Research Article

Current Landscape of Molecular Targeting Therapy in HER2 Positive Breast Cancer Cell Lines Using Monoclonal Antibodies

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Submission Date: 15-11-2024; Revision Date: 02-12-2024; Accepted Date: 25-12-2024.

ABSTRACT

Different target approaches such as nanocarriers and molecular targeting are used in the treatment of HER2 positive breast cancer. The present review summarizes the most significant updated research on the monoclonal antibodies used for the treatment of HER2 positive cell lines. Now a day's combination therapies are used by drugs with nanocarriers which enhance its high therapeutic outcome by targeting features. Incorporation of the monoclonal antibodies along with the drugs will reduce the concentration of active moiety and morbidity rate. This review concludes monoclonal antibodies suggested for HER2 positive breast cancer cell lines. Among the different monoclonal antibodies Trastuzumab, Pertuzumab, Bevacizumab, Pembrolizumab shows more targets on HER2 cell lines. From the kinase inhibitors Imatinib, Lapatinib, Nevatinib are the best one, where Erlotinib, Crizotinib, Vemurafenib shows poor candidates for the HER2 targeting cancer cell line.

Keywords: HER2, Monoclonal antibody, Nanocarriers.

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INTRODUCTION

Breast cancer occurs due to the unregulated proliferation of cancer cells. Typical signs of breast cancer involve the detection of a noticeable lump in the breast, changes in breast contour and the appearance of rough patches on the skin and the occurrence of fluid discharge from the nipple. Breast cancer occurs both in man and is most common in women.[1]

The decline in death by the breast cancer is by earlier detection and personalized approaches for the treatment. The uncontrolled division of breast cancer more rapidly and continue to accumulate for the lump of mass. The cancer cells may spread through the brain and reaches to lymph node where it moves to all part of the body.[2-4]

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DOI: 10.5530/ajbls.2024.13.80

Types of breast cancer

In situ breast cancer refers to the early stage of cancer that develops in the milk ducts and has not yet disseminated to the surrounding breast tissue.Invasive breast cancers are types which have the capacity in spreading to the surrounding tissue. Among the invasive ductal and the lobular carcinoma, invasive carcinoma is common. Some special invasive ductal carcinoma includes the triple negative breast cancer in which the cells have no estrogen and progesterone receptors and have no capacity to make HER2 protein. Inflammatory breast cancer is the type in which the proliferated cancer cell causes the blockage of lymph vessel in skin and make the breast look more inflamed.[5-7]

Other less common type of breast cancer includes Paget disease which started from the breast duct and spread to the nipple skin and to the aerola. Angiotarcoma which starts from the cell that lines blood vessels. Phyllode tumor is another rare tumor which develop in the stroma of the connective tissue.[8]

Treatments for breast cancer

First lines of the treatment include mastectomy and the lumpectomy along with the radiation therapy. The patients after the lumpectomy were recommended for the radiation therapy for treating the chest wall lymph node.[9,10] Most patients will start the drug therapy after surgery which include the combination of chemotherapy and hormone therapy. HER2 targeted therapy, immunotherapy and PARP inhibitors therapies are used.[11,12]

Nanocarriers are being selected for the targeted drug delivery. The bioavailability of the drug can be increased by liposomes, dentrimer, nano crystals, magnetic nanoparticle, Nano gel and the biodegradable nanoparticle. The encapsulating material used for the preparation is the biodegradable polymer.[17-19] The surface modifier makes the nanocarrier an efficient delivery system. Different nanocarriers used include.[20,21] Figure 1 shows nanocarriers used in breast cancer therapy.

Exploring molecular targeting strategies for breast cancer

Targeting is the process of minimising toxicity. The breast cancer is targeted by many receptors, including as HER2, Vascular Endothelial Growth Factors (VEGF), insulin-like Growth Factor Binding Protein-3 (GFBP-3) and Oestrogen Receptor (ER).[22,24]

APTAMER

Aptamer are short sequences oligonucleotides DNA, RNA, XNA or peptides which is used for the molecular regeneration of their respective target. They mainly used for the cancer reorganization, pathogen reorganization and for environmental contamination. They form strong and particular bonds with the target by adopting a complex three-dimensional structure.They recognize and bind to target agent like antibodies which is more convenient due to its short generation time low cost of manufacturing with high stability.[25,27-29] Figure 2 shows the 3D structure of RNA Binding Aptamer.

Figure 2: 3D structure of RNA Binding Aptamer (https://www.rcsb.org/).

VEGF

VEGF, Vascular endothelial growth factor, is a signalling protein that promotes the development of new blood vessels, a phenomenon called angiogenesis. This protein is essential for improving blood vessel function after injury and physical activity.[30,31] The application

Figure 1: Exploring the potential of nanocarriers in breast cancer therapy.

of VEGF in the cancer treatment is by reducing the blood supply which leads to the tumor death. VEGF stimulates the vasculogenesis and angiogenesis. Human monoclonal antibodies against VEGF Beracizumab are clinically most mature angiogenic agent and are used to improve the outcome-based treatment in the first line metastatic breast cancer.[30,31]

The VEGF family consists of VEGF-B, VEGF-C and VEGF-D. VEGF-C and VEGF-D[46] act as ligands for the VEGF-receptor-3, which is specifically expressed in endothelium of lymphatic vessels. VEGF-A and VEGF-B can identify both positive and negative cases of breast cancer, while VEGF-D is only recognised in cases of inflammatory breast cancer.[30,31] Figure 3 depicts the three-dimensional arrangement of VEGF-B when it is bound to an antibody.

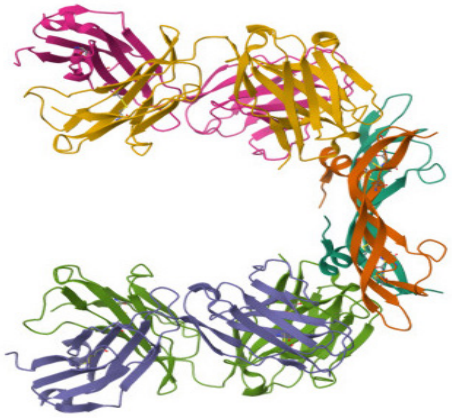

Figure 3: 3D structure of VEGF-B in complex with antibody (https://www.rcsb.org/).

IGFBA-3

Insulin-like Growth Factor (IGF) plays a significant function in cell proliferation and programmed cell death,[41] energy metabolism and aging. IGF have the receptor (IGF-IR and II-R). Insulin receptors have high affinity binding proteins (IGFB-1 to 6). IGFBP related proteins IGFBP-rps binds to the low affinity protein. It is high affinity binding proteins which have more affinity towards the breast cancer cells. IGF-IGFBP-3 complex will prevent the binding of IGFBP-3 to its reception.[32-34]

SiRNA

This is the synthetic small interfering non coding RNA molecule also called silencing RNA involves in the inhibiting of expression of a gene. For efficient delivery of SiRNA several non-viral vectors likes liposomes, micelle, nanoparticle, dentrimers, nanorod are used for the safer delivery. SiRNA is highly effective in treating triple-negative breast cancer, a type of breast cancer that lacks the ER receptor, progesterone receptor and HER2 receptor.[1] It also more efficient to overcome the drug resistant in breast cancer.[35-38]

ER

The Oestrogen Receptor (ER) consists of two subtypes, ERα and ERβ, which primarily function as G-protein coupled receptors and are activated by oestrogen. The endoplasmic reticulum is capable of regulating the production of RNA through genomic mechanisms without directly interacting with DNA.Post-menopausal women frequently develop breast tumours that are characterised by the presence of ER. Specific treatment options include the use of selective ER modulators, selective ER down regulators, aromatase inhibitors and sulphatase inhibitors.[39-41]

Therapeutic Approach for Her2 Positive Breast Cancer

Targeted treatment medications specifically target the protein found in breast cancer cells. Targeted drugs function by either eradicating cancer cells or impeding their proliferation. Various forms of targeted therapy are employed to specifically target cancer cell lines in breast cancer. Some treatment options are available for different types of breast cancer, such as HER2 positive breast cancer, BRCA gene mutation, triple negative breast cancer and hormone receptor-positive breast cancer.HER2 is a growth-promoting protein produced by breast cancer cell types. They have more robust growth compared to HER-2 negative breast cancer.[42,44,46,49]

Monoclonal Antibody drug targeting

They also called the immunotherapy in which they combine with the HER-2 protein. They can focus particularly to a specific target. Monoclonal antibody can able to target tumor cells and simultaneously it promotes the induction of antitumor immune response for long time. Mechanism of targeted antibodies is by blocking the growth factor receptor ligand signaling. Various types of cancer exhibit overexpression of the EGFR, which in turn triggers cellular proliferation and invasion.[50-52,55,56]

Trastuzumab

Herceptin, a drug widely recognised by its brand name, is routinely used to treat specific forms of cancer. The treatment will specifically focus on inhibiting the Human EGFR-2 (HER2) proteins, especially in situations when the cancer cells excessively produce the HER2 protein. It is efficacious in treating both early-stage and metastatic HER2-positive breast cancer.

The method of action of trastuzumab involves binding to the HER2 protein located on surface of cancer cells.[23] This interaction inhibits the signals that facilitate the growth and division of these cells, while also activating immune system to target and destroy the cancer cells. The medication is typically administered through Intravenous (IV) infusion in combination with other chemotherapy drugs.[57-58,60,61] Trastuzumab has demonstrated significant efficacy in the treatment of HER2-positive breast cancer, while it may have certain Typical adverse reactions consist of fever, chills, nausea, tiredness, diarrhoea and muscular or joint discomfort. Occasionally, it may result in more severe adverse effects such as cardiac complications or hypersensitivity reactions.[62,63,60]

Pertuzumab (Perjeta)

Pertuzumab specifically targets the HER2 protein. It functions by attaching to a distinct area of the HER2 protein compared to trastuzumab, thus inhibiting the creation of HER2-HER3 receptor complexes. Pertuzumab is frequently administered alongside trastuzumab and chemotherapy to treat HER2-positive breast cancer,[67] both in the neoadjuvant (pre-surgery) and metastatic stages.[64-67] Ado-trastuzumab emtansine, also known as T-DM1 or Kadcyla, is a combination of a monoclonal antibody called trastuzumab with a chemotherapeutic agent called emtansine.[43]

Trastuzumab acts as a vehicle to deliver emtansine specifically to the HER2-positive cancer cells, where it releases the chemotherapy drug to exert its anticancer effects. T-DM1 is commonly employed for the management of metastatic breast cancer that is HER2-positive and unresponsive to trastuzumab monotherapy.[78,79]

Bevacizumab (Avastin)

Bevacizumab is a monoclonal antibody that specifically targets the VEGF, a protein that plays a crucial role in the process of angiogenesis, which is the development of new blood vessels.[10] Bevacizumab hinders the activity of VEGF, hence impeding the development of blood vessels that provide nourishment to tumours.It has been utilised in conjunction with chemotherapy to treat specific forms of metastatic breast cancer.[70,71]

Pembrolizumab (Keytruda) and Atezolizumab (Tecentriq)

These monoclonal antibodies belong to a class known as immune checkpoint inhibitors. They work by blocking the PD-1 and PD-L1 proteins, which are involved in suppressing the immune response against cancer cells.[67] While pembrolizumab and atezolizumab are primarily used in other types of cancer, they have shown some promising results in certain subsets of breast cancer, particularly in tumors with high levels of PD-L1 expression. The use of these monoclonal antibodies may vary depending on the specific subtype and stage of breast cancer, as well as individual patient characteristics. Treatment decisions are typically made by healthcare professionals based on clinical guidelines and the patient's unique situation. Figure 4 represents 3D structures of trastuzumab, pertuzumab, pembrolizumab and atezolizumab conjugated with antibody.

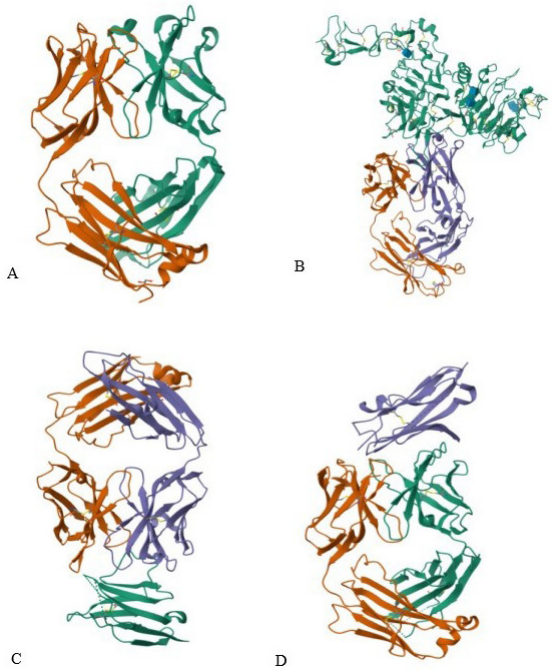

Figure 4: 3D structures of trastuzumab (A), pertuzumab (B), pembrolizumab (C), atezolizumab (D) conjugated with antibody (https://www.rcsb.org/).

Kinase Inhibitors

These drugs belong to a category that specifically targets enzymes known as kinases. Kinases are proteins that have a vital function in multiple biological processes, such as signal transmission and cell development.[1] These drugs can disrupt the signalling pathways that promote the growth and multiplication of cancer cells by blocking the activity of kinases.Kinase inhibitors have been formulated to treat several types of malignancies and other disorders characterised by aberrant kinase activity.[72,73]

Imatinib (Gleevec)

Imatinib was among the initial kinase inhibitors to be created and authorised for the therapy of cancer. The drug specifically targets the BCR-ABL fusion protein, which is a distinguishing feature of Chronic

Myeloid Leukaemia (CML) and a specific type of Acute Lymphoblastic Leukaemia (ALL). Imatinib has demonstrated effectiveness in treating Gastrointestinal Stromal Tumours (GISTs) by blocking the function of the KIT kinase. The mechanism by which Imatinib works is through the specific inhibition of the BCR-ABL tyrosine kinase, which is constantly active in CML as a result of the Philadelphia chromosome. Imatinib inhibits the activity of this kinase, hence disrupting the signalling pathways responsible for the aberrant proliferation and division of cancer cells.[56,49]

Imatinib has primarily been studied in patients with the "triple-negative" subtype of breast cancer. Triple-negative breast cancer is characterised by the absence of oestrogen receptor, progesterone receptor and HER2/neu receptor expression, which presents difficulties in treating the disease with targeted therapy.[75,76] The adverse effects of imatinib are typically well-tolerated. Typical adverse effects may encompass tiredness, queasiness, muscular spasms, fluid accumulation, skin irritation, digestive disturbances and swelling. [53] Serious side effects are rare which include severe liver toxicity, heart problems and low blood cell counts.[77] Regular monitoring and communication with a healthcare provider are essential during treatment. Some patients may develop resistance to imatinib over time, leading to disease progression. In such cases, alternative Tyrosine Kinase Inhibitors (TKIs) with different binding properties or new treatment strategies may be considered. Dasatinib, nilotinib, bosutinib and ponatinib are second- and third-generation TKIs that have been created to address the issue of imatinib resistance. These TKIs are utilised in certain clinical situations.

Erlotinib (Tarceva) and Gefitinib (Iressa)

These kinase inhibitors specifically target the overexpressed EGFR (Epidermal Growth Factor Receptor) in some kinds of lung cancer.They are utilised in the management of Non-Small Cell Lung Cancer (NSCLC) that contains activating mutations in the EGFR gene.Erlotinib is mainly employed for the management of advanced or metastatic NSCLC that possesses particular EGFR, such as exon 19 deletions or exon 21 L858R point mutations.These genetic changes cause cancer cells to rely more on EGFR signalling and erlotinib aids in blocking that pathway. Erlotinib is authorised for the therapy of locally advanced, inoperable, or spreading pancreatic cancer.

Patients with NSCLC who have EGFR mutations tend to have a higher response rate to erlotinib treatment compared to those without these mutations.[73] Some patients may develop resistance to erlotinib due to additional mutations or alterations in the EGFR gene. In such cases, alternative treatment options or second-generation EGFR inhibitors may be considered. Erlotinib specifically targets the EGFR, a protein that is involved in the proliferation and metastasis of several types of malignancies. Some breast cancer subtypes, such as Triple-Negative Breast Cancer (TNBC) and basal-like breast cancer, may have elevated EGFR expression, making them potential candidates for EGFR-targeted therapies like erlotinib. The clinical trials assessing the efficacy of erlotinib in breast cancer may demonstrate varying outcomes. Several studies have shown limited effectiveness in certain groups of patients with TNBC or breast cancer that is positive for the EGFR, while other studies have not found any substantial advantages. The diversity of breast cancer subtypes and the intricate nature of EGFR signalling in breast cancer are factors that contribute to the different outcomes observed.[73,75]

It's important to note that erlotinib is not a standard or first-line treatment for breast cancer and its use in this setting is still under investigation.[68] The primary treatment options for breast cancer typically include surgery, radiation therapy, chemotherapy, hormonal therapy and targeted therapies specific to the subtype and receptor status of the tumor. Erlotinib can cause side effects that vary among individuals. Common side effects may include skin rash, diarrhea, nausea, fatigue, loss of appetite and nail changes. More severe side effect includes interstitial lung disease and liver toxicity.[76]

Crizotinib (Xalkori)

Crizotinib is a pharmaceutical compound that functions as a kinase inhibitor, specifically targeting the Anaplastic Lymphoma Kinase (ALK) and c-Ros Oncogene 1 (ROS1) kinases. It is mostly employed in the management of advanced NSCLC that exhibits ALK gene rearrangements or ROS1 gene fusions.[15] Crizotinib is mostly employed for treating advanced NSCLC that exhibits certain genetic abnormalities, such as ALK gene rearrangements or ROS1 gene fusions.[31,72] These genetic alterations result in abnormal activation of ALK or ROS1 kinases and crizotinib helps inhibit their activity. Crizotinib acts as a potent inhibitor of ALK and ROS1 kinases by binding to their active sites, thereby preventing the downstream signaling pathways that promote cancer cell growth. By blocking these kinases, crizotinib helps to slow down tumor growth and potentially shrink the tumors. Patients with NSCLC who have ALK or ROS1 genetic alterations tend to have a higher response rate to crizotinib treatment compared to those without these alterations. In breast

cancer, certain subtypes may harbor ALK or ROS1 genetic alterations, making them potential candidates for crizotinib therapy.[71,72]

Clinical studies exploring the use of crizotinib in breast cancer have shown limited success. The presence of ALK or ROS1 gene rearrangements in breast cancer is relatively rare compared to lung cancer. Therefore, the number of breast cancer patients who may benefit from crizotinib is quite small. In general, crizotinib is not a standard therapy for breast cancer and is not currently approved for use in this disease. Some patients may develop resistance to crizotinib due to acquired mutations in the ALK or ROS1 genes. In such cases, alternative treatment options, such as next-generation ALK inhibitors, may be considered. Crizotinib can cause side effects, although they vary among individuals. Common adverse effects may encompass fatigue, diarrhoea, nausea, vomiting, edoema and vision impairments. Other less common side effects include liver toxicity, lung problems and abnormal heart rhythms.[15] Regular monitoring and communication with a healthcare provider are important to manage and address any potential side effects.[73,74]

Vemurafenib (Zelboraf) and dabrafenib (Tafinlar)

These kinase inhibitors specifically target mutated forms of the BRAF kinase, which are found in certain types of melanoma. These drugs are utilised to treat metastatic melanoma in individuals with BRAF V600 mutations. Vemurafenib, marketed under the brand name Zelboraf, is a targeted therapy and kinase inhibitor used in the treatment of melanoma, particularly melanomas that have specific genetic alterations. It specifically targets mutated forms of the BRAF kinase, which are found in approximately 40-50% of melanoma cases. Vemurafenib is primarily indicated for the treatment of unresectable or metastatic melanoma that harbours particular mutations in the BRAF gene, specifically the BRAF V600E or BRAF V600K mutations. These mutations result in the abnormal activation of the BRAF kinase and vemurafenib helps inhibit its activity. Vemurafenib is a selective inhibitor of mutated BRAF kinases. It works by binding to the active site of the mutated BRAF protein, blocking it signaling pathway and inhibiting the abnormal growth and proliferation of melanoma cells with these genetic alterations. Patients with melanoma who have BRAF V600 mutations tend to have a higher response rate to vemurafenib treatment compared to those without these mutations.[72,73]

It is not a standard treatment for breast cancer and its use in this context is limited. Breast cancer typically has different molecular characteristics and genetic alterations compared to melanoma. While BRAF mutations are common in melanoma, they occur in only a small subset of breast cancers, specifically in TNBC and rare cases of other breast cancer subtypes. Clinical trials assessing the efficacy of vemurafenib in breast cancer patients with BRAF mutations have demonstrated restricted effectiveness. Although certain individuals with BRAF-mutant TNBC have had tumour responses to vemurafenib, the overall response rates have been rather low. In the context of breast cancer, hormone therapies (e.g., tamoxifen) and HER2-targeted therapies (e.g., trastuzumab) are frequently employed, mostly depending on the presence of ER, Progesterone Receptors (PR), or overexpression of Human EGFR-2 (HER2).[76,77]

Vemurafenib can cause side effects, which can vary among individuals. Common side effects may include skin rash, fatigue, joint pain, fever, photosensitivity and hair loss. Other less common side effects include liver toxicity, cardiovascular events and the development of squamous cell carcinoma. Regular monitoring and communication with a healthcare provider are important to manage and address any potential side effects.[76,77]

Lapatinib (Tykerb)

Lapatinib is a pharmaceutical compound that acts as a dual kinase inhibitor, specifically targeting the EGFR and HER2 kinases. It is employed in conjunction with other medicines to treat HER2-positive breast cancer that has advanced or spread to other parts of the body. Lapatinib functions by suppressing the activity of both HER2 and EGFR, which play a role in stimulating the proliferation and viability of cancerous cells. Lapatinib can effectively inhibit the progression of HER2-positive breast cancer by specifically targeting these receptors.[78,79]

Lapatinib is typically administered alongside other treatments, such as chemotherapy or hormone therapy, based on the unique attributes of the breast cancer and the disease's stage. It is commonly recommended in instances where the cancer has developed resistance to earlier treatments or has metastasized to other regions of the body. Healthcare professionals establish the treatment approach, which may use lapatinib, depending on unique patient criteria such as disease stage, hormone receptor status and overall health.[80-82]

Neratinib (nerlyx)

Neratinib, marketed as Nerlynx or Neratinib Tablets, is an authorised targeted therapy drug for the treatment of HER2-positive breast cancer. HER2-positive breast

cancer is a specific form of breast cancer characterised by an excessive presence or increase in the human HER2 protein within the cancer cells.[83,84]

Neratinib is coming under Tyrosine Kinase Inhibitor (TKI) and works by blocking multiple receptors, including HER2, HER1 (EGFR) and HER4. By inhibiting these receptors, neratinib helps to slow down the growth and spread of HER2-positive breast cancer cells. Neratinib is commonly administered as an adjunctive therapy. It can be utilised following initial treatment with surgery and/or chemotherapy to mitigate the likelihood of cancer recurrence. It is approved for use in patients who have previously completed trastuzumab-based (Herceptin) therapy. Neratinib is generally taken orally as a daily treatment for one year.[83,84]

Side effect of neratinib include diarrhea. Prophylactic measures, such as the use of antidiarrheal medications, are often taken to manage this side effect. The advantages of neratinib over other antibodies is the ability to overcome the resistance by targeting the HER2 signelling.[85,86,87]

CONCLUSION

A highly standard and specific target therapy can be offered using monoclonal antibody and nanocarrier. Preparation of antibody targeted nanocarrier labeling technique provides a novel drug design that emphasis on target delivery. Nanocarrier has the advantage of loading cytotoxic drug and monoclonal antibody has desired cite specific activity for targeting the breast cancer cell lines. From the list of monoclonal antibodies mentioned above Trastuzumab, Pertuzumab, Bevacizumab, Pembrolizumab, Imatinib, Lapatinib, Nevatinib shows better result in targeting breast cancer cell lines.

ACKNOWLEDGEMENT

The authors express their gratitude to all the faculties and the Department of Pharmacy at Karpagam Academy of Higher Education for their support of the study.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in the manuscript.

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Cite this article: Aswathy Balan, Saravanan Gopal. Current Landscape of Molecular Targeting Therapy in HER2 Positive Breast Cancer Cell Lines Using Monoclonal Antibodies. Asian J Biol Life Sci. 2024;13(3):658-66.