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Haramine-Mediated Anticancer Effects in Breast Cancer Cells: Targeting TAZ as a Therapeutic Strategy

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Abstract: *Breast cancer is still one of women's greatest life-threatening diseases on the planet today, urgently requiring sheer innovations in therapeutic means such as these.The aim of this research was to study the anti-cancer effect of haramine and its ability to suppress breast cancer cells, with a special interest in TAZ (Transcriptional Co-activator with PDZ binding motif), an oncogenic protein that is involved in both cell survival and migrating invasive potential. Our results indicate that haramine inhibits breast cancer cells from growing tumours, and also that it causes apoptosis by acting upon the TAZ pathway. Diverse a variety of in vitro assays gave us an idea about haramine; there was a marked decrease in both cell viability and metastatic potential among breast cancer cells after being treated with haramine. These findings suggest that haramine represents a potential candidate for cancer treatment and targeting TAZ is therefore an exciting innovation in the fight against breast cancer. Electrical mechanisms of haramine's effect, and its clinical potential to cure breast cancer, remain areas for future study.*

Keywords: Breast-cancer, Haramine , Neoplasm , TAZ

I. INTRODUCTION

Breast cancer is the life-threating disease in worldwide at present time in women. breast cancer has been reported resulting from mammography and by physical examination as well as prophylactic mastectomy or development in therapy .breast cancer begins in lobules in the ducts the connect the lobules to the nipples .Breast cancer is the most common cancer among women in US, accounting for 268,600 of all new cancer cases detected in women in 2019and approximately 2,670 cases were diagnosed in men .In India breast cancer is second most common cancer in women . within four minute one woman is diagnosed with breast cancer , and one woman dies from it every eight minutes. In 2018, an estimated 162,468 women in India were newly diagnosed with breast cancer, and 87,090 women died from the disease. It was second highest mortality rate in the world for that year. In India's predominantly young population, the number of women in this age group being diagnosed with breast cancer is expected to rise. These statistics highlight the growing and alarming prevalence of breast cancer in India. Unfortunately, curative effect of all kinds of traditional chemotherapeutic agents is not ideal and some patients with advanced‐stage breast cancer are resistant to existing chemotherapy drugs . It is a tumour with multiple risk factors and complex pathogenesis molecular mechanisms. Consequently, novel anticancer mechanisms have become the focus of growing attention.

Harmaline, a beta-carboline, is widely distributed in the plant kingdom. Plants within over eight botanical families manufacture harmaline, harmine, harmalol, harman, and related hallucinogenic alkaloids Many plants have it, but the Syrian rue and Banisteriopsis caapi are the most common ones. Harmine is a reversible inhibitor of monoamine oxidase A (RIMA) because it reversibly inhibits the enzyme monoamine oxidase A (MAO-A), which breaks down monoamines. MAO-B is not inhibited by harmine. Other names for harmine include leucoharmine, telopathine, telepathine, banisterin, and yagin, yageine. Harmine (HM) is a β-carboline alkaloid first isolated in 1847 from the seeds of Peganumharmala and Banisteriopsis caapi. It is found in various medicinal plants and has been used in traditional medicine across the Middle East and Asia for centuries. Research has shown that HM has significant antitumor effects both in lab studies and in living organisms. It can inhibit the proliferation, migration, and invasion of cancer cells, promote apoptosis, and prevent tumour formation. HM has been effective again arresting the cell cycle at the G0/G1

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phase and reducing cyclin-dependent kinase activity. HM also induces autophagy and apoptosis through the AktmTOR and ERK1/2 signalling pathways and increases the expression of related proteins

II. BIOSYNTHESIS OF HARMINE

The biosynthesis of harmine begins with the aromatic amino acid L-tryptophan, which is produced via the shikimate pathway. The enzyme aromatic L-amino acid decarboxylase (AADC) decarboxylates L-tryptophan to yield tryptamine (I).Tryptamine contains a nucleophilecenter at the C-2 carbon of the indole ring due to the adjacent nitrogen atom, making it capable of participating in a Mannich-type reaction. In the subsequent steps, tryptamine is converted into a Schiff base through rearrangements. This Schiff base then combines with pyruvate (II) to produce β-carboline carboxylic acid. The carboxylic acid group of β-carboline is decarboxylated to form 1-methyl β-carboline (III). Following this, hydroxylation and methylation reactions occur to produce harmaline (IV). It has been shown that the sequence in which O-methylation and hydroxylation take place is not critical for the formation of the harmaline intermediate.In the final step (V), harmaline undergoes oxidation to complete the biosynthesis of harmine..

III. HARMINE CLINICALLY USES

Harmine is a reversible inhibitor of monoamine oxidase A (MAO-A), meaning it specifically targets MAO-A without affecting MAO-B. When taken orally or intravenously in doses ranging from 30 to 300 mg, harmine can cause various side effects such as agitation, bradycardia or tachycardia, blurred vision, hypotension, and paresthesias. To confirm a diagnosis of harmine exposure, serum or plasma harmine concentrations can be measured. The plasma elimination half-life of harmine is approximately 1 to 3 hours. Harmine is also valuable as a fluorescent pH indicator. As the pH of its surrounding environment increases, its fluorescence emission decreases. Because of its specific binding to MAO-A, carbon-11 labelled harmine can be used in positron emission tomography (PET) to study MAO-A dysregulation in various psychiatric and neurologic conditions. Historically, harmine was used as a medication for Parkinson's disease from the late 1920s until the early 1950s, when it was replaced by other treatments.

Natural Sources of Harmine

Approximately thirty different species, including seven butterfly species from the Nymphalidae family, have been identified by Alexander Shulgin as containing harmine. This compound is found in several plants, including tobacco, Peganumharmala, and two varieties of passiflora. Lemon balm (Melissa officinalis) also contains harmine. In addition to B.caapi, at least three members of the Malpighiaceae family contain harmine, including two other Banisteriopsis species and the plant Callaeum antifebrile. In samples of B. caapi, researchers Callaway, Barito, and Neves (2005) discovered harmine levels ranging from 0.31 to 8.43%.Peganum nigellastrum and Zygophyllumfabago, which belong to the same family as Peganumharmala (Zygophyllaceae), are additional plants known to contain harmine.

IV. TAZ AND HUMAN CANCERS

Many human cancers, such as breast cancer, glioblastoma, lung cancer, colorectal cancer, and oral squamous cell carcinoma, exhibit high or activated levels of TAZ. High-grade metastatic breast tumours exhibit elevated levels and activities of the TAZ protein. Overexpression of TAZ is sufficient to induce epithelial-mesenchymal transition (EMT), cell transformation, and proliferation in breast cancer cells. Additionally, TAZ is crucial for breast cancer stem cells, enabling them to retain their self-renewal capacity and initiate tumours. Research by Bartucci and colleagues has shown that higher TAZ expression is linked to shorter disease-free survival in breast cancer patients. TAZ is also essential for the metastatic activity and chemoresistance of breast cancer stem cells.Furthermore, TAZ serves as a biomarker for a lower pathological complete response rate in individuals with luminal B/HER2-positive breast cancer undergoing chemotherapy or neoadjuvanttrastuzumab treatment. In human invasive ductal breast cancer, TAZ expression is strongly associated with GPER, the G protein-coupled receptor for estrogen. In a study, apoptotic activity was identified using flow cytometry and DAPI labelling, while cell migration was investigated through a wound healing assay. Cell proliferation was measured with the CCK-8 assay. Western blotting was employed to assess the expression of several proteins, including B cell lymphoma 2 (Bcl-2), phosphorylated Erk (p-Erk), protein kinase B (Akt), phosphorylated Akt (p-Akt), and Bcl-2-associated X protein (Bax). The mRNA expression of TAZ was analyzed using

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reverse transcription quantitative polymerase chain reaction (RT-qPCR). Additionally, immunohistochemistry was used to investigate the expression of proteins in mouse tumor tissues.The primary function of the Hippo-YAP/TAZ pathway is to coactivate and interact with TEAD transcription factors, modulating the transcription of downstream target genes. Compounds that disrupt the interaction between TEADs and TAZ are believed to inhibit TAZ's carcinogenic effects. The porphyrin family, which includes verteporfin (VP), hematoporphyrin (HP), and protoporphyrin IX (PPIX), has shown promise in this regard. Liu-Chittenden et al. evaluated approximately 3,000 compounds and identified these porphyrins as excellent candidates for YAP/TAZ inhibitors.

Verteporfin, a therapeutic photosensitizer used in photocoagulation therapy for macular degeneration, significantly disrupts the interaction between YAP/TAZ and TEADs, thereby inhibiting the transcription of downstream target genes. Notably, verteporfin has demonstrated an anti-tumour effect on uveal melanoma cells with GNAQ mutations and has been shown to inhibit YAP-induced liver carcinogenesis. However, further studies are needed to fully understand the scope and limitations of verteporfin's anti-cancer properties.Disrupting upstream regulators is another effective strategy to inhibit TAZ activity. As previously mentioned, the actin cytoskeleton and Rho GTPase are crucial in regulating the Hippo-YAP/TAZ pathway in response to various signals. Therefore, blocking Rho GTPase can increase LAT1/2 kinase activity, effectively halting TAZ function. Recent research by Sorrentino et al. has shown that statins, which inhibit HMGCR—the rate-limiting enzyme of the mevalonate pathway—can significantly reduce YAP/TAZ nuclear localization. The mevalonate pathway is essential for Rho GTPase activation, membrane attachment, and prenylation.

By significantly activating LATS1/2 and reducing TAZ's transcriptional activity, HMGCR inhibition exerts anti-proliferative and apoptotic effects on breast cancer cells. It would be worthwhile to investigate whether other clinically used mevalonate pathway inhibitors can achieve similar results.It would be interesting to explore whether statins have similar effects to other clinically utilized inhibitors of the mevalonate pathway, such as fatostatin (an SREBP inhibitor), GGTI-2133 (a GGPP inhibitor), and zoledronic acid (an FDPS inhibitor). Investigating these compounds could provide valuable insights into their potential to inhibit YAP/TAZ activity and offer new avenues for cancer treatment.

V. CONCLUSION

The promising potential as an anticancer agent is underscored by our study particularly in the treatment of breast cancer. TAZ, which is a critical promoter in breast cancer cell proliferation and metastasis, suitably suppressed tumourgrowth and induced apoptosis by haramine. The results of this study suggest that with haramine switched on, manipulation of the TAZ pathway could constitute a brand new form of therapeutic intervention. For various approaches to tailor breast cancer treatments, this provides to look through detours out of impasse. To fully realize haraminetherapeutic potential, future research should aim at elucidating its molecular mechanisms and testing its effectiveness in clinical trials.

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