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REVIEW ON ANGIOTENSIN RECEPTOR BLOCKERS IN BREAST CANCER

Mrs. Rupitha N S[1], Mrs. Aswathy SS[2], Mrs. Savitha Mol G M[3], Dr. Silviya Navis A[4], Dr. Prasobh G R[5], Ms. Surabhi G S[6], Ms. Jiji Mohan M U[7]

[1] Assistant Professor, Department of Pharmacology, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram

[2]Assistant Professor, Department of Pharmacology, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram

[3]Associate Professor, Department of Pharmacology, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram

[4]Head of Pharmacology Department, Sree Krishna college of Pharmacy and Research centre, Parassala, Thiruvananthapuram

[5]Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram

[6]Assistant Professor, Department of Pharmacognosy, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram

[7]Assistant Professor, Department of Pharmacognosy, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram

Abstract:

Drug discovery is a time-consuming, costly and high-risk process. It usually takes 10-15 years to develop a new drug. Drug repurposing is an alternative approach of drug discovery. Drug Repurposing (DR) can be defined as a process of identification and discovery of new therapeutic uses, outside the scope of the original pharmacological indication, for already approved drugs. Cancer is a group of diseases caused by loss of cell cycle control. It is associated with uncontrolled growth of abnormal cells with the ability to invade local tissues and metastasis which are proliferating individually throughout the body. These abnormal cells are termed cancer cells, malignant cells, or tumor cells.

Corresponding author:

Mrs. Rupitha N S,
Assistant professor,
Department of Pharmacology,
Sree Krishna college of Pharmacy and Research centre,
Parassala, Thiruvananthapuram

QR code

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INTRODUCTION:

Cancer is a leading cause of death worldwide. It accounted for 8.2 million deaths (around 22% of all deaths not related to communicable diseases; most recent data from WHO). Lung, stomach, liver, colon, and breast cancer cause the most cancer deaths each year. Deaths from cancer worldwide are projected to continue rising, with an estimated 13.1 million deaths in 2030 (about a 70% increase). This usually represents a combination of environmental and genetic factors[1].

Cancer is the uncontrolled growth of abnormal cells anywhere in a body. These abnormal cells are termed cancer cells, malignant cells, or tumor cells. These cells can infiltrate normal body tissues. Many cancers and the abnormal cells that compose the cancer tissue are further identified by the name of the tissue that the abnormal cells originated from (for example, breast cancer, lung cancer, colorectal cancer). Cancer is not confined to humans; animals and other living organisms can get cancer[2,3].

BREAST CENCER

Breast cancer is a type of cancer that starts in the breast. Cancer starts when cells begin to grow out of control. Breast cancer cells usually form a tumor that can often be seen on an x-ray or felt as a lump. Breast cancer occurs almost entirely in women, but men can get breast cancer, too. It's important to understand that most breast lumps are benign and not cancer (malignant). Non-cancerous breast tumors are abnormal growths, but they do not spread outside of the breast. They are not life threatening, but some types of benign breast lumps can increase a woman's risk of getting breast cancer. Any breast lump or change needs to be checked by a health care professional to determine if it is benign or malignant (cancer) and if it might affect your future cancer risk[4].

Breast cancer is the most common cancer to affect women worldwide. While the age adjusted incidence rates of breast cancer in India is lower than the western countries, because of the large population the burden of breast cancer is high. Surgery, chemotherapy and radiotherapy are potentially curative methods that have been used for decades, with success in some cases. However, they are unsuccessful in controlling advanced metastatic breast cancer, as well as some aggressive subtypes of cancers. Fortunately, recent advances in basic research opened new possibilities to attack tumors via the drug repurposing approach[5,6].

Breast Cancer Signs and Symptoms

Knowing how your breasts normally look and feel is an important part of breast health. Although having regular screening tests for breast cancer is important, mammograms do not find every breast cancer. This means it's also important for you to be aware of changes in your breasts and to know the signs and symptoms of breast cancer.

The most common symptom of breast cancer is a new lump or mass. A painless, hard mass that has irregular edges is more likely to be cancer, but breast cancers can be tender, soft, or round. They can even be painful. For this reason, it's important to have any new breast mass, lump, or breast change checked by an experienced health care professional.

Other possible symptoms of breast cancer include:

- Swelling of all or part of a breast (even if no lump is felt)
- Skin dimpling (sometimes looking like an orange peel)
- Breast or nipple pain
- Nipple retraction (turning inward)
- Nipple or breast skin that is red, dry, flaking or thickened
- Nipple discharge (other than breast milk)
- Swollen lymph nodes (Sometimes a breast cancer can spread to lymph nodes under the arm or around the collar bone and cause a lump or swelling there, even before the original tumor in the breast is large enough to be felt.)

Although any of these symptoms can be caused by things other than breast cancer, if you have them, they should be reported to a health care professional so the cause can be found[7].

1.2.2 HOW DOES BREAST CANCER STARTS?

Changes or mutations in DNA can cause normal breast cells to become cancer. Certain DNA changes are passed on from parents (inherited) and can greatly increase your risk for breast cancer. Other lifestyle-related risk factors, such as what you eat and how much you exercise, can increase your chance of developing breast cancer, but it's not yet known

exactly how some of these risk factors cause normal cells to become cancer. Hormones seem to play a role in many cases of breast cancer, but just how this happens is not fully understood [8,9].

- **Proto-oncogenes**

Proto-oncogenes are genes that help cells grow normally. When a proto-oncogene mutates (changes) or there are too many copies of it, it becomes a "bad" gene that can stay turned on or activated when it's not supposed to be. When this happens, the cell grows out of control and makes more cells that grow out of control. This can lead to cancer. This bad gene is called an oncogene. Think of a cell as a car. For the car to work properly, there need to be ways to control how fast it goes. A proto-oncogene normally functions in a way that's much like a gas pedal. It helps control how and when the cell grows and divides. An oncogene is like a gas pedal that's stuck down, which causes the cell to divide out of control[10].

- **Tumor suppressor genes**

Tumor suppressor genes4 are normal genes that slow down cell division (cell growth), repair DNA mistakes, or tell cells when to die (a process known as apoptosis or programmed cell death). When tumor suppressor genes don't work properly, cells can grow out of control, make more cells that grow out of control, and cells don't die when they should, which can lead to cancer. A tumor suppressor gene is like the brake pedal on a car. It normally keeps the cell from dividing too quickly, just as a brake keeps a car from going too fast. When something goes wrong with the gene, such as a mutation, the "brakes" don't work and cell division can get out of control[11].

- **Inherited gene changes**

Certain inherited DNA mutations (changes) can dramatically increase the risk for developing certain cancers and are linked to many of the cancers that run in some families. For instance, the BRCA genes (BRCA1 and BRCA2) are tumor suppressor genes. When one of these genes changes, it no longer suppresses abnormal cell growth, and cancer is more likely to develop. A change in one of these genes can be passed from a parent to a child.

Women have already begun to benefit from advances in understanding the genetic basis of breast cancer. Genetic testing5 can identify some women who have inherited mutations in the BRCA1 or BRCA2 tumor suppressor genes (or less commonly in other genes such as PALB2, ATM or CHEK2). These women can then take steps to reduce their risk of breast cancer by increasing awareness of their breasts and following appropriate screening recommendations6 to help find cancer at an earlier, more treatable stage. Since these mutations in BRCA1 and BRCA2 genes are also associated with other cancers (besides breast), women with these mutations might also consider early screening and preventive actions for other cancers.

Mutations in tumor suppressor genes like the BRCA genes are considered "high penetrance" because they often lead to cancer. And although many women with high penetrance mutations develop cancer, most cases of cancer (including breast cancer) are not caused by this kind of mutation.

More often, low-penetrance mutations or gene variations are a factor in cancer development. Each of these may have a small effect on cancer occurring in any one person, but the overall effect on the population can be large because the mutations are common, and people often have more than one at the same time. The genes involved can affect things like hormone levels, metabolism, or other factors that impact risk for breast cancer. These genes might also cause much of the risk of breast cancer that runs in families[12].

- **Acquired gene changes**

Most DNA mutations related to breast cancer take place in breast cells during a woman's life rather than having been inherited. These acquired mutations of oncogenes and/or tumor suppressor genes may result from other factors, like radiation or cancer-causing chemicals. But so far, the causes of most acquired mutations that could lead to breast cancer are still unknown. Most breast cancers have several acquired gene mutations[13].

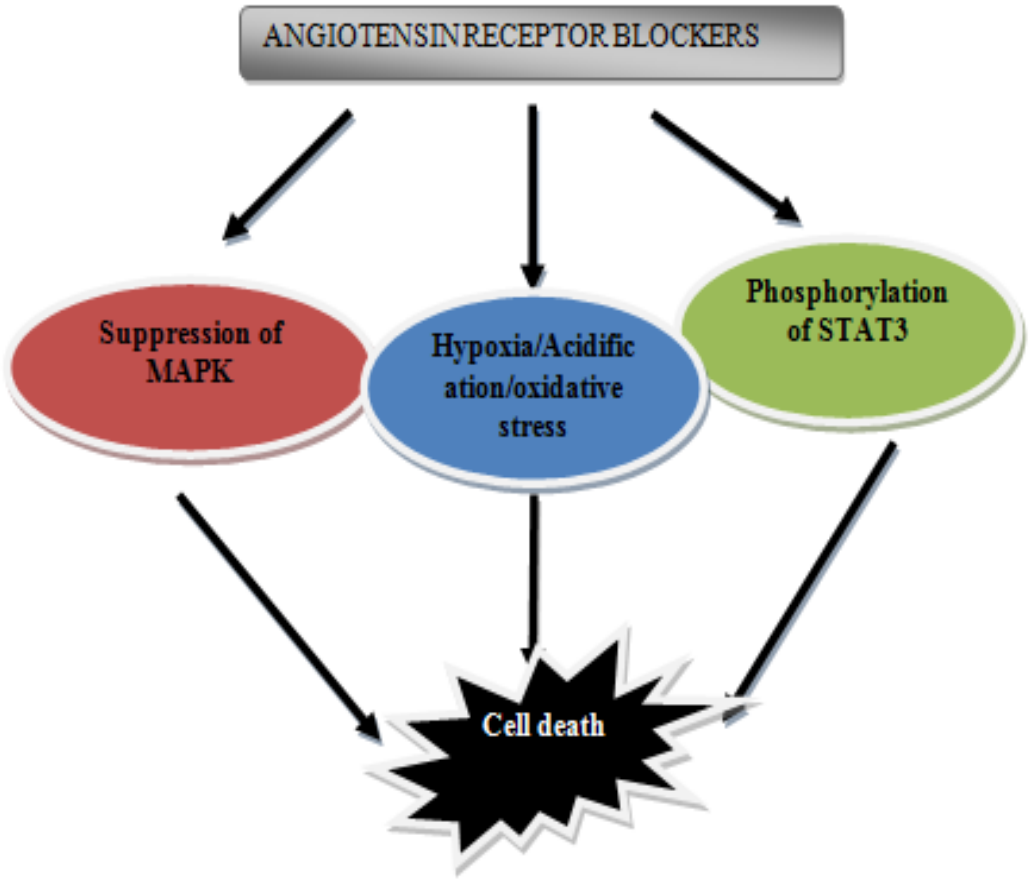
ANGIOTENSIN II RECEPTOR BLOCKERS IN CANCER

The angiotensin II receptors, and, are a class of G protein-coupled receptors with angiotensin II as their ligands. They are important in the renin–angiotensin system: they are responsible for the signal transduction of the vasoconstriction stimulus of the main effector hormone, angiotensin II exist in two types of receptor termed AT_1 and AT_2. It plays a role in the central nervous system and cardiovascular functions that are mediated by the renin–angiotensin system. This receptor mediates programmed cell death (apoptosis)[14].

The "classical" renin-angiotensin system is known to maintain blood pressure and body fluids. However,

increased understanding of its individual components and their structures and regulatory mechanisms, and the convergence and crosstalk with related pathways has resulted in the appreciation of a much more complex system. the renin-angiotensin system is implicated in a wide range of biological processes and diseases. This review provides an update on recent research into the structures, functions and metabolism of components of the renin-angiotensin system and its related pathways, and its role in biological processes such as angiogenesis, tumorigenesis, metastasis and cellular proliferation [15,16].

Previous studies have indicated that angiotensin II promotes the proliferation and metastasis of tumors, and that ARBs exhibit antiproliferative and antimetastatic effects on tumors. In addition, it has been reported that ARBs inhibit the growth of cancer cell lines via suppression of the mitogen-activated protein kinase (MAPK) or signal transducer and activator of transcription 3(STAT3) phosphorylation and exhibited an antitumor effect on patients with cancer. The ultimate aim of cancer therapy is the death of cancer cells, which may be induced by apoptotic or necrotic pathways. However, cancer cells are able to evade cell death mechanisms; therefore, a novel approach to target anti-apoptotic mechanisms in cancer is required. Previous reports have indicated that the induction of autophagic signals led to the death of cancer cells, despite autophagy being used as a survival strategy in cells experiencing insufficient supply of nutrients under hypoxic conditions. The phenomenon is termed autophagy-induced cell death, and is an alternative therapeutic approach to apoptosis-resistant cancer cells[17]



PPAR-γ in cancer

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a ligand-dependent transcription factor and a member of the nuclear receptor superfamily. Acting as sensors of hormones, vitamins, endogenous metabolites, and xenobiotic compounds, the nuclear receptors control the expression of a very large number of genes. Peroxisome proliferator-activated receptor (PPAR) is a Double-Edged Sword in Cancer Therapy. PPAR-γ not only controls the expression of genes involved in differentiations but also negatively regulates the cell cycle and contributes to their

antiproliferative activity. PPAR-γ activation inhibits the proliferation of malignant cells, including those derived from liposarcoma, breast adenocarcinoma prostate carcinoma, colorectal carcinoma, non-small-cell lung carcinoma, pancreatic carcinoma, bladder cancer, gastric carcinoma, and glial tumors of the brain[18].

PARP IN CANCER

The poly (ADP-ribose) polymerases (PARPs) are an emerging family of enzymes that share the ability to catalyze the transfer of ADP-ribose to target proteins (poly ADP ribosylation). There are at least 18 members of the PARP family that are encoded by different genes, and share homology in a conserved catalytic domain. Although some isoforms including PARP1 and PARP2 are best known for their involvement in DNA repair processes, it is now clear that these and other PARPs have an important role in several cellular processes including cell proliferation and cell death. A number of cellular substrates for PARP have been defined, and a majority of these proteins are nuclear proteins that are involved in nucleic acid metabolism, modulation of chromatin structure, DNA synthesis, and DNA repair.

ROLE OF m-TOR IN CANCER

Mechanistic target of rapamycin (mTOR) is a protein kinase regulating cell growth, survival, metabolism, and immunity. mTOR is usually assembled into several complexes. Activation of m-TOR promotes tumor growth and metastasis. Many mTOR inhibitors have been developed to treat cancer.

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that senses growth factor cues, nutrient and oxygen status, and directs appropriate changes to maintain cellular and tissue homeostasis. The mTOR signalling pathway is recognised as a key driver and regulator of cell growth and proliferation, cell survival, metabolism, and protein synthesis. mTOR belongs to the phospho-inositide 3-kinase (PI3K)-related kinase family, and consists of two distinct complexes; mTOR complex 1 (mTORC1) and complex 2 (mTORC2). Whilst both complexes are tightly regulated in a normal context, they are often deregulated in multiple disease-associated metabolic alterations and in cancer development. In normal conditions, activation of mTOR signalling occurs in response to the binding of specific growth factors to their cognate receptor tyrosine kinases (RTKs), including insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF).

The ligand-activated receptors recruit PI3K, which converts phosphatidylinositol bisphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3), and provides binding sites for phosphoinositide-dependent protein kinase 1 (PDK1). PDK1 then phosphorylates and activates, which in turn phosphorylates several downstream substrates that engage multiple pathways, including mTORC1. On the other hand, mTORC2 has been known to phosphorylate and activate members of the kinase family, including AKT, serum and glucocorticoid-induced kinase, and protein kinase whereby inhibition of these kinases results in tumour suppression

CONCLUSION:

The angiotensin receptors, and, are a class of G protein-coupled receptors with angiotensin II as their ligands. They are important in the renin–angiotensin system: they are responsible for the signal transduction of the vasoconstricting stimulus of the main effector hormone, angiotensin II exist in two types of receptor termed AT_1 and AT_2. FMN is an ATII receptor blocker it inhibit the growth of cancer cell lines via suppression of the mitogen-activated protein kinase (MAPK) or signal transducer and activator of transcription 3 (STAT3) phosphorylation and exhibited an antitumor effect on patients with cancer.

The ultimate aim of cancer therapy is the death of cancer cells, which may be induced by apoptotic or necrotic pathways. However, cancer cells are able to evade cell death mechanisms, therefore a novel approach to target anti-apoptotic mechanisms in cancer is required. Previous reports have indicated that the induction of autophagic signals led to the death of cancer cells, despite autophagy being used as a survival strategy in cells experiencing insufficient supply of nutrients under hypoxic conditions. The phenomenon is termed autophagy-induced cell death, and is an alternative therapeutic approach to apoptosis-resistant cancer cells.

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