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Research Article

In vitro analysis of silkworm sericin induced modifications in migration related genes in colorectal cancer cells

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Abstract
Background: Colorectal cancer is a leading cause of cancer-related deaths worldwide. The search for natural compounds with anticancer activity has gained increasing interest. Sericin, a silk-derived protein, has demonstrated various biological properties, including potential anticancer effects. This study aimed to evaluate anticancer effects of sericin and influence on the expression of genes associated with cancer progression in colorectal cancer cells.
Methods: Colorectal cancer cells (SW620, SW480, HCT116) were treated with different concentrations of sericin. Effects on cell viability were monitored and confirmed by MTT assay. The expression levels of focal adhesion kinase (FAK) and Ras-related C3 botulinum toxin substrate (RAC1) genes were analyzed using real-time quantitative polymerase chain reaction. Online data tool (STRING software) was used to assess the protein-protein interactions, biological processes and molecular functions associated with the two genes.
Results: Sericin treatment resulted in reduced cellular viability and downregulation of FAK and RAC1 gene expression compared to untreated control cells. The inhibition of these genes indicates suppression of signaling pathways involved in migration and invasion of the colorectal cancer cells. Bioinformatics showed important protein interactors of the genes with the involvement of key biological and molecular functions including growth signaling pathways, secondary messenger networks and kinase activities.
Conclusion: The findings suggest that sericin exhibits anticancer activity against colorectal cancer and deregulate the expression of FAK and RAC1 genes. Further *in vitro* studies are required to investigate the fine cellular tunings to confirm the efficacy.
Key Words: Colorectal cancer, Metastasis, Genes, Migration

INTRODUCTION

Sericin is a water-soluble globular protein derived from the silkworm (*Bombyx mori*) cocoon, accounting for approximately 20-30% of total silk protein [1]. Its amino acid composition, dominated by serine, glycine, and other polar residues, confers high hydrophilicity and strong free-radical scavenging ability, which are relevant to its biological activity [2]. In past regarded as an industrial by-product, sericin has gained scientific interest recently due to biocompatibility, biodegradability, antioxidant capacity and emerging anticancer properties [3]. Preclinical studies are consistently reporting its antiproliferative effects against cancer cell lines, including colon, breast, and liver cancer [4].

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In vitro experiments demonstrate that sericin suppresses tumor cell growth by inducing cell-cycle arrest and promoting apoptosis, primarily through the intrinsic mitochondrial pathway. This process is characterized by mitochondrial membrane depolarization accompanied by upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins. Importantly, sericin shows relatively low cytotoxicity toward normal cells, suggesting a degree of selectivity for malignant cells [5, 6].

Beyond direct cytotoxic effects, sericin exhibits significant antioxidant activities. It reduces oxidative stress by scavenging reactive oxygen species and enhancing endogenous antioxidant defenses, thereby limiting oxidative DNA damage responsible for carcinogenesis [7]. *In vivo* studies using chemically induced carcinogenesis models, particularly in the colon, reveal that dietary sericin reduces tumor incidence and suppresses the formation of aberrant crypt foci [8, 9]. Recent advances have further

expanded the relevance of sericin in cancer research through its application as a biomaterial for drug delivery. Sericin-based nanoparticles and matrices have been shown to improve drug solubility, enable controlled release, and reduce systemic toxicity of conventional chemotherapeutic agents, highlighting its potential as an adjunct in cancer therapy [10-12]. Overall, existing literature indicates that sericin possesses significant anticancer and chemo preventive potential, warranting further standardized and translational research.

As far as cellular environment is concerned, sericin has attracted increasing attention for its potential anticancer properties, particularly through modulation of gene expression in tumor cells. *In vitro* studies indicate that sericin promotes apoptosis by regulating pro-apoptotic genes such as BAX, P53, and Caspase-3, while downregulating anti-apoptotic mediators including *BCL-2*, thereby increasing the BAX/BCL-2 ratio and activating the mitochondrial apoptotic pathway [13, 14]. Additionally, sericin has been reported to induce cell cycle arrest through enhanced expression of cyclin-dependent kinase inhibitors (P21, P27) and suppression of cyclins (Cyclin D1, Cyclin E) and CDKs [15]. Beyond effects on proliferation and survival, sericin modulates oxidative stress-responsive genes and inhibits metastasis-associated factors. These gene-level alterations are often associated with suppression of key oncogenic signaling pathways [16-18]. Although current evidence is largely limited to cell culture models, these findings suggest that sericin may exert multifaceted anticancer effects through coordinated regulation of genes involved in apoptosis, cell cycle progression, redox balance and tumor invasion.

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that plays a pivotal role in cancer progression by integrating signals from integrins and growth factor receptors to regulate cell adhesion, migration, proliferation and survival. FAK is frequently overexpressed and hyperactivated in multiple malignancies including breast, colorectal and ovarian cancer, where elevated FAK activity correlates with poor prognosis and increased metastatic potential [19]. Emerging evidence further implicates FAK in shaping tumor microenvironment by promoting angiogenesis and immunosuppressive signaling [20]. Collectively, aberrant activation of FAK signaling contributes to oncogenic transformation, tumor progression, metastasis and therapeutic resistance, positioning FAK as a promising target for anticancer drug development.

RAC1 family of Rho GTPases, comprising RAC1, RAC2, and RAC3 plays a central role in tumorigenesis through regulation of cytoskeletal dynamics, cell proliferation, survival signaling and reactive oxygen species production [21]. Among these, RAC1 is the most extensively characterized in solid tumors, where gain-of-function alterations result in constitutive activation of downstream effectors, including PAK kinases, the PI3K/AKT pathway, and NF-κB signaling [22]. Overexpression or hyperactivation of RAC1 has also been implicated in progression of cancers [23]. Dysregulation of RAC1 signaling enhances oncogenic transformation, tumor progression and therapeutic resistance, highlighting the RAC1 GTPases as critical modulators of cancer pathobiology and potential targets for therapeutic intervention [24].

Current study was mainly designed to investigate effects of sericin exposure on expression of FAK and RAC genes in colorectal cancer cells. The outcomes will compel the attention of scientific community to regulate metastatic related genetic factors by using sericin in cancer cells.

METHODS

Growth Curve Analysis

Colorectal cancer cells (SW480, SW620, HCT116) were cultured under standard conditions in growth medium RPMI-1640 supplemented with 10% fetal bovine serum and antibiotics (streptomycin and penicillin). Cultures were maintained at 37 °C in a humidified incubator with 5% CO_2. Cells were passaged at 50-70% confluency prior to growth curve experiments. For growth curve analysis, cells were seeded at an initial density of 1000-6000 per 100 µl in each well of a 96-well plate. Cells were allowed to adhere for overnight periods and growth pattern was monitored for 1-3 days. Measurements were taken for proliferation index by using MTT assay as described earlier [13]. Growth curves were generated by plotting absorbance in comparison to time. Data were fitted to growth model using GraphPad Prism software v8.

Cytotoxicity of Sericin Assay

Antiproliferative effect of sericin was evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, which assesses cell metabolic activity as an indirect measure of cell viability and proliferation as reported earlier [13]. Human colorectal cancer cells were cultured under standard conditions into 96-well plates at a predetermined density (4000 per 100 µl in each well) and allowed to adhere overnight. Sericin, extracted (from local cocoons) and purified (commercially available) as described previously [13], was dissolved in sterile culture medium and applied to the cells at two concentrations (0.5 and 1.0 mg/ml) to assess dose-dependent effects. Control wells received culture medium without sericin. Following treatment for a defined incubation period (24-72 h), MTT solution was added to each well and the plates were incubated to allow metabolically active cells to reduce MTT into insoluble formazan crystals. After incubation for 3 h,

the culture medium was carefully removed, and the formazan crystals were solubilized using dimethyl sulfoxide (DMSO). The absorbance was measured at 570 nm using a microplate reader. Cell viability was expressed as percentage relative to untreated control cells. Inhibitory effect of sericin on cell proliferation was quantified by comparing absorbance values across treatment groups and dose-response relationships were determined. All experiments were performed in triplicate and results were reported as mean ± standard deviation. This assay provided quantitative evidence of cytotoxic and antiproliferative effects of sericin on colorectal cancer cells by reflecting changes in mitochondrial metabolic activity following treatment.

Real Time PCR Assessment

The effects of sericin on the expression of migration related genes (FAK and RAC) were evaluated using quantitative real-time polymerase chain reaction. Human colorectal cancer cells were cultured under standard conditions and treated with sericin at selected concentrations (0.5 and 1.0 mg/ml). Untreated cells served as controls. After the treatment period (48 h), total RNA was extracted from cells using a commercial RNA isolation reagent according to the manufacturer's instructions (Thermo Fisher Scientific, Cat#K0731) and RNA concentration was assessed spectrophotometrically. Complementary DNA (cDNA) was synthesized from equal amounts of total RNA using a reverse transcription kit (Thermo Fisher Scientific, Cat#K1622). Quantitative real-time PCR was performed using gene-specific primers (Table 1) and a SYBR Green master mix on a real-time PCR system. Relative gene expression levels were calculated using the comparative Ct ($2^{-\Delta\Delta Ct}$) method. All reactions were conducted in triplicate and results were expressed as average of standard deviation. This assay enabled quantitative assessment of sericin-mediated modulation of gene expression in terms of fold changes, providing insight into potential antimigratory effects in colorectal cancer cells.

Bioinformatics

To investigate molecular interactions and functional relationships among the genes, a bioinformatics-based gene interaction analysis was performed. Protein-protein interaction analysis was performed using the STRING database (STRING v11.x; https://string-db.org). Analysis was restricted to *Homo sapiens,* and interactions were retrieved based on both direct (physical) and indirect (functional) associations. The minimum required interaction confidence score was set to 0.4 (medium confidence). Evidence based channels included experimental data, curated databases, co-expression and text mining as specified for the analysis. The resulting interaction network was visualized using the STRING network view, where nodes represent proteins encoded by the input genes and edges represent predicted or known functional associations.

Statistical Analysis

All experiments evaluating the effects of sericin via MTT assay and real-time PCR were performed in triplicate. Data are presented as mean ± standard deviation. For MTT assay, cell viability was expressed as a percentage relative to untreated control cells, while for real-time PCR, relative gene expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method after normalization to the housekeeping gene (HPRT1). Comparisons involved only two groups and student's *t*-test was applied. A *p*-value of less than 0.05 was considered statistically significant and reflected as asterisk.

RESULTS

Growth Patterns of Cells

Selected cell lines were cultured in 96-well culture plates (1000-6000 cells/well/100 µl medium) followed by incubation for three different time points (24, 48 and 72 h) at standard cell culture incubation conditions and then incubated with MTT solution. Afterwards, crystals formed by the viable cells were dissolved in DMSO and optical densities were measured by an ELISA plate reader. Growth curves were generated with time intervals on X-axis and number of cells on Y-axis as shown in Figure 1. The data identified 3000-4000 cells as optimal number of cells to be used in subsequent experiments in 96 well plates as this number showed exponential growth during the selected time intervals particularly the middle period (48 h).

Toxicity of Sericin

The antiproliferative effect of sericin on colorectal cancer cells was evaluated using the MTT assay. Treatment with sericin resulted in a significant reduction in cell viability compared with untreated control cells. This inhibitory effect was observed in a dose-dependent manner as increasing concentrations of sericin led to progressively lower metabolic activity (Figure 2). At lower concentrations, sericin induced a modest decrease in cell viability, whereas higher concentrations caused a pronounced reduction, indicating strong growth-inhibitory effects. Decrease in MTT absorbance suggests that sericin impaired mitochondrial metabolic activity, reflecting reduced cell proliferation and increased cell death. In contrast, control cells maintained high viability throughout the experimental period. Analysis demonstrated sericin-treated group exhibited significantly lower percentage of viability compared with controls ($p < 0.05$). These findings indicate that sericin effectively suppresses the growth of colorectal cancer cells *in vitro*. Overall,

MTT assay results provided clear evidence of the cytotoxic and antiproliferative effects of sericin, supporting its potential role as an anticancer agent against colorectal cancer.

Table 1: Primer sequence for amplification of selected genes

Gene	Forward	Reverse
RAC1	TGGCTAAGGAGATTGGTGCT	TCTCTTCCTCTTCTTCACGGG
FAK	TGTCAGGGGCATCATTCAGA	AGCAAGCTCATACTTCTCCCT
HPRT1	GACCAGTCAACAGGGGACAT	CTTGCGACCTTGACCATCTT

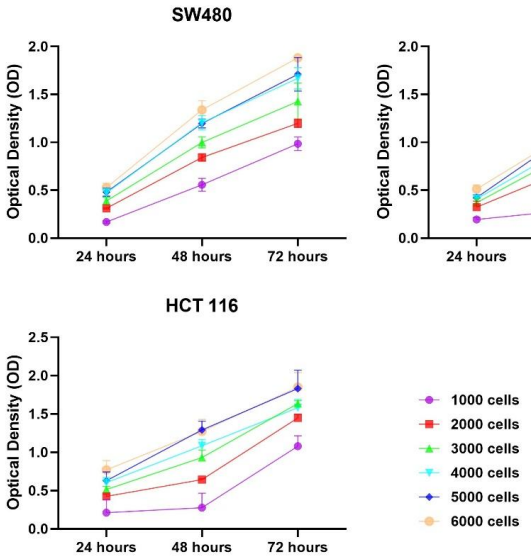


Figure 1: Growth curve generation for three different time points. Cells were incubated for three-time intervals with various cell numbers and viability were assessed by using MTT dye reduction assay.

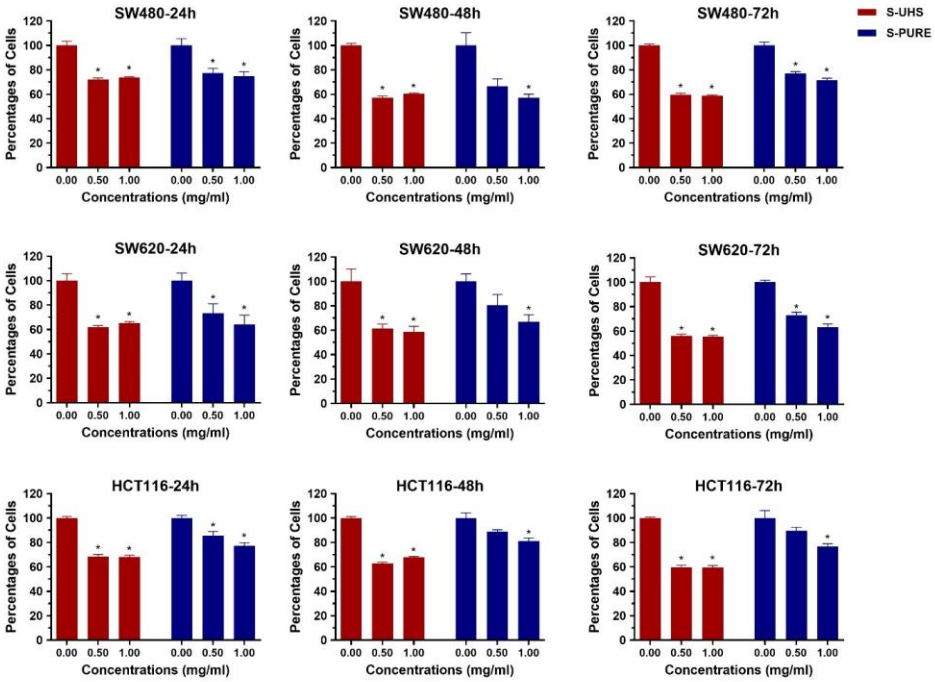


Figure 2: Cytotoxicity of sericin against colorectal cancer cells. The cells were incubated for three-time intervals and exposed to sericin (S-UHS: Local extracts, S-PURE: Commercially available) followed by viability assessment by using MTT dye reduction assay.

Expression Modulation by Sericin

Effect of sericin on the expression of genes associated with cell adhesion and migration was evaluated by quantitative real-time PCR, with a specific focus on FAK (PTK2) and RAC1 (AKT1). Gene expression levels in sericin-treated colorectal cancer cells were normalized to the housekeeping gene and compared with untreated control cells. The analysis revealed that sericin treatment resulted in a significant downregulation of FAK mRNA expression compared with control group. This reduction was concentration dependent as with higher sericin dose producing more pronounced decrease in FAK expression. However, the cell lines with different origins (primary) and molecular features responded differentially in this context. Given the established role of FAK in promoting proliferation and metastasis, its suppression suggests that sericin interferes with focal adhesion-mediated signaling pathways in colorectal cancer cells (Figure 3A).

Similarly, expression of RAC1 gene was inhibited following sericin treatment relative to untreated cells. The downregulation of RAC1 indicates inhibition of signaling pathways involved in the cytoskeletal reorganization and the cell motility (Figure 3B). Specifically, RAC1 gene was downregulated in primary colorectal cancer cells (SW480 and HCT116), while it was induced in metastatic cells (SW620). This variable response could be due to different molecular features of the cancer cell lines originating from different original sites. The coordinated suppression of FAK and RAC1 suggests that sericin may impair cancer cell migration and invasive potential in addition to its antiproliferative effects (Figure 3).

Overall, the real-time PCR results demonstrated that sericin modulates the genes involved in adhesion and migration signaling. These molecular changes provide mechanistic support for the observed inhibitory effects of sericin on colorectal cancer cell growth and highlight its potential role in suppressing tumor progression.

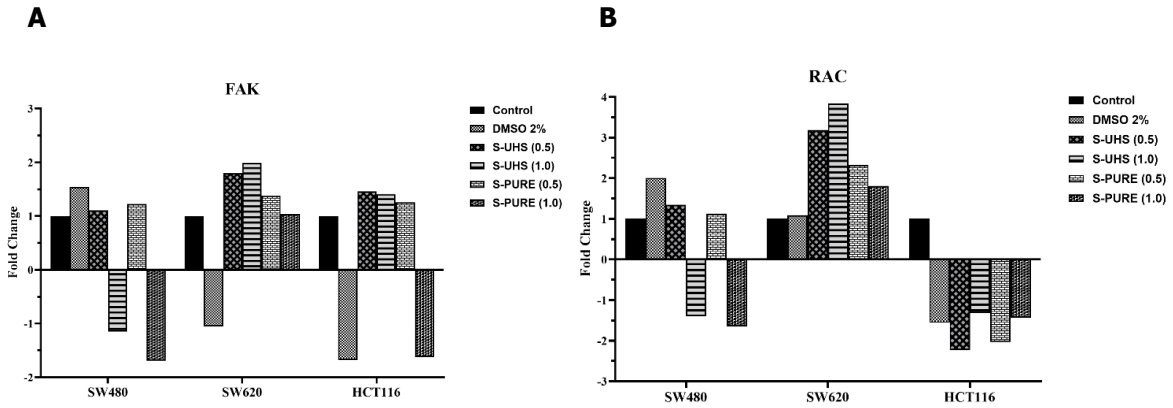
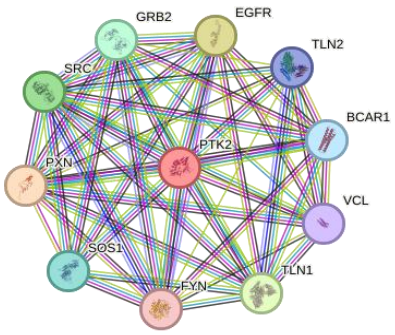


Figure 3: Expression analysis of genes. The cells were exposed to sericin followed by expression analysis of the genes by using real time PCR method. Data was reflected as fold changes in comparison to untreated controls.

Molecular Interactions of Genes

Bioinformatics-based signaling network analysis was performed to elucidate the molecular interactions and functional aspects associated with FAK (PTK2) and RAC1 (AKT1). Interacting networks of the two genes are shown in Figure 4 and 5 respectively. For FAK gene, the total number of nodes, edges along with average node degree was 11, 51 and 9.27 respectively. With a medium level of confidence (0.4), 10 interacting proteins with FAK on evidence based are shown in 4. For RAC1 gene, the total number of nodes, edges along with average node degrees was 11, 49 and 8.91 respectively. With a medium level of confidence (0.4), 10 interacting proteins with RAC1 on evidence based are shown in 5.

According to network analysis, two most important biological process of FAK gene were related to epidermal growth factor and vascular endothelial growth factor signaling pathways. As far as molecular functions are concerned, receptor binding, kinase activity and interactions with phosphatases were the most important features associated with FAK gene. For RAC1 gene, two most important biological processes were regulation of lamellipodium assembly responsible driven by actin polymerization and anoikis (programmed cell death after detachment from ECM). Among the molecular functions, NO signaling, dATP and CTP binding activities were the top three in the analysis. Overall, the analysis revealed that FAK (PTK2) and RAC1 (AKT1) functions as a central hub linking multiple interactors responsible for various functional aspects of a cell life.



Network Stats

number of nodes: 11
number of edges: 51
average node degree: 9.27
avg. local clustering coefficient: 0.941

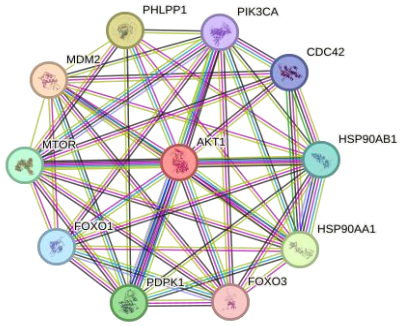
Biological Process (Gene Ontology)

GO-term	description	count in network	strength	signal	false discovery rate
GO:0007173	Epidermal growth factor receptor signaling pathway	6 of 49	2.34	4.25	2.55e-09
GO:0048010	Vascular endothelial growth factor receptor signaling pathway	4 of 33	2.34	2.65	7.69e-06
GO:0007172	Signal complex assembly	3 of 8	2.83	2.51	2.57e-05
GO:0007169	Transmembrane receptor protein tyrosine kinase signaling pathway	8 of 425	1.53	2.4	4.14e-08
GO:0038093	Fc receptor signaling pathway	4 of 51	2.15	2.34	2.31e-05

Molecular Function (Gene Ontology)

GO-term	description	count in network	strength	signal	false discovery rate
GO:0046875	Ephrin receptor binding	3 of 31	2.24	1.6	0.00095
GO:0004715	Non-membrane spanning protein tyrosine kinase activity	3 of 45	2.08	1.53	0.0011
GO:0019903	Protein phosphatase binding	4 of 152	1.67	1.39	0.0010
GO:0004713	Protein tyrosine kinase activity	4 of 146	1.69	1.39	0.0010
GO:0005178	Integrin binding	4 of 159	1.65	1.37	0.0010

Figure 4: Protein-Protein interactions along with biological processes and molecular functions of the gene (PTK2/FAK) were identified by using STRING software.



Network Stats

number of nodes: 11
number of edges: 49
average node degree: 8.91
avg. local clustering coefficient: 0.922

Biological Process (Gene Ontology)

GO-term	description	count in network	strength	signal	false discovery rate
GO:0010592	Positive regulation of lamellipodium assembly	4 of 29	2.39	2.92	2.40e-06
GO:0043276	Anoikis	3 of 12	2.65	2.48	2.57e-05
GO:0071453	Cellular response to oxygen levels	5 of 152	1.77	2.21	8.39e-06
GO:0006970	Response to osmotic stress	4 of 78	1.96	2.15	3.35e-05
GO:0051896	Regulation of protein kinase B signaling	5 of 166	1.73	2.11	1.22e-05

Molecular Function (Gene Ontology)

GO-term	description	count in network	strength	signal	false discovery rate
GO:0030235	Nitric-oxide synthase regulator activity	3 of 8	2.83	2.19	0.00010
GO:0032564	dATP binding	2 of 2	3.25	1.42	0.0028
GO:0002135	CTP binding	2 of 2	3.25	1.42	0.0028
GO:0017098	Sulfonylurea receptor binding	2 of 3	3.08	1.41	0.0028
GO:0002134	UTP binding	2 of 3	3.08	1.41	0.0028

Figure 5: Protein-Protein interactions along with biological processes and molecular functions of the gene (AKT1/RAC1) were identified by using STRING software.

DISCUSSION

The present study demonstrates that sericin exerts a significant cytotoxic effect on colorectal cancer cells, as evidenced by the MTT assay. The dose-dependent reduction in cell viability indicates that sericin interferes with key cellular processes essential for cancer cell survival, suggesting its potential as a bioactive compound for colorectal cancer therapy. These findings align with prior studies indicating that sericin possesses anticancer properties in various malignancies, including breast and colorectal cancer, where it has been shown to induce apoptosis, inhibit proliferation, and impair metabolic activity in tumor cells [5, 6]. The MTT assay results in our study further confirm that sericin negatively affects cellular metabolic activity, which may reflect both impaired mitochondrial function and reduced proliferation.

At the molecular level, our results show that sericin treatment significantly downregulates the expression of FAK and RAC1 genes in colorectal cancer cells depending upon nature of the cell line. FAK is a non-receptor tyrosine kinase that plays a central role in regulating cell adhesion, migration, invasion, and survival. Overexpression of FAK in colorectal cancer is associated with tumor progression, metastasis, and poor prognosis [19, 20]. By inhibiting FAK, sericin likely disrupts focal adhesion signaling pathways, impairing integrin-mediated survival and motility signals. This could also explain the decreased viability observed in the MTT assay and suggests that sericin may prevent not only tumor growth but also the invasive potential of colorectal cancer cells.

Similarly, RAC1, a member of the Rho family of small GTPases, regulates actin cytoskeleton organization, cell mobility, and proliferation. RAC1 signaling is critical for lamellipodia formation and migration in cancer cells and is often hyperactivated in colorectal tumors [22]. Our findings suggest that sericin-mediated suppression of RAC1 could impair cytoskeletal dynamics and reduce migratory capacity, potentially limiting metastatic spread. Importantly, the simultaneous downregulation of both FAK and RAC1 indicates that sericin may target multiple interconnected pathways that drive colorectal cancer progression. FAK and RAC1 are known to cooperate in controlling cytoskeletal rearrangements, cell adhesion turnover and survival signaling; thus, their dual inhibition may produce synergistic anticancer effects [21]. However, the mechanisms through which sericin downregulates FAK and RAC1 expression remain to be fully elucidated. Further mechanistic studies, including protein-level analyses and pathway-specific assays, are warranted to clarify these interactions.

Another noteworthy observation is potential selectivity of sericin toward cancer cells. While our study focused on colorectal cancer lines, previous reports indicate that sericin exhibits minimal cytotoxicity in normal cells, suggesting a favorable therapeutic index [9]. This selectivity could be attributed to differential uptake, metabolic processing, or reliance of cancer cells on FAK and RAC1 signaling for survival and metastasis. As far as functional importance of the selected genes are concerned, FAK and RAC1 genes are central regulators of key cellular signaling networks that control adhesion, migration, proliferation and survival in cells. FAK functions as a non-receptor tyrosine kinase localized at focal adhesions, which are specialized structures that mediate cell-extracellular matrix interactions. Upon activation, FAK recruits and phosphorylates multiple adaptor proteins, initiating downstream signaling cascades, including the PI3K/AKT, which promote cell survival, proliferation, and motility [22]. RAC1, a member of the Rho family of small GTPases, acts as key mediator of actin cytoskeleton remodeling and lamellipodia formation, processes essential for cell migration and invasion [23].

Overall, these results support the potential of sericin as a multi-target anticancer agent that exerts cytotoxicity and may work through the inhibition of FAK and RAC1, thereby impairing colorectal cancer cell survival, proliferation, and motility. Future studies should include *in vivo* models to validate these effects, investigate the pharmacokinetics and bioavailability, and explore combination therapies with conventional chemotherapeutic agents. Such studies will provide a clearer understanding of sericin's therapeutic potential and may establish it as a candidate for natural-based colorectal cancer treatment strategies.

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Competing Interests: Authors declare no competing interests.

Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.