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Anti-Cancer Activity of Andrographolide: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author VY designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors VY, KW and SH managed the analyses of the study. Authors VY and NJPS managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Andrographolide, is a chemical compound obtained from the *Andrographis paniculata* (Family-Acanthaceae), maybe a diterpene lactone ring is responsible for various biological activities like anti-inflammation, anti-microbial anti-cancer, anti-obesity, anti-diabetes, anti-oxidant immunomodulatory, antiseptic, hypolipidemic, cardioprotective, hepatoprotective, neuroprotective effects and other biological activities. In Current research activities worldwide to exhibit the beneficial role of Andrographolide are continuously enriching the therapeutic arsenal of this important Phyto molecule. For this purpose, several databases were accustomed explore for the anticancer/cytotoxic effects of the andrographolide in pre-clinical and clinical studies. During this report, an attempt has been given to spotlight the research findings, related to therapeutic potentials and up-to-date development within the pharmacological activities of andrographolide. Andrographolide is often one of the potential agents within the treatment of cancer.

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1. INTRODUCTION

Plants were the basis of advanced systems of traditional medicine that have existed for thousands of years. Herbal and botanical ingredients from traditional health care still play an important role in medicine in many countries. Andrographis paniculata. (Family- Acanthaceae) is one of the most important plants traditionally used for geographic distribution in Ayurvedic (India) and herbal medicine in Thailand and Chinese. Andrographolide is an active substance extracted from the above-ground parts of this plant and has a very bitter taste. It is a two-dimensional bicyclic lactone with many pharmacological activities (Fig. 1). This diterpene lactone belongs to the family of natural isoprenoid products. Isopentenyl pyrophosphate and dimethylallyl pyrophosphate are usually synthesized from isoprenoids via the mevalonic acid route.

However, the majority of andrographolide precursors are synthesized through the mevalonic acid pathway. Recent researches conducted to elicit newer therapeutic activities and the mode of action has lead to open a new avenue for potential future applications of this useful Phyto molecule. An approach to sum up the therapeutic potentials of andrographolide was made in the light of traditional uses as well as evidence-based research findings for providing a strong database for the future development in herbal drug research [1-9].

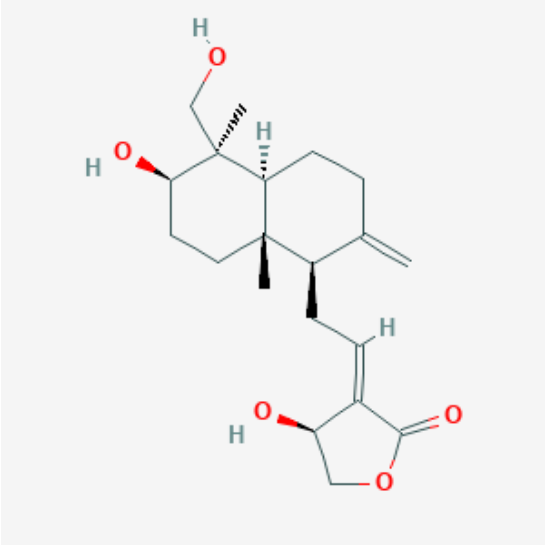

Fig. 1. Andrographolide

2. THE BIOLOGICAL ROLE OF ANDROGRAPHOLIDES

Andrographolide extract was shown to be impressive in the treatment of cancer in different experiments. A. paniculata and andrographolide worked in two ways. These are Activation of antigen-specific response that involves antibodies, which are made to counteract the invading microbes, and activation of the nonspecific immune response, which deals with the destruction of invaders by macrophage cells. Activation of both the responses by A. paniculata makes it effective against various infections as well as cancer. Andrographolide treatment inhibited the in-vitro proliferation of different cytotoxic cell lines, representing various types of cancers.

2.1 Lung Cancer

The anti-lung cancer effect of andrographolide was studied in a human vascular endothelial growth factor (VEGF-) -induced lung tumor mouse model. These results are indicate that the andrographolide significantly reduced the expression of VEGF- in Clara cells of the lung compared to the sham group. Similarly, andrographolide reduces tumor formation by reducing the expression of VEGF, EGFR, Cyclin A, and Cyclin B at the transcriptional & translational levels. These results indicate that andrographolide overexpression of VEGF can prevent cell cycle and induce lung tumors in transgenic mice. In conclusion, the anti-angiogenesis and chemotherapy potential of andrographolide may provide help for the treatment of lung tumors in the future [10].

To determine the effect of andrographolide on the growth of H3255 non-small cell lung cancer cells(NSCLCC). The expression of vascular endothelial growth factor (VEGF), and transforming growth factor β1 (TGF-β1), and protein kinase C (PKC) activity was also tested. H3255 cells were treated with 1.0, 2.5, or 5.0 μ MAD for 24 hours. Perform the MTT assay to check cell viability. The levels of VEGF and TGF-β1 were detected by ELISA. ATPase activity and PKC activity were tested. Treatment with EA reduces cell viability in a concentration-dependent manner, resulting in a decrease in Na (+) - K (+) - ATPase activity ($P < 0.05$). EA also increases the level of DNA fragmentation and the release of lactate dehydrogenase. EA also

reduced VEGF and TGF-β1 levels in H3255 cells and inhibited protein kinase C activity (P <0.05). EA inhibits the proliferation of lung cancer cells in a concentration-dependent manner through mechanisms related to the reduction of VEGF and TGF-β1 levels. Therefore, EA may be an effective drug against lung cancer [11].

Andrographolide is one of the major diterpene lactones of the plant of andrographis paniculata and has a significant inhibitory effect on many cancers. The effect of andrographolide on lung cancer in a rat model of lung tumors induced by human vascular endothelial growth factor A165 (hVEGF-A165). These results showed that the androgen system significantly reduced VEGF-A-165 expression in Clara's lung cells compared to the placebo group. Andrographolide also reduced tumorigenesis by reducing the expression of EGFR, VEGF, cyclin A, and cyclin B at the level of transcription and translation. These results suggest that androgenic treatment of may interfere with the cell cycle leading to lung tumors in transgenic mice when VEGF is overexpressed. As a result, the potential of antiangiogenic andrographolide and chemotherapy has the potential to treat lung cancer in the future [12].

2.2 Breast Cancer

The investigated andrographolide potential effects on breast cancer development and inhibition of neovascularization and the precise mechanisms involved. This study demonstrates the andrographolide potential anticancer effect, which can inhibit COX-2 expression by reducing PX-HAT activity and inhibiting angiogenesis through the VEGF pathway. Cancer drugs can help treat breast cancer [13].

The effect of andrographolide on NFkB activation mediated by caspase-8 apoptosis, pyroptosis, and axon matrix degradation (ECM) in MW-MB231 of A431 and the SKOV-3 cell line. The results showed that andrographolide inhibits the growth and growth of tumor cell lines by inhibiting NFRB signaling. As the concentration of andrographolide increases, the expression of the tissue inhibitor metalloproteinase-1 (TIMP1) increases significantly. Induction of TIMP1 inhibits the activity of matrix metalloproteinase-7 (MMP-7) and inhibits ECM degradation. Andrographolide does not cause microbial toxicity to tumor cells, it exhibits cytotoxicity through the NFkB signaling pathway, and inhibits the development of ovarian and breast cancer by inhibiting MMP-7 expression through TMPP1 overregulation. This drug is made for ovarian cancer and breast cancer [14].

Andrographolide diterpene lactone from Andrographis paniculata exhibits antimatter activity against cellular models of breast cancer and myeloid leukemia (M1) in vitro and in vivo. This study reported a semisynthetic Andrographis derivative that was active in vitro against the A549 cell line (ATCC) (NSCL carcinogenesis). During differential testing, compounds 3-5 showed maximum activity with IC50 values of 21-31 µl. G / ml [15].

Breast cancer is the leading cause of death in women. It occurs due to the uncontrolled proliferation of breast epithelial cells. Herbal therapy is more effective than synthetic drugs because it has no side effects. Andrographolide contains the active substance. It is an effective treatment for breast cancer. Inhibition of the cell cycle inhibitor protein p27 interferes with the G0/G1 phase of the breast cancer cell cycle and reduces the expression of four cyclin-dependent kinases (CDK4). It also activates the congenital apoptosis pathway through the box and dorsal induction. It increases the production of caspase and the expression of the p53 gene. Andrographolide inhibits blood vessel formation and metastasis in breast cancer. Synergistic androgenic therapy in combination with the production of androgenic nanoparticles and other chemotherapy agents represents a breakthrough in the treatment of breast cancer [16].

2.3 Gastric Cancer

Mechanism of inhibiting androgens from proliferation, & metastasis of gastric cells. the SGC7901 infected cell line to study the anti-cancer effects of andrographolides. Cell survival, cell migration and matrix invasion, cell cycle, cell death, and protein-mineral activity were investigated. also used Western blot and real-time PCR to assess protein and mRNA expression levels, respectively. Cell viability decreased dose-dependently with increasing androgen concentration. Consistent results were obtained by apoptosis as determined by flow cytometry. The G2/M2 cell cycle was blocked by andrographolide treatment, and the improvement of G1/M wound healing by increasing the capacity ratio of retained cells also showed reduced cell migration and invasion. Gastric cancer cells with different andrographolide concentrations. andrographolide can inhibit cell

proliferation, invasion, and migration in SGC7901 cells, disrupt the cell cycle, and induce apoptosis. Mechanisms include down-regulated expression of the TIMP-1/2, cyclin B1, p-Cdc2, Bax and Bc, top-down expression of MMP-2/9, and cellular protein Bcl-2 [17].

2.4 Cholangiocarcinoma

An extract of *Andrographis Paniculata* effectively inhibits the growth of cancer cells in the liver - HepG2 and SK-Hep1. Bile ducts (HuCCA-1 and RMCCA-1 14-deoxy-11,12-didehydro andrographolide, neo andrographolide, and 14-deoxyandrographolide, It includes a variety of developmental inhibitory activities. Inhibited the G0/G1 and G2/M phase cell cycles and induced apoptosis in HuCCA-1 and RMCCA-1 cells. The expression of cyclin D1 and Bcl-2 and the inactive enzymatic form of caspase-3 were reduced by ethanol extract of Ae. True leaf stage treatment was accompanied by increased fear during apoptosis protein acquisition. herbal plant for the alternative treatment of intrahepatic cholangiocarcinoma [18].

Andrographolide is a chemically active compound found in *Andrographis paniculata*, has the potential for a variety of cancers. To evaluate the anti-tumor activity of andrographolide against cholangiocarcinoma (CCA) and to understand the underlying mechanisms. The antiproliferative activity of andrographolide has been studied in a group of cholangiocarcinomas (CCA) cell lines such as Huanga-1, KKU-100, KKU-M213, and RMCCA-1. This same mechanism has been studied in the same migration and metastatic activity of KKU-M213 cells. The results showed that andrographolide inhibited CCA cell proliferation at inhibitory proliferation concentrations of 50% (IC50) of ~120 μM. andrographolide also inhibits the migration and penetration of CCA cells. other findings have shown that andrographolide reduces the expression of the tightly bound protein, claudin-1, and regulates the expression of snails. Also, andrographolide induced the phosphorylation of N-terminal kinase (JNK) and protein kinase P-38 using metabolic methods (MAPK). Treatment with a P-38 inhibitor restored claudin-1 expression and the ability of CCA cells to migrate. This study demonstrates the potential anticancer effects of andrographolide to inhibit CCA cell translation by activating the MAPK C-38 signaling pathway and inhibiting claudin-1. This combination helps to create an alternative remedy for CCA [19].

2.5 Leukemic Cancer

The cytotoxicity of *Andrographis paniculata* ethanol extract and major diterpenoid components in various tumor cells was evaluated in vitro. After 24 hours of treatment, it was shown to be a major inhibitor of HL-60 cell development in human acute myelogenous leukemia with an IC 50 of 14.01 μmol/mL. Among the three major dimers, Andrographis paniculata and andrographolide showed the highest level of cytotoxicity, followed by deoxyandrographolide, followed by neoandrographolide, which was the least effective. Confocal laser microscopy and gel electrophoresis show the presence of fragments of the dye in the DNA, suggesting cell death. An increase was observed from 51.88% to 78.69% in G(0)/G(1) phase cells after 36 hours of treatment with andrographolide. G(0)/G(1) phase arrest and apoptosis were associated with loss of C mitochondria and an increase in Bax but decreased expression of Bcl-2 protein in inhibitory cells. The sequence of all these events is unknown, but we concluded that EPA and andrographolide influence the endogenous mitochondrial pathway by inhibiting the cell cycle and regulating the expression of certain pro-apoptotic markers in HL-60 cells [20].

Compared with the application of each compound separately, pre-treatment of U937 with andrographolide first with a low dose of TP showed an enhanced apoptosis induction effect. The synergy of this combination appears to involves more intrinsic mitochondrial pathway of the including upregulation of Bax, cleavage of the PARP with the release of cytochrome C, and cleavage of different caspases into their active forms, especially, caspase -3 and -9. This new combination can be used as a new clinical chemotherapy strategy to treat AML and enhance the therapeutic effect of PT with less toxicity. Also, after further research and investigation, it can be used as an option for the treatment of other drug-resistant cancers [21].

2.6 Renal Carcinoma

TRAIL- Tumor necrosis factor-related apoptosis-inducing ligand induces apoptosis in tumor cells with little toxicity to normal tissue. However, accumulated evidence suggests that some cancers are not resistant to TRAIL signaling. Human kidney cancer (CRC) cells are generally resistant to TRAIL-mediated growth. RCC rejects the test resistor. The combination of TRAIL and Andrographolide inhibits MTS crystalline cell

viability and EdU crystalline dose-dependent growth, preventing RCC birth and migration. Andrographolide significantly improves TRAIL-mediated cell cycle arrest during the G2/M phase as determined by flow cytometry and aging. 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

Tumor necrosis factor-related apoptosis-inducing ligand-TRAIL, is an effective chemotherapy that specifically weakens cancer cells while keeping the cells normal. However, some cancer cells are resistant to TRAIL. Here, we identified Andrographolide, which is a diterpenoid lactone extracted from Andrographis paniculata, a traditional herbal medicine, which is a TRAIL sensitive agent ideal for combating bladder cancer. It results show that the combination of Andrographolide and TRAIL slows the growth of T24 cells, inhibits proliferation, reduces colonization, inhibits migration, and improves caspase-mediated apoptosis. How to rely on TRA53 to p53. Importantly, Andrographolide could also downgrade the p65/Rela transcript to disable the NF-B signaling pathway. This contributes to an increase in TRAIL-mediated cytotoxicity. These results suggest that the non-toxic dose of TRAIL-mediated endoscopic-sensitive bladder cancer cells is TRAIL-mediated and is an effective therapeutic agent for TRAIL-resistant human bladder cancer [23].

2.8 Prostate Cancer

Tumor necrosis factor-related apoptosis-inducing ligand -TRAIL, is a promising factor in cancer treatment. The identification of small molecules that can determine the susceptibility of prostate cancer (PCA) cells to TRAI-induced apoptosis is essential for the targeted treatment. It was developed a nude mouse PCA xenograft dissection model using flow cytometry to measure caspase-3 activity in cancer cells. Results showed that andrographolide increased the sensitivity of PCa cells at TRAIL-induced apoptosis, preferably at anti-toxic concentrations, and that the regulatory mechanism was associated with increased DR4 regulation. It also increases the expression of p53 and triggers the production of reactive oxygen species (ROS) in cells. That inhibition of DR4 expression, p53 expression, and ROS production can significantly reduce TRAIL and andrographolide-induced cell death in PCa cells. As a result, ANDRO increases PCA cell death associated with DR4 activation by sensitizing PCA cells to TRAIL-induced apoptosis by generating ROS and rearranging p53 [24].

2.9 Osteosarcoma

Osteosarcoma is the most common primary bone weakness and the long term survival of the patients with this disease over the past decades is insufficient. Andrographolide is a traditional drug used in herbal medicine and has remarkable anticancer effects against various cancers. However, little is known about the effectiveness of andrographolide on osteosarcoma and its underlying mechanisms. This study demonstrated that andrographolide inhibits osteosarcoma cell proliferation by the arresting cell cycle during the G2/M phase and increasing caspase-mediated apoptosis. Also, andrographolide treatment JNK activated, it's increased the production of reactive oxygen species (ROS). Andrographolide induced apoptosis in osteosarcoma cells, which was partially reversed by the JNK inhibitor and completely reversed by the ROS scavenger. Also, at the GOS/M phase, the ROS sensor was used to stop JNK activation & the cell cycle arrest, and in-vivo, andrographolide was shown to increase ROS levels and activate JNK to inhibit tumor growth. Thus, it causes cytotoxicity in early osteosarcoma cells, that andrographolide interferes with G2/M by regulating the ROS/JNK signaling pathway in osteosarcoma cells. Thus, andrographolide may act as a promising anticancer agent against osteosarcoma [25].

2.10 Colon Cancer

The Wnt/W chain signaling pathway plays an important role in the development of human colorectal cancer (CRC) and is a major target for CRC chemotherapy agents. The effects of cancer and molecular mechanisms to confirm its activity in the andrographolide analogue, 19-O-triphenylmethyl andrographolide (RS-PP-050) and the Wnt/β-catenin pathway. RS-PP-050 has been shown to inhibit the proliferation and survival of CR-HT-29 cells. It disrupts the cell cycle and induces cell death associated with the

activation of PARP-1 and p53. Also, RS-PP-050 inhibits the activity of intracellular T cell factor/lymphocyte growth factor (TCF / LEF), increases N-catenin expression, and increases N-catenin expression, thereby inhibiting catenin transcription. There is. Endogenous expression of the target. Inconvenience RS-PP-050 also reduces the expression of the active catenin protein but acts independently of the GSK-3ive Wnt inactivity modulator. Interestingly, RS-PP-050 primarily inhibits the phosphorylation of Ser675-catenin. This can interfere with the nuclear transport of the chain and contribute to its inactivation. Overall the anticancer mechanisms of andrographolide analogs and provide useful information on the recent use of chemotherapy agents in Wnt/catenin overexpressing CRC cells [26].

The effect of andrographolide on colon cancer is not fully understood. Therefore, we investigated the possibility of chemical protection of the andrographolide in HT-29 colon cancer cells. The cytotoxic potential of andrographolide against HT-29 cells was determined using MTT, trypan dehydration, colony composition, and morphological analysis. Apoptosis was generally determined by DAPI and Hoechst staining, DNA fragmentation test, and Caspase-3 test. Changes in mitochondrial potential by flow cytometry analysis using Rytamine 123 and Mito Tracker Red CMX Ros staining and cell cycle regulation characteristics Studies have shown that andrographolide decreases the viability of HT-29 cells as a function of dose and time. Also, andrographolide induces apoptosis in HT-29 cells. This appears to be associated with elevated intracellular levels of ROS and inactivation of mitochondrial membrane potential. Interestingly, andrographolide causes significant cell cycle arrest at low doses in the G2/M phase and high doses in the G0/G1 phase. In summary, our results show that andrographolide has anti-proliferative and apoptotic properties against HT-29 colon cancer cells [27].

2.11 Ovarian Cancers

The effect of andrographolide on the activation of NFkB that mediates caspase-8 apoptosis in MR-MB231 of the A431 extracellular matrix (ECM). And the SKOV-3 cell line. The results showed that ANDR inhibited the growth and growth of tumor cell lines by inhibiting NFkB signaling. With increasing ANDR levels, a significant decrease in phosphodiesterase p65 was observed in melanoma and breast cancer cells A431 and MDA-MB231, respectively. Consequently, andrographolide treatment increased caspase-8 expression, but no significant inclusion of caspase-1 expression. That increasing the concentration of andrographolide significantly increased the expression of tissue inhibitors of metalloproteinase-1 (TIMP1). TIMP1 induction inhibits matrix metalloproteinase-7 (MMP-7) activity and inhibits ECM degradation. Andrographolide is most likely in the ovary because it is cytotoxic to cancer cells through the NFkB signaling pathway without prostatitis and suppresses the development of breast and ovarian cancer attacks by inhibiting MMP-7 expression through overregulation of TIMP1 [28].

2.12 Other Cancers

The anticancer and immunosuppressive activity of methanol extract and human immune cells, Andrographis paniculata. Andrographis paniculata methanol extracts were separated into dichloromethane, petroleum ether, and aqueous extracts and tested for their bioactivity. the dichloromethane fraction of methanol extract contains effective compounds that support anticancer activity and activate the immune system. The dichloromethane fraction inhibits the growth of HT-29 cells (colon cancer) and increases the growth of human peripheral blood lymphocytes (HPBL) at low concentrations. When separating the dichloromethane extract, three compounds, namely, andrographolide, 14-deoxyandrographolide, 14-deoxy-11,12-didehydroandrographolide. Andrographolide has been shown to have anticancer activity against different cancer cells representing different types of human cancer. All three molecules showed proliferation and induction of interleukin-2 (IL-2) in HPBL [29].

3. CONCLUSION

Andrographolide is a well-known herbal compound isolated from Andrographis paniculata, a versatile treatment for cancer and other diseases. Discover the therapeutic potential of plant materials and see if pharmacodynamic research is currently a major concern for natural resource drug development. Therefore, it is worth evaluating the therapeutic potential based on the clinical efficacy of andrographolide. The pharmacodynamic potential of these plant molecules in the fight against various types of cancer and other diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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