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# THERAPEUTIC POTENTIAL OF BILWADI GUTIKA IN BREAST CANCER –A BRIEF REVIEW

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## ABSTRACT

**Introduction:** Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Breast cancer is the most common malignancy in women in the developing countries and the second commonest malignancy in women in India. In 2020, there were 2.3 million people diagnosed with breast cancer and 68500 deaths globally. Now a days due to Increasing Age, Inherited Genes (most well-known gene mutations are BRCA1 and BRCA2.), Radiation Exposure, Obesity, Early Menstruation or Late Menopause, Postmenopausal Hormone Therapy, drinking alcohol, physically inactive, long-term Use of Oral Contraceptives, Diet rich in fat, Smoking are some of the causes which are known to cause breast cancer. Despite the fact that contemporary science has developed powerful anticancer medications like cisplatin, and other conventional methods like surgery, radiation therapy, hormonal therapy and palliative therapy, causing many negative side effects. **Methodology:** *Agada Tantra* is a specialized branch of *Ayurveda* which deals with the management of toxicity

with numerous formulations. *Bilwadi gutika* is one such formulation mentioned in classics in *Ashtanga Hridaya* in *Sarpa Visha pradhishedha adhyaya.* It is an herbal formulation containing 13 ingredients in equal quantity and Goat's urine used as *Bhavana dravya* (Liquid media for trituration) **Result:** *Bilwadi Gutika*, may offer supportive care in cancer management, by playing a valuable role in reducing toxicity, managing inflammation, and supporting the immune system during conventional cancer therapies like chemotherapy and radiation. **Discussion:** Its detoxifying and restorative properties align with the needs of cancer patients who face significant side effects from aggressive treatments.

**Keywords: Cancer, Breast cancer, Conventional methods, *Bilwadi gutika***

**INTRODUCTION-**

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body **[1]**. Factors such as life style, level of physical activity, food, personal hygiene, and environmental pollution are the major causing factors of cancer. Every person nowadays is constantly exposed to a variety of harmful compounds, the majority of which are cancer-causing **[2]**. According to World Health Organization, more than 80% of people in developing countries depend on traditional Medicine for their primary health needs **[3]**. Breast cancer is the commonest malignancy among women globally and is the leading cause of cancer **[4]**. In 2020, there were 2.3 million people diagnosed with breast cancer and 68500 death globally **[5]**. It has been estimated that by 2022, 287850 new cases have been reported representing about 15% of cases and 43,250 death cases representing 7.1% among all death cases **[6]**. Every four minutes, a woman is diagnosed with breast cancer, and every 15 minutes, a woman dies from breast cancer in India **[7]**. One in 28 Indian women is likely to develop breast cancer during her lifetime. It is more (1 in 22) for urban women than the rural group (1 in 60) **[8]**. Based on the clinical features such as Lump of mass present in breast which is hard, Irritation of breast, Hard swelling, Pain, Deeply rooted, Discharge from the nipple with suppuration, Tenderness, Redness, Chest pain and Haemoptysis, Bone pain tenderness **[9]**. Now a days due to Increasing Age, Inherited Genes **(**most well-known gene mutations are BRCA1 and BRCA2.), Radiation Exposure, obesity, Early Menstruation or Late Menopause, Postmenopausal Hormone Therapy, Drinking alcohol, Long Term Use of Oral Contraceptives, Smoking are some of the causes which are known to cause breast cancer **[10]**.

**Risk factors**

**Hormonal Factors**: **[11]**

- **Estrogen Exposure**: Prolonged exposure to estrogen, either due to early menarche, late menopause, or hormone replacement therapy (HRT), increases breast cancer risk. Estrogen stimulates the growth of breast cells, and long-term exposure can lead to mutations in DNA.
- **Pregnancy and Breastfeeding**: Women who have their first child after age 30 or who do not have children at all are at a higher risk. On the other hand, breastfeeding reduces the risk by lowering estrogen levels and facilitating the shedding of breast tissue.

**Genetic Factors**: **[12]**

- **BRCA1 and BRCA2 Mutations**: Women who inherit mutations in the BRCA1 and BRCA2 genes have a significantly higher risk of developing breast cancer. These genes typically help repair damaged DNA, and mutations can lead to uncontrolled cell growth.
- **Family History**: A strong family history of breast cancer can indicate the presence of inherited genetic

**Lifestyle Factors**: **[13]**

- **Diet and Obesity**: High-fat diets and obesity, especially after menopause, increase breast cancer risk by elevating estrogen levels produced by adipose tissue.
- **Alcohol Consumption**: Alcohol raises estrogen levels and can contribute to the development of breast cancer. Even moderate alcohol intake has been linked to an increased risk.
- **Physical Activity**: Lack of physical activity is associated with a higher risk of breast cancer due to its effect on weight gain, hormonal balance, and immune system regulation.

**Proliferative Breast Disease (PBD): [14]**

Proliferative Breast Disease (PBD) increases the risk of breast cancer, with different types carrying varying levels of risk. Usual Ductal Hyperplasia (UDH) raises the risk 1.5 to 2 times due to increased, though normal-looking, cell growth in the breast ducts. Atypical Ductal Hyperplasia (ADH) and Atypical Lobular Hyperplasia (ALH) both elevate the risk s4 to 5 times, as these involve abnormal cell growth that resembles early cancerous changes in the ducts and lobules, respectively. Lobular Carcinoma in Situ (LCIS) presents a 7 to 12 times higher risk since it involves abnormal cells in the lobules that have a strong potential to become invasive cancer. Sclerosing Adenosis and Radial Scars increase the risk by 1.5 to 2 times due to benign tissue overgrowth and structural changes that can indicate a higher likelihood of malignancy.

Regular monitoring is recommended for individuals with these conditions to manage breast cancer risk

**Environmental Factors**: **[15]**

- **Radiation Exposure**: Exposure to radiation, particularly at a young age, can increase the risk of breast cancer by causing DNA mutations in breast cells.
- **Endocrine Disruptors**: Chemicals like bisphenol A (BPA) found in plastics can mimic estrogen and promote the growth of breast tissue, increasing cancer risk.

**Mechanisms of Breast Cancer Development: [16]**

Breast cancer arises from genetic and epigenetic changes that alter cell behavior, allowing for uncontrolled growth and invasion. The following are key mechanisms involved in breast cancer development:

**Hormonal Influence on Cell Proliferation**: Estrogen and progesterone play crucial roles in stimulating breast tissue proliferation. Breast cancers that are estrogen receptor-positive (ER+) depend on estrogen for growth. When estrogen binds to its receptor on breast cells, it activates signaling pathways that promote cell division. Over time, repeated cycles of cell proliferation can result in mutations, leading to cancer.

- **DNA Damage and Repair Deficiency**: Normal cells have mechanisms to repair damaged DNA, such as the BRCA1 and BRCA2 pathways. When these pathways are disrupted (either through inherited mutations or acquired alterations), cells are more likely to accumulate DNA errors. These mutations can lead to the activation of oncogenes (e.g., HER2) or inactivation of tumor suppressor genes (e.g., p53), promoting the development of breast cancer.
- **Chronic Inflammation**: Inflammatory processes can promote cancer development by releasing cytokines and growth factors that stimulate cell proliferation and survival. Chronic inflammation, whether due to obesity, infection, or other factors, is linked to a higher risk of cancer through mechanisms such as oxidative stress, which damages cellular DNA.
- **Angiogenesis and Metastasis**: As a tumor grows, it requires more oxygen and nutrients, leading to the activation of angiogenesis (formation of new blood vessels). Vascular endothelial growth factor (VEGF) is often upregulated in breast cancer cells, allowing them to recruit blood vessels to support tumor growth. This also

facilitates metastasis, the process by which cancer cells spread to distant organs like the lungs, bones, and liver. Breast cancer cells can break through the basement membrane, invade surrounding tissues, and enter the bloodstream or lymphatic system.

- **Epigenetic Modifications**: In addition to genetic mutations, epigenetic changes such as DNA methylation and histone modifications can alter gene expression without changing the DNA sequence itself. For example, hypermethylation of tumor suppressor genes can silence them, contributing to unchecked cellular growth.
- **Immune Evasion**: The immune system plays a key role in identifying and destroying abnormal cells. However, cancer cells can develop mechanisms to evade immune detection, such as downregulating antigen presentation or creating an immunosuppressive microenvironment. Some breast cancers overexpress proteins like PD-L1, which inhibit immune responses and allow tumors to grow unchecked.

**Treatment- [17]**

Depending on the type and stage of cancer, patients are treated with either traditional therapies (such as surgery, chemotherapy, and radiation therapy) or newer forms of treatment (such as immunotherapy, targeted therapy, hormone therapy, gene therapy and photodynamic therapy. Surgery is the process of removing cancer by doing operation and it is generally used only when cancer is localized. Radiation therapy uses high doses of radiation to shrink or kill cancer cells. On the other hand, chemotherapy is an effective and widespread way of cancer treatment in which one or more chemotherapeutic or alkylating agents are used.

**Cisplatin:**

Cisplatin, a key chemotherapy drug, causes DNA damage and triggers apoptosis but faces challenges like severe side effects (nephrotoxicity, ototoxicity) and drug resistance **[18]**. **Resistance** mechanisms include enhanced DNA repair, drug inactivation, altered transport, and apoptosis evasion, limiting its effectiveness in cancer treatment **[19]**.

**Oxidative Stress:** Cancer cells' high metabolism raises ROS levels, activating growth pathways and preventing apoptosis. Cisplatin generates ROS, causing lipid peroxidation and malondialdehyde (MDA) production, which supports cancer cell damage and metastasis **[20]**.

**Calcium Signaling:** Cisplatin induces apoptosis through calcium-dependent pathways, activating caspase-3 and ER

stress marker Grp78/BiP. In MCF-7 cells, $Ca^{2+}$ levels increase dose-dependently, suggesting treatment variability **[21]**.

**Apoptosis Induction:** Cisplatin triggers apoptosis via ROS generation, DNA cross-links, calcium disruption, and ER stress, collectively activating apoptotic pathways **[22]**.

**Gene Expression Modulation:** Cisplatin alters gene expression by forming DNA cross-links, activating damage response pathways, and affecting cell cycle and apoptosis genes. It also induces inflammation and epigenetic changes, influencing long-term gene expression **[23]**.

**Cisplatin causing toxicity-**

Cisplatin, while effective for cancer treatment, can cause significant toxicity in normal cells. Major concerns include nephrotoxicity leading to acute kidney injury, ototoxicity causing hearing loss, and hematologic toxicity resulting in anemia and increased infection risk. It can also induce peripheral neuropathy, gastrointestinal issues like severe nausea, and electrolyte imbalances **[24]**.

**METHODOLOGY:**

*Agada Tantra* is a specialized branch of *Ayurveda* which deals with the management of toxicity with numerous formulations. *Bilwadi gutika* is an herbal preparation explained in *Astanga hrudaya* **[25]**. It is having many chemical constituents which are proven to have anticancer potentials which includes, antioxidant activity, inhibition of cancer cell growth, induction of apoptosis, antitumor activity, cancer cell cytotoxicity, etc. without harming normal cells **[26]**. In this article, a comprehensive pharmacological review is done to understand the anticancer potentials of ingredients of *Bilwadi Gutika.* It is an herbal formulation containing 13 ingredients in equal quantity and Goat`s urine used as *Bhavana dravya* (Liquid media for trituration) **[27]**.

**Ingridents of Bilwadi Gutika:[28]**

**Table 1: Ingridents of Bilwadi Gutika**

| S. No. | Drug | Botanical Name | Part Used |
|---|---|---|---|
| 1 | Bilwa | *Aegle marmelos Corr* | *Moola* (Root) |
| 2 | Surasa | *Ocimum sanctum Linn* | *Pushpam* (Inflorescence) |
| 3 | Karanja | *Pongamia pinnata Merr* | *Phala* (Fruit) |
| 4 | Natam | *Valeriana wallichii DC* | *Moola* (Root) |
| 5 | Surahwam | *Cedrus deodara Roxb* ) | *Kanda sara* (Heartwood) |
| 6 | Haritaki | *Terminalia chebula Retz* | *Phala* (Fruit) |
| 7 | Vibitaki | *Terminalia bellirica Roxb* | *Phala* (Fruit) |
| 8 | Amalaki | *Emblica officinalis Gaertn* | *Phala* (Fruit) |
| 9 | Pippali | *Piper longum Linn* | *Phala* (Fruit) |
| 10 | Maricha | *Piper nigrm Linn* | *Phala* (Fruit) |
| 11 | Shunti | *Zingiber officinale* | *Kanda* (Rhizome) |
| 12 | Haridhra | *Curcuma longa Linn* | *Kanda* (Rhizome) |
| 13 | Daruharidhra | *Berberis aristata* | *Kanda sara* (Heartwood) |
| 14 | Basta mutra | | |

**RESULTS:**

**Probable mode of action of *Bilwadi gutika***

*Bilwadi Gutika* is an *Ayurvedic* formulation traditionally used for various health conditions, including digestive disorders and cancer. Its probable mode of action includes antioxidant activity that helps reduce oxidative stress by combating elevated reactive oxygen species (ROS) levels commonly found in cancer cells. Additionally, the formulation may possess anti-inflammatory effects that inhibit tumor progression and support overall health. Bilwadi Gutika may also enhance immune function, allowing the body to better fight cancer cells and infections. By promoting digestive health, it improves nutrient absorption, indirectly supporting cancer treatment. Some components may trigger apoptotic pathways in cancer cells, leading to programmed cell death, while others may directly inhibit the proliferation of cancer cells or disrupt key signaling pathways involved in cancer progression

The predominant rasas of *Bilwadi Gutika* are *Tikta* (36%), *Katu* (32%) and *Kashaya* (29%), predominant *Gunas* are *Laghu* (44%)*, Ruksha* (26%) and *Teekshna* (11%), predominant *Virya* is *Ushna* (85%) and predominant *Vipaka* is *Katu* (71%). Majority of ingredients (61%) have *Kapha vata* hara properties.

**Probable mode of action of *Aja mutra-***

*Aja Mutra* (goat's urine) in *Bhavana Samskara* helps in improving the bioavailability by increasing the solubility, cellular penetration, and absorption of active phytochemicals. Its alkalinity, detoxifying properties and its ability to enhance membrane permeability and transport processes make it an effective medium for enhancing the potency of *Bilwadi Gutika.* These processes together help ensure that the medicinal compounds are more efficiently absorbed, retained, and utilized by the body for therapeutic benefit.

**Table 2: Drug Properties**

| DRUGS | PROPERTIES |
|---|---|
| ***Bilwa, Surahwa, Karanja, Nata, Haritaki, Maricha, Haridra,Daruharidra*** **[29]** | **vishagna** |
| ***Amalaki, Haritaki*** **and** ***Bilwa*** **[31]** | **immunostimulant** |

- The *Laghu, Ruksha and Teekshna guna* makes the drug potent in action and helps for speedy action of the drug **[30]**.

*Bilwadi Gutika* is having chemical constituents like Tannic acid, Marmelosin, Ascorbic acid, Stearic acid, Linoleic acid, Karanjin, Pongapin, Valtrate, Linarin, Atlantone, Himachalol, Taxifolin, Chebulagic acid, sorbitol, Gallic acid, Ellagic acid, Ethyl gallate, Zingiberene, Gingerol, Piperine, Piperidine, Piperlongumine, Pipernonaline, Curcumin,

Camphene, Berberine, Berbamine, etc. which are proven to have different effect against cancer cells, which includes antioxidant activity, inhibition of cancer cell growth, induction of apoptosis, antitumor activity, cancer cell cytotoxicity, etc. and many were harmless to normal cells **[32]**.

**DISCUSSION:**

All ingredients are proven to have selective cytotoxic activity against cancer cells through various mechanisms like, Cell cycle arrest Targeting Growth Signaling Pathways DNA Synthesis Inhibition Increase in caspase 3 activity Inhibition of Telomerase Activity Modulation of Growth Factors Increase in ROS (reactive oxygen species), Bax - intrinsic pathway Downregulation of Bcl 2, Antioxidant Activity. TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) to induce Apoptosis. So the formulation might have caused cancer cell death by its synergistic action **[33]**.

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