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Mini-review

From derma to nervous system: Exploring the therapeutic efficacy of azelaic acid in Neuroblastoma and Glioblastoma

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The study explores the potential of a naturally occurring phytochemical, azelaic acid (AZA) as an immunomodulator against two aggressive forms of cancer in the nervous system, such as Neuroblastoma and Glioblastoma. Neuroblastoma affects the peripheral nervous system in children below the age of five. Genetic mutations such as overexpression of gene functions like MYCN, which regulates cell growth and proliferation under normal conditions, or deletion of chromosomal subunits are demonstrated as the predominant cause of neuroblastoma. Glioblastoma, tumorigenesis in glial cells affects the central nervous system. The Isocitrate dehydrogenase (IDH1) enzyme mutation is a critical marker for detecting glioblastoma. As the brain is immunologically inert, prognosis becomes even more difficult, causing death. Available drugs fail to cross the blood-brain barrier, thus lowering the efficacy. Additionally, chemotherapy and radiation therapy come with a lot of side effects, with increased cases of relapse. Hence, the requirement of a new therapeutic option is the need of the hour. Phytochemicals are natural compounds with therapeutic properties. AZA, a dicarboxylic acid naturally found in barley, wheat, and rye, is a known compound used in skin care products and helps cure acne vulgaris. Recently, *in vitro* studies have observed that Azelaic acid exhibits anti-proliferative and immunoregulatory effects on Acute Myeloid leukemia. However, a detailed mechanistic insight into the mode of action of neuroblastoma and glioblastoma is unexplored. In this review, we intend to discuss the known antineoplastic activities of azelaic acid in cancer and thereby design a hypothesis. Furthermore, a wide range of questions on the underlying mechanisms and whether AZA plays any role in the immunostimulatory effects on a tumor microenvironment in the immunologically inert brain will also be discussed and reviewed in this paper.

Keywords: Neurotrophic factors, MYCN alteration, IDH1 mutation, tumor microenvironment, immune escape, immunomodulatory pathways

Cancer is one of the world's leading conditions, causing thousands of deaths every year. According to the World Health Organization, there were up to 10 million deaths due to cancer in the year 2020[1]. There have been several reasons that have been associated with cancer, which include genetic mutations, familial inheritance, food choices, and lifestyle changes. Factors like smoking, consumption of alcohol, obesity, diet, and physical inactivity have also been considered as contributors to cancer[2]. However, there is still no definitive cure in the medical field. While treatments do exist, a definitive and universal cure for all cancer types remains a question yet to be answered[1,2].

Chemotherapy and radiotherapy are effective but have high chances of relapse and other symptoms associated with them. Amongst the most fatal cancers, tumorigenesis in the Nervous system is considered one of the most lethal ones as it has a low prognosis rate, consequently leading to lower chances of survival. Neuroblastoma, mainly found in the peripheral nervous system in children, is a highly malignant pediatric cancer caused by the amplification of genes responsible for the growth and proliferation of neural crest cells of the sympathetic nervous system[3]. Meanwhile, Glioblastoma multiforme is a tumor found in the brain with early symptoms like headache and fever, making it very difficult to diagnose early. Glioblastoma multiforme mainly occurs due to an Isocitrate dehydrogenase mutation in the neurons, causing tumor formation[4]. Both cancers in the nervous system are considered highly malignant and aggressive. Hence, effective drugs/ treatments are crucial to improve survival rates of patients suffering from these conditions, opening a wide scope of questions to be answered by researchers.

Neuroblastoma

High-risk neuroblastoma is defined as metastatic disease in a child ≥18 months or a patient of any age

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with L2, M, or MS (International Neuroblastoma Risk Group Staging system) disease with amplification of the MYCN oncogene[5].

Common molecular markers to detect neuroblastoma are mentioned below:

1. MYCN gene amplification is one of the markers of aggressive disease and poor prognosis in neuroblastoma[5], which is measured by fluorescent in situ hybridization (FISH) as a fourfold increase in the MYCN signal number compared with the reference probe located on chromosome 2q[6].
2. Cell ploidy is also a prognostic marker in neuroblastoma, with triploidy or hyperdiploidy having a better prognosis than diploidy [6].
3. Segmental chromosomal copy number alterations like gain of 17q, loss of 1p, and loss of 11q are also seen in neuroblastoma[7].
4. Mutations in specific genes in neuroblastoma are not common, but the presence of these alterations is being discovered at an increasing rate with the next-generation sequencing becoming more accessible[8].
5. ALK gene mutation in the germline DNA in families with heritable neuroblastoma has also been shown to be somatically mutated spontaneously in a subset of neuroblastomas[9] along with PHOX2 B germline mutations[10]
6. Other markers include TP53, NF1, BRCA1/2, NRAS, APC, and PTPN11[11] .
7. PTEN/MMAC1 alteration in neuroblastoma.

Genomic alterations in these above-mentioned markers result in disruption of the typical programming of the neural crest cell migration, differentiation, and maturation. Subsequently, the cells proliferate in an immature and proliferative neural crest like stage.

Neural Crest Migration: Altered Signaling in Neuroblastoma

Neural crest (NC) cells are a part of neuroepithelium and have the same morphology as other neuroepithelial cells. However, due to certain signals from the ectoderm cells and mesoderm cells, the neural crest originates and transforms from epithelial cells to mesenchymal cells[12].

The neural plate and epidermis interact for the induction of neural crest cells thus, it is known as neural plate-epidermal interaction[13,14]. NC cell specification and migration are guided by transcription factors such as Snail, FoxD3, and Sox8/9/10, whose expression is promoted by the canonical Wnt signaling pathway, which is essential for NC cells induction from the neural plate border[15].

To promote detachment of NC cells from the neural tube and for the cells to migrate away and differentiate into different cell types, Bone Morphogenic Protein (BMP) signaling cooperates with Wnt to initiate the transfer of NC cells from epithelial to mesenchymal cells[16,17]. Additionally, FGF signaling acts in concert with Wnt and BMP to maintain the NC progenitor population during early development in zebrafish[18]. However, pathogenesis of neuroblastoma is known to be caused due to aberrant regulation of these signaling pathways. For instance, the tumorigenic potential of neuroblastoma is enhanced by maintaining stem-like properties caused by persistent activation of Wnt signaling. Neuroblastoma cell fate is altered and proliferation is inhibited when β-catenin expression is disrupted, which is the central mediator of Wnt signaling[19]. Given the role of BMP in epithelial to mesenchymal transition during NC cell migration, abnormal signaling may contribute to altered cell fate and invasive behaviour as observed in neuroblastoma[19]. While neuroblastoma demonstrates the consequences of flawed neural crest development in the peripheral nervous system, aberrant signaling in the central nervous system result in Glioblastoma.

Glioblastoma multiforme (GBM)

Gliomas are tumors that primarily occur in the Central nervous system (CNS). They are the accumulation of tumor cells exhibiting glial differentiation. Molecular alterations in specified gliomas have led to better classification of gliomas in the fifth edition of the World Health Organization (WHO) classification of gliomas, hence providing a better understanding of the pathogenesis and inclusion of molecular markers in tumor classification[20].

GBM is the most aggressive, grade IV type of primary brain tumor and is associated with a poor clinical prognosis (Table 1). According to the WHO 2021 classification of central nervous system (CNS) tumors, glioblastomas are defined as isocitrate dehydrogenase (IDH) wild-type (WT) diffuse astrocytic tumors[21]. IDH-wildtype glioblastomas have a multifocal and non-lobular location. Based on clinical characteristics, GBM can be associated with

1) No mutation in IDH1 or IDH2, hence IDH wildtype
2) Necrosis or microvascular proliferation in histopathology
3) Telomerase reverse transcriptase (TERT) promoter mutation

Table 1 — List of immunosuppressive proteins during GBM prognosis

Component	Function/Interaction
Tryptophan	Converted into kynurenine by TDO/IDO
Kynurenine	Promotes the conversion of T cells into T regulatory (T reg) cells
TDO / IDO	Enzymes involved in tryptophan metabolism produce immunosuppressive metabolites
T reg	Immunosuppressive T cells present in the tumor microenvironment
MDSC (Myeloid-Derived Suppressor Cells)	Contribute to immunosuppression in the tumor environment
M2 Mφ (M2 Macrophages)	Immunosuppressive macrophages promote tumor growth
Secreted Molecules	IL-6, IL-10, TGF-β, CCL22, VEGF, PGE2, CSF-1, IL-1β, Gal-1 (support immunosuppressive microenvironment)
Receptors/Interactions with T cells	
- Fas / FasL	Induces T cell apoptosis
- NKG2A/D – HLA-E	Inhibitory signal to T cells
- PD-1 – PD-L1	Inhibitory checkpoint pathway
- ILT2/4 – HLA-G	Inhibitory signal to T cells
- CD27 – CD70	T cell co-stimulation/inhibition
- HVEM – BTLA/CD160	T cell inhibitory signaling

4) Epidermal growth factor receptor (EGFR) amplification
5) Combined chromosome 7 gain and chromosome 10 loss (+7/-10)
6) O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation[20].

Given that both neuroblastoma and glioblastoma comprise of dysregulation of cell differentiation and proliferation it is imperative to understand the role of neurotrophic factors in disease progression.

Neurotrophic factors (NTFs)

Neurotrophic factors help in the formation of neuronal networks and synaptic plasticity. The neurotrophins family is one of the major neurotrophic factors, consisting of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4). Other neurotrophic factors include insulin-like growth factor (IGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF)[22].

Brain-derived neurotrophic factor: It is known for promoting survival and differentiation of the neuronal population. BDNF is mostly found in the hippocampus, amygdala, cerebellum, and cerebral cortex of the brain. Initially, proBDNF is synthesized, stored in dendrites and axons, and undergoes cleavage to form mature BDNF protein. ProBDNF and Mature BDNF have opposing roles under pathological or non-pathological activity. ProBDNF binds to p75 NTR receptor, which facilitates long-term depression (LTD), hence causing apoptosis. Mature BDNF binds to Tyrosine kinase receptor, TrkB, which promotes cell survival and facilitates long-term potentiation[23,24]. p75 Neurotrophin receptor activates NFkB in fibroblasts, Schwann cells, and oligodendrocytes[25].

Nerve growth factor (NGF) is essential for maintaining peripheral nervous system function and synaptic interactions between cholinergic neurons in the central nervous system. It is known to activate various signaling pathways like the MAPK, ERK, and PI3K pathways. NGF binds to p75NTR and activates further signaling. NGF receptors are also expressed in immune cells and organs, hence allowing them to modulate cell differentiation and immune responses[26].

Neurotrophins NT-3 aids in the development and functioning of the nervous system. NT3 promotes the survival of neurons and nerve repair. NT3 promotes the differentiation of progenitor bone marrow-derived mesenchymal stem cells (BMSC) into neurons. It is also involved in the recovery of locomotor function and nerve regeneration. NT3 binds to BDNF to jointly regulate neurogenesis[27].

Neurotrophins NT-4 plays a pivotal role in the neuronal differentiation and survival in the CNS and PNS, follicular development, and oocyte maturation. The interaction between Epidermal growth factor EGF-like peptides and epidermal growth factor receptor (EGFR) is closely related to cell proliferation, survival, adhesion, and invasion. EGFR receptors play an important role in cellular response, cell proliferation, differentiation, and survival[28].

The glial cell line-derived neurotrophic factor (GDNF) family helps in the neural development of astrocytes. Neurturin (NRTN), artemin (ARTN), and persephin (PSPN) are members of the family. Their respective receptor interactions can be seen below[29,30] in Figure 1, 2 and 3. These neurotrophic factors have specific receptors, activating different signaling pathways that help regulate neural differentiation or proliferation. However, in neuroblastoma and glioblastoma, these functions are hampered by other factors, such as MYCN overexpression in Neuroblastoma.

Dysregulated neurotrophic signaling drives cancer progression and therapeutic resistance. Although, the robust blood brain barrier partially compromised

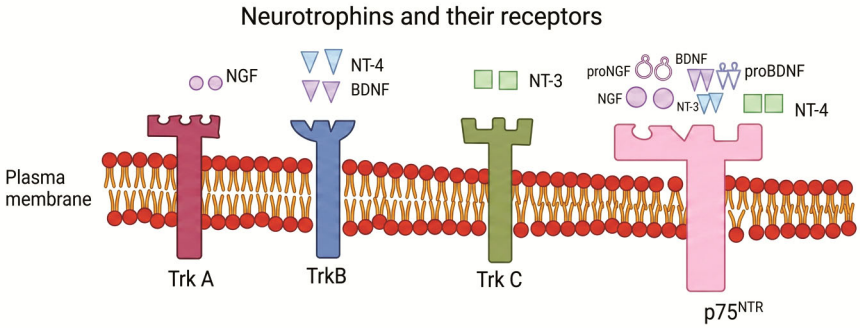

Fig. 1 — Neurotrophins (NT) and neurotrophin receptors (NTR) in Neuroblastoma. Source:[22]

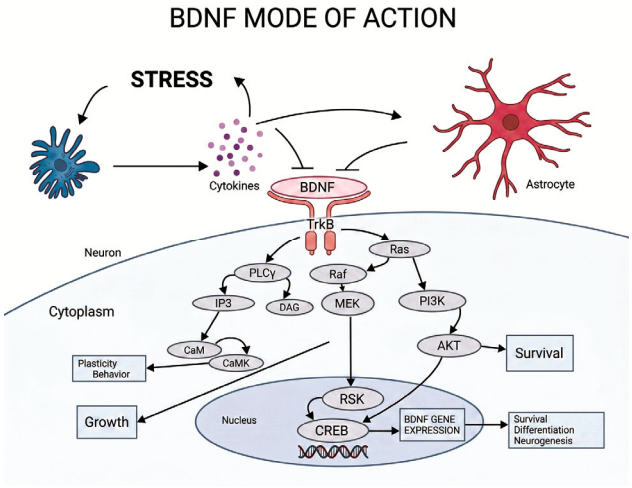

Fig. 2 — BDNF mode of action. Source:[23,24]

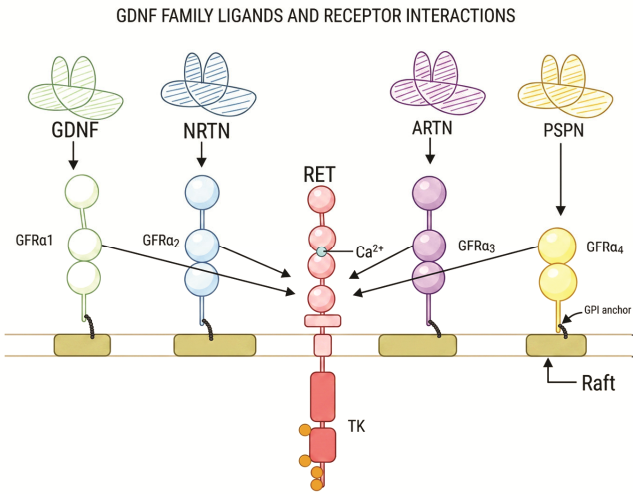

Fig. 3 — GDNF family ligands and receptor interactions. Source: [30]

during these cancer types but the permeability of the available drugs remains heterogenous. Additionally, conventional therapies result in higher toxicity and inevitable recurrence thus, phytocompounds are promising avenues that addresses cancer progression,

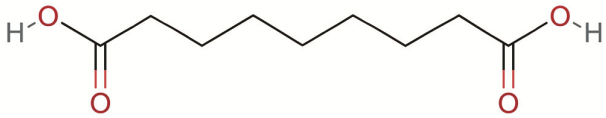

Fig 4 — Structure of Azelaic acid. Source: PubChem

targeted effect, bioavailability, and toxicity. In this review we discuss the potential role of azelaic acid in modulating tumor microenvironment.

Azelaic acid and its effect on tumor cell lines

Introduction as a phytochemical

Azelaic acid (AZA) or 1,7-heptane dicarboxylic acid, nonanedioic acid: HOOC-(CH2h-COOH) has a molecular weight of 188.22 as shown in Figure 4. Azelaic acid occurs in nature as a straight-chained 9-carbon dicarboxylic acid obtained by nitric acid oxidation of oleic acid or by chemical, physical, or biological oxidation of free esterified fatty acids[31,32]. It is generated *in vivo* by the lipoperoxidation of unsaturated fatty acids and acts as a natural antioxidant. Azelaic acid is produced by omega-oxidation of saturated odd monocarboxylic fatty acids followed by their β-oxidation. Normal individuals have small amounts of AZA present in the urine, while patients with ketosis have excessive amounts present in the urine with an inability to β-oxidation of monocarboxylic acids. AZA, when not eliminated in the urine, is metabolized by mitochondrial β-oxidation, which can enter the Krebs cycle and give rise to CO_2 and to malonyl coenzyme A, which ultimately is involved in fatty acid biosynthesis[32]. Azelaic acid lacks acute or chronic toxicity and is a non-teratogenic and non-mutagenic compound. It is also known to have antiviral and antibacterial effects on various microorganisms and hence is one of the most common treatments for skin-related ailments[33].

Azelaic acid has little or no effect on normal cells, but can selectively penetrate tumoral cells [33]. Azelaic

acid decreased intracellular ROS levels and increased antioxidant capacity. It was also found to be less toxic to peripheral blood mononuclear cells in comparison to cancerous cells, like that of Azelaic acid. Azelaic acid caused cell apoptosis in Acute myeloid leukemia cells. Mitochondrial membrane potential was significantly lost followed by the subsequent arrest of the AML cells at the G0 phase of the cell cycle after Azelaic acid treatment. Hence, suggesting that Azelaic acid can act as an agent responsible for decreasing intracellular ROS levels in a potential method of treating cancer[34].

Azelaic acid and its role in cellular differentiation

Scientific research now demonstrates keen interest in studying how AZA might affect neuroblastoma cells throughout neuronal differentiation processes. The chemical interactions between azelaic acid enable it to affect various cellular pathways through which differentiation processes take place. Research studies the effects of AZA on epigenetic regulation along with cellular signaling and oxidative stress because these mechanisms control cellular maturation and development processes [34]. Research findings demonstrate that AZA affects Notch signaling, which functions as a primary mechanism in cellular differentiation and neurogenesis processes. When Notch signaling becomes active, it shapes progenitor cell fate decisions that lead cells toward developing into either neuronal or glial cells[35]. Scientific evidence suggests that this path may drive neuronal differentiation, which implies AZA can steer neuroblastoma cells toward becoming mature neurons. In a study conducted on Acute Myeloid Leukemia (AML), AZA induced proliferation of NK and T cells and secretion of TNF-α and IFN-γ, causing activation of the cytotoxic ability of T-lymphocytic cells and large granular lymphocytes[34]. Azelaic acid has been proven to show antileukemia effects in clients suffering from acute myeloid leukemia by suppressing cell viability by activating apoptosis[36].

Immunomodulatory effects and the tumor microenvironment

Tumor microenvironment and immune escape

In most cancers, T cells become exhausted and dysfunctional due to persistent stimulations, causing T cell death, which can be detected using the presence of CD57. C57+ T cells release cytokines when activated by specific peptides; however, after activation, they do not divide. These T cells with the residing tumor downregulate CD27 and CD28 costimulatory molecules, causing immune dysfunction by changing the APC phenotype.

Glioblastoma multiforme finds different approaches to weaken people's immune system and evade being destroyed by it as shown in Figure 5. GBM result in elevated production of Intercellular

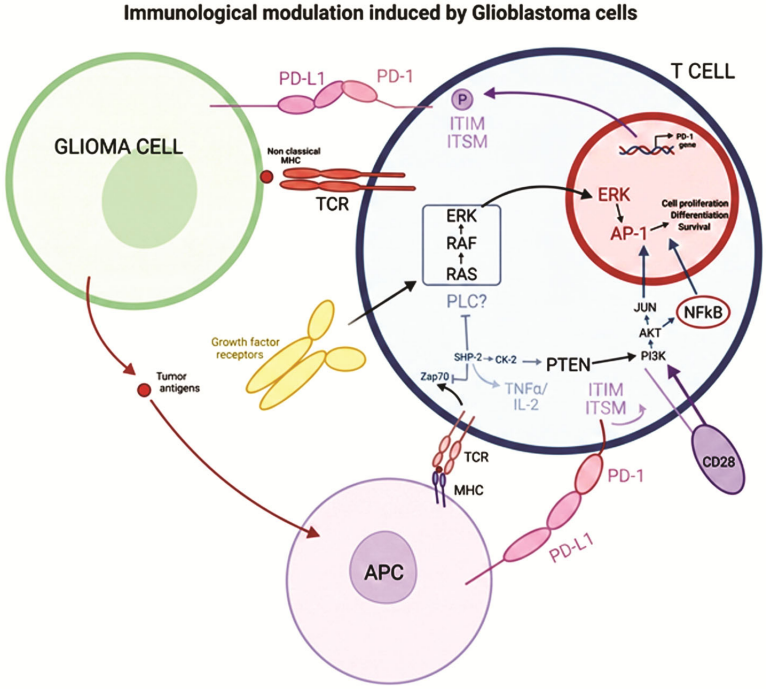

Fig. 5 — Immunological modulation induced by Glioblastoma multiforme cells. Source: [37, 38]

Adhesion Molecule-1 ICAM-11) thereby permitting increased infiltration of myeloid cells to the tumor environment. The process supports lowering the immune response by setting off Myeloid-Derived Suppressor Cells (MDSCs). In GBM tumors, MDSCs mainly prevent the immune system from working properly by secreting TGF-β and arginase. GBM overexpresses Galectin-1, thereby making the T cell subset weaker, as a result the body's immune response is limited and the cancer can successfully evade the tumor immune surveillance. Furthermore, Galectin-1 suppresses Natural Killer (NK) cells activity suppressing the immune function further. GBM is associated with the overexpression of non-classical MHC molecules namely Human Leukocyte Antigen-G (HLA-G) and Human Leukocyte Antigen-E (HLA-E). Interestingly, is known to HLA-G suppresses NK cell activity further contributing in evasion of the tumor immune surveillance. It attaches to the ILT2 receptor on the cell surface and stops cytolytic granules from being released and the Microtubule-Organizing Center (MTOC) from working properly, which weakens the NK cells' ability to destroy cells. HLA-E prevents NK cells from functioning normally, thus giving more protection to cancer cells[37].

Besides, both Fas Ligand (FasL) and Cluster of Differentiation 70 (CD70) are present on GBM cell surfaces, and they help to kill T cells at the tumor site. GBM secretes PD-L1, and this links to PD-1 on T cells, to prevent them from responding and growing further, so they cannot effectively attack the tumor. As a consequence of interfering with the immune system in several ways, GBM makes the tumor area very immune-resistant[38].

The body's immune system may be evaded in neuroblastoma due to specific gene activity patterns. These studies have shown that there is a higher amount of transforming growth factor beta 1 (TGF-β1) and interleukin-10 (IL-10) mRNA involved in these cases. Because of TGF-β1, the immune system is less effective in fighting the tumor since it inhibits the activity of immune cells and decreases the levels of interferon-gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF). In almost one-fifth of neuroblastoma cases, an extra copy of the MYCN oncogene occurs, and this is usually connected to a poor outcome. Such tumors contain increased amounts of genes that relate to B cells, macrophages, and cytokines. Additional research shows that CD68+ TAMs are present in neuroblastomas, and they also have IL-6. Just like CD33-positive blasts, IL-6-producing myelomonocytic cells can also be found in the bone marrow of patients with metastasis. *In vivo* research has found that neuroblastoma prompts PBMCs to release IL-6 and pulls in TAMs, especially in mice that do not have a complete immune system[8].

Neuroblastomas can release C-C motif chemokine ligand 2 (CCL2), a molecule that appeals to uncommon natural killer T (iNKT) cells in the environment surrounding the tumor. Such iNKT cells are marked by having an invariant TCRα chain, however, rearranged with Jα18 and Vβ11. They can detect glycolipids that are shown on the surface together with a CD1d molecule, which is similar to MHC class I. As soon as iNKT cells are stimulated, they produce IL-2, which then triggers NK cells to work more efficiently at eliminating monocytes with antigens from the tumor.

Neuroblastoma can avoid being spotted by the immune system in two major ways.

1 Loss of MICA and MICB ends in undetectable expression of genes like ULBP1, so NKG2D receptors on NK cells ignore the cancer species.
2 The production of soluble MICA results in its attachment to NKG receptors, lowering the number of these receptors and weakening how well NK cells can kill dangerous cells.

The variety of immune escape strategies plays a key role in keeping and accelerating neuroblastoma, mainly when the cancer has advanced or become metastatic[39].

Azelaic acid causes modulation of immune cells

Azelaic acid exhibits antitumor effects on several tumor cells by inhibiting Trx reductase activity, ROS generation, and DNA synthesis in tumor cells. It was found that Azelaic acid suppresses Acute myeloid leukemia cell proliferation and is also responsible for sensitizing AML cells to chemotherapy. Several immune-related signalling pathways were activated by Azelaic acid treatment, the most common one being the Notch signalling pathway. Notch can maintain low ROS levels to promote cell development and survival[35].

Azelaic acid and the azelates are potent modulators of the immune system in array of organisms ranging from plants to higher-order animals. In plants, AZA aids in mobilizing the plant hormone salicylic acid, thereby inducing immune response by defensive responses. In humans, it was found recently that

Diethyl azelate (DAE), an azelate of azelaic acid known to show immunomodulatory effects in human skin[32,40].

Change in lipid bilayer structure and composition can affect inflammatory signaling and innate immune response. Modulation of Plasma Membrane fluidity using lipid-soluble molecules as a treatment for human diseases is now being looked at. Azelates modify PM fluidity in a structure-related manner and have further effects on the activity of the various surface proteins, which are relevant for innate immune responses, ultimately causing varied patterns of signalling molecules. Azelaic acids showing fluidizing effects on Human PBMCs open a wide range of questions yet to be answered in the case of Neuroblastoma and glioblastoma cell lines[41].

In a research study, human plasmacytoid dendritic cells were investigated to find out what role the pattern recognition receptors (PRRs) play in immune activation. TLRs aid signals through the plasma membrane, as they detect the presence of extracellular materials, such as pathogen RNA or DNA, especially found during bacterial and viral infections in the body or after cell damage. The research discovered that using azelaic acid-based esters in skin reduced the impact of PAMP receptors and lowered the body's danger response due to damaged or stressed cells[41].

DAE was also seen to modulate cytokines and growth factor receptor signaling. This was detected by doing a cytokine multiplex immunoassay with 57 cytokines for TLR 1 to 6. There were elevated levels of multiple inflammatory markers like interleukin (IL) 12, IL6, Macrophage inflammatory protein (MIP) 1 alpha, Regulated on activation of normal T cell expressed and secreted proteins (RANTES), Tumor necrosis factor (TNF) alpha, Interferon gamma induced protein 10 (IP 10) and matrix metalloproteinase (MMP) 9, but upon treatment with DAE all these markers were brought back nearly to control levels[41].

Discussion

The effect of Azelaic acid on neuronal and glial cell lines is yet unexplored. Understanding whether azelaic acid induces cell death or cell differentiation would broaden the perspective in cancer research. Depending on which various Neurotrophic factors can be studied to understand the various pathways it might possibly follow. The tumor microenvironment is crucial in regulating cell proliferation. Understanding various cytokines, chemokines, and regulatory proteins pre- and post-treatment would help us identify if Azelaic acid can mitigate anti-tumorogenic effects in Neuronal/ glial cell lines or not. Membrane proteins determine the type of cells and the neurotransmitter the cells will release upon excitation. Understanding the various membrane receptor expression levels would give a deeper understanding of the functional metabolism of the cells. In short, Azelaic acid, as a drug for better recovery along with Chemotherapy and radiation, can potentially improve patients' quality of life.

Conclusion

The review explores and discusses the complex biology of neuroblastoma and glioblastoma multiforme, which are aggressive tumors with poor outcomes. The molecular processes are explored, such as MYCN amplification in neuroblastomas and IDH-wildtype mutations found in glioblastoma, and the role played by neurotrophic factors and evasion of the immune system that enables tumor growth and resistance. The author intends to comprehend the potential role of phytocompounds in reducing the aggressive nature of the tumor cells. Earlier studies with very familiar phytocompounds like curcumin, resveratrol have been known curb the invasiveness. However, reports suggests that these are ineffective in in vivo settings because of their poor bioavailability, rapid metabolism and less permeable via the BBB. Thus, it is inevitable that new phytocompounds such as azelaic acid is studied in these cancer types. The prospects of utilizing azelaic acid to subvert the cancer progression are the central focus here, since it is naturally present, selectively slows tumor growth, promotes cell death in cancer cells, and influences the immune response without harming normal cells. Furthermore, azelaic acid could be studied for its role in redifferentiation of immature neural cells and astrocyte differentiation in neuroblastoma and glioma cells respectively. Exploring the role of neurogenic transcription factors and cell cycle arrest post treatment would aid in validating role of AZA as immunomodulatory molecule. In conclusion, this inspires more research into developing new and less dangerous treatments for these serious cancer types.

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References

1 Kamita M, Waweru H, Githinji M, Kibiro E & Makokha F. Establishing a cancer registry and baseline data for Nyandarua County, Kenya: A step towards establishing a central cancer registry. *Heliyon*, 10 (2024) e39056.

2 Marino P, Mininni M, Deiana G, Marino G, Divella R, Bochicchio I, Giuliano A, Lapadula S, Lettini AR & Sanseverino F. Healthy Lifestyle and Cancer Risk: Modifiable Risk Factors to Prevent Cancer. *Nutrients*, 16 (2024) 800.

3 Chung C, Boterberg T, Lucas J, Panoff J, Valteau-Couanet D, Hero B, Bagatell R & Hill-Kayser CE. Neuroblastoma. *Pediatr Blood Cancer*, 68 (2021) e28473.

4 Liu Y, Lang F, Chou FJ, Zaghloul KA & Yang C. Isocitrate Dehydrogenase Mutations in Glioma: Genetics, Biochemistry, and Clinical Indications. *Biomedicines*, 8 (2020) 294.

5 Yang Y, Zhao J, Zhang Y, Feng T, Yv B, Wang J, Gao Y, Yin M, Tang J & Li Y. MYCN protein stability is a better prognostic indicator in neuroblastoma. *BMC Pediatrics*, 22 (2022) 404.

6 Kevin C, Naranjo A, Hibbitts E, Gastier-Foster JM, Bagatell R, Irwin MS, Shimada H, Hogarty M, Park JR & DuBois SG. "Association of heterogeneous MYCN amplification with clinical features, biological characteristics and outcomes in neuroblastoma: A report from the Children's Oncology Group." *Eur J Cancer,* 133 (2020) 112.

7 Geng J, Wang X, Zhao L, Zhang J & Niu H. Segmental chromosome aberrations as a prognostic factor of neuroblastoma: a meta-analysis and systematic review. *Transl Pediatr*, 13 (2024) 1789.

8 Irwin MS & Goldsmith KC. Current and Emerging Biomarkers: Impact on Risk Stratification for Neuroblastoma. *J Natl Compr Canc Netw*, 22 (2024) e247051.

9 Bu L, Hameed NUF, Luo C, Hong P, Zhou X, Wang S & Wu S. Germline ALK variations are associated with a poor prognosis in glioma and IDH-wildtype glioblastoma. *J Neurooncol*, 152 (2021) 27.

10 Peggion S, Najem S, Kolman JP, Reinshagen K & Pagerols Raluy L. Revisiting Neuroblastoma: Nrf2, NF-κB and Phox2B as a Promising Network in Neuroblastoma. *Curr Issues Mol Biol*, 46 (2024) 3193.

11 Nokchan N, Suthapot P, Choochuen P, Khongcharoen N, Hongeng S, Anurathapan U, Surachat K & Sangkhathat S. Whole-Exome Sequencing Reveals Novel Candidate Driver Mutations and Potential Druggable Mutations in Patients with High-Risk Neuroblastoma. *J Pers Med*, 14 (2024) 950.

12 Leathers TA & Rogers CD. Time to go: neural crest cell epithelial-to-mesenchymal transition. *Development*, 149 (2022) dev200712.

13 Esmaeli M, Barazesh M, Karimi Z, Roshankhah S, & Ghanbari A. Molecular signaling directing neural plate border formation. *Int J Dev Biol*, 68 (2024) 65.

14 Cao Y. Neural induction drives body axis formation during embryogenesis, but a neural induction-like process drives tumorigenesis in postnatal animals. *Front Cell Dev Biol*, 11 (2023) 1092667.

15 Mehrotra P, Tseropoulos G, Bronner ME & Andreadis ST. Adult tissue–derived neural crest-like stem cells: Sources, regulatory networks, and translational potential. *Stem Cells Transl Med*, 9 (2020) 328.

16 Manzari-Tavakoli A, Babajani A, Farjoo MH, Hajinasrollah M, Bahrami S & Niknejad H. The Cross-Talks Among Bone Morphogenetic Protein (BMP) Signaling and Other Prominent Pathways Involved in Neural Differentiation. *Front Mol Neurosci*, 15 (2022) 827275.

17 Perera SN & Kerosuo L. On the road again: Establishment and maintenance of stemness in the neural crest from embryo to adulthood. *Stem Cells*, 39 (2021) 7.

18 Sutton G, Kelsh RN & Scholpp S. Review: The Role of Wnt/β-Catenin Signalling in Neural Crest Development in Zebrafish. *Front Cell Dev Biol*, 9 (2021) 782445.

19 Ahmad MH, Ghosh B, Rizvi MA, Ali M, Kaur L & Mondal AC. Neural crest cells development and neuroblastoma progression: Role of Wnt signaling. *J Cell Physiol*, 238 (2023) 306.

20 Park YW, Vollmuth P, Foltyn-Dumitru M, Sahm F, Ahn SS, Chang JH & Kim SH. The 2021 WHO Classification for Gliomas and Implications on Imaging Diagnosis: Part 1—Key Points of the Fifth Edition and Summary of Imaging Findings on Adult-Type Diffuse Gliomas. *J Magn Reson Imaging*, 58 (2023) 677.

21 Khabibov M, Garifullin A, Boumber Y, Khaddour K, Fernandez M, Khamitov F, Khalikova L, Kuznetsova N, Kit O & Kharin L. Signaling pathways and therapeutic approaches in glioblastoma multiforme (Review). *Int J Oncol*, 60 (2022) 69.

22 Panvino F, Paparella R, Tarani F, Lombardi C, Ferraguti G, Pisani F, Fiore M, Pancheva R, Ardizzone I & Tarani L. Neurotrophins in Neurodevelopmental Disorders: A Narrative Review of the Literature. *Int J Mol Sci*, 26 (2025)

23 Colucci-D'Amato L, Speranza L & Volpicelli F. Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. *Int J Mol Sci*, 21 (2020) 7777.

24 Camuso S, La Rosa P, Fiorenza MT & Canterini S. Pleiotropic effects of BDNF on the cerebellum and hippocampus: Implications for neurodevelopmental disorders. *Neurobiol Dis*, 163 (2022) 105606.

25 Yang L, Zheng YX, Liu JP, Xu YS, Zhu FQ, Zhang WJ & Zou R. Schwann cells drive tumor progression through neuro-tumor crosstalk. *Int J Surg*, 112 (2026) 4510.

26 Capossela L, Gatto A, Ferretti S, Di Sarno L, Graglia B, Massese M, Soligo M & Chiaretti A. Multifaceted Roles of Nerve Growth Factor: A Comprehensive Review with a Special Insight into Pediatric Perspectives. *Biology (Basel)*, 13 (2024) 546.

27 Yan Z, Shi X, Wang H, Si C, Liu Q & Du Y. Neurotrophin-3 Promotes the Neuronal Differentiation of BMSCs and Improves Cognitive Function in a Rat Model of Alzheimer's Disease. *Front Cell Neurosci*, 15 (2021) 629356.

28 Kim M, Hwang SU, Yoon JD, Lee J, Kim E, Cai L, Kim G, Choi H, Oh D & Hyun SH. Beneficial Effects of Neurotrophin-4 Supplementation During in vitro Maturation of Porcine Cumulus-Oocyte Complexes and Subsequent Embryonic Development After Parthenogenetic Activation. *Front Vet Sci*, 8 (2021) 779298.

29 Kotliarova A & Sidorova YA. Glial Cell Line-Derived Neurotrophic Factor Family Ligands, Players at the Interface of Neuroinflammation and Neuroprotection: Focus Onto the Glia. *Front Cell Neurosci*, 15 (2021) 679034.

30 Mol P, Balaya RDA, Dagamajalu S, Babu S, Chandrasekaran P, Raghavan R, Suresh S, Ravishankara N, Raju AH, Nair B,

Modi PK, Mahadevan A, Prasad TSK & Raju R. A network map of GDNF/RET signaling pathway in physiological and pathological conditions. *J Cell Commun Signal*, 17 (2023) 1089.
31 Sieber MA & Hegel JKE. Azelaic acid: Properties and mode of action. *Skin Pharmacol Physiol*, 27 (2014) 9.
32 Feng X, Shang J, Gu Z, Gong J, Chen Y & Liu Y. Azelaic Acid: Mechanisms of Action and Clinical Applications. *Clin Cosmet Investig Dermatol*, 17 (2024) 2359.
33 Álvarez-Rodríguez S, Senizza B, Araniti F, Lucini L, Lucchini G & Sánchez-Moreiras AM. Evaluating the effects of azelaic acid in the metabolism of Arabidopsis thaliana seedlings through untargeted metabolomics and ionomics approaches. *Physiol Plant*, 176 (2024) e14550.
34 Agostino S Di, Vito A Di, Aloisio A, Piazzetta GL, Lobello N, Bria J, Chiarella E, Agostino S Di, Vito A Di, Aloisio A, Piazzetta GL, Lobello N, Bria J & Chiarella E. Harnessing Azelaic Acid for Acute Myeloid Leukemia Treatment: A Novel Approach to Overcoming Chemoresistance and Improving Outcomes. *Int J Mol Sci*, 26 (2025) 4362.
35 Gonzalez R & Reinberg D. The Notch pathway: A guardian of cell fate during neurogenesis. *Curr Opin Cell Biol*, 95 (2025) 102543.
36 Zhang D, Luo Z, Jin Y, Chen Y, Yang T, Yang Q, Wu B, Shang Y, Liu X, Wei Y & Zhou F. Azelaic Acid Exerts Antileukemia Effects against Acute Myeloid Leukemia by Regulating the Prdxs/ROS Signaling Pathway. *Oxid Med Cell Longev*, 2020 (2020) 1295984.
37 Basheer AS, Abas F, Othman I & Naidu R. Role of inflammatory mediators, macrophages, and neutrophils in glioma maintenance and progression: Mechanistic understanding and potential therapeutic applications. *Cancers (Basel)*, 13 (2021) 4226.
38 Puviindran BJ, Wallace S, Ayasoufi K, Lerner E & Fecci PE. Within and beyond the tumor: Mechanisms of glioblastoma-induced immunosuppression. *Neuro-Oncology Adv*, 7 (2025) iv4.
39 Wienke J, Dierselhuis MP, Tytgat GAM, Künkele A, Nierkens S & Molenaar JJ. The immune landscape of neuroblastoma: Challenges and opportunities for novel therapeutic strategies in pediatric oncology. *Eur J Cancer*, 144 (2021) 123.
40 Izbicka E & Streeper RT. Azelaic Acid Esters as Pluripotent Immunomodulatory Molecules: Nutritional Supplements or Drugs. *Nutraceuticals*, 1 (2021) 42.
41 Izbicka E & Streeper RT. Adaptive Membrane Fluidity Modulation: A Feedback Regulated Homeostatic System Hiding in Plain Sight. *In Vivo (Brooklyn)*, 35 (2021) 2991.