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Review of Pumpkin Anticancer Effects

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ABSTRACT

Context: In the earlier times, many people used plants to cure diseases just by experimental data without knowing anything about its compounds. As regards cancer was the most concerning disease in the past (same as now), so recognizing plants with anticancer agents was vital. The first search for herbal anticancer agents had been done in 1950s when vinca alkaloids (Vinblastine and Vincristine) were discovered and cytotoxic podophyllotoxins were isolated. One of these plants is pumpkin. In the past only sick people used pumpkin and then they found it was edible for everyone, and so pumpkin usage became widespread. In the Holy Quran (Sura 37, As-Saaffat, Verse 144-146), Allah said to Jonah:" But we cast him upon the shore when he was ill, and we made a pumpkin tree grow over him ". In North of Iran, pumpkins was the main dietary food which was ordinarily used by people; interestingly the level of cancers, especially gastrointestinal cancers and some of other diseases, were lower than other regions of Iran. Now because of industrialism and lifestyle changes the presence of pumpkin in the diet of families really has decreased, and in parallel the prevalence of variety of cancers, especially gastrointestinal cancers, has increased. Qua Northern provinces have become the gastric cancer belts of Iran. Pumpkin is one of foods that are well known for its healing effects especially on cancers. As we see from the pumpkin diet history, there is an inverse relationship between its usage and cancer prevalence.
Evidence Acquisition: Now by knowing pumpkin's history and its Quranic reference, we want to collect scientific evidences about healing effect of pumpkin on diseases like cancers, especially gastrointestinal cancer. These evidences prove the truth of this inverse relation and surely declare pumpkin as an anticancer plant.
Results: Pumpkin consists of many beneficial nutrients such as phytoestrogen, selenium, fiber, cucurbitacin E, calcium, zinc, other vitamins and minerals, etc. These are not only beneficial for cancer prevention, but also for curing many diseases as many researches and scientific methods prove their effective roles. This article will clarify the existence of certain nutrients in pumpkin and explain their roles in cancer prevention and curing diseases by describing their signaling pathways and molecular mechanisms of action. In addition the pumpkin plant possesses flowers, leaves, roots, and seeds which all have healing nutrients. Therefore we can consider this fruitful plant as a beneficial medicinal herb with certain anticancer aspects.
Conclusions: The pumpkin plant with all its parts consists of highly effective nutrients, where it is considered as a super food for many diseases and cancers, especially gastrointestinal cancer.

Keywords: Pumpkin; Nutrients; Cancers Prevention; Gastrointestinal

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Implication for health policy/practice/research/medical education:
Pumpkin consists of highly effective nutrients; surely it is a super food for many diseases like cancers, especially gastrointestinal cancer.

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1. Context

Plants have a long history in curing diseases and cancers. By the time lapse, healing nutrients and anticancer agents were extracted from plants. The first search for anticancer agents had been done in 1950s when vinca alkaloids "Vinblastine and Vincristine" were discovered and cytotoxic podophyllotoxins were isolated (1). One of these plants that have been used for medicinal purposes was pumpkin.

1.1. History

Pumpkin was cultivated in Mexico in 5500 years B.C. for the first time (2) when beans and corn were the main food of North Americans (3). Mayan people used pumpkin and its roasted seeds for healing many diseases and in their cooking (2). After centuries Christopher Columbus for the first time in 1492 reported the implant of pumpkin in his itinerary and then Gasper de Espinosa reported the implant of pumpkin in his itinerary in traveling to , but he named it Indian water-melon and described it as very delicious and is used in curing many diseases. Then pumpkin cultivation started in Europe for the first time (4).

1.2. Properties

Pumpkin is a yearling, grassy plant with twiner, ascendant (flagellum) or decumbent on the ground. Agricultural pumpkins are monoecious and most of them are long crawl vine on the ground (5).

1.3. Taxonomy

Pumpkin is an herbaceous plant of the genus *Cucurbita* and the family of *Cucurbitaceae* (6) (Table 1).

Table 1. Scientific Classification of Pumpkin

Kingdom	*Plantae*– Plants
Subkingdom	*Tracheobionta*
Superdivision	*Spermatophyta*
Division	*Magnoliophyta*
Class	*Magnoliopsida*
Subclass	*Dilleniidae*
Order	*Violales*
Family	*Cucurbitaceae*
Genus	*CucurbitaL.*
Species	*CucurbitapepoL.*
Variety	*Cucurbitapepo L.var. pepo*

All pumpkin species possess different varieties. Its edible species is divided to four groups: *Cucurbitapepo L.* (summer pumpkin); *Cucurbita maxima duch* (winter pumpkin); *Cucurbitamixta pang*; and *Cucurbitamoschata-duch* (summer or winter pumpkin). Pumpkin is called to all species in *Cucurbita* genus (7). In Iran they are called *Cucurbitapepo* or informally "Kadu Tanbal".

1.4. Different Types of Pumpkin

Winter and summer squash:

Table 2. Different Types of Winter Squashand Descriptions

Type Name[a]	Description	Image
Acorn squash	Its name is because for its shape that looks like an acorn. The skin has distinct ribs from one side to other with hard, dark-green, or yellow color. The flesh is sweet, dry, and fibrous.	
Fairytale pumpkin squash	It is thick and tender; its orange flesh is thick, firm, and sweet. The fruits are flattened and it is an ornamental pumpkin.	
Amber cup squash	This squash is a relative of buttercup squash. This is a small squash with orange color skin and its flesh is bright orange and sweet.	
Gold nugget squash	Sometimes it refers to as an Oriental pumpkin, this is small in shape and both skin and flesh are orange.	
Autumn cup squash	It is a hybrid of buttercup and kabocha and is a dark green squash. Its flesh is yellow/orange, dry, and sweet.	

Hubbard squash (gray and green)	They have too hard skin so they are best squash for keeping in winter. They are very large and their shape is irregular and taper at the end, their skin is blue/gray, wart, and not edible. Its flesh is dense, yellow, and damp.	 
Banana squash	Its shape and skin color is same as banana and its flesh is bright orange and sweet.	
Butternut squash	This is vase or bell shaped squash or like a large pear with beige color. This watery squash has bulbous end, creamy skin, and orange flesh with sweet taste.	
Kabocha squash	Its other names are Ebisu, Delica, Hoka, Hokkaido, or Japanese pumpkin. Kabocha is a common Japanese word for naming most common type of buttercup squash. Its skin is green, bluish-gray, or orange and the flesh is yellow. Its seeds are removed.	
Buttercup squash	It is hard-shelled with turban-like shape (is part of the Turban squash family) and has dark-green skin sometimes with light-green streaks. The flesh is creamy orange and sweet (sweeter than other winter specious).	
Spaghetti squash	It is also called vegetable spaghetti, vegetable marrow, or noodle squash because after cooking, its inside looks like cooked noodles. It is similar to small water-melon and has elliptical shape with golden yellow skin. Its seeds are not edible.	
Carnival squash	It is cream colored squash with orange spots or light-green with dark green spots in vertical stripes. The skin is hard and thick and its flesh is edible and sweet. Sometimes it is labeled as a type of acorn squash.	
Sweet dumpling squash	It is a small squash and similar to miniature squash with its top pushed in. The skin color is cream with green ribs and the flesh is orange and sweet	
Delicate squash	Originally it was introduced by Peter Henderson Company in New York City in 1894 and became popular in 1920s. It was obscured for 75 years for its thin and tender skin that make it not proper for transportation for far distances and storage for months. Other name is Peanut and Bohemian.	
Turban squash	Its name is for its shape. This squash has various colors from orange to dark and light green and white. The flesh is golden-yellow and its taste is like hazelnut. It has a bizarre shape that makes it sharvest ornamental.It has a cap like a bulb that swells from its fruit end.	
Lumina squash	This is grown like orange skin pumpkin and its flesh is orange and edible. By keeping it in cool and indirected light setting it will remain fresh for several weeks.	
Red Kuri squash	It is a red-orange pumpkin. It has a hard and thick skin, and the flesh sweet flavor.	
Calabaza squash	It belongs to both summer and winter squashes depending on its stage of harvest. Its name is derived from the Persian term for melon (kharbuz). The skin color reflects hybrids, varying from dark green to light yellow and the flesh is varying in color too.	

[a] Source: Melissas/World Variety Produce, Inc. (8) & Squash article by Linda Stradley (9)

1.4.1. Winter Squash

Winter squash is varying in shapes and colors and it belongs to vine type. Its fruits are harvested when they mature completely (*Table 2*).

1.4.2. Summer Squash

Summer squash belongs to the *Cucurbitaceae* family and is related to the winter type, but summer squashes are more delicate and eaten freshly shortly after harvest (*Table 3*).

Table 3. Different Types of Summer Squash and Descriptions

Type Name[a]	Description	Image
Zucchini Squash	This is one of the summer type squash; its skin's color varies from yellow to light and dark green. It grows on the flowering plant with edible flowers.	
Tatume Squash	It has a creamy texture and buttery flavor, and it is also called calabacita. It is similar to zucchini; it has thin and spotted light green skin.	
Yellow Crookneck	This squash usually is yellow and has a curved neck that is almost like a swan. Sometimes it has bright green skin.	
Gold Ball Squash	This squash is unique and is a new variety of hybrid of gold zucchini. It is round with shiny gold exterior, green stems, and green underside. It has a bright color and is soft to touch.	
Cushaw Squash	These squashes are special varieties of crookneck squashes but much larger than others. They have bulb like shaped like crookneck squashes.	 
8 ball Squash	This is unique and a new hybrid of zuchini and is round with shiny specked dark exterior. Its taste is similar to zuchini.	
Scallop Squash	Its other name is Pattypan squashes. Their shapes are similar to saucers with a variety of colors and sometimes they have sweeter taste than other types of summer squashes. In different countries they may have different names such as button squash orscallopini.	
Chayote Squash	It is similar to pear in shape and has a light to dark green color. It has a smooth skin with slight ridges running from stem to end. Its seeds are also edible.	
Cucuzza Squash	It is also known as: Italian squash, bottle gourd, zucca, suzza melon, tasmania bean, and New Guinea bean. It has light green, inedible skin with white flesh that contains many seeds. Its taste is similar to sweet summer squash and can grow 3 feet long.	

[a] Sources: Melissas/World Variety Produce, Inc 2012 8(8) 8812 Melissas/ World Variety Produce, Inc 2012, http://melissasfarmfreshproduce.com/pumpkin (8) ; Squash article by Linda Stradley Stardly 9(9) 9912 Stardly, L. Squash article of whats cooking America, http://whatscookingamerica.net/ (9)

1.5. Different Parts of Pumpkin

Pumpkins have different parts including: root, flower, leaf, fruit, and seeds (10). All parts of this plant are used. Its seeds or green skin are anti-tapeworm. Its skin and the flower are useful for healing wounds, especially burning wounds. The benefits of the fleshy portion are mentioned above. Pumpkin flower infusion is curative for sore throat or angina.

1.6 Nutrients in Pumpkin

The data are shown in Table 4.

1.7. Pumpkin Flowers

As mentioned before pumpkin flowers are edible. They can be used in salads with other vegetables. See the active compounds of pumpkin flower in Table 5 (10).

Table 4. Nutrients in Pumpkin

Variable[a]	Nutritional value
Energy, KJ	109
Carbohydrates, g	6.5
Sugars, g	1.36
Dietary fiber, g	0.5
Fat, g	0.1
Saturated, g	0.05
Monounsaturated, g	0.01
Polyunsaturated, g	0.01
Protein, g	1.0
Vitamin A, μg	369 (46%)
Beta-carotene, μg	3100 (29%)
Thiamine (vit.B1), mg	0.05 (4%)
Riboflavin (vit.B2), mg	0.110 (9%)
Niacin (vit.B3), mg	0.6 (4%)
Pantothenic Acid (B5), mg	0.298 (6%)
Vitamin B6, mg	0.061 (5%)
Folate(vit.B9),μg	16 (4%)
Vitamin C, mg	9 (11%)
Vitamin E, mg	1.06 (7%)
Calcium, mg	21 (2%)
Iron, mg	0.8 (6%)
Magnesium, mg	12 (3%)
Phosphorus, mg	44 (6%)
Potassium, mg	340 (7%)
Sodium, mg	1 (0%)
Zinc, mg	0.32 (3%)

[a] Nutritional value per 100 g (3.5 oz); Source: USDN Nutrient database

1.8. The Properties of the Seeds

Unsaturated fatty acids, ω6 and ω9 convert to prostaglandin in body and then to thromboxan, these hormones increase HDL and prevent deposit of fat in arteries, decreasing the risk of a heart stroke. Pumpkin seeds possess oleic acid and linoleic acid which have beneficial effects on people with hypertrophy. Phytosteroles in seeds play a role in treatment of prostate problems. Pumpkin oil contains vitamins like A, D, and E. Vitamin E and vitamin A are antioxidant and inhibit free radical action, so they prevent cancer, especially prostate cancer. Pumpkin seed is full of potassium, calcium, magnesium, phosphor, zinc, and selenium which are all useful for intestinal and bladder infections. Pumpkin seed contains phytosterols and cytostrols that have anticancer properties. Pumpkin seed has been proven to help in preventing prostate and colon cancer.

Pumpkin has excellent action against intestinal parasites due to its seeds, both tapeworms and roundworms, which are very common helminthes endo-parasites that can be expelled and eliminated by intake of pumpkin seeds. Pumpkin has a special amino acid known as Cucurbitin in its seeds (by scientific name: [(-)-3-amino-3-carboxypyrrolidine]). This amino acid is the main and most active compound and is necessary for anti-helminthic actions, and is capable of eliminating worms. Cucurbita species have different concentration of this amino acid.

2. Evidence Acquisition

Pumpkin is full of many healing nutrients and we want to clarify these nutrients and express their mechanisms of action to observe and conclude their prevention effects on cancers.

3. Results

3.1. Vitamin A

Vitamin A belongs to a group of fat-soluble retinoids like retinal, retinol, retinoic acid, and retinal esterase (11, 12). Its main role is in the visual pigments in retina and in addition it has role in regulation of gene expression, cell differentiation, immune system, reproduction, cellular communication, cell growth, and normal formation and maintenance of organisms (12, 13). Two types of vitamin A exist in human diet: vitamin A functional (retinal and retinal ester) and carotenoids (beta and alpha carotene) (12, 14). As vitamin A has role in regulation of cell growth and differentiation, so there is relationship between vitamin A consumption and some cancers like lung and prostate. The main relationship is unclear but many experiments prove that. For example experiments on smokers and non-smokers showed that high intake of carotenoids are associated to low risk of cancer (12). Another evidence

showed the relationship between beta-carotene and prostate cancer, people who took daily supplements of beta-carotene and retinyl palmitate had 35% lower risk of prostate cancer than who did not take (15).

3.2. Beta-carotene

It is an organic compound that is a pro-vitamin A and it is an orange pigment that exists in yellow, orange, and dark green vegetables. It acts as an antioxidant in body, so it can scavenge the free radicals from body (16). These biopigments are fat-soluble and take part in the cell membrane and protect cell from the action of free radicals (17). Caroteniods help the normal function of *connexin-46* gene and protect sensitivity between cells in order to prevent uncontrollable growth (17).

3.3. Phytoestrogen

Phytoestrogens can be divided into four classes: isoflavones, coumestans, lignans (18), and mycoesterogens (19). Phytoestrogens are bioactive compounds that are derived from plants like pumpkin and soy beans and have estrogenic activity. The mechanisms of action: a) mimicking the action of endogenous estrogens, b) function as compounds that are same as estrogens or estrogens antagonist, c) affect on endogenous hormones synthesis and metabolism, d) altering the biochemistry of hormone receptor (20, 21). Phytoestrogens have different structures, but the presence of phenol ring is their main property that is necessary for binding to estrogen receptor (22). The mechanism of action of phytoestrogen in preventing breast cancer is due to its similarity to estradiol in chemical structure, so they bind to estrogen receptors. In addition they have another activity as antioxidants, they protect the body from the destruction effects of free radicals, and they have anti-proliferative effect on tumor cells to prevent tumor growth (23). A member of phytoestrogens, Genistein, has inhibitory effects on tyrosine kinase (24) and topoisomerases (25, 26), so it arrests cell growth by interfering in signaling pathways (26-28). Therefore, this pathway can increase the expression of proto-oncogenes like *C-Jun*, *C-Fos*, and *C-Myc* (29). Phytoestrogen also inhibits sulphotransferase (enzyme that is involved in activation of pro-carcinogen compounds of diet) (30). Estrogen receptor has a unique property and it binds to a wide variety of compounds because of its hormone binding cavity size (it is large). Estrogen and estradiol have mitogenic effects, steroid hormones are hydrophobic and can pass through membrane and bind to its receptor (transcription factors) in cytoplasm or nucleus (29). As mentioned above phytoestrogens have the ability to bind to estrogen receptor and act as a weak estrogen and decrease breast cancer risk (31, 32). Sometimes they can compete with endogenous estrogen for binding to receptor (33, 34). When the level of endogenous is low, phytoestrogens act as estrogen and bind to receptor but in high level, phytoestrogens occupy receptor and act as anti estrogen and can protect against breast cancer (35).

3.4. Zinc

Zinc (Zn) is an essential metal. Zinc is important for male reproductive system, and is involved in sperm generation, testosterone metabolism, and sperm movements. Low levels of zinc cause low level of seminal volume and testosterone, leading to a higher risk of prostate cancer (36). Zinc contributes in development and progression of some cancers (37) like stomach and colon carcinoma, and is involved in advanced stages of cancers (38). Zn incorporates in enzymes and proteins. More than 300 enzymes need Zn as a cofactor for action (39), and many of them have a role against oxidative stress like metallothionein (40), these enzymes decrease disruptive effect of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). ROS and RNS induce DNA damage and cancer. Zn is the cofactor of P53 that is essential for DNA repair in response to DNA damage (40). In addition P53 is related to cell cycle checkpoint regulation and apoptosis induction (41). When DNA is damaged, P53 induces the transcription of *p21* (cyclin-dependent kinase inhibitor), and G1 phase cell cycle arrests to repair DNA or for apoptosis (42). Protein kinase ATM (Ataxia Telangiectasia Mutated) is activated in oxidative stress (43) and double stranded DNA break via the signaling pathway of Mre 11 complex (is a protein that participate in activating ATM in response to DNA damage and repair DNA double- strands break), and this complex binds activated ATM to free ends of damaged DNA in a Zn dependent manner (44). So low levels of Zn can weak mechanisms in response to DNA damage, decreases the integrity of DNA, and increase cancer risk (45). Oxidative stress induces mutation in DNA, and if the mutation is not repaired due to low level of Zn, it will cause the initiation and progression process of cancer (46). Tumor suppressor BRCA-1 has a RING finger domain with several cysteine residues in the N-terminal, these cysteine motifs form two potential Zn binding motifs (47). BRCA-1 has a suppression effect on breast cancer and has other roles in: regulation of chromatin remodeling, transcription of regulatory factors, control of cell cycle (48), and maintenance of chromosomal stability (49). Zinc can suppress cell proliferation and induce apoptosis in gastric cancer by incorporating in Zinc-finger protein 545 structures; ZNF545 inhibits the transcription of ribosomal RNA (rRNA). This inhibition is result of the hypermethylation promoter rDNA. So ZNF545 acts as a tumor suppressor in gastric cancer (50). Zinc ribbon domain-cotaining1 (ZNRD1) can suppress the growth of gastric cancer cells (51). This motif can arrest G1 cell cycle and inhibit angiogenesis. The p27kip1 (cyclin dependent kinase inhibitor- 1B) is a tumor suppressor and its phosphorylated form is recruited by Skp2 (S- phase kinase association protein 2) and then

degraded (52), so low level of p27kip1 causes growth in cancer cells, but ZNRD1 inhibits the expression of Skp2 by increasing its protein instability (51). The reduction in Skp2 related to increase in p27kip1 causes a decrease in cell proliferation (51).

Table 5 . Active Compounds in Pumpkin Flowers

Pumpkin **Flower Composition Per 100 g**[a]			
Energy , Kcal	14	**Niacin (vit.B3), mgs**	0.690
Carbohydrates, g	3.28	**Pantothenic acid (B5)**	-
Sugars	-	**Vitamin B6**	-
DietaryFiber	0	**Folate(vit.B9), mgs**	59
Fat, g	0.24	**Vitamin C, mgs**	28
Saturated	-	**Vitamin E**	-
Monosaturated	-	**Calcium, mgs**	39
Polysaturated	-	**Iron, mgs**	0.70
Protein, g	1.16	**Magnesium, mgs**	24
Vitamin A	195	**Phosphorus, mgs**	49
Beta-carotene	-	**Potassium**	173
Thiamine (vit.B1), mgs	0.042	**Sodium, mgs**	3
Riboflavin (vit.B2), mgs	0.075	**Zinc**	-

[a] Nutritional value per 100 g (3.5 oz); Source: USDN Nutrient database

3.5. Cucurbitacin E

Cucurbitacin E (Cu E, α elaterin), (C32H99O8) is a tetra cyclic triterpenoid that is extracted from plants especially from cucurbitaceae family (53, 54). Cucurbitacin E prevents cancer by inhibiting the action of JAK2 and STAT3 phosphorylation so affect on downstream genes. STAT3 binds to promoter of *Bcl-xl*, *CyclinD1*, and *VEGFR2* and actives them (29). Cu E suppresses the expression of *VEGF*/*VEGFR2*, *Bcl-xl*, and *Cyclin D1* (55). The major protein that is induced by active STAT is Bcl-xl, an anti-apoptotic factor (29). Tumor cells need blood vessels for migration and metastasis, and they need new vascularization for oxygen and nutrients, new blood vessels are made by VEGF. So Cu E inhibits angiogenesis significantly (55). Phospho-STAT3 activates the Bcl2 and Bcl-xl and they inhibit the caspase 3, but Cu E removes the inhibited effect of Bcl2 and Bcl-xl leading to the activation of caspase 3 and the occurrence of apoptosis (55).

P38 causes migration and ERK (Extracellular signal- regulated kinase) is causes proliferation when they are phosphorylated, and they are angiogenic factors, and Cu E has a strong effect on p38 and ERK, it suppresses their phosphorylation and inhibits the tumor cells growth (56, 57). Cucurbitacin E has anti-proliferating effect via its effect on actin filament in endothelial cells (58). Actin is an important intermediate in signaling pathways of cell division control (59, 60), so cucurbitacin E has an inhibitory effect on cell growth. For example in prostate carcinoma, Cu E induces cell growth inhibition (58). In addition Cu E binds to F-actin at residue Cys257 and occupies a different binding site on actin filaments so thedepolymerization of actin inhibited by Cu E and this cause on many processes in cells that involve to actin like cytokines. (61).

3.6. Fiber

Fiber is a non-starch polysaccharide and lignin that is derived from plants that are non-digestible in small intestines, because mammals do not produce its hydrolysis enzymes. Fiber is one of the well-known anti-cancer nutrients. Fiber mechanisms of action include: binding to bile acids and absorb it, increasing the water of feces and diluting the carcinogens, and decreasing transit time (62, 63). Fiber is a substrate for bacteria; these bacteria produce short chain fatty acids, including butyrate, by fermentation in large intestine. Butyrate has anti-carcinogenic effect on cancer cells, especially on colon cells (62). Butyrate has an ambiguous role, in normal cells it causes cell growth, but in cancer cells it inhibits cell proliferation, differentiation, and induces apoptosis (64).This contradictory is called the butyrate paradox (65). The major mechanism of butyrate action in colon cancer cells is inhibition of histone deacetylase, so it can regulate transcription and silence genes that are involved in control of cell cycle progression, differentiation, and apoptosis (66). This inhibition increases the expression of P21 and induces G1 cell cycle arrest (67). Neuerophilin-1 promotes cell migration in response to VEGF and butyrate down regulates this apoptotic and angiogenic regulator (68).

TGF-β is expressed in gut epithelium and it is a tumor suppressor. During colon cancer TGF-β inhibits cell pro-

liferation (69, 70). Butyrate can increase the expression of Smad3 (derived from sma gene + mad gene in drosophila) and empower the TGF-β signaling pathway in colon carcinoma (71). Butyrate expresses the Smad3, and TGF-β phosphorylates this Smad3 and arrests cell cycle and promotes apoptosis through the repression of Id2 (DNA-binding proteim inhibitor) (72), butyrate and TGF-β synergistically act in carcinoma cells. Many studies showed that foods with fiber have healing effects on both colon and rectum cancer (73). Intestinal butyrate modulates Wnt signaling pathway and promotes apoptosis in tumor cells in colon cancer by hyper- activation and highly changing protein folds in Wnt (refers to mammalian integrin 1 that homolog to Wingless gene in drosophila) signaling pathway (74). Two types of fiber exist: soluble and insoluble.

Soluble fibers absorb water in intestines and soften the stool so that stool defecates more quickly. Insoluble fiber absorbs water but preserves their form and structure so increasing the food bulk (75). Insoluble fiber increases the growth of beneficial bacteria and makes waste material soft and bulky, which helps waste material and undigested foods to exit more quickly from the body. Constipation will happen when a person cannot defecate because stool is small, hard, and dry.

Many scientists believe that fibers bind to estrogen in intestines and prevent tumor growth, leading to the acknowledgement of a reverse relationship between fiber consumption and breast cancer occurrence.

3.7. Selenium

Selenium (Se) is a trace mineral that is incorporated into proteins to make seleno-proteins, which are important enzymatic antioxidants, actually Se is not itself an antioxidant. This property prevents cellular damage from free radicals (76). More than 13 proteins and enzymes in human need selenium. The mechanism of action includes: induction and promotion of apoptosis, inhibition of the growth of cancer cells, induction the activity of P53, and protection of DNA from damage (77-79). Selenium has protective effects on many cancers, such as: it reduces the risk of prostate, lung, ovarian, and colorectal cancer, and its low level is correlated with stomach cancer. Animal studies showed that selenium treatment can reduce tumor growth, cell growth, and angiogenesis, promote apoptosis, and increase immune function (80). Seleno-enzyme mechanisms can reduce DNA damage, and this was proven in animal and human studies (81-83). Some inflammation can promote tumor growth, selenium as seleno-enzymes reduces hydroperoxide intermediates in cycloxygenase and lipoxygenase pathways, so the production of pro-inflammatory prostaglandins and leukotrienes are prevented and tumor growth will be decreased (84). Seleno -compounds like methyl selenol (CH_3SeH) can regulate and induce phase II conjugating enzymes like glutathione-S-transferase and detoxify carcinogens in order to reduce DNA adduct formation (85). Se supplementation enhances immune response by increasing cytotoxic lymphocytes and natural-killer cells, and these cells can destroy tumor cells (86, 87). Selenomethionine (Se-Met) activates P53 by redox regulation in cysteine residues of P53. Methyl- seleninic acid (CH_3SeO_2H) and sodium- selenite (Na_2SeO_3) regulate P53 by phosphorylation (88). Methyl- seleninic acid inactivates PKC so tumor promotion and cell growth will be inhibited (89). Se alters DNA methylation and activity of DNA methyl transferase, abnormal methylation is correlated with neoplasia and inactivation of tumor suppressor genes (90, 91). CH_3SeH precursors induce cell cycle arrest, inhibit growth, and allow DNA repair with or without any breakage in single strand DNA (92). CH_3SeH precursors induce DNA double strand breaks for apoptosis will be occurred and reduce VEGF and matrix metalloproteinase so inhibit angiogenesis (93). P38 protein is a member of the MAP-kinase proteins (MAPKs), which is a key mediator for CH_3SeH that induces vascular endothelial caspase-dependent apoptosis (94). Selenium reduces the production of matrix metalloproteinase 2 and matrix metalloproteinase 9 (MMP-2 and MMP-9) (95). They can degrade intercellular matrix so migration and metastasis will be easy for cancerous cells. MMPs degrade extra cellular matrix (ECM), and then hidden integrin binding sites become exposed leading to the triggering of integrin signals. MMPs facilitate endothelial cell migration by removing adhesion sites and cleavage cell-cell and cell-matrix receptors. So selenium interferes with activity of MMP-9 and reduces endothelial cells migration (96). Selenium decreases expression of MMP-2 and secretion of VEGF in prostate and breast cancer cell lines, which is a critical process for reduction of angiogenesis.

3.8. Calcium

Calcium (Ca^{2+}) is a mineral that is essential for contracting muscles, releasing hormones, transmitting signals, and strengthening bone and teeth. Tight junctions are present in the stomach, intestines, and blood. These junctions keep the cells near each other in the tissue. They are like a belt that localizes under the microvilli and blocks soluble transportation between epithelial cells. The presence of Ca^{2+} is necessary for formation and firmness of tight junctions; this is proven in experiments on cell cultures, MDCK. In intestinal epithelial cells there are so many finger like protrusions of membrane called "microvilli" that are important for food digestion. Their structure consist of actin filaments that are cross-linked with villin and fimbrin as width bridges in lateral arms of actin filaments and cross-linked proteins attached to myosin I and calmodulin. Calmodulin is a Ca^{2+} binding protein and Ca^{2+} can regulate the formation and function of microvilli in intestines. Cadherin is a key protein in cell-cell junction and cell signaling. Digestive system is full of E-cadherin. Adhesiveness of cadherins depends

on the presence of intercellular Ca^{2+} and so the naming of cadherin comes from this property. Each classical cadherin has one trans-membrane domain, one c-terminal cytosolic domain, and five intercellular domains that are for attaching Ca^{2+} and is necessary for cell-cell junction. In addition, another protein called integrin exists in the hemi-desmosome junction of epithelial cells. It has a main role in attaching the cell to matrix, and this attachment needs Ca^{2+} (29). The presence of the lining surface and epithelial cells causes digestive system to act more efficiently in intake and digestion of foods, because they increase the intake surface areas and elongate the time of food passage in the system, leading to more absorption. Moreover, pumpkin is also able to promote the secretion of bile, which enhances stomach wriggling and increase digestion. Many studies prove that calcium consumption helps in preventing cancers like prostate, colorectal, lung, ovarian (97), and breast cancer. In fact, it has been found that women with higher dietary intake of calcium have a lower risk of breast cancer (100). In addition calcium might reduce the risk of colorectal cancer (98, 99). Chemotherapy medications, besides its effect on cancerous cells, have adverse effects like osteopenia. Actually hormonal therapies in breast and prostate cancers and radiation therapies have the same effect on bones. As calcium is important for normal people, adequate intake of calcium is important for people under the chemotherapy medication and especially for people with osteoporosis.

3.9. Potassium

Potassium (K^+) is an essential mineral, low blood levels of it may cause cancer, heart disease, high blood pressure, osteoporosis, depression, or schizophrenia; and a diet high in sodium and low in potassium promotes tumor growth by changing the normal pH and water balance in human cells (101, 102). One type of ATPase family is H^+/K^+ATPase that exists in the stomach (29). By increasing K^+, this pump imports K^+ into the stomach and exports H^+ out in order to decrease the acidic state of the gastric. This pump is the well-proven target in peptic ulcers to decrease H+ and increase the pH of gastric.

3.10. Unsaturated Fatty Acids

Linoleic acid belongs to n-6 or omega 6 polyunsaturated fatty acid that is an essential fat for the body (103). Essential fatty acids and their metabolites suppress tumor growth by producing free radicals in tumor cells (104). Linoleic acid induces formation of lipid peroxidase and apoptosis. The n-6 fatty acids decrease human lung cell growth in a limited concentration. High concentration induces apoptosis in colorectal cancer and induces toxicity effect on tumor cells. Linoleic acid alters the potential of mitochondrial membrane, generates ROS compounds, releases cytochrome C, and activates caspase 9 and 3 to induce apoptosis in colorectal cancer (105).

3.11. Vitamin C

Vitamin C performs its action through taking part in non-enzymatic antioxidants (76). It acts in the hydrophilic phase. It scavenges and balances the free radicals that damages DNA and vital genes which may causes cancer (106).

3.12. Magnesium

Magnesium is the second most abundant cation that takes part in more than 300 enzymes (107), such as sodium-potassium-ATPase, adenylate-cyclase, creatine-kinase activation, and ATP metabolism (108). Glutathione (scavenges the free radicals) needs magnesium for its synthesis (109), where low magnesium is associated with an increase in free radical generation. Lack of magnesium may be carcinogenic; and in solid tumor, high level of magnesium inhibits carcinogenesis (110). Magnesium has a critical role in cell cycle and DNA synthesis. It controls cell growth, spindle timing, and chromosome cycle by changing its concentration, so lack of magnesium may cause uncontrollable cell growth and cancer (111). It is also found that magnesium intake is associated with lower risk of colorectal adenoma.

3.13. Phosphorus

Beside many critical roles of phosphorus like building strong bones and teeth, filtering out the waste material from the kidney, helping in muscle contraction, and supporting nerve conduction; phosphorus has a role in tissues' and cells' growth and repair and also is needed for producing the genetic building blocks DNA and RNA. So its deficiency may damage DNA and cause cancer. Low level of phosphorus increases the risk of colon-rectal cancer (112).

4. Conclusions

In the past many people used plants like pumpkin to cure diseases, and then they found pumpkin is edible and all its parts are beneficial. In especially in the North pumpkin was one of the main foods of local people and the level of cancers, especially gastrointestinal cancers were lower than other regions of but now it changed inversely. In addition the Holy Quran mentioned this plant to his prophet Jonah when he was ill. With this bright history scientists started to extract its nutrients to examine them on different diseases and cancers. We collected this information and explained its molecular mechanism of action on cancers, especially gastrointestinal cancer and came to a conclusion that low level of pumpkin usage is related with high risk of cancers. As pumpkin and its different parts have healing and beneficial nutrients, surely

it could be considered as a super food for many diseases and cancers, especially gastrointestinal cancer.

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