Fermented Foods: The Pharmacological and Anticancer Therapeutic Potential

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Abstract: Globally, dietary and environmental changes have been recognized as major causes of noncommunicable diseases such as malignancies, with ongoing research on modifiable risk factors, including eating habits, estimating that 30–40% of cancer formation can be avoided with behavioral adjustments. According to estimates from the World Health Organization (WHO), cancer is the second leading cause of death worldwide, with 9.6 million fatalities projected in 2018. Cancer accounts for nearly 1 in every 6 deaths especially in females. In a survey of year 2019 within Indian subcontinent about 20% (one in five) female suffers from one of the symptoms of ovarian disorders which further turns into tumors such as ovarian epithelial cells, endometriosis. More effective cancer treatments with lower toxicity are required. Natural foods have become increasingly popular in the treatment and prevention of cancer. Some nutrient components in fermented foods are referred to be "naturally fortified functional nutrients" because they assist to maintain a healthy gut microbiome, which protects against disease and physiology and could prove to be boon for those females by boosting metabolism because such women have lower healthy gut microflora as compared to other females as fermented foods have higher probiotic value which enhance the gut flora. The epidemiological studies suggest the evidences that lactic acid bacteria present in fermented foods plays an important role in preventing breast cancer. This review article summarizes the health benefits of fermented food to certain cancer which has been scientifically proven.

Keywords: Fermented foods, Endometriosis, Microbiome, Cancer, Microflora


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Introduction

Fermentation is a process in which microorganisms consume susceptible organic substrate as part of their own metabolic process. The study of fermentation is called Zymology by Robert et al. (2005). The term “ferment” derived from the fervere, a Latin word means to “boil it”. Louis Pasteur (1850-1860) was the one who discovered the process of fermentation. Eduard Buechner (1897) had clarified the chemistry of fermentation i.e. reaction mixture of sugar solution and yeast for the very first time. His invention opened a new door in biochemistry and selected for Nobel Prize in Chemistry 1907 (Helmenstin, 2020) It is one of the oldest and natural methods of preserving food before refrigeration. Fermentation Technology is an emerging field in Food microbiology (Sande, 1997; Terefe et al., 2022). With the increasing population food scarcity is also a major issue and this led to malnutrition due to lack of healthy balanced diet. Fermented foods are rich in vitamins and essential amino acids. Therefore, it can fulfill the urge of nutritional deficiency and has the potential to reduce several diseases like hypertension, high cholesterol, diabetes, obesity and mental anxiety (Some and Mandal, 2020).

Most prominent group is of adolescent girls (14-18 years) in which symptoms of ovarian disorders are found, one out of three girl suffering from Polycystic ovarian syndrome or disease (pcod or pcos) which causes gain in weight or obesity (Pirotta et al., 2022), acne and facial hair problems (Raak et al., 2014). In adult females it causes severe problems such as diabetes (type 1 and type 2), cardiovascular diseases, high cholesterol level, thyroid, anxiety - depression and mood swings sometimes pain in lower abdomen region, cancers and infertility. There are some scientific reasons behind using fermented foods in curing or reducing the chances of ovarian disorder. There is a positive link between dairy consumption and acne and hormone influx in females who are suffering from ovarian disorders (Burris et al., 2013).

Scientific Reasons:

Improves digestive issues and maintains gut flora:

Since fermented foods like yoghurt are good sources of probiotics helps in killing harmful bacteria present in gut. Bloating could be avoided by taking fermented foods in daily diet. If gut flora is healthy then there would be no problem of lactose intolerance, gluten sensitivity and allergies (Ridaura et al., 2013).

Prevent chronic diseases:

Diseases like diabetes, cancer are linked to gut microbes. There is no such medication or vaccination that could completely finishes diabetes but it has been reported that including fermented foods in daily diet helps to control blood-glucose level and helps in preventing gastric cancer by suppressing Helicobacter pyroli. It has been seen that patients who are under observation during this experiment has shown certain changes in gut bacteria and helps in boosting up immunity (Zhao, 2013).

Fermented foods help to feel happy:

Ovarian disorders are caused due to hormonal imbalance and stress could be one reason for hormonal influx. In a survey, females suffer from mental stress and depression more than males. According to doctors females should avoid mental stresses who are suffering from this problem. Lactobacillus plantarum (Raak et al., 2014) is a bacteria present in sauerkraut which have shown to produce neurotransmitter that helps to reduce depression and females who consume fermented food in comparison with those who does not are physically and mentally healthy.

Reduces Allergies:

Female’s especially adolescent girls suffer from facial problems like acne and hairs on face and sometimes food allergy (Yazdanbakhehsh et al., 2002). In fermented food presence of lactic acid bacteria is associated with changing gut bacteria to be favorable for reducing allergies.
There are some known fermented products (Table 1) which will definitely bring better results in curing ovarian disorders.

**Yoghurt:**

Yoghurt is made up of bacterial fermentation of milk by adding yoghurt culture (*Lactobacillus bulgaricus* and *Streptococcus thermophiles*) and a probiotic which is good for gut microflora (Ardo et al., 2006; Hao et al., 2011). Dairy consumption seems to be most discussed topic for females who are diagnosed with ovarian diseases. Milk consumption in these patients lead to increase in androgens and insulin levels (Burris et al., 2013). Body needs calcium and vitamin D especially in women after the age of 30 as their bone density starts decreasing. Yoghurt contains higher protein and lower carbohydrates (low glycemic index) which is again helpful in weight loss. *Lactobacillus*, *Leuconostoc*, *Pediococcus*, *Streptococcus*, *Micrococcus* and *Bacillus* species are common fermentation microorganisms. *Paecilomyces*, *Aspergillus*, *Fusarium*, *Cladosporium*, *Penicillium* and *Trichothecium* are examples of fungus (Gupta and Abu-Ghannam, 2012).

Probiotic cultures are thought to minimise exposure to chemical carcinogens. By altering the intestinal environment and thereby lowering the population or metabolic activity of bacteria capable of producing carcinogenic compound (Saxami et al., 2017), detoxifying carcinogens (Lili et al., 2018), producing metabolic products such as butyrate, which increases apoptosis ability (Parvez et al., 2006), and stimulating the immune system against cancer cell IFN-c, TNF-, and cytokines are examples of cytotoxic mediators (Kinouchi et al., 2012). Another proposed mechanism, according to Parvez et al. (2006), is that probiotics can reduce the number of carcinogens in the intestine by limiting the bacterial growth that modifies the carcinogens. Probiotics also have antimutagenic, antimicrobial, anticarcinogenic, anti diarrheal activity, advancement in lactose intolerance, decrease in serum cholesterol level, immune system stimulation, and suppression of *Helicobacter pylori* infection (Walia et al., 2015).

Yoghurt could be used in preventing lung cancer, with the combination of dietary fibers (prebiotics) and yoghurt (probiotic) not only enhance gut microflora ecosystem but also act as immunomodulator which secretes cytokine which proliferates immune cells. Bacterial strains *Lactobacillus* and *Bifidobacterium* change the gut and lung ecosystem (Trompette et al., 2016).

**Sauerkraut:**

Sauerkraut or kimchi are fermented cabbage leaves which convert natural sugars to lactic acid. It contains *Lactobacillus plantarum* which helps in reducing depression, anxiety and inflammation in gastrointestinal tract (Levit et al., 2017). In binary logistic regression study 81 women were assessed using the statistical analysis by using SPSS ver.13 (SPSS Inc. Chicago, Ill, USA). The results showed that about 38.6% suffered from anxiety and 25.7% were suffering from depression and diagnosed with ovarian disorders symptoms.

On contrary, Kimchi is an Asian version of sauerkraut, fermented cabbage with daikon, radish, ginger, garlic and spices. According to a Korean medical report, regular consumption of kimchi by a group of obese women showed changes in gut bacteria that leads to weight loss (Han et al., 2015). Sauerkraut is rich in antioxidants, calcium, magnesium, vitamin C, vitamin D, vitamin K and dietary fibers. Consumption of sauerkraut foods either during adolescence or adulthood significantly reduced breast cancer risk among Polish migrant women (Pathak et al., 2021).

However, it should be consumed in limited amount as it contains high amount of histamine which may increase allergy problems (Katrina Pace, 2017). The kynurenine concentration was decreased by *Lactobacillus plantarum* 299v (LP299v) while this bacterial strain improves cognitive functions in patients with major depression. Placebo controlled study (a double-blind, randomized) was conducted in Medical
In this study 79 patients were randomized with major depressive disorder (MDD). Patients received either a Selective serotonin reuptake inhibitors (SSRI) with the placebo of the robiotics (n=39) or SSRI with the LP299v (n=40) for a period of 8 weeks. The severity was assessed by using three parameters like Perceived Stress Scale (PSS-10), hamilton depression rating scale (HAM-D 17) and symptom checklist (SCL-90) while cognitive functions were assessed by using several parameters viz., stroop test parts A and B, attention and perceptivity test (APT), trail making test (tmt) parts A and B, ruff figural fluency test (RFFT), and california verbal learning test (CVLT).

Many biochemical parameters were assessed such as kynurenine (KYN), anthranilic acid (AA), tryptophan (TRP), tumor necrosis factor-alpha (TNF-α), kynurenic acid (KYNA), 3-hydroxy anthranilic acid (3HAA), cortisol plasma concentrations, 3-hydroxykynurenine (3HKYN), interleukin 6 (IL-6) and interleukin 1-beta (IL-1b). After 8 weeks out of 60 patients, 30 in the LP299v group and 30 in the placebo group finished the study and were analyzed. There was a significant decrease in KYN concentration in the LP299v group while significant increase in 3HKYN:KYN ratio in the LP299v group compared with the placebo group was recorded. ANOVA studies revealed a significant effect but there were no significant changes in concentrations of TNF-α, IL-6, IL-1b and cortisol in neither LP299v nor placebo groups. Hence, this study concluded that LP299v decreased KYN concentration and improved cognitive performance in MDD patients due to robiotics bacteria. Decreased concentration of KYN could contribute to the improvement of cognitive functions in the LP299v group compared to the placebo group.

Kefir:

Kefir was originated in Russia, this is a traditional drink made by fermentation of milk. Fermentation is done by clusters of bacteria called “grains” which are matrix of polysaccharides, proteins and lipids containing bacteria (Leuconostoc acetobacter, Lactobacillus kefiri and Lactobacillus kefrianoacines) and yeast (Candia kefyr) and digest lactose while the remaining liquid gives slight sour and fizzy in taste which makes kefir drink lactose free (Angulo et al., 1993; Marquina et al., 2002; Latorre-Garcia, 2007; Disoma et al., 2013). Kefir helps to prevent diabetes and reduce cardiovascular diseases (WHO, 1982) and oxidative stress and has antioxidant capacity. Kefir is capable of having anti-carcinogenic effect because of its antioxidant and reducing DNA damage property (Grishina et al., 2011). It increases the glutathione peroxidase and decreases malon-dialdehyde level which controls oxidative stress. Kefir inhibits the linoleic acid peroxidation by binding DPPH (1,1-diphenyl-2-picrylhydrazyl) and superoxide radicals (Cevikbas, 1994). It is suggested that bacteria in kefir reduces allergies in body as well as change the immune signals sent out by body (Bourrie et al., 2016). University of Medical Sciences, Dezful, Iran conducted the work on anti-carcinogenic properties of Kefir. It is capable to prevent cancer in females such as breast cancer and colon cancer. One of the most common cancers among women is breast and ovarian epithelial cancer and the treatment as well as prevention are very substantial. Sharif et al. (2017) and Chen et al. (2007) showed that kefir extracts induce apoptosis, cell cycle which reduces tumor growth in breast cancer cells which is a strong method of preventing breast cancer. The supernatants of kefir contained high amounts of acetic and lactic acid and showed meaningfully antioxidant capacity and this evidence suggests that kefir can decrease DNA damage, which might be due to their antioxidant properties and its anticancer potential on CRC cell line (Caco -2 and HT -29) at G-1 phase arrest cell cycle. In addition, kefir decreases the expression of Transforming Growth Factor (TGF-β1) and (TGF-α) in human colorectal adenocarcinoma cell line (HT-29 cell line). It has also been reported that kefir can reduce sleep disturbance in patients treated for colorectal cancer.
Kombucha:

Kombucha is a kind of black tea fermented together by using Symbiotic Culture of Bacteria and Yeast (SCOBY). This special type of black tea has antioxidant as well as antimicrobial properties (Chakravorty et al., 2016; Kaewkod et al., 2022) and also helpful to reduce gastric ulcers, diabetes risk and cholesterol because this drink contains polyphenols and organic acid all of which could affects digestion (Banerjee et al., 2010; Aloulou et al., 2012). This could be easily made at home by keeping 7 to 10 days for fermentation and then it is served. Tea fungus makes black tea ingredients to undergo various progressive modification (Blanc, 1996). The main metabolites identified in the Kombucha beverage are glucuronic acid, gluconolactone, glucaric acid, gluconic acid, 2-keto-D-gluconic acid and usnic acid (Fig. 1). The composition of metabolite as well as concentration depends on the source of tea fungus, concentration of sugar and the fermentation time. There are different ways to prepare. Glucose and fructose are formed from sucrose because yeast cells hydrolyze and produce ethanol. In the study, LAB (lactic acid bacteria) produces lactic acid and acetic acid and vitamin B complexes and folic acid are produced by the fermentation. If organic acid content increases during the fermentation process then pH of kombucha decreases simultaneously.

Since 1852, mainly in Europe Kombucha has been studied and reviewed by Allen (1998) which proved that kombucha reduce menstrual disorders and menopausal hot flashes, improve hair, skin and nail health, stress and nervous disturbances, insomnia, help for headaches, improve eyesight problems and also enhance general metabolism. Kombucha has anti-carcinogenic effect in body because of tea polyphenols and metabolites like oxalic acid, lactic acid, citric acid (Watawana et al., 1998). Kombucha also inhibit rapid multiplication of cancer cells, induce cancer cell apoptosis, gene mutation and ability to end metastasis and in cancer patients it prevents stomach cancer. Kombucha contains D-saccharic acid-1,4-lactone (DSL) which is helpful in boosting the activity of doxorubicin antitumor agent in colorectal cancer (Watawana et al., 1998).

Soy based food:

Soy (Glycine max) comes from soyabean originated from China, which can be consumed in the form of soy protein, fiber and contains many essential amino acids that is complete protein source (Shurtleff et al., 2007). Soy contains isoflavones which is converted into phytoestrogens in human body. These phytoestrogens are similar in molecular structure to estrogens (Toi et al., 2013).

Genistein, Daidzein and Glycitein are the soy isoflavones. Daidzein and genistein are the prominent in soy products. Genistein is obtained through diet in soy products like tofu, tempeh exists as conjugated form, genistin in the primary chemical form (Zhang et al., 2013). This is an active flavonoid which participates in the activity of altering estrogen related malignancies which is related to apoptosis, cell cycle and inhibition of metastasis which helps in preventing cancer cells and also shows synergistic properties with anticancer drugs such as doxorubicin for therapy. Caspases, Bcl2-associated X protein, Bcl-2, kinesin-like protein 20A, extracellular signal-regulated kinase 1/2, nuclear transcription factor B (NF-B), mitogen-activated protein kinase, inhibitor of NF-B, Wingless and integration 1 -catenin, and phosphoinositide 3 kinase/Akt signaling pathways have all been implicated in the anticancer and therapeutic effects of genisten (Sarkar et al., 2003; Spagnuolo et al., 2015). Its ability to inhibit NF-B is particularly essential because this inhibits inflammation. Both the NF-B and the serine/threonine-specific protein kinase Akt keep a homeostatic equilibrium between cell survival and apoptosis in place.

Soy isoflavones, particularly genistein, decrease cell growth and facilitate apoptosis and cell cycle arrest in the G2/M phase in patients with colon cancer (Zhang et al., 2013). As shown by quantitative polymerase chain reaction and immunoblotting, cell cycle arrest in the G2/M
Table 1: Mechanism of fermented foods in cancer patients

<table>
<thead>
<tr>
<th>Fermented foods</th>
<th>Anticancer component</th>
<th>Types of Cancer</th>
<th>Binding sites</th>
<th>Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoghurt</td>
<td>Lactobacillus and Bifidobacterium</td>
<td>Gastric cancer and Lung cancer</td>
<td>IFN-γ, TNF-α, and cytokines</td>
<td>Binding the cancerous cells and act as immune-modulator</td>
<td>Nout et al. (2005)</td>
</tr>
<tr>
<td>Soy Tofu and Tempeh</td>
<td>Genistein and daidzein</td>
<td>Colon cancer and Breast cancer</td>
<td>Caspases, Bcl2-associated X protein, Bcl-2, kinesin-like protein 20A, extracellular signal-regulated kinase 1/2, nuclear transcription factor B (NF-B), mitogen-activated protein kinase, inhibitor of NF-B, Wingless and integration 1 - catenin, and phosphoinositide 3 kinase/Akt</td>
<td>Genistein triggered G2/M cell cycle arrest in a p53-dependent manner, implying that the ATM/p53-p21 cross-regulatory network is critical in mediating genistein's anticarcinogenic activity as well as binding the Tyrosine Protein Kinase responsible for transduction cell growth factor</td>
<td>Zhang et al. (2013); Cappelletti et al. (2000)</td>
</tr>
<tr>
<td>Kefir</td>
<td>Lactic acid</td>
<td>Breast cancer and colon cancer</td>
<td>CRC cell line (Caco-2 and HT-29) at G-1 phase arrest cell cycle.</td>
<td>It increases the glutathione peroxidase and decreases malon-dialdehyde level which controls oxidative stress. decreases the expression of Transforming Growth Factor (TGF-β1) and (TGF-α) in human colorectal adenocarcinoma cell line (HT-29 cell line).</td>
<td>Chen et al. (2007); Sharifi et al. (2015)</td>
</tr>
<tr>
<td>Kombucha</td>
<td>D-saccharic acid-1,4-lactone (DSL)</td>
<td>Colon Cancer</td>
<td>Strengthen antitumor agent doxorubicin and inhibits the multiplication of cancer cell gene mutation</td>
<td></td>
<td>Watawana et al. (2015)</td>
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</tbody>
</table>

Fig. 1: Chemical structure of Kombucha constituents (source: Dufresne and Farnworth, 2000).
phase is associated with activation of ATM/p53, p21waf1/cip1 and GADD45, as well as downregulation of cdc2 and cdc25A. Genistein triggered G2/M cell cycle arrest in a p53-dependent manner, implying that the ATM/p53-p21 cross-regulatory network is critical in mediating genistein’s anticarcinogenic activity. Genistein was discovered to work with the histone deacetylase inhibitor vorinostat to promote cell death in PCa cells (Phillip et al., 2012). This significant isoflavonoid has recently been found to boost radiosensitivity of PCa cells in a synergistic manner.

Another study revealed that high concentrations of probiotics may alter the metabolism of isoflavones. The consumption of beverages containing L. casei Shirota (probiotic bacteria) and soy isoflavone was inversely associated with the incidence of breast cancer in Japanese women consuming such beverages regularly since adolescence and has least chance of breast cancer. Then this incidence evaluated through rat carcinogenic model by taking soy isoflavone supplement like soymilk and observed that it prevented the development of mammary tumors (Kaga et al., 2013).

There is another setup that looked at the relation of soy phytoestrogen intake in 315 women undergoing infertility treatment with assisted reproductive technology (ART) (Vanegas et al., 2015). As per this study soy not only improved the fertility rate but also improves pregnancy and birth rate. Hence, we could conclude that soy reduces the chances of infertility as well in women who are diagnosed with ovarian disorders.

Tofu and Tempeh:

Tofu is a processed fermented curdled bean form of soy. It contains isoflavones which possess both dependent and independent characteristics which restricts the development of breast cancer. The mechanism of isoflavones in inhibiting is by competitive binding of estrogen receptors (Jamilian et al., 2016). Genistein, an isoflavonoid found in soy is another inhibitory factor of tumor growth in various breast cancer through the restriction of TPK (Tyrosine Protein Kinase) which is responsible for transduction cell growth factor (Cappeletti et al., 2000; Zhang et al., 2013). Tofu is a staple food in western Asian countries, therefore probably females in western countries reports more cases of breast cancer comparatively the western Asian females. Soy helps in reducing cholesterol, triglycerides, inflammatory markers and hormone influx. It has low calorie count, high protein and little fat but good source of iron, calcium and magnesium.

Tempeh is the best alternative of protein for females who are non–vegetarian, dietary fibers and vitamins to control cholesterol to avoid obesity or weight gain. It is originated from Indonesia and made from fermented soybeans like tofu but differ in nutritional properties and textural feature. It is made by a natural culturing and controlled method of fermentation that binds soybeans in cake form. The starter culture used is Rhizopus oryzae (Shurtlaff and Aoyagi, 2007).

It has been found that tempeh can help in restricting breast cancer being a fermented form of soy which has abundant isoflavones-- Genistein and Daidzein. These isoflavonoids has the potential to inhibit the angiogenesis, since proliferation of cancer cells depends on adequate amount of oxygen and nutrients by restricting the oxygen demand to cancerous cells growth of breast cancer cells could be terminated to certain extent (Nishida et al., 2006; Varinska et al., 2015).

Conclusion

With the growing population, fermented foods demand also increasing in India. Fermented foods are not new generation food but it is an ancient practice of preserving food, increases nutritive value, flavours and reduces cooking times. Moreover, fermented foods are functional food which helps in curing or helps in reducing the adverse effects of ovarian disorders along with medical prescription. The foods which are discussed here are easily available in market and could be used in daily life. Apart from this it is
necessary to give time on physical exercise and adapt healthy eating pattern such as fresh fruits, green leafy vegetables and keep mind stress free.

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