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The impact of interaction between verteporfin and yes-associated protein 1/transcriptional coactivator with PDZ-binding motif-TEA domain pathway on the progression of isocitrate dehydrogenase wild-type glioblastoma

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ABSTRACT

Verteporfin and 5-ALA are used for visualizing malignant tissue components in different body tumors and as photodynamic therapy in treating isocitrate dehydrogenase (IDH) wild-type glioblastoma (GBM). Additionally, verteporfin interferes with Yes-associated protein 1 (YAP)/Transcriptional coactivator with PDZ-binding motif - TEA domain (TAZ-TEAD) pathway, thus inhibiting the downstream effect of these oncogenes and reducing the malignant properties of GBM. Animal studies have shown verteporfin to be successful in increasing survival rates, which have led to the conduction of phase 1 and 2 clinical trials to further investigate its efficacy in treating GBM. In this article, we aimed to review the novel mechanism of verteporfin's action, the impact of its interaction with YAP/TAZ-TEAD, its effect on glioblastoma stem cells, and its role in inducing ferroptosis.

KEYWORDS: Glioblastoma, verteporfin, YAP/TAZ-TEAD pathway, glioblastoma stem cells, ferroptosis

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Introduction

Isocitrate dehydrogenase wild-type glioblastoma (GBM) is an incurable malignant neoplasm with high invasive properties.^{1–3} GBM is the most common malignant brain neoplasm accounting for approximately 45.2% of malignant primary brain tumors and 16% of all CNS neoplasms with a median survival of 15-months.⁴ GBM has been classified as the most frequent adult-type diffuse gliomas and has a poor prognosis with a 5-year survival rate of 4%–5.5%.^{1,4–6} Despite advances in surgical techniques and adjuvant therapies, the tumor still has high recurrence rates. Almost 85% of the recurrences emerge from the residual malignant cells adjacent to the resection cavity.^{7,8} Maximal resection of the tumor would decrease recurrence rates. One of the ways of maximal resection is better visualization of tumor cells via fluorophores such as 5-ALA and verteporfin (Visudyne).^{9,10} Besides conveying maximal tumor resection, verteporfin is useful as a treatment modality for GBMs. Verteporfin is a

benzoporphyrin derivative; it produces reactive oxygen radicals following activation by a laser light with a wave length of 690 nm and causes cell apoptosis, destroys neo-vascular membranes, and inhibits angiogenesis and tumor cell proliferation.^{11–13}

A new novel therapeutic modality of verteporfin has been revealed, recently.^{14,15} Gene therapies and therapeutic molecules targeting oncogenic networks and intricate pathways have been shown to be effective in reducing GBM progression following surgical resection. Many oncogenes are implicated in enhancing GBM progression such as AEG-1, AK2, YAP, TAZ, and TEAD.^{16,17} Verteporfin has been shown to inhibit YAP/TAZ-mediated transcription of oncogenes, thus inducing apoptosis of malignant cells and preventing abnormal vascularization, invasion, and metastasis.^{14,15,18,19} Hippo pathway, an important tumor suppressor pathway, mediates the phosphorylation of YAP/TAZ transcriptional factors by means of TEA domain (TEAD) pathway, thereby inactivating them and



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preventing their accumulation in the GBM cells.²⁰ Deactivation of the Hippo tumor suppressor pathway results in YAP and TAZ activation, leading to an increment in expression of other oncogenes such as C-MYC, EGFR.^{21–23} As YAP and TAZ are main targets of verteporfin, elucidating structure, function, downstream effects, and interactions of YAP and TAZ with other oncogenes is essential in understanding the role of verteporfin in treatment of GBM. On the other hand, verteporfin has been reported to possess YAP-independent mechanism of action via inducing ferroptosis and decreasing glioblastoma stem cells (GSCs) (Figure 1). Animal studies have shown promising findings for verteporfin that led to conduction of phase 1 and 2 clinical trials to further investigate its efficacy in treating patients with GBM.¹⁴ Herein, we aimed to narratively review mechanism, effects, route of administration, and outcome of verteporfin in the treatment of GBM.

YAP/TAZ-TEAD pathway and microenvironment of IDH wild-type glioblastoma

Environmental factors (ionizing radiation) and genetic factors (EGFR overexpression, PTEN gene mutations, loss of chromosome 10q) contribute to the development of GBMs.^{24,25} Secondary GBMs evolve from pre-existing low-grade glial tumors (diffuse astrocytoma, anaplastic astrocytoma) via loss of chromosome 19q, isocitrate dehydrogenase 1 (IDH1) mutation, and p53 gene mutation. Additionally, certain genetic syndromes (tuberous sclerosis, neurofibromatosis type I and II, and Li Fraumeni syndrome) could accompany GBMs.^{26,27} The GBM has a highly infiltrative nature and indefinite borders making it difficult to distinguish from the surrounding normal brain

parenchyma. The YAP and TAZ oncogenes enhance GBM progression, abnormal vascularization, and invasiveness by activating other oncogenes such as SNAIL, C-MYC, EGFR, MCL-1, KIF23, and Wnt/ β -catenin (Figure 2).^{14,17,28–30}

High level of expression of YAP/TAZ is not unique for the GBMs. The YAP/TAZ has been observed in many types of solid tumors such as lung, liver, colon, breast, and ovarian cancers.^{31–33}

YAP and TAZ are small proteins acting as transcriptional co-activators. They are considered the main downstream effectors in the Hippo signaling pathway. This pathway is a signal cascade that plays a vital role in tumorigenesis and controls organ size. Activation of the Hippo pathway leads to degradation of YAP and TAZ proteins in cytoplasm.^{23,34} If the Hippo pathway is deactivated, YAP and TAZ are translocated into the nucleus, leading to transcription of downstream genes through formation of complexes with transcription factors, such as TEAD, also known as TEF, and Runx (runt-domain transcription factors) (Figure 2).^{23,34,35}

This pathologic process has been defined in many other cancer types.^{32,35} Therefore, the Hippo pathway is considered a potent target of anticancer drug development.^{35,36}

The structure of YAP contains a proline-rich region at the N-terminal, the transcription factor binding domain of the TEAD family (TB). In the middle, there are 2 tandem WW domains, followed by an Src homology domain 3 binding motif (SH3 BM), a coiled-coiled motif (CC) in the transactivation domain (TA), and, finally, a PDZ-binding motif (PDZ-BM) in the C terminal.^{37–41} TAZ, also known as WWTR1 (WW-domain containing transcriptional regulator 1), has a similar structure to YAP, but the proline-rich domain, the second WW domain, and the SH3-binding motif are absent.^{37,42} (Figure 3).

Verteporfin Mechanism of Action

YAP/TAZ inhibition

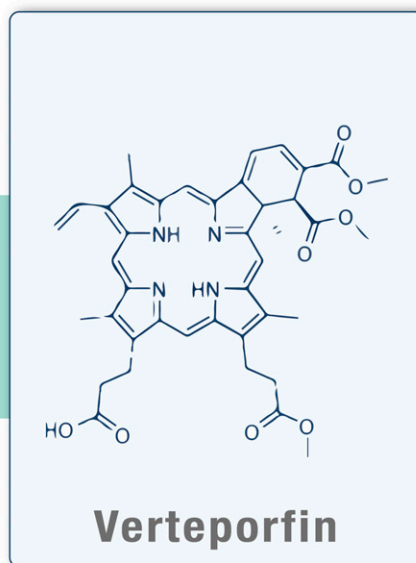
- Irreversibly inhibits YAP-TEAD domain.
- Inhibits transcriptional activation, thus decreasing cell proliferation and tumor progression.

Glioblastoma Stem Cells

- Inhibits YAP protein, thus decreasing stem cell activity, reduced tumor growth, and increased sensitivity to other cancer treatments.
- Inhibits oxidative phosphorylation and induces cell death in GSCs.

Ferroptosis

- Induces ferroptosis.
- Inhibits glutathione peroxidase 4, thus leading to accumulation of lipid peroxides, which are lethal to GBM cells.
- has a synergistic effect with other ferroptosis-inducing agents, such as erastin and RAS-selective lethal 3 (RSL3).



Mahmoud Osama

Figure 1. The mechanism of verteporfin's action.

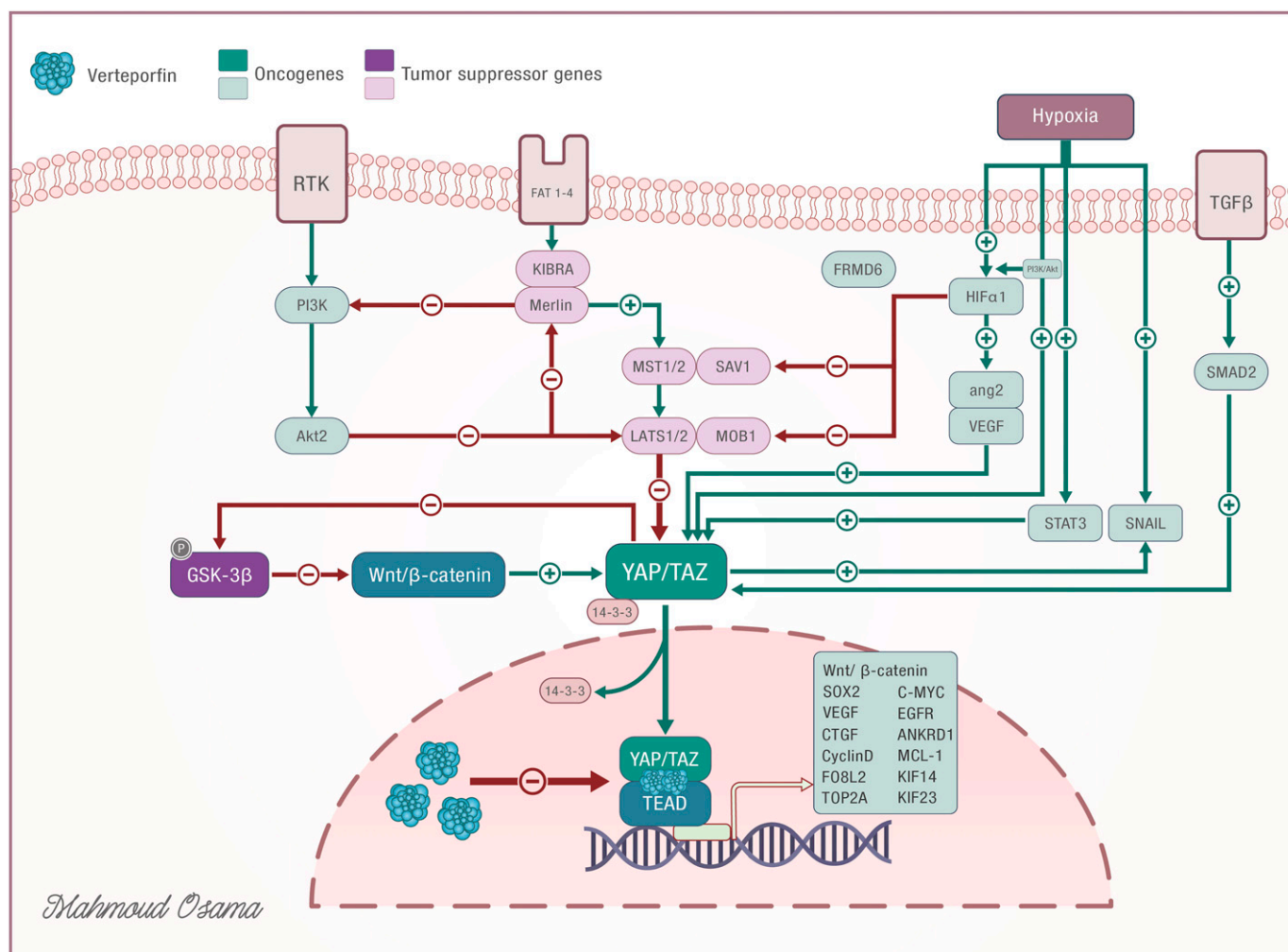


Figure 2. Demonstrates the interaction between verteporfin and YAP/TAZ-TEAD in the nucleus; Verteporfin prevents YAP/TAZ activation of TEAD complex. Hippo pathway, represented by MTS1/2 and SAV1, is phosphorylated and activated by FAT 1-4 receptors, leading to phosphorylation and activation of LATS1/2, which in turn deactivates YAP and TAZ proteins and permits the attachment between them and 14-3-3 protein. 14-3-3 labels YAP and TAZ for proteasome degradation in the cytoplasm. In contrary, activation of RTK leads to dephosphorylation and inhibition of Hippo pathway downstream signals. As a result, YAP and TAZ proteins are dephosphorylated; their dephosphorylation leads to the detachment of 14-3-3 protein. Consequently, YAP and TAZ translocate into the nucleus and form YAP/TAZ-TEAD complex, leading to increased expression of oncogenes such as EGFR, C-MYC, SOX2, Wnt, B-catenin, and cyclin-D.

The 2 WW domains of YAP protein consist of 2 Tryptophan residues (W); these 2 domains are separated from each other by 20-23 amino acids and interact with PPXY motifs present in some transcriptional factors.⁴³⁻⁴⁷ TEAD family of transcription factors is recognized by TB binding domain. They lead to activation of target gene expression. The 14-3-3 binding motif is important for regulation of YAP and TAZ as 14-3-3 protein leads to deactivation of YAP and TAZ proteins in the cytoplasm, thus preventing their translocation to the nucleus.^{39,42,48} The PDZ-binding motif, found in a lot of transmembrane or cytoskeleton-associated proteins, binds to the PDZ domain and causes direct YAP and TAZ translocation.⁴⁸⁻⁵⁰ Once YAP and TAZ proteins translocate to the nucleus, they immediately interact with transcriptional factor partners and act as transcription co-activators.^{41,48}

Mammalian genome includes 4 homologous members of the TEAD protein family (TEAD1-4), which are the main targets of the YAP and TAZ to regulate cells contact inhibition, oncogenic transformation, epithelial-mesenchymal transition (EMT), and apoptosis inhibition.⁵¹⁻⁵³ The binding and interaction of the TEAD with the TB domains of YAP and TAZ leads to activation of downstream gene transcripts, such as Wnt/ β -catenin, C-MYC, EGFR, CTGF, SOX2 and Cyr61.^{52,54-57} Therefore, disrupting the binding of YAP or TAZ to TEAD will inhibit their ability to promote cell proliferation and tumorigenesis, thereby slowing down tumor progression. Several porphyrin compounds, such as, verteporfin, have been found to target YAP and TAZ proteins and inhibit the interaction between YAP and TEAD.¹⁴

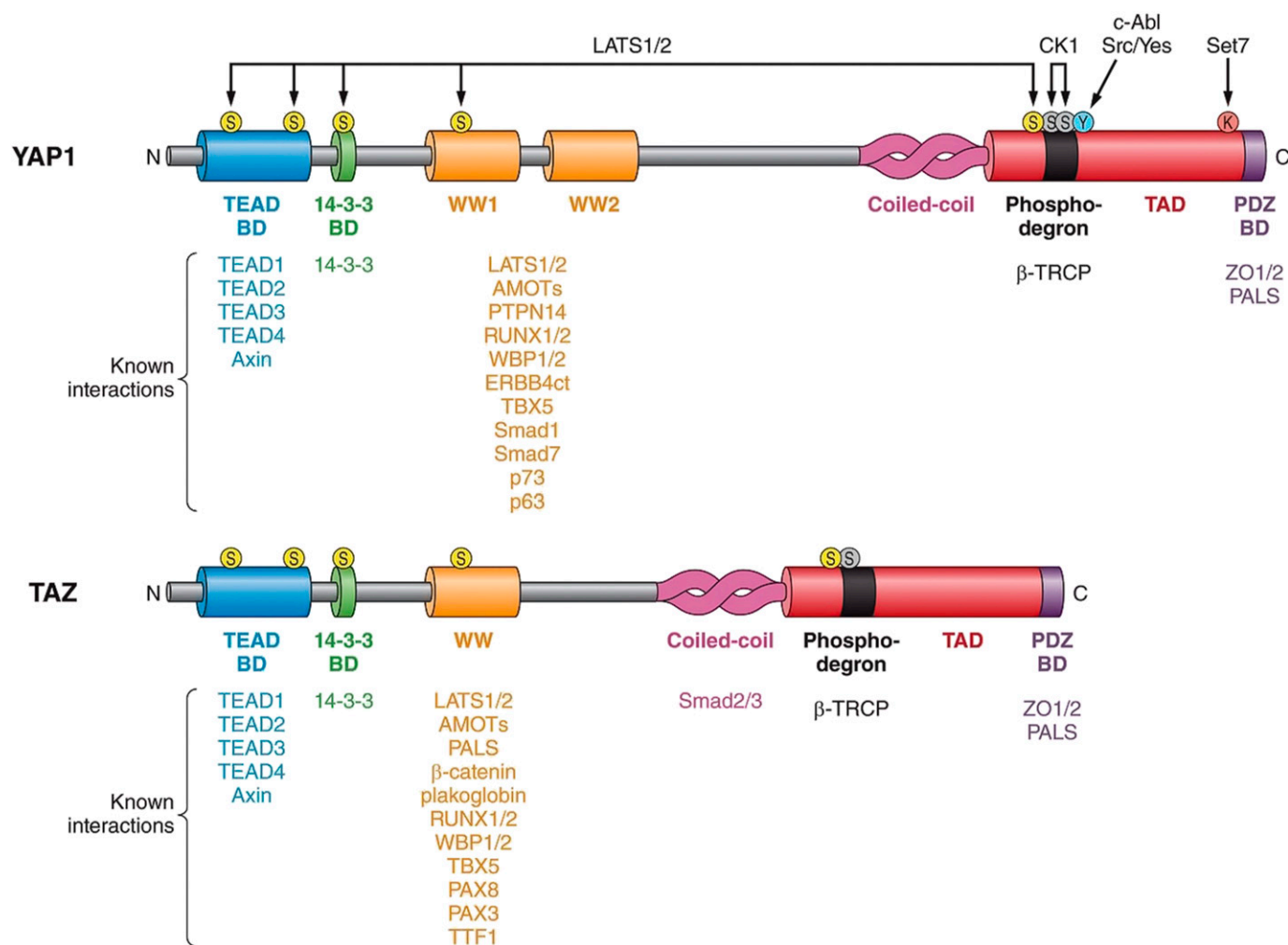


Figure 3. The structure of YAP and TAZ proteins. With courtesy of Piccolo et al. The biology of YAP/TAZ: Hippo signaling and beyond. *Physiological Reviews*. 2014;94 (4):1289 (page: 1289).³⁷

Verteporfin structure, function, interaction with YAP/TAZ-TEAD pathway, and its effect on glioblastoma stem cells

The activity of some essential enzymes responsible for heme metabolism, such as ferrochelatase, is decreased in malignant cells, causing intermediate metabolites of heme such as verteporfin to accumulate.⁵⁸ Verteporfin consists of a porphyrin ring, C₄₁H₄₂N₄O₈, and produces reactive oxygen radicals upon exposure to a wave length of 690 nm that result in cell apoptosis and prevents angiogenesis and tumor proliferation.^{18,59,60}

Verteporfin is used intraoperatively to visualize and delineate the tumor margins under blue light (with a wavelength of 400-410 nm).¹⁴ This enables the surgeons to maximize the extent of resection and spare the normal brain parenchyma as much as possible. A novel mechanism of verteporfin has recently been discovered.^{14,15} Verteporfin has been found to inhibit YAP/TAZ-TEAD interaction. It targets the TEAD binding domain in YAP and TAZ, degrades YAP/TAZ protein, and inhibits transcriptional activation.^{14,15,20,37,61} Moreover verteporfin has been reported to increase the level of 14-3-3 protein, which in

turn leads to proteasome sequestration of YAP and TAZ proteins, inhibiting their transcriptional co-activation function.⁶²

Receptor Tyrosine Kinases (RTK) and Hippo pathway are the main 2 pathways that act oppositely through their transcriptional co-factors in the cells of GBM.^{14,63} Hippo pathway deactivates YAP/TAZ transcriptional factors and prevents their accumulation in the GBM cells.²⁰ In contrast, RTK promote overexpression of YAP/TAZ proteins, particularly in EGFR-amplified GBM cells, leading to their accumulation in GBM cells which enhance aggressiveness, hypoxic characteristic, and immortality of GBMs.^{23,34,63-67} Vigneswaran et al¹⁴ did experiments in gliosphere cultures and showed that verteporfin blocked interaction between TAZ and TEAD4. Verteporfin likely inhibited TAZ-mediated transcriptional activation of TEAD targets. They used verteporfin at a dose of .5-2 mg/ml on representative gliosphere cultures to determine the verteporfin effect on YAP/TAZ-TEAD transcriptional activation in RTK-dependent GBM cells. The dose was successful to inhibit YAP-TEAD-dependent growth of tumor cells, as well

as was not toxic to non-tumor cells. Animals, treated with intraventricular verteporfin for 14 days, were shown to have verteporfin (.67-1.46 ng/mg) through mass spectrometry quantification in their brain parenchyma.¹⁴ To prove the therapeutic effects of verteporfin, GBM xenograft-bearing mice were treated with verteporfin by intraventricular osmotic pump, which pumped drug continuously for 14 days or more. Verteporfin had a high rate (86%) of tumor necrosis in those animals. Long-term reduction in EGFR, C-MYC, and SOX2 expression in tumor tissue was observed near pump implantation sites. Reduction in proliferation of tumor bulk, and significantly increased median survival of 30% were observed in treated animals compared to the controls. These experiments illustrated that verteporfin is absorbed into GBM xenograft tumors in vivo, downregulates YAP/TAZ target genes expression, and significantly slows down tumor progression in xenograft models of EGFR-mutant GBM.¹⁴

The YAP/TAZ-negative gliomasphere cultures did not undergo significant apoptosis and growth arrest with prolonged verteporfin treatment at 3 mg/mL. This means that YAP/TAZ expression largely regulates the proapoptotic and anti-proliferative effects of verteporfin on GBM cells.¹⁴ In contrast, other studies reported YAP-independent mechanisms of action of verteporfin.⁶⁸⁻⁷⁰ Eales et al⁶⁸ found that verteporfin kills GBM cells, only under hypoxic environments, concluding that the drug acts independently of YAP/TAZ-TEAD pathway. Given the similarity of verteporfin structure with iron-binding porphyrins, the authors pioneeringly hypothesized that verteporfin acts not through YAP/TAZ-TEAD-dependent mechanism but through free iron binding and production of oxidative oxygen species.⁶⁸ The authors also suggested that the hypoxic glial cells already experience heightened oxidative stress, making them vulnerable to Verteporfin, which by triggering ROS production, initiates endoplasmic reticulum (ER) stress and DNA damage, ultimately inducing glioma cells death. Nevertheless, the weaker effects of Verteporfin on YAP/TAZ-negative GBM, as described earlier, arise questions about the validity of this hypothesis. The current evidence seems to be contradictable and insufficient to make significant conclusions.

Verteporfin has shown promising effects against GSCs, which exhibit high self-renewing and tumorigenic capacity and are widely recognized for their contribution to the heterogeneity, initiation, migration, and recurrence of GBM.⁷¹ Verteporfin appears to inhibit the activity of a YAP protein, which plays a role in promoting the self-renewal and survival of stem cells. It inhibits the activity of YAP through a direct interaction with the protein which is a transcriptional co-activator that crucially controls cell growth and proliferation and regulates gene expression by translocating into the cell nucleus and interacting with transcription factors. By inhibiting YAP, verteporfin may disrupt the signaling pathways that contribute to the maintenance of GSCs. This disruption could potentially lead to decreased stem cell activity, reduced tumor growth, and increased sensitivity to other cancer treatments.

On the other hand, recent studies have shown that verteporfin inhibits oxidative phosphorylation and induces cell death specifically in GSCs independently of YAP.^{71,72} The study by Kuramoto et al. showed that verteporfin induced selective cell death in GSCs and had a minimal effect on differentiated glioma cells due to the high mitochondrial oxidative phosphorylation of GSCs.⁷¹ The mechanism of action of verteporfin in GSCs involves, in a dose-dependent manner, reducing oxidative phosphorylation, inhibition of mitochondrial respiration, and induction of ROS production. In addition, verteporfin has been reported to reduce mitochondrial membrane potential (MMP) and intracellular ATP in GSCs without photoactivation.⁷¹ Moreover, verteporfin has been shown to have a synergistic effect with radiation and temozolomide chemotherapy in a GSCs xenograft model of primary GBM.⁷² The combination of verteporfin with radiation and temozolomide chemotherapy had transient pro-survival effects and significantly increased tumor necrosis in tumor mass of GBM compared to radiation and temozolomide treatment alone.⁷³

Another YAP-independent mechanism that verteporfin work with is its role on ferroptosis, a recently discovered form of programmed cell death.⁷⁴ Ferroptosis is an iron-dependent pathway driven by intracellular alterations in iron metabolism resulting in lipid peroxidation and subsequently cellular death.^{74,75} Recent studies have demonstrated that verteporfin can induce ferroptosis in cancer cells.⁷⁶ The mechanism of action of verteporfin in inducing ferroptosis involves the inhibition of glutathione peroxidase 4 (GPX4), which is a key enzyme that protects cells from lipid peroxidation.^{77,78} The inhibition of GPX4 leads to the accumulation of lipid peroxides, which are lethal to GBM cells.^{75,76} Moreover, verteporfin has been shown to have a synergistic effect with other ferroptosis-inducing agents, such as erastin and RAS-selective lethal 3 (RSL3), in inducing ferroptosis in GBM cells.^{78,79} The combination of verteporfin with erastin or RSL3 resulted in a significant increase in lipid peroxidation and cell death compared to either agent alone.^{77,78} These findings suggest that verteporfin may be a promising therapeutic agent for the treatment of GBM.

Verteporfin as a promising therapy for GBM

Hyperactivation of YAP/TAZ pathway demonstrated in GBM cells has derived the efforts of scientists towards development and testing of their inhibitors as a potential treatment for GBM. Drug reprofiling is a current trend aiming to identify novel possible therapeutic scales for available and approved indications of that medication.⁸⁰ Verteporfin is used mainly in the treatment of neurovascular age-related macular degeneration (AMD) in the clinical practice.⁶⁰ Verteporfin has been shown to significantly decelerate tumor growth in vitro studies.^{18,63,81} Verteporfin and other YAP-TAZ inhibitors have demonstrated efficient therapeutic effects on solid tumors such as GBM, esophageal, pancreatic, and ovarian cancers.^{15,20,82-84} The GBM is the most aggressive brain tumor of solid nature and rich in hypoxic cells and stem cells that contribute to GBM

recurrence and are considered a major obstacle behind the cure. Verteporfin has been reported to inhibit proliferation, migration, and invasion of GBM in several studies through interaction with YAP/TAZ-TEAD pathway, inducing ferroptosis, and decreasing stem cells activity.^{20,71} Although low-energy, nonthermal infrared laser light is required for the optimal efficacy of verteporfin in treatment of AMD, its use as a stimulator and activator to verteporfin in the treatment of brain tumor is debatable.^{18,85} A previous study reported no effect of light during verteporfin administration in GBM patients.¹⁸ Shah et al¹⁹ reported a low access of verteporfin to the brain parenchyma due to its hydrophobic nature and suggested the use of microparticles to deliver verteporfin to the brain parenchyma, thus preventing systemic accumulation and toxicity of verteporfin.¹⁹ On contrary, Barette et al⁷³ did not find any systemic toxicity following prolonged administration of verteporfin for 39 days with frequent different doses in an experimental study evaluating 8 low-passage patient-derived orthotopic xenograft (PDX) models of GBM cell lines.⁷³ The authors also demonstrated a high penetration of verteporfin to the brain parenchyma, which was directly dependent on the drug dose and daily injection. They underlined a significant decrease in drug effect when given through a vehicle or carrier. Efficacy of verteporfin in management of GBM has been demonstrated in the literature with positive effects on the survival of GBM patients, particularly when combined with standard chemotherapy and radiotherapy.¹⁴

Conclusion and future perspectives

Gross total resection of GBMs is difficult due to the infiltrative nature and unclear borders of the tumor tissue. Molecular therapies aid in surgical success following maximal resection of GBMs by destroying the residual malignant cells, preventing local recurrences, and improving survival rates of the patients. Verteporfin has been shown to be a promising therapeutic molecule besides its usefulness during resection of GBMs, and better understanding of verteporfin mechanism of action and pathogenetic profile of gliomas is essential to develop highly penetrating and efficacious generic forms of verteporfin.

Further studies are necessary to resolve issues related to the best method of verteporfin administration in GBM patients and to determine the optimal dose and frequency patterns.

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Mahmoud Osama: conceptualization, literature search, screening, writing, editing, and visualization; Muhammed Amir Essibayi: literature search, screening, writing, and editing; Mona Osama: literature search, screening, writing, and editing;

Ismail A. Ibrahim: literature search, writing, and editing; Mostafa Nasr Mostafa: writing, and editing; Murat Şakir Ekşi: supervision, writing, and editing.

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Appendix

Abbreviations

GBM	Glioblastoma
YAP	Yes-associated protein
TAZ	Transcriptional co-activator with PDZ-binding motif
TEAD	Transcriptional enhanced associated domain
TEF	Transcriptional enhancer factors
Runx	Runt-domain transcription factors
GPX4	glutathione peroxidase 4
GSCs	Glioblastoma stem cells
MMP	Mitochondrial membrane potential.