AminoTriComplex: Preclinical and Clinical Evidence for a Multi-Component Phytochemical Formulation Targeting Oxidative Stress, Mitochondrial Function, and Cancer-Related Pathways

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Abstract: ***AminoTriComplex (ATC, also referred to as AminoSineTriComplex) is a multi-component phytochemical formulation in which epigallocatechin gallate (EGCG), resveratrol, and berberine are recurrently emphasized as key mechanistic constituents across the available literature. This narrative translational review summarizes preclinical and clinical evidence regarding its potential effects on oxidative stress, mitochondrial function, inflammatory signaling, and cancer-related pathways. In a CCl4-induced oxidative stress rat model, ATC was associated with lower lipid peroxidation, restoration of antioxidant enzyme activity, and improved mitochondrial respiration. In carcinogen-induced rat tumor models, ATC-related reports described modulation of inflammatory, metabolic, and tumor-associated biomarkers. A prospective controlled study in 266 patients with advanced, refractory triple-negative breast cancer receiving metronomic cyclophosphamide and propranolol with or without ATC reported higher objective response rate and longer progression-free survival in the ATC arm. A randomized, double-blind, placebo-controlled study in metastatic colorectal cancer has also been reported, but the current evidence remains limited to an early single-study experience. Overall, the available findings suggest multi-targeted biological activity and possible adjunctive oncological benefit; however, interpretation is constrained by limited independent replication, incomplete methodological reporting, variation in formulation description across reports, and the need for larger randomized studies with overall survival, quality-of-life, pharmacokinetic, and long-term safety endpoints.***

Keywords: AminoTriComplex; EGCG; resveratrol; berberine; oxidative stress; mitochondrial protection; triple-negative breast cancer; metastatic colorectal cancer; polypharmacology; metronomic therapy; translational oncology; nanodelivery systems

1. Introduction

Oxidative stress and mitochondrial dysfunction are central features of many chronic disorders, including metabolic disease, cardiovascular pathology, neurodegeneration, and cancer [6,12]. Persistent reactive oxygen species production can damage lipids, proteins, and DNA, while mitochondrial injury further amplifies redox imbalance and bioenergetic failure [6,12].

Because these processes operate through interconnected signaling networks rather than a single linear pathway, reductionist antioxidant strategies have often produced inconsistent clinical benefit. This has increased interest in multi-component phytochemical approaches that can influence redox regulation, inflammation, mitochondrial homeostasis, and tumor-associated signaling in parallel [8-11,17]. At the same time, the translational value of such agents depends heavily on formulation quality, bioavailability, and reproducible manufacturing [13-16].

AminoTriComplex (ATC) has been presented as a phytochemical platform intended to address this multi-target problem. The current manuscript is framed as a narrative translational review rather than a systematic review or meta-analysis. Its objective is to summarize the available preclinical and clinical evidence on ATC, place those findings in the context of broader literature on phytochemicals and nanodelivery, and identify the main methodological limitations that must be addressed before definitive therapeutic claims can be made.

2. Review Objective and Evidence Synthesis Approach

This article is a narrative review. PubMed, Google Scholar, and other publicly accessible biomedical sources were consulted through March 2026 using combinations of the terms "AminoTriComplex," "AminoSineTriComplex," "EGCG," "resveratrol," "berberine," "oxidative stress," "mitochondria," "triple-negative breast cancer," "metastatic colorectal cancer," "nanodelivery," and related pathway terms. ATC-specific original reports were prioritized for direct evidence, while independent reviews and context articles on constituent compounds, natural-product nanodelivery, metronomic chemotherapy, and propranolol were included to support mechanistic and clinical interpretation [8-22].

Because the ATC-specific literature remains limited and is largely derived from one investigative program, the present synthesis gives explicit attention to study design, reproducibility, and reporting quality. No formal meta-analysis was attempted, and no quantitative risk-of-bias instrument was applied. Conference-style summaries, non-peer-reviewed promotional materials, and unpublished claims were not treated as confirmatory evidence.

3. Composition and Mechanistic Rationale

Across the ATC literature, EGCG, resveratrol, and berberine are repeatedly highlighted as major mechanistic constituents [1-4]. However, not all reports describe the formulation identically; some publications refer to broader multi-phytochemical compositions that include additional agents [2]. For that reason, the mechanistic discussion below focuses on the three most consistently emphasized compounds and treats the precise pharmaceutical composition as an area that requires fuller standardization and batch-level reporting in future publications.

EGCG has been associated with direct free-radical scavenging, modulation of Nrf2-related antioxidant responses, and attenuation of NF-kB-mediated inflammatory signaling [8]. Resveratrol has been linked to SIRT1 activation, mitochondrial biogenesis, and broader effects on redox and metabolic regulation, although its clinical translation remains limited by pharmacokinetic constraints [9,11,16]. Berberine has been widely studied for AMPK-related metabolic effects, inflammatory modulation, and potential influence on mitochondrial stress pathways [10]. The theoretical appeal of ATC is that these mechanisms may converge on overlapping nodes relevant to oxidative injury and cancer biology.

The formulation has also been described as nano-enhanced. This is a potentially important feature because natural products often suffer from poor aqueous solubility, rapid metabolism, variable absorption, and inconsistent tissue exposure [13-16]. Nanodelivery systems may improve stability, oral uptake, and target-site delivery, but those benefits cannot be assumed without detailed pharmaceutical characterization. For ATC specifically, future reports should state particle composition, loading efficiency, release behavior, batch reproducibility, and pharmacokinetic data in a transparent manner.

From a systems perspective, the rationale for ATC is polypharmacology: a combination strategy intended to influence oxidative stress, inflammatory signaling, mitochondrial homeostasis, metabolic adaptation, and tumor-survival pathways at the same time [17]. This rationale is biologically plausible. Nevertheless, true synergy should be demonstrated empirically rather than inferred from the known actions of the individual compounds alone.

Table 1: Reported mechanistic framework of ATC and its recurrently emphasized constituents [1-4,8-17].

Component or feature	Mechanistic relevance	Appraisal / caveat
EGCG	Associated with antioxidant activity, Nrf2-related responses, and attenuation of inflammatory signaling [8].	Frequently presented as a key ATC constituent, but not all studies report identical formulation composition [1-4].
Resveratrol	Linked to SIRT1 activation, mitochondrial biogenesis, and redox regulation [9,11].	Biological plausibility is strong, yet clinical translation is limited by bioavailability unless formulation issues are addressed [11,16].
Berberine	Associated with AMPK-related metabolic regulation, inflammatory modulation, and effects on mitochondrial stress pathways [10].	Potential contribution is plausible, but specific in-formulation exposure data for ATC are not yet adequately reported.
Nano-enhanced delivery	In principle may improve stability, absorption, tissue exposure, and controlled release for natural products [13-16].	ATC publications should report particle composition, loading, release profile, reproducibility, and pharmacokinetics explicitly.
Polypharmacology	Combination design may influence oxidative stress, inflammation, mitochondrial homeostasis, and tumor-signaling networks simultaneously [17].	Synergy should be demonstrated experimentally; it should not be inferred only from the known actions of individual constituents.

4. Preclinical Evidence

The strongest ATC-specific preclinical signal currently comes from a CCl4-induced oxidative stress study in male Wistar rats (n = 40), in which animals were allocated to control, oxidative stress, oxidative stress plus ATC, and ATC-alone groups [1]. ATC was administered orally at 75 mg/kg for 14 days. Compared with untreated oxidative-stress animals, the ATC-treated group reportedly showed lower hepatic malondialdehyde levels, restoration of reduced glutathione content, recovery of superoxide dismutase and catalase activity, and improved mitochondrial state 3 respiration and respiratory control ratio [1]. These findings support a possible antioxidant and mitochondrial-protective effect under experimentally induced oxidative injury.

A separate 2024 preclinical report evaluated ATC in carcinogen-induced rat cancer models and described changes in biomarker profiles linked to tumor growth, inflammation, angiogenesis, and metabolic reprogramming [2]. A related NMU rat study from the same research program linked tumor progression to NF-kB activation, altered melatonin secretion, and lactate dehydrogenase dynamics, thereby providing biological context for the circadian-metabolic biomarker framework used in later translational work [5]. Together, these reports suggest that ATC-related investigations are attempting to connect redox biology with broader tumor signaling and host-response pathways.

However, the preclinical evidence base remains limited. The currently available publications do not fully resolve issues such as randomization procedures, allocation concealment, blinding of outcome assessment, a priori power calculation, inter-batch formulation consistency, or independent laboratory replication. Accordingly, the animal data should be interpreted as supportive but preliminary.

Table 2: Summary of reported preclinical evidence relevant to ATC [1,2,5].

Model / source	Main reported findings	Critical appraisal
CCl4-induced oxidative stress in Wistar rats [1]	ATC was associated with lower MDA, higher GSH, improved SOD and CAT activity, and recovery of state 3 respiration and respiratory control ratio.	Supportive for antioxidant and mitochondrial-protective activity, but fuller reporting of randomization, blinding, and power calculation is needed.
Carcinogen-induced rat tumor models [2]	Reported modulation of inflammatory, angiogenic, metabolic, and tumor-related biomarkers across several rat cancer models.	Promising but heterogeneous; formulation description and cross-model comparability require clearer standardization.
NMU breast-cancer biomarker study [5]	Linked tumor progression with NF-kB activation, altered melatonin signaling, and LDH dynamics, providing biological context for translational biomarker work.	Primarily contextual rather than definitive proof of ATC efficacy; external replication remains necessary.

5. Clinical Evidence

The most developed clinical report concerns advanced triple-negative breast cancer (TNBC). In a prospective, open-label, controlled, multicenter study, 266 heavily pretreated patients with advanced, refractory, PD-L1-positive, stage IV TNBC received either ATC plus metronomic cyclophosphamide and propranolol (n = 147) or the metronomic backbone alone (n = 119) [3]. The reported primary endpoint was objective response rate at week 12 according to RECIST v1.1, with progression-free survival, biomarker dynamics, performance status, and safety as secondary outcomes.

According to the published report, the ATC-containing arm achieved a higher objective response rate than control (46.3% vs 12.6%) and longer median progression-free survival (8.9 vs 3.4 months), with an adjusted hazard ratio for progression of 0.42 (95% CI 0.30-0.60; $p < 0.001$) [3]. Paired biopsy analyses also showed larger reductions in Ki-67 and greater increases in CD8-positive tumor-infiltrating lymphocytes in the ATC arm [3]. The study further proposed a translational biomarker triad- Survivin downregulation, Cystatin C upregulation, and MT1 receptor re-expression - as a potential predictor of response [3]. Safety reporting did not indicate a disproportionate increase in exposure-adjusted adverse events attributable to the addition of ATC [3].

A randomized, double-blind, placebo-controlled trial in metastatic colorectal cancer (mCRC) has also been published [4]. This is important because it moves the program toward a higher-evidence design. Even so, the current mCRC literature remains limited to an early, single-study report from the same broader investigative group, and independent validation has not yet been established. For that reason, the colorectal data should be regarded as preliminary rather than practice-defining.

Overall, the clinical signal is encouraging but not yet definitive. The TNBC study is not sufficient on its own to establish routine clinical use because the evidence base remains small, largely single-group derived, and not yet anchored by independent confirmatory trials or overall survival data.

Table 3. Summary of available clinical evidence on ATC [3,4].

Clinical setting	Main reported findings	Critical appraisal
Advanced refractory TNBC [3]	Prospective controlled study (n = 266) reported ORR 46.3% vs 12.6% and median PFS 8.9 vs 3.4 months for ATC plus metronomic backbone versus backbone alone. Biomarker changes included reduced Ki-67, increased CD8-positive TILs, and the proposed Survivin/Cystatin C/MT1 response triad.	Most informative clinical dataset currently available, but open-label design, lack of independent replication, and absence of overall survival data limit definitiveness.
Metastatic colorectal cancer [4]	A randomized, double-blind, placebo-controlled clinical trial has been reported, indicating that higher-level testing has begun.	At present, interpretation is limited by the early single-study nature of the evidence and the absence of independent confirmatory reports.

6. Translational Interpretation and Clinical Context

One of the more original aspects of the ATC program is its attempt to bridge molecular biomarkers with clinical response. The proposed Survivin/Cystatin C/MT1 triad links apoptosis resistance, protease regulation, and circadian signaling, which is biologically interesting in a disease such as TNBC where immune modulation, metabolic adaptation, and proliferative escape are tightly interconnected [3]. Even so, biomarker panels can appear highly predictive in derivation cohorts and then lose performance when tested externally. Independent prospective validation is therefore essential before such a triad can be considered clinically actionable.

The breast-cancer backbone used in the TNBC study also deserves contextualization. Metronomic chemotherapy has a biologically plausible role in breast cancer because of its anti-angiogenic, immunomodulatory, and tolerability advantages, particularly in advanced or resistant disease settings [18-20]. Propranolol has likewise attracted interest as an adjunctive anticancer agent, but the broader literature remains mixed and does not yet support uniform conclusions across tumor types or treatment settings [21,22]. This context is relevant because

Paper ID: SR26302015636 DOI: https://dx.doi.org/10.21275/SR26302015636

any observed treatment effect in the ATC arm must be interpreted against an active metronomic platform rather than against no therapy.

More broadly, ATC sits within a wider translational movement toward multi-target phytochemicals and enhanced delivery systems [13-17]. That direction is scientifically reasonable, especially when poor bioavailability, multidrug resistance, and network-level signaling plasticity are considered. Still, successful translation depends on rigorous formulation science, reproducible pharmacology, and careful separation of mechanistic plausibility from demonstrated patient benefit.

7. Limitations of the Current Evidence

First, the ATC-specific evidence base is small and largely derived from the same investigative network [1-5]. This limits confidence in reproducibility and increases the importance of external confirmation.

Second, methodological reporting is incomplete in several reports. Key details such as randomization methods, blinding procedures, sample-size justification, protocol registration, and predefined statistical analysis plans are not always described with sufficient precision for critical appraisal.

Third, formulation description is not fully harmonized across publications. Some reports emphasize a tri-constituent core, whereas others describe broader multi-phytochemical compositions [2]. Without standardized pharmaceutical reporting, it is difficult to attribute observed effects to a stable and reproducible formulation.

Fourth, the available clinical evidence emphasizes response and progression-based endpoints, whereas overall survival, long-term toxicity, pharmacokinetics, drug-drug interactions, and patient-reported quality of life remain incompletely defined.

Fifth, the present article is itself a narrative review. It was designed to improve transparency and balance, but it does not provide the formal comprehensiveness, protocol registration, or quantitative synthesis of a systematic review.

8. Future Research Priorities

Future work should prioritize independent, multicenter randomized trials that evaluate ATC against clearly defined standard or backbone regimens and include overall survival, quality-of-life, and long-term safety endpoints.

Equally important is transparent pharmaceutical characterization. Future publications should specify full composition, manufacturing standardization, nanodelivery architecture, stability, bioavailability, pharmacokinetics, and pharmacodynamic markers.

The proposed biomarker triad should be tested prospectively in external cohorts and ideally across more than one tumor type before being used for patient selection or treatment monitoring.

Expansion into other oxidative-stress-related disorders or cancer settings should remain hypothesis-generating until indication-specific human data become available.

9. Conclusion

AminoTriComplex integrates multiple bioactive phytochemicals within a formulation intended to modulate oxidative stress, mitochondrial function, and cancer-related signaling pathways. The available preclinical literature suggests antioxidant and mitochondrial-protective activity, and early clinical data in refractory TNBC suggest possible adjunctive benefit when ATC is combined with a metronomic treatment backbone. However, the present evidence base remains limited, largely single-group derived, and incompletely standardized at both the methodological and formulation levels.

Independent replication, larger randomized trials with overall survival endpoints, transparent reporting of formulation and study methods, and long-term safety assessment are required before definitive therapeutic positioning can be established.

Acknowledgments
The authors thank the staff of the Institute for Personalized Medicine, Tbilisi, for their contribution to the clinical and research programs summarized in this review. Appreciation is also extended to the patients and research participants involved in the studies discussed.

Funding
This work was supported by the Institute for Personalized Medicine, Tbilisi, Georgia. No external commercial funding was reported.

Disclosure Statement
The authors report no external commercial conflicts of interest. Several authors were involved in the development or evaluation of the formulation discussed in this review.

References

[1] Tavartkiladze A, Simonia G, Reiter RJ, Lou R, Okrostsvaridze N, Kasradze D, et al. Antioxidant Activity of AminoTriComplex (AminoSineTriComplex) and Reduction of Oxidative Stress During Induced Stress. J Cancer Res. 2025;3(2):1-20.
[2] Tavartkiladze A, Simonia G, Lou R, Revazishvili P, Kasradze D, et al. Exploring AminoSineTriComplex (AminoTriComplex) for Multimodal Tumor Management in Carcinogen-Induced Rat Models: Insights from Blood Biomarker Analysis. J Cancer Res. 2024;2(1):1-18.
[3] Tavartkiladze A, Simonia G, Reiter RJ, Lou R, Okrostsvaridze N, Kasradze D, et al. AminoTriComplex Therapy in Advanced Triple-Negative Breast Cancer: A Translational Study Linking Survivin Downregulation, Cystatin C Upregulation, and MT1 Receptor Re-Expression to Clinical Outcomes. J Cancer Immunol. 2025;7(3):128-143.
[4] Tavartkiladze A, Simonia G, Reiter RJ, Lou R, Okrostsvaridze N, Revazishvili P, et al.

AminoSineTriComplex for Metastatic Colorectal Cancer: A Double-Blind, Placebo-Controlled Randomized Clinical Trial. J Cancer Res. 2025;3(1):1-12.

[5] Tavartkiladze A, Simonia G, Reiter RJ, Lou R, Okrostsvaridze N, et al. The Role of NF-kB, Melatonin, and LDH-A in Breast Cancer Initiation, Promotion, and Progression in Rats Exposed to N-Methyl-Nitroso-Urea: Implications for Tumor Metabolic Reprogramming. J Cancer Res. 2025;3(1):1-11.

[6] Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev. 2017; 2017: 8416763.

[7] Tungmunnithum D, Thongboonyou A, Pholboon A, Yangsabai A. Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects. Medicines (Basel). 2018;5(3):93.

[8] Legeay S, Rodier M, Fillon L, Faure S, Clere N. Epigallocatechin gallate: a review of its beneficial properties to prevent metabolic syndrome. Nutrients. 2015;7(7):5443-5468.

[9] Salehi B, Mishra AP, Nigam M, Sener B, Kilic M, Sharifi-Rad M, et al. Resveratrol: a double-edged sword in health benefits. Biomedicines. 2018;6(3):91.

[10] Imenshahidi M, Hosseinzadeh H. Berberine and barberry (Berberis vulgaris): a clinical review. Phytother Res. 2019;33(3):504-523.

[11] Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov. 2006;5(6):493-506.

[12] Brand MD, Nicholls DG. Assessing mitochondrial dysfunction in cells. Biochem J. 2011;435(2):297-312.

[13] Lv Y, Li X, Zhang Q, Zhao Y. Nano-Drug Delivery Systems Based on Natural Products. Int J Nanomedicine. 2024; 19: 541- 569.

[14] Huang L, Huang XH, Yang X, et al. Novel nano-drug delivery system for natural products and their application. Pharmacol Res. 2024; 201: 107100.

[15] Li B, Shao H, Gao L, Li H, Sheng H, Zhu L. Nano-drug co-delivery system of natural active ingredients and chemotherapy drugs for cancer treatment: a review. Drug Deliv. 2022;29(1):2130-2161.

[16] Annaji M, Poudel I, Boddu SHS, Arnold RD, Tiwari AK, Babu RJ. Resveratrol-loaded nanomedicines for cancer applications. Cancer Rep (Hoboken). 2021;4(3): e1353.

[17] Aljabali AAA, Obeid MA, Bashatwah RM, et al. Phytochemicals in Cancer Therapy: A Structured Review of Mechanisms, Challenges, and Progress in Personalized Treatment. Chem Biodivers. 2025;22(8): e202402479.

[18] Cazzaniga ME, Cortesi L, et al. Metronomic Chemotherapy in Triple-Negative Metastatic Breast Cancer: The Future Is Now? Int J Breast Cancer. 2017; 2017: 1683060.

[19] Cazzaniga ME, Vallini I, Montagna E, et al. Metronomic chemotherapy (mCHT) in metastatic triple-negative breast cancer (TNBC) patients: results of the VICTOR-6 study. Breast Cancer Res Treat. 2021;190(3):415-424.

[20] Guarini C, Santoro AN, Melaccio A, Lanotte L, Gadaleta-Caldarola G, Giuliani F, et al. Metronomic chemotherapy and breast cancer: a critical evaluation of its role in the new landscape of therapeutics. Expert Opin Drug Saf. 2025;24(1):9-16.

[21] Pantziarka P, Bryan BA, Crispino S, Dickerson EB. Propranolol and breast cancer-a work in progress. Ecancermedicalscience. 2018;12: ed82.

[22] O'Logbon J, Alizadeh A, et al. Does propranolol have a role in cancer treatment? A systematic review of the epidemiological and clinical trial literature on beta-blockers. J Cancer Res Clin Oncol. 2025;151(7):212.