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Article

The Dysbiosis-Urolithin A-Melatonin Axis in Advanced Solid Tumors: A Pilot Observational Study and Proposal of a Composite Biomarker Triad

Alexandre Tavartkiladze ^{1,2,4,*}, 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} and Rusudan Khutsishvili ²

- ¹ Tbilisi State Medical University, Tbilisi 0186, Georgia
- ² Institute for Personalized Medicine, Tbilisi 0160, Georgia
- ³ Department of Cellular and Structural Biology, University of Texas Health Science Center, San Antonio, TX 78229, USA
- ⁴ Foconsci Chemical Industry, Department of Biotechnology, China
- * Correspondence: alexandre.tavartkiladze@gmail.com

Abstract

Urolithin A (UA) is a gut microbiota-derived metabolite of dietary ellagitannins with anti-inflammatory, mitochondrial, and neuroprotective properties. Because systemic UA availability depends on specific microbial consortia, dysbiosis may lead to functional loss of urolithin production. Melatonin, assessed via its major urinary metabolite 6-sulfatoxymelatonin (6-SMT), has been linked to cancer risk modulation in epidemiologic studies. In this three-year pilot observational study in Caucasian adults, we compared Group 1 (n = 231) with aggressive stage IV tumors (colorectal, hepatic, pancreatic, NSCLC, SCLC, TNBC, or glioblastoma), Group 2 (n = 118) with less aggressive advanced tumors (stage IV ER/PR+++ HER2-negative breast cancer, WHO grade 2 astrocytoma, or stage IV carcinoid tumors), and healthy controls (n = 117). UA was quantified by HPLC in plasma and stool; stool microbiota were cultured with attention to *Streptococcus thermophilus*, *Enterococcus faecium*, and Bacteroidetes; serum IL-6, TNF- α , IL-8, and IL-10 and 24 h urinary 6-SMT were measured. Group 1 exhibited severe selective dysbiosis with loss of *S. thermophilus* and *E. faecium* and critical reduction in Bacteroidetes, accompanied by undetectable UA in plasma and stool, marked elevation of pro-inflammatory cytokines (IL-6, TNF- α , IL-8) with normal IL-10, and profoundly reduced 6-SMT. Group 2 showed an attenuated pattern (reduced but detectable UA, moderate dysbiosis, moderately elevated cytokines, and moderate 6-SMT reduction). We identify a reproducible dysbiosis-UA-melatonin triad associated with tumor aggressiveness and propose it as a candidate composite biomarker framework for prospective validation and mechanistic studies.

Keywords: urolithin A; ellagitannins; gut microbiota; dysbiosis; melatonin; 6-sulfatoxymelatonin; glioblastoma; colorectal cancer; NSCLC; composite biomarker

1. Introduction

Ellagitannins from pomegranate, walnuts, and some berries are converted by intestinal microbial consortia into urolithins, a family of dibenzopyran-6-one metabolites. Among these, urolithin A (UA) is the best characterized and has been extensively reviewed for its metabolism, bioactivity, and associated gut microbiota [1]. Interindividual differences in microbial composition lead to distinct urolithin metabolotypes (UMA, UMB, and UM0), ranging from robust UA producers to nonproducers [2]. A recent systematic review summarized bacteria implicated in ellagitannin

transformation to urolithins and highlighted the biological and technical sources of variability that underlie these metabotypes [3].

UA exhibits anti-inflammatory, antioxidant, and mitochondrial effects (including mitophagy induction) in experimental systems [4–6]. At physiologically relevant concentrations, UA and its conjugates can attenuate pro-inflammatory signaling, including TNF- α -driven endothelial activation [5] and broader inflammatory cascades [6]. Importantly, urolithins and their conjugates have been reported to cross the blood-brain barrier (BBB) and modulate stimulus-dependent microglial activation [7]. Reviews and preclinical studies position UA as a candidate postbiotic for brain aging and neurodegenerative trajectories, including Alzheimer's disease models [8,9].

Cancer-associated gut dysbiosis is well documented in colorectal cancer (CRC), where reduced diversity and altered microbial metabolite profiles are consistently reported [10,11]. Although evidence is less mature in extraintestinal cancers, associations between gut dysbiosis and non-small-cell lung cancer (NSCLC) risk have been described and may influence treatment response [12]. These observations support the concept that microbial metabolic capacity—not only taxonomic diversity—may modulate host inflammation and potentially tumor biology.

Melatonin is a pineal-derived hormone with pleiotropic immunomodulatory and oncostatic actions. Its major urinary metabolite, 6-sulfatoxymelatonin (6-SMT), is commonly used as a noninvasive surrogate of nocturnal melatonin secretion. Prospective studies have reported inverse associations between urinary 6-SMT and breast cancer risk in some cohorts [16–18], and night shift work is associated with reduced 6-SMT and altered cortisol profiles [19]. Urinary melatonin-sulfate has also been evaluated in prostate cancer [20,21] and prostate cancer risk studies [22].

Despite converging evidence linking (i) microbiota-dependent ellagitannin-urolithin metabolism, (ii) cancer-associated dysbiosis, and (iii) circadian/melatonin biomarkers, these dimensions have rarely been assessed together in advanced solid tumors. We hypothesized that a composite signature involving selective dysbiosis, systemic and fecal UA depletion, and decreased 6-SMT would track with tumor aggressiveness. Here, we report a three-year pilot observational study comparing two advanced tumor cohorts and healthy controls, and we propose an integrated dysbiosis-UA-melatonin triad as a candidate composite biomarker and mechanistic framework.

2. Materials and Methods

2.1. Study Design and Participants

This pilot observational study was conducted over a three-year period. Adult Caucasian oncology patients were prospectively observed and categorized into two cohorts based on tumor aggressiveness and clinical status, and compared to a healthy control cohort.

A total of 466 oncology patients were screened; 117 were excluded; and 349 were included and allocated to Group 1 ($n = 231$) or Group 2 ($n = 118$) (Figure 1). Group 1 (high aggressiveness) included stage IV colorectal, hepatic, pancreatic, NSCLC, SCLC, TNBC, and glioblastoma cases ($n = 231$; 107 male, 124 female). Group 2 (lower aggressiveness) included stage IV ER/PR+++ HER2-negative breast cancer, WHO grade 2 astrocytoma, and stage IV carcinoid tumors ($n = 118$; 77 male, 41 female).

Healthy controls were recruited as an age- and sex-matched Caucasian cohort without known malignancy ($n = 117$; 75 male, 42 female). Additional control blood specimens were available for some analyses (Figure 1).

Participant flow and specimen availability for blood, stool, and urine are summarized in Figure 1.

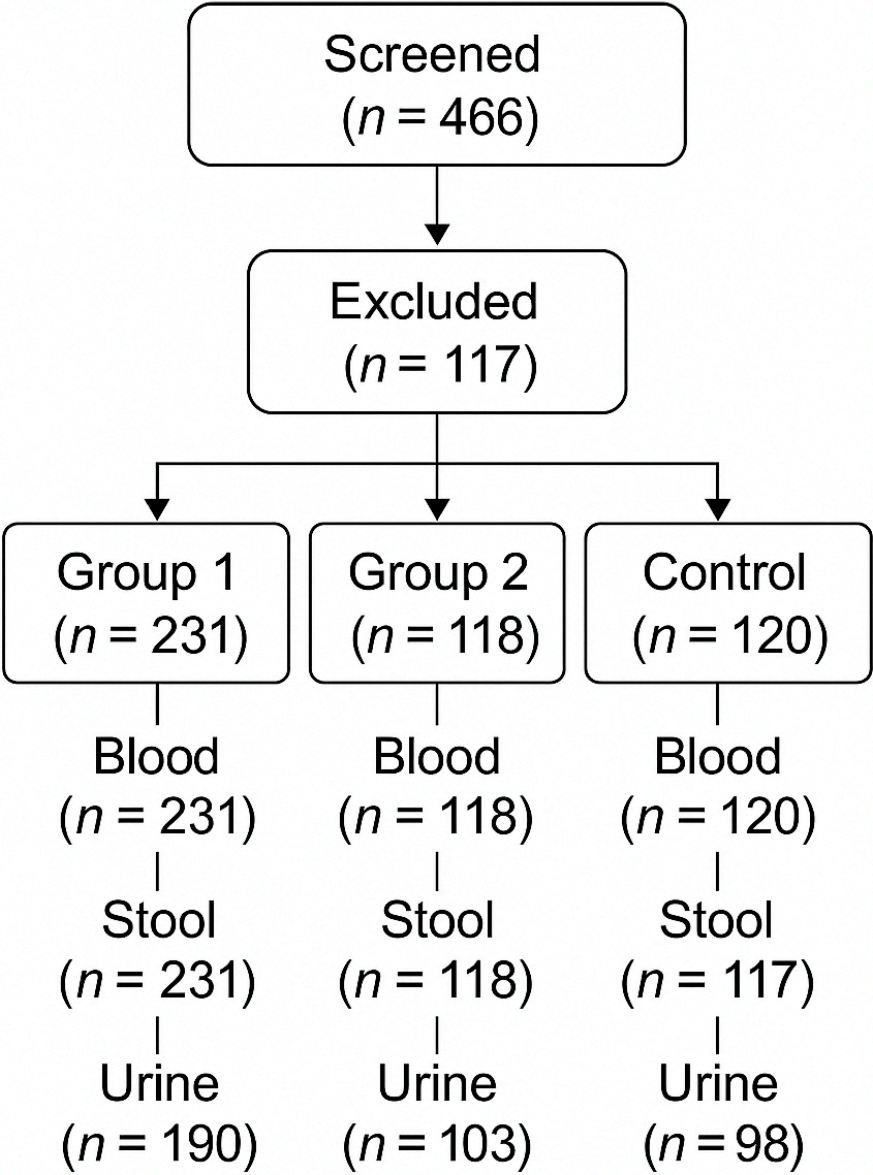


Figure 1. Study design and participant flow. Flow diagram showing numbers screened and excluded, allocation to Group 1 and Group 2, and control cohort, with numbers contributing blood, stool, and urine specimens.

2.2. Sample Collection and Processing

Blood, stool, and 24 h urine samples were collected according to a standardized protocol. Plasma was isolated from blood and stored under conditions appropriate for metabolite and cytokine analyses.

Stool specimens were processed for UA-related metabolite measurement and for culture-based microbiota assessment. Urine was collected over 24 h for quantification of 6-SMT.

2.3. Quantification of Urolithin A in Plasma and Stool

UA was quantified by high-performance liquid chromatography (HPLC) in plasma and stool extracts. The assay targeted UA and UA-related fecal metabolites; concentrations below the assay’s detection threshold were classified as undetectable.

All available plasma specimens were analyzed for UA. Stool UA analysis was performed for all available stool samples in each cohort (Figure 1).

2.4. Culture-Based Microbiota Assessment

Stool cultures were performed using selective and differential media with particular attention to *Streptococcus thermophilus*, *Enterococcus faecium*, and Bacteroidetes, taxa hypothesized to relate to urolithin production and/or dysbiosis severity. Results were interpreted qualitatively (present/depleted/absent) in relation to the clinical grouping.

2.5. Inflammatory Cytokines and Urinary 6-SMT

Serum IL-6, TNF- α , IL-8, and IL-10 were measured using immunoassays performed according to the manufacturers' instructions. Cytokine results were summarized as cohort-level distributions.

Twenty-four-hour urinary 6-SMT was measured as an index of melatonin output. All values were normalized to daily excretion (ng/day).

2.6. Statistical Analysis

Because this study was designed as a pilot observational investigation, analyses were primarily descriptive and focused on between-cohort contrasts. Continuous variables are reported using medians and interquartile ranges (IQRs) where available; categorical variables are reported as counts and percentages. Where comparisons were performed, nonparametric tests were used for continuous variables and χ^2 tests for categorical variables. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Study Design, Cohorts, and Specimen Availability

Oncology patients were screened (n = 466) and excluded (n = 117) according to protocol criteria, yielding 349 included patients allocated to Group 1 (n = 231) and Group 2 (n = 118). A healthy control cohort (n = 117) was enrolled in parallel.

Specimen availability for downstream analyses is summarized in Figure 1. Blood and stool samples were available for all participants in Groups 1 and 2. For controls, blood was available for 120 individuals and stool for 117 individuals (Figure 1). Twenty-four-hour urine samples were available for 190 participants in Group 1, 103 in Group 2, and 98 controls (Figure 1).

3.2. Plasma and Fecal Urolithin A Are Profoundly Depleted in the High-Aggressiveness Tumor Cohort

Plasma UA concentrations differed sharply across cohorts. In Group 1, UA was undetectable in plasma and fecal samples, consistent with a functional loss of urolithin-producing capacity. In Group 2, UA was reduced but remained detectable, whereas controls exhibited UA concentrations within the expected range (Figure 2).

These group-level patterns suggest that advanced, high-mortality tumors may be accompanied by a collapse of the ellagitannin-to-urolithin metabolic axis, potentially reflecting both taxonomic dysbiosis and metabolic dysfunction (Table 2).

3.3. Selective Dysbiosis of Putative Urolithin-Associated Taxa

Culture-based stool analysis showed marked depletion or absence of *Streptococcus thermophilus* and *Enterococcus faecium* in Group 1, along with a critical reduction in Bacteroidetes. Group 2 showed a moderate reduction in these taxa, while controls generally retained these groups (Table 2).

While culture-based approaches provide limited taxonomic resolution, the reproducibility of the selective depletion pattern across participants supports the hypothesis that specific taxa (or consortia) may be linked to UA production status and overall dysbiosis severity.

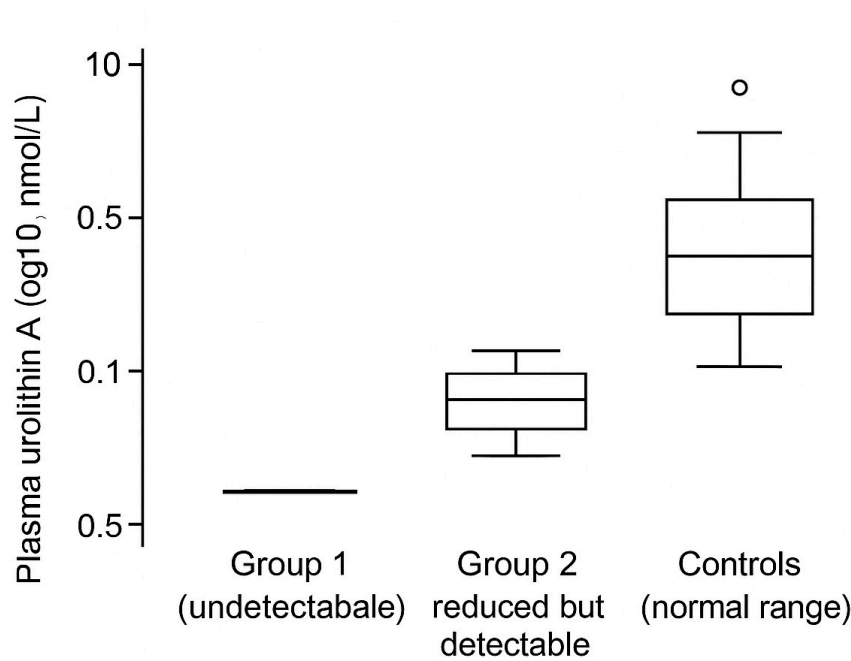


Figure 2. Plasma urolithin A concentrations across cohorts. Box-and-whisker plots (log scale) for plasma UA in Group 1 (undetectable), Group 2 (reduced but detectable), and controls (normal range).

3.4. Urinary 6-SMT Is Reduced in Parallel with UA Depletion

Twenty-four-hour urinary 6-SMT was critically reduced in Group 1 and moderately reduced in Group 2, compared with controls (Figure 3). This gradient suggests that diminished melatonin output may track with tumor aggressiveness and with the extent of UA depletion.

Notably, a subset of Group 1 exhibited near-zero 6-SMT excretion (Figure 3), consistent with profoundly impaired nocturnal melatonin production or altered metabolism/excretion in the setting of systemic illness.

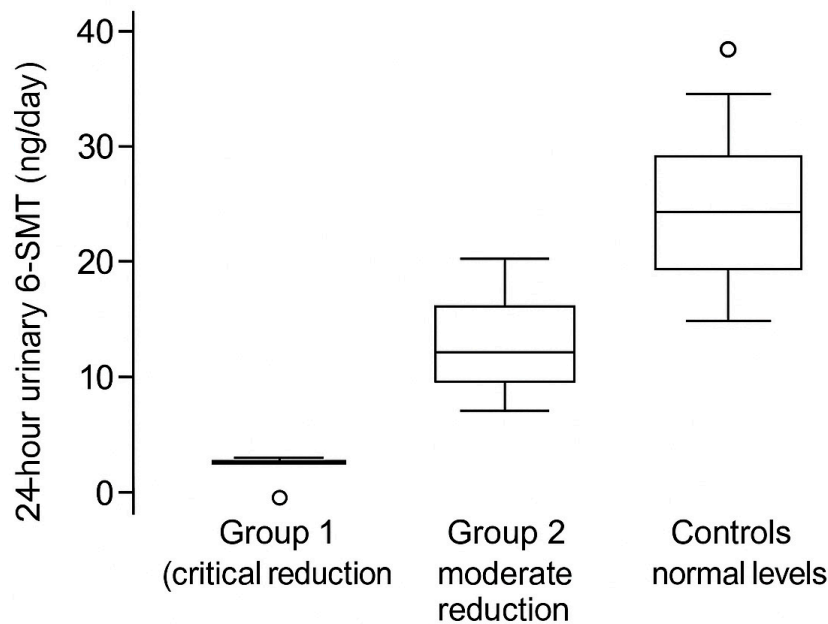


Figure 3. 24-hour urinary 6-sulfatoxymelatonin (6-SMT) across cohorts. Box-and-whisker plots of 6-SMT levels illustrating critical reduction in Group 1, moderate reduction in Group 2, and normal levels in controls.

3.5. Pro-Inflammatory Cytokines Are Elevated with Preserved IL-10, Defining a Composite Triad

Group 1 displayed markedly elevated serum IL-6, TNF- α , and IL-8, whereas IL-10 remained within the normal range. Group 2 showed the same directionality with a smaller magnitude of elevation. Controls exhibited low levels of pro-inflammatory cytokines. Together, these findings indicate chronic, low-grade systemic inflammation that accompanies the dysbiosis-UA-melatonin pattern.

Based on the concordant patterns across compartments, we propose a composite dysbiosis-UA-melatonin triad characterized by (i) selective dysbiosis with depletion of putative urolithin-associated taxa, (ii) systemic and fecal UA depletion, and (iii) reduced 6-SMT coupled to elevated pro-inflammatory cytokines (Figure 4; Table 3).

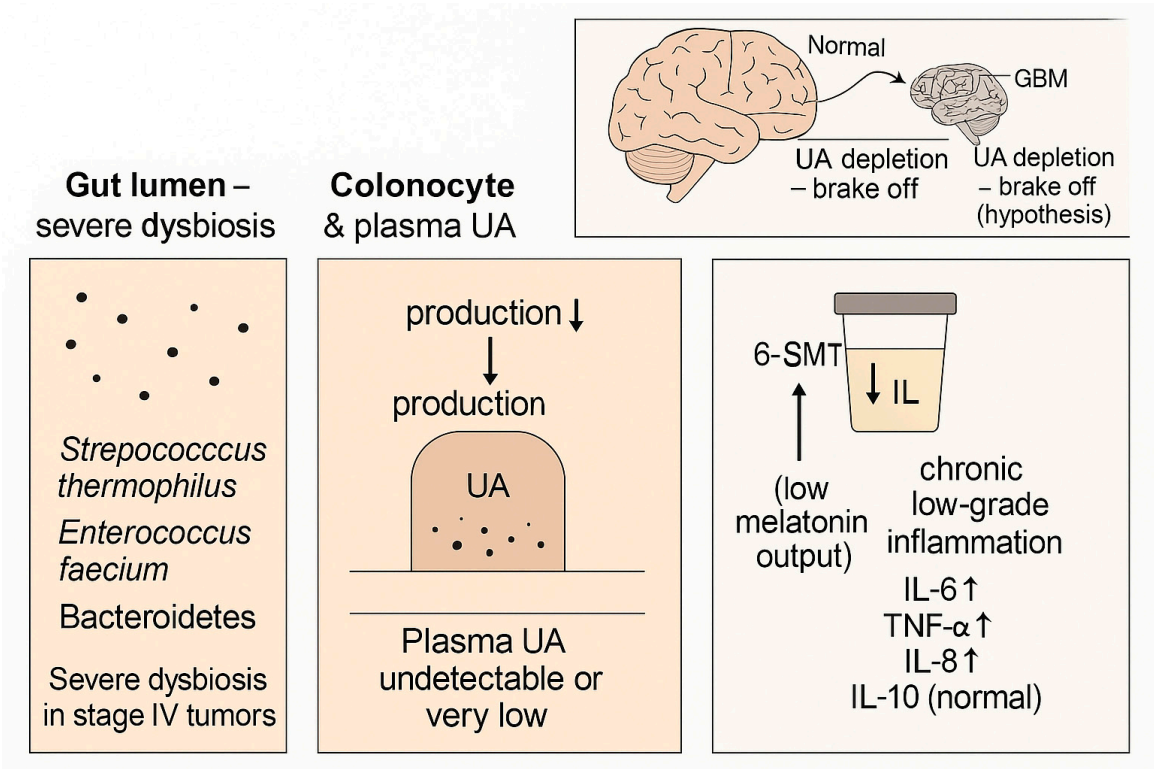


Figure 4. Schematic summary of the dysbiosis-UA-melatonin triad across compartments. Severe dysbiosis in the gut lumen is associated with reduced colonocyte and plasma UA, reduced melatonin output (low 6-SMT), and a chronic low-grade inflammatory cytokine profile. A putative ‘UA depletion-brake off’ hypothesis is depicted for glioblastoma (GBM).

Table 1. Cohort definitions and baseline clinical characteristics (summary).

Cohort	n	Sex (M/F)	Clinical definition / tumor types	Notes
Group 1 (high aggressiveness)	231	107/124	Stage IV colorectal, hepatic, pancreatic; NSCLC; SCLC; TNBC; glioblastoma	UA undetectable; low 6-SMT
Group 2 (lower aggressiveness)	118	77/41	Stage IV ER/PR+++ HER2-negative breast cancer; WHO grade 2 astrocytoma; stage IV carcinoid tumors	UA reduced; 6-SMT reduced
Controls	117	75/42	No known malignancy (healthy adults)	UA detectable; 6-SMT normal

Table 2. Qualitative summary of key features across cohorts.

Parameter	Group 1	Group 2	Controls
Plasma UA	Undetectable	Reduced but detectable	Normal range
Fecal UA metabolites	Undetectable	Reduced	Detectable
<i>Streptococcus thermophilus</i>	Absent/depleted	Reduced	Present
<i>Enterococcus faecium</i>	Absent/depleted	Reduced	Present
Bacteroidetes	Critical reduction	Moderate reduction	Preserved
24 h urinary 6-SMT	Critical reduction	Moderate reduction	Normal levels
IL-6, TNF- α , IL-8	Markedly elevated	Moderately elevated	Low/normal
IL-10	Normal range	Normal range	Normal range

Table 3. Proposed dysbiosis-UA-melatonin triad categories for future validation.

Category	UA status	6-SMT status	Dysbiosis	Cytokines	Interpretation
A (triad-positive, high-risk)	Undetectable	Critical reduction	Severe/selective depletion of taxa	High IL-6/TNF- α /IL-8; IL-10 preserved	Severe metabolic/inflammatory disruption
B (intermediate)	Reduced but detectable	Moderate reduction	Moderate depletion of taxa	Moderate elevation of IL-6/TNF- α /IL-8	Partial disruption; may track with lower aggressiveness
C (triad-negative)	Normal range	Normal levels	No severe dysbiosis	Normal cytokine profile	Physiologic host-microbe axis preserved

4. Discussion

4.1. Summary of Main Findings

This pilot observational study suggests that advanced solid tumors with high mortality are associated with a reproducible multi-compartment pattern: (i) selective severe dysbiosis with depletion of key taxa, (ii) collapse of systemic and fecal UA availability, and (iii) reduced melatonin output (as 6-SMT) accompanied by elevated pro-inflammatory cytokines with preserved IL-10. In a lower-aggressiveness tumor cohort, the same pattern was present but attenuated, whereas controls exhibited measurable UA and normal 6-SMT.

We propose that this dysbiosis-UA-melatonin triad may serve as a composite biomarker framework for disease severity and as a hypothesis-generating model that integrates microbial metabolic capacity, systemic inflammation, and neuroendocrine status (Figure 5).

4.2. Dysbiosis and Functional Loss of Urolithin Production

UA production depends on specific microbial consortia and is highly variable between individuals, giving rise to the recognized urolithin metabotypes [1–3]. The observation that UA was undetectable in both plasma and stool in Group 1 suggests that, in at least a subset of advanced cancer patients, dysbiosis may extend beyond taxonomic shifts to a functional collapse of ellagitannin-to-urolithin biotransformation.

Because diet was not controlled and metagenomic profiling was not performed, we cannot distinguish whether UA depletion reflects loss of urolithin-producing taxa, suppression of relevant metabolic pathways, reduced substrate availability, or combined effects. Nonetheless, the concordance between culture-based depletion of selected taxa and the UA phenotype supports the plausibility of a metabolic bottleneck.

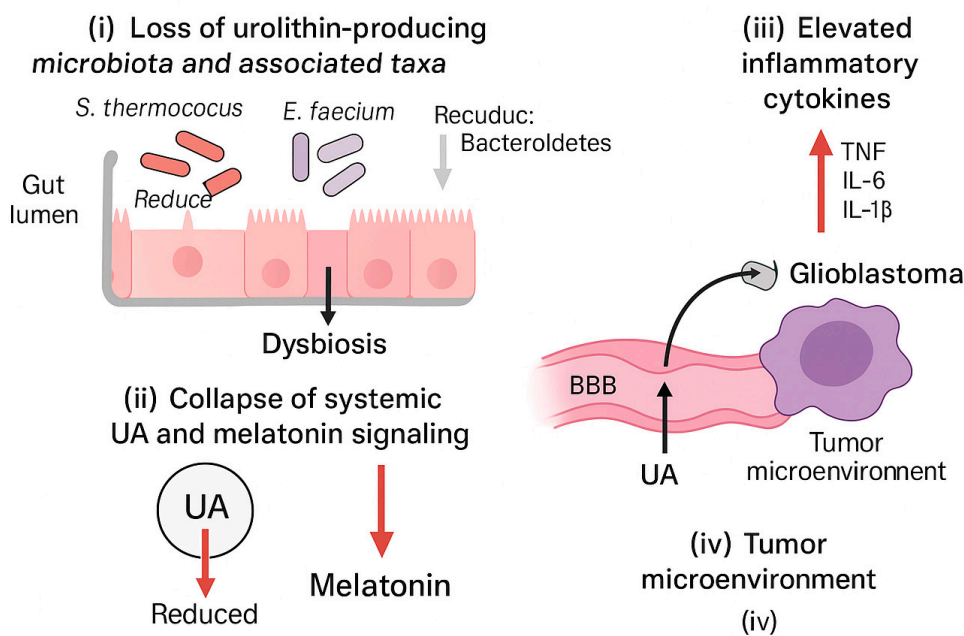


Figure 5. Conceptual model of the dysbiosis-UA-melatonin triad. Loss of urolithin-producing microbiota and associated taxa is proposed to contribute to dysbiosis, collapse of systemic UA and melatonin signaling, elevated inflammatory cytokines, BBB interactions, and tumor microenvironment changes (schematic).

4.3. Linking UA Deficiency to Systemic Inflammation

UA has been reported to modulate inflammatory signaling and endothelial activation, including pathways driven by TNF- α [5] and broader inflammatory cascades [4,6]. In our cohorts, UA depletion paralleled elevations in IL-6, TNF- α , and IL-8, consistent with a chronic inflammatory state. While causality cannot be inferred, one interpretation is that loss of a potentially anti-inflammatory postbiotic may contribute to a permissive cytokine milieu.

Alternatively, systemic illness, tumor burden, and therapy-related factors may drive both dysbiosis and inflammation, with UA depletion acting as a downstream marker of disrupted host-microbe metabolism. Longitudinal sampling will be required to determine temporality and directionality.

4.4. Potential Relevance to Glioblastoma and the BBB

A notable feature of our conceptual model is the potential intersection between UA availability and central nervous system (CNS) tumor biology. Urolithins and their conjugates have been reported to cross the BBB and to modulate microglial activation in experimental models [7]. In parallel, UA has been discussed as a candidate postbiotic for brain aging and neurodegeneration, including Alzheimer’s disease models [8,9].

These observations motivate the hypothesis that systemic UA depletion could remove a protective ‘brake’ on neuroinflammatory or metabolic processes relevant to glioblastoma progression. This remains speculative and requires direct mechanistic testing in GBM models, including measurements of UA (and conjugates) in CNS compartments and evaluation of tumor-microenvironment interactions.

4.5. Melatonin Output as a Companion Signal in the Triad

Reduced urinary 6-SMT has been linked to cancer risk modulation in several epidemiologic settings, particularly in breast cancer cohorts [16–18]. Circadian disruption and night shift work are associated with altered 6-SMT and cortisol profiles [19]. Studies in prostate cancer further suggest

that melatonin/6-SMT rhythms may relate to disease status [20,21], and urinary 6-SMT has been investigated in prostate cancer risk in a multiethnic cohort [22].

In our cohorts, the reduction in 6-SMT tracked with tumor aggressiveness and with the UA phenotype. Whether this reflects altered pineal output, systemic inflammation, medication effects, sleep disruption, or changes in metabolism/excretion cannot be determined from this design. Nonetheless, incorporating a circadian/neuroendocrine biomarker alongside microbial-metabolic and inflammatory readouts may improve composite risk stratification.

4.6. Clinical Implications and Future Directions

If confirmed, the triad could inform screening or monitoring strategies in advanced solid tumors. Interventions might include dietary ellagitannin optimization, microbiota-directed therapies (e.g., prebiotics or carefully selected probiotics), direct UA supplementation, and/or circadian alignment strategies aimed at restoring melatonin rhythms.

Any microbiota-directed intervention should consider safety and strain specificity. For example, while certain *Enterococcus* strains are used as probiotics and can produce bioactive exopolysaccharides [13], functional properties of *Streptococcus thermophilus* have been reviewed in food and industrial contexts [14]. At the same time, concerns regarding enterococcal probiotic risk and the need for strain-level safety assessment have been highlighted [15]. Future trials should prioritize well-characterized, nonpathogenic strains and incorporate metagenomic and metabolomic endpoints.

4.7. Limitations

This study has several limitations: (i) the observational design precludes causal inference; (ii) microbiota assessment relied on culture-based methods rather than sequencing; (iii) dietary intake of ellagitannins and use of antibiotics/probiotics were not quantitatively controlled; (iv) treatment exposures and other confounders were not modeled; and (v) detailed quantitative UA, cytokine, and 6-SMT distributions were not available for all participants in this report.

Accordingly, the findings should be interpreted as hypothesis-generating. Larger prospective cohorts with longitudinal sampling, comprehensive multi-omics profiling, and standardized dietary and circadian assessments are needed to validate the triad and clarify mechanisms.

5. Conclusions

In this pilot observational study, patients with highly aggressive advanced solid tumors exhibited a consistent triad comprising severe selective dysbiosis, collapse of systemic and fecal urolithin A availability, and reduced melatonin output (24 h urinary 6-SMT), accompanied by elevated pro-inflammatory cytokines with preserved IL-10. A lower-aggressiveness tumor cohort demonstrated an attenuated version of the same pattern, while controls showed measurable UA and normal 6-SMT.

These data motivate the dysbiosis-UA-melatonin triad as a candidate composite biomarker and a framework for mechanistic studies, including investigation of BBB-permeable postbiotics in glioblastoma biology. Prospective validation and intervention trials are warranted.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) under protocols #CN-2021-11 and #TX-UT-2021-08.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

UA, urolithin A; 6-SMT, 6-sulfatoxymelatonin; BBB, blood-brain barrier; CRC, colorectal cancer; GBM, glioblastoma; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer; ECOG, Eastern Cooperative Oncology Group; HPLC, high-performance liquid chromatography; IQR, interquartile range.

Appendix A. Figure Files for Submission

Table A1. Figure numbering, captions, and file names (submission index).

Item	Title (short)	File name	Notes
Graphical Abstract (optional)	Overview schematic	GraphicalAbstract.png	Optional MDPI graphical abstract
Figure 1	Study design and participant flow	Figure1.png	Flow diagram
Figure 2	Plasma urolithin A across cohorts	Figure2.png	Box-and-whisker plot (log scale)
Figure 3	Urinary 6-SMT across cohorts	Figure3.png	Box-and-whisker plot (ng/day)
Figure 4	Compartmental schematic of triad	Figure4.png	Summary schematic/hypothesis illustration
Figure 5	Conceptual model of dysbiosis-UA-melatonin triad	Figure5.png	Mechanistic/conceptual diagram

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