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Harnessing the Power of Alkaloids in Breast Cancer Treatment: A Review of Therapeutic Efficacy and Challenges

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Abstract

Cancer is a massive public health concern on a global scale. Developed nations have greater rates of breast cancer. Survival rates have increased as a result of early discovery. However, there are still major ongoing challenges which include variances in the availability of care, aggressive tumor subtypes, and the emergence of treatment resistance. These medical procedures have been linked with various adverse effects, prompting the usage of natural substances because they have less to no negative impact. Among these natural compounds is the class of alkaloids. These phytochemicals form a wide range of organic compounds that are naturally present and mostly derived from plant-kinds, but then they are also found in microbes, yeasts, and faunas. Characterized by nitrogen atoms, alkaloids exhibit more biological properties, making them of significant interest in various research fields. Alkaloids exhibit antiproliferative, antibacterial, and antioxidant properties and act as an abundant source for drug discovery and development. This study reviews the alkaloids matrine, noscapine, capsaicin, harmine, and Mahanine and describes their modes of action. These alkaloids can be utilized as tools of combination treatment and have been illustrated to initiate autophagy, reduce tumor volume, cause apoptosis, disrupt microtubule function, inhibit topoisomerase enzymes, and signaling pathway alterations involved in cell growth and survival to inhibit cell multiplication and migration. This review presents comprehensive data on the therapeutic potential of alkaloids against breast cancer.

Keywords: *Alkaloids, Anticancer Drugs, Bioactive Phytochemicals, Breast Cancer, Cellular Mechanism, Signaling Pathways.*

Introduction

Breast Cancer

Cancer - Hereditary changes that impact cell function, particularly cell division and proliferation, are the underlying cause of cancer. One among the most prevalent causes of mortality for womankind globally is breast cancer. The initial onset of this disease affects women's entire lifestyles and is associated with several risk features. Breast cancer can generally be categorized into invasive, non-invasive, or metastatic. The non-invasive breast cancer cells stay inside the ducts, while the

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neighbouring connective and fatty tissues of the breast are attacked by the invasive tumor cells when they burst out of the ductal and follicular walls [1].

Breast Cancer Progression Pathway

The progression of breast cancer typically follows a well-defined pathway. It begins with initiation, where DNA mutations or epigenetic changes cause normal breast cells to grow uncontrollably. This uncontrolled growth leads to promotion, where the abnormal cells continue to multiply, forming a localized mass known as a tumor. As the tumor develops, it undergoes invasion, growing into and disrupting nearby breast tissue. To sustain its growth, the tumor induces angiogenesis, a process where cancer cells facilitate the development of new vessels for blood stream to the tumor with necessary oxygen and nourishment. Finally, if the cancer advances, it may enter the stage of metastasis, where cancer cells spread through the lymphatic system or bloodstream to distant organs, leading to secondary tumor in other parts of the body [2]. Personalized therapy planning and the advancement of minimal intervention options are facilitated by the discovery of various genetic alterations across grades of oral squamous cell carcinoma by NGS analysis [3].

Breast Cancer Cell Lines

There are several subtypes of breast cancer, which is a genetically and clinically diverse illnesses. The most prevalent and typically recognised means for categorizing carcinoma of the breast is by immunohistochemistry, depending on the regulation of human epidermal growth factor (HER2), estrogen (ER), and progesterone (PR) hormone receptors. As a result, there are four kinds of breast tumours: triple-negative, HER2-positive, luminal A, and luminal B [4].

Among that the luminal subtype that is ER-positive is the most prevalent kind. ER+, PR-, and HER2 negative are the characteristics of Luminal A subtype breast cancer. It is represented by the cell lines MCF-7, T47D, and SU M185. Because of its high ER expression and significant hormone sensitivity, MCF-7 is the most often employed breast cancer cell line in studies. One of the other subtypes of breast cancer cells are claudin-low (triple negative), resembling basal subtypes that are distinguished by PR-, ER-, and HER2-. Among the claudin-low types, the most common is MDA-MB-231[5]. Severe oral epithelial dysplasia and OSCC both had markedly increased salivary MMP-9 levels, which may indicate that the substance is a marker for malignant transformation [6].

Nature's Therapeutic Agents

One of the most effective treatments amid the several therapy options presently existing for breast cancer, is the use of natural compounds/chemical combinations. Almost 60% of cancer medications present now are sourced from natural products. Phytochemicals have low adverse effects and a high anticancer potency. The World Health Organization (WHO) claims that, some countries solely use natural remedies as treatments. Alkaloids are one such class that has shown both anticancer and a broad range of medicinal properties [7]. By causing apoptosis, preventing glycolysis, and lowering migration and invasion in HSC-3 oral cancer cells, calotropin demonstrates anti-cancer potential [8].

Plant-derived treatments have made significant contributions to human health through their diverse medicinal properties. Aspirin, derived from the willow tree (Salix species), is extensively used to alleviate pain, reduce fever, and manage inflammation, as well as to prevent cardiovascular events. Quinine, extracted from the cinchona tree (Cinchona officinalis), has been a fundamental treatment for malaria for centuries, particularly important in combating drug-resistant strains. Aloe vera, applied topically, soothes burns and aids in wound healing. Ginger, from Zingiber

officinale, is valued for its anti-nausea and anti-inflammatory effects, while turmeric, from Curcuma longa, contains curcumin with anti-inflammatory properties. Higher DMFT scores, a plaque ecology that favors *Streptococcus mutans*, and increased caries severity are all associated with *H. pylori* in cavitated carious lesions [9]. These plant-based treatments highlight the importance of botanical sources in modern medicine, offering effective solutions for a wide range of health issues [10]. Because it inhibits apoptotic signaling and produces cytotoxic effects, β-sitosterol shows promise as a treatment for oral cancer [11].

Role of Alkaloids in Cancer Therapy

Discovering naturally occurring substances with anticancer characteristics in the plant world, aided in identifying anticancer alkaloids and developing novel drugs that have advanced treatment for cancer. An extensive group of compounds with an atom of nitrogen and a ringed structure called as alkaloids. Plants produce these as secondary metabolites for defence mechanisms, and in many cases, no biological function is assigned to the molecules [12]. The quantity of alkaloid synthesis varies based on the species and tissue of the tree; in some, it is more concentrated in the leaves, fruits, or seeds, while in others, it is highest in the bark or roots. In general, though, the yield is modest, results in the overexploitation of the natural population for the molecules [13]. Alkaloids play a multifaceted role in cancer therapy by directly killing cancer cells, inducing apoptosis, inhibiting metastasis and angiogenesis, overcoming drug resistance, and modulating the immune response. They are often used in combination therapies, to enhance treatment efficacy and reduce side effects [7]. Thus, phytochemicals modulate the cancer pathway, thereby act as anti-cancer drugs.

Classification of Alkaloids

Alkaloids has various classification which is given in the Table 1, Table 2 [7,16].

Challenges of using Alkaloids in Cancer Treatment

Alkaloids and their derivatives have made a major contribution to the treatment of cancer but there are still some pharmacological obstacles that limit their use. Some of the concerns includes bioavailability, toxicity, etc [14].

Alkaloids in Treatment of Other Diseases

In addition to breast cancer, alkaloids are utilized as therapeutic agents for various illness. Alkaloids have a variety of pharmaceutical properties, like antioxidant, anti-inflammatory, anti-hypersensitizing, anticancer, antibacterial, and anti-diarrheal qualities. Berberine can control blood sugar and cholesterol, and it is used for the treating Alzheimer's disease by inhibiting the progress and it can also arrest hippocampus neurodegeneration. Solanine has the ability to suppress the AChE enzyme, which makes it a potential therapeutic for Alzheimer's disease [7].

Alkaloid Effects on Cancer Progression: Signalling Pathways.

Cellular homeostasis is irreversibly disrupted by cancer. The circumstances that lead to tumour development includes six key characteristics:

1. Uncontrolled cell differentiation and division.
2. Enhanced angiogenesis.
3. Elevated proliferative signalling.
4. Reproducing immortality.
5. Metastatic invasion.
6. Resistance to cell death [15].

The alkaloids have the ability to induce autophagy, reduce tumour volume, impede cell migration and proliferation, and trigger apoptosis. They are suitable for combination treatment. The research aims to investigate the possible medicinal benefits of alkaloids in the management of cancer in the breast. This work analyses various methods by means of which alkaloids cause apoptosis, decrease cell growth,

and reduce tumour development. Additionally, it aims to tackle the pharmacological obstacles that restrict the application of alkaloids in cancer treatment. The alkaloids discussed in this paper are Matrine, Noscapine, Capsaicin, Harmine, and Mahanine. The Molecular structure of these alkaloids is given in Figures 1.

Table 1. Classification Depending upon their Origin and Structure

Type	Feature	Class	Example
True Alkaloids	They possess heterocyclic rings containing nitrogen and are formed from amino acids. They have significant metabolic activity and are quite sensitive in nature. They are primarily a result of a variety of amino acids, including L-ornithine, L-histidine, L-phenylalanine/L-tyrosine, and L-lysine.	Piperidine group of alkaloids	Piperine, Sedamine.
		Iso-quinoline alkaloidal group	Berberine, Noscapine.
		Tropane class of alkaloids	Scopolamine
		Quinoline alkaloidal class	Skimmianine, Cusparine.
		Quinolizidine Alkaloids	Matrine, Lupinine.
		Purine alkaloid	Caffeine, Theobromine.
		Pyrrolizidine alkaloid	Retronecine, Platyphyline.
		Imidazole alkaloids	Pilocarpine.
		Pyrrolidine alkaloids	Nicotine
Indole alkaloids	Among the alkaloid substances, it is the most significant group. They have a 5 membered pyrrole ring with a basic nitrogen atom and one pentacyclic ring.	Non-isoprene indole alkaloids	Harmine, Mahanine.
		Semi-terpenoid indole alkaloids	Ergotamine, Ergobasine.
		Mono-terpenoid indole alkaloids	Ajmaline, Vinca alkaloids, Ibogamine.
Pseudoalkaloids	They originate from precursors or post-cursors of amino acids through transamination or amination process linked to amino acid pathways rather than directly from them. It is also produced from non-amino-acid precursors. Both acetate and phenylalanine can be used for producing it.	Steroidal alkaloids	Solanidine, Cyclopamine.
		Diterpenes	Delphinine.
Proto-alkaloids	Their source is amino acids, and although they include a nitrogen group, but it is not found inside the heterocyclic ring. They help in treating a variety of health issues, including pain, mental illness, and neuralgia. Tyrosine, Tryptophan, or phenylalanine amino acids that has aromatic side chains are	Phenylethylamine derivatives	Tyramine, Mescaline.
		Colchicine derivatives	Colchicine, Colchamine.
		Muscarine	Muscarine, Allomuscarine.
		Benzylamine	Capsaicin, Vanillylamine.

	generally the chemical sources of Proto-alkaloids.		

Plant-Derived Alkaloids in Cancer Therapy

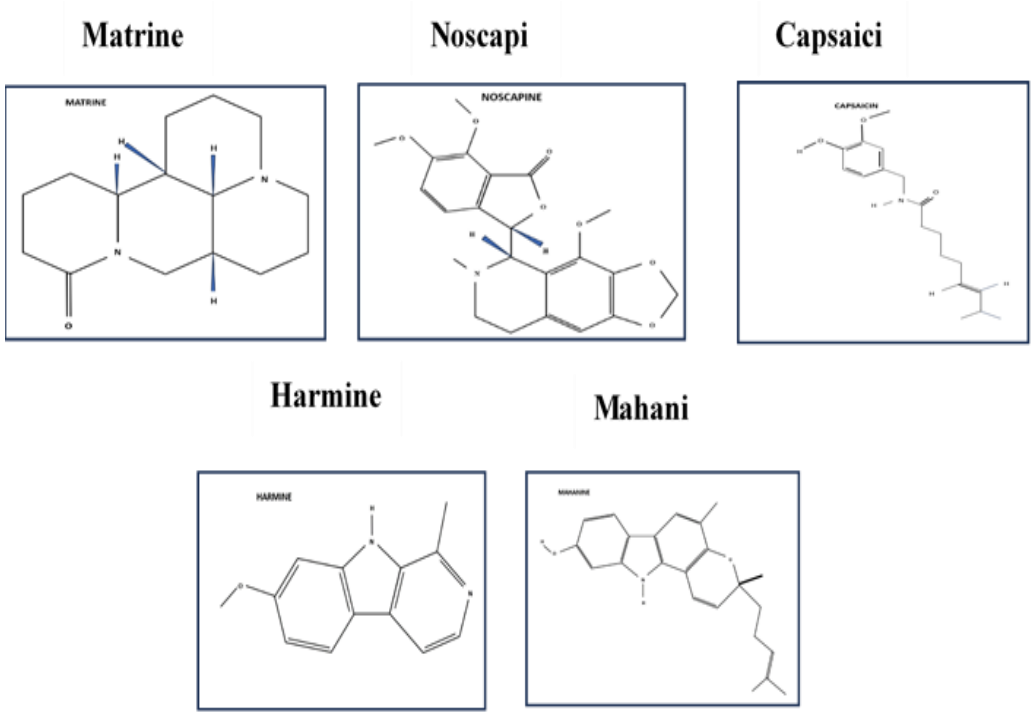

Figure 1. Molecular Structure Alkaloids

Table 2. Classification Based on Location of the Nitrogen Atom

Type	Feature	Group	Example
Heterocyclic alkaloid	The nitrogen atom is located within the heterocyclic ring.	Mononuclear	Boldine
		Polynuclear	Reserpine
Non-Heterocyclic alkaloid	Though it is not on the heterocyclic ring, the atom of nitrogen is there in the aliphatic chain.	Phenylethylamine Skeleton	Ephedrine
		Tropolone Skeleton	Colchicine
		Modified Diterpenes	Paclitaxel

Matrine (MT)

Symbolic Representation: $C_{15}H_{24}N_2O$,
Atomic Mass: 248.36 g/mol

Matrine is the most significant bioactive constituent in Kushen, which is an alkaloid referred to as tetracyclo-quinolizindine. It is found in the *Sophora flavescens* plant, which is broadly used in Chinese herbal medicine. Sophora root is utilized in herbal treatments in China, Japan, and certain European countries. More than 1g of matrine can be obtained from 1kg of Kushen[17].

Impact of Matrine on mda-mb-231 & mcf–7

According to new research, Matrine may have anti-tumor, anti-oxidant, anti-fibrotic, antiviral, anti-inflammatory, antimicrobial, anti-allergic, cardioprotective, antinociceptive, hepatoprotective, and neuroprotective characteristics which have been explored through experimental studies. These activities

include triggering apoptosis, inducing the differentiation of cancer cells into normal cells, blocking specific enzymatic actions, preventing DNA synthesis in cancer cells, influencing tumor metastasis and cell cycle arrest, controlling the expression of factors linked to tumours and telomerase activity [18]. It has been shown that matrine effectively inhibits the breast cancer development in MCF-7 cells in a dose- and time-dependent manner. The inhibition rates of MCF-7 cells were found to be 6.01%-37.01%, 7.56%-53.92%, and 10.86%-70.23% after 24, 48, and 72 hours, respectively, following matrine treatment [19].

Numerous studies have demonstrated that MT inhibits the progression of the cell cycle at many phases, resulting in an increase in the G0/G1 phase and a decrease in the S phase in MCF-7 and MDA-MB-231 cells, hence preventing cell division. It has been shown that MT efficiently inhibited the invasion of MDA-MB-231 cells in vitro by lowering the activation of MMP-2/MMP-9 (matrix metalloproteinase-2 and metalloproteinase-9) proteins, lowering the activities of p65, VEGFR1, and epidermal growth factor (EGF), and increasing AKT phosphorylation [20]. It was found that Bax (BCL2-associated X protein) and Bcl-2 (B-cell lymphoma 2) were both up-regulated in breast cancer MCF-7 cells, which promoted apoptosis. In MCF-7, MT administration inhibits the Bcl-2 protein linked to the AKT signaling pathway, which has anti-cancer properties. When the cancer cells were treated to matrine, their Bcl-2/Bax protein and mRNA proportions reduced, which in turn caused apoptosis and cell cycle inhibition [21].

This miR-21/PTEN/Akt pathway was discovered to be a signaling mechanism underlying the growth suppression mechanism of matrine's anticancer activity. Matrine also decreased MCF-7 cell growth in a time- and dose-dependent manner by inducing cell cycle arrest in the G1/S phase and promoting apoptosis. Furthermore, by decreasing the levels of miR-21, matrine resulted in the enhancement of PTEN (Phosphatase and Tensin homolog) [22]. IL-17A and salivary 1-25dihydroxycholecalciferol levels show a negative correlation during orthodontic treatment phases, indicating that vitamin D administration may hasten tooth movement while minimizing tissue injury [23]. It has been proposed that matrine regulated the downstream apoptotic components of the PI3K/AKT signal pathway to induce MCF-7 cell growth inhibition, and reversal of multidrug resistance for breast cancer cells [24].

Toxicity

The therapeutic use of MT has been limited due to reports of its neurotoxic effects and significant side effects, such as hepatotoxicity, neurotoxicity, and toxicity to the reproductive and developmental systems. A Research found MT suppressed the central nervous system of ICR mice. When given at doses of 10 and 40 mg/kg/day for 60 days, it reduced their coordination as well as balance, indicating that one of MT's main organs of concern is the neurological system [25]. miRNAs are important in OPMDs because they have the potential to be both therapeutic targets and diagnostic indicators [26].

Noscapine:

Molecular formula: $C_{22}H_{23}NO_7$

Molecular weight: 413.4 g/mol

Papaver somniferum, often known as the opium poppy, contains this phthalideisoquinoline alkaloid, which has a number of medical applications [27]. For decades, noscapine has been used to suppress coughs. Noscapine, a chemical, enhanced the expression of Bax protein in MCF-7, and MDA-MB-231, whereas decreased the Bcl-2 expression [28]. Noscapine, according to Quisbert-Valenzuela, increased the protein expression and expression of the Bax gene in three cell lines while decreasing the expression of the Bcl-2 protein and Bcl-xL gene in breast

cancer cell lines. This implies that noscapine was an efficient anticancer agent that initiated programmed cell death in breast cancer cells whereas having less toxicity in typical cells. Consequently, the Bax/Bcl-2 ratio increased in all three cell lines. This medication upregulated the expression of the caspase-8 and caspase-9 genes in MDA-MB-231 and MCF-10F. Additionally, it enhanced caspase-8 breakdown, showing that the presence of both intrinsic and extrinsic apoptosis pathways is likely responsible for the noscapine-induced apoptosis [28].

According to cell cycle analysis, Cancer stem cells (CSCs) treated with noscapine underwent a significant transition from a quiescent cell cycle state in G0/G1 (46% for MDA-MB-231 and 59% for MCF-7), S phase (42%, 35%), and G2/M (12%, 6%) to a cycling state with an increase in G2/M (32%, 37%) and a subsequent decrease in G0/G1 (40%, 43%). These discoveries demonstrate that noscapine causes CSC cell cycle inhibition in the G2/M phase. In MCF-7 and MDA-MB-231, noscapine has strong dose-dependent anti-proliferative effects [30]. Apart from triggering apoptosis, Noscapine also stops dividing cells in their metaphase and elevates them in the G2/M phase [31].

Toxicity

In general, a small proportion of people experience nausea and stomach pain after taking noscapine hydrochloride. Research conducted on people and animals has verified its incredibly low toxicity, minor side effects, and little to no influence on blood parameters and vital organs [32].

Capsaicin

Chemical formula: $C_{18}H_{27}NO_3$

Molecular Mass: 305.4 g/mol

The primary component of chilli peppers' fiery, pungent flavour, capsaicin, is an alkaloid (capsaicinoid) that belongs to the capsicum family.

Based on a range of studies, two apoptotic pathways—death receptor-dependent (extrinsic) and mitochondria-dependent (intrinsic) — have been identified based on the response to anticancer medications. These pathways are given below in Figure 2 and Figure 3 respectively [33].

Capsaicin hinders the survival of breast cancer cells by disrupting the signaling cascade of CDK8/PI3K/Akt/Wnt/β-catenin [34].

Paradoxical effects

Due to its irritating and spicy properties, capsaicin can lead to cancers. The impact of capsaicin on carcinogenesis from animal research discovered that capsaicin itself was mutagenic and enhanced tumor growth. Human cancer risk has been associated with consumption of chili peppers. However, some researchers demonstrated that capsaicin's in vitro action on apoptotic induction inhibits the proliferation of immortalized or malignant cells. Hence, proving capsaicin's anticarcinogenic and anti-mutagenic properties [35].

Toxicity

Consuming high quantities of peppers by adults or moderate amounts by children might result in nausea, vomiting, gastrointestinal discomfort, and extremely hot diarrhoea. Furthermore, they create undesirable burning or stinging effects on the skin [27]

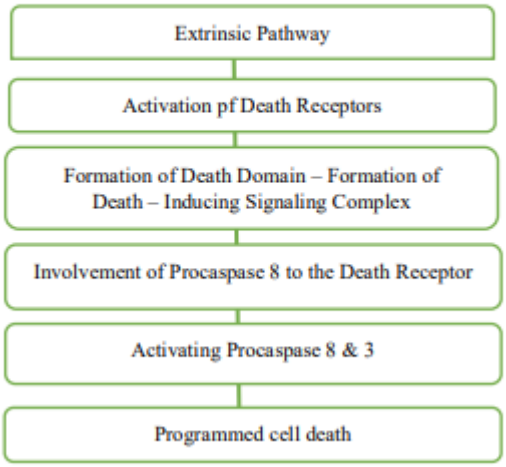

Figure 2. Extrinsic Pathway

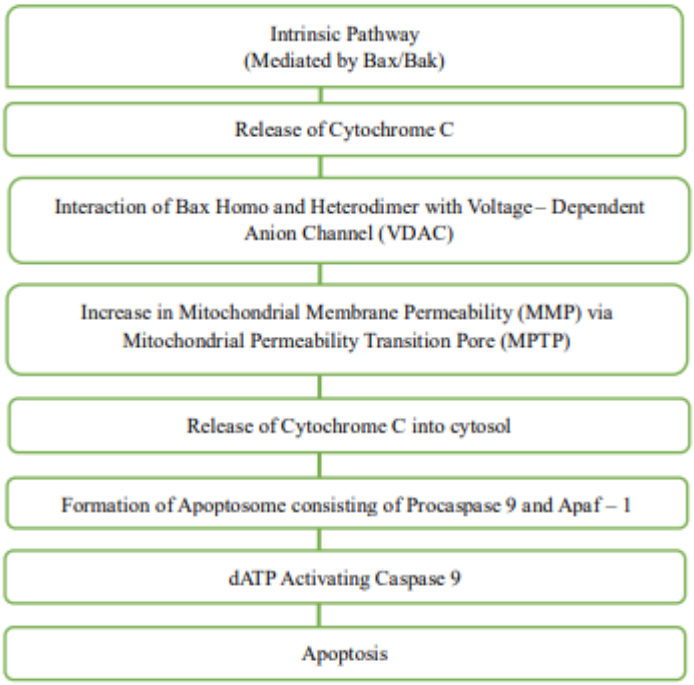

Figure 3. Intrinsic Pathway

Harmine

Symbolic Representation: $C_{13}H_{12}N_2O$

Molecular mass: 212.25 g/mol

The beta-carboline alkaloid known as "harmine" was extracted from Peganum harmal seeds. Various medicinal properties exhibited by harmine include antibacterial, hallucinogenic qualities, antifungal, anticancer, antioxidant, cytotoxic, antiplasmodial, antimutagenic, and antigenotoxic [36]. Breast Cancer Resistance Protein (BCRP) defends against cytotoxicity in healthy cells, tissues, and organs. It removes anticancer medications from the cells. To resensitize BCRP-mediated resistance, reversal drugs are required. Harmine decreased BCRP-mediated drug efflux and increased the cytotoxicity of anticancer drugs in the breast cancer cell line MDA-MB-231, which overexpresses BRCP [37].

It was discovered to decrease migration and proliferation in a dose- and time-dependent manner. Apoptosis of cells was markedly enhanced by HM. According to research, it is used in conjunction with further chemical medications to prevent the progression and spread of cancer by the downregulation of TAZ. Through experiments, it was revealed that overexpressing transcriptional co-activator with PDZ-binding motif (TAZ) reduced the antiproliferative and pro-apoptotic actions of HM [38].The proliferation and invasion of cancer cells are enhanced by the epithelial-mesenchymal transition (EMT). With the support of the EMT, cancer cells can attack and increase by breaking the cellular framework. The mesenchymal biomarkers N-cadherin and Vimentin were supressed after harmine administration, while the epithelial biomarker E-cadherin increased in a dose-dependent manner. Consequently, harmine could potentially stop breast cancer cells from undergoing EMT [39].

Harmine inhibits the EMT, invasion, and metastasis of MDA-MB-231 and MCF-7 breast cancer cells by raising the phosphorylation levels of TAZ and blocking its nuclear localization [40].

Toxicity

In spite of its unique anticancer efficacy, the application of harmine is restricted due to its and severe side effects including neurotoxicity, and low solubility [40]. Symptoms begin at 3 mg/kg of harmine which is highly toxic to humankind. These symptoms include behavioural changes such as restless nights, tremors, nausea, vomiting, and digestive issues [27].

Mahanine

Chemical formula: $C_{23}H_{25}NO_2$

Molecular mass: 347.4 g/mol

The *Murraya koenigii* (curry tree) leaves are abundant in alkaloids that possess anticancer, anti-analgesic, antiulcerogenic, and anti-obesity properties [41].

Cancer cells have been discovered to exhibit extremely increased proteasome activity, which is required for survival and growth. Tumour cell death is caused by proteasome inhibition, and the proteasome is considered the potential molecular target for anticancer medications [42]. A distinguished suppression of the 26S proteasome was associated with this growth-inhibitory activity [43]. MH has cytotoxic efficacy against several types of cancer cells by downregulating the STAT-3 pathway, releasing reactive oxygen species, and significantly activating extrinsic and intrinsic apoptotic signaling pathways including p53 signaling. After MH treatment, there was a reduction in the expression of the anti-apoptosis protein Bcl-xL and the initiator cascade Caspase 9[44], as well as a suppression of complex-III activity, AKT/mTOR signaling, RASSF1A, and Hsp90-Cdc37 complex activity [45].

Additionally, MH-mediated cleaved PARP at higher doses and decreased expression of the DNA-repairing enzyme PARP and enhanced the MDA-MB-231 and MCF-7 programmed cell death mechanism [46]. At higher doses, the MH induced cell cycle arrest in G0/G1 and apoptosis with reduced expression of Caspase 9, PARP, Bcl-xL, and elevated levels of cleaved p21Cip1, PARP, and p27Kip protein, indicating a common molecular mechanism [45].

The steady growth of the G1 phase in the cell cycle depends on cyclin D1, and its reduction resulted in the release of sequestered CDK inhibitors, p21Cip1, p27Kip1, and eventually G0/G1 arrest which leads to apoptosis [47]. One feature of CSCs, especially in breast cancer, is the capacity to develop into mammospheres. MH has the capacity to prevent breast cancer stem cells (bCSC) from proliferating. In both cell lines, MH produced dose-dependently significant reductions in the formation of both first and second generation mammospheres [48].

The plasma biomarkers miRNA 21, miRNA 184, and miRNA 145, which are circulating exosomal miRNAs, have the ability to detect leukoplakia, OSMF, and OSCC patients who are at a high risk of developing malignant transformation [49].

Conclusion

With increasing industrialization and changing lifestyles, the prevalence of cancer, particularly breast cancer, is expected to rise. Current anticancer therapies, though effective, face challenges such as high costs, toxicity, and adverse side effects. This underscores the need for alternative treatments, especially from plant-derived sources. Alkaloids, with their diverse biological activities—such as inducing apoptosis, reducing tumor growth, and inhibiting cell proliferation—show great promise as therapeutic agents for breast cancer. Alkaloids like matrine, noscapine, capsaicin, harmine, and Mahanine have demonstrated potential in targeting key cancer pathways and may be valuable in combination therapies. However, their pharmacological limitations including low bioavailability and potential toxicity, etc. necessitate future research and clinical trials to optimize dosage, administration, and safety. Ongoing research on alkaloids could lead to more effective and less toxic treatments, improving breast cancer outcomes.

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Conflict of Interest

There exist no conflicts of interest, as stated by the authors.

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