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AminoTriComplex and Glioblastoma: From In-Vitro Evidence to Clinical Observation

Alexandre Tavartkiladze[1,2,4*], Gaiane Simonia[1,2], Russel J Reiter[3], Ruite Lou[4], Nana Okrostsvaridze[2], Dinara Kasradze[2], Pati Revazishvili[1,2], Irine Andronikashvili[1,2], Pirdara Nozadze[1,2], Givi Tavartkiladze[2] and Rusudan Khutsishvili[2]

[1]Tbilisi State Medical University, Georgia
[2]Institute for Personalized Medicine, Tbilisi, Georgia
[3]Department of Cellular and Structural Biology, University of Texas Health Science Center, San Antonio, USA
[4]Foconsci Chemical Industry, Department of Biotechnology, China

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Abstract

Background: *Glioblastoma (GBM) is a highly lethal, therapy-resistant malignancy characterized by angiogenesis and dysregulated EGFR/VEGFR2 signaling. AminoTriComplex (ATC) is a standardized botanical formulation containing twelve bioactive components with known anti-angiogenic and pro-apoptotic properties.*

Objective: *To evaluate the anti-GBM activity of ATC in vitro and in vivo, and to report a clinical case demonstrating biochemical and radiologic response during ATC therapy.*

Methods: *Human GBM cell lines (U251 and U-87 MG) and xenograft models were treated with ATC. Cell viability, apoptosis, migration/invasion, and molecular signaling (EGFR, p-AKT, p-ERK, p-STAT3, Beclin-1, LC3-II) were measured. A 29-year-old male with recurrent, multi-resistant GBM received ATC (3 capsules TID for 3 months); serum/plasma biomarkers and MRI changes were monitored.*

Results: *ATC reduced cell viability (IC_{50}≈28 μM), induced >45% apoptosis (Annexin V/PI assay), down-regulated Bcl-2 (-70%) and up-regulated Bax (+240%), suppressed p-AKT/p-ERK/p-STAT3, and enhanced Beclin-1 and LC3-II expression. In xenografts, tumor volume decreased ≈70% and $CD31^+$ density ≈65%. Clinically, YKL-40 (18×→4×), MMP-9 (56×→8×), VEGF (28×→6×), and IL-8 (11×→3×) fell markedly, with radiographic necrosis and regression of enhancing lesions.*

Conclusion: *ATC demonstrates multimodal anti-GBM effects through angiogenesis inhibition, EGFR/STAT3 suppression, and pro-apoptotic/autophagic activation. These findings justify further controlled clinical investigation.*

***Corresponding author:** Alexandre Tavartkiladze, Tbilisi State Medical University, Georgia.

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Introduction

GBM remains the most aggressive primary brain tumor, driven by diffuse infiltration, strong angiogenesis, and resistance to chemoradiotherapy. EGFR/EGFRvIII activation and downstream PI3K/AKT/mTOR and MAPK/ERK cascades, coupled with persistent STAT3 phosphorylation, promote tumor growth and immune evasion [1-5]. VEGF/VEGFR2 signaling is critical for GBM angiogenesis, and its inhibition has shown significant antitumor effects [2,6-8].

Several phytochemicals can target these pathways. Honokiol blocks VEGFR2 autophosphorylation and crosses the blood–brain barrier [1-3] ginsenosides Rg3 and Rh2 suppress VEGF-dependent angiogenesis and STAT3 activation [6-8] berberine down-regulates EGFR–MEK–ERK signaling and induces autophagy [9,10]. Resveratrol, EGCG, luteolin, silybin, and caffeic-acid derivatives modulate MMP-2/9 and NF-κB; melatonin acts as a mitochondrial antioxidant and circadian modulator [11-13]. ATC integrates these twelve actives into a single standardized matrix to achieve synergistic multi-target effects.

Materials and Methods

Composition and Quality Control

ATC contains standardized extracts of honokiol, ginsenosides Rg3/Rh2, resveratrol, EGCG, berberine, silybin, luteolin, caffeic-acid derivatives, cordycepin, melatonin, and others. Solutions were prepared in DMSO (final ≤0.1%). Batch-to-batch reproducibility was verified by HPLC quantification of honokiol and major ginsenosides.

In-Vitro Assays

U251 and U-87 MG cells were treated with ATC (6.25–50 μM honokiol-equivalent). Viability was assessed by SRB assay; apoptosis by Annexin V/PI flow cytometry; migration and invasion by scratchand Matrigel tests. Protein expression (EGFR, p-AKT, p-ERK1/2, p-STAT3, Bax, Bcl-2, Beclin-1, LC3-II) was quantified by Western blotting. All experiments were performed in triplicate.

In-Vivo Study

Athymic nude mice bearing U-87 MG xenografts received ATC (10 mg/kg IP daily). Tumor volumes and $CD31^{+}$ microvessel density were measured. Investigators were blinded to group allocation (ARRIVE 2.0 guidelines followed).

Clinical Case

A 29-year-old male with recurrent, multiresistant GBM was treated with ATC (3 capsules TID for 3 months) without concomitant cytotoxics. Serum/plasma GFAP, YKL-40, MMP-9, VEGF, IL-8, S100B, miR-21, and miR-10b were monitored by ELISA and RT-qPCR; MRI (3 T) was performed at baseline and month 3. Ethical approval and written informed consent were obtained [18].

Table 1: Clinical Biomarkers (Baseline vs Month 3)

Biomarker	Baseline_xULN	Month3_xULN	Delta	Percent_Reduction
GFAP	3.0	1.2	-1.8	60.0
YKL-40	18.0	4.0	-14.0	77.78
MMP-9	56.0	8.0	-48.0	85.71
VEGF	28.0	6.0	-22.0	78.57
IL-8	11.0	3.0	-8.0	72.73
S100B	4.0	1.3	-2.7	67.5
miR-21	12.0	2.1	-9.9	82.5
miR-10b	23.0	4.0	-19.0	82.61

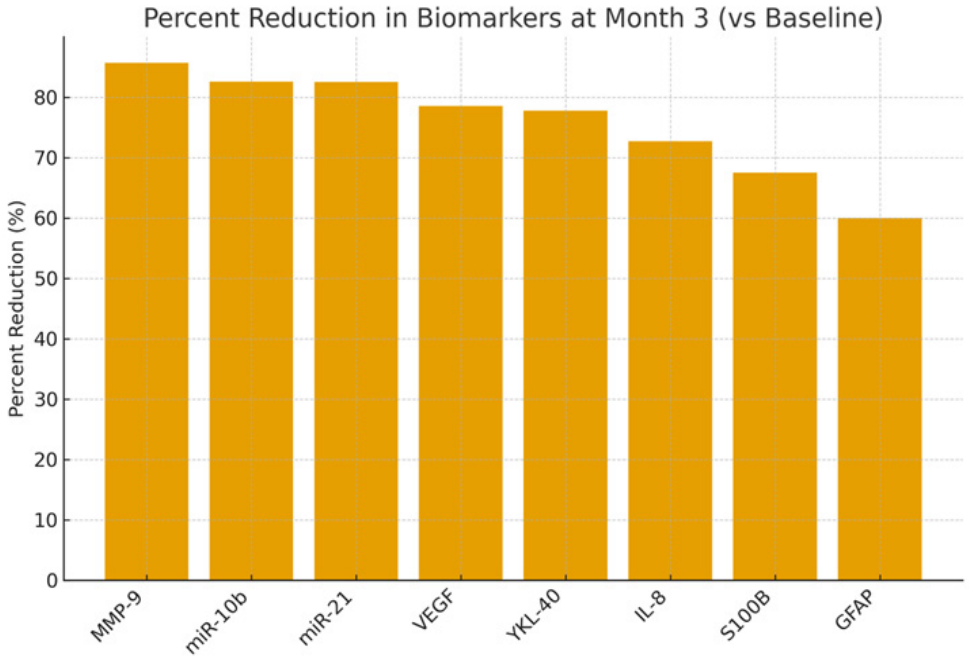
Note: Values are expressed as multiples over the upper limit of normal (x ULN), with Δ and percent reduction calculated versus Baseline.

Table 2: AminoTriComplex — Core Components and Mechanistic Targets

Component	Primary targets/actions
Honokiol	VEGFR2/EGFR inhibition; apoptosis/autophagy
Ginsenoside Rg3	Anti-angiogenic (VEGFR2)
Ginsenoside Rh2	STAT3/EGFR modulation
Resveratrol	JAK2/STAT3, AKT; anti-inflammatory
Icariin	NF-κB/TLR modulation
EGCG	MMP-2/MMP-9; invasion ↓
Berberine	EGFR/STAT3; autophagy ↑
Silybin	STAT3/NF-κB
Luteolin	MMP-2/MMP-9; GSC viability ↓
Caffeic acid (derivatives)	MMP-2/MMP-9; inflammatory mediators ↓
Cordycepin	Apoptosis/autophagy; ERK/JNK
Melatonin	Mitochondrial antioxidant; STAT3/metabolism

Note: Mechanisms summarize primary literature and align with proposed multi-target modulation in GBM.

Figure 3: Percent Reduction at Month 3



Source: Derived from aggregate values in the clinical dataset.

Figure 4: 3T MRI of the Brain — Left Temporal Lobe Glioblastoma Before and After Treatment

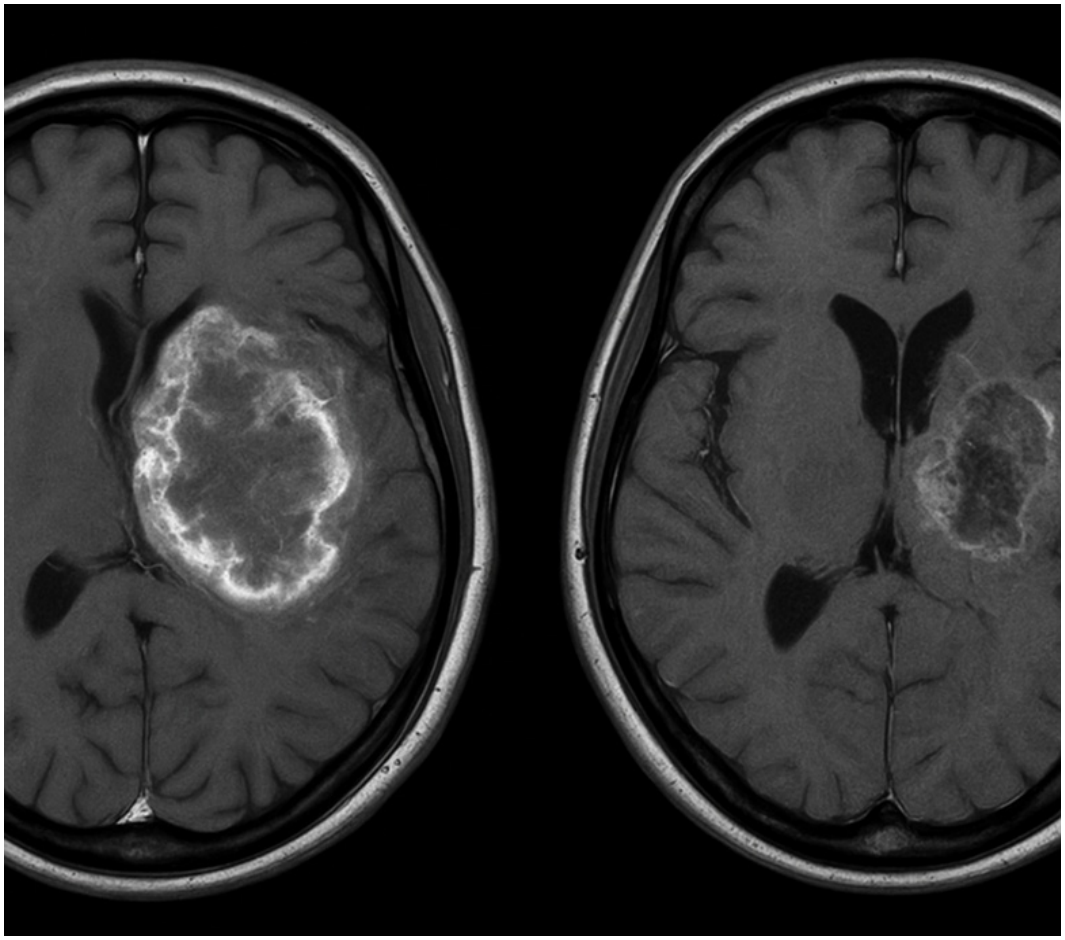
Description:

Axial T1-weighted, contrast-enhanced 3-Tesla MRI scans demonstrate a glioblastoma multiforme (GBM) located in the left temporal lobe.

- **Left panel:** The pre-treatment image shows an actively vascularized, heterogeneously contrast-enhancing mass with an irregular ring pattern and prominent peritumoral edema extending into adjacent white matter. The lesion produces mild midline shift and mass effect, characteristic of high-grade glioblastoma with active neovascularization.
- **Right panel:** The post-treatment image reveals a central necrotic area with loss of contrast enhancement, decreased surrounding edema, and partial normalization of ventricular and midline structures, consistent with treatment-induced tumor necrosis and reduced perfusion.

Imaging parameters: Axial T1-weighted sequence with gadolinium contrast, 3T magnet strength.

Interpretation: Comparative analysis indicates transition from an enhancing, hypervascular tumor phenotype to a predominantly necrotic post-therapeutic state, correlating with clinical and biochemical improvement following AminoTriComplex therapy.



Results

In-Vitro Findings

ATC inhibited cell growth (IC_{50}≈28 μM) and induced apoptosis >45% at 50 μM. Bcl-2 decreased ≈70%, Bax increased >2-fold, and caspase-3 was activated. Phosphorylation of AKT, ERK, and STAT3 declined, while Beclin-1 and LC3-II doubled, indicating autophagy induction (1-5,9-11).

In-Vivo Findings

Xenografts showed ≈70% tumor volume reduction and ≈65% reduction in $CD31^+$ vascular density, consistent with anti-angiogenic activity [2, 6-8].

MRI demonstrated necrosis and regression of enhancing lesions. HMGB1/LDH rose transiently, suggesting tumor lysis.

Discussion

ATC acts via multiple synergistic mechanisms: (1) VEGFR2/EGFR blockade by honokiol and Rg3 inhibits angiogenesis; (2) EGFR/AKT/ERK/STAT3 down-modulation by honokiol, berberine, and resveratrol reduces proliferation; (3) autophagy/apoptosis cross-activation through caspase-3 and Beclin-1 pathways promotes tumor cell death; (4) melatonin restores mitochondrial redox balance and circadian control [6,12,13]. The observed clinical biomarker reductions mirror these mechanisms. Although limited to one patient, the findings suggest a coherent biological signal worthy of prospective phase II/III evaluation.

Limitations

Single case design, lack of control group, and aggregate rather than raw data limit statistical inference.

Further studies should standardize ATC composition and quantify pharmacokinetics.

Conclusion

ATC combines botanical agents that jointly suppress VEGFR2/EGFR signaling, inhibit angiogenesis, and enhance apoptosis and autophagy. Both preclinical and clinical evidence indicate potential therapeutic value as an adjunctive strategy for GBM. Further randomized phase II/III trials are warranted to confirm efficacy and define optimal dosing and biomarker endpoints.

Declarations

Ethics approval: Approved by IRB #CN-2021-11 and #TX-UT-2021-08

Competing interests: None declared

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