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Bartogenic Acid: A Promising Pentacyclic Triterpenoid in Cancer Research and Possible Mechanism

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Abstract

Bartogenic Acid (BA) is a natural triterpenoid compound found in several plants, including *Barleria lupulina, Croton tiglium*, and *Euphorbia hirta.* It has been shown to exhibit a wide range of pharmacological activities, including anti-inflammatory, anti-cancer and anti-oxidant properties. BA has been shown to exhibit promising anti-cancer properties in various studies. In particular, BA is effective against a variety of cancer cell lines, including breast, lung, and colon cancer. Its ability to induce apoptosis, inhibit cell proliferation, and suppress tumor angiogenesis makes it a potential therapeutic agent for various cancers. BA has been demonstrated to induce apoptosis in cancer cells through various mechanisms, including activation of the caspase cascade, downregulation of Bcl-2, and upregulation of Bax. It also inhibits cell proliferation by arresting cell cycle progression at the G1/S checkpoint. Additionally, BA suppresses tumor angiogenesis by inhibiting the expression of Vascular Endothelial Growth Factor (VEGF). The molecular mechanisms underlying BA's anti-cancer effects are not fully elucidated, but several potential pathways have been identified. BA has been shown to interact with various signaling molecules, including nuclear factor-κB (NF-κB), Mitogen-Activated Protein Kinase (MAPK), and phosphatidylinositol 3-kinase/Akt (PI3K/Akt) pathways. BA is also a potent inhibitor of topoisomerase I and II, which are enzymes that are involved in DNA replication which suggests that BA may be able to prevent cancer cells from replicating and dividing. This review summarizes the current understanding of BA's anti-cancer effects and its possible mechanisms of action. Further research is warranted to fully elucidate the molecular mechanisms underlying BA's anti-cancer effects and to evaluate its potential for clinical development.

Keywords: Bartogenic acid • Pharmacology • Anti-cancer • Chemomodulation • Anti-inflammatory

Introduction

Globally, there is significant worry about the ongoing rise in cancer incidence and death in both developed and developing nations. After cardiovascular disorders, cancer is the second leading cause of death [1]. Cancer can develop due to several internal and external factors. Internal factors include genetic alteration, mutation in genetic material, abnormal hormonal conditions, and compromised immune systems. External factors include modern lifestyles and certain occupational conditions [2]. BA has a 30-carbon skeleton with 6-membered rings (oleanane type) and comes under the pentacyclic triterpenoid class [3]. BA is found in a variety of plants, including *Bartogensis ecklonii* and *B. gerardii*. It is a white, crystalline solid with a molecular weight of 458.61 g/mol. BA has a complex structure with five rings (Figure 1) and it is this structure that is thought to be responsible for its biological activity. It is poorly soluble in water, making it difficult for it to be absorbed into the bloodstream after oral administration. It undergoes extensive metabolism in the liver, reducing the amount of active compound that reaches the bloodstream. It is a substrate for *P*-glycoprotein, a transporter that pumps drugs out of cells, further reducing its bioavailability (Figure 1).

BA promotes apoptosis and inhibits angiogenesis, both of which are required for cancer initiation and progression. The methods by which BA exerts its anti-cancer benefits are not entirely known, however, it is considered to include many routes. BA has been found to reduce cancer cell proliferation *in vitro* and *in vivo*, as well as cause apoptosis and prevent angiogenesis. It is highly efficient against breast, colon, and lung cancer cells. BA also causes apoptosis, which is a type of programmed cell death that is necessary for the elimination of cancer cells. Furthermore, BA inhibits angiogenesis, which is the creation of new blood vessels required for tumor growth and dissemination. The methods by which BA exerts its anti-cancer properties are not entirely known. BA may block the activation of NF-B, a transcription factor implicated in cell proliferation, inflammation, and apoptosis, as one possible mechanism. BA may also activate the p53 tumor suppressor gene, which is in charge of initiating apoptosis in the presence of DNA damage. Furthermore, BA has been

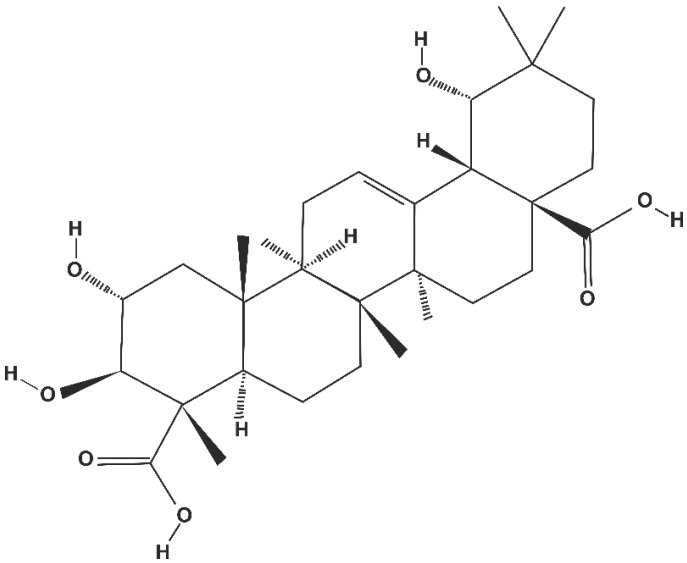

Figure 1. Chemical structure of Bartogenic acid.

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shown to block the Akt signaling pathway, which is crucial in cell proliferation and survival. BA has been shown to have anti-diabetic, anti-arthritic, anti-inflammatory, chemomodulatory and anti-tumor activities [4-7]. BA's anti-cancer actions are not entirely known, however, it is considered to engage many pathways. Further research is needed to determine the efficacy and safety of BA as a cancer treatment. This review aims to provide an overview of the current understanding of the purpose and goals of BA which shows a promising effect in cancer research.

Literature Review

Possible mechanistic approach of BA

BA has demonstrated promising anti-cancer properties in various preclinical studies [3]. Its proposed mechanisms of action involve multiple cellular pathways, including induction apoptosis, inhibition of angiogenesis, and anti-inflammatory and immunomodulatory potentials. BA has been shown to induce apoptosis in cancer cells through multiple mechanisms, including activation of caspases, mitochondrial dysfunction, and DNA damage (Figure 2). Caspases are enzymes that play a critical role in the execution of apoptosis. BA has been shown to enhance the expression and activity of these enzymes [8]. BA also disrupts mitochondrial function, leading to the release of cytochrome c, a protein that triggers apoptosis when released into the cytoplasm. Additionally, BA can induce DNA damage in cancer cells, which can lead to apoptosis if not repaired. Furthermore, angiogenesis is the formation of new blood vessels, which is essential for tumor growth and metastasis. BA has been shown to inhibit angiogenesis by targeting various factors involved in this process, including VEGF and Matrix Metalloproteinases (MMPs) [3]. VEGF is a key signaling molecule that promotes the formation of new blood vessels, and BA has been shown to downregulate its expression. MMPs are enzymes that break down the extracellular matrix, which is necessary for angiogenesis to occur. BA has been shown to inhibit the activity of MMPs, thereby preventing the breakdown of the extracellular matrix and hindering angiogenesis. Moreover, inflammation is associated with cancer development and progression. BA has been shown to possess anti-inflammatory properties by modulating the expression of inflammatory mediators, such as cyclooxygenase-2 (COX-2) and Nuclear Factor-κB (NF-κB). COX-2 is an enzyme that produces prostaglandins, which are inflammatory molecules [9]. BA has been shown to downregulate COX-2 expression, thereby reducing prostaglandin production. NF-κB is a transcription factor that plays a role in the expression of inflammatory genes. BA has been shown to inhibit NF-κB activation, thereby reducing the expression of inflammatory genes [10]. Additionally, BA has been shown to modulate the immune system by enhancing the activity of Natural Killer (NK) cells and dendritic cells. NK cells are immune cells that can directly kill cancer cells, and BA has been shown to increase the cytotoxicity of NK cells. Dendritic cells are immune cells that present antigens to T cells, which are essential for the adaptive immune response. BA has been shown to enhance the maturation and function of dendritic cells, thereby promoting the activation of T cells and the anti-tumor immune response [11]. These proposed mechanisms of action suggest that BA has the potential to be an effective anti-cancer agent. Further research is needed to fully elucidate the mechanisms of action and to evaluate the clinical efficacy of BA in the treatment of cancer (Figure 2).

BA has been shown to exhibit anti-tumor effects against various types of cancer, including ovarian, skin, and breast cancer. The mechanisms underlying BA's anti-cancer activity are multifaceted and involve multiple signaling pathways. BA induces apoptosis, programmed cell death, in cancer cells. It triggers the activation of caspase enzymes, which dismantle cellular components and lead to cell death [12]. BA inhibits the proliferation of cancer cells by arresting their cell cycle progression. It targets specific cell cycle checkpoints, such as G1/S and G2/M, preventing cancer cells from dividing uncontrollably. BA suppresses angiogenesis, the formation of new blood vessels, which is essential for tumor growth and metastasis. It inhibits the expression of angiogenic factors and disrupts the formation of vascular endothelial cells [13]. BA exhibits anti-inflammatory properties, which contribute to its anti-cancer activity. It modulates the expression of inflammatory mediators and reduces the infiltration of immune cells that promote tumor growth [9]. BA influences epigenetic mechanisms, such as DNA methylation and histone modifications, which can alter gene expression patterns. It promotes the expression of tumor suppressor genes and suppresses the expression of oncogenes. BA enhances the efficacy of conventional chemotherapy agents. It reduces the resistance of cancer cells to chemotherapy and increases the sensitivity of tumors to chemotherapeutic drugs. These mechanisms suggest that BA holds promise as a potential therapeutic agent for cancer treatment. Further research is warranted to fully elucidate its mechanisms of action and explore its potential for clinical application [14].

Downregulation or upregulation of transcription factors (NF-κB), Antiapoptotic Proteins (bcl-2, bcl-xL), promoters of cell proliferation (cyclooxygenase-2, cyclin D1, c-myc), Invasive and Metastatic Genes (MMPs), Intracellular Adhesion Molecule-1 (ICAM-1), cytokines (interleukin and growth factors), and angiogenic protein (VEGF) have all been shown to be a great potential in targeting different cancers [15]. IKK-mediated activation of the NF-κB pathway is inhibited by pentacyclic triterpenoids [16]. Pyruvate kinase M2 is inhibited by the synthetic oleanane triterpenoid (pentacyclic triterpenoids). The pyruvate kinase M2 is a critical regulator of cancer cell metabolism and one of the key components in the Warburg effect. PKM2 expression is upregulated in a lot of cancers [17]. Autophagy enhances cell survival in the normal state, but its dysregulation or over-activation causes death signals. Cell growth, differentiation, metabolism, and autophagy are all controlled by the PI3K/Akt/mTOR signaling pathway. It is frequently activated in a variety of cancer cells [18]. Autophagy is modulated by several pentacyclic triterpenoids such as Oleanolic Acid (OA) and Ursolic Acid (UA), which have a tumor suppressor effect. Modulating oxidative stress markers such as GSH content, activities of GSHPx, SOD, and catalase have a potential role in the management of cancer

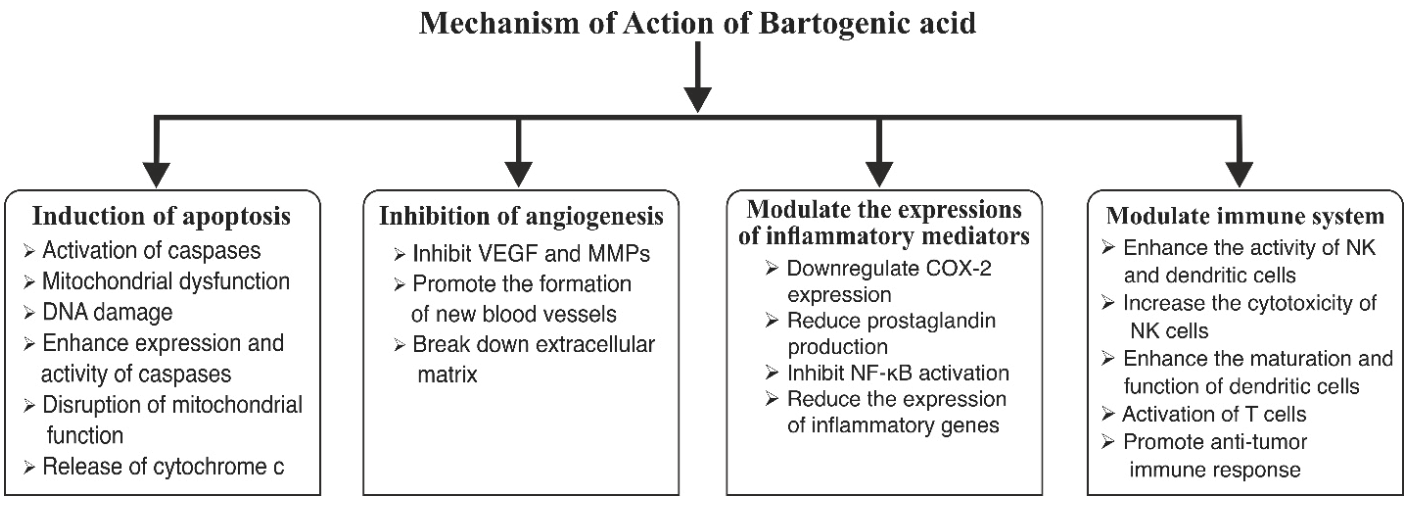

Figure 2. Mechanism of BA involving multiple cellular pathways.

progression [7]. Other pentacyclic triterpenoids with structural similarities to BA include OA and UA. In a clinical trial for cancer therapy, OA and UA are now being investigated [19-21]. Because of the abovementioned point, plant-oriented compounds are considered key compounds in various therapeutic research fields these days. Since conventional anti-cancer drugs are highly toxic, plant-derived herbal medicine is being investigated as an alternate therapy to target various types of cancer.

Discussion

Scientific validation of BA as an anti-cancer agent

Cancer is the second foremost non-communicable disease after cardiovascular diseases and emerged as a serious illness worldwide. The cause of the majority of cancers is genetic predisposition and exposure to environmental pollutants such as excessive tobacco or alcohol, exposure to harmful chemicals and radiation [22] which leads to either internal factors such as spontaneous mutations, hormones, and nutrient metabolism in the body or by external stimulators [23]. Ethnomedical survey has shown that the seeds of *Barringtonia racemosa* Roxb are traditionally used in certain remote villages of Kerala (India) to treat cancer-like diseases. BA has ample of useful therapeutic effects; including anti-diabetic, anti-arthritic, anti-inflammatory, and chemomodulatory properties. BA is efficacious against the proliferation of ovarian and skin cancer cells *in vitro* and *in vivo*. Inflammatory diseases are globally identified causes of morbidity among the population [24]. Inflammation is a natural protective response of the body to tissue injury caused by chemical, mechanical, or thermal stimuli, trauma, microbial agents, or autoimmune diseases [24,25]. BA enriched fraction was investigated for anti-inflammatory activity in experimental models of acute and chronic inflammation. Activity against acute inflammation was evaluated in inflammogens-induced rat paw edema models. Whereas, the effect in chronic inflammation was evaluated in cotton pellet granuloma and oxazolone-induced Delayed-Type Hypersensitivity (DTH) model in mice. The present investigation revealed that BA enriched fraction possesses potent anti-inflammatory activity in acute and chronic models of inflammation. Additionally, BA enriched fraction possesses an inhibitory effect on cell-mediated immunity as evident from its inhibition of oxazolone-induced DTH [6]. BA for anti-tumor potential in the preclinical model of skin carcinogenesis induced in mice by application of DMBA/Croton oil reveals that BA elicits selective cytotoxicity against cutaneous squamous cell carcinoma cell line and markedly suppresses the initiation and progression phases of DMBA/Croton oil-induced two-stage skin carcinogenesis by modulating the Phase II detoxification enzyme and improving anti-oxidant defense such as GSH content, activities of GSHPx, SOD and catalase [7]. Further, findings of the SKOV-3 xenograft ovarian cancer model using SCID mice suggest that the treatment of BA alone and in combination with paclitaxel has a significant anti-tumor effect by modulating TGF-β1 and MMP9, NF-κB [3]. By this, Thomas TJ, et al. [26] tested the seed extracts for anti-tumor activity against mice challenged with 1 million Dalton's Lymphoma Ascitic (DLA) and, found them efficacious in mice. In addition, BA (2 & 4 mg/kg; orally or topically) reduced precancerous skin lesions and tumor incidence in mice models of DMBA/croton oil-induced skin carcinogenesis, increased catalase and superoxide dismutase activities, and inhibited lipid peroxidation in the skin of mice.

Conclusion

Many studies have demonstrated that plants are widely spread, contain a wide variety of chemical compounds, and may affect several physiological processes in both healthy and diseased states. The key mechanisms of pentacyclic triterpenoids responsible for their anti-cancer actions are reviewed in this study. Pentacyclic triterpenoid may act on several molecular targets and cell proliferation regulatory pathways, which are crucial in uncontrolled cell proliferation, according to literature gathered from *in vitro* and *in vivo* investigations. In conclusion, BA is a promising pent acyclic triterpenoid with demonstrated anti-cancer activity against various cancer cell lines. It has been shown to induce apoptosis, inhibit cell proliferation, and suppress tumor growth *in vivo*. BA also exhibits anti-inflammatory and anti-oxidant properties, which may contribute to its anti-cancer effects. Additionally, BA appears to be non-toxic to normal cells, making it a potential therapeutic agent with minimal side effects. Further research is warranted to elucidate the precise molecular mechanisms underlying the anti-cancer effects of BA. This includes identifying the specific targets of BA in cancer cells and understanding how it modulates signaling pathways involved in tumorigenesis. Additionally, clinical trials are needed to evaluate the safety and efficacy of BA in cancer patients. If BA proves to be safe and effective in humans, it could represent a valuable addition to the arsenal of cancer therapies. While BA is effective against a variety of cancer cell lines, it is important to determine whether it is similarly effective against different types of cancer *in vivo*. BA could potentially be combined with other anti-cancer drugs to enhance their efficacy and reduce side effects. BA could be encapsulated in nanoparticles or liposomes to improve its solubility and bioavailability, which could enhance its therapeutic potential. Overall, BA is a promising natural compound with the potential to revolutionize cancer treatment. With continued research, BA could become a safe and effective therapy for a wide range of cancers.

Acknowledgement

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Conflict of Interest

None.

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