



Therapeutic Targeting on Death Pathways In Glioblastoma

Pavithra Suppiah¹, Julia Joseph¹, Rolla Al-Shalabi¹, Nik Nur Syazni Nik Mohamed kamal¹, Nozlana Abdul Samad*¹

Abstract

Glioblastoma multiforme (GBM) is a type of aggressive glioma composed of star-shaped glial cells; it is also known as grade IV astrocytoma. Alterations are enhancing therapeutic effectiveness for individuals with glioblastoma to several targeted medicines that target cell death pathways such apoptosis (type I), autophagic cell death (type II), and necrosis (type III). The purpose of this review was to compile information about the various methods of killing cancer cells in glioblastoma and the treatments currently being used. This review aimed to determine the effectiveness of targeted therapy on glioblastoma death pathways, both intrinsic and extrinsic. Furthermore, nanoparticles studies represented a significant advance in glioblastoma via combinatorial therapy. Targeting specific proteins or genes using drug-loaded nanoparticles has promise as a treatment for glioblastoma.

Key Words: Apoptosis; Astrocytoma; Blood-Brain Barrier; Glioblastoma; Nanoparticles.

Significance | Current drug discovery information for glioblastoma

*Correspondence: Nozlana Abdul Samad, Advanced Medical and Dental Institute, Sains@BERTAM, Universiti Sains Malaysia, Kepala Batas, Penang, Malaysia. Email: nozlana@usm.my

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Introduction

Glioblastoma multiforme (GBM) is a rapidly developing glioma composed of glial cells structured like stars (i.e., astrocytes and oligodendrocytes). It is also known as astrocytoma of grade IV (Goldsmith & Hogarty, 2005). The glial cells are responsible for the deterioration of the spinal cord and brain's nerve cells' health. This form of glial tumour is characterised by fast growth and subsequent dissemination to surrounding spinal and brain regions. The majority of glioblastoma (GBM) is located in the cerebral hemispheres, particularly the frontal and temporal lobes (Banu, 2019). Berns and Abernety described gliomas for the first time in 1800 and 1804, as documented in their respective works. These scientific results were published in British scientific publications, with Rudolf Virchow receiving credit for the first full histomorphological description in 1865. Glioblastoma (GBM) is an aggressive form of brain cancer that often results in death within 15 months after diagnosis (Stoyanov & Dzhenkov, 2018).

Glioblastoma (GBM) is a very aggressive and deadly brain tumour (Ohgaki & Kleihues, 2012). The cure and treatment of glioblastoma (GBM) tumours remain a big problem for researchers, as surgery, radiation, and chemotherapy are unlikely to induce long-term remission. Therefore, several targeted medicines are launched to target the cell death pathways, such as apoptosis (type I cell death), autophagic cell death (type II cell death), and necrosis (type III cell death), of tumour cells in an effort to enhance the treatment results for glioblastoma patients. For decades, these medicines have been accessible for the exploratory treatment of glioblastoma (GBM). However, there is no evidence-based evaluation of the new glioblastoma targeting death pathways. Therefore, this study aims to examine all forms of glioblastoma death mechanisms and existing treatments. The results of this study are anticipated to aid future researchers in improving treatment targeting in glioblastoma (GBM).

Author Affiliation:

¹Department of Toxicology, Advanced Medical and Dental Institute, Sains@BERTAM, Universiti Sains Malaysia, Kepala Batas, Penang, Malaysia

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Over the past three decades, several studies and research have been conducted on the cell death pathway in an effort to develop effective treatments for glioblastoma (GBM). According to clinical statistics, effective medicines have increased the median survival of glioblastoma (GBM) patients by three months. However, there is no evidence-based analysis of the unique targeting of glioblastoma cell death pathways. Essentially, a systematic review that seeks to extract meaningful lessons from the findings of a variety of research. At some point, the paucity of data, the length of time, and the difficulty of gathering genuine, trustworthy evidence about cell death pathways may have posed obstacles for researchers conducting evidence-based reviews. As an improvement, our study assisted in discovering and synthesising all the research publications pertaining to a broader range of inclusion criteria connected to targeting on glioblastoma-associated death pathways.

This study's primary purpose is to examine all sorts of cell death mechanisms in glioblastoma and existing treatments. The particular aims of this study were to examine papers published between 2010 and 2020 on the treatment of glioblastoma. The papers were chosen precisely within the last ten years to guarantee that the study evidence was current and connected with current research and development, hence eliminating doubt in the final outcomes of this systematic review. The second particular purpose was to establish the efficacy of treatment for glioblastoma. Last but not least, we compared the nanoparticles therapy trials for glioblastoma treatment. This comparative study examined the characteristics and responsiveness of nanoparticles as targeted therapeutics on glioblastoma cell death pathways.

Therapeutic Effectiveness on Targeting Apoptosis Pathways in Glioblastoma (GBM)

Several targeting pathways have been analysed in the research selected from the literature (Table 1).

According to the findings, gingerol's potential efficacy in TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis may be gained via reactive oxygen species (ROS) production in U87 glioblastoma cells. In a total of three further trials, the therapeutic targeted pathways that generated oxidative stress have been identified (Kusaczuk et al 2018; Cheng et al., 2020; Xu et al., 2010).

Targeting the corresponding proteins and genes decreased cell proliferation, metastasis, invasion, and glioblastoma (GBM) cell's apoptotic cycle, demonstrating their efficiency (apoptotic pathways). The targeted microRNA (miRNA) and protein overexpression has suppressed glioblastoma cell growth and affected apoptosis. This conclusion is based on cell transfection, real-time quantitative reverse transcription- polymerase chain (qRT-PCR), and Western Blot assays from three separate studies,

namely Lei et al. (2017), Wang et al. (2017), and Pall et al. (2017). (2019). Targeting the oncogene epidermal growth factor-containing, fibulin-like extracellular matrix protein 1 (EFEMP1) and microRNA-388-5p (miR-388-5p) decreased the proliferation, metastasis, invasion, and apoptotic cycle of glioblastoma (GBM) cells globally (Lei et al.,2017).

Similarly, overexpression of Fas-associated protein with death domain (FADD) and Caspase-8 promotes apoptosis in SHG 44. Even without death receptor ligands, Fas-associated protein with death domain (FADD) overexpression can trigger and increase cell apoptosis. Pall et al. (2019) showed that overexpression of Na⁺(K⁺)/H⁺ Exchanger Isoform 9 (NHE9) promoted glioblastoma cell proliferation and migration by increasing the density of epidermal growth factor receptors (EGFRs) in the plasma membrane. Na⁺(K⁺)/H⁺ Exchanger Isoform 9 (NHE9) overexpression is characterised by an increase in panspecific plasma membrane receptors. Surprisingly, the increase of function in Na⁺(K⁺)/H⁺ Exchanger Isoform 9 (NHE9) may be exploited to target and eliminate GBM cells successfully. When GBM cells overexpressing Na⁺(K⁺)/H⁺ Exchanger Isoform 9 (NHE9) were exposed to gold nanoparticles, they acquired much more gold via receptor-mediated endocytosis than control cells. Using near-infrared light to irradiate these cells led to the apoptotic death of cancer cells.

In addition, therapeutic pathways mediate temozolomide resistance and trigger cell cycle apoptosis, as proven by six studies (Xu et al., 2018; Cui et al., 2020; Trevisan et al., 2020; Forte et al., 2019; Vengoji et al., 2019; Avci et al., 2020). Mitogen-activated protein kinases (MAPK) have been identified as a signaling mechanism in cancer development. Moreover, cellular transformation drives the activation of mitogen-activated protein kinases (MAPK) pathways. TMZ-resistant glioblastoma cells were triggered through mitogen-activated protein kinases (MAPK) signaling pathways (i.e., overexpression of mitogen-activated protein kinases 8 (MAPK8)), hence inhibiting the apoptotic cell cycle (Xu et al., 2018). Furthermore, by inducing mitochondrial signal transducer and activator of transcription 3 (STAT3) translocation and respiratory chain malfunction, signal transducer and activator of transcription 3 (STAT3) was suppressed and temozolomide-resistant glioblastoma cell death was further promoted (Cui et al., 2020).

Apoptotic pathways in GBM

Based on the research conducted, (Table 2) summarised and presented a clear picture of the death pathways studied in the selected literature studies. Furthermore, knowing apoptosis pathways offered insight into the efficacy of targeted therapy on respective death pathways.

Mitochondria mediated pathways

A summary of selected literature research (Table 2) revealed eleven results targeting mitochondrial pathways. The majority of glioblastoma research have mostly focused on mitochondrial pathways, however in this study, the cell cycle controller, p53 expression, and the caspase-independent apoptosis marker, Cathepsin D, are highlighted and tend to demonstrate positive outcomes in apoptotic mechanisms (Lopez & Tait, 2015).

Epidermal growth factor receptor

According to the analysis, nine research focused on epidermal growth factor receptor (EGFR) pathways in treating and causing cell death. The epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and the primary downstream signaling pathway via phosphoinositide-3 kinase/protein kinase B (PI3K)/AKT are known to be changed in glioblastoma (Xu et al., 2017).

Death receptors pathways

Three research at most were found to have focused on the paths taken by death receptors. In this investigation, apoptosis was induced via extrinsic pathways by the death ligand tumour necrosis factor (TNF), Fas ligand (FasL), also known as TRAIL (15). D. H. Lee et al. (2014) found that glioblastoma (GBM) cells were amenable to tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis, and that gingerols impacting this molecular process activated TRAIL-induced apoptosis.

Intrinsic and Extrinsic pathways

Twenty out of the twenty-three studies that looked at therapeutic targeting in glioblastoma cells predominantly focused on intrinsic rather than extrinsic mechanisms (Figure 1). Death caspase 3, which is activated by both the intrinsic and extrinsic pathways, is ultimately triggered by caspase 8. Both paths appeared to be interconnected and could even have an effect on one another.

Nanoparticles targeted therapy approach in glioblastoma

Table 3 summarises the data from three studies that looked at the use of nanoparticles in the treatment of glioblastoma. Using silica nanoparticles, gold nanoparticles, and RNA nanoparticles to deliver antitumoral medicines or genetic material is a fresh and inventive approach to treating the tumour of glioblastoma, as demonstrated by the research.

Discussion

The majority of studies targeted specific proteins and genes, such as via overexpression of Na⁺(K⁺)/H⁺ Exchanger Isoform 9 (NHE9), Fas-associated protein with death domain (FADD) and Caspase-8 consequently, these studies clearly demonstrate a positive outcome for therapeutics targeting these specific death pathways. In addition, only a few published works address temozolomide (TMZ) resistance. Ultimately, temozolomide (TMZ), which is known to be a deoxyribonucleic acid (DNA)

alkylating agent, caused cell cycle arrest at gap 2/mitosis (G2/M) and apoptosis. By that time, it was also effective against brain tumours. Resistance to temozolomide (TMZ) is mediated by changes in the expression of DNA alkylating proteins and DNA repair enzymes and alterations in cell signalling pathways. Therefore, combinatorial treatments are more likely to be proposed as a therapy for glioblastoma.

Apoptosis is a crucial step to maintain the homeostatic balance of cell proliferation and death. It is a process in which cells start a biochemical pathway that leads to their death if they get injured and when the repair system fails (Valdés-Rives et al., 2017).

In cancer, apoptosis via the mitochondrial route is the most often dysregulated mode of cell death. This process is characterised by mitochondrial outer membrane permeabilization (MOMP), which permanently causes cell death (Lopez & Tait, 2015). The opening of the permeability transition (PT) pore results in the decoupling of oxidative phosphorylation, which is caused by the breakdown of the proton gradient created by electron transport. When the permeability transition (PT) channel develops, water enters the mitochondrial matrix, causing widening of the inner mitochondrial membrane gap and rupturing the outer membrane, eventually releasing apoptogenic proteins (Hooper & Killick, 2021). Consequently, active Bcl-2-associated X (BAX) is required to permeate the mitochondrial outer membrane. However, this action's mechanism remains uncertain. Bcl-2-associated X (BAX) activation is always contingent upon direct interaction with a Bcl-2 homology 3 (BH3)-only protein family member. This results in the oligomerisation of Bcl-2-associated X (BAX) within the mitochondrial outer membrane (Lopez & Tait, 2015). Eleven discoveries targeting mitochondrial pathways were described based on a summary of selected literature research (Table 2). The majority of glioblastoma studies focused on mitochondrial pathways. Silva et al. (2019) state that WIN55,212-2 (WIN) induces caspase-independent apoptosis in GBM cells. In this work, the cell cycle regulator, p53 expression, and the caspase-independent apoptosis marker, Cathepsin D, are discussed and tend to demonstrate positive outcomes in apoptosis processes.

According to Cui et al. (2020), SH-4-54 may concentrate on the mitochondrion to promote mitochondrial signal transducer and activator of transcription 3 (mitoSTAT3) translocation and enhance the integration of signal transducer and activator of transcription 3 (STAT3) and focused complexes, implying that SH-4-54 enhanced mitochondrial signal transducer and activator of transcription 3 (mitoSTAT3) may play a role in amplifying mitochondrial dysfunction.

Similarly, T. J. Lee et al. (2017) noted that the effect of the phosphatidylinositol-3 kinase (PTEN-AKT) (cell growth) mechanism, which increases the degree to which a cell cycle is paused, might be attributable to a considerable increase in this key

Table 1. Summary on the therapeutic targeting on death pathways in glioblastoma of literature studies.

Targeted therapy	Specific proteins/gene of death pathways	Types of studies	References
Gingerol	TRAIL-induced apoptosis	<i>In vitro</i>	(D. H. Lee et al., 2014)
MiR-338-5p	EFEMP1	<i>In vitro</i>	(Lei et al., 2017)
FADD Caspase 8	Proliferation of SHG44 cell line	<i>In vitro</i>	(Wang et al., 2017)
MAPK8	MAPK	<i>In vitro</i>	(Xu et al., 2018)
WIN55,212-2	HSP70 p53 Cathepsin D	<i>In vivo</i> <i>In vitro</i>	(Silva et al., 2019)
STAT3	mitoSTAT3 Respiratory dysfunction	<i>In vitro</i> <i>In vivo</i>	(Cui et al., 2020)
RNA nanoparticle	Oncogenic miR-21	<i>In vivo</i> <i>In vitro</i>	(T. J. Lee et al., 2017)
PIK3CB siRNA	P13K-AKT-mTOR	<i>In vivo</i> <i>In vitro</i>	(Cen et al., 2018)
LXR agonist	EGFR AKT SREBP-1 LDLR-Dependent Pathway	<i>In vivo</i> <i>In vitro</i>	(Guo et al., 2011)
P13K BCI-2	Apoptosis downregulation of <i>MCI-1 Phospho-BAD</i>	<i>In vitro</i> <i>Ex vivo</i>	(Pareja et al., 2014)
CD44	Mammalian HIPPO signalling pathway	<i>In vitro</i> <i>In vivo</i>	(Yin Xu et al., 2010)
RF-Id	IAP NF-κB	<i>In vitro</i>	(Zappavigna et al., 2016)
Lycorine	AKT MMP9 protein	<i>In vivo</i> <i>In vitro</i>	(Shen et al., 2018)
DGAT1	<u>Lipid homeostasis</u>	<i>In vitro</i> <i>Ex vivo</i>	(Cheng et al., 2020)
Cold Atmospheric Plasma Gold Quantum Dots	Fas/TRAIL	<i>In vitro</i>	(Kaushik et al., 2020)
Silica Nanoparticle (SiNPs)	LN229 cells	<i>In vitro</i>	(Kusaczuk et al., 2018)
Gold Nanoparticle (GNP)	NHE9 EGFR	<i>In vitro</i>	(Pall et al., 2019)
Cytoplasmic p53 couple's oncogene-driven glucose metabolism	EGFR-driven glucose	<i>In vivo</i> <i>In vitro</i>	(Mai et al., 2017)
Bay 11-7082 Temozolomide (TMZ)	NF-κB (p65)	<i>In vitro</i>	(Avci et al., 2020)
Temozolomide (TMZ)	p53	<i>In vitro</i>	(Maria Forte et al., 2019)
Ionising radiation Temozolomide (TMZ)	miRNAs MGMT gene	<i>In vitro</i>	(Trevisan et al., 2020)
Afatinib Temozolomide (TMZ)	EGFRvIII-cMet	<i>In vivo</i> <i>In vitro</i>	(Vengoji et al., 2019)
RND2	p38 MAPK	<i>In vivo</i> <i>In vitro</i>	(Yang Xu et al., 2020)

Table 1. Summary of the respective death pathways in regard of targeted therapies.

Death pathways	References
Death receptor pathways	(D. H. Lee et al., 2014), (Wang et al., 2017), (Kaushik et al., 2020)
Epidermal growth receptor pathways	(Lei et al., 2017), (P. Xu et al., 2018), (Cen et al., 2018), (Guo et al., 2011), (Shen et al., 2018), (Pall et al., 2019), (Mai et al., 2017), (Trevisan et al., 2020), (Vengoji et al., 2019)
Mitochondrial pathways	(Silva et al., 2019), (Cui et al., 2020), (T. J. Lee et al., 2017), (Pareja et al., 2014), (Yin Xu et al., 2010), (Zappavigna et al., 2016), (Cheng et al., 2020), (Kusaczuk et al., 2018), (Avci et al., 2020), (Maria Forte et al., 2019) (Yang Xu et al., 2020)

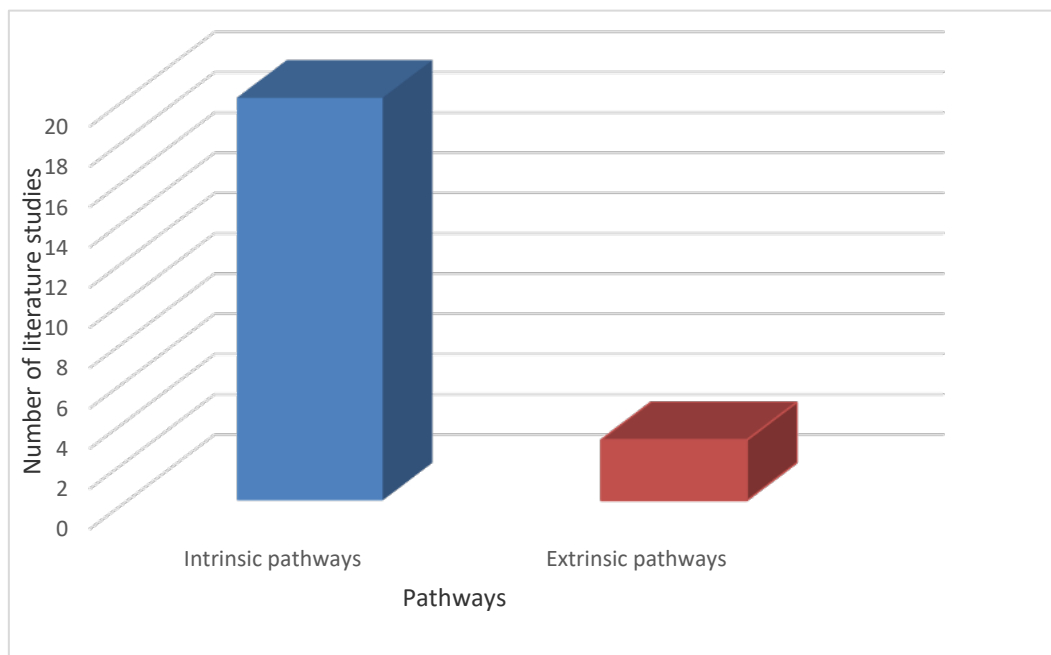


Figure 2. Selected literature studies relative to the extrinsic and intrinsic pathways.

Table 2. Summary on nanoparticles studies and the respective years of the selected literature studies.

Year published	2017	2018	2019
Nanoparticles studies	RNA Nanoparticle-Based Targeted Therapy for glioblastoma through Inhibition of Oncogenic miR-21	Silica nanoparticle-induced oxidative stress and mitochondrial damage is followed by activation of intrinsic apoptosis pathway in glioblastoma cells	A gain of function paradox: Targeted therapy for glioblastoma associated with abnormal NHE9 expression
Specific nanoparticles	RNA nanoparticle	Silica Nanoparticle (SiNPs)	Gold Nanoparticle (GNP)
References	(T. J. Lee et al., 2017)	(Kusaczuk et al., 2018)	(Pall et al., 2019)

signalling pathway. In the brains of mice treated with folic acid-3 Way Junction RNA- Locked Nuclei Acid-microRNA-21 ribonucleoprotein (FA-3WJ-LNA-miR21 RNP), the cleft variants of Caspase-3 and poly (ADP-ribose) polymerase (PARP) proteins were increased, indicating that this intervention accelerated cell apoptosis selectively at the tumour site. Pareja et al. (2014) reported elevated levels of the antiapoptotic Bcl-2 family of proteins and hyperactivity of the phosphatidylinositol 3-kinase, indicating that death pathways were dysregulated (P13K). Interfering with the phosphatidylinositol 3-kinase (P13K) pathway and the Bcl-2 protein family is a possible first-line treatment.

In vivo studies demonstrate that Cluster of Differentiation 44 (CD44) reduces the expression of the Hippo apoptotic signalling pathway in glioblastoma cells, functioning as a chemoprotector. CD44's role in shielding cancerous cells from oxidative and cytotoxic stress-induced apoptosis and its potential to increase receptor tyrosine kinases (RTK) signalling suggests that it may be a useful therapeutic target for sensitising malignant glioma to RTK inhibitors (Xu et al., 2010). According to Zappavigna et al., Radio Frequency Identification (Rf-Id) suppressed inhibitors of apoptosis proteins (IAP) family proteins and the nuclear factor kappa B (NF-Kb) pathway in glioblastoma cells, resulting in caspase-dependent death (2016).

The epidermal growth factor receptor (EGFR) signalling system is one of the most critical mechanisms that govern mammalian cell development, survival, proliferation, and differentiation (Oda et al., 2005). Glioblastomas are known to have altered outer membrane binding sites and downstream molecules, including the epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and the major downstream signalling pathway via phosphoinositide-3 kinase/protein kinase B (PI3K)/AKT. In addition, phosphatase and TENsin homolog deleted on chromosome 10 (PTEN), which inhibited the phosphoinositide-3 kinase/protein kinase B (PI3K)/AKT pathway, and mammalian target of rapamycin (mTOR), which includes the tumour suppressor molecule phosphatase and TENsin homolog deleted on chromosome 10, were identified (PTEN). Furthermore, overexpression of the gene encoding epidermal growth factor receptors (EGFR) was found in around 40% of initial glioblastomas, but in only a tiny percentage of secondary glioblastomas (Eisele & Weller, 2013).

Moreover, death receptors have a cytoplasmic region known as the "death domain" that enables them to create lethal signals when activated by their specific ligands. When a receptor connects to a ligand, it aggregates and interacts with adaptor proteins, which then bind and activate initiator caspases 8 and 10. These occurrences initiate a proteolytic cascade. Consistent evidence suggests that death receptors (Ectodysplasin-A Receptor) and nerve growth factor receptor (NGFR) are mostly responsible for

producing cytotoxic signals (Guicciardi & Gores, 2009). Following ligand contact, the intracellular death domain (DD) of death receptors links directly or indirectly with an adaptor protein known as Fas-associated death domain (FADD) through TNFR-associated death domain (TRADD). Fas-associated death domain (FADD) further interacts with procaspase-8 to produce the death-inducing signalling complex at the receptor (DISC). When the death-inducing signalling complex (DISC) is created, it activates caspase-8, which in turn activates effector caspases. Pro-caspase 8 cleaves the BH3-only protein BH3 interacting-domain death (Bid), which is subsequently translocated to the mitochondria and activates the intrinsic pathway, so uniting the two death processes (Hooper & Killick, 2021).

Similarly, the mitochondrial and epidermal growth factor receptor (EGFR) signalling pathways are essentially defined by the intrinsic route. Modifications in these pathways are well-known, but further combinatory therapies can be developed to boost efficacy via intrinsic pathways. The extrinsic mechanism of secondary hemostasis is simpler than the intrinsic system; transmembrane receptor-mediated interactions start apoptosis. Endothelial cells produce tissue factor following vascular injury, which increases factor VII to factor VIIa. The activated factor X is subsequently transformed into factor Xa by factor VIIa. At this time, both the extrinsic and intrinsic paths converge. The duration of prothrombin is a clinical sign of the extrinsic pathway. These investigations indicated that this route may enhance existing and future glioblastoma therapies. Importantly, tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) has emerged as the most promising therapeutic target for glioblastoma; however, more in vivo research is required to evaluate the viability of this approach further. However, initiating an energy-dependent cascade of metabolic processes requires a unique set of initiating signals. Each route (intrinsic and extrinsic) activates its own caspase (8, 9, 10) while caspase 3, the death caspase, is activated later. Evidently, the two paths are interconnected and may also impact one another.

Nanoparticles (NPs) have been found as potential "theranostics" for the diagnosis and treatment of glioblastoma cancers (Nduom et al., 2012). As delivery agents for glioblastoma cells, researchers have examined natural polymers, synthetic polymers, lipidic nanoparticles (NPs), poly(ethylenimine) derivatives, dendrimers, carbon-based nanoparticles, iron and zinc nanoparticles, gold and silver nanoparticles, silica and silicon nanoparticles. Aside from that, several research have established the effectiveness of delivering targeted medicines to glioblastoma cell lines in vitro, although just a handful have demonstrated the same effectiveness in brain xenografts. The addition of compounds designed to facilitate blood brain barrier (BBB) crossing onto nanoparticles (NPs) enhances the likelihood that nanoparticles (NPs) will

efficiently transport their therapeutic payload to glioblastoma brain xenografts. In terms of silica nanoparticles, polyphenols, and drug-resistant chemotherapeutic agents, docetaxel (Doc) can be coupled with functionalised silica-based nanoparticles to enhance the efficacy of polyphenols and chemotherapeutic medications in drug-resistant tumours, such as prostate cancer (Chaudhry et al., 2021). Silica nanoparticles (SiNP) induced oxidative stress by overproducing reactive oxygen species (ROS), which was then followed by an imbalance in the oxidant-antioxidant system, a decrease in mitochondrial function, and activation of the intrinsic apoptotic pathway.

Due to their outstanding biocompatibility, low toxicity, high atomic number, and high X-ray absorption coefficient, gold nanoparticles (GNPs) applications in the treatment of glioblastoma (GBM) have garnered considerable interest for usage in a range of imaging methods. Gold nanoparticle (GNPs) synthesis is both technically and commercially viable (Meola et al., 2018). Comparatively, to prevent the effects of serum proteins and changes in the net charge of gold nanoparticles (GNPs), gold nanoparticles (GNPs) absorb portions of the studies in serum-free media so that cell culture can be conducted under controlled conditions with potentially confounding variables. A tenfold rise in NHE9 transcript levels led to a seventeenfold increase in absorption of gold nanoparticles (GNPs) through clathrin-mediated endocytosis. In addition, the overexpression of Na⁺(K⁺)/H⁺ exchanger isoform 9 (NHE9) has increased the carcinogenic potential of a subset of glioblastoma GBMs, but it also offers chances for innovative targeted therapies. In addition, NEPTT enhances the effectiveness of erlotinib by many times (Pall et al., 2019). Na⁺(K⁺)/H⁺ exchanger isoform 9 (NHE9) expression using gold nanoparticles (GNPs) presents an interesting therapeutic target in treating glioblastoma, however more in vivo research with mice and incorporates ribonucleic acid (RNA) nanoparticles and Silica nanoparticles are required.

According to research, numerous elements of the cellular activity of glioblastoma LN229 cells are harmed by silica nanoparticles (SiNPs). In addition, excessive formation of reactive oxygen species (ROS), mitochondrial damage, and endoplasmic reticulum (ER) stress all lead to cell death.

In addition, folic acid (FA)-conjugated promoter-associated RNA-3-way junction ribonucleoprotein (pRNA—3WJ RNP) for glioblastoma (GBM) targeting therapeutics via folate receptor-mediated as a preferential delivery of an anti-microRNA-21 locked nucleic acid (miR-21 LNA) with therapeutic potential and biodistribution profiles. In addition to its accessibility and variety in therapeutic applications, RNA alterations in RNA nanoparticle research should be justified.

Compared to research involving silica nanoparticles and ribonucleic acid (RNA) nanoparticles, the application of gold

nanoparticles in the treatment of glioblastoma seems highly promising. In conjunction with Na⁺(K⁺)/H⁺ exchanger isoform (NHE9) expression, considerable gold accumulation via receptor-mediated endocytosis was observed. In addition, the transport of gold nanoparticles (GNPs) is aided by a tight connection between macrophages and (glioblastoma9+) GBM9+ cancer cells (Pall et al., 2019). Gold nanoparticles (GNPs) occur in malignancies due to enhanced permeability and retention due to passing through a damaged endothelial tumour vasculature, especially in the latter stages of malignancy. This work is a paradoxical gain, as the combinatorial therapy with gold nanoparticle-enabled photothermal therapy (NEPTT) boosted the effectiveness of an epidermal growth factor receptors (EGFR) inhibitor.

Each nanoparticles approach in glioblastoma demonstrated promising therapeutic efficacy, but it would be even better if more findings from in vivo studies were to provide and uncover the depth and insight of these approaches in terms of ribonucleic acid (RNA) nanoparticles, Gold Nanoparticles and Silica Nanoparticles

Conclusion

Overall, glioblastoma and other cancer cells have developed several ways to evade programmed cell death. A sophisticated regulatory network balanced pro-survival signals, controlled and regulated cell apoptosis, and two key active signalling pathways were responsible for this type of death mechanism (extrinsic and intrinsic pathways). In addition to promoting tumour development, dysfunction in apoptotic pathways also ensures resistance to already available anticancer drugs. This analysis concluded that glioblastoma treatment with targeted delivery of anticancer medicines over the blood-brain barrier (BBB) utilising drugs, nanoparticles, and focusing on particular proteins or genes appeared to be a potential therapy. However, as discussed in the literature reviews, focused medicines on cell death pathways have a variety of drawbacks. This is due to the possibility that targeted therapy may not be the optimum treatment for a patient who may have any sort of cancer. For instance, if the cancer cells do not have their specified targets, such as an organ, targeted therapy may not produce the optimum treatment results and outcomes.

Additionally, because targeted treatment for certain cell death pathways involves a great deal of complexity, it was determined that there was insufficient research on all related pathways because the complexity identified in this study is substantially higher. In vivo investigations have not yielded much insights into the mechanisms of targeted therapy for cell death pathways. One of the major limitations in this systematic review was the insufficient number of clinical studies that examined innovative drugs that influence cancer cells. Another was the identification of several glioblastoma cell lines and related metabolic pathways.

Author Contributions

NAS, supervised the project. NAS, PS, NNSNMK study conception, design and data collection. NAS, PS analysis and interpretation of results. PS, NAS, JJ, RAS, NSNMK draft manuscript preparation and correction. All authors reviewed the results and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest

Supplementary Information

Search strategy

Literature records were found by conducting searches against several online databases, including Google Scholar, PubMed, Science Direct, and Scopus, using the relevant common terms. To do this, researchers used thesaurus searches to find synonyms for the study's title and Boolean operators to broaden and focus their searches. The phrases "goal," "intent," "healing," "remedial," "cure," "treatment," "medication," "route," "channel," "passage," "cell death," "glioblastoma," "astrocytoma," "brain tumour," "glioma," and "malignance" were used to extract all of the included research. The elimination of duplicate research from the screening process was followed by an independent reviewer reviewing the recovered relevant articles by reading the "full copy" or "abstract." The subsequent procedures, known as eligibility, took both inclusion criteria and exclusion criteria into account. At this point, literature papers were carefully selected and vetted in accordance with the inclusion criteria. In order to find further information, a manual search from other sources was also conducted, including a list of the articles' references. A crucial element that has to be emphasised is that the screened study titles and abstracts were assessed by two reviewers who served as supervisor and co-supervisor in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards. As a reference manager, Endnote software Version X8 was supported, and the general screening and eligibility processes were demonstrated in (Figure 3).

Study selection and inclusion/exclusion criteria

Publications published before 2010 and after 2021 were not considered because the current analysis was centered on articles published between 1 January 2010 and 31 December 2020. The study containing glioblastoma therapeutic targets and the research on glioblastoma therapeutic treatments in both male and female candidates throughout the spectrum of individuals were included. Additionally, papers reporting on the therapies given to

glioblastoma patients worldwide were included in the current analysis. English-language research of all kinds were included, including in vivo, ex vivo, and in vitro experiments. Articles published in a language other than English, review articles, conference proceedings papers, publishing of books, and abstracts were all omitted from this study.

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