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Breast cancer prevention: A *Unani* approach

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Abstract: Breast cancer is an increasing public health problem. In India breast cancer is the 2nd most common cancer after cancer cervix. Obesity and a sedentary lifestyle are two modifiable risk factors. Advances have been made in the treatment of breast cancer, but the introduction of methods to predict women at elevated risk and prevent the disease has been less successful. Plants have a long history of use in the treatment of cancer. In the recent years, a number of herbs have been found to possess anti-cancer potential. In the *Unani* system of medicine, breast cancer is described as *warme sulabe pistan or sartane pistan. Unani* physicians have mentioned in the texts that the *warme sulab* usually develops in the *az'ae ratba*. Various herbal formulations in *Unani* system of medicine have been used for the prevention. A number of herbal drugs such as *rehan, mulaithi, methi, alsi* etc are being researched and reviewed for their anti-cancerous properties. This review expands the concept of *warme sulabe pistan* in *Unani* system of medicine and anticancer effects and related mechanisms of some common natural herbs in the prevention of breast cancer. Details will be presented in full length paper along with scientific research.

Key words: Breast cancer, *Unani* herbs, women health, *warme sulb*.

Introduction:

The incidence of breast cancer is increasing, with an estimated 80,000 new cases diagnosed annually.[1] There are 458,000 deaths per year from breast cancer worldwide making it the most common cause of female cancer death in both the developed and developing world.[2] The most profound breast cancer risk

factor is female gender. A woman's life time risk of developing breast cancer is about 1in 8 or approximately 12%.[3, 4] In the classical *unani* literature it is described as *warme sartaane pistan*. It is a form of *auraame baridah* classified as *warme saudawi. Unani* physicians have mentioned in the texts that the *warme sulb* usually develops in the *az'ae ratba* such as breast(pistaan), uterus(rehm), intestines, throat & lungs etc. which is why they are a common finding in females.[5]

Modern concept:

Cancer breast is the commonest cancer in women in Europe, USA and Australia. In India it is second commonest cancer after cancer cervix.[6] The treatment of breast cancer is based on the stage of diagnosis, a multidisciplinary approach involving surgery, radiation and medical oncology including chemotherapy or hormonal therapy is employed. A combination of local treatments that remove or destroy cancer in the breast (such as surgery and radiation) and systemic treatments that destroy or control cancer cells throughout the body (such as chemotherapy and hormonal therapy) is being undertaken.[7] A constellation of breast cancer risk factors have been identified and are classified as[8];

Table 1. Risk factors:

Not modifiable	**Modifiable**	**Potentially modifiable**
Genetics/family history.	Diet.	Age at first birth.
Age.	BMI.	Age at menopause.
Race/ethnicity.	Exercise.	Breast feeding.
Height.	Smoking.	_____
Age at menarche.	Exogenous estrogen use.	_____
_____	Alcohol consumption.	_____
_____	Reproductive history.[8]	_____

The prevention of breast cancer can be achieved by reducing the modifiable and the potentially modifiable risk factors. Further many women worry about the potential impact of a breast cancer diagnosis on themselves and their families. As a result interest in strategies to prevent breast cancer remains strong.[9]

Conventional breast cancer prevention:

It includes mammography, BSE(breast self examination), CBE(clinical breast examination), chemoprevention, diet and physical activity.

Mammography: Regular mammography as an important part of preventive care. However, while it is true that screen-detected breast cancers are associated with reduced morbidity and mortality, the majority of women who participate in screening will not develop breast cancer in their lifetime. Screening also will not benefit all women who are diagnosed with breast cancer, and it leads to harms in women who undergo biopsy for abnormalities that are not breast cancer, as well as those who are over-treated for ductal carcinoma in situ (DCIS) that might have been non-progressive.[10] With advancing age, incidence of breast cancer remains high, breast cancer mortality rate increases, but overall life expectancy decreases. Because the survival benefit from screening mammography takes several years to emerge. [11,12]

Breast self examination/ Clinical breast examination:

Beginning in their 20s, women should be told about the benefits and limitations of BSE. The importance of prompt reporting of any new breast symptoms to a health professional should be emphasized. The logic for the earlier detection in an average-risk women under age 40, of palpable tumors with CBE or BSE can lead to earlier therapy. The evidence supporting the value of CBE and BSE as methods of reducing breast cancer mortality is limited and mostly inferential.[11]

Chemoprevention:

Uptake of tamoxifen and raloxifen as chemo preventive agents is variable and optimal methods needs to be developed to explain the risk, the benefit/risk ratio of treatment. Further these agents have their own side effects. An issue is predicting those women who will benefit from SERM treatment.[13]

Diet:

The effect of individual components of diet is controversial. The risk of ER negative tumors may be reduced by high vegetable intake while lowering fat intake may reduce both cancer risk and relapse after surgery.[14]

Physical activity:

Observational evidence shows that a physically active lifestyle after cancer treatment prevents relapse and reduces the risk of all cause mortality. However, the optimal exercise regime and timing are uncertain and randomized trials are required to assess the preventive benefits.[15]

Hence, when it comes to breast cancer it's important to understand that getting regular mammogram screenings is not going to prevent the entity. Further the use of chemo preventive agents has issues determining risk estimation in women and who will benefit with the treatment.

It is not a preventive measure but is a screening procedure. This helps in early detection of cancer but cannot prevent it. Therefore, there is a great need for more effective and less toxic therapeutic and preventive strategies. A growing interest in medicinal herbs as part of complementary medicine has been seen in the recent years. The high cost, side effects, and therapeutic limitations of conventional medicines are the key factors that are driving, the revival of herbal remedies. [16]

Although some risk reduction can be achieved with the use of herbal drugs, complete prevention cannot be gained.

Certain herbs defend the body from malignancy by augmenting detoxification or cleaning role of the body. Some biological response modifiers, derivatives of herbs, are recognized to hinder the growth of cancer by modifying the activity of precise hormones and enzymes, while other herbs diminish lethal side effects and complications of chemotherapy and radiotherapy.[9]

***Unani* concept:**

Breast cancer in *unani* concept has been described under the heading of *warme saudawii.*

Table 2. Classification of *auraame baridah* [17]:

Warme balghami	***Warme saudawii***	***Warme reehii***
Warme rakhu	*Saqeeroos*	*Tahabbuj*
Warme maii	*Sartan*	*Nafkha*
Silate'layyena		
Khanazeer		

Unani physicians defined cancer under the headings of *warme salb* or *sartan*. The humour responsible for the development of *sartan* is the *maddae saudawiya*. The *saudawi madda* exists in two forms;

1. *Tabaii maddae sauda.*

2. *Saudae mutaharriqa.*

When the *madda* (humour) is *tabaii* (physiological) it causes *warme sulb* and is termed as *saqeerus.* If this *tabaii madda* becomes *mutaharriq* it results in *sartan* (cancer).[18] Hence, *warme sulb* is classified into two according to the *maddae saudawi:*

Table 3. Classification of *warme saudawi/warme sulb* [17]*:*

Saqeerus	***Sartan***
Saudae akaruddam.	*Saudae akri.*
Khalis sauda.	*Saudae ehteraqi.*
Saudae makhlute balgham.	
Khaalis balgham.	

Sartan is an exhaustive disease. It is easier to manage if diagnosed in the initial stages and its progression to other sites can be ceased. However, when diagnosed late it is incurable and fatal.[19] *Sartan* is mobile, growing and has extensions inside the organ and the surrounding tissue.[20] The *warm* or the *sartan* is surrounded by green colored vessels. Although pain is not a common finding in *sartan*, it develops and increases when the size enlarges. In the beginning the *sartan* is the size of gram seed but can grow to the size of a watermelon in the later stages.[21] *Sartan* usually develops in the *azae' mutkhalkhala* (loose organs with spaces) and *azae'ratba* such as breast (*pistaan*), uterus (*rehm*), intestines, throat & lungs etc. which is why they are a common finding in females.[22]

Pathogenesis:

Sartan develops from *saudae' ehteraaqi* (*khilte mutaharriq), maddae' safrawi* and *maddae' saudawi* together undergoes *ehteraaq* (oxidation) to produce *maddae' ehteraaqi*. This *madda* is the precursor for *sartan* formation. In the initial stages *sartan* is mild (*khafeef*) and difficult to diagnose whereas in the later stages it becomes difficult to manage as it insinuates deep into the surrounding tissue. The course of the disease is first *warme sartani* develops and later the symptoms start appearing. *Sartan* is a fast growing tumor and can metastasize to distant organs as well as to the surrounding tissues.[23]

Sartan may present in three forms;

1. *Sartan* may present with severe pain.
2. *Sartan* may be painless and static.
3. *Sartan* may present with *taqarreh*. This form develops from *hararate' safrae' khalis*.

Prevention:

To prevent progression of *warme sulab* following measures should be undertaken;

Istefraagh of the *khilte ghalib.*

Detoxification of the body and blood of the *sauda.*

Calorie restriction to prevent accumulation of *maddae sauda*.

Drugs and diet possessing hot temperament are to be avoided.

Anti-inflammatory and laxatives should be advised.[24]

Ghizae' saleh should be advised.[23]

Unani physicians have mentioned that *istefragh* and calorie restriction is helpful in the treatment of *warm* of any etiology.[25]

Management:

Measures should be taken to prevent *mutaqarreh* in the *sartan* irrespective of the site of the tumor. This ensures that *sartan* can be treated. However, when *sartan* becomes *mustehqam* (established) it is difficult to manage and cannot be cured. *Buqrat* has clearly stated that any attempt to produce *tehreeq* in the *madda* should be avoided as it would cause *behlaaq* and worsen the condition, whereas if left as such the *sartan* remains static for longer duration and chances of survival of the patient increases. This is commonly seen in patients advised to take *ghizae' saleh.*

The role of surgery in the management of *sartan* is conflicting. Unani physicians mentioned a case of *jarahat* (surgery) in a woman who suffered from *sartaane pistaan* (breast cancer), the affected breast was excised completely. However, after surgery she developed *warme sartaani* in the other breast which was otherwise healthy. This lead to the confusion that *maddae sartani* gets spread to the healthy breast due to *jarahat* (surgery). They concluded that the cancer tissue must have been already metastasized to the other breast, before surgery was performed and the disease manifested after it.[23] *Ibne sina* has mentioned in his treatise *al-qanoon, jarahat* should be performed if the tumor size is small. The excision should be performed in such a way that the *urooq* (vessels) and the *gh'dood* (glands) supplying nutrition to the *sartan* should be removed.[23] The wound after excision can be left as such for free flow of blood or is immediately cauterized following excision when no *tanqiae mawad* is required.[26] When *sartan* lies in close proximity with *azaae shareefa* (vital organs) excision and cauterization should not be opted as it aggravates the condition and becomes incurable. Therefore the principle of treatment should be *tanqiae mawade sauda* irrespective of its location. For the same, regular use of *maul jubn* admixed with *afteemoon* and *maul usl* seems efficacious.[27]

A number of *unani* herbs are potential anti cancerous agents and when used in crude form may prevent cancer. Below is a list of plants with their chemical constituents and activity menstioned in Table 4.

Table 4. List of plants with anti cancer activity.

Botanical name	**Chemical constituent**	**Activity**
Belgiri (Aegle marmelos)	Lupeol	Anti cancer[28]
Aelwaa (Aloe vera)	Acemanon	Anti cancer[29]
Khoolanjaan (Alpinia galangal)	Acetoxy-chavicol-acetate, galangin.	Anti cancer
Neem (Azadirachta indica)	Liminoids, nimbolide(triterpenoids)	Antimutagenic Antimetastatic.[30]
Zarishq (Berperis vulgaris)	Berberine, Cannabisin-G, tyramine, lyoniresinol (phenolic compounds).	Anti cancer.

Soya (Glycine max)	Genistein and diadzein (isoflavones).	Anti cancer[31]
Ginkgo biloba	Ginkgetin, ginkgolides(A&B)	Anti cancer[31]
Amla (Emblica officinalis)	Emblicanin A&B (tannins), Ellagic acid**.**	Anti cancer.[32]
Rubia cordifolia	Rubidianin, rubiadin, RA- 7, RA-700, RC-18.	Anti cancer.
Qust (Saussurea lapa)	Sesquiterpenes, costunolide, dehydrocostuslactone.	Anti cancer.
Viscum album	Viscumin(lectins), Viscotoxins (polypeptides)	Anti cancer.
Asgand (Witthania somnifera)	Withaferin A,SitoindosideIX, Physagulin-D withamosideIV,viscosalactone.	Anti cancer.[31]
Garcinia cambogia	Xanthones & garcenols.	Anti cancer.[33]
Hasha (Thymus serpyllum)	Thymol & carvacarol.	Anti cancer.
*Dhaniya (*Coriandrum sativum)	Quercetin, rutin & beta carotene.	Anti cancer.[31]
Mulaithii (Glycrrhiza glabra)	Glycyrrhizin, aglycone and glycyrrhetinic acid.	Anti cancer.
Tamatar (Lycopersicum esculentum)	Leaves extract.	Anti cancer.
Mako (Solanum nigrum)	Solamargine and solasonine.	Anti cancer.
Alsi (Linum usitassimum)	Secoisolariciresinol diglucoside (SDG)	Anti cancer.
Lehsun (Alium sativa)	Organic sulfides, polysulfides.	Anti cancer.
Haldi (Curcuma longa)	Curcumin(di-feruloyl-methane).	Anti cancer.
Banafsha (Viola odorata)	Cycloviolacin O2 (CyO2).	Anti cancer.
Rehan (Ocimum sanctum)	Flavonoids (orientin, vicenin, cirsilineol, cirsimaritin, isothymusin, isothymonin & apigenein).	Anti cancer.

Methi (Trigonella foenum)	4-hydroxyisoleucine (amino acid), steroidal sapogenins, galactomannans.	Anti cancer.
Sheetraj (Plumbago zeylanica)	Plumbagin.	Anti cancer.
Mac (Myristica fragrans)	Myristicin.	Anti cancer, anti neoplastic.
Adraq (Curcuma zeodoria)	Isocurcumenol.	Anti cancer.[34]

In-vivo, In-vitro antitumor activity of common *unani* herbs:

1. ***Licorice roots* (Glycrrhiza glabra):** Licorice (*mulaithii*) is a perennial plant found in Asia, Mediterranean and parts of southern Europe. The peeled roots (dried) of *mulaithii* are used in the crude form. The temperament is 2°hot and dry. It is commonly used in the treatment of lung, liver and bladder diseases. It causes *nuzj* in the *akhlat* (humours), is an expectorant and also has emmenogogue properties. The chemical constituents of the root are glycrrhizin, asparagin, sugar, starch, resin, gum, mucilage, calcium and magnesium salts etc.[31] Experimental studies have recognized a number of substances in *mulaithii* that may help event DNA mutations, reduce tumor development or even destroy cancer cells including breast cancer.[35] Glycyrrhizin along with its aglycone and glycyrrhetinic acid have also been stated to encourage activity of interferon, supplement the movement of natural killer cells and modulate the growth response of lymphocytes through augmentation of IL-2 production.[36, 37,38] The liquorice extract induced the Bc12 phosphorylation in breast and prostate tumor cells and G2/M cycle arrest, apoptosis demonstrated by annexinV and TUNEL assay. In studies with mice, glycrrhizin and glycrrhic acid decreased the

initiation of colon, uterine and breast cancers. Licorice root also contains powerful antioxidants as well as certain phytoestrogens. Research has demonstrated that this estrogenic effect of licorice components helps to slow the progression of breast cancer.[35]

2. **Tomato leaves (Lycopersicum esculentum):** The cytotoxicity effect of tomato leaves (methanol extract) on cancer cells to address potential therapeutic in MCF-7 breast cancer cell lines and its toxicity towards Vero cells was studied. The effect of extract towards MCF-7 breast cancer cell lines and Vero cells were observed using in vitro cytotoxicity assay to indicate its active fractions and its half maximal inhibitory concentration (IC50). Purified sample gave a rational effect towards MCF-7 breast cancer cells with IC50 value of 5.85 μg mL.[39]
3. ***Mako* (Solanum nigrum *L*):** It has been traditionally used as a herbal plant, whose fruit is believed to have anti-tumor properties, although the mechanism for the activity remains to be elucidated. An ethanol extract from ripe fruits of SNL was prepared and investigated the mechanism involved in its growth inhibitory effect on MCF-7 human breast cancer cells. Results from proliferation assay using tritium uptake showed that the proliferative capacity of MCF-7 cells was strongly suppressed in the presence of SNL ethanol extract. This was further confirmed through MTT assay and trypan blue exclusion experiments, which showed a very close correlation between the SNL extract concentration and the surviving cell numbers. The SNL extract-mediated suppression of cell growth was verified to be apoptotic, based on the appearance of DNA laddering, increase in DNA fragmentation, and low fluorescence intensity in nuclei after propidium iodide staining of the cells. Furthermore, the SNL extract was revealed to be a potential scavenger of hydroxyl radicals and DPPH radicals

rather than superoxide anions. Collectively, findings suggest that SNL fruit extract could be used as an antioxidant and cancer chemo-preventive material.[40]

4. ***Flaxseeds*** **(Linum usitassimum):** Flaxseed is the richest source of the lignan secoisolariciresinol diglucoside (SDG). Flax lignans may be protective against some cancers (i.e. breast, lung and colon) because of their antioxidant, antiproliferative, anti-oestrogenic or anti-angiogenic properties or possibly due to their ability to inhibit certain enzymes. A series of studies have examined the effect of flaxseed and SDG on breast cancer risk using a rat model. Tou et al. (1998) summarized that flaxseed and SDG appeared to delay the progression of N-methyl-N-nitrosourea-induced mammary tumor genesis. Further, SDG altered mammary gland structure by reducing terminal end buds and alveolar buds which may reduce mammary cancer risk. The mechanism by which SDG protects against breast cancer is unknown. Insulin-like growth factor I is associated with increased risk for breast cancer and SDG has been shown to lower plasma insulin-like growth factor I concentrations.[41] The concentration of Zn is higher in breast cancer tissues than in normal breast tissues. Thus, another mechanism could be related to the ability of SDG to regulate the expression of Zn transporters.[42] Lastly, vascular endothelial growth factor stimulates the production of new blood vessels (i.e. angiogenesis), which is critical in the progression of cancer. In vitro and in vivo evidence suggests that ED and EL may provide protection against breast cancer by limiting angiogenesis.[43]
5. ***Garlic*** **(Alium sativum):** Medicinal properties of garlic have been widely known. It possesses multiple beneficial effects such as hypolipidemic, anti thrombotic and antitumor activities. Anti cancer properties of garlic was first described by Weisberger and Pensky in 1958. They reported an inhibitory effect of garlic extract on cancer cells both in vitro and in vivo. The antitumor property

of Garlic is attributed to its high level of a wide-ranging diversity of organic sulfides and polysulfide's. It is known to augment action of the immune system by activating lymphocytes and macrophages to kill cancer cells. It is also identified to interrupt the metabolism of tumor cells [36][44]. The ripened extract of garlic shields DNA from the harmful influence of carcinogens, surges activity of detoxifying enzymes, hustles up elimination of chemical carcinogens and boost body's immune system. Further, (mature garlic extract) it is known to prevent development of several tumors including those of the breast, lungs, stomach, colon and bladder. An investigation done at the National Medical Centre and Hospital in Japan has shown that the Garlic extract lessens complications of radiotherapy and chemotherapy as well.[45,46,47, 48]

6. ***Turmeric*** **(Curcuma longa):** Its anti-mutagenic action as well as cancer inhibition activity is attributed to its phenolic constituents. Turmeric has been shown to curb the progress of cancer breast as well as lung, stomach and skin malignancies.[49] Its antioxidant curcumin (a diferuloylmethane), has been shown to be a successful anti-inflammatory agent in humans and slows down the development of cancer by averting the production of toxic eicosanoid such as PGE-2 [50]. This anticancer outcome has been established in all the phases of tumor growth, i.e. initiation, promotion and progression. Curcuma longa increases levels of glutathione and other nonprotein sulphahydryls and acts directly on several enzymes.[51, 52] Numerous research also advocates that curcumin hampers the initiation of cancer as well as encourages its deterioration.[51] Laboratory studies support that curcumin interferes with several important molecular pathways involved in cancer development, growth, and spread while researchers report that curcumin inhibits the formation of cancer causing enzymes in rodents.[53]

7. ***Banafsha* (Viola odorata):** Cycloviolacin O2 (CyO2), a cyclotide from Viola odorata (Violaceae) has antitumor effects and causes cell death by membrane permeabilization. In the breast cancer line, MCF-7 and its drug resistant subline MCF-7/ADR, the cytotoxic effects of CyO2 (0.2-10 microM) were monitored in the presence and absence of doxorubicin (0.1-5 microM) using cell proliferation assays to establish its chemosensitizing abilities. SYTOX Green assays were performed to verify membrane permeabilization and showed cellular disruption correlates with cyclotide chemosensitization. Fluorescence microscopy studies demonstrated increased cellular internalization of doxorubicin in drug resistant cells when coexposed to CyO2. Interestingly, CyO2 did not produce significant membrane disruption in primary human brain endothelial cells, which suggested cyclotide specificity toward induced pore formation in highly proliferating tumor cells. This study documents CyO2 as a promising chemosensitizing agents against drug resistant breast cancer.[54]
8. ***Fenugreek* (Trigonella foenum):** Trigonella foenum (Fenugreek) is traditionally applied to treat disorders such as diabetes, high cholesterol, wounds, inflammation, and gastrointestinal ailments. Fenugreek is also reported to have anticancer properties due to its active beneficial chemical constituents.[55] A potential protective effect of Fenugreek seeds against 7, 12-dimethylbenz(α)anthracene (DMBA)-induced breast cancer in rats. At 200 mg/kg b.wt. Fenugreek seeds' extract significantly inhibited the DMBA-induced mammary hyperplasia and decreased its incidence. Epidemiological studies also implicate apoptosis as a mechanism that might mediate the Fenugreek's anti-breast cancer protective effects.[56]
9. ***Sheetraj* (Plumbago zeylanica):** Plumbagin exhibited cell proliferation inhibition by inducing cells to undergo G_2-M arrest and autophagic cell death.

Blockade of the cell cycle was associated with increased p21/WAF1 expression and Chk2 activation, and reduced amounts of cyclin B1, cyclin A, Cdc2, and Cdc25C. Plumbagin also reduced Cdc2 function by increasing the association of p21/WAF1/Cdc2 complex and the levels of inactivated phospho-Cdc2 and phospho-Cdc25C by Chk2 activation. Plumbagin triggered autophagic cell death but not predominantly apoptosis. Pretreatment of cells with autophagy inhibitor bafilomycin suppressed plumbagin-mediated cell death. We also found that plumbagin inhibited survival signaling through the phosphatidylinositol 3-kinase/AKT signaling pathway by blocking the activation of AKT and downstream targets, including the mammalian target of rapamycin, forkhead transcription factors, and glycogen synthase kinase 3β. Phosphorylation of both of mammalian target of rapamycin downstream targets, p70 ribosomal protein S6 kinase and 4E-BP1, was also diminished. Overexpression of AKT by AKT cDNA transfection decreased plumbagin-mediated autophagic cell death, whereas reduction of AKT expression by small interfering RNA potentiated the effect of plumbagin, supporting the inhibition of AKT being beneficial to autophagy. Furthermore, suppression of AKT by plumbagin enhanced the activation of Chk2, resulting in increased inactive phosphorylation of Cdc25C and Cdc2. Further investigation revealed that plumbagin inhibition of cell growth was also evident in a nude mouse model. Taken together, these results imply a critical role for AKT inhibition in plumbagin-induced G_2-M arrest and autophagy of human breast cancer cells.[57]

Conclusion: There has been a recovery of attention and interest, both scientifically and in terms of recognition, in the consumption of natural approaches in the prevention of cancer. Science has long accepted the importance of natural substances. Experimentations have shown that herbal drugs can play anticancer role by stimulating

apoptosis and differentiation, augmenting the immune system, hindering angiogenesis and reversing multidrug resistance. Nevertheless, the mechanism of the anticancer function has not yet been completely illuminated. Further research is required to evaluate the use of *unani* herbs as potential agents in the prevention of breast cancer.

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