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Umbilical Cord Wharton's Jelly–Derived Mesenchymal Stem Cells and Their Applications in Cancer: A Systematic Review

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Abstract: Mesenchymal stem cells derived from Wharton's Jelly (WJ-MSCs) and their cell-free products are emerging candidates for cancer therapy but show context-dependent effects. This systematic review synthesized preclinical *in vitro* and *in vivo* evidence on the anticancer and protumorigenic roles of WJ MSCs, their secretome, and extracellular vesicles (EVs) across diverse malignancies. Searches of PubMed, Scopus, and Springer Nature Link (English, up to August 2025) followed PRISMA guidance. Experimental studies using WJ-MSC-based interventions in cancer models were included, and two reviewers independently screened, extracted data, and assessed risk of bias using SYRCLE for animal studies and a QUIN-type tool for *in vitro* work. Twenty-six preclinical studies were eligible, predominantly *in vitro* with limited *in vivo* validation. Most reported antitumor effects—reduced proliferation, induction of apoptosis, inhibition of migration/epithelial–mesenchymal transition, and modulation of PI3K/AKT, NF-κB, and STAT3 pathways—whereas a smaller subset described enhanced growth, EMT, or activation of HGF–AKT/ERK and β-catenin signaling. Overall methodological quality was moderate to high, although reporting of randomization and blinding was often incomplete. Current evidence supports WJ MSC-derived secretome and EVs as promising, potentially safer anticancer and drug-delivery platforms, but standardized production protocols, rigorous safety evaluation, and well-designed animal and clinical studies are required before clinical translation.

Keywords: exosome; secretome; extracellular vesicle; WJ-MSC; EVs; cancer.

1. Introduction

Cancer is a non-communicable disease (NCD) health problem in the 21st century, with a mortality rate of almost one in six deaths (16.8%). This disease causes 10 premature deaths globally due to NCDs. It is one of the top 3 causes of death in the 30-69 age group in 177 of 183 countries [1]. Chemotherapy is the most effective treatment at this time, but it has problems with the emergence of resistance and rapid relapse. Conventional chemotherapy currently targets rapidly dividing cancer cells, accompanied by side effects due to its low specificity,

including nausea, hair loss, immunosuppression, and evasiveness [2]. As a result, knowledge is needed regarding effective alternative therapies. The latest strategy is to modify the ability of tumor cells to respond to effective treatments for aggressive cancers such as triple-negative breast cancer (TNBC) [3]. Modification of tumor cell capabilities can be achieved with a renewable therapeutic approach, one of which involves genetic modification of stem cells (e.g., ESCs, MSCs) through genetic engineering. One of the therapies is by utilizing Wharton's Jelly (WJ), which is a gelatin layer found in the umbilical cord. WJ is rich in mesenchymal stem cells (MSC) with bioactive content, such as secretome and exosomes, that have the potential for cancer therapy. WJ-MSCs can differentiate into multiple cell types, including adipocytes, osteocytes, and hepatocyte-like cells, making them versatile for regenerative medicine [4-7]. WJ-MSC is a medical waste that can be used as an innovative approach to stem cell therapy without the ethical considerations of embryonic stem cells.

Currently, WJ-MSC has been used in several therapeutic applications due to its regenerative ability in graft-versus-host-disease (GvHD) or organ transplantation, neurological disorders, organ damage, wound healing, and COVID-19 [8,9]. The role of WJ-MSCs in cancer is dual and context-dependent. Several studies report tumor-suppressive effects, whereas others show tumor-promoting actions. WJ-MSCs can inhibit tumors by modulating the tumor microenvironment and enhancing antitumor immune responses. They secrete bioactive molecules with cytotoxic activity against cancer cells; for example, conditioned medium from WJ-MSCs inhibits the proliferation of breast cancer cell lines and induces apoptosis via upregulation of genes such as p53, Bax, and Casp9 [10].

Conversely, some studies indicate that WJ-MSCs can promote cancer growth under specific conditions. WJ-MSC-derived microvesicles increase the aggressiveness of renal cancer cells by enhancing hepatocyte growth factor production, which in turn activates AKT and ERK1/2 signaling [11]. This duality requires further study and consideration to apply WJ-MSC and microvesicles to cancer therapy. Current preclinical evidence suggests that WJ-MSCs have a favorable safety and efficacy profile, with low immunogenicity and limited tumorigenic potential [12,13]. Their exosomes exert potent immunomodulatory effects, supporting the development of regenerative and anticancer applications [14]. However, careful clinical evaluation is still required to confirm effectiveness and to minimize the risk of cancer promotion. However, careful evaluation of the effectiveness and safety in clinical use is needed to utilize the potential of WJ-MSC and reduce the risk of cancer promotion. This review aims to systematically evaluate the current evidence on the dual roles of WJ-MSCs and their extracellular vesicles in cancer therapy, highlighting their tumor-suppressive mechanisms and their potential tumor-promoting effects. This study aims to provide a comprehensive understanding of WJ-MSC-based therapies, identify key information gaps, and inform the formulation of safe and effective therapeutic guidelines for their application in cancer.

2. Materials and Methods

This study used a systematic review to analyze research on Wharton's jelly mesenchymal stem cells for therapy. This systematic review was conducted according to the PRISMA statements [15]. By looking at journal citations, editorial input, and other metadata, it assessed the impact and value of publications and researchers in the field. The methodology of this systematic review used several databases, namely PubMed, Scopus, SAGE, Springer Nature Link, and DOAJ, across all categories. Keywords were formulated to facilitate the process of searching for articles and achieving the desired target. In this study, the keywords

used are "Wharton's Jelly Mesenchymal Stem Cells", "secretome", "extracellular vesicles", "exosome", "microvesicles", AND "cancer". Inclusion criteria included articles about Wharton's jelly mesenchymal stem cells AND cancer. Exclusion criteria included articles that used Wharton's Jelly Mesenchymal Stem Cells for non-cancer applications, review articles without original data, conference abstracts, and non-English publications. This was performed on a single day to avoid daily updating bias since the database is still open. A flow diagram

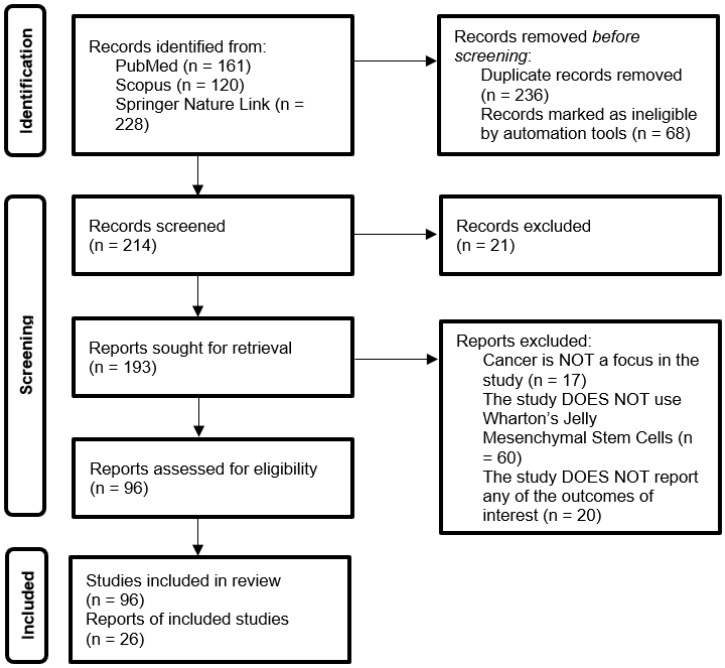

Figure 1 shows the record selection process. To capture the latest advancements, including studies published up to 2025, only recent and English-language papers were included. To enhance transparency of the results and underscore the potential risk of bias in the included studies, two quality assessment tools were used. For *in vivo* studies that investigated WJ-MSC products using the SYRCLES' RoB checklist [16]. Risk of bias for animal (*in vivo*) studies was assessed using the SYRCLE Risk of Bias tool. Two reviewers (SK and AH) independently evaluated each included *in vivo* study across all SYRCLE domains, including sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias. For each domain, judgments were assigned as *low*, *unclear*, or *high* risk based on the information reported in the article. Any disagreements between reviewers were resolved through discussion, and a third reviewer (RM) adjudicated unresolved items to reach consensus. *In vitro* studies were evaluated separately using the *in vitro* risk-of-bias tool appropriate for cell-based experiments. The same reviewer procedure (two independent reviewers with a third as arbitrator) was applied to the *in vitro* assessments. For *in vitro* studies, we utilized a QUIN tool (Quality Assessment Tool For *In vitro* Studies) for assessing the potential risk of bias among *in vitro* studies [17-19].

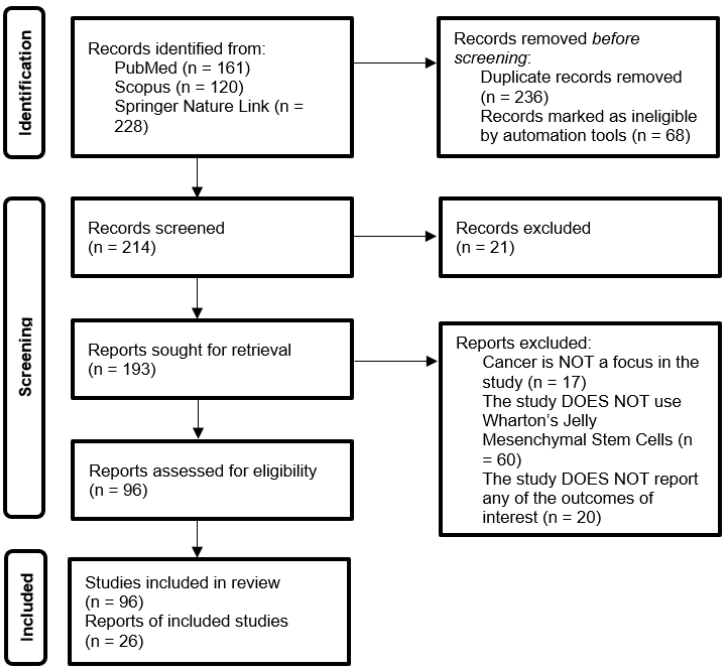

Figure 1. A flow diagram outlining the record identification and selection process.

3. Results and Discussion

3.1. Study selection.

The database search identified 509 records, of which 236 were duplicates, and 68 were excluded by automated tools during initial screening. The remaining 214 records were screened by title and abstract, resulting in the exclusion of 21 clearly irrelevant articles (e.g., non-WJ MSC sources, non-cancer indications). Full texts were sought for 193 records; 97 could not be retrieved or did not meet basic eligibility criteria, and 70 were excluded after detailed assessment because they did not use WJ-MSCs or their derivatives as the primary intervention, lacked cancer-related outcomes, or were non-original articles (reviews, editorials, conference abstracts). Ultimately, 26 preclinical studies fulfilled all inclusion criteria and were included in the qualitative synthesis, comprising predominantly *in vitro* experiments and a small number

of *in vivo* components, as summarised in the PRISMA flow diagram and Table 1 (Table 1;

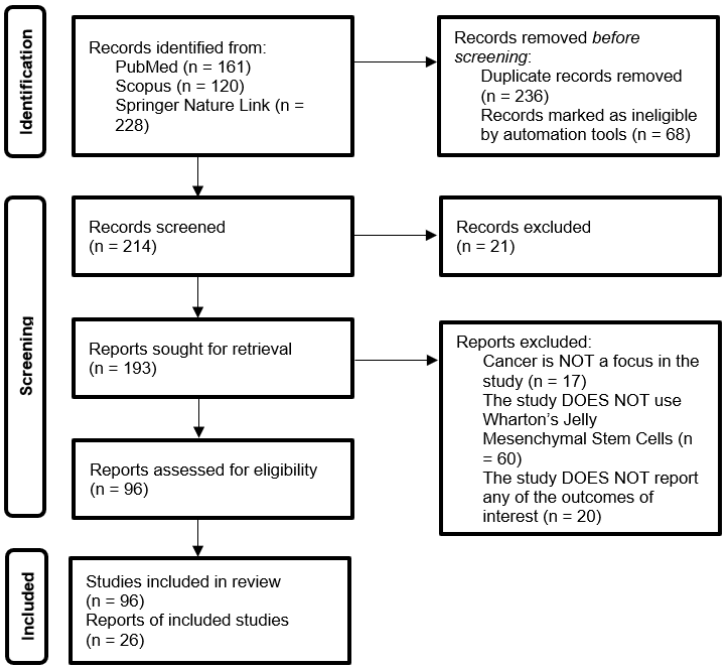

Figure **1**).

Table 1. Summary of included studies and essential characteristics.

No.	Author (Year)	Model	WJ-MSC product/intervention	Cancer type	Key outcomes	Direction of effect
1	Vahdanikia *et al*., 2020 [20]	*In vitro* (MDA-MB-231)	WJ-MSC conditioned medium	Breast cancer	Suppress tumor growth by reducing CXCR4 and VLA-4 expression	Anticancer
2	Iranifam *et al*., 2020 [21]	*In vitro* (DU145)	WJ-MSC conditioned medium	Prostate Cancer	Suppress tumor growth by reducing CXCR4 and VLA-4 expression	Anticancer
3	Abbasi *et al*., 2021 [22]	*In vitro* (AGS cells)	WJ-MSC conditioned medium and conditioned lysate	Human gastric adenocarcinoma	Downregulation of NF-κB and MAPK modification	Anticancer
4	Alidadi *et al*., 2024 [23]	*In vitro* (HT-29)	WJ-MSC conditioned medium	Colon carcinoma	Suppressing mitophagy	Anticancer
5	Hendijani *et al*., 2015 [24]	*In vitro* (A549)	WJ-MSC secretome	Lung cancer	Inhibit proliferation, apoptosis, and drug resistance	Anticancer
6	Kalamegam *et al*., 2019 [25]	*In vitro* (OVCAR3)	WJ-MSC conditioned medium	Ovarian cancer	Inhibit proliferation	Anticancer
7	Lin *et al*., 2017 [26]	*In vitro* (Ramos, CRL 1596)	WJ-MSC conditioned medium	Burkitt's Lymphoma	Induction of immunogenic cell death	Anticancer
8	Widowati *et al*., 2021 [10]	*In vitro* (T47D and MCF7)	WJ-MSC conditioned medium	Breast cancer	Inhibition of proliferation and induction of apoptosis	Anticancer
9	Gauthaman *et al*., 2012 [12]	*In vitro* (TOV-112D, MG-63, and MDA-MB-231)	WJ-MSC conditioned medium and conditioned lysate	Ovarian, osteosarcoma, and breast cancer	Increase in apoptosis	Anticancer
10	Said *et al*., 2022 [27]	*In vitro* (Scorpion Venom Breast Cancer)	WJ-MSC conditioned medium	Breast cancer	Increase in apoptosis	Anticancer
11	Ahmadpour *et al*., 2023 [28]	*In vitro* (SK-BR3)	WJ-MSC secretome	Breast cancer	Inhibit metastasis	Anticancer

No.	Author (Year)	Model	WJ-MSC product/intervention	Cancer type	Key outcomes	Direction of effect
12	Lin *et al*., 2014 [29]	*In vitro* (Human Burkitt's lymphoma cells)	WJ-MSC conditioned medium and conditioned lysate	Lymphoma	Increase in apoptosis	Anticancer
13	Rezaei-Tazangi *et al*., 2020 [30]	*In vitro* (HT-29)	WJ-MSC secretome	Colon carcinoma	Increase caspase and Bax/Bcl	Anticancer
14	Huwaikem *et al*., 2021 [31]	*In vitro* (K562)	WJ-MSC conditioned medium	Leukemia	Inducing Cell Cycle Arrest and Apoptosis	Anticancer
15	Aslam *et al*., 2021 [32]	*In vitro*	WJ-MSC conditioned lysate	Glioma	Downregulates KITLG (stem-cell factor)	Anticancer
16	Galliou *et al*., 2025 [33]	*In vitro* (RKO)	WJ-MSC conditioned medium	Colorectal cancer	Metabolic reprogramming, laminin-integrin adhesion signalling	Anticancer
17	Mirabdollahi *et al*., 2020 [34]	*In vivo* (murine with 4T1 cells) and *In vitro* (MCF-7 and 4T1)	WJ-MSC conditioned medium	Breast cancer	Inhibit cancer growth by paracrine delivery of bioactive cargo	Anticancer
18	Ababneh *et al*., 2025 [35]	*In vitro* (MCF-7 and A549)	WJ-MSC exosome	Breast cancer	Promote senescence-like features and migration	Pro-tumorigenic
19	Kaçaroğlu *et al*., 2025 [36]	*In vitro* (CRL 1469)	WJ-MSC exosome	Pancreatic ductal adenocarcinoma	Suppress tumor growth and modulate EMT	Anticancer
20	Chang *et al*., 2022 [37]	*In vitro* (MDAMB-231)	WJ-MSC exosome	Breast cancer	Inhibit tumor environment via miR-125b/HIF1 α signaling pathway	Anticancer
21	Karaoz *et al*., 2019 [38]	*In vitro* (ATCC CCL-218, ATCC CRL-1803, ATCC HTB-26)	WJ-MSC exosome	Epithelial Cancer: Human Colorectal Adenocarcinoma (HCA), Human Thyroid Carcinoma (CGTH), Mammary Gland Adenocarcinoma (MDA), Malignant breast stromal cell (MBSC)	Not promoting the proliferation	Anticancer
22	Du *et al*., 2014 [11]	*In vivo* (RCC line in male BALB/c nu/nu mice)	WJ-MSC secretome	Renal cancer	Induction of Hepatocyte Growth Factor	Protumorigenic
23	Abas *et al*., 2022 [39]	*In vitro* (HeLa and L929)	WJ-MSC exosomes loaded with Paclitaxel	Cervival cancer cells	Induce apoptosis and suppress EMT signaling	Anticancer
2	Sharif *et al*., 2017 [40]	*In vitro* (HEK293T and U87)	WJ-MSC transduced with miR-124	Glioblastoma Multiform Cells	Decreases proliferation and migration, and confers chemosensitivity	Anticancer
25	Seydi *et al*., 2024 [41]	*In vitro* (Huh-7 and HepG2)	WJ-MSC transduced with mir-29a	Hepatocelullar carcinoma	Induced apoptosis through autophagy blockage	Anticancer

No.	Author (Year)	Model	WJ-MSC product/intervention	Cancer type	Key outcomes	Direction of effect
26	Hosseini *et al*., 2024 [42]	*In vitro* (4TI) and *in vivo* Balb/C mice	WJ-MSC exosome loaded with S3I-201 (STAT3 inhibitor)	Breast cancer	Induced apoptosis through STAT3	Anticancer

3.2. Risk of bias and methodological quality assessment.

Risk of bias for animal (*in vivo*) studies was assessed using the SYRCLE RoB tool [16]. Two reviewers independently assessed each included animal study across the SYRCLE domains (sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias) (Table 2). For Du *et al*. (2014) [11], we judged sequence generation as low risk because the authors explicitly reported random allocation to groups and reported blinding of the histology assessor; however, allocation concealment, random housing, and blinding of caregivers/other outcome assessors were not reported (unclear) [11]. For Hosseini *et al*. (2024) [42], animals were stated to be randomly assigned to groups (low risk for sequence generation), but descriptions of allocation concealment, random housing, and assessor blinding were not provided (unclear) [42]. Overall, while ethical standards and comprehensive outcome reporting were evident, methodological details concerning randomization and blinding were limited, reflecting common challenges in preclinical animal research. These gaps underscore the importance of improving experimental transparency and bias mitigation strategies in future studies.

Table 2. Summary SYRCLE *risk of bias table for in vivo* studies.

Reference	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Performance blinding	Random outcome assessment	Detection blinding	Attrition bias	Reporting bias	Other sources of bias
[11]	+	?	?	?	+	?	?	?	+	?
[42]	+	?	?	?	?	+	?	?	?	?
[34]	+	+	?	?	?	?	+	+	?	?

(+) indicates low risk of bias; (-) indicates high risk of bias; (N.A.) Not applicable; (?) indicates unclear risk of bias.

Table 3. Summary of QUIN tool for *in vitro* studies.

Reference	Study objectives	Sample/source characterization	Experimental procedures	Controls and Comparators	Replicates/repeatability	Blinding	Randomization	Outcome assessment	Data/ statistics	Reporting transparency	Reproducibility	Conflict of interest
[10]	2	2	2	2	2	0	0	2	2	2	2	2
[11]	2	2	2	2	2	2	1	2	2	2	2	2
[12]	2	2	2	2	2	0	0	2	2	1	2	2
[42]	2	2	2	2	2	1	2	2	2	2	2	2
[34]	2	2	2	2	2	1	1	2	2	2	2	2
[43]	2	2	2	2	2	0	0	2	2	2	2	2
[44]	2	2	2	2	2	0	0	2	2	2	2	2
[45]	2	2	2	2	2	0	0	2	2	2	2	2
[36]	2	2	2	2	1	0	1	2	2	2	1	2
[41]	2	2	2	2	2	2	2	1	1	2	2	2
[22]	2	2	2	2	2	2	0	1	2	2	2	2
[30]	2	2	2	2	2	0	1	2	2	2	2	2
[37]	2	2	2	2	2	0	1	2	2	2	2	2
[29]	2	2	2	2	2	0	0	2	2	1	2	2

Reference	Study objectives	Sample/source characterization	Experimental procedures	Controls and Comparators	Replicates/repeat ability	Blinding	Randomization	Outcome assessment	Data/ statistics	Reporting transparency	Reproducibility	Conflict of interest
[25]	2	2	2	2	2	0	0	2	2	2	2	2
[20]	2	1	2	2	1	0	0	2	2	2	1	2
[31]	2	2	2	2	2	0	0	2	2	2	2	2
[35]	2	2	2	2	2	1	0	2	2	2	2	2
[28]	2	2	2	2	1	0	0	2	2	2	2	2
[46]	2	2	2	2	2	1	0	2	2	2	2	2
[38]	2	2	2	2	2	0	0	2	2	2	2	1
[32]	2	2	2	2	2	0	0	2	2	2	2	2
[47]	2	2	2	2	2	0	0	2	2	2	2	2
[39]	2	2	2	2	2	0	0	2	2	2	2	2
[40]	2	2	2	2	2	0	0	2	2	2	2	2

0 = not specified; 1 = inadequately specified, 2 = adequately specified.

Across all included *in vitro* studies evaluating Wharton's jelly mesenchymal stem cells (WJ-MSCs), their conditioned media, exosomes or microvesicles against diverse cancer models (glioma, lung, cervical, renal, gastric, colorectal, ovarian and breast cancer), methodological quality by the 12-item QUIN tool was consistently high, with total scores typically between 17–22/24, indicating overall low risk of bias (Table 3). Most studies clearly defined objectives, thoroughly characterized WJ-MSCs and their derivatives (surface markers, tri-lineage differentiation, and EV markers), detailed preparation of secretome/lysate/exosomes including loading procedures for drugs or miRNAs, used appropriate cancer and control cell lines (and in several cases *in vivo* tumor models), and applied validated outcome assays (MTT/BrdU, apoptosis by Annexin V/7-AAD, cell-cycle, migration/scratch, clonogenic, Western Blot, qPCR, cytokine/chemokine profiling, and, where relevant, xenograft growth and survival). Statistical methods (ANOVA or equivalent with post hoc tests, clear reporting of n, variance, and p values) and reporting transparency were generally robust, with sufficient procedural detail to permit replication. The main recurrent weaknesses across papers were a lack of explicit blinding of outcome assessment and limited reporting of randomization at the well/plate level, which reduced scores in those domains but did not critically undermine internal validity given predominantly automated readouts. Overall, the QUIN assessments support that the body of WJ-MSC–based *in vitro* evidence is methodologically sound, with reproducible protocols and biologically coherent effects, making these studies suitable for inclusion in higher-level syntheses while acknowledging the usual *in vitro* limitations regarding blinding and random sequence generation.

3.3. Mesenchymal stem cells from Wharton's jelly.

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that can differentiate into mesodermal lineages, including osteoblasts, adipocytes, and chondrocytes [48-50]. They can be extracted from many tissues, including bone marrow, adipose tissue, liver, amniotic fluid, lung, skeletal muscle, and kidney, each source providing distinct biological properties and therapeutic possibilities [51]. In addition to their anticancer properties, WJ-MSCs are attractive because they can be collected without ethical or invasive concerns, expanded *in vitro* at scale, and used as carriers for gene or drug delivery. Compared with embryonic stem cells, they produce higher levels of anti-inflammatory cytokines and carry a lower risk of tumor

formation [52-55]. Their origin from youthful perinatal tissue confers strong regenerative potential and low immunogenicity, and safety studies suggest a more favorable safety profile than other MSC sources, with a reduced likelihood of adverse events or tumorigenicity [56]. Their combined attributes have established MSCs as favorable candidates for cell-based treatments for a wide array of illnesses.

Wharton's Jelly mesenchymal stem cells (WJ-MSCs), obtained from the gelatinous matrix of the umbilical cord, have garnered significant attention as a promising and beneficial alternative [57,58]. In contrast to bone marrow MSCs (BM-MSCs), which are extracted invasively from the iliac crest, and adipose-derived MSCs (AT-MSCs), usually procured via liposuction, WJ-MSCs are isolated non-invasively and have superior *in vitro* expansion capabilities. BM-MSCs and AT-MSCs have use in hematopoietic support and regenerative applications, respectively [59-61]. Still, their application in oncology is constrained by challenges such as tumor-promoting effects and donor-dependent variability. Conversely, WJ-MSCs exhibit reduced immunogenicity, higher proliferation rates, and greater antitumor efficacy, rendering them particularly appropriate for oncological applications [62,63].

Their unique secretome profile underpins the therapeutic superiority of WJ-MSCs. Conditioned media derived from Wharton's Jelly mesenchymal stem cells (WJ-MSCs) have demonstrated the ability to inhibit the proliferation and migration of glioblastoma cells, specifically arresting U87MG cells in the G1 phase. In contrast to the secretome of bone marrow-derived mesenchymal stem cells (BM-MSCs), it does not stimulate fibroblast growth, underscoring a more selective and potent anti-glioma effect [46]. Moreover, WJ-CM specifically stimulates the TREM1 and NF-κB pathways, as well as the complement and coagulation cascades, thereby augmenting innate immune activation. This results in enhanced recruitment of macrophages and platelets, and the inhibition of glioma stem cell-associated genes, including LIN28B, ABCG2, and EPCAM [32].

Evidence also corroborates the application of WJ-MSCs in hematological malignancies. Wharton's jelly-derived mesenchymal stem cells from the umbilical cord inhibit the proliferation of multiple myeloma by upregulating p53 and downregulating CDK6 and Cyclin E1, thus generating G0/G1 cell cycle arrest and apoptosis. They also impede migratory and metastatic capability by regulating epithelial–mesenchymal transition, diminishing N-cadherin and elevating E-cadherin, while decreasing stemness-associated markers NANOG, SOX2, and OCT4. Moreover, WJ-MSCs reduce the release of pro-tumor cytokines, including IL-6 and VEGFA, and inhibit the PI3K/AKT/NF-κB signaling pathway, a significant contributor to myeloma progression [64].

In addition to their anticancer properties, WJ-MSCs are beneficial since they may be obtained without ethical or invasive issues, cultured *in vitro* for scalability, and utilized as effective carriers for gene or drug delivery in cancer treatment [65]. In contrast to embryonic stem cells, they generate elevated quantities of anti-inflammatory cytokines while presenting a minimal risk of tumor formation [12]. Their derivation from biologically advantageous, youthful tissue confers significant regenerative potential and minimal immunogenicity [66]. Significantly, safety studies indicate that WJ-MSCs possess a superior safety profile relative to alternative MSC sources, exhibiting a diminished likelihood of adverse effects or tumorigenicity [67]. Collectively, these data establish WJ-MSCs as a preeminent source of MSCs for cancer treatment. Although BM-MSCs and AT-MSCs are significant in regenerative and hematopoietic contexts, WJ-MSCs offer distinct advantages, combining accessibility,

safety, and robust antitumor properties, making them exceptionally promising for direct cancer intervention and supportive tissue regeneration post-conventional therapies.

3.4. Source and isolation of WJ-MSCs.

Wharton's Jelly (WJ) is a gelatinous connective tissue within the umbilical cord and represents a rich source of mesenchymal stem cells (MSCs), which can be collected at birth. Several techniques have been developed to isolate WJ-MSCs, primarily categorized into explant-based and enzymatic digestion–based methods. The explant method involves excising small fragments of Wharton's jelly tissue and directly culturing them, allowing MSCs to migrate out into the surrounding medium [68,69]. Culture conditions are critical for maximizing yield and maintaining MSC characteristics. Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% human platelet lysate (HPL) has been identified as particularly effective, supporting robust proliferation, preservation of MSC markers, and multilineage differentiation [70]. For translational and clinical applications, xeno-free media are strongly recommended to avoid animal-derived components and further enhance the immunomodulatory properties of WJ-MSCs [71].

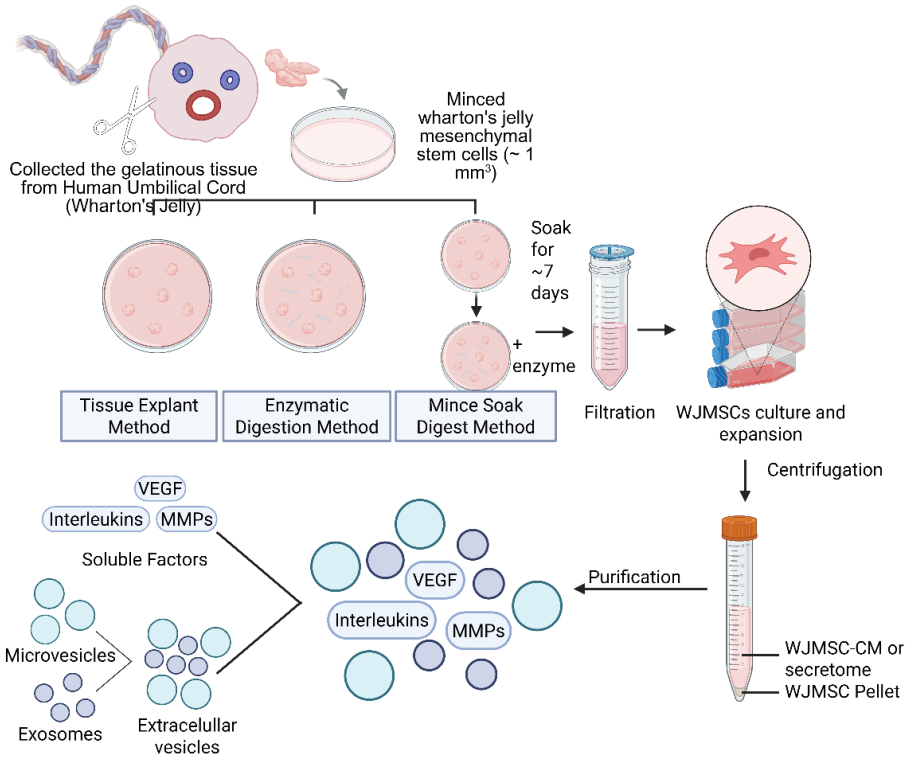

Figure 2. Wharton's Jelly Mesenchymal Stem Cells (WJ-MSC) extraction process. Created in BioRender. (https://BioRender.com/325ddqe)

In contrast, the enzymatic digestion method accelerates MSC release by exposing minced Wharton's jelly tissue to proteolytic enzymes such as trypsin, hyaluronidase, and collagenase [68]. Each enzyme plays a complementary role: collagenase cleaves collagen fibers forming the structural backbone; hyaluronidase degrades hyaluronic acid to reduce viscosity and improve penetration; trypsin disrupts adhesion proteins to facilitate single-cell suspension; and DNase I removes extracellular DNA from lysed cells to prevent clumping. Compared with the explant method, enzymatic digestion requires only hours rather than days, yields significantly higher cell numbers, and reduces the risk of microbial contamination from prolonged tissue culture [66]. Notably, this approach yields highly viable MSCs that meet

International Society for Cellular Therapy (ISCT) criteria and achieve confluent cultures up to three times faster than those obtained through explantation [72]. A more recent refinement, the Mince–Soak–Digest (MSD) method, incorporates a soaking step before enzymatic digestion, thereby enhancing matrix breakdown and improving enzyme efficiency. This technique has been reported to increase cell yield by 4- to 10-fold compared to conventional methods while maintaining high purity and consistency [66]. The MSD method, therefore, offers a promising strategy for standardizing MSC isolation and minimizing inter-laboratory variability. As shown in Figure 2, WJ tissue obtained from the umbilical cord can be processed using various methods, including tissue explant, enzymatic digestion, and mince-soak digest.

3.5. Surface markers and differentiation capabilities.

Wharton's Jelly mesenchymal stem cells (WJ-MSCs) have a unique immunophenotype, marked by heightened expression of CD44, CD73, CD90, CD105, and CD166 *[70,73]*. According to the criteria established by the International Society for Cellular Therapy (ISCT), they lack hematological and endothelial markers, including CD34, CD45, CD116, CD19, and HLA-DR [70,74-76]. The lack of these markers is clinically significant, as hematopoietic and endothelial indicators are often associated with tumor proliferation, angiogenesis, and metastasis. Their lack in WJ-MSCs underscores the comparative safety of these cells in oncological applications [77]. In addition to their immunophenotype, WJ-MSCs exhibit remarkable multilineage differentiation potential. In appropriate culture conditions, they can differentiate into adipocytes, chondrocytes, osteocytes, myocytes, cardiomyocytes, neurogenic lineages (neurons and glial cells), and even oocyte-like cells [70,78]. This plasticity increases their relevance in regenerative medicine and experimental oncology. The expression of stemness-associated markers, the lack of hematopoietic and endothelial antigens, and significant differentiation potential highlight the dual therapeutic potential of WJ-MSCs: they are adaptable for tissue regeneration and relatively safe for cancer therapy due to their non-tumorigenic immunophenotype. Moreover, their marker profile suggests potential interactions with tumor microenvironments, making them a crucial model for studying cancer progression and treatment techniques.

3.6. Immunomodulatory and secretory characteristics.

Wharton's Jelly mesenchymal stem cells (WJ-MSCs) exhibit significant immunomodulatory properties, making them highly beneficial for immune-related conditions. They can inhibit lymphocyte proliferation and facilitate the expansion of regulatory T cells, which is especially advantageous in the management of graft-versus-host disease and autoimmune disorders [79]. WJ-MSCs modulate innate and adaptive immunological responses, inhibiting T cell proliferation and differentiation, particularly of pro-inflammatory Th1 and Th17 subsets, while increasing macrophage polarization towards the anti-inflammatory M2 phenotype [71,80]. The effects are partially mediated by the release of immunoregulatory cytokines, such as IL-10, HGF, VEGF, and TGF-β. WJ-MSCs and their conditioned supernatants may markedly suppress phytohemagglutinin-induced T lymphocyte proliferation, with inhibition rates dependent on concentration [81]. The immunomodulatory actions of WJ-MSCs are chiefly ascribed to their paracrine activity, facilitated by bioactive compounds and extracellular vesicles (EVs), including exosomes and microvesicles. These vesicles function as transporters of cytokines, chemokines, growth factors, lipids, and

regulatory nucleic acids, thereby modulating the immunological milieu and affecting tissue healing [82-84].

Expanding on this paracrine process, attention has shifted to cell-free therapies derived from MSCs, which aim to leverage their therapeutic potential while mitigating the risks associated with live-cell transplantation. The products encompass conditioned lysate, conditioned medium, the secretome, exosomes, and microvesicles, each comprising a diverse array of bioactive molecules, including proteins, nucleic acids, and signaling factors [82]. Conditioned medium comprises soluble components secreted during culture, whereas conditioned lysate denotes intracellular contents released upon cell destruction. The secretome includes all secreted compounds, such as soluble factors and vesicles. Exosomes are nanoscale carriers within these vesicles that facilitate intercellular communication through the transfer of RNAs and proteins, while microvesicles are larger entities released from the plasma membrane [85-89]. Compared with whole-cell transplantation, cell-free products derived from WJ-MSCs offer numerous advantages, including limited tumorigenicity, negligible immunogenicity, ease of storage and transport, reduced risk of rejection, and maintenance of regenerative and anti-inflammatory properties. These cell-free products can collectively control inflammation, enhance angiogenesis and tissue healing, and alter tumor microenvironments. This renders them appealing and pragmatic substitutes for direct MSC therapy, with enhanced safety profiles and translational potential for clinical applications.

3.7. Antitumorigenic effects of Wharton's jelly mesenchymal stem cells.

Wharton's Jelly Mesenchymal Stem Cells (WJ-MSCs) have attracted considerable interest in oncology due to their unique biological properties and promising preclinical results. Unlike other specific sources of mesenchymal stem cells (MSCs), such as bone marrow or adipose tissue, Wharton's Jelly-derived MSCs (WJ-MSCs) are relatively primitive, exhibit low immunogenicity, and have a reduced propensity to develop into tumor-associated fibroblasts. These attributes provide a theoretical foundation for their enhanced application in cancer therapy [39]. Experimental investigations increasingly demonstrate that WJ-MSCs, their conditioned media, and their extracellular products, including exosomes, microvesicles, and secretomes, exhibit notable anticancer properties [29]. The effects are mediated by several mechanisms, including the induction of apoptosis, inhibition of proliferation, suppression of metastasis, modulation of the immune environment, and decrease of pro-survival signaling pathways. At the cellular level, WJ-MSCs have cytotoxic and proapoptotic effects on many cancer cell lines, including leukemia, glioma, colorectal carcinoma, and breast carcinoma. For instance, direct co-culture or treatment with WJ-MSC preparations has been shown to reduce cell viability and induce traditional apoptotic characteristics, such as nuclear condensation, membrane blebbing, and DNA fragmentation [82]. These advantages appear to depend on both dosage and duration, underscoring the therapeutic potential of WJ-MSCs and the importance of precise dosing protocols in translational applications.

WJ-MSCs demonstrate their anticancer effects via direct cell–cell interactions and paracrine signaling pathways. The paracrine effects are enabled by the secretion of many bioactive molecules, including exosomes abundant in tumor-suppressive miRNAs, cytokines exhibiting anti-proliferative properties, and soluble factors that can disrupt cancer-promoting pathways such as PI3K/Akt and MAPK. In prostate cancer models, the administration of 15–30% WJ-MSC preparations to DU145 cells led to a substantial, dose-dependent reduction in cell viability, accompanied by the downregulation of CXCR4 and VLA-4, two essential

homing receptors involved in metastatic colonization via the SDF-1/CXCR4 axis. This finding highlights the ability of WJ-MSCs to inhibit both primary tumor growth and metastatic dissemination [21]. Comparable results have been attained in breast cancer models. The administration of human Wharton's jelly mesenchymal stem cells (hWJSCs) to the aggressive triple-negative breast cancer cell line MDA-MB-231 significantly reduced cell viability in a dose- and time-dependent manner, resulting in IC_{50} values of 40 μM at 24 hours and 20 μM at 48 hours. Migration tests demonstrated a notable reduction in cell motility, suggesting that hWJSCs interfere with critical molecular processes that facilitate metastasis. Gene expression profiling confirmed the downregulation of pro-metastatic genes, including CXCR4 and VLA-4, supporting the idea that WJ-MSCs exhibit anti-metastatic effects by disrupting adhesion and migration processes [20]. The commencement of apoptosis is acknowledged as one of the most dependable anticancer mechanisms of WJ-MSCs. Multiple studies demonstrate that exposure to WJ-MSC secretome elevates reactive oxygen species (ROS) levels and disrupts mitochondrial membrane potential in cancer cells, hence triggering the intrinsic apoptosis pathway. This entails the overexpression of the proapoptotic gene Bax, downregulation of the anti-apoptotic protein Bcl-2, and activation of caspase-9 and caspase-3, culminating in DNA fragmentation and cellular death. In colon carcinoma cells (HT-29), the secretome of WJ-MSC suppressed proliferation and colony formation in a dose-dependent manner, while sparing normal fibroblasts, suggesting a degree of cancer selectivity [23,30].

WJ-MSC secretome induces mitochondrial apoptosis across several cancer models, typically accompanied by ROS increase, loss of mitochondrial membrane potential, and modulation of Bax/Bcl-2 and caspases, as outlined in the mechanistic overview section. In HT-29 colon carcinoma cells, WJ-MSC secretome reduced proliferation and colony formation in a dose-dependent manner while sparing normal fibroblasts, indicating selective cytotoxicity [31,47]. In K562 leukemia cells, WJ-MSC-derived conditioned media and lysate increased G_2/M arrest and strongly upregulated BAX and CASP3 while reducing BIRC5, together with a shift from pro-inflammatory (IFN-γ, TNF-α, IL-1β, IL-6, IL-8, IL-12) to anti-inflammatory cytokines (IL-4, IL-10), which supports both direct cytotoxic and microenvironment-modulating antileukemic effects [40,46].

Besides apoptosis, WJ-MSCs and their derivatives have anti-angiogenic and immunomodulatory characteristics. For example, intratumoral administration of WJ-MSC secretome in mice with breast cancer significantly reduced tumor size, inhibited angiogenesis, and improved hematological parameters, hence enhancing survival rates. The secretome is rich in cytokines, including IL-1α, IL-1β, IL-6, IL-8, and GM-CSF, which can modulate the tumor immune microenvironment in a context-dependent fashion. At high doses, specific pro-tumorigenic cytokines may emerge; nevertheless, balanced secretome formulations have shown efficacy in augmenting anticancer immunity by upregulating IL-2 and GM-CSF, which activate cytotoxic T cells and NK cells [34,43]. This dualistic effect underscores the need for dose adjustment and cytokine assessment prior to therapy initiation.

Exosomes derived from WJ-MSCs exhibit significant therapeutic potential. Extracellular vesicles can transmit tumor-suppressive miRNAs, such as miR-125b, to triple-negative breast cancer (TNBC) cells, resulting in the downregulation of HIF1α and the inhibition of pathways associated with stemness and metastasis [90]. In bladder cancer, WJ-MSC microvesicles induced apoptosis and cell cycle arrest, reducing tumorigenicity both *in vitro* and *in vivo* [91]. Alginate-encapsulated WJ-MSCs (eWJ-MSCs) demonstrated substantial anticancer stem cell efficacy by obstructing migration, invasion, and angiogenesis in breast

cancer stem cell models. They mechanistically impaired Wnt/β-catenin signaling, diminished epithelial-mesenchymal transition indicators such as N-cadherin, and elevated epithelial markers like E-cadherin, hence rectifying drug-resistance traits [92].

These data collectively highlight the several anticancer mechanisms of WJ-MSCs, including the induction of apoptosis, inhibition of proliferation and migration, immunological modulation, and anti-angiogenic effects. Notably, WJ-MSCs generally avoid developing into tumor-promoting fibroblasts, a common drawback linked to other MSC sources. The selective anticancer characteristics, along with low immunogenicity and abundant availability from umbilical cords, position WJ-MSCs as a highly attractive stem cell platform for oncology. The variability in results across different cancer types and experimental conditions indicates that their effects are context-dependent. Certain data indicate that under specific tumor microenvironmental settings, WJ-MSCs may adopt pro-tumorigenic roles, facilitating immune evasion or enhancing angiogenesis. Future investigations should clarify the molecular switches that regulate this dual behavior, ensuring that therapy formulations consistently emphasize tumor suppression over tumor promotion.

3.8. Pro-tumorigenic risks linked to Wharton's jelly mesenchymal stem cells.

Although Wharton's Jelly Mesenchymal Stem Cells (WJ-MSCs) exhibit promising anticancer properties, growing evidence also highlights their potential pro-tumorigenic effects. These hazards appear to be dependent on context, varying with cancer subtype, tumor microenvironment, and specific cellular or vesicular products produced. WJ-MSCs can affect lung cancer stem cells (LCSCs) in a subtype-specific manner. Treatment with WJ-MSC-conditioned medium significantly enhanced cell proliferation, S-phase entry, and the proportion of CD133 and ALDH-positive cells in adenocarcinoma-derived LCSCs. The co-transplantation of these cells with WJ-MSCs *in vivo* accelerated tumor progression, increased xenograft size, and amplified stem-like subpopulations. In contrast, squamous cell carcinoma-derived LCSCs showed unique responses, including growth inhibition, induction of apoptosis, and reduced stemness, although their tumorigenic capacity remained mostly unaffected by co-transplantation [93]. This duality underscores the importance of cancer subtype in influencing the effects of WJ-MSCs. Besides lung cancer, WJ-MSCs have shown the capacity to promote tumor proliferation in several other malignancies. Gastric cancer exhibits an overexpression of stemness-associated genes and the activation of oncogenic signaling pathways, such as NF-κB, STAT3, and β-catenin [94]. Mesenchymal stem cells can facilitate tumor progression by promoting immunosuppression, angiogenesis, epithelial–mesenchymal transition (EMT), and the proliferation of cancer stem cell populations [95,96]. In some environments, they may differentiate into cancer-associated fibroblasts, hence providing structural and paracrine support for tumor advancement.

Extracellular vesicles (EVs) produced by WJ-MSCs promote pro-tumorigenic activity. Microvesicles (MVs) originating from WJ-MSCs have demonstrated the ability to augment proliferation, migration, and invasion of renal cell carcinoma (RCC) by facilitating cell cycle progression and activating the AKT and ERK1/2 signaling pathways. These vesicles further augment the expression of hepatocyte growth factor (HGF) in renal cell carcinoma (RCC) cells, leading to expedited and amplified tumor progression *in vivo*. Significantly, WJ-MSC-conditioned medium had similar effects, suggesting that MVs are essential mediators of these

responses [11]. WJ-MSC-derived EVs have been shown to enhance breast cancer cell migration and invasion by promoting epithelial-mesenchymal transition through ERK signaling [97,98]. Recent research demonstrates that exosomes derived from WJ-MSCs enhance the migratory capacity of MCF-7 breast cancer and A549 lung cancer cells, highlighting their role in facilitating invasive phenotypes [35].

These data collectively suggest that while WJ-MSCs and their derivatives have therapeutic promise, they also pose risks by promoting tumorigenesis, stemness, angiogenesis, and invasion through paracrine signaling and the activation of oncogenic pathways. The therapeutic use of WJ-MSCs in oncology requires careful consideration, with rigorous preclinical assessments necessary to minimize risks and define the conditions under which their application may be safe and effective.

3.9. Composition of WJ-MSC-derived secretome.

The secretome of Wharton's Jelly Mesenchymal Stem Cells (WJ-MSCs) comprises a complex array of soluble proteins, cytokines, chemokines, growth factors, and extracellular vesicles (EVs), including exosomes and microvesicles. These bioactive constituents are widely acknowledged as the principal mediators of WJ-MSC paracrine activity, providing a cell-free treatment strategy with extensive anticancer potential (Table 4). Hendijani *et al*. (2015) initially documented quantifiable protein levels in WJ-MSC conditioned media (CM), which augmented upon stimulation, underscoring its dynamic reactivity [24]. Subsequently, Hendijani *et al*. (2015) [47] revealed that the WJ-MSC secretome reduced leukemia cell proliferation by approximately 50% and augmented the cytotoxic effectiveness of liposomal doxorubicin to exceed 90%, indicating that secretome-based therapy may diminish chemotherapy dosages and related toxicities while maintaining efficacy [47].

Numerous investigations show that WJ-MSC-conditioned medium induces apoptosis through intrinsic mitochondrial pathways in breast and other solid tumors, consistent with the mechanisms summarised in the mechanistic overview. In MCF-7 cells, this is accompanied by changes in Bax, Bcl-2, and caspases [27], while in osteosarcoma WJ-MSC products activate both apoptosis and autophagy (ATG5, ATG7, Beclin-1) [12], suggesting complementary death programs triggered by the secretome. Metabolic reprogramming constitutes another essential target of the WJ-MSC secretome. Said *et al*. (2021) indicated that CM administration inhibited critical glycolytic enzymes, including ALDOA and PKM2, in MCF-7 cells, hence undermining the Warburg effect and depriving tumor cells of their preferred energy source [27]. Likewise, hypoxia-preconditioned cardiomyocytes elicited heightened death in lymphoma cells by augmenting oxidative stress, elevating caspase activation, and intensifying lipid peroxidation, thereby combining direct cytotoxicity with metabolic disturbance [44]. These findings highlight the impact of oxygen tension and preconditioning on the composition and efficacy of the secretome.

In addition to direct lethal effects, the WJ-MSC secretome influences the tumor microenvironment by altering cytokine profiles. In ovarian cancer cells, both conditioned media and cell lysate decreased pro-tumor cytokines (IL-1β, IL-6, TNF-α, G-CSF) and chemokines (MCP-1, RANTES, MIG/CXCL-9) while slightly increasing antitumor cytokines such as IL-2, IL-12, and IFN-γ [25]. Lin *et al*. (2017) [26] demonstrated that WJ-MSC-CM prompted immunogenic cell death (ICD) in lymphoma, characterized by the exposure of calreticulin, HSP70, and HMGB1 as "eat-me" signals, while concurrently downregulating PD-

L1 and CD47 [26]. This dual action not only eradicated tumor cells but also augmented their detection by dendritic cells, thereby triggering adaptive immune activation.

The influence of oxygen circumstances on secretome composition underscores its plasticity. Widowati *et al*. (2021) [99] demonstrated that normoxia-conditioned medium (norCM) inhibited breast cancer proliferation more effectively than hypoxia-conditioned medium (hypoCM), attributable to reduced concentrations of angiogenic and survival cytokines, including VEGF and IL-6, in norCM. In contrast, hypoCM released elevated quantities of VEGF and inflammatory interleukins, which can inhibit apoptosis via PI3K/AKT activation [99]. These data highlight that normoxic CM may constitute a safer, more tumor-suppressive alternative for therapeutic use.

Table 4. Secretions of Wharton's jelly mesenchymal stem cells affect cancer.

Effect	Mechanism of Action	Cancer Model	Reference
Apoptosis effects	Modification of MAPK and NF-κB signaling pathways	Human gastric adenocarcinoma (AGS cells)	[22]
Cytotoxic effects	Disruption of the PINK1/Parkin pathway, increased BAX/BCl2 ratio.	Colon carcinoma (HT-29)	[23]
No tumorigenic effect and no drug resistance	MSC-derived protective factors that buffer drug-induced ROS or block caspase activation.	Lung cancer (A549)	[47]
Cytokine modulation	Decrease in oncogenic cytokines, increase in antitumor cytokines.	Ovarian cancer (OVCAR3)	[25]
Induction of ICD	Apoptosis, mitochondrial stress, and DAMP release.	Burkitt's Lymphoma (Ramos, CRL 1596)	[26]
Gene Expression Modulation	Apoptosis and autophagy-related genes.	Breast cancer (T47D and MCF7)	[10]
Growth inhibition,	Induction of apoptosis, induction of autophagy, inhibition of migration, and cell cycle arrest.	Ovarian, osteosarcoma, and breast (TOV-112D, MG-63, and MDA-MB-231)	[12]
Apoptosis via Gene Regulation	Apoptosis, cell cycle arrest, and glycolytic metabolism.	Scorpion Venom Breast Cancer Cell Line	[27]
Anti-proliferative, pro-apoptotic, antioxidant enhancement, and EMT modulation	Paracrine signaling enhances antioxidant defenses, restoring redox balance, and inhibits the transition that enables metastasis.	Breast cancer (SK-BR3)	[28]
Reduced proliferation and apoptosis	Oxidative stress induced apoptosis and cell cycle arrest.	Human Burkitt's lymphoma cells	[29]
Apoptosis Induction	Increasing caspase and Bax/Bcl activity to prevent cell growth also enhanced colon cancer cell death.	Colon carcinoma (HT-29)	[30]
Inducing Cell Cycle Arrest and Apoptosis	increasing the expression of pro-apoptotic genes such as BAX and CASP3, while decreasing anti-apoptotic genes like BIRC5 (Survivin).	Chronic myeloid leukemia (CML) (K562)	[31]
Cell Cycle Arrest	Downregulates KITLG (stem-cell factor) to blunt PI3K/AKT, Ras/MAPK, Rap1, and PLD signaling.	Glioma Cells (U87MG)	[46]
Suppress growth	Metabolic reprogramming, laminin-integrin adhesion signaling, oxidative stress resistance.	Colorectal Cancer (RKO)	[33]
Inhibit proliferation and slow tumor progression	Paracrine delivery of bioactive cargo, epigenetic and hematologic restoration.	*In vivo* murine breast carcinoma cells 4T1 cells, and *in vitro* breast cancer (MCF-7 and 4T1)	[43]
Induction of apoptosis	Downregulation of metastasis-related genes of CXCR4 and VLA-4	*In vitro* breast cancer (MDA-MB-231)	[20]

Effect	Mechanism of Action	Cancer Model	Reference
Induction of apoptosis	Downregulation of metastasis-related genes of CXCR4 and VLA-4	*In vitro* prostate cancer (DU145)	[21]

The WJ-MSC secretome exhibits effectiveness across a wide range of malignancies. In colorectal cancer, WJ-MSCs polarized to the MSC1 phenotype released proteins that diminished tumor viability while reprogramming metabolism and maintaining extracellular matrix connections [33]. In HER2-positive breast cancer, secretome treatment induced apoptosis, reduced colony formation, and modulated epithelial-to-mesenchymal transition (EMT) markers by downregulating E-cadherin and β-catenin and upregulating N-cadherin and vimentin, thereby inhibiting metastatic potential [28]. The multimodal effects indicate that the WJ-MSC secretome not only exhibits direct cytotoxicity but also affects invasion, metabolism, and immune response, rendering it a multifaceted candidate for cancer therapy.

Wharton's jelly mesenchymal stem cells (hWJSCs), delivered as either conditioned medium or cell-free lysate, exert potent anticancer effects on AGS gastric cancer cells by reducing viability, migration, and invasion in a time- and dose-dependent manner; inducing apoptosis via upregulation of pro-apoptotic genes (BAX, SMAC) and downregulation of anti-apoptotic genes (BCL2, SURVIVIN); suppressing NF-κB signaling (decreased p65, increased IκB); and activating MAPK signaling (increased total and phosphorylated p38, JNK, and ERK1/2), together highlighting their promise as a natural, non-toxic therapeutic strategy against gastric cancer [22].

The secretome generated from WJ-MSCs presents a versatile, cell-free therapeutic platform. Its anticancer mechanisms include mitochondrial apoptosis, production of oxidative stress, metabolic disruption, cytokine modulation, immunological activation, and regulation of epithelial-mesenchymal transition (EMT). The incorporation of soluble components and extracellular vesicles facilitates synchronized tumor reduction by direct cytotoxicity and indirect immune-mediated mechanisms. Nonetheless, pinpointing the exact bioactive compounds, standardizing secretome preparation, and assessing safety in preclinical models are crucial further stages prior to clinical application.

3.10. Composition of WJ-MSC-derived extracellular vesicles.

Extracellular vesicles are crucial in conveying signals originating from WJ-MSCs. Exosomes and microvesicles transport tumor-suppressive microRNAs, including miR-146a and miR-126, which modulate the NF-κB and angiogenesis pathways, respectively, so facilitating the prolonged inhibition of cancer cell viability [26]. Extracellular vesicles (EVs) also convey ligands such as TRAIL, BMPs, and THBS1, which facilitate apoptosis and inhibit tumor development [33]. Size-fractionation tests indicated that the most tumoricidal activity is found in secretome fractions exceeding three kDa, implying that proteins, vesicles, and regulatory RNAs are the primary effectors [29].

Exosomes originating from Wharton's Jelly mesenchymal stem cells (WJ-MSCs) are nanoscale extracellular vesicles (30–150 nm) that transport a diverse array of bioactive chemicals essential for intercellular communication. These vesicles encompass proteins, including fibrinogen, which is pertinent to wound healing and keratinocyte proliferation, as well as nucleic acids, lipids, and signaling molecules that affect the behavior of recipient cells [82]. The broader secretome includes cytokines, chemokines, growth factors, metabolites, and

larger extracellular vesicles such as microvesicles (100 nm–1 μm), which have overlapping contents with exosomes but vary in size and biogenesis [100].

Recent evidence underscores the multifaceted involvement of WJ-MSC-derived exosomes (WJ-MSC-Exos) in cancer biology (Table 5). These vesicles are laden with microRNAs (miRNAs) that produce context-specific effects on tumor cells. For instance, miR-125b has been demonstrated to inhibit the proliferation of breast cancer (MDA-MB-231), epithelial–mesenchymal transition (EMT), and angiogenesis by directly targeting HIF1α. Pathway analysis discovered other HIF1α-regulating miRNAs, including let-7a, miR-7a, miR-9, miR-17, miR-21, miR-30c, miR-100, miR-191, miR-221, miR-146a, miR-503, and miR-504, which contribute to intersecting signaling networks. Notably, tumor-suppressive miRNAs such as miR-148a, miR-200b, miR-452, miR-548d-1, miR-2682, and miR-5094 are upregulated in WJ-MSC-Exos, whereas several pro-tumorigenic miRNAs including miR-18a, miR-29b-1, miR-382, miR-4521, miR-505, miR-579, and miR-6501 are downregulated, indicating a net antitumorigenic profile. The molecular alterations are associated with diminished secretion of pro-inflammatory cytokines, including IL-6 and TGF-β, and reduced expression of CXCR4 in breast cancer cells, consequently inhibiting angiogenesis and the development of cancer-associated fibroblasts within the tumor microenvironment [37].

Notwithstanding these tumor-suppressive actions, WJ-MSC-Exos have intricate and occasionally contradictory roles. In MCF7 breast cancer and A549 lung cancer cells, they elicit senescence-like states marked by SA-β-Gal activity and elevation of p53/p21^Cip1, although this impact is temporary in A549 cells. Furthermore, WJ-MSC-Exos can augment cell migration, prompting apprehensions about their dual function in cancer advancement [35]. Du *et al*. (2014) [11] similarly demonstrated that microvesicles (MVs) derived from WJ-MSCs convey HGF mRNA to renal carcinoma cells, resulting in HGF protein expression and the activation of AKT and ERK1/2 pathways, hence enhancing proliferation, migration, and tumor aggressiveness *in vivo* [11].

Proteomic and immunological analysis further highlights the therapeutic intricacy of vesicles produced from WJ-MSCs. Li *et al*. (2021) [101] found exosomal markers (CD9, CD63, CD81), chaperones (HSP70), and immune checkpoint ligands (PD-L1, PD-L2) in WJ-MSC exosomes, indicating immunomodulatory potential. Exosomes carrying PD-L1 have been suggested to mitigate graft-versus-host disease (aGvHD) and may intriguingly modulate tumor immune evasion through PD-L1/CD80 interactions [101]. Kaçaroğlu *et al*. (2025) [36] measured the cytokine composition of WJ-MSC exosomes, indicating substantial levels of IL-1RA, IL-6, TNF-α, IL-1β, and IL-10, and revealed their capacity to inhibit epithelial-mesenchymal transition (EMT), induce G1 phase arrest, and facilitate apoptosis in cancer cells [36]. Nonetheless, their immunosuppressive cytokine profile suggests the potential to inhibit antitumor immunity, suggesting a more prudent application as drug delivery vehicles rather than as direct treatments.

Table 5. Extracellular vesicles derived from Wharton's jelly-derived mesenchymal stem cells affect cancer.

Part	Effect	Mechanism	Cancer Type	Reference
Exosome	Promotes senescence-like features and migration in cancer	Induced senescence-associated secretory phenotype (SASP).	Breast cancer (MCF7 and A549 cells).	[35]
Exosome	Suppress tumor growth and modulate EMT	Inducing G1 cell cycle arrest, promoting early apoptosis, reversing epithelial–mesenchymal transition, and modulating immune responses through	Pancreatic ductal adenocarcinoma (Panc-1/ATCC: CRL 1469)	[25]

		downregulation of pro-inflammatory cytokines and upregulation of IL-10.		
Exosome	Inhibit the tumor environment	HIF1α signaling pathway by miR-125-b.	Breast cancer (MDAMB-231)	[37]
Exosome	Not promote proliferation	Paracrine signaling via exosomes, downregulation of phosphorylated Akt, and induction of apoptosis via caspase-3 activation.	Epithelial Cancer: Human Colorectal Adenocarcinoma (HCA), Human Thyroid Carcinoma (CGTH), Mammary Gland Adenocarcinoma (MDA), Malignant breast stromal cell (MBSC)	[38]
Microvesicle	Promote cell growth and aggressiveness	Induction of hepatocyte growth factor.	Human renal cancer cell (RCC) line in male BALB/c nu/nu mice.	[11]

Additional studies support an overall antitumor profile of many WJ-MSC-derived vesicles: WJ-MSC exosomes are internalised by colorectal, thyroid and breast cancer cells without stimulating proliferation [38], and WJ-MSC microvesicles can induce G0/G1 arrest, increase p53 and cleaved caspase-3, and reduce Akt phosphorylation in bladder cancer models, thereby limiting tumor growth *in vitro* and *in vivo* [91]101]. These effects are partly mediated by transferred miRNAs, such as miR-124, miR-146b, and miR-16, which converge on Akt and the angiogenic pathways already discussed in the mechanistic overview [40,91,102].

Collectively, these data highlight the dual and context-dependent function of WJ-MSC-derived vesicles in cancer. Although their miRNA and protein cargos can reduce proliferation, angiogenesis, and epithelial-mesenchymal transition, they may also promote migration or establish immunosuppressive microenvironments. Therefore, meticulous mechanistic analysis and *in vivo* validation are crucial to ascertain whether WJ-MSC-Exos serve more effectively as direct anticancer agents or as bioengineered delivery systems for targeted therapeutics.

3.11. Wharton jelly mesenchymal stem cells and their products in drug delivery or combinational therapy.

Mesenchymal stem cells generated from Wharton's Jelly (WJ-MSCs) and their secretome present considerable potential as vehicles for sophisticated drug administration in oncology. Their minimal immunogenicity, capacity for tissue engraftment, and prolonged release of medicinal agents render them adaptable bioreactors. For instance, the intramuscular implantation of about 7×10^6 hWJ-MSC-EPO exhibited prolonged secretion of physiological erythropoietin (EPO), maintaining high hemoglobin and hematocrit levels for more than ten weeks in both cancer-bearing and tumor-cleared mice. The modified cells operated as immunoprivileged factories, evading rejection and bypassing the dosage variability associated with recombinant protein infusions. This method not only rectified cancer-associated anemia but also demonstrated the capacity of WJ-MSCs as sustained delivery systems for therapeutic proteins [103].

Table 6. Effect of Exosomes derived from WJ-MSC as a drug carrier on cancer.

Loaded Compound	Mechanism of Action	Cancer Model	Reference
Paclitaxel	Induce apoptosis and suppress EMT signaling	Cervical cancer cells (HeLa and L929)	[39]
miR-124	Decreases cell proliferation and migration	Glioblastoma Multiform Cells (HEK293T and U87)	[40]
mir-29a	Autophagy blockade, apoptosis induction,	Hepatocelullar carcinoma (Huh-7 and HepG2)	[41]

S3I-201 (STAT3 inhibitor)	Suppressing STAT3 activity, inducing apoptosis, inhibiting migration, and modulating immune responses.	*In vitro* TNBC cells (4TI) and *in vivo* Balb/C mice	[42]

WJ-MSC secretome can act as a chemosensitizer, increasing doxorubicin cytotoxicity in leukemia cells without inducing resistance, thereby supporting its role as an adjuvant to standard chemotherapy. WJ-MSC-derived exosomes have been used as nanocarriers, for example, to deliver the STAT3 inhibitor S3I-201 in TNBC and paclitaxel in cervical cancer, leading to enhanced apoptosis, reduced migration, and modulation of EMT-related pathways in line with the signaling mechanisms summarised in the mechanistic overview [39]. In addition to medication loading, WJ-MSC exosomes function as miRNA delivery systems, facilitating targeted genetic modification of cancer cells. Sharif *et al*. (2018) [40] revealed that WJ-Exos effectively targeted glioblastoma multiforme (GBM) cells and delivered miR-124, resulting in the downregulation of CDK6, inhibition of proliferation and migration, and increased sensitivity of GBM cells to temozolomide, thereby markedly augmenting apoptosis *[40]*. In a similar vein, Seydi *et al*. (2024) [41] created EV20K-miR-29a, extracellular vesicles derived from WJ-MSCs and infused with miR-29a, a potent autophagy inhibitor. These modified vesicles triggered apoptosis and inhibited proliferation, migration, and colony formation in hepatocellular carcinoma cells by obstructing autophagy regulators (ATG9A, TFEB) and oncogenic factors (MCL1, SIRT1, MMP9). *In vivo*, EV20K-miR-29a therapy resulted in significantly smaller xenograft tumors with diminished Ki-67 indices, highlighting the clinical promise of engineered WJ-Exos in inhibiting tumor growth [41].

These results collectively demonstrate that exosomes produced from WJ-MSCs constitute a next-generation platform for combinatorial cancer therapy (Table 6). Their capacity to (i) reliably deliver therapeutic proteins, (ii) augment the efficacy of chemotherapeutic drugs, (iii) transport targeted miRNAs to modify tumor signaling pathways, and (iv) selectively localize to tumor tissues establishes them as a formidable asset in nanomedicine. Although promising, additional efforts are needed to improve their loading efficiency, biodistribution, and immunological safety before clinical application.

3.12. Preclinical studies and clinical applications of Wharton's jelly mesenchymal stem cells and their products.

Mesenchymal stem cells produced from Wharton's Jelly have emerged as intriguing options for cancer therapy due to their cytotoxic, immunomodulatory, and non-tumorigenic characteristics. In preclinical studies, WJ-MSCs have exhibited direct cytotoxic and proapoptotic actions against various cancer cell types. For instance, they were demonstrated to induce apoptosis in leukemic cell lines (K562, HL-60), colorectal cancer cells (HT-29), and breast cancer cells (T47D and MCF7), highlighting their extensive antitumor efficacy across hematologic and solid tumors [104,105]. In addition to their inherent tumor-suppressive properties, WJ-MSC-derived secretomes have been shown to enhance the cytotoxic effects of standard chemotherapeutics. Conditioned media from WJ-MSCs significantly improved the effectiveness of doxorubicin in leukemia cells without causing drug resistance, indicating its potential in combinational therapy [47].

The safety profile of WJ-MSCs has been thoroughly assessed in animal models. Acute and sub-chronic toxicity investigations in rats demonstrated no significant alterations in physical, biochemical, or hematological parameters relative to controls, hence affirming their systemic safety [106]. Similarly, Kathivaloo *et al*. (2025) [107] validated the lack of

detrimental or toxic effects subsequent to WJ-MSC delivery in preclinical environments [107]. Significantly, WJ-MSCs maintain their tumor-targeting capability *in vivo*, moving to tumor locations and demonstrating inhibitory effects on tumor proliferation in xenograft models [108]. These findings bolster the justification for their clinical application.

Preliminary clinical investigations provide additional evidence for the use of WJ-MSC therapy. In breast cancer contexts, WJ-MSCs combined with vitamin E enhanced cell survival and proliferation under stressful circumstances, underscoring their potential for supportive and regenerative applications [109]. Significantly, in patients with hematologic malignancies such as AML, MDS, and T-cell lymphoma receiving allogeneic hematopoietic cell transplantation (HCT), treatment with WJ-MSC–derived exosomes did not elevate relapse rates, assuaging concerns about their potential pro-tumorigenic risks. This work highlighted the intricate equilibrium between graft-versus-leukemia and graft-versus-host responses in hematopoietic cell transplantation, emphasizing the immunological safety of Wharton's jelly mesenchymal stem cell-derived products in clinical cancer [101].

Preclinical studies demonstrate substantial evidence supporting the antitumor efficacy of exosomes and secretome derived from Wharton's Jelly mesenchymal stem cells (WJ-MSC) [23,34,42]. Nonetheless, their utilization in cancer treatment faces significant obstacles. The dual role of WJ-MSC products raises a notable concern. Multiple studies emphasize their cytotoxic, proapoptotic, and immunostimulatory properties. In contrast, other research suggests that under certain conditions, these products may enhance tumor progression through mechanisms such as angiogenesis, migration, or immune evasion [35,47]. This paradox underscores the importance of a comprehensive evaluation of context-specific effects, as tumor type, stage, and microenvironment considerably influence therapeutic outcomes.

3.13. Mechanistic pathways underlying antitumor and protumor effects.

Wharton's Jelly Mesenchymal Stem Cell (WJ-MSC) derivatives, including extracellular vesicles, conditioned medium, and secretome, have emerged as pivotal modulators of cancer cell behavior, displaying dual functions in tumor suppression and the regulation of critical cellular processes such as proliferation, apoptosis, and migration. Figure 3maps how secreted factors influence cancer via several signaling cascades. For instance, modulation of the MAPK pathway (JNK, ERK, p38) and downregulation of tumor growth and invasion via DKK1/Wnt and PI3K/Akt [22]. Activation of IL-6/JAK2/STAT3 signaling boosts proliferation and cell activation, while BIRC5/survivin contributes to cell cycle arrest [31]. The secretome also modifies the tumor microenvironment by reducing inflammatory cytokines (IFN-γ, TNF-α, IL-1β, IL-6, IL-8, IL-12) and increasing anti-inflammatory cytokines (IL-4, IL-10), shifting the balance toward apoptosis (activation of caspase-9, caspase-3, and reduced Bcl-2) [23]. These processes collectively contribute to either tumor suppression (through apoptosis and cell cycle arrest) or, less commonly, support for tumor survival, depending on the prevailing molecular cues in the tumor milieu.

WJ-MSC-derived extracellular vesicles can induce G0/G1 cell cycle arrest in cancer cells. Key molecules such as p21, p53, and PI3K/Akt are shown to regulate the cell cycle and promote apoptosis via cleaved caspase-3 [38]. This pathway ultimately inhibits cancer cell proliferation and migration by shifting epithelial cells toward a mesenchymal phenotype, modulating adhesion molecules (like increasing E-cadherin and decreasing CD44, vimentin, and MMP9) [36]. These changes reduce cell growth and metastatic potential. EV-WJ-MSC also works as a delivery vehicle for anti-cancer agents. Here, EVs carry miRNAs (like miR-

124 and miR-29a) or chemotherapeutic agents (S3I-201, paclitaxel), leading to increased cancer cell apoptosis and autophagy [39-42] (Figure 3). The vesicles enter cancer cells by endocytosis or membrane fusion, enhancing anti-tumor effects by suppressing proliferation and promoting programmed cell death.

The lack of standardized protocols for the isolation, characterization, and storage of secretomes and exosomes poses a significant challenge. Variations in MSC origin, culture conditions (including normoxia and hypoxia), and passage number can markedly influence the molecular composition and therapeutic efficacy of the resultant product [67,82,110]. The optimal dosage, administration route, and treatment schedule remain undefined, limiting reproducibility across studies. Long-term safety requires a comprehensive investigation, particularly regarding biodistribution, off-target effects, and possible immunosuppression that could inadvertently diminish antitumor immune responses. Regulatory obstacles present considerable challenges in the context of translation. Exosome- and secretome-based therapies integrate biologics, cell-based products, and nanomedicine, leading to a lack of a universally accepted framework for clinical approval [111]. Addressing these issues requires developing consensus guidelines for quality control, potency assays, and large-scale manufacturing that ensure therapeutic activity is preserved.

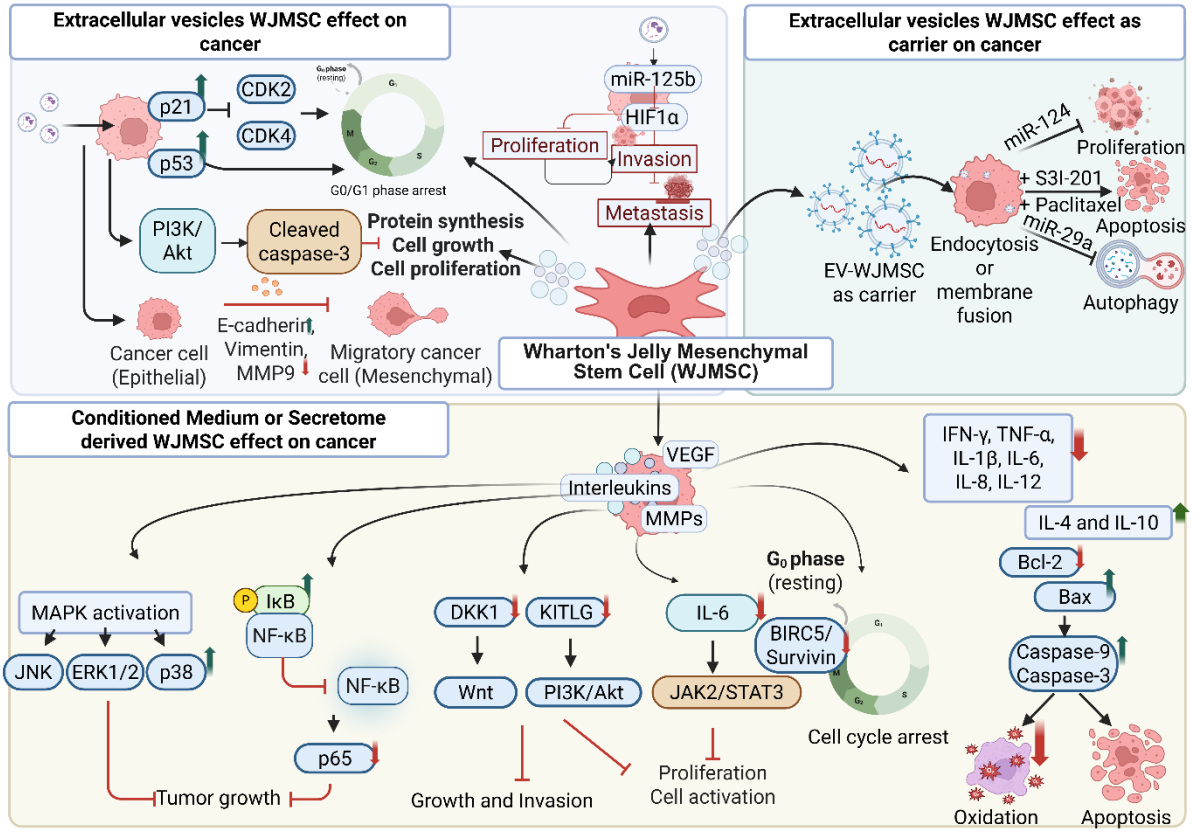

Figure 3. Schematic Representation of the Effects of Wharton's Jelly Mesenchymal Stem Cells (WJ-MSCs) and their derivatives on cancer progression and therapy. Created in BioRender. https://BioRender.com/e4r04st

This review synthesizes mainly *in vitro* and a few *in vivo* preclinical studies, so the relevance of WJ-MSC-based interventions to human cancer patients remains uncertain. Marked heterogeneity in WJ-MSC sources, culture conditions, preparation and characterization of secretome/EVs, dosing, and outcome measures, together with incomplete reporting of randomization and blinding, limits comparability and introduces potential risk of bias. Finally, the context-dependent duality of WJ-MSC effects and the paucity of clinical data constrain firm conclusions about net antitumor benefit, underscoring the need for standardized protocols

and well-designed clinical trials. Future research should focus on clarifying the molecular mechanisms underlying the dual effects of the WJ-MSC secretome and exosomes, enabling the identification of components that may act as either tumor-suppressive or tumor-promoting. Engineering approaches offer substantial opportunities, including the genetic modification of WJ-MSCs to improve exosome enrichment with tumor-suppressive miRNAs, the application of preconditioning strategies (such as hypoxia or inflammatory priming) to optimize secretome composition, and the incorporation of drugs into WJ-MSC–derived vesicles for targeted delivery [108,112]. The integration of WJ-MSC products with established cancer therapies, such as chemotherapy, radiotherapy, and immune checkpoint inhibitors, may enhance therapeutic efficacy while mitigating toxicity.

4. Conclusions

The therapeutic potential of WJ-MSC secretome and exosomes is considerable; however, careful refinement, standardization, and comprehension of mechanisms are essential for their safe and effective use in clinical applications. Addressing these challenges will determine whether WJ-MSC–derived products can advance from preclinical potential to established next-generation cancer therapies.

Author Contributions

Conceptualization, S.K. and R.M.; methodology, S.K. and A.H.; software, A.H.; validation, A.H. and R.M.; formal analysis, S.K.; investigation, S.K.; resources, S.K. and R.M.; data curation, S.K., A.H., and R.M.; writing—original draft preparation, S.K.; writing—review and editing, R.M.; visualization, S.K.; supervision, R.M.; project administration, R.M.; funding acquisition, R.M. All authors have read and agreed to the published version of the manuscript.

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This article is based solely on previously published studies, all of which are available through the DOIs and links provided in the References section. No new data were generated or analyzed in this work.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ABCG2	ATP-Binding Cassette Subfamily G Member 2
ALDOA	Aldolase A
ALDH	Aldehyde Dehydrogenase
ATG	Autophagy-related protein
ATMSC	Adipose-Derived Mesenchymal Stem Cell
BAX	BCL2-Associated X protein
BCL2	B-cell Leukemia/Lymphoma 2
BIRC5	Baculoviral IAP Repeat Containing 5
BMMSC	Bone Marrow Mesenchymal Stem Cell
Casp9	Caspase 9
CDK6	Cyclin-Dependent Kinase 6
CGTH	Human Thyroid Carcinoma
COVID-19	Coronavirus Disease-19
CXCR4	C-X-C chemokine receptor type 4
DMEM	Dulbecco's Modified Eagle's Medium
DNA	Deoxyribonucleic Acid
DOAJ	Directory of Open Access Journals
EMT	Epithelial-Mesenchymal Transition
EPCAM	Epithelial Cell Adhesion Molecule
EPO	Erythropoietin
ERK	Extracellular Signal-Regulated Kinase
ESC	Embryonic Stem Cell
EVs	Extracellular Vesicles
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GvHD	Graft-Versus-Host-Disease
HGF	Hepatocyte Growth Factor
IFN	Interferon
IκB	Inhibitor of Nuclear Factor Kappa-B
IL	Interleukin
ISCT	International Society for Cellular Therapy
LCSCs	Lung Cancer Stem Cells
MBSC	Malignant Breast Stromal Cell
MAPK	Mitogen-Activated Protein Kinase
MCF-7	Michigan Cancer Foundation-7
MCP-1	Monocyte Chemotactic Protein-1
MDA	Mammary Gland Adenocarcinoma
miRNA	microRNA
MSC	Mesenchymal Stem Cell
MSD	Mince–Soak–Digest
MV	Microvesicles
NCD	Non -communicable Disease
NF-κB	Nuclear Factor Kappa B
NK Cells	Natural Killer Cells
HCA	Human Colorectal Adenocarcinoma
HCT	Hematopoietic Cell Transplantation
HIF	Hypoxia-Inducible Factor
HSP	Heat Shock Protein

Abbreviation	Definition
HPL	Human Platelet Lysate
OCT4	Octamer-Binding Transcription Factor 4
PI3K	Phosphatidylinositol 3-kinase
PD-L1/2	Programmed Death Ligand 1/2
PKM2	Pyruvate Kinase M2
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RANTES	Regulated upon Activation, Normal T-cell Expressed and Secreted
RCC	Renal Cancer Cell
SASP	Senescence-Associated Secretory Phenotype
SDF-1	Stromal Cell-Derived Factor-1
STAT	Signal Transducer and Activator of Transcription
SYRCLES	Systematic Review Centre for Laboratory Animal Experimentation
TNBC	Triple Negative Breast Cancer
TNF	Tumor Necrosis Factor
TGF	Transforming Growth Factor
TRAIL	Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand
TREM1	Triggering Receptor Expressed on Myeloid cells 1
TME	Tumor Microenvironment
VEGF	Vascular Endothelial Growth Factor
U87MG	Uppsala 87 Malignant Glioma
VLA-4	Very Late Antigen-4
WJ	Wharton's Jelly
WJ-MSC	Wharton Jelly Mesenchymal Stem Cells
WJ-MSC-EV	Wharton Jelly Mesenchymal Stem Cells-derived Extracellular Vesicles
WJ-MSC-exo	Wharton Jelly Mesenchymal Stem Cell-derived Exosome
WJ-MSC-CM	Wharton Jelly Mesenchymal Stem Cell Conditioned Media

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