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IN-SILICO AND *EX-VIVO* ANALYSIS OF ANTI-CANCER ACTIVITY OF SOLASODINE AGAINST BREAST CANCER- A REVIEW

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ABSTRACT

Cancer kills almost millions of people per year. Fatal breast cancer can result in death. The early diagnosis of breast cancer and treatment can increase the survival rate. Breast cancer is the second most disease spreading worldwide. The pink ribbon day campaign focuses on creating acknowledgment among people about breast cancer. Chemotherapy can create adverse side effects and selective novel anticarcinogens are required to treat them. Solasodine obtained from medicinal plants helps in curing malignant skin cancer and several types of cancer. It mostly affects women above the age of 40. *Solanum nigrum*, also known as the poisonberry, involves various traditional treatments such as treating ringworm, bacterial infection, cough, and indigestion. Major components are glycoalkaloids, glycoproteins, and polysaccharides. The proliferation activity of the *Solanum nigrum* helps to fight against various tumor cell lines including HepG2, and HT29. MDA-MB-231 is a cell line that can induce cancer in the breast.

Keywords: Solasodine, Anticancer activity, *Solanum nigrum,* breast cancer.

1. INTRODUCTION

Cancer is a complex disease that is characterized by uncontrolled growth and division of abnormal cells These cells can form tumors invade nearby tissues, and can even spread to other parts of the body through the bloodstream or lymphatic system, a process called metastasis. Cancer can affect any part of the body and can occur in any tissue or organ, such as the lungs, breast, colon, or skin. There are many different types of cancer, each with its own set of causes, symptoms, and treatment options [1]. Some common risk factors for developing cancer include age, family history, exposure to certain chemicals or substances, and lifestyle factors such as smoking, poor diet, and lack of physical activity. Some types of cancer can also be caused by infections, such as human papillomavirus (HPV) and hepatitis B and C [6]. Cancer is typically treated with a combination of therapies, such as surgery, radiation, chemotherapy, and immunotherapy. The specific treatment approach depends on the type and stage of cancer, as well as the patient's overall health and preferences. Prevention is an important aspect of cancer management, and it often involves adopting a healthy lifestyle, such as eating a balanced diet, getting regular exercise, avoiding tobacco and excessive alcohol consumption, and getting screened for certain cancers [4]. Early detection and treatment can greatly improve the chances of successful cancer treatment and recovery. Despite advances in cancer treatment, it remains a major public health problem worldwide. Traditional chemotherapeutic agents have many side effects and are often limited by drug resistance [4]. Therefore, there is a need for the development of new and effective anticancer agents. Solasodine is a steroidal alkaloid found in plants of the Solanaceae family, which has been reported to have anticancer activity against various types of cancer cells. This paper will review the anticancer activity of solasodine against MCF-7 cells, a breast cancer cell line, and summarize the underlying mechanisms [18].

2. TYPES OF CANCER

There are many different types of cancer, each with its own unique characteristics, risk factors, and treatment options. Breast cancer is a type of cancer that develops in the breast tissue. It is the most common cancer among women worldwide [1]. Lung cancer occurs when abnormal cells grow out of control in the lungs. It is often associated with smoking, but can also occur in non-smokers. Prostate cancer affects the prostate gland in men. Colorectal cancer affects the colon or rectum and is often preceded by the growth of precancerous polyps in the lining of the colon. Melanoma or skin cancer develops in the cells that produce pigment in the skin. It can be spread to other parts of the body if left untreated. Leukemia or cancer in the blood or bone marrow, and involves the abnormal production of white blood cells [3]. Lymphoma is a cancer of the lymphatic system, which is part of the body's immune system. It can occur in the lymph nodes, spleen, bone marrow, and other organs. Pancreatic cancer affects the pancreas, an organ that produces hormones and enzymes to aid in digestion. Ovarian cancer affects the ovaries, which are part of the female reproductive system. These are just a few examples of the many different types of cancer that can occur. It is important to consult with a healthcare professional for information about a specific type of cancer and its treatment options [2].

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3. BREAST CANCER

Breast cancer is a type of cancer that develops in the breast tissue, most commonly in the ducts or lobules that produce milk. Breast cells are more prevalent in women than in men [1].The cause of breast cancer is not fully understood, but there are several known risk factors, including age, family history, genetic mutations, hormonal factors, and lifestyle factors such as alcohol consumption and lack of physical activity. Some common symptoms of breast cancer include a lump or thickening in the breast or underarm area, changes in breast size or shape, changes in the skin texture or color of the breast, and nipple discharge or inversion [2]. Breast cancer is typically diagnosed through a combination of methods, including mammography, ultrasound, and biopsy. Treatment options may include surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy, depending on the stage and type of cancer. Prevention and early detection are important aspects of breast cancer management. This may include regular breast self-exams, clinical breast exams, and mammography screening for women who are at increased risk. Lifestyle changes such as maintaining a healthy weight, avoiding excessive alcohol consumption, and getting regular physical activity may also reduce the risk of developing breast cancer [5].

4. BREAST CANCER TREATMENT

The treatment of breast cancer depends on various factors, such as the stage of cancer, the size and location of the tumor, the grade of the cancer cells, and the patient's overall health and preferences. The primary treatments for breast cancer include surgery and radiotherapy. The most common surgical option is a lumpectomy or partial mastectomy, which involves removing only the tumor and a small amount of surrounding breast tissue. Mastectomy, which involves removing the entire breast, may be necessary in some cases. Sentinel lymph node biopsy or axillary lymph node dissection may also be performed to assess whether cancer has spread to nearby lymph nodes. In radiation therapy, High-energy radiation is used to destroy cancer cells in the breast tissue after surgery, or in combination with chemotherapy before surgery [5]. Radiation therapy may also be used to relieve symptoms of advanced cancer. In chemotherapy, powerful drugs are used to kill cancer cells throughout the body, often before surgery to shrink the tumor or after surgery to destroy any remaining cancer cells. Chemotherapy may also be used to treat advanced or metastatic breast cancer. Hormone therapy is used for breast cancers that are hormone receptor-positive, which means the cancer cells have receptors for estrogen or progesterone. Hormone therapy may involve medications that block the hormones or medications that reduce the body's production of hormones [4]. Targeted therapy involves targeting the specific proteins or genes that are involved in the growth and spread of cancer cells. Targeted therapy may be used for certain types of breast cancer that overexpress HER2 protein, such as Herceptin. In addition to these primary treatments, there are several other types of therapies that may be used for breast cancer, such as immunotherapy, alternative medicine, or palliative care. The treatment plan for breast cancer should be individualized and discussed with a healthcare provider.

5. TAXONOMY

Solanum nigrum, commonly known as black nightshade, is a plant species in the family Solanaceae. It is a widespread plant that can be found throughout many regions of the world. The taxonomy of *Solanum nigrum* is a subject of ongoing research, as there are many different varieties and subspecies of the plant. The scientific classification of *Solanum nigrum* is as follows:

Kingdom: Plantae
Clade: Tracheophytes
Clade: Angiosperms
Clade: Eudicots
Clade: Asterids
Order: Solanales
Family: Solanaceae
Genus: Solanum
Species: *Solanum nigrum*

Within the species *Solanum nigrum*, there are several different varieties and subspecies that have been identified. *Solanum nigrum var. nigrum* is the most common variety of Solanum nigrum and is found throughout much of the

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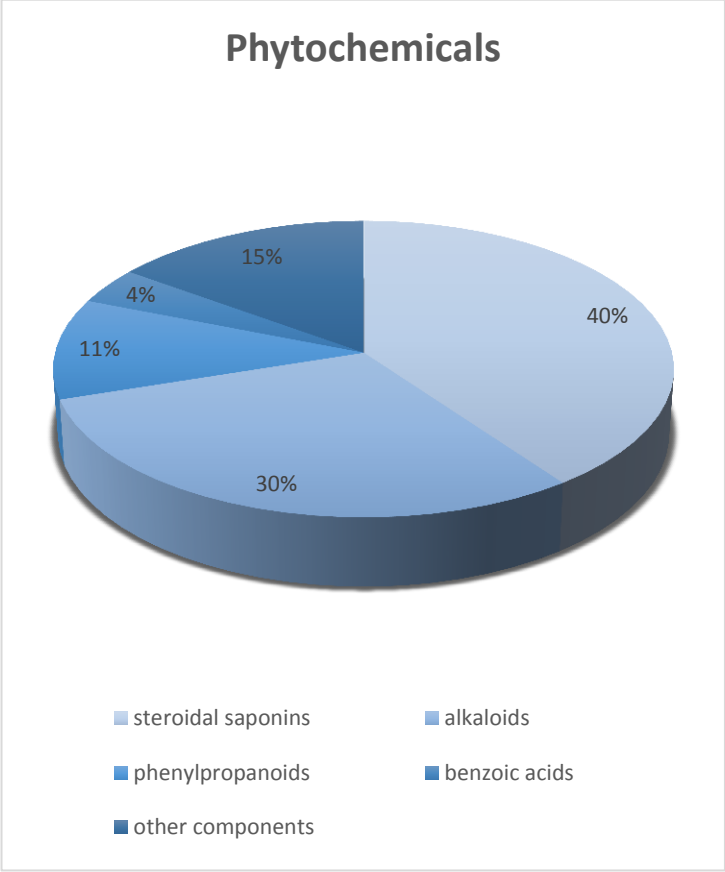
world.[25] It is an annual plant that can grow up to 1 meter in height and produces small black berries that are edible when ripe. *Solanum nigrum var. Americanum* is found primarily in North and South America.[25] It is a perennial plant that can grow up to 2 meters in height and produces larger berries than the nigrum variety.[22] *Solanum nigrum subsp. Schultesi*i is found in Central and South America. It is a shrub that can grow up to 4 meters in height and produces large, fleshy berries that are used in traditional medicine. The taxonomy of *Solanum nigrum* is complicated by the fact that there are many different varieties and subspecies, as well as the fact that the plant can hybridize with other members of the Solanum genus. As a result, there is ongoing research into the classification of the plant and its relationships with other members of the Solanaceae family [26].

5.1. MORPHOLOGY

The morphology of *Solanum nigrum* is variable, with characteristics that can vary depending on the environmental conditions, cultivar, and age of the plant. The root system of *Solanum nigrum* is fibrous, with numerous fine roots that grow close to the soil surface [20]. The stem is herbaceous, with a cylindrical or angular shape, and can grow up to 1-2 meters in height. The stem and branches are often green, sometimes purplish, with a fine layer of pubescence. The leaves are alternate, simple, and ovate to elliptic in shape, with a length of up to 10 cm. The leaves are green on the upper surface and slightly paler on the lower surface, with a distinct petiole. The inflorescence of *Solanum nigrum* is a cyme or a raceme, with several flowers that are pedicellate and often nodding. The flowers are small, with a diameter of about 5 mm, and are usually white or pale blue in color, with a yellow center [21]. The calyx is five-lobed, and the corolla is five-lobed and rotates, with the lobes often reflexed. The stamens are five in number, with the anthers arranged in a cone-shaped structure around the style. The ovary is superior, with two chambers, and the stigma is capitate. The fruit of *Solanum nigrum* is a shiny, black, or dark purple berry, about 1 cm in diameter, which is toxic when unripe. The fruit contains many small, flattened seeds that are yellowish-brown in color, and the fruit remains on the plant after maturing [22]. The entire plant is known to be poisonous, with the highest concentration of the toxin in the unripe berries and leaves.

5.2. PHYTOCHEMICAL

Solanum nigrum has been used for various medicinal purposes due to its numerous bioactive compounds [20]. The phytochemical analysis of *Solanum nigrum* has identified a wide range of chemical constituents, including alkaloids, flavonoids, saponins, phenolic acids, and steroids. Alkaloids are among the most studied and abundant classes of compounds *in Solanum nigrum*. Various types of alkaloids have been identified in the plant, including solasodine, solanine, solasonine, and solamargine [29]. These alkaloids have been reported to have a range of pharmacological activities, including anti-cancer, anti-inflammatory, and anti-microbial properties. Flavonoids, which are known for their antioxidant properties, have also been identified in *Solanum nigrum*. These include quercetin, rutin, kaempferol, and luteolin. Flavonoids have been shown to have a range of beneficial effects, including anti-inflammatory and anti-cancer activities. Saponins, another class of compounds found in *Solanum nigrum,* have been shown to have a range of pharmacological properties, including anti-inflammatory, anti-tumor, and immunomodulatory effects. The main saponins identified in the plant are solanomargin and solasonine. Phenolic acids, including gallic acid, protocatechuic acid, and caffeic acid, have also been identified in Solanum *nigrum*. These compounds have been reported to have anti-inflammatory and anti-cancer activities, as well as antioxidant properties. Steroids, such as β-



sitosterol and stigmasterol, have also been identified in *Solanum nigrum* [50]. These compounds have been shown to have a range of beneficial effects, including anti-inflammatory, anti-cancer, and anti-diabetic activities. Overall, *Solanum nigrum* is a rich source of bioactive compounds that have various pharmacological properties. The plant has been used for centuries in traditional medicine to treat various ailments, and its bioactive compounds have been the subject of numerous studies. However, more research is needed to fully understand the mechanisms of action and potential therapeutic applications of these compounds [14].

6. SOLASODINE

The chemical structure of solasodine is characterized by a steroidal nucleus, which consists of four fused rings (three six-membered and one five-membered ring), and a nitrogen-containing pyrrolidine ring that is attached to the C-3 position of the steroid nucleus [30]. The pyrrolidine ring contains a primary amino group, which is responsible for the basic nature of solasodine. The basic structure of solasodine is similar to that of other steroid alkaloids, such as solanine and solasonine, which are also found in plants of the Solanaceae family. However, solasodine differs from these compounds in the substitution patterns on the steroid nucleus. Specifically, solasodine has a double bond between the C-22 and C-23 positions, as well as a hydroxyl group at the C-22 position[31]. The chemical formula for solasodine is C27H43NO, and its molecular weight is 413.64 g/mol. The compound is soluble in ethanol, methanol, and chloroform, but is insoluble in water. Solasodine has been the subject of numerous studies due to its potential medicinal properties, particularly its anti-cancer activity [32]. It has been shown to inhibit the growth and proliferation of various cancer cell lines, including MCF-7 breast cancer cells, through a variety of mechanisms, such as inducing apoptosis and cell cycle arrest. In addition to its anti-cancer properties, solasodine has also been reported to have anti-inflammatory, anti-microbial, and anti-fungal activities [10].

6.1. APPLICATION

Solasodine, a naturally occurring steroid alkaloid, has been used for medicinal purposes in traditional medicine systems for centuries. It is found in various plant species, including *Solanum nigrum*, Solanum dulcamara, and Solanum lycopersicum [27]. Here are some of the traditional applications of solasodine:

- Anti-cancer: In traditional medicine, solasodine has been used as an anti-cancer agent. The steroidal alkaloid has been shown to exhibit anti-cancer activity by inducing apoptosis and cell cycle arrest in various cancer cell lines, including MCF-7 breast cancer cells, HepG2 liver cancer cells, and A549 lung cancer cells.
- Anti-inflammatory: Solasodine has been used traditionally to treat inflammation-related disorders such as arthritis and gout. It is believed to exert its anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and enzymes, such as interleukin-1β and cyclooxygenase-2 (COX-2).
- Anti-microbial: Solasodine has been traditionally used for the treatment of various infectious diseases caused by bacteria, viruses, and fungi. It has been reported to exhibit broad-spectrum antimicrobial activity against various pathogenic microorganisms, including Staphylococcus aureus, Escherichia coli, Candida albicans, and Aspergillus niger.[24]
- Skin diseases: Solasodine has been traditionally used for the treatment of various skin diseases, such as psoriasis, eczema, and dermatitis. It is believed to exert its therapeutic effects by inhibiting the growth and proliferation of skin cells and reducing inflammation.
- Wound healing: Solasodine has been used in traditional medicine for the treatment of wounds and burns. It is believed to promote wound healing by stimulating the growth of new tissue and enhancing the activity of enzymes involved in tissue repair.

Solasodine has been used for centuries in traditional medicine for its various therapeutic properties, including anti-cancer, anti-inflammatory, anti-microbial, and wound healing properties. While some of these traditional uses have been scientifically validated, further research is needed to fully understand the mechanisms of action and potential therapeutic applications of solasodine.[26]

7. COMPUTER-AIDED DRUG DESIGN

Computer-aided drug design (CADD) is a technique that uses computational methods to discover, design, and optimize small molecules that can interact with biological targets such as proteins or nucleic acids. The goal of CADD is to expedite the process of drug discovery and development by providing a more cost-effective and efficient approach [17].

The process of CADD involves several steps, including:

- Target identification: Identifying a specific biological target that is involved in a disease or disorder.
- Target validation: Confirm that the selected target is indeed responsible for the disease or disorder and that it is a suitable target for drug development.

- Virtual screening: Using computational methods to screen a large number of small molecules to identify those that have the potential to bind to the target.
- Molecular modeling: Using computational techniques to simulate the interactions between the small molecule and the target in order to optimize the design of the small molecule.
- Lead optimization: Refining the structure of the small molecule to improve its efficacy, safety, and pharmacokinetic properties.
- Experimental validation: Testing the selected small molecules in vitro and in vivo to confirm their activity and safety.[30]

CADD can be used in a variety of applications, such as discovering new drugs, optimizing existing drugs, and identifying new targets for drug development [19]. It has become an essential tool in modern drug discovery and development, allowing researchers to more efficiently explore the vast chemical space of potential drug molecules and accelerate the process of drug discovery.

7.1 MOLECULAR DOCKING

Molecular docking can be used to predict the binding of ligands, such as solasodine, to a target protein of interest. In order to perform molecular docking against solasodine, the 3D structure of solasodine should first be obtained or generated using a computational method. Once the 3D structure of solasodine is available, it can be docked against the target protein using a molecular docking software tool [19]. The target protein can be selected based on its relevance to the biological activity of solasodine, such as an enzyme or receptor that solasodine is known to interact with. During the docking process, the software tool will generate a set of possible binding conformations for solasodine within the binding site of the target protein [17]. These confirmations will be scored based on a scoring function that estimates the binding affinity of the solasodine-protein complex. The best binding pose(s) will be selected based on the highest-scoring conformations. It is important to note that molecular docking is a computational method, and the predicted binding affinity and mode of interaction between solasodine and the target protein should be validated experimentally. This can be done through techniques such as biochemical assays, X-ray crystallography, or NMR spectroscopy [18].

7.2. CELL LINE

Cancer cell lines are cells that have been derived from cancerous tissues and are grown in vitro (in a laboratory setting) for research purposes. These cells are often used to study the biology of cancer, as well as to develop and test new anti-cancer drugs [16]. There are many different cancer cell lines available, each of which has its own unique characteristics and can be used to study different aspects of cancer. For example, some cancer cell lines are known to be particularly aggressive, while others are more sensitive to certain types of chemotherapy drugs. Some commonly used cancer cell lines include HeLa, MCF-7, A549, PC-3, and SK-MEL-28 [17]. MCF-7 is a breast cancer cell line that was first established in 1970 from the breast tissue of a 69-year-old woman with infiltrating ductal carcinoma. MCF-7 is widely used as a model for studying breast cancer biology and developing new breast cancer therapies [18].

MCF-7 cells are estrogen receptor (ER) positive, which means they express the ER protein and are responsive to estrogen. They are also progesterone receptor (PR) positive and HER2/neu negative. MCF-7 cells are sensitive to anti-estrogen drugs such as tamoxifen and fulvestrant, which are commonly used in the treatment of ER-positive breast cancer. Researchers use the MCF-7 cell line to study various aspects of breast cancer biology, including the mechanisms of estrogen signaling, the role of various oncogenes and tumor suppressor genes in breast cancer, and the development of resistance to anti-cancer drugs [6]. MCF-7 cells are also commonly used to screen and develop new anti-cancer drugs for the treatment of breast cancer. It's important to note that while cancer cell lines such as MCF-7 are useful for studying cancer biology and testing new therapies, they may not fully represent the complexity of cancer as it occurs in the human body. Therefore, the findings obtained from research with cancer cell lines must be validated through further testing in animal models and human clinical trials.

7.3 ANTI-CANCER ACTIVITY ASSAY

To evaluate the potential anti-cancer activity of solasodine against MCF-7 breast cancer cells, a variety of assays can be used. MTT assay measures the ability of cells to survive and proliferate in the presence of a compound [37]. In the MTT assay, cells are treated with solasodine at different concentrations and the viability of the cells is measured by the ability of the cells to convert a yellow MTT dye to a blue formazan product. The amount of formazan produced is directly proportional to the number of viable cells. Cell cycle assay is used to measure the effect of solasodine on the cell cycle progression of MCF-7 cells [45]. The cells are treated with solasodine and then analyzed by flow cytometry to determine the percentage of cells in each phase of the cell cycle. Apoptosis assay measures the ability of solasodine to induce apoptosis, or programmed cell death, in MCF-7 cells. The cells are treated with solasodine and then stained

with Annexin V and propidium iodide to identify apoptotic cells by flow cytometry [45]. Caspase activity assay measures the activity of caspases, which are enzymes involved in the process of apoptosis. The cells are treated with solasodine and then the activity of caspases is measured using a fluorescent substrate. Wound healing assay is an assay that measures the ability of solasodine to inhibit the migration of MCF-7 cells. The cells are allowed to grow to confluence and then a scratch is made in the cell layer. The cells are then treated with solasodine and the closure of the scratch is monitored over time[50]. These assays can provide valuable information about the potential anti-cancer activity of solasodine against MCF-7 breast cancer cells. However, it's important to note that the results obtained from in vitro assays must be confirmed in animal models and human clinical trials before the efficacy and safety of solasodine as an anti-cancer agent can be established [37].

7.4 ANTI-CANCER ACTIVITY OF SOLASODINE AGAINST MCF-7 CELLS

Solasodine has been reported to exhibit anti-cancer activity against MCF-7 cells through various mechanisms. One of the main mechanisms by which solasodine exerts its anti-cancer effects is by inducing apoptosis, a programmed cell death that is essential for maintaining tissue homeostasis. Solasodine has been shown to induce apoptosis in MCF-7 cells by activating the intrinsic apoptotic pathway, which is mediated by the release of cytochrome c from the mitochondria [46]. In addition to inducing apoptosis, solasodine has also been reported to inhibit cell proliferation and induce cell cycle arrest in MCF-7 cells. Cell cycle arrest is a mechanism by which cells stop dividing and is essential for preventing the proliferation of cancer cells [33]. Solasodine has been shown to induce cell cycle arrest in MCF-7 cells at the G2/M phase, which is associated with the inhibition of cyclin-dependent kinases (CDKs) and the upregulation of CDK inhibitors. Solasodine has also been reported to modulate various signaling pathways involved in cancer development and progression. For example, solasodine has been shown to inhibit the PI3K/Akt/mTOR signaling pathway, which is involved in cell growth and survival and is frequently dysregulated in breast cancer. In addition, solasodine has been shown to downregulate the expression of matrix metalloproteinases (MMPs), which play a critical role in cancer invasion and metastasis. Moreover, solasodine has been reported to sensitize MCF-7 cells to chemotherapy and radiotherapy [34]. It has been shown to enhance the cytotoxic effects of chemotherapeutic drugs, such as doxorubicin and paclitaxel, in MCF-7 cells, and to sensitize MCF-7 cells to ionizing radiation [45].

8. CONCLUSION

In conclusion, solasodine has been shown to have anticancer activity against MCF-7 cells, a breast cancer cell line. Solasodine inhibits cell proliferation, induces apoptosis, and causes cell cycle arrest in MCF-7 cells. The underlying mechanisms include the downregulation of anti-apoptotic proteins, upregulation of pro-apoptotic proteins, and inhibition of the PI3K/Akt/mTOR signaling pathway. Solasodine also has synergistic anticancer activity when combined with other agents. These findings suggest that solasodine has the potential as a novel anticancer agent for the treatment of breast cancer.

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