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A meta-perspective on the application of *Withania somnifera* in breast cancer: Unveiling its role as a complementary therapeutic agent

Prabha Chauhan[1], Surbhi Srivastava[2], Akanksha[3], Vikas[4] and Vinod Kumar Gupta[5]

Rapture Biotech International Pvt. Ltd., Noida, Uttar Pradesh-201301

*Corresponding author's E-mail: prabhac589@gmail.com

ABSTRACT

Since the days of Ayurveda, the plant *Withania somnifera* (WS), commonly referred to as Ashwagandha, has been used in traditional Indian medicine. Studies on WS and their chemical constituents, such as withaferin A and withanolide D, have shown promise in the prevention and treatment of a number of cancer cells, including those of the colon, blood, lung, skin, breast, kidney, prostate, fibrosarcoma, pancreatic, and other types. Breast cancer is the second leading cause of cancer deaths among women. The development of breast cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. Approximately 6%-10% of patients have metastatic disease at the time of diagnosis and Among other things, by stopping the growth and spread of cancer cells, changing conditions related to kidneys, malignant melanoma, hematological disorders, and osteosarcoma, as well as by modifying biochemical and cell cycle markers are some of the efforts. Since radiation and chemotherapy kill the body's natural cells and weaken immunity, patients can utilize this medicinal plant WS as an alternative cancer treatment. *Withania somnifera* helps patients heal more quickly and have better lives by preventing these harmful effects. To substantiate our assertions, multicentric long-term clinical investigations by oncologists on WS are necessary.

Keywords: *Withania somnifera,* Breast Cancer, Ayurveda, Phytochemistry.

1. INTRODUCTION

Ayurveda is an age-old medicinal practice that uses natural medicines to treat a variety of illnesses [1]. In addition to treating physical ailments, Ayurveda also treats mental and spiritual issues. Ayurveda holds that imbalances in the three doshas—pitta, kapha, and vata—cause the majority of disorders related to pathologic and psychophysiologic alterations in the body [2]. According to Ayurvedic literature, the body is controlled by three systems: the venous system (Pitta, or fire), the artery system (Kapha, or water), and the nerve system (Vata, or air). Together, these systems allow the body to operate normally. Any disturbance of these body-control systems could result in a disease condition. Restoring balance to these three is the main objective of Ayurvedic medicine. natural basic body systems [3]. Malignant tumors are extremely dangerous because they cause the three main body systems to lose their ability to coordinate with one another, which makes it impossible to stop tissue destruction and can lead to a fatal morbid condition. Plants have an edge over synthetic pharmaceuticals because of their higher molecular variety. This is crucial because new drugs must be brought to market, and the resulting changes in cellular function are more intricate. The development of synthetic drugs with a range of traits, chemical structures, and qualities of unknown physicochemical processes is often based on

biodiversity and plant resources [4]. Although science has made great strides in understanding the genetic causes of cancer, we still don't fully understand how to prevent and treat it [1].
WS, A member of the Solanaceae family is a green shrub that grows throughout the drier parts of India, Balochistan, Pakistan, Afghanistan, Sri Lanka, the Congo, South Africa, Egypt, Morocco, and Jordan. According to [5]. It is widely grown in the Indian provinces of Madhya Pradesh, Uttar Pradesh, Punjab plains, and the northwest, which includes Gujarat and Rajasthan [6]. Reaching a height of 30 to 150 cm, it is a woody pubescent shrub with upright branches. Ovoid leaves have complete margins, alternate in arrangement, and are 2.5–5 cm long and up to 10 cm wide. The red globose fruits that develop from the green or yellow blossoms are born in axillary fascicles. The roots are 6–12 mm in diameter and 20–30 cm long. They have two to three slightly smaller, straight, unbranched lateral roots. The outer surface is buff to greyish-yellow with longitudinal wrinkles, and the center is a soft, solid mass with sporadic pores. It is caustic, tastes unpleasant, and has a unique scent. Although the entire plant—leaves, roots, stem, green berries, fruits, seeds, and bark—is used medicinally, the most commonly used part is the roots [7]. Numerous pharmacological studies have been carried out to outline the different biological characteristics of *Withania somnifera*, and the findings of these studies indicate that it may be useful in the treatment of senile dementia, cancer, bronchitis, asthma, ulcers, and emaciation [8]. Because of its chemopreventive qualities, Ashwagandha may be a helpful addition to cancer patients receiving chemotherapy and radiation therapy [9]. Picture of the plant can be seen in fig. 1

Fig. 1. Picture of *Withania somnifera* plant.

Numerous preclinical and clinical trials have demonstrated the additional multipurpose medicinal uses of *Withania somnifer*a, which include antidiabetic, immunomodulatory, hemopoietic, neurological inflammatory disorders, Parkinson's disease, and as an antioxidant, abortifacient, antibiotic, aphrodisiac, DE obstruent, diuretic, and sedative [10].

2. Chemical composition of *Withania somnifera*

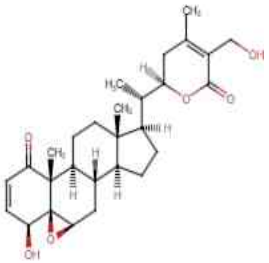
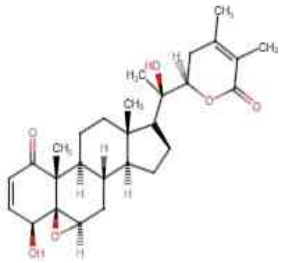
Phytochemicals are the non-nutritive compounds that are present in plants and give them their medicinal properties. Extensive phytochemical research resulted in the isolation and identification of about 35 chemical components from WS. Ashwagandha's primary components are steroidal lactones and alkaloids. In addition to withanine, alkaloids also include the following substituents: 3-a-gloyloxytropane, choline, cuscohygrine, isopelletierine, anaferine, somniferine, somniferinine, withananine, pseudo-withanine, tropine, and pseudo-tropine. Ergostane type steroidal lactones,

withaferin A, withanolides A-Y, withasomniferin-A, withasomidienone, withasomniferols A-C, withanone, and others are examples of steroidal lactones [11]. Triterpenoids, commonly referred to as withanoids, and C-28 steroidal lactones are the most well-known of these substances. Withanoid A and Withanoid D are the most prevalent. The ergostane backbone that makes up withanoids' structure is distinguished by the lactone ring's C-8 or C-9 side chain. Various plant components also include other bioactive substances, including alkaloids, flavonoids, steroids, withanamides, withanosides, withanolide, glycosides, and steroids. The phytoconstituents of W. somnifera are primarily composed of withanolides and alkaloids [12]. Plants are also a major source of iron, withaniol, acylsteryl glucosides, starch, reducing sugar, hantreacotane, and ducitol in addition to these chemical components. Numerous amino acids, including aspartic acid, proline, tyrosine, alanine, glycine, glutamic acid, and tryptophan, are also present in them [6]. The two main withanolides that account for a significant amount of W. somnifera's pharmacological activity are withaferin A and withanolide D [13]. Fourth, 27-dihydroxy-5b-6b-epoxy-1-oxowitha-2, 24-dienolide is the chemical definition of withaferin-A. and a potent inhibitor of angiogenesis that has also been shown to induce apoptosis [14]. The plant's phytochemical composition changes as it spreads geographically. Withanine is the main component among the several alkaloids. The Indian variety has been found to have thirteen distinct positive alkaloids. WS showed chemo genetic variety, and three chemotypes—I, II, and III—have been identified thus far. Withaferin A is one of the main withanolidal active compounds found in the plant. Despite having similar chemical characteristics, they vary, especially in the quantity of withanolide [6]. Important Active ingredients, their molecular formulae and location in plants are shown in table 1.

3. BREAST CANCER

Globally, cancer causes a great deal of pain and financial loss. The incidence and mortality rates for the majority of cancer types remain high despite notable improvements in cancer treatment [16]. Numerous alterations brought on by a direct interaction between dangerous chemicals and DNA and chromosomal mutations result in cancer. The expression of tumor suppressor and oncogene genes varies throughout cancer types. Consequently, growth signals are released by the tumor cells themselves, leading to uncontrolled growth, resistance to antigrowth signals, and inhibition of apoptosis [17]. Among the potential treatment options for cancer include surgery, radiation, chemotherapy, and targeted therapy. The quality of life of the patient is impacted by the adverse effects of chemotherapy and radiation on neighboring healthy cells [18]. Usually, cancer is named after the body part in which it originated; thus, breast cancer refers to the erratic growth and proliferation of cells that originate in the breast tissue [19]. The development of breast cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. Early diagnosis of breast cancer is one of the best approaches to prevent this disease [20]. Approximately 6%-10% of patients have metastatic disease at the time of diagnosis and approximately 30% of patients initially diagnosed with earlier-stage breast cancer will eventually develop recurrent advanced or metastatic disease [21]. Women are most commonly diagnosed with breast cancer around menopause. It is notably less common in women under the age of 45 [22]. Additional risk factors for breast cancer in both sexes include elevated estrogen levels brought on by obesity and hormone function in the testicles such as the Klinefelter syndrome or impairment [23]. In recent decades, much research has been carried out, resulting in the discovery of genes whose dysfunction is linked to an elevated possibility of developing ovarian or breast cancer. The two most crucial genes are BRCA1 and BRCA2, which stand for breast cancer susceptibility 1 and 2, and they serve as tumor suppressor genes in cells [24]. Mammography is a commonly used screening method for breast cancer detection that has been shown to significantly lower mortality.Other screening techniques, like the more sensitive magnetic resonance imaging (MRI) than mammography, have also been carried out and researched throughout the past ten years [25]. The pathogenesis and tumor drug-resistant mechanisms are revealed by discovering breast cancer stem cells, and many genes are found related to breast cancer. Currently, people have more drug options for the chemoprevention of breast cancer, while biological prevention has been recently developed to improve patients' quality of life [20].

Table 1. important Active ingredient, their molecular formulae and location in plant.

Active Ingredient	Molecular formulae	Structure	Location	Reference
Withaferin A	**C28H4OO6**		**Roots**	**[15]**
Withanolide A	**C28H38O6**		**Roots**	**[16]**
Withanolide D	**C28H38O6**		**Roots and leaves**	**[7]**

Most breast cancers begin in the cells that line the ducts (ductal cancers). Some begin in the cells that line the lobules (lobular cancers), while a small number start in the other tissues There are various risk factors for Breast Cancer, a woman who has had breast cancer has an increased risk of getting breast cancer in the other breast [26]. Breast cancer in a male increases the risk for all his close female relatives. BRCA1 and BRCA2 are abnormal genes that, when inherited, markedly increase the risk of breast cancer to a lifetime risk estimated between 40 and 85%. Women who have the BRCA1 gene tend to develop breast cancer at an early age Breast cancer may develop more quickly if the hormonal level changes. One way to attend to it would be to begin and stop the menstrual cycle, early pregnancy, hormone replacement treatment, using oral medications, etc. [27]. Five to ten percent of instances of breast cancer may be heritable, with BRCA1/2 mutations accounting for up to thirty percent of these cases. New genes have been identified as risk factors for breast cancer, including uncommon germline mutations in high penetrant genes like TP53 and PTEN and more common mutations in moderate genetic penetrant genes like PALB2, ATM, and CHEK2. Current information on novel discoveries in breast cancer susceptibility genes will be compiled in this review [28]. Based on the presence or absence of molecular markers for the estrogen, progesterone, and human epidermal growth factor 2 receptors, breast cancer is divided into three major subtypes: triple-negative (15%), hormone receptor positive/ERBB2 negative (70% of patients), and ERBB2 positive (15%–20%) [29].

Different signs of Breast Cancer include lump in the breast or underarm. Breast self-examination on a monthly basis is an excellent approach to become acquainted with the texture, size, cyclical changes,

and skin condition of your breasts. Breast cancer is generally indicated by symptoms like breast swelling, nipple soreness, inverted (retracted) nipple, lymph node Swelling in the armpit, clear or red discharge or skin on the nipple that is pitted or scaly, ongoing breast tenderness, and uncommon breast pain or discomfort. Underarm lymph nodes are found in the advanced stage (metastatic) of the disease along with additional symptoms like headaches, weakness or neurological pain,[30]. Effect of *Withania somnifera* on Breast Cancer cell lines are shown in fig. 2.

4. MODE OF ACTION

Purified from the plant *Withania somnifera*, withaferin A (WA) inhibits the vimentin cytoskeleton. The findings demonstrated that WA maintained strong anti-invasive effect at low concentrations while exhibiting mild cytotoxic and apoptotic activity at concentrations less than or equivalent to 500 nm. Vimentin depolymerization occurs quickly after perinuclear vimentin buildup. Parallel to vimentin breakdown, there was an observed rise of vimentin ser56 phosphorylation. These relationships demonstrated that the anticipated vimentin-binding region of WA is required for both the anti-invasive effect of the compound and to cause vimentin ser56 phosphorylation. With no harm to lung tissue, WA demonstrated dose-dependent suppression of metastatic lung nodules and increased vimentin ser56 phosphorylation It infers that WFA is a strong anti-metastatic drug for breast cancer and that its effects on vimentin and vimentin ser56 phosphorylation, at least in part, mediate its anti-metastatic activity [31]. In a concentration-dependent way, the WA treatment reduced the viability of human breast cancer cells MCF-7, which is estrogen-responsive, and MDA-MB-231, which is estrogen-independent. There was a correlation between the induction of apoptosis, which is characterized by DNA condensation and cytoplasmic fragmentation of histone-associated DNA and poly-(ADP-ribose)-polymerase cleavage. The production of Bim-s and Bim-L isoforms in MCF-7 cells and the induction of Bim-s and Bim-EL isoforms in MDA-MB-231 cells occurred concurrently with the WA-mediated apoptosis. A significant defence against WA-mediated increase of Bim expression was provided by FOXO3a knockdown. When compared to the tumors from control mice, the tumors from WA-treated mice showed higher apoptosis and decreased cell proliferation [32]. The anti-breast cancer cytotoxic evaluation with the help of WS extract was carried out using the MCF-7 cell line, and the results showed significant cytotoxic effects in a dose-dependent manner [33].

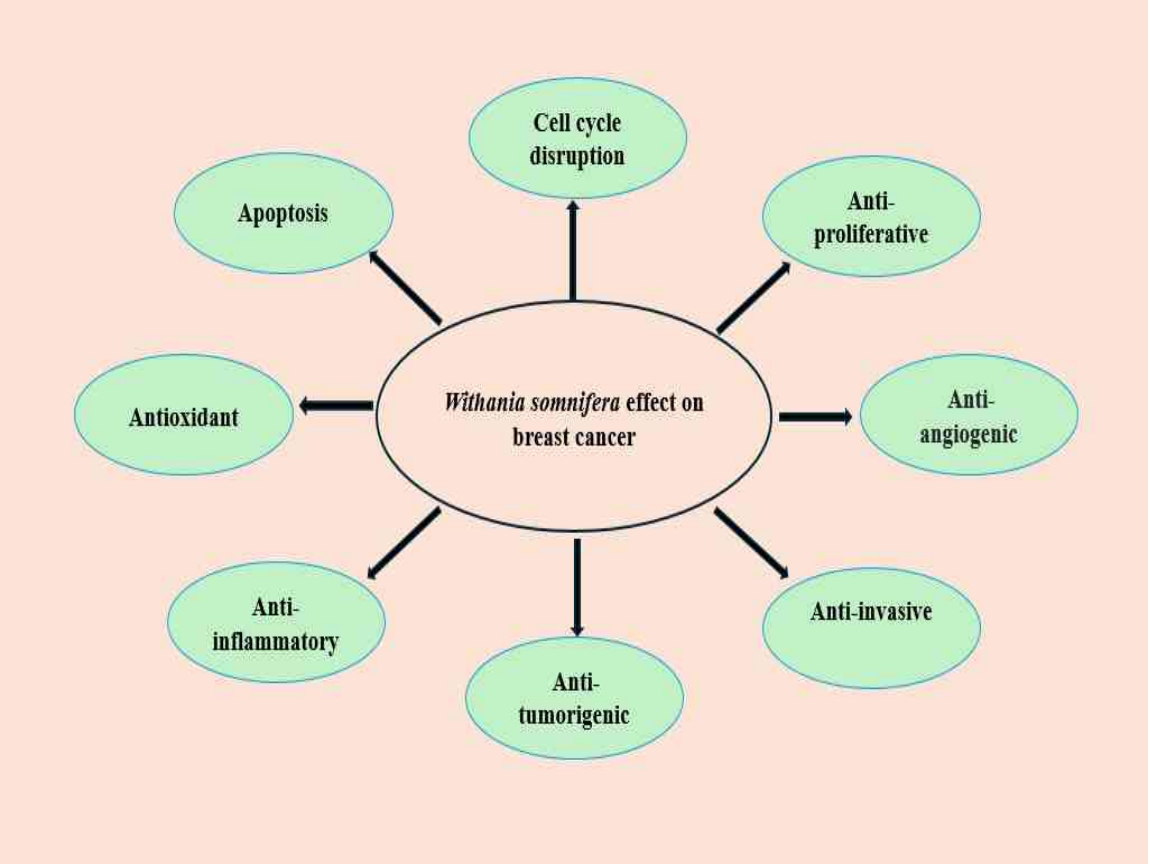


Fig .2. *Withania somnifera* effect on breast cancer cell line.

Three fractions A4, A5, and A6 and two extracts (WS and WS-chloroform) adversely impacted Hep2 and these were further studied pharmacologically. Cell cycle disruption and a build-up of hypoploid (sub G1) cells were identified A chickchorio-allantoic membrane (CAM) was used to examine their anti-angiogenic capability. The results showed a significant decrease of vascular endothelial growth factor (VEGF) These results imply that *Withania somnifera's* roots have anti-angiogenic and cell cycle disruption properties, which may be a key mechanism behind their anti-cancer properties [34]. Desoxywithaferin A (Twelve withanolides, including withaferin A (1), sitoindoside IX (2), 4-(1-hydroxy-2, 2-dimethylcyclpropanone)-2, 3-dihydrowithaferin A (3), 2, 3, and 4, have been identified. Physagulin D (1!6), 24, 25-dihydro-27-), and dihydrowithaferin A (5)-h-D-glucopyranosyl- (1!4)From the leaves of this plant, researchers have isolated 27-O-h-D-glucopyranosylphysagulin D (7), physagulin D (8), withanoside IV (9), 27-O-h-D-glucopyranosylviscosalactone B (10), 4, 16-dihydroxy-5h, 6h-epoxyphysagulin D (11) and viscosalactone B (12). The antiproliferative effects of compounds 1 through 12 and diacetyl withaferin A (13), on the human tumour cell lines MCF-7 (Breast) were seen [16].

WS root extract concentrations prevent cancer spread by inhibiting EMT. Additionally, dosages of WS root extract exhibit little toxicity in typical mouse organs, indicating the possibility of therapeutic application for orally taken *Withania somnifera* root extract (WRE) capsules [35]. When the effects of a methanolic extract of WS leaves were studied against MCF-7, HCT116, and HepH2 cell lines, all cell lines were sensitive to the extract's potent antiproliferative effects Results from flow cytometry revealed that the extract stopped the cell cycle at the S phase and increased the caspase The extract may be able to cause cell death through a caspase-mediated route [36]. WS has been found to inhibit constitutive as well as interleukin-6 (IL-6)-inducible activation of signal transducer and activator of transcription 3 (STAT3), which is an oncogenic transcription factor activated in many human malignancies including breast cancer. The IL-6-stimulated activation of STAT3 conferred a modest protection against WA-mediated suppression of MDA-MB-231 cell invasion. The results of the study indicate that WA can

trigger apoptosis and largely inhibit cell migration/invasion of breast cancer cells even after IL-6-induced activation of STAT3, which should be viewed as a therapeutic advantage for this agent [37]. Mode of action of *Withania somnifera* on Breast Cancer cell line are shown in fig 3.

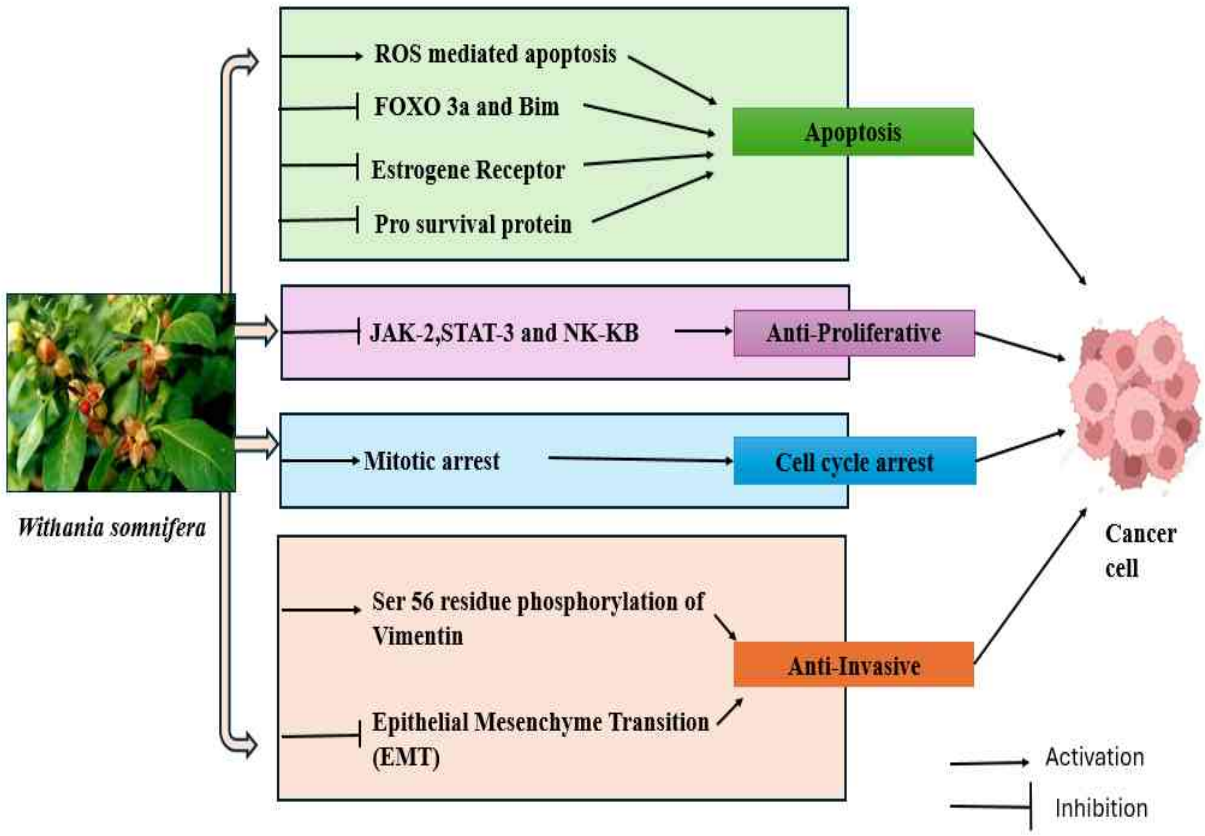


Fig. 3. *Withania somnifera*'s mode of action on cancer cells.

5. CONCLUSION

Breast cancer is among the most prevalent and life-altering forms of cancer globally, contributing to immense physical, emotional, and financial burdens. Despite progress in therapeutic approaches, including surgery, radiation, chemotherapy, and targeted treatments, the incidence and mortality rates for many cancers, including breast cancer, remain high. Moreover, these conventional therapies often lead to adverse side effects, significantly affecting patients' quality of life. Cytotoxic chemotherapy, though widely used, faces challenges such as toxicity and the emergence of drug resistance in cancer cells. Ayurveda, a traditional system of medicine, takes a holistic view of health—addressing the mind, body, and spirit—and relies on natural remedies to treat various ailments. *Withania somnifera* (commonly known as Ashwagandha), a cornerstone of Ayurvedic medicine, has been employed for centuries and has shown promising therapeutic effects in both clinical and preclinical studies. Its benefits span conditions such as anxiety, neurological and cognitive disorders, and inflammation. Notably, it has also demonstrated potential as a supportive agent for patients undergoing chemotherapy and radiation therapy. One of its key bioactive compounds, Withaferin A, has shown significant anti-tumorigenic action against Breast cancer cells, such as Par-4-dependent apoptosis, cell cycle arrest, cytotoxicity, ROS production, anti-proliferative qualities, etc. against breast cancer cells. The integration of traditional medicinal knowledge with modern oncology, particularly through the use of plant-derived compounds like *Withania somnifera*, offers a promising path forward in enhancing cancer treatment and overcoming some of its most pressing challenges.

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EXPLORING THE HEALING SYNERGY OF NATURE AND SCIENCE IN BREAST CANCER CARE

Plot no 977, GMS Road, near Balliwala Flyover, opposite Cubic Plaza,
Dehradun, Uttarakhand 248001

admin@reboin.com

www.rebioin.com