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Nutritional Recommendations for Breast Cancer Treatment: a Review of Persian and Conventional Medicine Resources

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ABSTRACT

Background: Breast cancer is the most common neoplastic cancer of women in the world, which counts for approximately a quarter of all cancers.

Methods: In the present review, we aim to evaluate the most common plant and animal products in the food diet recommended for breast cancer treatment in Persian Medicine manuscripts. The findings reveal the retrieved links from the electronic databases between diet, plant and animal products, and cancer through key terms such as plant and animal products; diet and cancer.

Results: The study findings found 17 types of plant and animal products in the food diet. Scientific evidence has investigated that these products can be as anticancer agents through several mechanisms including cytotoxicity against MCF cells, antiproliferative activity, containing phytosterol, polyphenol, β-sitostrol, flavonoid, antioxidants, as well as having anti-inflammatory and anticancer activities.

Conclusion: Nutritional factors play an important factor in the incidence of cancer. In this regard, Persian Medicine mentions nutrition as the first line therapy. Moreover, pharmacological studies are required to help in identification of related molecular mechanisms in the plant and animal products and their possible side effects.

Keywords: Traditional Persian medicine; Neoplasm; Nutritional plant and animal products; Food Plant

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Introduction

Breast cancer is the most common neoplastic cancer of women in the world [1-3]. While it is the second most common reason of death due to cancer in the world after lung cancer, breast cancer (BC) is the most common cause of cancer death in women [2,3]. This highly prevalent cancer in women worldwide, counts for approximately a quarter of all cancers. Incidence rates of BC are different across the globe, ranging from 25 per 100,000 in Middle Africa as well as Eastern Asia to 92 per 100,000 in Western Europe. It is estimated that by the year 2040, incident cases will increase globally by 46.5% [4]. There are various methods used to treat breast cancer, including hormone therapy, radiation, chemotherapy, and surgery; but the side effects of treatment make one think of complementary and alternative therapies, including the use of plants that have a natural potential to help in treating breast cancer [5]. On the other hand, research has been conducted on the relationship between diet and cancer in recent decades [6]. Nutrition therapy plays a key role in all stages of care and life cycle. It is evaluated that at least 1.3 million cancer deaths per year, as well as 30% of total cancer cases can be prevented via healthy living and controlling environmental factors [7]. It is reported that quality of diet is another risk factor of BC which is changeable. Dietary modifications can result in prevention of about one-third of BC cases. In addition, individuals with cancer often seek information about food choices, physical activity, and supplements that improve outcomes and are very effective in increasing quality of life and overall survival [8].

On the other hand, poor nutrition is associated with adverse outcomes including morbidity, poor prognosis and resistance to treatment, reduced quality of life and increased health costs. The effect of proper nutrition on immune system stimulation or modulation is also a beneficial effect that we expect in cancer patients. Therefore, evaluation of nutritional conditions is indicated in all cancer patients receiving anticancer treatment [9]. Good nutrition can play a positive role in preventing cancer recurrence and progression. Most anti-cancer nutrients should be obtained through a healthy diet. As a result, it is important to take diet and nutritional planning into consideration in palliative care, with a focus on foods and supplements that provide anti-cancer nutrients, decrease oxidative damage and inflammation, improve the patients' quality of life and have beneficial effects on cancer and other medical problems [10].

Recently, more attention is paid to traditional and complementary medicines because of fewer side effects and lower costs [11]. Ancient medical systems like Egyptian, Unani, Chinese Indian, and Persian Medicine (PM) (Iranian traditional medicine) provide further notes to understand cancer [12]. PM is an ancient medical school with known scholars such as Avicenna (980–1037 AD) [13]. This comprehensive medical school has valuable and applicable notes regarding cancer with especial concentration on dietary considerations. The goal of this paper is investigating the recommended foods in PM for breast cancer and comparing them with findings of contemporary medicine.

Materials and Method

This article is a qualitative study (review-descriptive) of content analysis conducted based on Persian Medicine texts and pharmaceutical manuscripts from the 10th to the 19th century,

including *Al-Hawi* (10th century), *Al-Qanun fi al-Tib* (11th century), *Kamil al-Sanaah al-Tibbiyah* (10th century), *Zakhireye Kharazmshahi* (11th century), *Akbari's Tebb-e-Akbari* (18th century) and *Exir-e Azam* (19th century) for words related to "*saratan*" (cancer), "*thady*" (breast), "*waram ol-solb*" (swelling). Furthermore, databases were searched in PubMed, Google Scholar and Scopus until 2020-April with the key term of "nutrition in breast cancer", "meat", "MCF-7", "polyphenol" and gathered the data on the associated food groups and cancer. Finally, the findings of modern medicine were compared with the outcomes of Persian medicine.

Results and Discussion

In this study, the Persian diets have claimed to be effective for breast cancer treatment. Data have been collected from PM texts and pharmaceutical manuscripts and their pharmacodynamics and possible efficacy in modern medicine were evaluated. Persian physicians strongly believe that modifying diets should be used as a first-line treatment in the diseases [14,15]. Nutritional factors play a notable role in the cancer development and prevention [16]. In this article, we aimed to explore cytotoxicity against MCF7 cells, antiproliferative activity, phytoestrol, polyphenol, β-sitostrol, flavonoid, antioxidants, anti-inflammatory and anticancer activities of animal and plant-based foods and drinks as antitumor agents in PM. Persian scholars recommended anticancer foods and drinks for patients treatment including medical barley, yogurt taken from cow's milk , butter, *Ma'ol jobon*, fresh and small fish, goat and lamb meat, half roasted eggs, chicken, mung bean, peas, almonds, spinach, Common Purslane, donkey's milk, sumac [14,15]. In 2020, World Cancer Research Fund [17] reported the diet quality as a another risk factor of BC which is changeable. Dietary modifications can result in prevention of about one-third of BC cases. Meta-analytic results on effective dietary in Breast Cancer treatment showed that, the prudent diet, had only an %11 reduction risk of Breast Cancer. This diet is from foods naturally rich in vegetables, fruits, low fat dairy, fish, poultry, whole grains, and legumes [18] The prudent diet components were very similar to the Persian diet. The difference is that in this diet, goat meat and viper stew are also ordered and the type of spice in the food is also mentioned. Hot-cold and wet-dry temperaments are the basic concepts on the knowledge of PM. This recommended dietary based on cold and wet temperaments. PM texts report high consumption of hot / dry - temperament foods as the causative factors of cancer and removing its causes is the best therapeutic strategy. Therefore, cold and wet temperament foods are recommended [14,15]. Diets containing were surveyed to exhibit temperament and bioavailability of anticancer foods *in vivo* and/or *in vitro*. All the recommended dietary components have been investigated to show the anti-cancer properties in the present study were proven. Among them, the effect of food compounds on human breast cancer cells (MCF-7) are as follows: the chickpea via the inhibitory effect of reactive oxygen species; the honey [19], portulaca, whey protein and donkey milk via cytotoxic activity; egg yolks via reduction in the proliferation; *Vigna radiata*, *Rhus coriaria* and spinach [20] via apoptosis induction; and also *Rhus coriaria* with dependent inhibitory effect on the viability of MCF-7 cells; yogurt drink via reduced cell growth; *Hordeum vulgare* via using MTT assay. Cucurbita via inhibitory effects on the growth of (MCF-7) human breast cancer cells, while almonds [21] inducing the quinone reductase enzyme activity, are stronger in this regard.

Diet modification and or combination with standard management can be a very important

strategy in controlling and preventing breast cancer. It is suggested that further assessment be done on diets referenced in PM as a helper-therapy and be used in clinical practice.

Table 1. *In vitro* studies on nutritious plants mentioned for treatment of breast cancer or cancer in Persian Medicine

Scientific Name of Plant	Part/Active constituent	effect	mechanism	Reference
Hordeum vulgare	barley grass extract	apoptosis of breast and prostate cancer cells	↑intracellular levels of reactive oxygen species (ROS)	[46]
	β-D-glucan isolated from barley treated with γ-rays	- enhanced antioxidant & antiproliferative activities - dose dependent cancer cell growth inhibition	irradiation causes formation of low molecular weight β-D-glucan with antioxidant & antiproliferative characteristics	[71]
	Gramine, a natural indole alkaloid	Inhibition of MDA-MB-231 & MCF-7 cells growth	- Acts as an adiponectin receptor 2 agonist	[72]
Portulaca oleracea Linn.	Whole plant/ Total phenolics	- Cytotoxic effect on MCF-7 cells - High antioxidant effect	- Superoxide dismutase (SOD) enzyme inhibition - neutralization of free radicals or reactive oxygen species by phenolic compounds through donating a hydrogen atom or an electron chelating metal ion in aqueous solutions - A strong relationship between phenolic content of the plant, antioxidant, and inhibitory activity of enzyme	[73,74]
	Leaves/ phenolic compounds	antioxidant and antiproliferative activity on MCF-7	Phenolic compounds show antioxidant activity because of the reactivity of the phenol moiety & can scavenge free radicals through hydrogen or electron donation	[75,76]
	air-dried aerial parts/ four compounds including two new alkaloids	cytotoxic activities against human lung cancer cell lines (K562: weak cytotoxic activities and A549: moderate cytotoxic activities)	NS	[65]
Cucurbita andreana Trichosanthes cucumerina L.	Cucurbitacin B (an oxygenated tetracyclic triterpenoid compound)	strong antiproliferative effects against breast cancer cells MCF-7 & MDA-MB-231 in a dose-dependent manner. cell cycle arrest at G2/M phase & enhancement of apoptosis	- disruption of the microtubule network - ↓c-Myc & nucleophosmin/B23 - perturbation in nucleophosmin/B23 trafficking from the nucleolus to nucleoplasm, ending in G2/M arrest	[23]
	Cucurbitacin B (CuB)	6 human breast cancer cell lines represent a various mix of breast cancer subtypes different in expression of estrogen receptor (ER), Her2/neu, & p53 mutation. cells underwent rapid morphologic changes post-exposure to 5 × 10−7 M CuB ()	disruption of F-actin & the microtubules	[24]
	cucurbitacins B (1), D (2), E (3), and I (4)	inhibitory effects on the MCF-7 cancer cell lines	- COX-2 enzyme inhibition - lipid peroxidation inhibition by some compounds	[25]
	23,24-Dihydrocucurbitacin B (DHCB) extracted from root	- proliferation inhibition of MCF-7 cell line in a dose- and time-dependent way - apoptosis induction in human breast cancer cell line Bcap37	- G2/M cell-cycle arrest induction - mitochondria-dependent apoptosis	[26]
	Cucurbitacin B	cytotoxic effect on breast cancer cell lines SKBR-3 & MCF-7	- G2/M phase arrest & apoptosis - ↓Cyclin D1, c-Myc, & β-catenin - ↑ PARP cleavage & ↓ Wnt-associated signaling molecules β-catenin, galectin-3, cyclin D1 & c-Myc, corresponding changes in phosphorylated GSK-3β levels - inhibition of translocation to the nucleus of β-catenin & galectin-3	[27]

Table 1. *In vitro* studies on nutritious plants mentioned for treatment of breast cancer or cancer in Persian Medicine

Scientific Name of Plant	Part/Active constituent	effect	mechanism	Reference
Cicer arietinum L.	isoflavones extracted from chickpea sprouts (ICS)	proliferation inhibition of SKBr3 & MCF-7 cell lines in a time-dependent and dose-dependent fashion	- significant increase of cytoclasis and apoptotic body formation - ↑apoptosis-promoting gene Bcl-2-associated X protein, ↓expression of the antiapoptotic gene Bcl-2 - ↑caspase 7, caspase 9, P53, and P21 - ↓mitochondrial membrane potential ↑reactive oxygen species	61
	lectin	significant inhibition of the survival of MCF-7 breast cancer cells in a dose dependent manner, apoptosis induction, S and G2 phase cell cycle arrest	- lactate dehydrogenase leakage - cell cycle arrest reactive oxygen species generation	60
	protease inhibitor concentrates (PIC)	Significant viability inhibition of MDA-MB-231 breast cancer cells at all concentrations tested (25–400 µg/ml)	may possess similar anticancer properties to that of soybean Bowman-Birk inhibitor	64
Rhus coriaria	*Rhus coriaria* ethanolic extract	↓cancer cell viability in dose & time-dependent manners	- induction of cell cycle arrest at G1 phase, with ↑p21, ↓cyclin D1, p27, PCNA, c-myc, phospho-RB. - activation of p38 and ERK1/2 signaling pathways. - ↑DNA damage and ↓mutant p53 (two events preceding autophagy)	44
	Rhus coriaria ethanolic extract	- antiproliferative activity against MDA-MB-231 breast cancer cells in a concentration-dependent manner - angiogenesis and metastasis suppression of MDA-MB-231 cells	- promoting cell cycle arrest & autophagic cell death - attenuating the migration ability & inhibiting the invasive capability & transendothelial migration of MDA-MB-231 breast cancer cells - inhibition of the invasive potential of MDA-MB-231 cells, downregulating MMP-9 & prostaglandin E2 & ↓adhesion of the breast cancer cells to fibronectin - attenuating STAT3 activation & inhibiting NFκB pathway in MDA-MB-231 cells - ↓TNF-α protein & ↓levels of IL-6 and IL-8 ↓Nitric Oxide, ↓VEGF production	43
	Rhus coriaria ethanolic extract	inhibition of MDA-MB-231 & MCF-7 cell lines proliferation in a time- and concentration-dependent way	- cell cycle arrest induction at G1, ↑p21, ↓cyclin D1, p27, PCNA, c-myc, phospho-RB and expression of senescence-associated β-galactosidase activity. - activation of p38 & ERK1/2 signaling pathways , induction of autophagy. autophagy induction via DNA damage induction & ↓mutant p53	44
	Silver nanotechnology and nanoparticles AgNPs synthesised from sumac fruit aqueous extract (AgSu/NPs)	a concentration-dependent inhibiton of MCF-7 cells in a dose dependent manner	apoptosis through ↑Bax & ↓Bcl-2	45
Cucumis sativus	methanolic extract of leaves	cell shrinkage, cell wall blebbing and reduction in breast cancer cell population	NS	77
	pulp & peel of *Cucumis sativus* L. fruit, aqueous solution	cytotoxic effect against MCF-7 cell line	NS	78
Almond	biogenic core-shell nanoparticles (polyphenols with additional vitamin E flavonoids)	significant inhibition of MCF 7 cell growth	NS	31
Spinach / *Spinacia oleracea*	methanol extract of spinach	inhibiting MDA-MB-231 cell proliferation	induction of apoptosis	79
NS: Not Stated				

Tables 1-6 include some of the studies recommended by PM for breast cancer. confirming antiproliferative effect of some foods

Table 2. *In vivo* studies on nutritious plants used for treatment of breast cancer in Persian Medicine

plant	Active constituent	Animal	Intervention	Result	mechanism	References
Cucurbita andreana	Cucurbitacin B (CuB)	female nude mice	Intraperitoneal application of either CuB 1.0 mg/kg or vehicle to animals with MDA-MB-231	↓Tumor volume by 55% in treatment group receiving CuB for six weeks	targeting the microtubules	[24]
Rhus coriaria	*Rhus coriaria* ethanolic extract (RCE)	chick embryo model	Grafting MDA-MB-231 cells on the chorioallantoic membrane, then treating the formed tumors every 48 hours with 50 & 150 µg/mL RCE, 2 µM colchicine, vehicle (ethanol).	significant inhibition of tumor growth	- angiogenesis inhibition, -↓VEGF production - ↓MMP-9, PgE2, TNF-α, IL-6 & IL-8.	[43]

Table 3. Clinical studies on plants used for treatment of breast cancer in Persian Medicine

plant	Treatment group	Control group	Study design	Result	References
almond	97	104	Prospective study	high consumption of almonds, walnuts or peanuts reduced breast cancer risk by 2-3 times, which is significant.	[29]

Cucurbita andreana

According to PM, the Mizaj of *Cucurbita andreana* is cold and wet [22]. Some plants produce Cucurbitacin. These plants include especially members of the family Cucurbitaceae, such as the common pumpkins. Cucurbitacin is any of a class of biochemical compounds produced from these plants.

Cucurbitacin B showed proliferation restriction of human breast cancer cell in cellular [23-27] and animal models[24]. It showed significant anticancer and anti-inflammatory activity [28].

Prunus dulcis

Consuming almond has a protective effect on development of breast cancer [29]. Also, antiproliferative terpenoids have been identified in almond [30]. Anticancer/ bactericidal functions were seen in core-shell nanoparticles, which were greenly synthesized within almond [31].

Yogurt drink

In a study, the antiproliferative effect of extract of kefir and yogurt extract on human mammary cancer cells (MCF-7) and normal human mammary epithelial cells was studied. After six days of culture, it was seen that yogurt extract blocked the growth of MCF-7 cells by altering peptide profiles [32].

Spinacia oleracea

This plant, with the common name Spinach plays an important role in cancer. Its glycoglycerolipids serve as angiogenesis inhibitors based on the selective inhibition of DNA polymerase activity [33,34]. Its anti-tumor activity is known [33]. *In vivo* antitumor effect of liposomes with sialyl Lewis X including monogalactosyl diacylglycerol, which

is a replicative DNA polymerase inhibitor derived from spinach, has been proved [35].

Honey

In different cellular studies, it is seen that honey can induce apoptosis and disturb the potential of mitochondrial membrane in human breast and cervical cancer cell lines [36,37]. Also, honey promotes apoptotic cell death induced by tamoxifen in breast cancer cell lines [38]. In PM, *Ma-ol-asal* is used for different purposes of improving health and making disease prognosis better. Different probable mechanisms by which honey might block proliferation of tumors are: regulating cell cycle, activating mitochondrial pathway, inducing permeabilization of mitochondrial outer membrane, inducing apoptosis, modulating oxidative stress, ameliorating inflammation, modulating insulin signaling as well as angiogenesis inhibition. Honey is very cytotoxic against cancer cells, while being non-cytotoxic to normal cells. The data of studies reveal that honey is able to block carcinogenesis through modulation of the molecular processes including initiation, promotion, and progression stages [39].

Egg yolk

Birds have been widely used in recent years to produce antibodies, which are used instead of serum in mammals. Large amounts of antibodies can be produced from egg yolks in a cost-effective way [40]. Some studies have been performed to evaluate the anticancer effect of egg yolk. The IgY antibody isolated from the yolk induced apoptosis in breast cancer cells and show obvious toxic effects against MCF-7 human breast cancer cell line [40,41]. Also, conjugated linoleic acid (CLA)-enriched egg yolks (EFA-CLA) which contain the two important isomers: *cis9, trans11* (80–90% of total CLA) and *trans10, cis1,* has been able to lower the proliferation of MCF-7 breast cancer cells [42]. Finally, the results of these studies suggest that egg yolk can be used as a potential drug in cancer control [40].

Rhus coriaria

In Iranian traditional medicine Rhus coriaria is a plant with cold and dry temperament, and tonic properties [22]. *Rhus coriaria* is a plant of Anacardiaceae family which belongs to Mediterranean area and its common name is Sumac. According to previous studies *Rhus coriaria* containing flavonoids, phenolic acids, and tannins, has many special effects, including anti-fibrogenic, antimicrobial, antifungal, anti-inflammatory, and anti-atherogenic characteristics. These features make it a good candidate for the treatment of many diseases. To further investigate the effects of *Rhus coriaria*, the in vivo study was done on MDA-MB-231 breast cancer cells, and it was found that *Rhus coriaria* can have anti-cancer effects by causing cellular arrest and autophagy of metastatic cells. *Rhus coriaria* successfully lowered inflammatory cytokines TNF-α, IL-6 and IL-8, weakened and stopped nitric oxide (NO) and NFκB, STAT3 pathways [43,44]. In addition, it has been observed that aqueous extract of *Rhus coriaria* is able to block the proliferation and induce apoptosis in of MCF-7 breast cancer cells [45].

Hordeum vulgare

According to Iranian traditional medicine, *Hordeum vulgare* has a cold and dry temperament that can wash out wastes from body, and the water obtained after boiling it, does the same thing [22]. *Hordeum vulgare* L. has long been used in food and is a source of various biological compounds such as various proteins, minerals, carbohydrates,

amino acids and phenolic compounds that can be used in the treatment of diseases [46,47]. Studies have shown that barley has beneficial effects on the immune system by altering the expression of cytokines and suppressing inflammation caused by lipopolysaccharides. Also, to study anti-cancerous effects of barley, it was seen that it could have anti-cancer effects on breast cancer and prostate cancer by inducing apoptosis via increasing reactive oxygen species (ROS) in MDA-MB-231 and DU145 cells [47]. In another study, *Hordeum vulgare* inhibited the proliferation of colon cancer cells by inducing apoptosis [48].

Whey protein

In Iranian traditional medicine, whey protein has a warm and wet temperament and can subtilize dense maters, helps expel wastes, and is very useful in the treatment of diseases caused by yellow bile and black bile [49]. Whey protein is subset of dairy products that derived from milk, which is a source of cysteine amino acid proteins like serum albumin, lactoferrin, and α-lactalbumin, which have role in glutathione production as an important antioxidant. And in previous studies, whey protein had been shown the ability to rise antioxidant activity in human peripheral blood mononuclear cells and also in alcohol-treated rats. Besides whey protein could increase the PTEN-positive cell line MDA-MB-231 response to rapamycin [50]. Also, Seleno-β-lactoglobulin (Se-β-Lg) compound, which contains seleninic acid and β-lactoglobulin (β-Lg), which is a major whey protein of milk, showed anti-cancer effects on two lines of breast cancer cells, (MDA-MB-231, MCF-7), and apoptosis was observed after Seleno-β-lactoglobulin (Se-β-Lg) treating [51].

Vigna radiata

Vigna radiata is a kind of bean with cold and dry temperament that can decrease heat and inflammation from the perspective of Iranian medicine [22]. *Vigna radiate* is widely used in Asia due to its low price and high protein content. Also, it is rich in minerals, dietary fiber, vitamins, and some bioactive compounds like phenolic acids, tannins and flavonoids [52,53]. The results of studies have shown that mung bean has beneficial uses such as antihypertensive, anti-melanogenesis, hepatoprotective, immunomodulatory and anticancer effects. Studies have shown that mung bean has anticancer effects on breast adenocarcinoma cells (MDA-MB-231andMCF-7) via inhibiting cell proliferation, also its methanolic extract can cause apoptosis on cancer cells. And its aqueous extract has been successful in inhibiting breast cancer formation and inhibiting mitosis by stimulating the secretion of T cell cytokines (IL-2 and IFN-γ) [53]. Besides, studies have proven that mung bean protein has an ACE inhibitory and antioxidant effects that makes it a good candidate for the prevention and treatment of cancers, including breast cancer [54,55].

Donkey milk

Donkey milk is a dairy product that according to the Persian alchemist and physician, al-Razi (865-930), is an anti-poisoning (theriac)[14] and has been used in cancer treatment due to its high moisture content [22]. Donkey milk had shown dose-dependent cytotoxic activity against MCF7 cells [56] Active fractions derived from donkey milk reduced the viability of A549 cells in time-dependent and dose-dependent ways [57]. Also, Lactoferrin in donkey milk is protective against cancer metastasis and development [58]. According to a meta-analysis done in 2011, more usage of total dairy food, but not milk, might be associated with less risk of breast cancer [59].

Chickpea

Chickpea is a plant of the family Fabaceae that in the viewpoint of persian physicians, has potent phytonutrients.They have applied it with honey as a topical paste to clean purulent and malignant wounds[22].

Chickpea reduced breast cancer cells (MCF-7 cells) proliferation by inducting apoptosis [60,61]. Bowman-Birk inhibitor is a new cancer chemopreventive agent that was isolated from Chickpea [62,63] and show inhibitory effects on proliferation of breast and prostate cancer cells *in vitro* [64].

Table 4. *In vitro* studies on nutritional animal products used for treatment of breast cancer in Persian Medicine

Animal product	Part/Active constituent	effect	mechanism	References
Donkey milk	casein and whey proteins	strong cytotoxic effect against MCF7 cells in a dose dependent way	correlation between anti-cancer activity of milk caseins and their physicochemical characteristics like alpha helix structure, positive/negative charges	80
Whey protein	Seleno-β-lactoglobulin (Se-β-Lg)	potent anticancer effect on MCF-7 and MDA-MB-231 cells	activating apoptotic signaling pathway by Se-β-Lg and involvement of reactive oxygen species (ROS)	51
	lanthanum (III)-amino acid complex utilizing cysteine	cytotoxic activity on MCF-7 breast cancer cell lines in a time- and dose-dependent way	the binding of the La (III) complex to residues in bovine serum albumin and Bovine β-lactoglobulin may cause micro-environmental and conformational changes of the proteins	81
	Whey protein concentrate	- Induction of rapamycin sensitivity in MDA-MB-231 cells - Depletion of GSH levels & reduction of Nrf2 nuclear accumulation induction of mTORC1 activation	changing the redox state of cells & activation of GSK3β/mTOR signaling	50
Egg yolk	Immunoglobulin Y (IgY) (An agonistic egg yolk antibody)	significant toxicity against MCF7 cells	activating TRAIL death receptors like TRAIL-2 (DR5) & therefore apoptosis signaling	40
	IgYs	anticancer effect on MCF7 cells	Apoptosis induction	41
	fatty acids extract from CLA-enriched egg yolks	reduction in viability and proliferation of MCF-7 cells	- EFA-CLA being PPAR ligands with agonistic activity for all PPAR isoforms EFA-CLA-mediated regulation of PPAR-responsive genes being probably facilitated by cis9, trans11CLA isomer incorporated in egg yolk	42
Yogurt drink	yogurt extracts	antiproliferative effects on MCF-7 cell	change in peptide profiles	32
honey	Tualang honey	- cytotoxicity to MCF-7 and MDA-MB-231 breast cancer cells activation of caspase-3/7 and -9	- apoptosis induction via mitochondrial apoptotic pathway ↓potential of mitochondrial membrane and ↑ in lactate dehydrogenase (LDH) leakage from the cell membranes	37
	Tualang honey	Promotion of anticancer activity of tamoxifen in MCF-7 and MDA-MB-231	- ↑apoptotic cell death induced by tamoxifen in breast cancer cell lines with activating caspase-3/7, -8 & -9 ↑Depolarization of the mitochondrial membrane	38
	Indian honey	Inhibition of MCF-7 cancer cell growth	- antioxidant effect - free-radical scavenging activity ↑accumulation of cells at the sub-G1 phase	82

GSH: glutathione, Nrf2: nuclear factor (erythroid-derived 2)-like 2, GSK3β: glycogen synthase kinase 3 beta, mTOR: Mammalian target of rapamycin, TRAIL: tumor necrosis factor (TNF)-related apoptosis-inducing ligand, CLA: conjugated linoleic acid, EFA-CLA: fatty acids from CLA-enriched egg yolks, PPARs: peroxisome proliferator-activated receptors

Table 5. *In vivo* studies on nutritional animal products used for treatment of breast cancer in Persian Medicine

product	Active constituent	Animal	Intervention	Result	mechanism	References
Whey protein	α-lactalbumin	BALB/c mice	immunization of female SWXJ mice with recombinant mouse α-lactalbumin	- effective and safe protection and therapy against breast cancer development - dose-dependent proliferation of lymph node cells	involvement of CD4+ and CD8+ T cells, showing a proinflammatory phenotype involving ↑production of interferon-γ & IL-2, ↓production of IL-4, IL-5 and IL-10	[83]
	α-lactalbumin	Female rats	consumption of standard AIN-76A diet with 20% α-lactalbumin	- significantly lower proliferative index anti-proliferative effect in breast cancer development & in controlling tumor aggressiveness	NS	[84]
	lycopene loaded whey protein isolate nanoparticles (LYC-WPI-NPs)	female wistar rats	Consumption of powdered LYC-WPI-NPs (equivalent to 15 mg/kg free LYC) orally	- prophylactic anticancer effect - decrease tumor proliferation increase the survival rate of treated animals	scavenging of ROS	[85]
Cow ghee	Cow ghee	Female rat	Animals were fed for 44 weeks diet containing cow ghee	- less tumor incidence, tumor weight & tumor volume - ↑Tumor latency period ↓progression of carcinogenesis	- ↓expression of cyclooxygenase-2 - ↑expression of PPAR-γ	[86]
honey	honey	Rat and mice	Honey was given honey peroral, once a day for 10 consecutive days	anti-metastatic effect when given peroral before tumor-cell inoculation	NS	[87]
	Malaysian jungle Tualang Honey	Female rats	Three treatment groups received 0.2, 1.0 or 2.0 g/kg bodyweight/day honey, for 150 days	- ↓size increment & smaller mean tumor size compared to controls - significantly fewer number of cancers developed in TH-treatment groups ↓grade of tumor in treatment groups compared to control	↑apoptotic index in treatment groups with ↑ dosage of honey	[88]

NS: not stated, ROS: reactive oxygen species, PPAR: peroxisome proliferator-activated receptor

Portulaca (*Portulaca oleracea)*

It is one of the best vegetables in Iranian nutrition, which has good effects on the liver and female reproductive system. Antioxidant and antiproliferative activity of Portulaca oleracea L. extracts against (MCF-7) cell line and their cytotoxic activities against (MCF-7 and MDA-MB-435(has been confirmed in vitro [65]. Water-soluble polysaccharide derived from it has been shown to inhibit cervical cancer cell proliferation [66].

Table 6. Clinical studies on nutritional animal products used for treatment of breast cancer in Persian Medicine

Animal Product	Treatment group	Control group	Study design	Number of patients	Treatment duration	Result	Reference
poultry-chicken	---	---	Prospective cohort study	2830 cases of breast cancer	20 years of follow-up	↓risk of breast cancer in postmenopausal women	[70]
Whey protein	Consumed 30 grams of whey protein concentrate daily	---	Prospective study	five patients with metastatic carcinoma of the breast, one of the pancreas, and one of the liver	6 months	Two patients with breast cancer showed signs of tumor regression, normalization of hemoglobin and peripheral lymphocyte	[89]

A- tocopherol, b-sitosterol and polyphenolic contained in Purslane effect on serum level of lipids, lipoproteins and paraoxanase 1(PON1) activity in hypercholesterolemia patients [67,68].

Goat meat

Weight loss can result from the side effects of cancer or its treatment. Goat meat contains a large amount of protein and is rich in many nutrients such as iron, zinc and selenium, and can therfore improve strength and endurance. However, there is no evidence for goat meat in current literature; lamb or goat meat consumption reveal low rates of colorectal cancer in several Arabic countries [69].

Poultry-chicken

Of the meat food group Chicken soup is used to treat patients. In a prospective cohort study, poultry-chicken has reduced the risk of breast cancer in postmenopausal women [70].

Conclusion

Persian physicians strongly believe that modifying diets should be used as a first-line treatment in diseases [15]. Nutritional factors play a notable role in the cancer development [16]. In this regard, focusing on plant and animal products with anti-cancer properties can be considered. This study has been conducted to explore evidence-based medicine for Persian knowledge based on experience. According to the data, in addition to patient eating habits,their views about these factors should be evaluated to give the best nutritional counseling and dietary therapy for cancer patients. In conclusion, it reduces health care costs in the future.

Declaration of Interest

There is no conflict of interests regarding the publication of this study.

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