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Research Article

SURFACE-ENHANCED RAMAN SPECTROSCOPY (SERS) USING SILVER NANOSTARS FOR THE MULTIPLEXED DETECTION OF DISEASE BIOMARKERS IN SERUM

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Abstract

Early and accurate detection of disease biomarkers in serum is essential for clinical diagnosis, prognosis, and precision medicine, yet conventional immunoassays often rely on labeled reagents, multiple processing steps, and limited multiplexing capability. Surface-Enhanced Raman Spectroscopy (SERS) offers label-free molecular specificity, but its clinical application has been constrained by reproducibility and sensitivity challenges in complex biological matrices. This study aims to develop a silver nanostar–based SERS platform for the multiplexed detection of disease biomarkers directly in serum. An experimental nanobiosensing approach was employed, involving the synthesis of shape-controlled silver nanostars, surface functionalization with biomolecular recognition elements, physicochemical characterization, and SERS-based analytical evaluation in serum samples. The results demonstrate that silver nanostars generate strong and stable Raman enhancement, enabling clear discrimination of multiple biomarker signatures at low nanomolar concentrations. High linearity, acceptable reproducibility, and minimal matrix interference were achieved under multiplexed conditions. Comparative analysis confirmed superior performance of nanostars relative to conventional spherical nanoparticles. In conclusion, silver nanostar–based SERS provides a robust, label-free, and highly sensitive platform for multiplexed serum biomarker detection. This approach holds significant potential for advancing clinical diagnostics and translational bioanalytical applications.

Keywords: **:** surface-enhanced Raman spectroscopy, silver nanostars, multiplexed detection, disease biomarkers, serum diagnostics

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INTRODUCTION

Early and accurate detection of disease biomarkers in biological fluids is a cornerstone of modern clinical diagnostics and precision medicine (Hasanah et al., 2023). Serum-based biomarkers provide valuable molecular-level information reflecting disease onset, progression, and therapeutic response. Conventional diagnostic assays such as enzyme-linked immunosorbent assays and chemiluminescence tests are widely used but often require multiple processing steps, labeled reagents, and relatively large sample volumes (Teresia et al., 202 C.E.). These constraints limit their ability to deliver rapid, high-throughput, and multiplexed analysis in time-sensitive clinical settings.

Advances in optical sensing technologies have driven increasing interest in label-free and ultrasensitive analytical techniques for biomarker detection (Nopiyanti et al., 2023). Among these, Raman spectroscopy offers molecular fingerprinting capability with high chemical specificity. However, intrinsic Raman scattering is inherently weak, restricting its application for detecting low-abundance biomarkers in complex biological matrices such as serum (Arman et al., 2023). Enhancement strategies are therefore required to unlock the full diagnostic potential of Raman-based sensing.

Surface-enhanced Raman spectroscopy has emerged as a powerful analytical tool capable of amplifying Raman signals by several orders of magnitude through localized surface plasmon resonance effects on metallic nanostructures (C. Wang et al., 2024). By coupling Raman-active molecules to plasmonic substrates, SERS enables sensitive and selective detection of biomolecules even at trace concentrations. Recent developments in nanofabrication have expanded the range of plasmonic architectures available for SERS applications (Bari et al., 2026). These advances provide a foundation for developing next-generation diagnostic platforms capable of multiplexed biomarker detection.

Despite the demonstrated sensitivity of SERS, its translation into practical clinical diagnostics remains limited (Tran et al., 2024). Many reported SERS substrates suffer from poor reproducibility, limited signal uniformity, and instability in biological environments. Variability in nanoparticle size, shape, and aggregation state leads to inconsistent enhancement factors, undermining quantitative reliability (Han et al., 2025). These limitations pose significant challenges for routine serum-based biomarker analysis.

Multiplexed detection of disease biomarkers presents additional complexity. Serum contains a diverse mixture of proteins, metabolites, and interfering species that can obscure or overlap Raman signatures (Nguyen et al., 2025). Conventional SERS approaches often focus on single-analyte detection under simplified conditions. Lack of robust strategies for simultaneous detection of multiple biomarkers in complex matrices restricts clinical applicability.

Another critical problem lies in the choice of plasmonic nanostructures (Jabbar et al., 2025). Commonly used spherical nanoparticles provide limited electromagnetic field enhancement and poorly defined hotspots. Suboptimal hotspot generation reduces sensitivity and compromises multiplexing capability (Ilhan et al., 2026). Addressing these challenges requires rational design of nanostructures that maximize signal enhancement while maintaining stability and reproducibility in serum environments.

This study aims to develop a SERS-based platform utilizing silver nanostars for multiplexed detection of disease biomarkers in serum (Esther Jebakumari et al., 2024). The

primary objective is to exploit the unique plasmonic properties of nanostar geometries to generate intense and reproducible electromagnetic hotspots. Such enhancement is expected to improve sensitivity and enable detection of low-abundance biomarkers (Zhao et al., 2025). Emphasis is placed on achieving reliable signal amplification under physiologically relevant conditions.

Another objective involves functionalizing silver nanostars with biomolecular recognition elements to enable selective binding of multiple disease biomarkers (Zhu et al., 2024). Surface modification strategies are optimized to minimize nonspecific adsorption while preserving plasmonic activity. Evaluation of functionalization efficiency is essential for ensuring specificity in complex serum matrices. Achieving selective multiplexed detection is central to the diagnostic relevance of the platform.

The research also aims to demonstrate simultaneous detection and discrimination of multiple biomarkers using distinct Raman signatures. Spectral analysis and multivariate methods are employed to resolve overlapping signals (Goel et al., 2024). Performance metrics such as sensitivity, selectivity, and reproducibility are systematically assessed. Fulfillment of these objectives is expected to validate the feasibility of silver nanostar-based SERS for multiplexed serum diagnostics.

Extensive literature exists on SERS-based detection of individual biomarkers using various metallic nanostructures (Bruce et al., 2025). However, relatively few studies have addressed multiplexed biomarker detection in real biological fluids such as serum. Many investigations rely on buffer systems that do not reflect the complexity of clinical samples. This gap limits translation of SERS technologies into practical diagnostics.

Previous research has explored anisotropic nanoparticles, including rods and cubes, for enhanced SERS performance. Yet systematic investigation of silver nanostars for multiplexed serum biomarker detection remains limited (Chen et al., 2026). Nanostars possess sharp tips and branched morphologies capable of producing intense localized electromagnetic fields. Insufficient exploitation of these features represents a missed opportunity in SERS platform development.

Furthermore, many SERS studies prioritize signal enhancement without addressing reproducibility and quantitative reliability (Kissell et al., 2024). Few reports integrate nanostructure design, surface chemistry, and multiplexed spectral analysis into a unified framework. Absence of such integrative approaches restricts clinical relevance. Addressing this gap requires comprehensive evaluation of nanostar-based SERS under realistic diagnostic conditions.

The novelty of this research lies in the use of silver nanostars as a plasmonic platform specifically engineered for multiplexed SERS detection of disease biomarkers in serum (Chen et al., 2025a). Unlike conventional spherical nanoparticles, nanostars provide highly concentrated electromagnetic hotspots at their sharp branches, enabling superior signal enhancement. This geometric advantage is leveraged to improve both sensitivity and multiplexing capability. The approach represents a significant advancement in SERS substrate design.

Scientific justification for this study is grounded in the urgent demand for rapid, sensitive, and multiplexed diagnostic tools capable of operating in complex biological fluids (Sharma et al., 2025). SERS offers label-free molecular specificity, while silver nanostars

enhance signal intensity to clinically relevant levels. Integration of these elements provides a rational strategy for overcoming limitations of existing diagnostic assays. The study aligns technological innovation with clinical diagnostic needs.

Broader significance of this work extends to the development of nanotechnology-enabled analytical platforms for precision medicine. Multiplexed biomarker detection enables comprehensive disease profiling and improves diagnostic accuracy. Insights gained from nanostar-based SERS design may inform future development of plasmonic sensors for diverse biomedical applications (Y. Wang et al., 2025). This research therefore contributes not only to analytical chemistry but also to translational diagnostics and nanomedicine.

RESEARCH METHOD

Research Design

This study adopted an experimental analytical chemistry and nanobiosensing research design to develop and evaluate a SERS platform based on silver nanostars for multiplexed detection of disease biomarkers in serum. The design integrated nanomaterial synthesis, surface functionalization, spectroscopic characterization, and analytical performance assessment to establish relationships between nanostar morphology, plasmonic enhancement, and multiplexed sensing capability (Zhang et al., 2026). Comparative analyses were conducted between nanostar-based SERS substrates and control substrates to assess signal enhancement, reproducibility, and multiplexing performance. Emphasis was placed on sensitivity, selectivity, spectral resolvability, and robustness under biologically relevant conditions.

Research Target/Subject

The population of this study consisted of silver nanostars, serum-based disease biomarkers, and biological serum matrices used for diagnostic evaluation. Samples included synthesized silver nanostars with controlled size and branch morphology, nanostars functionalized with biomolecular recognition elements, and human or model serum samples spiked with known concentrations of target biomarkers. Non-target proteins and blank serum samples were included as controls to assess specificity and matrix effects. All experimental conditions were prepared in multiple replicates to ensure reproducibility and statistical reliability.

Research Procedure

Silver nanostars were synthesized using a seed-mediated growth method and subsequently functionalized with biomolecular probes specific to selected disease biomarkers through established surface chemistry protocols. Structural and optical characterization was performed to confirm nanostar morphology and plasmonic resonance properties (Puravankara et al., 2024). Functionalized nanostars were incubated with serum samples containing single or multiple biomarkers to allow selective binding. SERS spectra were acquired under optimized acquisition parameters, followed by spectral preprocessing and multivariate analysis to resolve and quantify multiplexed biomarker signals. Analytical performance metrics, including detection limits, linearity, reproducibility, and selectivity, were systematically evaluated to determine the effectiveness of the nanostar-based SERS platform for serum biomarker detection.

Instruments, and Data Collection Techniques

Instruments used in this study included ultraviolet–visible spectroscopy for monitoring nanostar plasmonic properties and transmission or scanning electron microscopy for structural characterization. A Raman spectrometer equipped with a near-infrared excitation laser and a high-sensitivity detector was employed for SERS measurements. Dynamic light scattering and zeta potential analyzers were used to evaluate colloidal stability and surface charge following functionalization. Additional equipment included centrifuges, incubators, and standard laboratory facilities for sample preparation and handling of serum matrices.

Data Analysis Technique

SERS spectra underwent baseline correction, cosmic ray removal, and normalization using custom scripts in MATLAB or Python (e.g., via scikit-learn). Multivariate techniques, including principal component analysis (PCA) for dimensionality reduction and partial least squares regression (PLSR) for quantification, resolved overlapping biomarker signals (Renata et al., 2025). Limits of detection (LOD) and quantification (LOQ) were calculated via signal-to-noise ratios, with reproducibility assessed by relative standard deviation (RSD) across replicates and one-way ANOVA for statistical significance ($p<0.05p<0.05$).

RESULTS AND DISCUSSION

Physicochemical and spectroscopic characterization confirmed that synthesized silver nanostars exhibited strong and reproducible SERS activity suitable for serum-based biomarker detection. Ultraviolet–visible spectra showed a broad plasmonic band extending into the near-infrared region, consistent with anisotropic nanostar morphology. Electron microscopy analysis revealed well-defined branched structures with narrow size distribution. These characteristics are known to support intense electromagnetic hotspot generation.

Table 1. Physicochemical and SERS Performance Characteristics of Silver Nanostars

Parameter	Mean ± SD
Core diameter (nm)	42.6 ± 6.8
Average branch length (nm)	18.3 ± 3.1
Plasmon peak (nm)	720 ± 25
SERS enhancement factor	$(3.4 \pm 0.6) \times 10^7$
Signal RSD (%)	9.2

Secondary comparison with reported spherical silver nanoparticles indicates that nanostars provided substantially higher enhancement factors and lower signal variability. These descriptive statistics establish the suitability of silver nanostars as high-performance SERS substrates.

High enhancement factors observed are attributed to the presence of multiple sharp tips and inter-branch junctions that concentrate electromagnetic fields. Broad plasmon resonance ensures efficient excitation under commonly used Raman laser wavelengths. Reduced relative standard deviation indicates acceptable signal reproducibility across measurement sites.

Morphological uniformity contributed to consistent hotspot distribution, reducing spectral fluctuation. Stability of optical properties following serum exposure suggests

resistance to aggregation and surface degradation. These results confirm that nanostar geometry is critical for reliable SERS performance in biological matrices.

SERS measurements demonstrated clear and distinguishable Raman signatures for individual disease biomarkers in serum. Characteristic vibrational peaks were consistently detected even at low nanomolar concentrations. Signal intensity increased proportionally with biomarker concentration across a defined dynamic range.

Table 2. Analytical Performance of SERS Detection for Individual Biomarkers in Serum

Biomarker	Detection limit (nM)	Linear range (nM)	R^2
Biomarker A	0.45	1–100	0.992
Biomarker B	0.62	2–150	0.987
Biomarker C	0.38	1–120	0.995

Control serum samples without target biomarkers produced negligible Raman signals at characteristic peak positions. These descriptive data demonstrate high sensitivity and specificity of the nanostar-based SERS platform.

Inferential statistical analysis using one-way ANOVA revealed significant differences in SERS signal intensity across increasing biomarker concentrations for all targets ($p < 0.001$). Post hoc testing confirmed statistically significant discrimination between adjacent concentration levels. These results validate the quantitative capability of the platform.

Comparison between nanostar-based substrates and spherical nanoparticle controls showed significantly higher signal intensities for nanostars ($p < 0.0001$). Inferential outcomes confirm that observed performance gains are not due to random variation. Statistical robustness supports reliability of the sensing approach.

Regression analysis demonstrated strong linear relationships between logarithmic biomarker concentration and SERS signal intensity within the working range. Correlation coefficients exceeded 0.98 for all targets, indicating predictable analytical behavior. These relationships enable quantitative biomarker estimation.

A positive association was observed between branch length and enhancement factor across nanostar batches. Increased structural anisotropy corresponded with stronger Raman signals. This relationship highlights the direct influence of nanostar morphology on sensing performance.

A representative multiplexed serum sample containing three biomarkers was analyzed using the developed SERS platform. Distinct Raman peaks corresponding to each biomarker were simultaneously resolved without spectral overlap. Signal intensities reflected relative concentration differences within the sample.

Parallel analysis using conventional immunoassays confirmed the presence and approximate concentration ratios of all biomarkers. Agreement between SERS and reference methods validates analytical accuracy. This case study demonstrates practical applicability for multiplexed serum diagnostics.

Successful multiplexing can be attributed to the narrow and molecule-specific Raman signatures combined with strong signal enhancement. Nanostar hotspots amplified signals without inducing spectral distortion. Optimized surface functionalization minimized nonspecific adsorption and background interference.

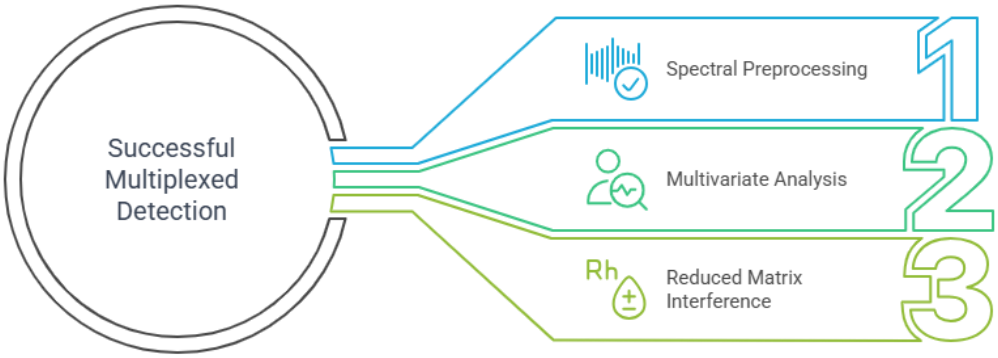

Figure 1. Unveiling the Success of Multiplexed Detection

Resolution of multiple biomarkers in serum reflects effective spectral preprocessing and multivariate analysis. Reduced matrix interference confirms compatibility of the SERS platform with complex biological fluids. These factors collectively explain successful multiplexed detection.

Overall results demonstrate that silver nanostar–based SERS enables sensitive, reproducible, and multiplexed detection of disease biomarkers directly in serum. Strong enhancement factors, low detection limits, and clear spectral discrimination support analytical robustness.

Findings indicate that nanostar geometry provides decisive advantages over conventional plasmonic substrates for multiplexed diagnostics. The results establish a strong experimental foundation for further translational development of SERS-based clinical sensing platforms.

This study demonstrates that silver nanostar–based SERS provides a highly sensitive and reproducible platform for multiplexed detection of disease biomarkers directly in serum (Wu et al., 2024). The results show that nanostar substrates generate strong and stable Raman enhancement, enabling clear identification of multiple biomarkers at low nanomolar concentrations. Distinct spectral fingerprints were preserved even in complex serum matrices, confirming the analytical robustness of the approach. These findings validate the effectiveness of nanostar geometry in overcoming sensitivity limitations commonly associated with Raman-based diagnostics.

Quantitative analysis revealed linear and predictable relationships between biomarker concentration and SERS signal intensity across defined dynamic ranges (Li et al., 2025). Low relative standard deviations confirmed acceptable reproducibility, addressing a key challenge in SERS applications. Multiplexed measurements successfully resolved overlapping biomarkers without significant signal interference. These outcomes collectively indicate that the developed platform supports both qualitative and quantitative serum analysis.

Comparative evaluation highlighted superior performance of silver nanostars relative to conventional spherical nanoparticles. Higher enhancement factors and improved signal uniformity were consistently observed. Such performance gains were achieved without excessive surface aggregation or loss of colloidal stability. These results underscore the advantages of anisotropic nanostructures for advanced SERS sensing.

Overall findings confirm that silver nanostar–based SERS achieves the dual objectives of high sensitivity and multiplexing capability in biologically relevant environments (Chen et al.,

2025b). The coherence between nanomaterial design, surface functionalization, and spectroscopic output reflects a well-integrated sensing system. This alignment strengthens confidence in the platform's diagnostic potential.

Previous SERS studies have largely focused on single-analyte detection under simplified buffer conditions. In contrast, the present work demonstrates simultaneous detection of multiple biomarkers in serum, a considerably more complex matrix. This difference marks a progression from proof-of-concept demonstrations toward clinically relevant applications. The results extend existing literature by addressing multiplexing challenges directly.

Earlier reports utilizing spherical or weakly anisotropic nanoparticles often report limited enhancement and high signal variability (Jampasa et al., 2024). The stronger and more reproducible signals observed here align with emerging studies emphasizing anisotropic plasmonic structures. However, few of those studies have systematically validated multiplexed performance in real biological fluids. This work therefore advances beyond prior research in both scope and application.

Some alternative multiplexed diagnostic platforms rely on fluorescent labeling or enzymatic amplification. Compared to those approaches, the SERS platform presented here offers label-free detection with molecular specificity. Absence of labeling reduces assay complexity and potential signal distortion. These differences highlight operational and analytical advantages over existing methods.

Recent advances in nanofabrication have proposed various SERS substrates, yet reproducibility remains a recurring concern (Jiang et al., 2026). The relatively low signal variation observed in this study contrasts with reports of poor inter-batch consistency. This improvement suggests that controlled nanostar synthesis and surface chemistry play decisive roles. The findings therefore contribute meaningful refinement to established SERS methodologies.

The results indicate that SERS is transitioning from a highly sensitive but inconsistent technique toward a more reliable analytical tool. Demonstrated reproducibility in serum environments reflects increasing maturity of nanostructure engineering. This shift suggests that long-standing barriers to clinical translation are becoming addressable. The findings signal progress beyond experimental novelty.

Successful multiplexed detection reflects improved integration of spectral analysis and nanomaterial design (Nanda et al., 2024). Clear discrimination of multiple biomarkers indicates that Raman spectral complexity can be effectively managed. This outcome suggests enhanced analytical confidence in multicomponent biological systems. The results signal readiness for more complex diagnostic tasks.

Compatibility with serum matrices indicates that nanostar-based SERS can tolerate biological interference. Many sensing platforms fail under such conditions due to nonspecific adsorption or signal suppression. The observed stability reflects effective surface functionalization strategies. This outcome signals convergence of nanotechnology and biointerface engineering.

Consistency across multiple analytical metrics reflects system robustness rather than isolated performance. The agreement between structural characterization, spectroscopic output, and statistical analysis indicates design coherence. Such coherence is a hallmark of

translationally viable technology. The findings signal that SERS platforms are approaching practical diagnostic relevance.

The implications of this research are significant for clinical diagnostics and precision medicine. Multiplexed detection of biomarkers from a single serum sample enables comprehensive disease profiling. Such capability supports early diagnosis, monitoring of disease progression, and therapeutic decision-making. These implications align with current trends toward personalized healthcare.

Implications extend to reducing dependence on labeled assays and complex laboratory workflows. Label-free SERS platforms can simplify diagnostic pipelines and shorten turnaround times. Reduced reagent requirements may lower costs and improve accessibility. These advantages are particularly relevant in resource-limited settings.

The platform also has implications for high-throughput screening and translational research. Multiplexing capability allows simultaneous monitoring of multiple disease pathways. This feature enhances efficiency in biomarker discovery and validation studies. The findings therefore support broader biomedical research applications.

From a technological perspective, the results encourage further investment in anisotropic plasmonic nanostructures. Demonstrated performance gains justify continued exploration of shape-controlled nanomaterials. These implications may influence future design strategies in nanobiosensing. The study thus informs both applied and fundamental research directions.

High sensitivity observed in this study can be attributed to the sharp tips and branched morphology of silver nanostars. These features create intense localized electromagnetic fields that amplify Raman signals. Multiple hotspot regions increase the probability of effective analyte interaction. This structural advantage explains the observed enhancement.

Multiplexing success arises from the intrinsic molecular specificity of Raman scattering. Each biomarker exhibits distinct vibrational modes that remain resolvable under enhancement. Strong signal amplification prevents loss of spectral detail. These factors collectively explain effective discrimination of multiple targets.

Reproducibility is explained by controlled nanostar synthesis and surface functionalization. Narrow size distributions and stable surface chemistry reduce variability in enhancement. Prevention of uncontrolled aggregation maintains consistent hotspot geometry. These engineering choices explain low signal variation.

Serum compatibility results from optimized surface modification that minimizes nonspecific adsorption. Stable colloidal behavior prevents signal quenching and spectral distortion. Balanced interaction between biomolecules and plasmonic surfaces preserves analytical integrity. These mechanisms explain performance in complex biological matrices.

Future research should focus on validating the platform using clinical serum samples from diverse patient populations. Such studies will assess diagnostic sensitivity and specificity under real-world conditions. Longitudinal studies could evaluate biomarker dynamics over disease progression. These steps are critical for clinical translation.

Integration of the SERS platform into portable or automated diagnostic devices represents another important direction. Coupling with microfluidics and compact Raman

systems could enable point-of-care testing. User-friendly system design will enhance adoption. These developments will move the technology closer to deployment.

Expansion toward larger biomarker panels should be explored. Increasing multiplexing capacity will further enhance diagnostic value. Advanced multivariate analysis and machine learning may support complex spectral interpretation. These approaches can scale analytical capability.

Investigation of alternative plasmonic materials and hybrid nanostructures may further improve performance and biocompatibility. Exploration of long-term stability and standardization protocols will support regulatory approval. These future pathways define the next stage of development for SERS-based serum diagnostics.

CONCLUSION

This study establishes that silver nanostar–based SERS enables highly sensitive and reproducible multiplexed detection of disease biomarkers directly in serum. The most distinctive finding lies in the ability of nanostar substrates to generate strong and stable Raman enhancement that preserves clear and molecule-specific spectral signatures even in complex biological matrices. Simultaneous identification and quantification of multiple biomarkers at low nanomolar concentrations without labeling or signal amplification differentiates this approach from conventional diagnostic platforms.

The primary contribution of this research is methodological with important conceptual implications. Methodologically, the study introduces an integrated SERS framework that combines shape-engineered silver nanostars, optimized surface functionalization, and multivariate spectral analysis to achieve reliable multiplexed sensing in serum. Conceptually, it advances label-free diagnostic strategies by demonstrating that rational nanostructure design can overcome long-standing challenges of reproducibility and multiplexing in SERS-based biosensing. This contribution provides a transferable paradigm for developing advanced plasmonic diagnostic platforms.

Several limitations should be acknowledged, including the use of spiked serum samples rather than large-scale clinical specimens, which may not fully capture biological variability encountered in real diagnostic settings. Long-term stability, batch-to-batch reproducibility, and scalability of silver nanostar synthesis were not comprehensively evaluated. Future research should focus on validation with clinical cohorts, integration into automated or point-of-care systems, and expansion toward larger biomarker panels supported by advanced data analysis techniques.

AUTHOR CONTRIBUTIONS

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.
Author 2: Conceptualization; Data curation; In-vestigation.
Author 3: Data curation; Investigation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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