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From silk waste to cancer therapy: a review of the therapeutic potential and in vitro cytotoxicity of sericin

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ABSTRACT

Cancer is a disease characterized by uncontrolled cell growth, often leading to death. The high incidence of cancer has led to continued exploration of potential therapeutics, particularly those derived from natural products. One of the potential natural products is sericin, which has been shown to have anticancer effects against several types of cancer through various in vitro studies. Previous studies generally indicate that sericin's anticancer effects are reflected in its ability to reduce cancer cell viability and induce apoptosis by regulating the expression levels of its related proteins. Studies have suggested that the expression levels of apoptosis-related proteins are known to influence the metastatic potential of cancer cells. Although the specific antimetastatic effects of sericin, an industrial waste by-product, remain largely unexplored, this review comprehensively evaluates its role as an anticancer agent and its underlying cellular mechanisms. Sericin modulates the apoptotic pathway by shifting the Bax/Bcl-2 ratio, specifically through upregulating the pro-apoptotic Bax and suppressing the anti-apoptotic Bcl-2, leading to the sequential activation of pro-caspase-9 and downstream effector caspases. Beyond its established pro-apoptotic activity, we highlight the ability of sericin to restore the apoptotic threshold, which may effectively limit the survival of circulating tumour cells and their capacity to metastasize. Consequently, while sericin offers a promising frontier for future therapeutic investigation, realizing this remarkable potential requires addressing critical experimental gaps, specifically the current lack of dedicated in vitro migration/ invasion assays and in vivo metastasis models to evaluate sericin impact on disrupting the metastatic cascade.

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1. Introduction

Cancer is a condition characterized by uncontrolled cell growth and spread, which leads to death if remain untreated (Arianto et al., 2024). Based on data collected in 2022, there were 20 million new cases of cancer diagnosed, and 9.7 million deaths caused by cancer worldwide (Bray et al., 2024). The high incidence of cancer is the reason why various studies are continuously conducted to explore the potential of various cancer therapy options. Current forms of cancer therapy often involve surgical removal and radiation, which are usually followed by systemic chemotherapy treatment to maintain the patient's condition (Rayan et al., 2017). However, the use of chemically synthesized anticancer drugs has caused adverse effects for cancer patients, especially in suppressing the immune system (Rayan et al., 2017). Therefore, the discovery and development of cancer therapies from natural products continue to be carried out to achieve high efficacy while maintaining relatively low toxicity.

Some of the natural products with anticancer effects are curcumin, a phenolic pigment in turmeric (Calaf et al., 2018), and caffeine that contained in various types of drinks (Liu et al., 2017). However, there are several obstacles that arise in the use of natural

products as anticancer drugs, including the difficulties of accessing the sources of the sample or synthesizing the target compound in the necessary quantities (Da Rocha et al., 2001). Another natural product that is known to have anticancer potential is sericin, which for years has been discarded and considered as textile industry waste (Elahi et al., 2021; Liu et al., 2022). Although sericin is generally unused and even considered waste in the textile industry, several studies have shown that sericin has benefits in the biomedical field, such as anti-inflammatory, antioxidant, and accelerating the wound healing process (Munir et al., 2023; Rahimpour et al., 2023). In addition, there are also studies reported that sericin can provide anticancer effects observed through in vitro studies (Niu et al., 2021)

1.1. Review Methodology

This narrative review provides a comprehensive overview of the therapeutic potential of sericin in cancer treatment, focusing specifically on in vitro evidence. Relevant literature was identified through searches of electronic databases, using keywords including sericin, anticancer, metastasis, and migration. Literature was screened and selected based on relevance, historical significance, and a contribution to understanding sericin's efficacy against cancer, ensuring comprehensive coverage of both the foundational background and recent advancements.

2. Sericin

Sericin is one of the proteins that make up silk fiber along with fibroin (Lamboni et al., 2015; Seo et al., 2023). Silk fiber is produced by the fifth instar larval phase of silkworms, which then forms a cocoon, a place for the larvae to develop and metamorphosis into adults (Cao and Zhang, 2016; Kunz et al., 2016). The percentage of sericin in silk fiber is 20-30%, while the percentage of fibroin is 70-80% (Kundu et al., 2008; Wang and Zhang, 2011). Sericin functions as an adhesive that maintains the structure of the silkworm cocoon (Babu and Suamte, 2024). Sericin is located on the outside of the silk fiber surrounding fibroin, which is located on the inside (Cao and Zhang, 2016; Sobajo et al., 2008) (Fig. 1).

Sericin is divided into 3 layers based on its location, namely the outermost sericin (sericin A), sericin that located in the middle (sericin B), and sericin that is located on the inside, which is directly adjacent to and surrounds fibroin (sericin C) (Wang and Zhang, 2011; Cao and Zhang, 2016). Research by Wang and Zhang (2011) shows that the three layers of sericin in silk fiber obtained from cocoons have different percentages (Wang and Zhang, 2011). The composition of the sericin layers can be seen in Fig. 2.

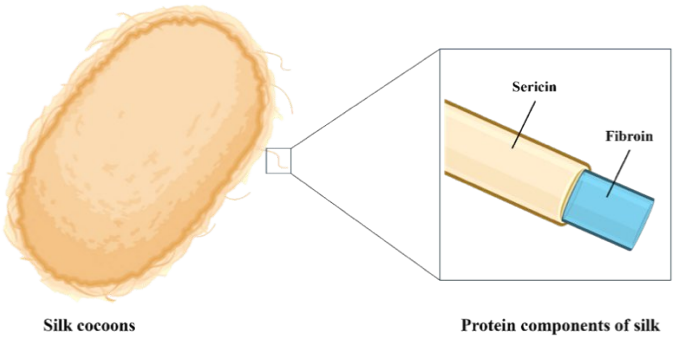

Fig. 1. Structure of silk fiber components

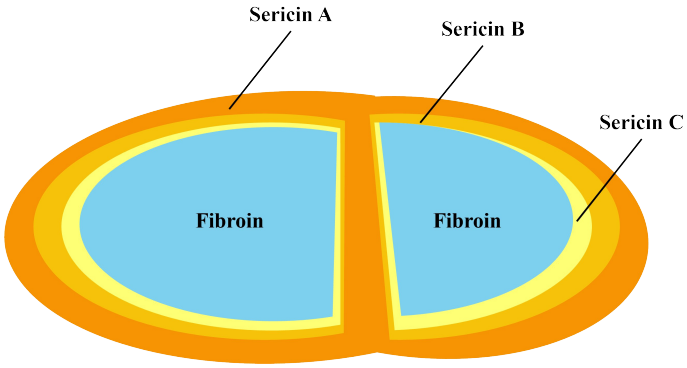

Fig. 2. Structure of the sericin layer

Sericin A is known to have a percentage of 50% compared to the total sericin present; this shows that sericin A has the largest amount compared to the other 2 sericin layers. Meanwhile, sericin B has a percentage of 35%, and sericin C has the smallest percentage (15%) (Wang and Zhang, 2011).

2.1. Sericin sources

Sericin is a protein produced by silkworms, one of which is the *Bombyx mori* species, which has been generally domesticated (Kundu et al., 2008). The production of sericin and fibroin in sufficient quantities is found in the 5th instar larval phase, which will then form a cocoon for metamorphosis (Kundu et al., 2008). In addition to being obtained from the cocoon, sericin produced by *Bombyx mori* can also be obtained directly from its silk gland (Kunz et al., 2016). The *Bombyx mori* silk gland is divided into three main areas, that is the Anterior Silk Gland (ASG), middle silk gland (MSG), and Posterior Silk Gland (PSG) (Akai, 1983; Kunz et al., 2016) (Fig. 3). The MSG part is responsible for secreting sericin, while PSG is responsible for secreting fibroin (Kunz et al., 2016). The ASG is where silk protein flows, and excess water is absorbed, so that dense filaments can be formed (Kunz et al., 2016).

2.2. Sericin extraction method

In the textile industry, while making silk cloth, sericin is separated from fibroin through a degumming process and then discarded, leaving only fibroin used as silk (Gupta et al., 2013). Sericin makes silk fibers have a hard and stiff structure, while without sericin, the silk fibers will be smoother and shinier (Padamwar and Pawar, 2004). This character causes the sericin separation process to be carried out to obtain shiny, soft, smooth, and dyeable silk (Gupta et al., 2013). Fibroin is a single protein that has characteristics that are not soluble in water, while sericin is a gummy protein that can be dissolved in water, so that the separation of sericin (degumming) will be easy to do without causing damage to the fibroin (Yuksek et al., 2012). The degumming process in the textile industry is usually carried out by boiling silkworm cocoons in a solution containing sodium carbonate and Marseille soap to separate sericin from fibroin (Liu et al., 2022). Although this method is effective in obtaining relatively clean isolated fibroin for further use, it is very difficult to separate sericin from soap and other chemicals, because sericin has been emulsified and causes it to dissolve in wastewater (Lamboni et al., 2015; Yuksek et al., 2012).

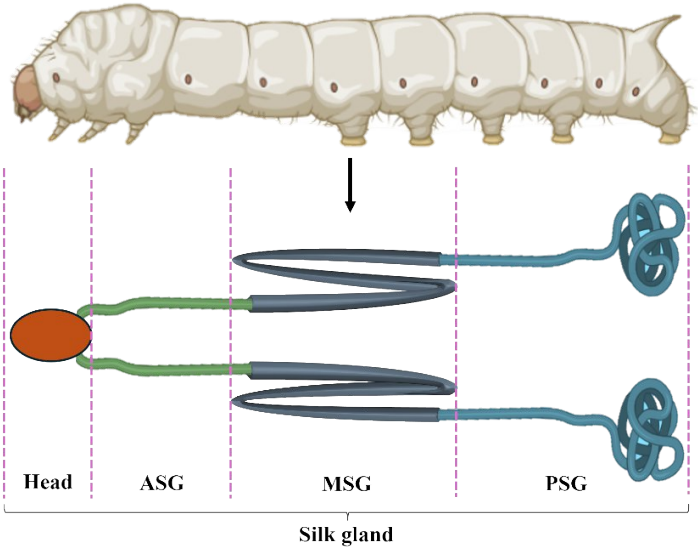

Fig. 3. Anatomy of the silk gland of *Bombyx mori*

Four primary methodologies are currently employed for extracting sericin from cocoons, such as high temperature associated with high pressure by autoclaving, acid-mediated extraction with citric acid, alkaline treatment using sodium carbonate, and urea-based solubilization (Kunz et al., 2016). While autoclave-assisted thermal extraction remains the most prevalent laboratory protocol, the choice of extraction technique profoundly influences the biological efficacy of the recovered product. This methodological impact is highlighted by Ratanabunyong et al. (2024), which demonstrated that sericin obtained through these varying protocols exhibit distinct IC_{50} values when evaluated across four different cell lines.

2.3. Various forms of sericin utilization

The separation of sericin in the silk manufacturing process has made sericin considered a textile industry waste for many years (Elahi et al., 2021; Liu et al., 2022; Yuksek et al., 2012). However, several studies provide information on the utilization of sericin in various fields, for example in cosmetics, pharmacology, biomedicine, and biotechnology applications (Aramwit et al., 2012; Kundu et al., 2008; Lamboni et al., 2015; Padamwar and Pawar, 2004; Seo et al., 2023). The use of sericin in 2-dimensional (film) and 3-dimensional (hydrogel and scaffold) forms has been widely reported (Kundu et al., 2008), specifically to observe the ability of sericin as a wound dressing applied in the wound healing process (Munir et al., 2023). Sericin hydrogel as a wound dressing in test animals (mice) can accelerate wound healing, when compared with the use of saline solution only, which in the study acted as a negative control (Munir et al., 2023).

In addition, sericin is also known to have the ability to be used as a proliferation substrate, so it can be an alternative to collagen, which has been widely used as a substrate for adherent mammalian cell cultures (Zhang, 2002). The use of sericin films to culture L929 cells showed that sericin was able to support higher cell attachment and proliferation compared to cells grown in culture plate that were not coated with sericin films (Aramwit et al., 2010). A similar finding was also found in the study of Tsubouchi et al. (2005) which stated that human skin fibroblast cells cultured in petri dishes that had been coated with sericin experienced an increase in cell number of up to 250% after incubation for 72 hours due to accelerated attachment. In addition, it was also reported that there were differences in cell morphology between cells grown in sericin-coated dishes and non-coated dishes. Cells on sericin-coat dishes appear to have a well-extended fibrous shape similar to that on the collagen-coat, while on non-coat dishes the cells appear round (Tsubouchi et al., 2005).

3. Anticancer efficacy of sericin

3.1. Anticancer effect of sericin on colorectal cancer

The biomedical utility of sericin is increasingly defined by its considerable therapeutic promise in oncology (Kundu et al., 2008). The in vivo evaluation that Zhaorigetu et al. (2001) did have demonstrated the potent anticancer efficacy of sericin. The research indicates that dietary sericin supplementation for 115 days, resulting in a marked decrease in adenoma occurrence, observed in only 38% of the treated group versus 100% of the control, while concurrently preventing the development of advanced adenocarcinomas (Zhaorigetu et al., 2001).

Expanding upon its therapeutic profile, Kaewkorn et al. (2012) characterized the biological properties of sericin by evaluating the impact of molecular weight (MW) on its cytotoxic efficacy. Their comparative analysis of large-sized sericin (191-339 kDa) and small-sized sericin (61-132 kDa) across a broad concentration range (25-1,600 mg/mL) revealed significant growth inhibition in SW480 colorectal adenocarcinoma cells. Notably, small-sized sericin exhibited a slightly higher antiproliferative effect (62% viability) compared to its large-sized counterpart (69%) in SW480 cells. However, large-sized sericin demonstrated superior selective toxicity, maintaining significantly higher viability in normal FHC cells (81%) compared to SW480 cells (69%)—a distinction that was less pronounced with small-sized sericin (Kaewkorn et al., 2012). Mechanistically, only low-MW sericin significantly increased the percentage of late apoptosis in SW480 cells. This pro-apoptotic activity was further validated by a significant upregulation of Caspase-3 activity and a concomitant downregulation of the anti-apoptotic protein Bcl-2, confirming that sericin-induced cell death occurs through the activation of established apoptotic cascades. Both protein expression levels showed significant differences when compared to the control (Kaewkorn et al., 2012).

Further investigation into the colorectal anticancer potential of sericin was also conducted by Ratanabunyong et al. (2024), who evaluated the efficacy of four distinct extraction methodologies (acid, alkaline, heat, and urea-based protocols) across a panel of four cell lines. Comparative analysis of the half-maximal inhibitory concentration (IC_{50}) revealed that urea-extracted sericin exerted the most potent effect on cell viability. Specifically, in HCT116 cells, sericin treatment induced apoptosis in a dose-dependent manner, characterized by the significant upregulation of both initiator caspases (CASP8, CASP10) and executioner caspases (CASP3, CASP7). The activation of these specific caspases indicates that sericin may trigger both the extrinsic and intrinsic apoptotic pathways, providing a multi-targeted mechanism for inhibiting malignant progression (Ratanabunyong et al., 2024).

3.2. Anticancer effect of sericin on breast cancer

The potential efficacy of sericin in breast cancer therapy was explored by Mumtaz et al. (2023), who utilized a nanotechnology-based approach by synthesizing sericin-capped silver nanoparticles (Ser-AgNPs). The cytotoxic impact was evaluated via MTT assay on two distinct breast cancer phenotypes: the hormone-responsive MCF-7 line and the highly aggressive, Triple-Negative MDA-MB-231 line. Treatments included varying concentrations of sericin and Ser-AgNPs (0.1-1 mg/mL), with Tamoxifen serving as a clinical positive control (1-10 µg/mL). Results indicated that a significant reduction in cell viability compared to the negative control was only achieved at the maximum sericin concentration of 1 mg/mL.

Interestingly, a dose-dependent inhibitory response was exclusively observed in MDA-MB-231 cells, whereas MCF-7 cells exhibited a less sensitive reaction to increasing concentrations. This variation suggests that sericin's anticancer bioactivity may be modulated by the specific molecular subtype of the breast cancer cells (Mumtaz et al., 2023).

The subtype-specific efficacy of sericin was further elucidated by Niu et al. (2021), who evaluated its impact across a panel representing diverse molecular subtypes. This study utilized Triple-Negative Breast Cancer (TNBC) models, specifically the MDA-MB-468 and MDA-MB-453 lines, alongside the Luminal A (non-TNBC) subtype represented by MCF-7 cells (Dai et al., 2017; Niu et al., 2021). To establish a baseline for biocompatibility, the MCF-10A normal breast epithelial cell line was employed as a non-malignant control. The inclusion of these distinct genotypes allows for a critical assessment of whether sericin's cytotoxic effects are broad-spectrum or selective toward aggressive, hormone-independent phenotypes like TNBC (Niu et al., 2021).

The classification of breast cancer into clinically relevant subtypes is determined by the immunohistochemical expression of three key molecular markers: Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) (Elkholi et al., 2022; Kumar and Aggarwal, 2016). The Triple-Negative Breast Cancer (TNBC) subtype is characterized by the characteristics of ER negative, PR negative, and HER2 negative (Dai et al., 2017; Krishnamurti and Silverman, 2014; Kumar and Aggarwal, 2016; Rakha et al., 2010). Examples of cell lines included in the TNBC subtype are MDA-MB-468 and MDA-MB-231 cells (Dai et al., 2017; Niu et al., 2021). Meanwhile, Luminal A subtype breast cancer is characterized by ER positive, and/or PR positive, and HER2 negative (HER2 not amplified) (Dai et al., 2017; Kumar and Aggarwal, 2016). Several cell lines included in the Luminal A subtype are MCF7, BT483, and HCC712 cells (Dai et al., 2017).

Experimental results further substantiate the subtype-specific potency of sericin, which demonstrated a markedly higher efficacy in reducing the viability of TNBC cell lines (MDA-MB-468 and MDA-MB-453) compared to the Luminal A (MCF-7) and normal epithelial (MCF-10A) lines. In the TNBC cohort, sericin elicited a dose-dependent cytotoxic response, a phenomenon particularly pronounced in MDA-MB-468 cells. Conversely, the non-TNBC MCF-7 line exhibited significant resistance to treatment, while the normal MCF-10A line remained entirely unaffected, confirming sericin's high biocompatibility and selective index (Niu et al., 2021). These findings were corroborated by a clonogenic (colony formation) assay, which assessed the long-term proliferative capacity of the malignant cells. Sericin administration resulted in a significant, dose-dependent reduction in colony counts in MDA-MB-468 cells. Specifically, treatment with 8 mg/mL of sericin reduced the colony count to 215,000±8,544 ($P<0.001$), representing a dramatic decline compared to the negative control 459,667±24,132). This potent inhibition of anchorage-independent growth underscores sericin's potential to disrupt not only immediate cell survival but also the regenerative capacity of aggressive breast cancer phenotypes (Niu et al., 2021).

Complementing the phenotypic observations, molecular analysis provides further evidence that sericin-induced cell death in MDA-MB-468 cells is driven by the modulation of key apoptotic regulators. Western blot results revealed a significant downregulation of the anti-apoptotic protein Bcl-2, coupled with a concomitant increase in Bax and Cytochrome-c (Cyto-c) levels. This shift in the pro-apoptotic balance triggers the intrinsic mitochondrial pathway, as corroborated by flow cytometry, which demonstrated a clear dose-dependent increase in apoptotic cell populations. Notably, high-throughput gene profiling identified the PI3K/Akt signalling pathway as the primary therapeutic target of sericin in TNBC models. Administration of 8 mg/mL of sericin resulted in a significant suppression of proteins within this axis, suggesting that sericin exerts its anticancer effects by inhibiting the PI3K/Akt survival pathway, thereby sensitizing aggressive TNBC cells to programmed cell death (Niu et al., 2021).

3.3. Anticancer effect of sericin on lung cancer

Beside colorectal and breast malignancies, the therapeutic potential of sericin also demonstrating considerable promise in the management of lung cancer. Research conducted by Mehak and Iqbal (2024) systematically demonstrated that sericin exerts concentration- and time-dependent inhibitory effects on H1299, lung cancer cells, with concentrations ranging from 0.03 to 1.0 mg/mL over 24-72 hours. This study validated the reliability of the degumming extraction process by showing comparable results between locally extracted and commercially available sericin, while further identifying a dual-action mechanism where sericin arrests the cell cycle and triggers cellular stress responses. Specifically, sericin treatment was found to upregulate cell cycle inhibitor genes such as *CDKN1A* (up to 2.7-fold) and *CDKN2A* (up to 3-fold), alongside stress-related genes *GADD45A* and *GADD45B*, which increased up to 2.9-fold. It is noteworthy that this induction exhibited greater potency at a sericin concentration of 0.25 mg/mL (Mehak and Iqbal, 2024). This coordinated upregulation of cytostatic and cytotoxic effectors suggests that sericin exerts its antiproliferative activity through dual mechanisms, simultaneously arresting cell cycle progression and activating cellular stress responses that lead to cancer cell death.

Complementing these findings, additional studies have further elucidated the molecular basis of sericin anticancer activity against lung cancer cells. Ratanabunyong et al. (2024) established that urea-extracted sericin possesses potent cytotoxicity against NCI-H1975 cells, achieving an IC_{50} value at 43 µg/mL and inducing over 80% apoptosis at a dosage of 100 µg/mL. This apoptotic response is driven by the activation of the extrinsic pathway, characterized by the upregulation of death receptor ligands like FASLG and TNFSF10 and a comprehensive cascade involving caspases 8, 10, 3, and 7 (Ratanabunyong et al., 2024). The versatility of sericin is further highlighted by its efficacy when derived from alternative sources, such as the bacterial-derived sericin (BNES) studied by El-Fakharany et al. (2020). BNES demonstrated selective cytotoxicity against A549 lung adenocarcinoma cells with an IC_{50} of 0.55 mg/mL, notably maintaining a high selectivity index of 7.62 which indicates minimal toxicity toward normal W138 lung fibroblasts. This anticancer activity was confirmed to be apoptosis-dependent, evidenced by morphological alterations, nuclear DNA fragmentation, and cell cycle arrest at the sub-G1 phase (El-Fakharany et al., 2020). Adding to this repertoire, Devi et al. (2023) explored sericin from the non-mulberry silkworm *Antheraea proylei* J. (APS), which exhibited an IC_{50} value of 3.8 µg/µL (equivalent to 3.8 mg/mL) against A549 cells after 24 hours of treatment. Their analysis revealed that APS induces significant dose-dependent DNA fragmentation and triggers apoptosis through the activation of caspase-3 and PARP cleavage, specifically involving the modulation of the ERK signalling pathway. Furthermore, APS was found to induce cell cycle arrest at the S phase in A549 cells, which contributed to its antiproliferative effects (Devi et al., 2023). These findings reinforce the concept that sericin, regardless of its origin as bacterial-derived or silkworm-derived (including both mulberry and

non-mulberry species), consistently suppresses lung cancer cell growth through the sophisticated coordination of extrinsic apoptotic pathways and the induction of cell cycle arrest.

3.4. Anticancer effect of sericin on other cancers

Beyond colorectal, breast, and lung models, the anticancer potential of sericin has been investigated across a broader spectrum of human malignancies, including epidermoid carcinoma (A431) and tongue squamous cell carcinoma (SAS). A critical dimension of this research involves the comparative analysis of sericin extracted from diverse lepidopteran species: the domesticated *Bombyx mori* (BM) and the wild silkworms *Antheraea assamensis* (AA) and *Philosamia ricini* (PR). MTT assays conducted across a concentration gradient (500-4,000 µg/mL) revealed that while concentrations up to 1 mg/mL maintained cell viability, higher dosages elicited a significant dose-dependent cytotoxic response. Notably, all three sericin variants (BMS, AAS, and PRS) at 4 mg/mL reduced the viability of A431 and SAS cells to below 50%. However, *Antheraea assamensis* sericin (AAS) demonstrated superior potency in breast adenocarcinoma (MCF-7) models, being the only variant to achieve a sub-50% viability threshold at the 4 mg/mL concentration, suggesting that wild silk proteins may possess unique bioactive properties compared to their domesticated counterparts (Kumar and Mandal, 2019).

To further delineate the mode of cell death, Annexin V/Propidium Iodide (PI) dual staining was performed via flow cytometry to quantify the distribution of cell populations across apoptotic stages. In this assay, early apoptosis is defined by Annexin V positivity (indicating phosphatidylserine externalization), while late apoptosis is marked by both Annexin V and PI positivity. Cells staining positive only for PI are classified as necrotic (Alshehade et al., 2024). Kumar and Mandal (2019), demonstrated that *Bombyx mori* sericin (BMS) elicited the highest percentage of early apoptotic populations in both A431 and SAS cells. However, the induction of late-stage apoptosis varied by species: *Antheraea assamensis* sericin (AAS) was most effective in A431 cells, whereas BMS remained more potent in SAS cells. Notably, the MCF-7 breast cancer line showed a distinct sensitivity to wild silk; significant transitions into early and late apoptosis were exclusively observed following AAS administration. Compared to the untreated control, AAS induced a 9.5-fold increase in early apoptosis and a 9.2-fold increase in late apoptosis in MCF-7 cells, underscoring the superior pro-apoptotic potential of non-mulberry sericin in specific adenocarcinoma models (Kumar and Mandal, 2019; Ratanabunyong et al., 2024). The anticancer efficacy of sericin across various malignancies, along with the specific concentrations evaluated in these studies, is summarized in Table 1.

4. Mechanisms of sericin-mediated inhibition in cancer cells

The antineoplastic efficacy of sericin is characterized by its capacity to concurrently activate both the extrinsic and intrinsic apoptotic cascades. Genomic analysis in colorectal cancer models has demonstrated that sericin treatment significantly upregulates the expression of pro-apoptotic ligands and receptors, including FASLG and TNFSF10 (TRAIL) (Ratanabunyong et al., 2024). This activation initiates the extrinsic pathway via the formation of the Death-Inducing Signaling Complex (DISC). The recruitment of the Fas-Associated Death Domain (FADD) and the subsequent activation of initiator caspases (CASP8 and CASP10) facilitate the direct proteolytic maturation of effector caspases (CASP3, CASP6, and CASP7) (Su et al., 2015).

Simultaneously, sericin modulates the intrinsic pathway by altering the rheostat of the Bcl-2 protein family. Bax and Bcl-2 proteins are members of the B-cell lymphoma-2 (BCL-2) protein family, which have opposing functions. Bcl-2 proteins function to inhibit apoptosis (anti-apoptotic), while Bax supports the initiation of apoptosis (pro-apoptotic) (Youle and Strasser, 2008). Bax and Bcl-2 protein levels correlate with apoptosis regulation; if Bax levels increase, apoptosis will also increase. Conversely, increased Bcl-2 levels will inhibit apoptosis (Qian et al., 2022). By inducing a shift in the Bax/Bcl-2 ratio, specifically through the upregulation of pro-apoptotic Bax and the suppression of anti-apoptotic Bcl-2, sericin promotes the permeabilization of the outer mitochondrial membrane (OMM) (Niu et al., 2021). This results in the cytosolic release of Cytochrome-c, which assembles with APAF-1 to form the apoptosome complex. This complex recruits and activates Procaspase-9, further amplifying the downstream effector caspase cascade (Adams and Cory, 2007; Youle and Strasser, 2008). The convergence of these two pathways underscores sericin's role as a potent coordinator of programmed cell death in malignant cell lines. The general apoptosis pathway can be seen in Fig. 4.

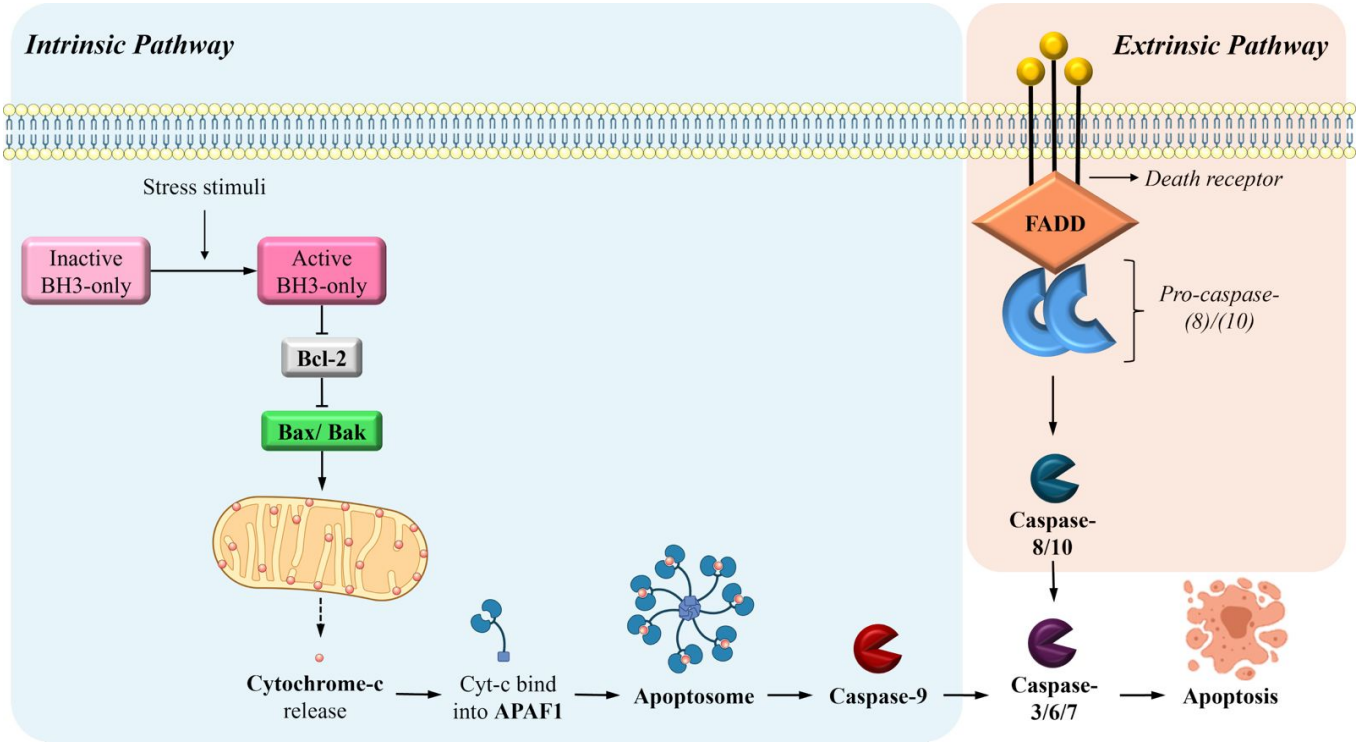

Fig. 4. Apoptosis activation pathways

Table 1. Anticancer efficacy of sericin across various types of cancer

Cancer Type	Cell Line	Sericin Concentration (mg/mL)	Key Findings	Ref
Liver Cancer	HepG2	0.03 – 1.00	- Inhibited cell proliferation in a concentration- and time-dependent manner (48-72 hours) - Induced *GADD45B* and *CDKN1A* expression, while *GADD45A* was moderately inhibited - Comparable cytotoxic effects between locally extracted and commercially available sericin confirmed the reliability of the degumming extraction method	(Mehak et al., 2025)
Colorectal Cancer	SW620, SW480, HCT116	0.50 – 1.00	- Downregulated *FAK* gene expression, which is involved in cell adhesion, migration, and invasion in colorectal cancer cells - Downregulated *RAC1* gene expression in SW480, HCT116, but induced it in metastatic cells (SW620)	(Iqbal and Numan, 2025)
Colorectal Cancer	SW480, FHC	25 – 1,600	- Small-size sericin (61–132 kDa) reduced SW480 cell viability more effectively than large-size sericin (191–339 kDa) - Induced apoptosis in SW480 cells via increased caspase-3 activity and downregulation of Bcl-2 expression - Caused S-phase cell cycle arrest in SW480 cells	(Kaewkorn et al., 2012)
Lung, Cholangio, Colorectal, and Liver Cancer	NCI-H1975, RBE, HCT116, and HepG2	0.04 – 0.10[a]	- Urea-extracted sericin showed the highest cytotoxicity against HCT116 cells (IC_{50} = 0.042 mg/mL[a]) and induced apoptosis in over 80% of cells at 0.10 mg/mL[a] - Activated the extrinsic apoptosis pathway by upregulated the death receptors (FASLG, TNFSF10) and caspase cascade (CASP8, CASP10, CASP3, CASP7)	(Ratanabunyong et al., 2024)
Colorectal, Breast, Liver, Lung Cancer	Caco-2, MCF-7, A549, Huh-7	0.07 – 1.33	- Bacterial sericin (BNES) showed selective cytotoxicity against cancer cells (IC_{50} = 0.41–0.55 mg/mL) with no toxicity to normal cells - BNES induced apoptosis via sub-G1 cell cycle arrest and DNA fragmentation - BNES exhibited antioxidants (DPPH IC_{50}: 0.38 mg/mL) and antimicrobial activities	(El-Fakharany et al., 2020)
Breast Cancer	MCF-7	20.00	- DOX-loaded sericin nanoparticles (15 – 40 nm) significantly decreased MCF-7 cell viability after 24 hours compared to unloaded nanoparticles - DOX-loaded sericin nanoparticles induced DNA damage in MCF-7 cells - Unloaded sericin nanoparticles showed good biocompatibility with no significant cytotoxicity or DNA damage in MCF-7 cells	(Radu et al., 2021)

Cancer Type	Cell Line	Sericin Concentration (mg/mL)	Key Findings	Ref
Breast Cancer	MCF-7	0.005 – 1.00[a]	- Melatonin/resveratrol-loaded sericin nano capsules (MR-SNC) showed pH-dependent drug release (maximum at pH 6) - MR-SNC at pH 6 induced DNA fragmentation, chromatin condensation, and efficient cellular uptake via charge reversal mechanism	(Aghaz et al., 2023)
Breast Cancer	MCF-7, MDA-MB-231	0.10 – 1.00	- Sericin and Sericin-AgNO3 NPs (1 mg/mL, 72 h) reduced cell viability by 41% in MCF-7 and 26% in MDA-MB-231 breast cancer cells - Induced *GADD* family genes (*GADD45A*, *B*, *G*, *34*, *153*) and *CDKN1A*/*B* (2.5 to 34.3-fold) in both cell lines	(Mumtaz et al., 2023)
Lung Cancer	H1299	0.03 – 1.00	- Sericin induced expression of *CDKN1A*, *CDKN2A*, *GADD45A*, *GADD45B* with cytotoxic effects were concentration-dependent with similar results between local and commercial sericin.	(Mehak and Iqbal, 2024)
Gastric Cancer	AGS, MKN45	1.00 – 30.00	- APS (*Antheraea proylei J.* sericin) inhibited proliferation, migration, and colony formation of gastric cancer cells (AGS, MKN45) at 4 mg/mL - APS induced mitochondrial apoptosis pathway by upregulating Bax, caspase-3/7/9 and downregulating Bcl-2 - APS showed no toxicity to normal gastric mucosal cells (GES1) and mice, and suppressed cisplatin-resistant MKN45/CDDP cells	(Wei et al., 2025)
Breast Cancer	4T1	0.0005 – 0.01[a]	- Sericin-Ce6 nanoparticles (SSC NPs) showed enhanced cellular uptake, - SSC NPs with NIR laser (660 nm) induced high ROS generation, and reduced 4T1 cell viability to 11% at 0.01 mg/mL[a] Ce6, - SSC NPs accumulated effectively in tumors of 4T1-bearing mice and suppressed tumor growth without systemic toxicity	(Gao et al., 2021)
Colorectal Cancer	SW480, SW620, HCT116	0.25 – 2.00	- Sericin and SChiAgNPs (65.8 nm) inhibited cell viability by 35 – 43% in SW480, SW620, and HCT116 colorectal cancer cells at 2 mg/mL - Sericin and SChiAgNPs induced *GADD45A*, *BCL2*, and *TNF* gene expression - Extracted sericin showed comparable or slightly better antiproliferative effects than commercial sericin	(Ijaz et al., 2025)
Squamous, Oral, Breast Cancer	A431, MCF-7, SAS, HaCaT, MCF-10	0.5 – 4.00	- Sericin (4 mg/mL) reduced cancer cell viability >50% (A431, SAS, MCF-7) with minimal toxicity to normal cells - Sericin induced apoptosis via increased ROS, sub-G1 arrest, and mitochondrial membrane depolarization - AAS sericin upregulated p53/Bax and downregulated Bcl-2, while suppressing SOD activity	(Kumar and Mandal, 2019)
Lung, Cervical, Prostate Cancer	A549, HeLa, PC3 cells	0.17 – 11[b]	- APS reduced cell viability in A549, HeLa, and PC3 cells with IC50 values of 3.4 – 3.9 mg/mL[b] - APS activated caspase-3/PARP in A549 and HeLa cells (caspase-dependent), but induced apoptosis via p38 pathway independent of caspase/PARP in PC3 cells	(Devi et al., 2023)

[a]Original data reported in µg/mL and converted to mg/mL for consistency.
[b]Original data reported in µg/µL and converted to mg/mL for consistency.

5. The potential of sericin against metastasis in cancer

Metastasis represents the terminal stage of malignant progression and remains the primary driver of cancer-related mortality (Park et al., 2022). The successful colonization of secondary organs requires cancer cells to bypass multiple biological checkpoints, including the evasion of programmed cell death (Owen-schaub et al., 1998; Park et al., 2022). Current evidence suggests that apoptosis induction serves as a critical internal safeguard against metastatic dissemination (Mehlen and Puisieux, 2006). For instance, Del Bufalo et al. (1997) demonstrated that the overexpression of the anti-apoptotic protein Bcl-2 in MCF-7 cells significantly increased the incidence of pulmonary metastases and nodule formation in vivo (Del Bufalo et al., 1997). Conversely, the inactivation of pro-apoptotic genes, such as *FASL*, has been shown to facilitate lung metastasis in melanoma models, whereas wild-type subjects remained resistant (Owen-schaub et al., 1998).

Given that sericin has been established to significantly downregulate Bcl-2 and upregulate FasL and caspase activity in various adenocarcinoma lines, there is a compelling biochemical rationale to suggest that sericin may possess antimetastatic potential. By restoring the apoptotic threshold, sericin may effectively limit the survival of circulating tumour cells and their ability to establish secondary niches. While a gap remains in the literature concerning the direct antimetastatic activity of sericin, this established association justifies future studies into its role in inhibiting the metastatic cascade.

6. Conclusion

In summary, sericin exhibits significant anticancer potential across various human cancer cell lines, primarily driven by its ability to suppress cell viability and re-establish the apoptotic threshold. By modulating the intricate balance between pro-apoptotic (Bax, Caspases) and anti-apoptotic (Bcl-2) proteins, sericin effectively initiates programmed cell death through both intrinsic and extrinsic pathways. Given the established correlation between apoptotic regulation and the suppression of the metastatic cascade, sericin represents a promising multi-targeted candidate for inhibiting cancer dissemination. However, as direct empirical evidence regarding sericin's impact on secondary colonization is currently non-existent, future research must prioritize rigorous in vitro functional assays. Specifically, studies focusing on cell migration and invasion potential are essential to determine if sericin can physically disrupt the movement of cancer cells. Such studies will be pivotal in transitioning sericin from a laboratory-observed bioactive protein to a viable clinical strategy for advanced oncology.

Future perspectives and challenges

While the exploration of natural products for cancer therapy has expanded significantly, the limited availability and unsustainable sourcing of many bioactive compounds remain major obstacles. In contrast, within the worldwide production of I million tons (fresh weight) of cocoons, roughly 50,000 tons of sericin are released into aquatic environments each year (Aramwit et al., 2012; Gupta et al., 2013). Nevertheless, sericin, an abundant silk industry by-product, presents a promising and sustainable alternative, showing significant efficacy in modulating cellular death pathways. Its ability to modulate the Bax/Bcl-2 ratio underscores its potential as a broad-spectrum anticancer agent, as evidenced by numerous in vitro studies across various malignancies. Furthermore, evidence from animal models has established a clear link between apoptotic protein regulation and metastatic capacity. Although sericin's specific role in this process has yet to be investigated, its established ability to modulate these same proteins provides a strong theoretical basis for its potential antimetastatic effects. To date, sericin application remains strictly within the pre-clinical phase. As summarized in Fig. 5, key pre-clinical milestones, such as in vitro migration/ invasion assays and in vivo metastasis models, must be prioritized in future investigations. To move beyond the laboratory bench, future research must prioritize robust in vivo studies to evaluate sericin's efficacy in complex biological systems. A critical next step involves determining how sericin survives metabolic degradation, specifically, whether its peptide fragments retain the ability to trigger the intrinsic apoptosis pathway once they enter the bloodstream.

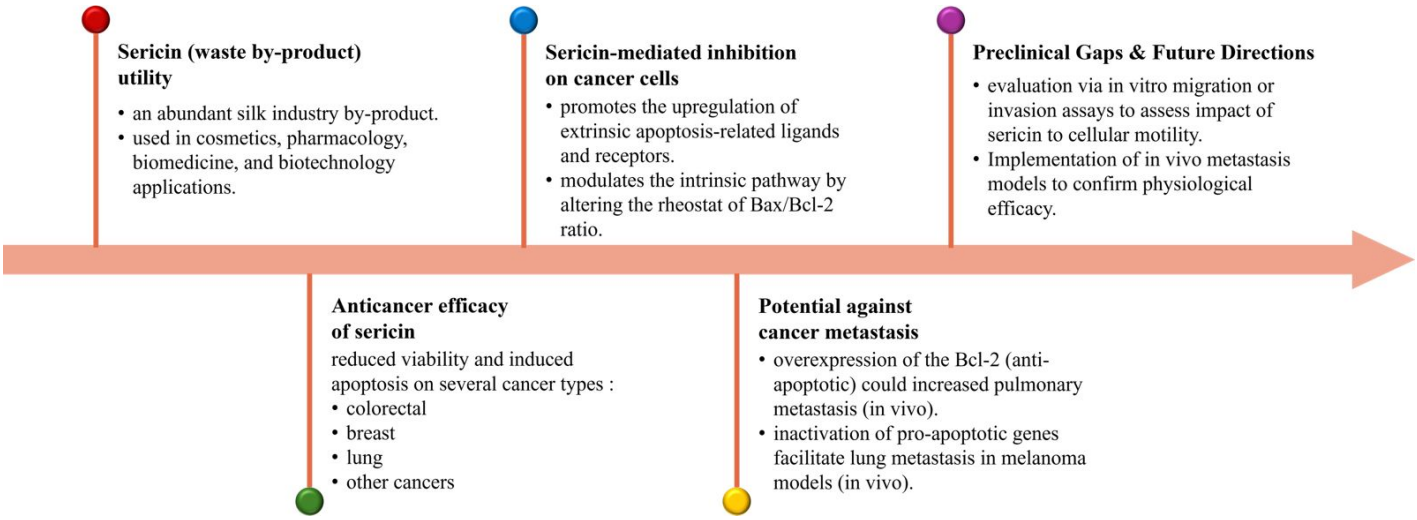

Fig. 5. Conceptual framework and future roadmap of sericin in cancer therapeutic development

A primary challenge in establishing sericin as a clinical anticancer agent relies on the structural variability resulting from different extraction methods. Since sericin's bioactivity, including its ability to influence apoptosis, is highly dependent on its molecular weight, standardizing production is essential for achieving reproducible results. Furthermore, while the pro-apoptotic effects of sericin from in vitro studies are well-documented, there is currently a total absence of metastasis-specific models, even at the in vitro level. Basic assays for cell migration and invasion have yet to be conducted to determine if sericin can disrupt the initial stages of the metastatic cascade. However, the necessity for research extends beyond in vitro assays; in vivo models are urgently required to validate these findings within a complex physiological system. Unlike isolated cell cultures, animal models are essential to determine if sericin can survive systemic circulation and effectively inhibit the 'seeding' of secondary tumours in distant organs. Consequently, bridging this gap, by integrating both in vitro migration studies and in vivo metastatic assays, remains a fundamental hurdle for validating sericin's broader therapeutic potential.

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Conflict of interest

The authors declare no conflict of interest in this research.

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