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ANDROGRAPHIS PANNICULATA: A REVIEW ON ITS ANTICANCER POTENTIAL

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ABSTRACT

Since the beginning of time, people have utilized medicinal herbs to heal various ailments. People all across the world are impacted by the common problem of cancer. Research into new drugs to combat cancer is still underway, although the use of natural chemicals derived from plants in cancer chemotherapy has increased significantly in recent years. Andrographis paniculata (Brum. F) Nees is a well-known plant that has been studied as a possible cancer treatment in traditional Chinese and Indian medicine.

Owing to these characteristics, A. paniculata is a viable choice for a plant-based anticancer drug. A. paniculata has a variety of pharmacological actions. This overview includes comprehensive information on the primary phytochemicals, their historical applications, pharmacology, and the purifying procedure used to extract them from A. paniculata. Its main active phytochemical, andrographolide, has been shown to have significant anticancer effects. These characteristics of A. paniculata make it a strong contender for a potential anticancer medication produced from plants.

Medicinal plants have been used to treat illnesses since the prehistoric era. Cancer is a widespread issue that affects people all around the world. Recent years have seen a significant increase in the use of plant-derived natural compounds in cancer chemotherapy, and research into novel cancer-fighting medications is still ongoing. Researchers are looking into the highly known plant Andrographis paniculata (Brum. F) Nees

in the context of traditional Chinese and Indian medicine as a potential cancer therapy. Due to these qualities, A. paniculata is a promising option for an anticancer medication generated from plants.

The pharmacological effects of A. paniculata are multifaceted. In-depth details about the main phytochemicals, historical uses, pharmacology, and purification process of phytochemicals from A. paniculata are provided in this overview. There have been notable anticancer effects demonstrated by its primary active phytochemical, andrographolide. These qualities of A. paniculata make it a potent candidate as a prospective plant derived anticancer drug.

Keywords: Medicinal plants; Phytochemicals; Andrographis paniculata; Anti-cancer; Andrographolide; Immunomodulatory

1. INTRODUCTION

Since ages, traditional medicinal system has been built on the foundation of plants. Worldwide, the use of herbal and botanical compounds from traditional medicine has prominant effects on health alignments. One of the most significant plants utilised historically for geographic dispersion in Ayurvedic (Indian medicine) and herbal medicine in Thailand and China is Andrographis paniculata (Family: Acanthaceae). The active ingredient, andrographolide, is taken from the portions of the plant that are above ground and tastes quite bitter. It is a bicyclic lactone that is two-dimensional and has a wide range of pharmacological actions **(Figure 1)**. This diterpene lactone is a member of the naturally occurring isoprenoid product family. Typically, isoprenoids are converted to isopentenyl and dimethylallyl pyrophosphates by the mevalonic acid pathway.

All andrographolide precursors are synthesized via the mevalonic acid pathway. Current studies aimed at eliciting novel therapeutic actions and their mode of action have opened up new possibilities for its possible future uses. In order to create a solid foundation for future advancements in the study of herbal drugs, an approach was taken to summarise the therapeutic potentials of andrographolide in both conventional applications and evidence-based research findings **[1-9]**.

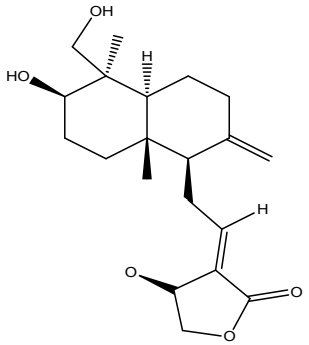

Figure 1: Andrographolide

2.The role of Andrographolides in biology

Various investigations have demonstrated the outstanding effects of andrographolide extract

in the treatment of cancer. Andrographolide and A. paniculata both functioned in two ways. These are the induction of the nonspecific immune response, which deals with the killing of invaders by macrophage cells, and the induction of the antigen-specific immune response, which involves antibodies produced to combat the invasive bacteria. It works well against cancer and a variety of infections because A. paniculata activates both responses. Treatment with andrographolide decreased the proliferation of several cytotoxic cell lines, which represent distinct cancer types, in vitro.

2.1 Lung Cancer

By using a lung tumour mouse model produced in human vascular endothelial growth factor (VEGF-), 's anti-lung cancer activity of andrographolide was investigated. These findings show that, andrographolide decreased the expression of VEGF- in lung Clara cells. Similar to this, andrographolide inhibits the growth of tumours by lowering the transcriptional and translational levels of VEGF, EGFR, Cyclin A, and Cyclin B expression. These findings suggest that in transgenic mice, over expression of VEGF can inhibit the cell cycle and cause lung tumours. In conclusion, andrographolide's ability to inhibit angiogenesis and act as a chemotherapeutic agent may prove useful in the future for the treatment of lung tumours **[10]**.

To demonstartae andrographolide's impact on the proliferation of H3255 non-small cell lung cancer cells (NSCLCC), testing was also done on the expression of transforming growth factor β1 (TGF-β1), vascular endothelial growth factor (VEGF), and protein kinase C (PKC) activity. For this, throught a full day, H3255 cells were exposed to 1.0, 2.5, or 5.0 μ MAD. To verify the vitality of the cells, the MTT experiment was done. Using ELISA, the levels of TGF-β1 and VEGF were found. Testing was done on PKC and ATPase activity. Cell viability is decreased by EA treatment in a concentration-dependent manner, which lowers Na (+) - K (+) - ATPase activity ($P < 0.05$). Moreover, EA causes more DNA fragmentation and lactate dehydrogenase to be released. Lung decreased protein kinase C activity and TGF-β1 and VEGF levels in H3255 cells ($P < 0.05$). By reducing the levels of VEGF and TGF-β1, EA inhibits the growth of lung cancer cells in a concentration-dependent way. As a result, EA is found to be a useful medication to treat lung cancer **[11]**. Andrographolide is found to be one of the main diterpene lactones in the plant andrographis paniculata which is a powerful inhibitor of numerous malignancies. The effect of andrographolide on lung cancer in a

rat model of lung tumours is produced by human vascular endothelial growth factor which is A165 (hVEGF-A165). These findings demonstrated that, in contrast to the placebo group, Clara's lung cells' production of VEGF-A-165 was considerably decreased by the androgen system. By decreasing EGFR, VEGF, cyclin A, and cyclin B expression at the transcriptional and translational levels, andrographolide also inhibited the growth of tumours. According to these research, androgenic therapy disrupt the cell cycle, causing lung tumours in transgenic mice with elevated VEGF expression. Because of this, chemotherapy plus antiangiogenic andrographolide may one day be used to treat lung cancer **[12]**.

2.2 Breast Cancer

Researchers looked into the precise processes underlying andrographolide's possible impacts on the development of breast cancer and its ability to block neovascularization. The results of this study highlight the potential anticancer effect of andrographolide, which can suppress COX-2 production by lowering PX-HAT activity and preventing angiogenesis via the VEGF route. Treatment for breast cancer may involve cancer medicines **[13]**.

The impact of andrographolide on MW-MB231 of A431 and the SKOV-3 cell line on NFkB activation mediated by caspase-8 apoptosis, pyroptosis, and axon matrix breakdown (ECM). The findings demonstrated that andrographolide blocks NFRB signalling, which in turn prevents tumour cell lines from growing. The expression of tissue inhibitor metalloproteinase-1 (TIMP1) increases considerably with increasing concentrations of andrographolide. TIMP1 induction prevents ECM breakdown and matrix metalloproteinase-7 (MMP-7) from acting on the cells. Andrographolide demonstrates cytotoxicity via the NFkB signalling pathway and does not produce microbial toxicity to tumour cells so prevents the growth of breast and ovarian cancer by suppressing the expression of MMP-7 by overregulating TMPP1. This medication is intended to treat breast and ovarian cancer **[14]**.

In vitro and in vivo studies of andrographolide diterpene lactone demonstrates anticancer activity against cellular models of myeloid leukaemia (M1) and breast cancer. A semisynthetic derivative of andrographis was found to be effective in vitro against the A549 cell line (ATCC) (NSCL carcinogenesis) in this investigation. Compounds 3-5 exhibited the highest activity during differential testing, with IC50 values of 21–31 µl G/ml **[15]**.

The most common cause of mortality for women is breast cancer. It happens as a result

when breast epithelial cells proliferation reaches out of control. Because herbal medicine has no negative side effects, it is more successful than synthetic drug therapy. As cleared by several experiments andrographolide is the active ingredient which can prove a successful tool for treatment of breast cancer. When the cell cycle inhibitor protein p27 is inhibited, four cyclin-dependent kinases (CDK4) are less expressed and the G0/G1 phase of the breast cancer cell cycle is disrupted. Additionally, by means of the box and dorsal induction, it triggers the congenital apoptotic pathway. It raises the expression of the p53 gene and caspase synthesis. Andrographolide prohibits the blood vessel growth and metastasis in breast cancer. A significant advancement in the management of breast cancer has been made possible by the use of synergistic androgenic therapy in conjugation with the synthesis of androgenic nanoparticles and other chemotherapy drugs **[16]**.

2.3 Gastric Cancer

The mechanism which prevents androgens from causing gastric cell growth and metastasis is the SGC7901 infected cell line to investigate andrographolides' anti-cancer properties. Investigations were conducted on protein-mineral activity, cell death, cell cycle, cell migration and matrix invasion, and cell survival. Furthermore, evaluated the levels of mRNA and protein expression using real-time PCR and Western blot, respectively. As the concentration of androgen increased, cell viability reduced in a dose-dependent manner. Using flow cytometry, apoptosis was observed to produce consistent findings. In addition to improving G1/M wound healing by increasing the capacity ratio of retained cells, andrographolide therapy also inhibited the G2/M2 cell cycle and decreased cell invasion, migration, proliferation, and cell cycle disruption in addition to death. Among all, the mechanisms include top-down expression of MMP-2/9, down-regulated expression of TIMP-1/2, cyclin B1, p-Cdc2, Bax, and Bc, and cellular protein Bcl-2 **[17]**.

2.4 Cholangiocarcinoma

HepG2 and SK-Hep1 cancer cells in the liver are successfully inhibited from growing by an extract of Andrographis paniculata. A range of developmental inhibitory activities are included in the bile ducts (HuCCA-1 and RMCCA-1 14-deoxy-11, 12-didehydro andrographolide, neo andrographolide, and 14-deoxyandrographolide) caused apoptosis in HuCCA-1 and RMCCA-1 cells and inhibited the G0/G1 and G2/M phase cell cycles. The ethanolic extract of andrographis P. decreased the expression of Bcl-2, cyclin D1, and caspase-3's inactive enzymatic form

and9 increase in anxiety coincided with the true leaf stage therapy during the acquisition of apoptotic proteins **[18]**.

The chemically active substance andrographolide, is responsible for a number of malignancies to assess and comprehend the underlying mechanisms of andrographolide's anti-tumor effect against cholangiocarcinoma (CCA). A variety of cholangiocarcinoma (CCA) cell lines, including Huanga-1, KKU-100, KKU-M213, and RMCCA-1, have been used to study the antiproliferative action of andrographolide. Likewise mechanism has been investigated in relation to KKU-M213 cell migration and metastatic activity. The findings demonstrated that at inhibitory proliferation concentrations of 50% (IC50) of approximately 120 μM, andrographolide lowered the proliferation of CCA cells. Furthermore, andrographolide prevents CCA cells from migrating and penetrating. According to previous research, andrographolide controls and lowers the expression of the tightly bound protein claudin-1.

Andrographolide phosphorylated protein kinase P-38 and N-terminal kinase (JNK) (MAPK), CCA cells' capacity to migrate and express claudin-1 were both restored after receiving treatment with a P-38 inhibitor with the help of metabolic mechanisms. This study shows that andrographolide may have anticancer effects by blocking claudin-1 and stimulating the MAPK C-38 signalling pathway, which in turn inhibits CCA cell translation. This contributes to the development of a different CCA treatment **[19]**.

2.5 Leukemic Cancer

In vitro tests were performed to determine the cytotoxicity of Andrographis paniculata ethanol extract and main diterpenoid components in different tumour cells. Following a 24-hour treatment period, it had a significant inhibitory effect on the growth of HL-60 cells in human acute myelogenous leukaemia, with an IC 50 of 14.01mol/mL. Andrographis paniculata and andrographolide had the maximum amount of cytotoxicity among the three primary dimers, followed by deoxyandrographolide and the least effective neoandrographolide. The presence of dye fragments in the DNA is indicated by confocal laser imaging and gel electrophoresis, which suggests cell death. G(0)/G(1) phase cells showed a rise from 51.88% to 78.69% following a 36-hour Andrographolide therapy.

In inhibitory cells, G(0)/G(1) phase arrest and apoptosis were linked to the loss of C mitochondria, a rise in Bax, and a decrease in Bcl-2 protein expression. Although the exact

order of all these events is uncertain, we deduced that andrographolide and EPA suppress the cell cycle and control the expression of specific pro-apoptotic markers in HL-60 cells, which in turn affects the endogenous mitochondrial pathway **[20]**. The pre-treatment of U937 with andrographolide first at a low dose of TP demonstrated an improved apoptosis induction impact when compared with the application of each chemical independently. This combination seems to work better together because it activates more intrinsic mitochondrial pathways, such as upregulating Bax, breaking up of PARP to release cytochrome C, and cleaving various caspases into their active forms, particularly caspase -3 and -9. With minimal toxicity, this new combination can be employed as a novel clinical chemotherapeutic approach to treat AML and improve PT's therapeutic efficacy. Additionally, it may be utilised as a treatment option for additional drug-resistant malignancies after more study and analysis **[21]**.

2.6 Renal Carcinoma

With minimal damage to healthy tissue, TRAIL—tumor necrosis factor-related apoptosis-inducing ligand—induces apoptosis in tumour cells. Accumulating data, however, indicates that not all tumours are resistant to TRAIL signalling. TRAIL-mediated growth typically inhibits the development of human renal carcinoma (CRC) cells. In RCC, the test resistor is rejected. Inhibiting MTS crystalline cell viability and EdU crystalline dose-dependent growth, TRAIL and andrographolide together stop RCC birth and migration. According to flow cytometry and ageing, andrographolide dramatically enhances TRAIL-mediated cell cycle arrest during the G2/M phase. Also, Andrographolide has access to the TRAIL signal transmission. It activates the apoptotic copy determined by immunoblotting. The TRAIL receptor, a non-DR5 death receptor (DR) 4, has been shown to interact significantly with Andrographolide in RCC cells and contribute to Andrographolide's role as a sensitizer to TRAIL. The study showed that the combination of Andrographolide and Trail has potential therapeutic value in kidney cancer **[22]**.

2.7 Bladder Cancer

An effective treatment that specifically destroy cancer cells while sparing healthy cells is called tumour necrosis factor-related apoptosis-inducing ligand, or TRAIL and TRAIL resistance is observed in certain cancer cells. Some scientists discovered andrographolide, a diterpenoid lactone that is isolated from the traditional herbal remedy

Andrographis paniculata. This drug is TRAIL sensitive and is excellent for treating bladder cancer. The combination of andrographolide and TRAIL lowers colonisation, slows down T24 cell development, prevents proliferation, blocks migration, and fastens caspase-mediated death, according to the data. How to rely on p53 and TRA53. It's significant to note that andrographolide may also inhibit the NF-B signalling pathway by downregulating the p65/Rela transcript.

This results into a rise in cytotoxicity mediated by TRAIL. These outcomes imply that TRAIL-mediated endoscopic-sensitive bladder cancer cells have a non-toxic dosage that is TRAIL-mediated and can effectively treat TRAIL-resistant human bladder cancer **[23]**.

2.8 Prostate Cancer

A potential therapeutic for cancer is factor-related apoptosis-inducing ligand, or TRAIL. The targeted treatment requires the identification of small compounds that can ascertain whether prostate cancer (PCA) cells are susceptible to TRAI-induced apoptosis. Using flow cytometry, a model of nude mouse PCA xenograft dissection was created to assess caspase-3 activity in cancer cells. The findings indicated that andrographolide enhanced PCa cells' susceptibility to TRAIL-induced apoptosis, ideally at anti-toxic doses, and that enhanced DR4 regulation was linked to the regulatory mechanism. In addition, it causes cells to produce reactive oxygen species (ROS) and upregulates the expression of p53. The reduction of TRAIL and andrographolide-induced cell death in PCa cells can be achieved by dramatically lowering the expression of DR4, p53, and ROS generation. Thus, by producing ROS and rearranging p53, ANDRO sensitises PCA cells to TRAIL-induced apoptosis, increasing PCA cell death linked to DR4 activation **[24]**.

2.9 Osteosarcoma

Insufficient long-term survival has been observed in patients with osteosarcoma over the previous few decades, despite it being the most frequent primary bone weakening. Andrographolide is known for its amazing anticancer properties against a variety of malignancies and a classic herb used in herbal medicine. That being said, not much is known about the mechanisms underlying andrographolide's usefulness in treating osteosarcoma. By inhibiting the cell cycle at the G2/M phase and promoting caspase-mediated apoptosis, andrographolide limits the growth of osteosarcoma cells, as per the studies. Reactive oxygen species (ROS) were also produced at higher levels when andrographolide treatment JNK was activated. In osteosarcoma cells,

andrographolide triggered apoptosis, which was entirely reversed by the ROS scavenger and somewhat reversed by the JNK inhibitor. Additionally, the ROS sensor was utilised to halt JNK activation and the cell cycle arrest during the GOS/M phase. Andrographolide was also demonstrated to raise ROS levels and activate JNK in vivo to restrict the growth of tumours. Andrographolide disrupts G2/M in osteosarcoma cells by controlling the ROS/JNK signalling pathway, which results in cytotoxicity in early osteosarcoma cells. As a result, andrographolide shows promise as an anticancer treatment for osteosarcoma **[25]**.

2.10 Colon Cancer

Human colorectal cancer (CRC) is largely driven by the Wnt/W chain signalling system, which is also a primary target for CRC chemotherapeutic drugs. The impact of cancer and the molecular processes that validate its involvement in the Wnt/β-catenin pathway and 19-O-triphenylmethyl andrographolide (RS-PP-050), an analogue of andrographolide. It has been demonstrated that RS-PP-050 inhibits CR-HT-29 cell survival and proliferation.

It causes cell cycle disruption and cell death linked to p53 and PARP-1 activation. Additionally, RS-PP-050 enhances N-catenin expression and inhibits the activity of intracellular T cell factor/lymphocyte growth factor (TCF / LEF), which in turn prevents catenin transcription. It functions independently of the GSK-3ive Wnt inactivity modulator, RS-PP-050 also lowers the expression of the active catenin protein. It's interesting to note that RS-PP-050 mostly prevents Ser675-catenin from being phosphorylated. This may cause disruptions to the chain's nuclear transport and ultimately lead to its deactivation **[26]**.

To know how andrographolide affects colon cancer, researchers looked at the potential for andrographolide to provide chemical defence in HT-29 colon cancer cells. Using MTT, trypan dehydration, colony composition, and physiological examination, the cytotoxic capability of andrographolide was ascertained against HT-29 cells. To identify apoptosis DAPI and Hoechst staining, DNA fragmentation testing, and the Caspase-3 test were commonly used. Alterations in mitochondrial potential was determined by flow cytometry analysis with the help of Mito Tracker Red CMX and Rytamine 123, features of cell cycle regulation and Ros staining. According to studies, andrographolide reduces HT-29 cell viability in a dose- and time-dependent manner.

Likewise, andrographolide causes HT-29 cells to undergo apoptosis. This seems to be connected to both the inactivation of the

mitochondrial membrane potential and increased intracellular ROS levels. It's interesting to note that andrographolide significantly arrests the cell cycle at high doses in the G0/G1 phase and low levels in the G2/M phase. The results of tests demonstrate that andrographolide inhibits the growth of HT-29 colon cancer cells and induces apoptosis **[27]**.

2.11 Ovarian Cancers

The influence of andrographolide on the caspase-8 apoptotic cascade in MR-MB231 of the A431 extracellular matrix (ECM) is investigated on the cell line SKOV-3. The result indicated that ANDR blocked NFkB signalling, which in turn restricted the tumour cell line growing. A significant decrease in melanoma and brest cancer was observed by Phosphodiesterase (P65) against A431 and MDA-MB231 with r ANDR levels, respectively.

So the, treatment with andrographolide boosted the expression of caspase-8 but did not significantly raise the expression of caspase-1. Tissue Inhibitors of Metalloproteinase-1 (TIMP1) expression was found to be remarkably elevated upon increasing the concentration of andrographolide. Matrix metalloproteinase-7 (MMP-7) activity is inhibited by TIMP1 upregulation, which also inhibits ECM breakdown. As andrographolide slows the growth of breast and ovarian cancer attacks by reducing MMP-7 expression through overregulation of TIMP1, which is likely to be present in the ovary as it is cytotoxic to cancer cells through the NFkB signalling pathway without causing prostatitis **[28]**.

2.12 Other Cancers

According to reaserch and studies Andrographis paniculata was found to possess anticancer and immunosuppressive properties in human immune cells. The methanolic extract of Andrographis paniculata was subjected to bioactivity check, for that the extract was divided into dichloromethane, petroleum ether, and aqueous extracts. The dichloromethane fraction of methanol extract has potent ingredients that boost immunological function and enhances anticancer action. The dichloromethane fraction promotes the proliferation of human peripheral blood lymphocytes (HPBL) at minimal concentrations, while suppressing the growth of HT-29 cells, which are associated with colon cancer**.** The three compounds—andrographolide, 14-deoxyandrographolide, and 14-deoxy-11,12-didehydro andrographolide, were extracted from the dichloromethane extract. Research has demonstrated that andrographolide exhibits anticancer activity against different

types of cancer cells that are indicative of several human cancer types **[29]**.

3. CONCLUSION

A Well-known herbal compound andrographolide, which was extracted from Andrographis paniculata, is used to treat a variety of illnesses, including cancer. After Examining the medicinal possibilities of plant materials and determining whether pharmacodynamic research is presently a top priority for the development of drugs derived from natural resources, it is considered that the therapeutic potential of andrographolide's demonstrated clinical efficacy against various types of cancer. The compounds possess pharmacodynamic promise in combating several forms of cancer and other illnesses.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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