RESEARCH ARTICLE

Editorial Process: Submission:07/18/2025 Acceptance:02/24/2026 Published:03/05/2026

Disruption of EMT Signaling and Migration by Moringa oleifera Leaf Powder-Silver Nanoparticles (MOLP-AgNPs) in HeLa Cervical Cancer Cells

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Abstract

Objective: This study aimed to evaluate the potential anticancer effect of Moringa oleifera leaf powder–silver nanoparticles (MOLP-AgNPs) by assessing their impact on epithelial–mesenchymal transition (EMT) markers and cell migration in HeLa cervical cancer cells. **Methods:** HeLa cells were treated with MOLP-AgNPs at concentrations of 2, 4, and 6 µg/mL, alongside an untreated control group. Cell viability was assessed using the trypan blue exclusion method to determine non-toxic concentrations. A scratch (wound-healing) assay was used to evaluate cell migration, while immunofluorescence staining was performed to detect the expression of EMT-related proteins Snail and vimentin. **Result:** MOLP-AgNPs significantly inhibited cell migration in a dose-dependent manner ($p < 0.05$). Additionally, the expression of Snail and vimentin was markedly downregulated following treatment, indicating suppression of EMT-related pathways ($p < 0.001$). **Conclusion:** These exploratory preclinical findings suggest that MOLP-AgNPs exert anti-migratory effects on cervical cancer cells by modulating EMT. Although HeLa is a non-metastatic cell line, this study highlights the potential of MOLP-AgNPs as a promising candidate for further investigation in metastatic cancer models.

Keywords: Cervical cancer- HeLa- Moringa oleifera- Snail- Vimentin

Asian Pac J Cancer Prev, **27 (3)**, 981-988

Introduction

Cervical cancer is a malignant disease initiated by dysplastic changes in the cervical epithelium, wherein abnormal cells undergo unregulated proliferation and evade apoptosis. The majority of cervical cancer cases are histologically classified as squamous cell carcinoma, accounting for approximately 90% of all diagnoses [1]. Globally, cervical cancer remains one of the leading malignancies affecting women. According to the World Health Organization (WHO), it ranks as the fourth most common cancer in women, with an estimated 660,000 new cases and 350,000 deaths reported in 2022. Notably, about 94% of these deaths occurred in low- and middle-income countries, where access to HPV vaccination, routine screening, and healthcare services remains limited [2, 3].

Persistent infection with high-risk Human Papillomavirus (HPV), particularly genotypes 16, 18, 31, and 33, represents the principal etiological factor for cervical cancer. Transmission is frequently associated with high-risk sexual behaviors, including early sexual debut and multiple sexual partners. HPV is capable of infecting mucosal epithelial cells in the oral, anogenital, and esophageal regions, where it may induce precancerous lesions over time. Additional risk factors include high parity, immunosuppression, and poor access to health services [4, 5]. Oncogenes E6 and E7 play pivotal roles in HPV-mediated carcinogenesis by dysregulating cell cycle control. These proteins interfere with tumor suppressor functions and facilitate immune evasion through mechanisms such as suppression of TLR9 expression and disruption of NF-κB signaling, ultimately enabling viral persistence and malignant transformation [6].

During HPV persistence and progression to cervical

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cancer, inflammatory cytokines such as IL-6, IL-8, TNF-α, and MIP-3α contribute to immune modulation and chronic inflammation [7]. Among the molecular drivers of cervical cancer metastasis, the epithelial–mesenchymal transition (EMT) pathway has garnered significant attention. EMT enables epithelial cells to acquire mesenchymal characteristics, promoting motility and invasiveness. This process is governed by transcription factors, such as Snail, which suppress the expression of epithelial markers, including E-cadherin, occludin, and claudin, while promoting mesenchymal traits [8]. E-cadherin, a key adhesion molecule, plays a central role in maintaining epithelial phenotype, and its downregulation, frequently driven by Snail, is considered a hallmark of EMT and tumor progression [8, 9].

The regulation of Snail itself is influenced by several upstream signaling molecules, including HIF-1α, STAT3, MTA3, and Egr-1, which modulate its transcriptional activity [9]. The culmination of these molecular events leads to cellular detachment, disruption of polarity, and a transition into invasive, migratory mesenchymal cells. Another key mediator of EMT is vimentin, a type III intermediate filament protein predominantly expressed in mesenchymal cells. Vimentin supports cellular integrity under mechanical stress and is essential for cytoskeletal remodeling and metastasis. Its expression is regulated by phosphorylation, which alters filament dynamics and promotes cellular plasticity [10, 11]. Moreover, vimentin interacts with proteins such as Scribble and modulates the expression of EMT-related genes, including Axl, ITGB4, and PLAU, thereby enhancing metastatic capacity [12, 13].

While chemotherapy remains a mainstay treatment for early-stage cervical cancer, its use is often limited by systemic toxicity and poor tumor selectivity. Adverse effects such as anemia, nausea, fatigue, and immunosuppression significantly impair quality of life [14]. In light of these limitations, interest has grown in the development of adjunct therapies using natural compounds with bioactive properties. Phytomedicine, although not intended to replace conventional treatments, may serve as a complementary strategy to reduce side effects and enhance therapeutic efficacy [15].

One promising candidate is Moringa oleifera, commonly known as the Moringa tree. This plant, widely distributed and used in traditional medicine, exhibits various pharmacological effects, including anticancer activity [16]. Its bioactive constituents, such as isothiocyanates (derived from glucosinolates), flavonoids, alkaloids, terpenoids, saponins, and polyphenols, have been reported to exert cytotoxic, pro-apoptotic, and antimetastatic effects [17]. However, the mechanistic role of M. oleifera in modulating EMT-related transcription factors and mesenchymal markers, particularly Snail and vimentin, remains underexplored [18-20].

Therefore, this study seeks to investigate the effect of M. oleifera leaf powder-silver nanoparticles (MOLP-AgNPs) on the EMT pathway in cervical cancer. Specifically, we evaluated the expression of Snail and vimentin, as well as cell migration, in HeLa cells. Given the need for more targeted, biocompatible, and less toxic therapeutic strategies, this study aims to elucidate the potential of MOLP-AgNPs as a natural antimetastatic agent in cervical cancer, with the ultimate goal of contributing to the development of novel adjunct therapies in oncology.

Materials and Methods

Preparation of Moringa oleifera Leaf Extract and Green Synthesis MOLP-AgNPs

Moringa oleifera leaf powder (MOLP), sourced from Madura Island, East Java, Indonesia, was used for nanoparticle synthesis. Ten grams of MOLP were suspended in 100 mL deionized water and stirred at room temperature for 30 minutes. The mixture was then filtered using Whatman No. 1 filter paper, and the aqueous extract was collected.

To synthesize silver nanoparticles, 200 µL of the MOLP extract was added dropwise to 10 mL of 1 mM $AgNO_3$ solution in a 15 mL Falcon tube. A visible color change to brown indicated the formation of MOLP-AgNPs via green synthesis.

Culture of HeLa Cancer Cells

HeLa cervical cancer cells (ATCC, USA) were cultured in DMEM (Gibco, Thermo Fisher Scientific) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin [9]. Cells were incubated at 37°C in 5% CO_2 and passaged when they reached 80% confluence. For experiments, cells were harvested using 0.25% trypsin-EDTA and seeded into appropriate plates: 96-well plates for migration and immunofluorescence assays. The overall experimental workflow and treatment design are illustrated in Figure 1.

Trypan Blue Exclusion Test for Dose Selection

Viability testing was conducted using the Trypan Blue exclusion method. Cells were mixed with 0.4% Trypan Blue (1:1 ratio), and viable versus non-viable cells were counted using a hemocytometer [21].

Initial testing used MOLP-AgNPs concentrations of 250, 500, and 1000 µg/mL. Based on viability data and nanoparticle characterization, final treatment doses were standardized to 1000, 2000, and 3000 µg/mL of nanoparticle solution, equivalent to 2, 4, and 6 µg/mL of pure MOLP extract (considering the extract was ~0.2% of nanoparticle mass). These doses were used in all assays.

Experimental Design

An in vitro exploratory design was implemented with four groups: one untreated control and three MOLP-AgNP-treated groups (2, 4, and 6 µg/mL). HeLa cells were treated for 24 hours once they reached 70–80% confluency to ensure consistent biological conditions.

Wound-Healing Assay

To assess antimigratory activity, a scratch assay was conducted. HeLa cells were grown in 96-well plates to ~90% confluence. A straight scratch was made with a sterile P10 pipette tip. After PBS washing, wells were replenished with MOLP-AgNP-containing media or

control media [22].

Scratch closure was photographed at 0 and 24 hours using an inverted microscope (Olympus CKX53, Japan). Wound areas were quantified using ImageJ, and percent wound closure was calculated.

Immunofluorescence Staining

For EMT marker analysis, immunofluorescence staining was performed. HeLa cells were seeded on sterile glass coverslips in 96-well plates and treated with MOLP-AgNPs for 24 hours. After fixation with 4% paraformaldehyde and permeabilization with 0.1% Triton X-100, blocking was done with 1% BSA [23].

Cells were incubated overnight at 4°C with primary antibodies targeting: Snail (Cell Signaling Technology) and Vimentin (D21H3 XP® Rabbit mAb, Cell Signaling Technology, Cat# 57415).

Subsequently, Alexa Fluor® 488-conjugated secondary antibodies were added for 1 hour at room temperature in the dark. Nuclei were counterstained with DAPI. Fluorescent signals were visualized under a fluorescence microscope. Semi-quantitative analysis was conducted using Corrected Total Cell Fluorescence (CTCF) in ImageJ.

Statistical Analysis

All data were derived from three independent experiments (n = 3 per group). Results are expressed as mean ± standard deviation (SD). Group comparisons were analyzed using one-way ANOVA with Tukey's post hoc test. Data normality and homogeneity were verified using Shapiro–Wilk and Levene's tests, respectively.

Statistical analyses were performed using GraphPad Prism v8.4 and SPSS v27. A p-value of <0.05 was considered statistically significant. Exact p-values are reported in figure legends. Given the exploratory nature of this preclinical in vitro study, power analysis was not applied, and standard triplicates were used for all assays.

Results

Effect of MOLP-AgNPs on HeLa Cell Migration

To explore the potential of MOLP-AgNPs in suppressing cervical cancer metastasis, a scratch wound healing assay was conducted as an exploratory preclinical approach to assess cell migration. HeLa cells were treated with MOLP-AgNPs at 2, 4, and 6 µg/mL for 24 hours. A negative control (untreated group) was included for comparison.

At 0 hours, all groups displayed uniform wound widths (Figure 2A), confirming the reliability of baseline conditions. After 24 hours, the untreated group showed substantial wound closure, while the treated groups demonstrated markedly delayed closure (Figure 2B).

Quantitative analysis (Figure 2C) using ImageJ and GraphPad Prism revealed a significant reduction in cell migration across all treatment groups compared to the control ($p < 0.05$, one-way ANOVA with Tukey's post hoc test). The most pronounced effect was seen at 2 µg/mL, with a 1.32-fold decrease in migration, followed by 1.20-fold and 1.22-fold reductions at 4 and 6 µg/mL, respectively. These findings indicate that MOLP-AgNPs inhibit cell motility in a dose-dependent manner, with a peak effect at the lowest tested dose.

These data suggest that MOLP-AgNPs may interfere with the EMT process, a critical mechanism in metastasis, and underscore their potential as antimetastatic agents in cervical cancer.

Effect of MOLP-AgNPs on Snail Protein Expression

To investigate the mechanism underlying the antimigratory effect, Snail expression, a master EMT transcription factor, was evaluated via indirect immunofluorescence. Snail represses epithelial markers and enhances mesenchymal traits, contributing to cancer

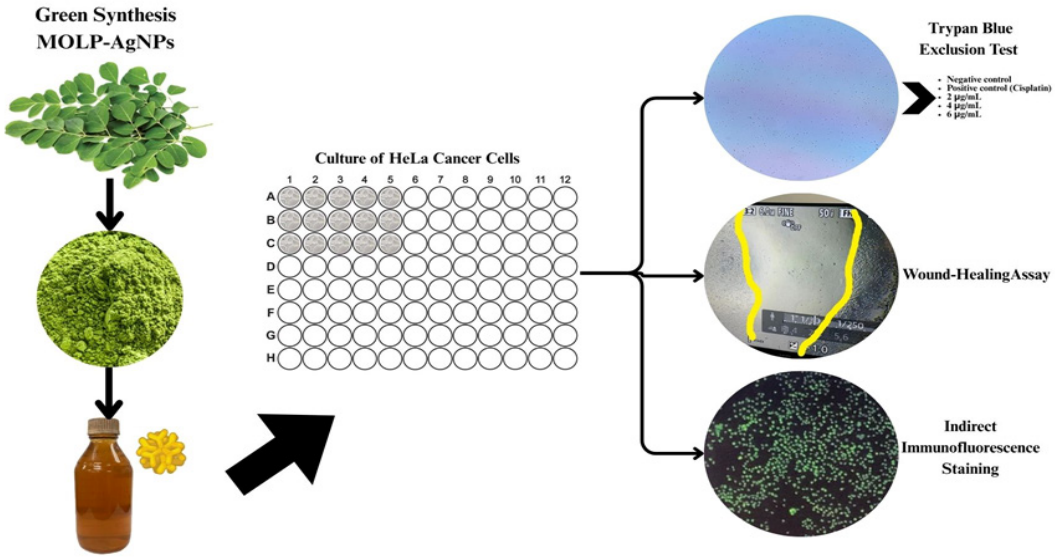

Figure 1. Schematic Representation of the Experimental Workflow. The biological effects of MOLP-AgNPs were evaluated through three main assays: (1) Trypan Blue Exclusion Test to determine cell viability and select appropriate treatment doses; (2) Wound-Healing Assay to assess the antimigratory effect of MOLP-AgNPs on HeLa cells; and (3) Indirect Immunofluorescence Staining to examine the expression of EMT-related markers, Snail and vimentin.

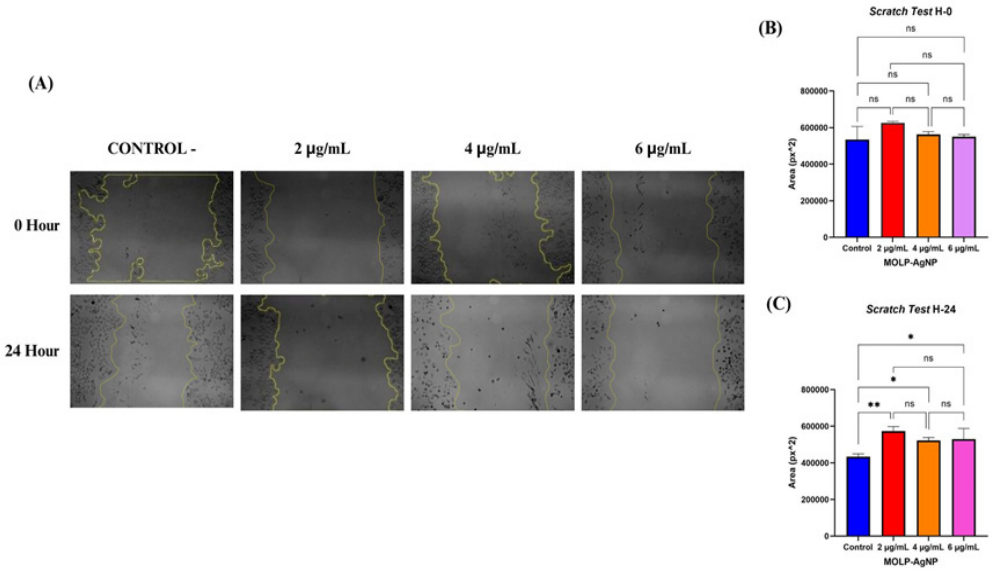

Figure 2. MOLP-AgNPs Suppress HeLa Cell Migration in a Scratch Test. (A) Representative images of HeLa cell migration at 0 and 24 hours post-treatment with MOLP-AgNPs (2, 4, 6 µg/mL) and untreated control. Yellow lines indicate wound margins. (B) Quantification of initial scratch areas (µm²) at 0 hour across all groups, confirming baseline uniformity (One-Way ANOVA; ns = not significant). (C) Quantification of wound closure at 24 h post-treatment. MOLP-AgNPs significantly inhibited HeLa cell migration in a dose-dependent manner (One-Way ANOVA with Tukey's test; *p ≤ 0.01, **p ≤ 0.001, ns = not significant).

progression [9].

Figure 3A shows a decrease in Snail fluorescence intensity in all treated groups compared to the control. While a concentration-dependent decline was visible, most notably at 6 µg/mL, the trend appeared to plateau above 2 µg/mL.

To control for potential differences in cell number, DAPI staining was used to confirm nuclear counts. The relatively uniform DAPI fluorescence across all groups supports the conclusion that the observed reduction in Snail signal resulted from actual biological effects.

Quantitative analysis using Corrected Total Cell Fluorescence (CTCF) in ImageJ revealed a consistent decrease in Snail intensity in treated groups (Figure 3B), though statistical significance was not reached (ns, $p > 0.05$). Despite this, the downward trend in Snail expression across increasing concentrations of MOLP-AgNPs suggests their potential to modulate EMT-related transcription factors.

These exploratory findings highlight the preclinical

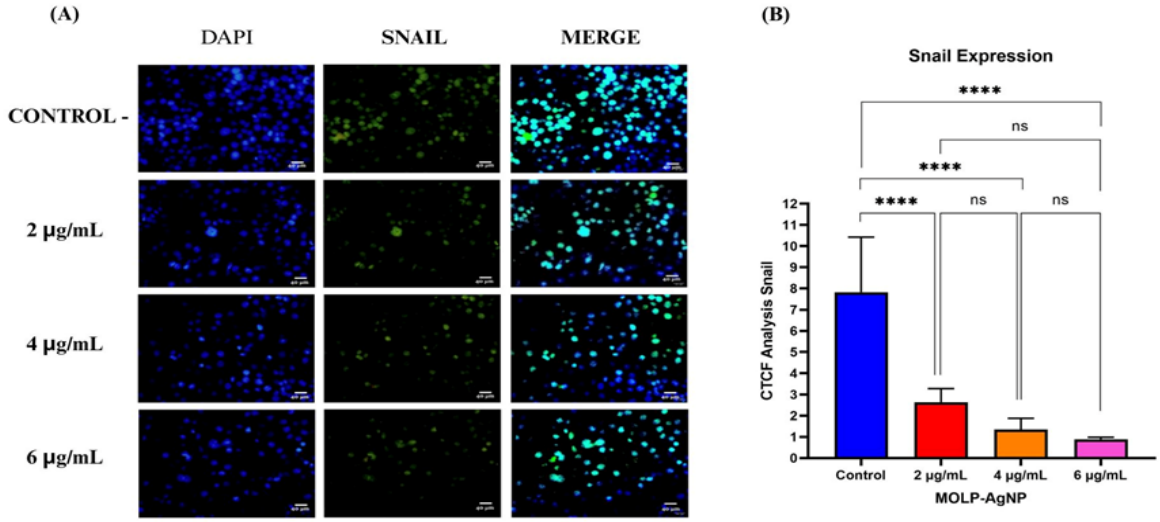

Figure 3. Snail Protein Suppression in HeLa Cells after MOLP-AgNPs Treatment. (A) Immunofluorescence images showing decreased Snail expression (green) in HeLa cells treated with MOLP-AgNPs (2, 4, and 6 µg/mL) compared to control. DAPI (blue) indicates nuclear staining. (B) Quantitative analysis of Snail expression based on Corrected Total Cell Fluorescence (CTCF) shows a significant dose-dependent reduction. Data represent mean ± SD; ****p ≤ 0.0001; ns = not significant (One-Way ANOVA, Tukey's HSD).

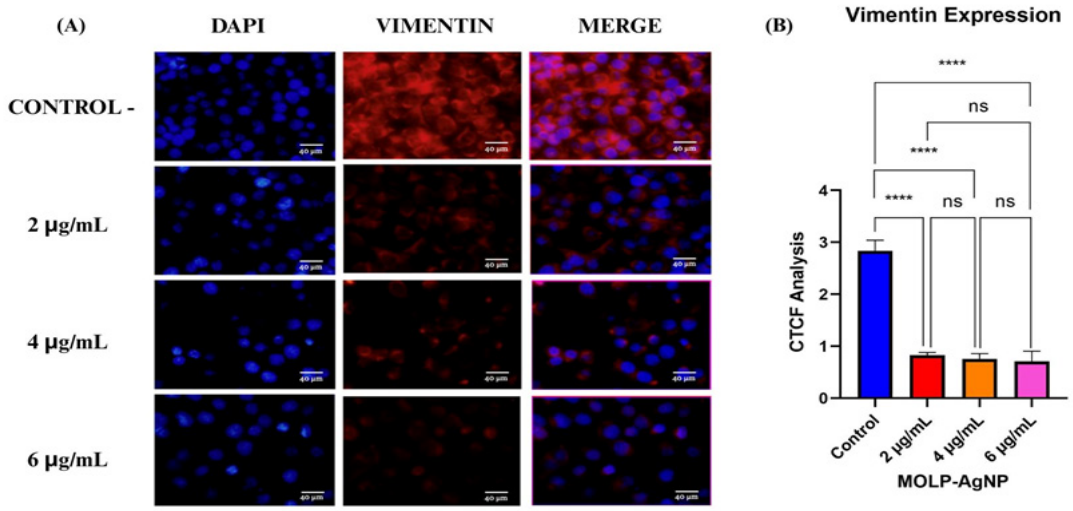

Figure 4. Vimentin Protein Suppression in HeLa Cells Following MOLP-AgNPs Treatment. (A) Immunofluorescence images showing reduced vimentin expression (red) in HeLa cells treated with MOLP-AgNPs at 2, 4, and 6 µg/mL compared to control. DAPI (blue) marks nuclear staining. (B) Quantitative CTCF analysis of vimentin expression reveals a significant dose-dependent decrease. Data shown as mean ± SD; ****$p \leq 0.0001$; ns = not significant (One-Way ANOVA, Tukey's HSD).

potential of MOLP-AgNPs to suppress EMT initiation through Snail downregulation, warranting further mechanistic validation.

Effect of MOLP-AgNPs on Vimentin Protein Expression

Vimentin, a structural protein involved in maintaining the mesenchymal phenotype, serves as another key EMT marker. Elevated vimentin expression is associated with cellular plasticity and metastatic capacity [12].

Indirect immunofluorescence (Figure 4A) demonstrated a dose-dependent reduction in vimentin signal following MOLP-AgNP treatment, with the most notable suppression at 6 µg/mL. As with Snail, DAPI staining confirmed comparable nuclear counts across

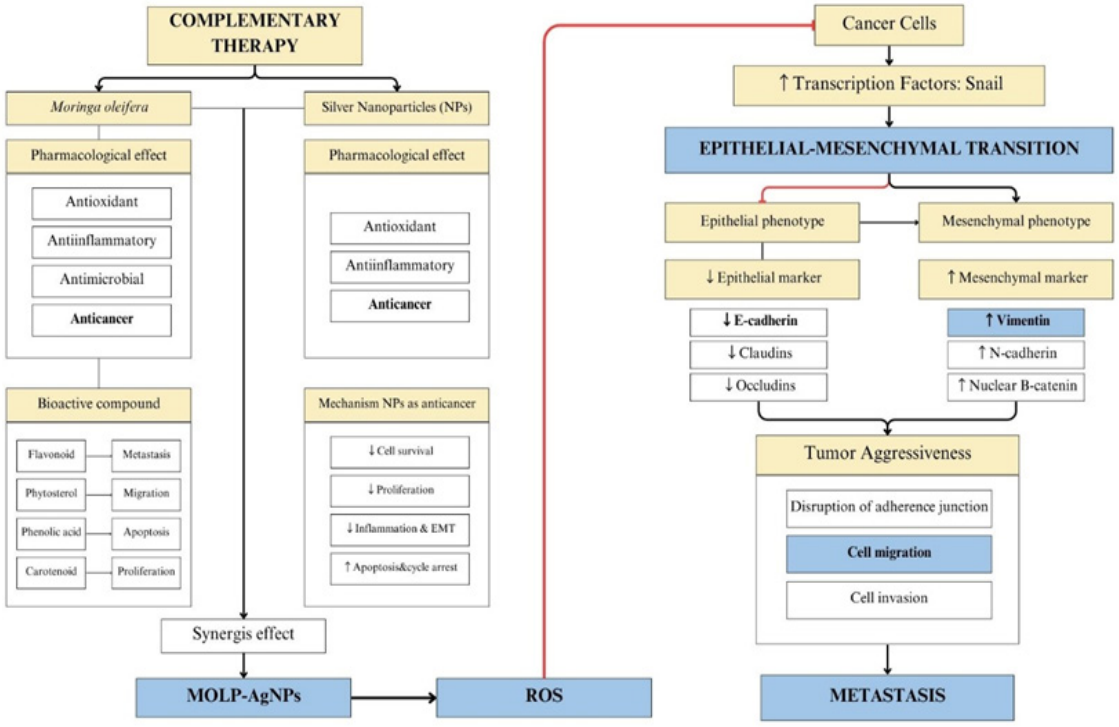

Figure 5. Proposed Mechanism of MOLP-AgNPs in Suppressing EMT. This figure illustrates the synergistic anti-cancer mechanism of Moringa oleifera bioactives and silver nanoparticles in MOLP-AgNPs, which together inhibit cancer cell migration and EMT.

groups.

CTCF-based quantification (Figure 4B) showed decreasing fluorescence intensity with increasing doses of MOLP-AgNPs, although the trend did not reach statistical significance (ns, $p > 0.05$). Nevertheless, the consistent reduction suggests that vimentin downregulation may be part of the molecular mechanism through which MOLP-AgNPs suppress EMT in HeLa cells.

These findings align with previous reports where Moringa-derived compounds and AgNPs were shown to inhibit EMT-related pathways in gastric and colorectal cancers [24, 25], and support the exploratory preclinical hypothesis that MOLP-AgNPs may interfere with mesenchymal transformation.

Discussion

EMT is a key biological process that drives cancer metastasis by enabling epithelial cells to acquire mesenchymal characteristics, enhancing motility, invasiveness, and resistance to apoptosis [8, 13]. EMT is orchestrated by transcription factors, such as Snail, which downregulates epithelial markers, like E-cadherin, and upregulates mesenchymal markers, like vimentin [9]. In this study, MOLP-AgNPs significantly downregulated Snail and vimentin expression in HeLa cervical cancer cells, indicating that these nanoparticles inhibit EMT-related pathways and may reduce metastatic potential.

The scratch assay confirmed that MOLP-AgNPs suppressed HeLa cell migration in a dose-dependent manner, with the most significant effect observed at 2 µg/mL ($p < 0.0332$). Interestingly, the inhibitory effect on migration at 2 µg/mL was more pronounced than at higher concentrations. This dose-dependent pattern may reflect an optimal bioactive window in which the phytochemical components of M. oleifera maintain maximal interaction with cellular signaling targets. At higher doses, mild cytotoxic stress or nanoparticle aggregation may reduce effective cellular uptake and thus attenuate the observed biological activity.

Cell migration is a hallmark of metastasis, and its inhibition is essential in cancer therapy. Our findings are consistent with prior studies demonstrating that M. oleifera and its nanoformulations reduce migration in gastric (AGS) and colorectal (HT-29) cancer cell lines by modulating EMT markers [24, 25]. Comparable findings have been reported with other plant-based nanomaterials such as Caulerpa racemosa extract nanoparticles and silver nanoparticles synthesized from Nostoc or Curcuma longa, which also demonstrated inhibition of EMT and migration in HeLa cells. These parallels suggest that biogenic nanoparticles derived from antioxidant-rich plant sources may share common molecular mechanisms in suppressing metastasis-related pathways. The potent antimigratory effect of MOLP-AgNPs may be attributed to the synergy between Moringa phytochemicals and the physicochemical properties of silver nanoparticles, which enhance cellular uptake and increase reactivity [26, 27].

Indirect immunofluorescence showed reduced expression of Snail and vimentin across all MOLP-AgNP concentrations tested (2–6 µg/mL), although no statistically significant differences were found between doses. CTCF quantification confirmed the downward trend, and DAPI staining verified consistent cell numbers across groups, validating that the decrease in EMT markers resulted from treatment effects rather than variations in cell density. The suppression of Snail, a master regulator of EMT [9], and vimentin, a cytoskeletal protein involved in metastasis [10, 12], highlights the potential of MOLP-AgNPs to disrupt EMT-driven cancer progression.

The dual anticancer action of MOLP-AgNPs arises from the combination of Moringa bioactive compounds and the unique properties of AgNPs, as illustrated in Figure 5 M. oleifera contains phytochemicals such as isothiocyanates, flavonoids (quercetin, kaempferol), alkaloids, and phenolic acids (gallic acid, p-coumaric acid), which are known to induce apoptosis, inhibit proliferation, and modulate signaling pathways related to cancer development [17, 28, 29]. Isothiocyanates and glucosinolates regulate pro-apoptotic genes [29, 30], while flavonoids suppress PI3K/Akt and MAPK pathways and downregulate Snail and vimentin [31, 32]. These phytochemicals may act in concert to impair EMT and migration.

Silver nanoparticles complement these effects by inducing oxidative stress, disrupting mitochondrial function, and modulating gene expression. AgNPs increase intracellular ROS levels, leading to oxidative damage and triggering apoptosis through mitochondrial pathways, including the release of cytochrome c and caspase activation [33-35]. Additionally, AgNPs influence epigenetic regulation, such as the downregulation of SOX4 through modulation of miR-338-3p and long non-coding RNAs [36]. These multifaceted actions enhance the cytotoxicity and therapeutic efficacy of MOLP-AgNPs in vitro.

AgNPs may also induce autophagy, which, when excessively activated, leads to autophagic cell death [37]. Their preferential activity against cancer stem-like cells further adds therapeutic value by potentially preventing tumor recurrence and treatment resistance [35]. The integration of these complementary mechanisms supports the significant anticancer and antimetastatic effects observed in this study.

This study highlights the potential of MOLP-AgNPs as an antimetastatic agent that targets EMT regulators in cervical cancer. The concurrent downregulation of Snail and vimentin, along with the inhibition of cell migration, suggests that MOLP-AgNPs can attenuate cancer invasiveness and progression [28]. These results contribute to the growing body of evidence supporting the use of phytochemical-based nanoparticles as adjunct or alternative therapeutic agents, particularly in light of the toxicity and limitations of conventional therapies [14].

Nonetheless, limitation must be acknowledged. This study utilized only one cancer cell line (HeLa) without comparing its effects in non-cancerous or metastatic cell lines, thereby limiting the generalizability of the findings. These design limitations should be addressed in future studies.

Importantly, these findings represent exploratory in

vitro data that lay the groundwork for future preclinical studies involving larger sample sizes, alternative cervical cancer models, and in vivo validation. Further research is warranted to optimize dosage, treatment duration, and clarify the contributions of Moringa phytochemicals versus the nanoparticle component.

In conclusion, this study demonstrates that MOLP-AgNPs effectively suppress HeLa cell migration by modulating the EMT pathway. MOLP-AgNPs significantly downregulated Snail and vimentin expression in a dose-dependent manner, suggesting potential antimetastatic activity. These findings support the role of MOLP-AgNPs as a natural agent targeting EMT-related mechanisms in cervical cancer.

Author Contribution Statement

Raisha Anis Fatiha: Project administration, Investigation, Methodology, Writing – original draft. Christian Kencana Ngabdi: Data curation, Methodology, Writing - review & editing. Jihan Salwa Azizah: Data curation, Methodology, Writing - review & editing. Bintang Sukma Natalsah Putri: Project administration, Investigation, Methodology, Writing – original draft. Bayu Lestari: Formal analysis, Validation, Supervision, Writing – review & editing. Nik Ahmad Nizam Nik: Validation, Resources. Hendra Susanto: Resources. Wibi Riawan: Formal analysis, Validation, Supervision, Writing – review & editing. Happy Kurnia Permatasari: Formal analysis, Supervision, Funding acquisition, Writing – review & editing, Writing – original draft.

Acknowledgements

General

The authors gratefully acknowledge all individuals and institutions whose invaluable support contributed to the successful completion of this study. Special appreciation is extended to those who provided technical assistance during the experimental procedures and to colleagues who offered critical input in the writing and refinement of this manuscript.

Funding Statement

This research was funded by the Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia, through the Community Research and Development Board (Badan Penelitian dan Pengembangan Masyarakat – BPPM) [Grant No. 3237/5/UN10.F08/PN/2024].

Scientific/Thesis Approval

This study was conducted as part of an approved undergraduate research project at the Faculty of Medicine, Universitas Brawijaya, Indonesia.

Ethical Declaration: The study was approved by the Ethics Committee of Faculty of Medicine, Universitas Brawijaya (Approval No.87/EC/KEPK/04/2024).

Conflict of Interest

The authors report no conflict of interest.

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