppression by inducing ROS in cancer cells (Karimvand et al. 2020). Luteolin and apigenin found in the Chinese variety of corn silk (Wang et al. 2019), are also potent anti-cancer agents. Apigenin can induce anti-cancerous effects through modulation in different pathways such as tumour suppressor genes, angiogenesis, cell cycle and apoptosis (Rahmani et al. 2022). The studies discussed above provide strong evidence for the anti-cancerous effect of corn silk. Compounds like epicatechin, maysin, maysin derivatives, rutin, apigenin, luteolin, quercetin, beta-sitosterol, kaempferol, chlorogenic acid and theaflavin have reported anti-cancerous effects through different modes of actions and all these compounds have been detected in corn silk.

Mechanism of action for anti-cancerous effect of corn silk

Cancer is usually caused by genetic and epigenetic alterations in the normal cells causing an imbalance in homeostasis by not inhibiting proliferation, invasion to other tissues and survival of aberrantly proliferative cells (Sever and Brugge 2015). The development of normal cells is controlled by many signalling pathways, in the case of cancer cells, these signalling pathways are altered resulting in abnormal cell growth and development (Feng et al. 2018). Mutations in proto-oncogenes cause tumour formation while mutations in tumour suppressor genes will inactivate them leading to uncontrolled cell proliferation and migration. These mutations can alter the activity of proteins involved in signalling pathways. Some of these proteins are epidermal growth factor receptors (EFGR), serine/threonine kinases (Akt), lipid kinases (PI3Ks), transcription factors (NF-kB) and cell cycle effectors (cyclins) (Sever and Brugge 2015). Mutations can inhibit the activity of tumour suppressor genes, for example, p53, p16, pRB and CKIs and PTEN (a negative regulator of PI3K-Akt).

Several studies have focussed on the therapeutic effects of corn silk. Corn silk exhibits anti-cancer activity by regulating one or more of these signalling pathways and thereby inhibiting proliferation, and migration and causing apoptosis of cancer cells. Figure 2 shows the mechanism behind the anti-cancer properties of corn silk and depicts the mode of action of corn silk compounds through different pathways in tumour suppression. Further, corn silk contains certain bioactive compounds which promote the anti-cancer effect. Maysin is one such compound from corn silk which induced mitochondrial-dependent apoptotic cell death and also downregulated Bcl-2 and pro-caspase-3 expression levels in prostate cancer cells (Salehi et al. 2019). The anti-cancer effect of corn silk and its bioactive compounds on different cancer types is shown in Table 3.

Corn silk induces anti-pancreatic cancer activity through EGFR/PI3K/AKT/CREB and CK-2 dependent signalling pathways

The effect of crude polysaccharides from corn silk on pancreatic cancer cell line BxPC-3, SW1990, PANC-1, normal pancreatic ductal epithelial cells (HPDE6-C7) and human liver cells (LO2) was studied by Tao et al. (2020). Crude polysaccharide (S1) inhibited proliferation in pancreatic cancer cells and did not cause any cytotoxicity in normal ductal epithelial cells and liver cells. S1 also inhibited metastasis by EMT and β-catenin signalling pathways. The study revealed that S1 arrested the cell cycle and induced apoptosis in pancreatic cancer cells by impairing the EGFR/PI3K/AKT/CREB pathway. The PI3-K/Akt pathway controls many cellular functions including cell growth, progression, and proliferation. Crude polysaccharides from corn silk inhibited the PI3-K/Akt signalling pathway and downregulated epidermal growth factor receptor (EFGR) and cyclic AMP (cAMP) response element binding protein (CREB). PI3-K/Akt inhibitors have been used in various cancer drugs like Buparlisib and PKI-587 (Mayer and Arteaga 2016).

The effect of beta-sitosterol was studied alone and in combination with Gemcitabine (GEM) on MIA-PaCa-2 and BXPC-3 pancreatic cancer cells (Cao et al. 2019). Beta-sitosterol is a plant compound also found in corn silk (Haslina et al. 2017) which is known for its anticancer effect. Beta-sitosterol inhibited proliferation, induced apoptosis, and arrested cell cycle progression at G0/G1 phase. It also inhibited EMT markers through the Akt/GSK-3β signalling pathways (Cao et al. 2019). Epithelial-mesenchymal transition (EMT) is an important event in cancer cell progression and invasion, transcriptional factors like snail and the E-cadherin gene control the transcription of EMT and suppress metastasis (Liu et al. 2014).

Another plant flavonoid, apigenin reported having anticancer properties due to its inhibitory effect on CK2-dependent signalling pathways (Nelson et al 2017). Panc02 murine pancreatic cancer cell line was used to study the effect of apigenin

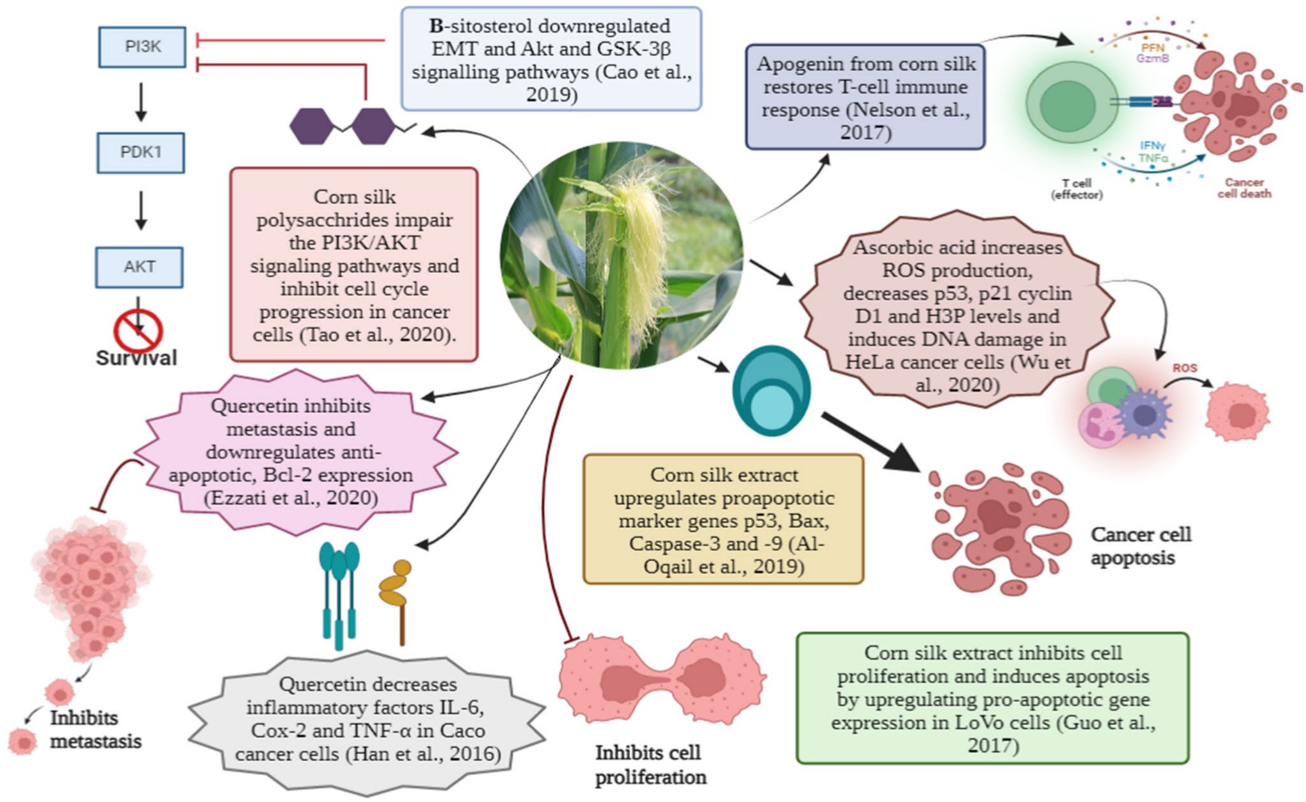

Fig. 2 The mechanism behind the anti-cancer property of corn silk. Corn silk compounds (rutin, quercetin, beta-sitosterol, ascorbic acid, apigenin) cause cancer cell apoptosis, inhibit proliferation and metastasis, increase the reactive oxygen species (ROS) in cancer cells. Corn silk extract and polysaccharides alter cell cycle pathway and upregulate the pro-apoptotic genes

in the inhibition of CK2, preventing degradation of Ikaros (transcriptional factors important for T cell development) and restoring immune responses. CD4+ and CD8+ T cells are highly important for tumour suppression in cancer cells; however, their response is diminished in cancerous cells. The study revealed that apigenin (plant flavonoid) stabilizes Ikaros which is important for T cell development. Apigenin effectively inhibited CK2 activity and upregulated PP1 expression which prevented Ikaros degradation. Stabilization of Ikaros further improved T cell development and restored immune responses.

It can be concluded from the above studies that corn silk showed anti-cancerous effect on pancreatic cancer cells due to the presence of compounds like beta-sitosterol, apigenin and its polysaccharides which alter the cell cycle, inhibit the EMT pathway and PI3-K/Akt signalling pathway and restores the T cell immune response.

Apoptotic and antiproliferative effect of corn silk on breast cancer cells by increasing ROS production, upregulating Bax, Bak, p53, pTEN, p21 proteins and downregulating Bcl-2 and cyclin B1

MCF-7 breast cancer cells and normal human mesenchymal cells (hMSC-TERT4) were used to detect the anti-breast cancer effect of corn silk extract. Corn silk extract induced cytotoxicity and reduced cell viability in MCF-7 cells in a dose-dependent manner while no cytotoxic effect was observed in TERT4 cells. The study revealed an increase in ROS production related to cell damage in cancer cells. Corn silk extract upregulated the expression of pro-apoptotic proteins, Bax, p53, caspase-9 and 3 while downregulating the anti-apoptotic, Bcl2 proteins (Al-Oqail et al. 2019).

Quercetin, a flavonoid found in many plants and herbs like corn silk, was studied for its antitumor potential in

Table 3 Effect of corn silk and its bioactive compounds on different types of cancers

Type of cancer	Study design	Objectives	Results and findings	References
Pancreatic cancer	Corn silk crude polysaccharides (CSP) were evaluated and their role in blocking EGFR/PI3K/AKT/CREB pathway was studied using BxPC-3, SW1990, PANC-1 cell lines	The mechanisms behind the inhibition of cancer cell proliferation, migration and apoptosis of cancer cells	Crude polysaccharides from corn silk impaired the EGFR/PI3K/AKT/CREB pathway CSP inhibited pancreatic cell proliferation, attenuated cancer migration and induce cell apoptosis	Tao et al. (2020)
	MIA-PaCa-2 and BXPC-3 cell lines were used to study the inhibitory role of beta-sitosterol	Beta-sitosterol in the inhibition of pancreatic cancer cells and the mechanisms behind it	Beta-sitosterol effectively inhibited cell proliferation and induced apoptosis in pancreatic cancer cells It also inhibited migration and downregulated EMT and Akt and GSK-3β signalling pathways	Cao et al. (2019)
	Inhibition of CK2 pathway by apigenin using Panc02 cell line	Apigenin in inhibition of CK2 and restoring immune responses	Apigenin inhibited CK2 signalling pathways and restored the Ikaros tumour suppressor It restored T cell immune responses	Nelson et al. (2017)
Breast cancer	Effect of methanolic extract of corn silk on human breast cancer (MCF-7) cells and normal human mesenchymal cells (hMSC-TERT4)	The cytotoxicity, effect on oxidative stress, and the mechanism behind apoptosis induced by corn silk extract (CSE)	CSE induced cytotoxicity in breast cancer cells It increased the lipid peroxidation levels and decreased the glutathione level CSE upregulated proapoptotic marker genes p53, Bax, caspase-3, and caspase-9	Al-Oqail et al. (2019)
	Anticancer properties of quercetin on breast cancer	The anticancer capacity of quercetin	Quercetin inhibited metastasis It decreased anti-apoptotic, Bcl-2 expression and increased pro-apoptotic proteins, Bax and Bak It stopped proliferation in MCF-7 cells	Ezzati et al. (2020)
	Anticancer effect of apigenin and rutin on MCF-7 and MCF-10A cell line	The pathways involved in apoptosis of breast cancer cells	Apigenin and rutin caused apoptosis and inhibited proliferation in MCF-7 cells Increased expression of p53, p21, PTEN and downregulation of cyclin B1	Hasani et al. (2018)
Colon Cancer	LoVo and HT-29 colon cancer cells and MGC-803 gastric cancer cells were used to study the anticancer effect of corn silk extract	The apoptotic and anti-proliferative effect of corn silk extract on colon cancer cells	LoVo cells were more sensitive to corn silk extract as compared to HT-29 and MGC-803 cells Corn silk extract has an inhibitory effect on cancer cell growth, its proliferation and causes apoptosis of LoVo cells CSE increases apoptotic protein expression and downregulates the anti-apoptotic proteins	Guo et al. (2017)
	Chlorogenic acid (CGA) and its metabolites inhibit proliferation and cancer progression in Caco-2 colon cancer cells	Anti-colon cancer effect of CGA and its metabolites	CGA and its metabolites, caffeic acid (CA), 3-phenyl propionic acid (3-PPA) and benzoic acid (BA) caused inhibition of the colon cancer cell progression, proliferation and induced apoptosis	Wu et al. (2018)

Table 3 (continued)

Type of cancer	Study design	Objectives	Results and findings	References
	Effect of quercetin on Caco-2 cancer cell line	Quercetin on migration and invasion of colon cancer cells	Quercetin decreased the invasive capacity of cancer cells and also has an antiproliferative effect Quercetin decreased inflammatory factors like IL-6, Cox-2 and TNF-α Metastasis protein expression of MMP-2 and MMP-9 was decreased while expression of E-cadherin was increased	Han et al. (2016)
Cervical Cancer	Analysis of corn silk polysaccharides to determine its effect on HeLa cells	Antioxidant potential of corn silk polysaccharides and to analyse their effect on HeLa cells	Corn silk polysaccharide, CSP-S2 showed a higher antioxidant activity as compared to CSP-1 CSP-2 showed an anti-proliferative effect on HeLa cells	Li et al. (2020)
	Role of rutin against Jab1 in SiHa cervical cancer cells	Anti-cancer effect of rutin and its effect on Jab1 protein	Rutin downregulated Jab1 expression and upregulated p27 expression It induced an anti-tumour effect by upregulation of p53 and Bax proteins, stimulating caspase-3 and -9 activities and downregulating Bcl-2	Pandey et al. (2021)
	Effect of ascorbic acid on HeLa cervical cancer cells and SiHa cells	The effect of L-ascorbic acid on cell proliferation, cell survival and apoptosis of HeLa and SiHa cells	L-ascorbic acid increased ROS production in cancer cells in pharmacological doses It decreased p53, p21, cyclin D1 and H3P levels and induced DNA damage in HeLa cells	Wu et al. (2020)

breast cancer in the work of Ezzati et al. (2020). Quercetin induced apoptosis, inhibited proliferation in the MCF-7 cell line and downregulated Bcl-2 expression and upregulated Bax and Bak proteins which are responsible for apoptosis. Quercetin causes the activation of apoptotic factors caspase-3 and -9 by the release of Bax and cytochrome c from mitochondria and it also decreases levels of Bcl2 which led to the death of cancer cells.

The mechanism and pathways involved in the anti-cancer activities of dietary polyphenols, rutin and apigenin on MCF-7 breast cancer cells and MCF-10A non-transformed breast cells were studied by Hasani et al. (2018). MCF-7 cells were more sensitive to apigenin and rutin than MCF-10A and hence proliferation was inhibited in MCF-7 cells. Apigenin and rutin induced apoptosis in cancer cells by upregulation of p53, pTEN and p21 expression and decreased cyclin B1 gene expression.

The above studies reveal that corn silk extract and the compounds quercetin, rutin and apigenin found in it show anti-cancerous effect against breast cancer cells by increasing the reactive oxygen species, increasing the expression of pro-apoptotic genes, and inhibiting the anti-apoptotic factors.

S-phase cell cycle arrest, upregulation of pro-apoptotic factors and inhibition of inflammatory factors in colon cancer cells by corn silk and its bioactive compounds

The antiproliferative and apoptotic effect of corn silk extract on LoVo and HT-29 colon cancer cells was reported by Guo et al. (2017). Corn silk extract-induced cell cycle arrest at S-phase inhibited cell proliferation and caused apoptosis. Corn silk extract increased the expression of pro-apoptotic factors caspase-3, caspase-9, cytochrome-c and Bax and downregulates anti-apoptotic factors like Bcl-2. Corn silk extract was found to decrease mitochondrial membrane permeability by reducing the levels of Bcl-2 and increasing Bax protein, this leads to the release of cytochrome-c and activation of caspase-3 and caspase-9 (apoptotic proteins).

The apoptotic, cell cycle arrest and antiproliferative effect of chlorogenic acid (CGA), a polyphenol found in plants like coffee and corn silk (Žilić et al. 2016), on Caco-2 colon cancer cells was studied by Sadeghi Ekbatan (2018). CGA and its metabolites, caffeic acid, 3-phenyl propionic acid and benzoic acid lead to cytotoxicity in Caco-2 cells and arrest cell cycle progression at S-phase.

The effect of quercetin on Caco-2 colon cancer cells was studied by Han et al. (2016), it was observed that quercetin decreased cell viability, inhibited cell migration and reduced invasion ability. Quercetin decreased expression of mitochondrial membrane potential-2 and -9, toll-like receptor 4 (TLR4), nuclear factor-kappa B (NF-κB) p65 and increased expression of E-cadherin protein. It also decreased inflammatory factors, tumour necrosis factor-α, cyclooxygenase-2 and interleukin-6 content.

Thus, the above findings suggest that corn silk extract and its compounds quercetin and chlorogenic acid suppress colon cancer cells by arresting the cell cycle, upregulating pro-apoptotic factors, increasing cytotoxicity and by decreasing the inflammatory factors.

Inhibition of cell proliferation and downregulation of Jab1 factor in cervical cancer cells

The corn silk polysaccharides for their antioxidant and anti-cervical cancer properties were analyzed by Li et al. (2020). Out of the three polysaccharides obtained only two were used for the study (CSP-S1 and CSP-S2). CSP-S2 showed higher scavenging activity than CSP-S1. CSP-S2 also inhibited the proliferation of HeLa cervical cancer cells in a dose-dependent manner.

Rutin, a flavanol from plants, is known for its therapeutic effect on numerous diseases. The effect of rutin on Jab1 (a protein involved in tumour development and progression) in SiHa cervical cancer cells and the mechanism behind it was studied by Pandey et al. (2021). Rutin reduced cell viability in SiHa cells and downregulated Jab1 expression. Downregulation of Jab1 by rutin caused an increase in levels of p53, p27, and Bax mRNA expression and a decrease in Bcl-2 levels.

Ascorbic acid in corn silk induced DNA damage in HeLa cervical cancer cells by decreasing levels of p53, p21, cyclin D1 and H3P. It also increased the production of ROS which further led to cancer cell apoptosis (Wu et al. 2020).

The studies above suggest that corn silk polysaccharides, rutin and ascorbic acid inhibit tumour progression in cervical cancer cells by increasing cytotoxicity and ROS production.

Prevention of side effects caused due to cancer therapy by corn silk bioactive compounds

As cancer rates are rising rapidly many cancer treatments have emerged ranging from invasive to non-invasive techniques. These include radiotherapy, chemotherapy, immunotherapy, gene therapy, hormone therapy etc. Radiotherapy and chemotherapy are among the conventional treatments for cancer (Rizeq et al. 2020). Despite major advances in cancer treatment, the side effects of these treatments still prevail. Radiotherapy can induce chromosomal abnormalities and DNA damage in patients (Mohan et al. 2019). Some of the other side effects of conventional therapy include erythema, hyperpigmentation, hypopigmentation, nausea, vomiting, gastritis, hair loss, soreness, tooth decay, hand and foot syndrome, cutaneous hypersensitivity etc (Rizeq et al. 2020; Mohan et al. 2019).

Recent research (Ghanadi et al. 2019; Toygar et al. 2020; Hussain et al. 2021) focuses on combining conventional therapies with dietary phytochemicals to increase the anti-cancer effect of drugs as well as minimize the side effects related to cancer. Various plant compounds like curcumin, quercetin, resveratrol, catechins etc., are claimed to have anti-tumour effects and are also known to stimulate immune responses against cancer (Zhang et al. 2018). Some of these phytochemicals like quercetin, ferulic acid, rutin, and epigallocatechin which are found in herbs like corn silk are discussed below with their proposed mechanisms against cancer side effects.

Quercetin

Oxaliplatin, one of the anti-cancer drugs used for gastrointestinal cancers can cause peripheral neurotoxicity in patients causing symptoms of paraesthesia, dysesthesia, and pain. Quercetin (50 μM) reduced the mitochondrial oxidative stress in neuronasl cells caused by oxaliplatin by decreasing lipid peroxidation, and protein oxidation and by strengthening levels of glutathione and nonprotein-bound thiols (Waseem and Parvez 2016). Quercetin has been identified in corn silk with a concentration of 0.11 mg/L in 80% ethanolic extract (Ismael et al. 2017). According to another study by Yang et al. (2019), 142.4 μg/100 g of quercetin was quantified in mature corn silk.

Another cancer treatment drug, cisplatin, can cause acute kidney injury in patients as the drug gets accumulated in kidney tissues. The effect of quercetin in reducing nephrotoxicity caused by cisplatin was analysed by Sanchez-Gonzalez et al. (2017). It was found that quercetin had a differential rate of accumulation in tumour tissues as compared to renal tissues. In kidneys, quercetin decreased the activation of inflammatory factors (platelet-activating factor and angiotensin II) and reduction of the glomerular filtrate by cisplatin thereby decreasing the nephrotoxic effects of the drug.

Ferulic acid

The effect of ferulic acid, a phenolic acid on cisplatin-induced nephrotoxicity was studied by Bami et al. (2017). Ferulic acid successfully reduced lipid peroxidation levels, increased the total antioxidant status (TAS) while reducing the total oxidant status, decreased apoptosis of renal cells and caused a reduction in neutrophil infiltration thereby suggesting the potential anti-nephrotoxic activity of ferulic acid against cisplatin. Ferulic acid has also been identified in corn silk. Around 356.6 μg/100 g of ferulic acid was found in immature corn silk and 591.1 μg/100 g was found in mature corn silk (Yang et al. 2019).

Rutin

Cyclophosphamide, an anticancer drug used for the treatment of breast cancer, lung cancer, systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis may cause side effects like nephrotoxicity, hepatotoxicity, mutagenicity and immunotoxicity (Nafees et al. 2015). These side effects are caused due to an increase in oxidative stress and activation of inflammatory factors like tumour necrosis factor-alpha (TNS-α), nuclear factor kappa B (NF-KB) and interleukin-6 (IL-6). Rutin, a dietary flavonoid, decreased the production of ROS thereby decreasing the oxidative stress in hepatic cells. It also downregulated the expression of i-NOS, COX-2 and P38-MAPK and decreased levels of TNF-α and IL-6. Corn silk contains 0.1398 mg/L of rutin (Ismael et al. 2017).

The anti-inflammatory and anti-oxidative role of rutin against the toxic effects of Methotrexate (used for cancer chemotherapy) was studied by Gautam et al. (2016). The use of methotrexate is related to side effects like hepatotoxicity, nephrotoxicity, mucosal barrier damage and intestinal injury. Rutin demonstrated protection against intestinal lesions caused by methotrexate, restored elevated levels of interleukins and decreased mucosal damage in a dose-dependent manner.

Epigallocatechin-3-gallate

Epigallocatechin gallate (EGCG) is the most abundantly found catechin. The protective effect of EGCG against the neurotoxicity, inflammation and oxidative damage induced by cisplatin was observed in a rat model by Arafa and Attia (2020). It was found that EGCG reduced the inflammatory cytokines produced by cisplatin, eliminated the nitro-oxidative stress, inhibited the elevation of acetylcholine levels and upregulated apoptotic proteins, Bax and caspase-3 in the cerebral cortex. Therefore, EGCG can effectively reduce cisplatin-induced neurotoxicity. EGCG has been identified in corn silk. According to a study around 1.89 mg/g of EGCG was found in corn silk flour (Rabi et al. 2022).

The role of EGCG was studied in reducing the ototoxicity (damage to outer hair cells and other regions of the cochlea) induced by cisplatin treatment by Borse et al. (2017). Cisplatin causes ototoxic effects due to the increase in oxidative damage. EGCG reduced cisplatin-induced damage to outer hair cells, spiral ligament, and stria vascularis of the cochlea by inhibiting apoptosis in these regions. The study revealed the antioxidant and anti-inflammatory effects of EGCG.

Safety evaluation and recommended dosage for corn silk consumption

In the above points, the potential health benefits of corn silk were discussed which included its apoptotic effect in cancer cells as well as its role in preventing cancer-related side effects. For the consumption of corn silk, the possible toxicity of corn silk should also be accounted. The toxicity effects of corn silk and its boiled aqueous extract were studied by Ikpeazu et al. (2018) in a rat model. It was found that a dose of corn silk up to 5 g/kg body weight produced no toxic effect in rats. However, the boiled aqueous extract of corn silk showed toxicity at doses equal to or greater than 1000 mg/kg body weight. Administration of aqueous corn silk extract for 28 days increased body weight, triglycerides, low-density lipoproteins, decreased high-density lipoproteins and caused alterations in hepatic markers AST and ALT.

The acute and subacute toxicity of corn silk extract in mice was analysed for 4 weeks by Ha et al. (2018). The acute toxicity analysis showed that a dose of 2000 mg/kg body weight per day showed no increase in either body weight or any toxic effects. For subacute toxicity analysis doses of 5 mg/kg, 50 mg/kg and 500 mg/kg of corn silk extract were administered every day for four weeks and the parameters for the test were changes in body weight, blood analysis, urine analysis and organ weight analysis. The study proved that a dose of 500 mg/kg showed no toxic effects in mice and had no adverse effects on the parameters stated above.

5 µg/mL of corn silk extract was defined as a safe dose at which no cytotoxic effects were observed (Kim et al. 2019). 500 mg/kg oral dose of corn silk extract was also considered safe in the study of Oyabambi et al. (2021). Normal human mesenchymal cells (TERT-4) showed no cytotoxic effects by corn silk extract at doses of 200 µg, 500 µg and 1000 µg while it decreased cell viability in human breast cancer (MCF-7) cells (Al-Oqail et al. 2019). The cytotoxic effect of corn silk polysaccharides was analysed at different concentrations of 40, 100, 200, 300 and 400 µg/mL in L6 skeletal muscle cells. No adverse toxic effect was observed for concentrations less than 400 µg/mL (Guo et al. 2017).

The above studies show that a dose of corn silk up to 500 mg/kg body weight has been defined as safe for consumption. However higher doses of up to 2000 mg/kg for longer durations can cause harmful effects and can prove to be toxic. So, to avoid any risk only lower doses of less than 1000 mg/kg body weight of corn silk should be consumed for its therapeutic uses (Singh et al. 2022a, b, c).

Future perspectives

Studies have revealed numerous health benefits of corn silk which include the ability to prevent and manage a vast number of illnesses like obesity, diabetes, hypertension, kidney diseases, urinary tract infections as well as cancer. Many of the diseases mentioned have interlinked causes. Corn silk is an abundant source of flavonoids, polyphenols, and other bioactive compounds. These compounds have earlier reported anti-diabetic, anti-obesity, antihypertensive and anticancer properties. Due to the presence of these compounds, corn silk helps in fighting against the diseases mentioned above by interfering in the development of the disease at various steps and by preventing other interrelated diseases.

Corn silk products like herbal corn silk tea, corn silk capsules, corn silk liquid extract and corn silk powder are already available in the market for healthcare uses. Plant-derived natural compounds like flavonoids and polyphenols have been studied for incorporation in drugs as well as food for anti-cancer therapeutic effects. Most of the new chemotherapeutic drugs have used these bioactive compounds which target cancer cell apoptosis and cell proliferation at various cancer stages. Corn silk flavones and flavonoids can also be extracted for this purpose by ethanol–water extraction or ultrasound-assisted extraction and then be used as a natural therapeutic drug. It can be combined and used with chemotherapy to reduce the toxic effects of chemotherapeutic drugs. Corn silk aqueous extract has been used to develop silver nanoparticles which showed antimicrobial as well as high cytotoxic effects on cancer cells. Hence corn silk extract can be used as a preventive or therapeutic step to cure cancer. Corn silk tea, having antioxidant properties, is also sold in the market and can be used as a herbal drink to fight against numerous infections. Some anticancer supplements are also available in the market which can include some natural vitamins, minerals or herb extracts having an anti-cancer effect. Corn silk can also be used as a supplement either in powder or extract form. Some new technologies for the transfer of anticancer agents to the site of tumour progression have been helpful in cancer treatment. Microspheres containing anticancer agents like corn silk active compounds can be used for intravenous or intra-arterial transport to specific sites. Novel products which incorporate corn silk with other natural anti-cancer products like turmeric, honey, cereals, green tea etc. need to be developed for use against cancer.

Conclusion

The anti-cancer effect of corn silk is attributable to the presence of various phytonutrients in it which inhibit cancer growth and proliferation and cause apoptosis of cancerous cells via complex signalling pathways. The bioactive compounds present in corn silk offer a wide range of pharmacological benefits. Cancer therapy is linked with numerous side effects. A combination of herbal and pharmaceutical drugs can provide new scope for cancer treatment. The phytonutrients of corn silk have also been studied for the prevention of cancer therapy-related side effects. Corn silk phytonutrients have proven to reduce chemotherapy side effects through various mechanisms. There is no toxicity associated with the consumption of low doses of corn silk as analysed by various studies. Hence, the incorporation of corn silk in the diet of cancer patients can increase survival rates and decrease the potential side effects of cancer therapy. Corn silk can also be used as a preventive step towards cancer. The anti-cancer property of corn silk promises a new scope for its use in anti-cancer drugs and therapy. More research is needed to investigate the acceptable dosage for cancer patients, the bioavailability of corn silk with chemotherapy drugs and the development of new technology for the transfer of phytonutrients from corn silk to human cells.

Acknowledgements The authors thank Lovely professional university for the support provided for the collection of data and writing of the manuscript.

Author contributions AG: writing-original draft. JS: conceptualization and supervision. PR: review, editing and supervision. SK: review, editing and supervision. JK: review and editing. VN: review and editing.

Funding This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no conflict of interest.

Research involving human and animal rights This article does not contain any studies with human or animal subjects.

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