REVIEW

A review on mesenchymal stem cells and their secretome in hepatocellular carcinogenesis and its related signaling pathways: recent update

Jayenth Jayachandran[1], A. T. Rithi[1], Abhijit Mitra[2], Arunkumar Radhakrishnan[1*], Antara Banerjee[2*] and Asim K. Duttaroy[3*]

*Correspondence:
Arunkumar Radhakrishnan
arunkumarr@care.edu.in
Antara Banerjee
antara.banerjee27@gmail.com;
antarabanerjee@care.edu.in
Asim K. Duttaroy
a.k.duttaroy@medisin.uio.no
[1]Department of Pharmacology, Chettinad Hospital and Research Institute (CHRI), Chettinad Academy of Research and Education (CARE), Chennai, India
[2]Medical Biotechnology Lab, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute (CHRI), Chettinad Academy of Research and Education (CARE), Chennai 603103, India
[3]Department of Nutrition, Institute of Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway

Abstract

Hepatocellular carcinoma (HCC) is a significant global health challenge, being one of the leading causes of cancer-related mortality. This review focuses on the intricate interactions within the tumor microenvironment and mesenchymal stem cells (MSCs) and it's secretome in HCC and possible therapeutic responses. MSCs, characterized by their multipotent differentiation and self-renewal capabilities, can influence tumor behavior maybe through its secreted factors, including cytokines, growth factors and extracellular vesicles. This review summarizes the recent findings on role of MSCs in HCC, highlighting its involvement in different cell signaling pathways, including NF-κB, Wnt/β-catenin, Notch1, Stat3, and TGF-β, which play a significant role in HCC and possibly exhibit both tumor-suppressive and/or tumor-promoting effects depending on the activation or deactivation of signaling pathways. Publications related to the topic between 2016 to 2025 were searched using databases like PubMed, Scopus, Google Scholar with keywords viz. HCC, mesenchymal stem cells, secretome, tumor microenvironment, and signaling pathways. Findings from different research studies depict that MSCs and their secretome can exert anti-tumor effects by inducing apoptosis and enhancing immune responses, they may also promote alternate effects like tumor proliferation and metastasis under certain conditions, related to the activation or deactivation of different signalling pathways. This review aims to provide a comprehensive understanding of the multifaceted roles of MSCs in HCC. The dual role and the complexities of MSCs is context dependent. However, advancements in MSC research showed that the modifications of MSCs and secretome-based therapies and targeting the signaling pathways may have the potential to overcome challenges like drug resistance in HCC treatment.

Keywords Hepatocellular carcinoma, Mesenchymal stem cells, MSC secretome, Tumor microenvironment, Extracellular vesicles, Therapeutic intervention

1 Introduction

Liver cancer is one of the leading causes of cancer-related deaths worldwide, with nearly 800,000 deaths reported each year [1]. Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for approximately 85–90% of primary liver cancers, and is associated with high recurrence rates and poor treatment outcomes. Various risk factors, including chronic liver diseases, hepatitis B/hepatitis C infection, alcohol use, and environmental exposures to carcinogens, influence the development and progression of HCC, as shown in Fig. 1 [2]. Liver diseases such as hepatitis C, alcoholic liver disease, and non-alcoholic fatty liver disease tend to develop and worsen with older age, leading to adverse outcomes. HCC is characterized by advanced pathophysiological interactions, a high malignancy rate, and a tendency to reoccur [3]. Liver transplantation, surgery, radiation therapy, immunotherapy, ablation therapy, and embolization are some of the treatment options for HCC [4]. Understanding the mechanisms driving HCC progression is crucial for the advancement of effective therapeutic approaches [5].

Mesenchymal stem cells (MSCs) are emerging as a promising therapeutic approach in treating diseases such as Neurodegenerative diseases, Cardiovascular diseases, Autoimmune diseases, Inflammatory diseases, hepatic disorders, and cancer [6, 7]. Some advantageous properties of MSCs include reduced immunogenicity, trans-differentiation ability to other lineage cells, especially neuronal cells, cardiomyocytes, hepatocytes, and epithelial cells, the ability of chemotaxis, and the ability to target tumor sites with precision [8]. MSCs are multipotent stromal cells present in multiple tissues, such as bone marrow and adipose tissue [9]. They can differentiate into multiple cell types and play significant roles in tissue homeostasis and repair [10, 11]. Studies have demonstrated that MSCs play a substantial role in oncogenesis and cancer cell dynamics by altering the tumor microenvironment (TME) [12]. Various factors influence the immune response and regulate tumor behavior by inhibiting or promoting tumor growth and progression [13]. Specifically, in HCC, MSCs have exhibited both tumor-suppressing
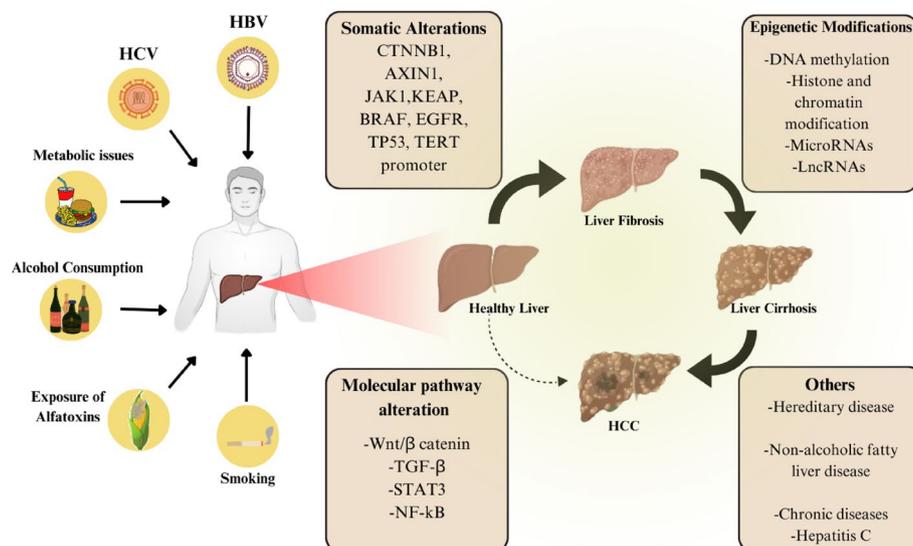
Fig. 1 An illustrative diagram showing the progression of Hepatocellular carcinoma from liver cirrhosis, highlighting key risk factors such as hepatitis B/hepatitis C Virus, diabetes, and alcohol consumption

and tumor-promoting properties [14]. MSCs can also alter the extracellular matrix (ECM), which subsequently influences tumor metastasis and cellular migration [15]. The secretome of MSCs, which collectively refers to the molecules they secrete, including proteins, lipids, nucleic acids, growth factors, cytokines, and extracellular vesicles (EVs), such as exosomes and microvesicles, may play an important role in mediating the effects [16]. MSCs secretomes and HCC interact through several signaling pathways, including Wnt/β-catenin, NF-κB, Notch1, STAT3, and Transforming Growth Factor-beta (TGF-β) [17]. This review aims to consolidate key findings from the most relevant recent research on the role of MSCs and it's secretome in HCC, highlighting the importance of targeting underlying signaling pathways in HCC. Additionally, we have summarised the role of MSCs and their secretome in the possible promotion and reduction of HCC depending on the activation/deactivation of the signaling pathways after doing a very rigorous literature review of the research evidence published by different researchers from 2016 to 2025 [18–27].

2　Soluble and vesicular components of MSC secretome

Currently, increasing attention has been directed toward investigating the secretome produced by MSCs and its use as an alternative therapeutic approach in some difficult-to-cure diseases. Limitations of only mesenchymal stem cell-based treatments include the possibility of tumorigenicity and cancer progression [28]. Additionally, heterogeneity and lack of standardization in MSC populations make it challenging to ensure consistent therapeutic outcomes after the treatments [29]. Another critical issue is unpredictable differentiation and integration, as MSCs may not always differentiate into the desired cell types or properly integrate into host tissues, potentially leading to unintended effects. Moreover, despite their immunomodulatory properties, MSC-based therapies can trigger an immune response against implanted MSCs [30]. Limited survival and engraftment post-implantation further reduce the long-term effectiveness of MSC treatments, as many implanted cells fail to persist in the host environment [31]. Given these challenges, researchers are increasingly focusing on the MSC secretome, comprising both the soluble factors, cytokines, chemokines, growth factors, and vesicular components like EVs are being explored as a potential approach to leverage the regenerative and immunomodulatory properties of MSCs [32].

MSC-derived soluble factors, including cytokines and chemokines, significantly influence various processes involved in disease progression, especially in conditions like cancer, liver fibrosis, neurodegeneration, and autoimmune disorders [33]. These small molecules can exert immunomodulatory effects by directly or indirectly regulating immune cell activity and their response to tissue or cellular damage [34]. Additionally, specific growth factors and cytokines present in the MSC secretome, such as transforming growth factor-beta isoform 3 (TGF-β3), hepatocyte growth factor (HGF), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α), are known to modulate key cellular signaling pathways [35]. These factors contribute to fibrogenesis and can reduce liver fibrosis by promoting tissue repair and reducing excessive scar formation [36].

MSC-derived extracellular vesicles (MSC-EVs) offer several advantages over their parent cells due to their unique cargo property, which includes mRNAs, microRNA, and proteins that can be effectively transferred to recipient cells, influencing various biological processes [37]. Compared to MSC-based therapies, MSC-EVs present significant

benefits in terms of storage, handling, and large-scale production, making them more practical for clinical application [38].

3 Current therapeutic strategies for HCC treatment

HCC remains a significant challenge, with existing therapeutic strategies demonstrating limited efficacy and posing substantial risks [39]. Treatments like liver transplantation, surgical resection, and local ablation are primarily effective in early-stage HCC but may have less efficacy in advanced cases [40]. The multi-kinase inhibitor Sorafenib tosylate was the first systemic therapy approved for advanced HCC, demonstrating a modest improvement in overall survival [41]. However, the development of drug resistance frequently restricts its efficacy, and significant adverse effects may include hand-foot skin reactions, diarrhea, and hypertension, and not all HCC tumors are equally responsive to systemic therapy or anti-angiogenic antibodies [42].

Recent advancements have introduced immune checkpoint inhibitors, including Nivolumab and Pembrolizumab, which function by targeting the PD-1/PD-L1 pathway for HCC treatment [43]. While these agents have shown promise, their response rates in HCC patients remain variable, and immune-related adverse events can occur, necessitating careful patient selection and monitoring [44]. The therapeutic combination of Atezolizumab, a monoclonal antibody targeting PD-L1, and Bevacizumab, an antibody that inhibits VEGF, has become the first choice for treating advanced HCC because it works better than Sorafenib tosylate [45]. Despite these advancements, challenges such as tumor heterogeneity and the development of resistance continue to impede long-term treatment success [46]. Stem cell therapy has recently emerged as a novel strategy for restoring deteriorated tissues and to manage HCC, especially those with end-stage liver disease.

Preclinical studies show that MSC secretomes support hepatocyte survival, lower oxidative stress, and protect against liver damage by switching immune responses and encouraging tissue regeneration [47]. For example, a conditioned medium made from MSCs derived from adipose tissue has been shown to aid tissues in healing and reduce inflammation in models of liver injury caused by drugs [47]. Similarly, MSC-derived EVs from human umbilical cord tissue have been shown to protect the liver by lowering apoptosis and oxidative stress in hepatocytes [48]. Further research is required to elucidate the way they function fully and to evaluate their safety as well as effectiveness in the setting of clinical use [49]. In summary, while recent advancements in newer therapies have enhanced the treatment of advanced HCC, they present limitations such as adverse effects and resistance [50]. Under these limitations, researchers have restored to cell-free regenerative therapies. One promising approach is exploring the secretome of MSCs, which is a complex mixture of soluble proteins, lipids, nucleic acids, and EVs, including exosomes. MSC secretome has multiple effects on hepatocytes and the tumour microenvironment via regulating paracrine signaling pathways [51]. In HCC models, components of the MSC secretome have been shown to reduce hepatocyte apoptosis, regulate oxidative stress, and inhibit pro-inflammatory and fibrotic signaling pathways. The delivery of certain microRNAs (e.g., miR-122, miR-199a-3p), growth factors (e.g., HGF, IGF-1), and anti-inflammatory cytokines (e.g., IL-10, TGF-β3) have been illustrated to promote liver regeneration and tumour suppression [52].

Moreover, the secretome modulates several oncogenic pathways such as PI3K/Akt, Wnt/β-catenin, and NF-κB, contributing to reduced cell proliferation, migration, and angiogenesis in HCC. Exosomal cargo has also been shown to reprogram immune cell behavior within the tumor microenvironment, promoting a shift from an immunosuppressive to an immune-reactive phenotype, thereby enhancing anti-tumor immunity [53]. In addition, MSC-derived secretome therapy offers significant translational advantages, including reduced immunogenicity, absence of tumorigenic risk, ease of storage and standardization, and potential for targeted delivery via engineered vesicles [54]. This therapeutic strategy indicates a significant change in advanced HCC treatment, moving away from generalised cytotoxic drugs and towards mechanism-based, precision regenerative medicine methods, both liver damage and tumour growth while reducing systemic toxicity.

4 MSCs secretome as a promising therapeutic option for HCC

MSC-derived conditioned medium (MSC-CM) contains a diverse range of bioactive molecules, such as cytokines, chemokines, immunomodulatory agents, and growth factors. These components contribute to immunomodulation, suppress cell death and fibrosis, and may also help reduce cancer progression, as shown in Fig. 2 [55].

In early-stage HCC, MSCs can reduce oxidative stress, reduce reactive oxygen species (ROS) accumulation, and maintain genomic stability [56]. MSC-secreted cytokines and EVs can also trigger immune activation and induce apoptosis in HCC cells [57]. For example, MSC-derived EVs containing miR-122 have been reported to enhance HCC sensitivity to chemotherapeutic agents like sorafenib by targeting cyclin G1 [58]. Additionally, miR-199a, another MSC-derived microRNA, downregulates the mTOR pathway, an essential regulator of cellular growth and metabolism, thereby inhibiting tumor proliferation [25, 59]. Furthermore, an HCC animal model was successfully created through the scaffold-free transplantation of three cell sheets into rats' livers: HCC cells alone, HCC cells with BMSCs, and HCC cells with UCMSCs [60]. All transplanted cell sheets induced tumors, but the addition of MSCs, particularly UCMSCs, reduced tumor size, suggesting an adverse effect on tumor development. This approach highlights the
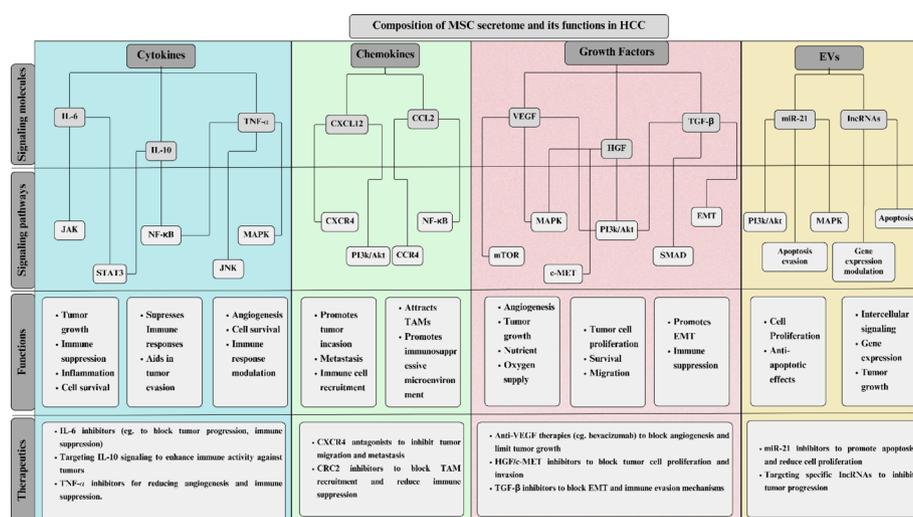
Fig. 2 A flowchart detailing the various components of the Mesenchymal stem cell and its secretome (cytokines, chemokines, growth factors, EVs) and their associated functions in Hepatocellular carcinoma

potential for using certain MSC subtypes in cancer treatment and offers a valuable method for creating solid tumor models for clinical research [61]. The study demonstrated that exosomes derived from human umbilical cord MSCs (hUCMSC-Ex) possess hepatoprotective properties by enhancing antioxidant defenses, thereby arresting the progression from liver injury to fibrosis and tumor development in HCC [62].

However, further research is required to figure out the mechanisms by which hUC-MSC-Ex exerts these antioxidant effects during liver disease development [63]. This highlights the complexity of hepatotropic networks involved in tissue regulation and homeostasis. Additionally, the study by Tang et al. (2016) and other researchers demonstrated that UC-MSCs effectively suppress the proliferation of HepG2 cells, and apoptosis is induced by decreasing the expression of AFP, Bcl-2, and Survivin, which are associated with apoptotic signaling pathways [20, 64]. These findings indicate that UC-MSCs could represent a potential and valuable cell source for MSC-based therapeutic strategies aimed at treating HCC. The study also demonstrated that human amniotic mesenchymal stem cells (hAMSCs) inhibit the proliferation of HepG2 cells and promote apoptosis by blocking the Wnt/β-catenin and IGF-1R/PI3K/AKT signaling pathways [23]. This suggests that the administration of hAMSCs and their conditioned medium (hAMSC-CM) could be a novel clinical strategy for treating HCC. Moreover, co-culturing HCC cell lines with adipose-derived mesenchymal stem cells (ADMSCs) or their conditioned medium significantly inhibited cell proliferation and increased apoptosis while also reducing migration and invasion. This effect was linked to changes in key gene expressions and the suppression of important HCC markers, indicating ADMSCs' potential as a therapeutic strategy for HCC [65].

In some recent comparative studies, it is illustrated that the therapeutic efficacy of MSCs derived from adipose tissue (AD-MSCs), bone marrow (BM-MSCs), and umbilical cord (UC-MSCs) in the treatment of HCC can vary, significantly as a result of their distinct biological properties and secretory profiles [66]. AD-MSCs have significant pro-apoptotic and anti-migratory effects on HCC cells by secreting specific microRNAs and bioactive compounds that control apoptosis-related genes such as *BAX*, *BCL-2*, and *Caspases*. These MSCs also produce paracrine factors that inhibit EMT markers, reducing the invasive and metastatic potential of HCC cells [20]. UC-MSCs are active immunomodulators, secreting anti-inflammatory cytokines such as IL-10, TGF-β, and PGE2. These factors contribute to immunological reprogramming by separating macrophages from M2 to M1, suppressing T cell proliferation, and modulating dendritic cell maturation. UC-MSCs also had a better proliferation index, more in vitro growth capability, and lower immunogenicity than AD-MSCs and BM-MSCs [22].

A selection of intrinsic and extrinsic variables, such as donor age, physiological status, tissue origin, and culture conditions, impact the functional heterogeneity of MSCs from various tissues. As a result of senescence-related alterations in their secretory nature, BM-MSCs generated from older persons frequently have reduced regenerative and anti-tumor activities. MSCs from younger or perinatal tissues, such as AD-MSCs and UC-MSCs, seem to have enhanced proliferative and bioactive characteristics [67]. Furthermore, external variables such as the composition of the culture medium, oxygen content, and passage number during in vitro growth can significantly modify the molecular composition of the MSC secretome, influencing therapeutic efficiency. Understanding these biological changes is important for selecting MSC sources adapted

to the different stages of HCC. Personalised therapies, derived from molecular analysis of the tumour microenvironment and patient-specific immunological characteristics, may improve therapy results [68]. Additional high-throughput proteome and transcriptome investigations of MSC-derived secretome are required to determine the most therapeutically beneficial MSC variation for clinical applications in HCC. Researchers have also emphasized the dual-edged sword behavior of MSCs and their secretome in both progression and as targeted therapy for cancer [69]. Exosomes derived from cancer tissues/tumors play an important role in immunomodulation, and cancer-derived exosomes play a critical role in immunomodulation [70]. The impact of MSCs and their secretome on cancer cells is complex and cancer stage dependent. TGF-β and IL-10 are the cytokines secreted by MSCs that contribute to an immunosuppressive TME that fosters tumor growth, while other factors like IFN-γ can enhance anti-tumor immune responses [71]. Additionally, MSC-derived EVs can influence the PI3K/AKT and Wnt/β-catenin, which regulate cancer cell survival and metastasis [72]. This dual nature underscores the importance and understanding of MSCs secretome for developing targeted cancer therapies [73].

Moreover, MSC-derived EVs containing microRNAs such as miR-21 and miR-1247 have been shown to enhance HCC cell proliferation and invasiveness via the PI3K/AKT and Wnt/β-catenin pathways, thereby contributing to treatment resistance [74]. Recent research has demonstrated that human MSCs (hMSCs) facilitate tumor growth through the activation of the MAPK signaling pathway and increase progression via epithelial-mesenchymal transition (EMT) in vivo [75]. Another study demonstrated that hMSCs when administered to the HCC group, CD56 expression showed a significant reduction, whereas levels of TNF-α and IL-6 exhibited an increase, potentially contributing to tumor progression. RNA sequencing revealed that hMSCs enhanced hepatocyte migration and invasion by targeting ITGA5 [76].

5 Mesenchymal stem cell-derived exosomes (MSCsEXOs) and HCC

MSC-based therapies face several limitations, including challenges in maintaining a consistent nature of cells with stable phenotypes and the high costs associated with their isolation, characterization, and maintenance [77]. Additionally, MSCs present potential risks such as immune rejection and the possibility of tumor formation [78]. On the other hand, MSC-EXOs offer distinct advantages unlike MSCs, exosomes are more readily produced and stored, and their cell-free nature helps to reduce immune rejection and tumorigenesis [79]. Furthermore, their nanoscale types and bilayer lipid development facilitate targeted delivery to organs by crossing biological barriers [80].

MSC-EXOs possibly exhibit therapeutic effects in HCC. However, their role in cancer regulation is complex, acting as a double-edged sword [81]. As part of the tumor stromal cell population, MSCs contribute to the formation of the TME [82]. Some studies indicate that MSC-EXOs can transfer tumor-associated factors, potentially promoting cancer cell proliferation [83]. Conversely, MSC-EXOs have also demonstrated therapeutic potential, as research has shown that animals treated with exosomes develop significantly smaller tumors with reduced volume ratios.

Compared to the control group, rats treated with exosomes displayed an increased proportion of circulating Natural Killer T (NKT) cells on day 5 and day 15 following treatment. Exosomes derived from adipose tissue mesenchymal stem cells (AMSC-EXOs)

have been shown to augment the anti-tumor activity of rat NKT cells, thereby facilitating the suppression of HCC and promoting low-grade tumor differentiation [84]. Similarly, exosomes derived from bone marrow mesenchymal stem cells (BMSC-EXOs) have been shown to induce apoptosis and suppress the cell cycle progression of HepG2 cells [85]. Furthermore, in HCC rat models, the injection of BMSC-EXOs significantly suppressed tumor angiogenesis, metastasis, and invasion in vivo [86]. hUCMSC-EXOs can treat CCl4-induced liver fibrosis in rats by significantly reducing type II and III collagen expression within three weeks of transplantation [87]. They also reduce liver damage by inhibiting the TGF-β1/Smad pathway and preventing EMT. Similarly, hBM-MSC-EXOs suppress Wnt/β-catenin signaling, reducing activation of hepatic stellate cells (HSCs), ultimately reducing CCl4-induced liver fibrosis [87]. Given the dual role of MSC-EXOs in tumor progression, exosomes that have been artificially engineered can also be used and offer greater advantages in HCC treatment [88]. miR-199a-3p-modified AMSC-EXOs enhance HCC cell chemosensitivity by delivering miR-199a-3p and targeting the mTOR pathway. Overexpression of mTOR counteracts AMSC-EXO-199a's effects on 4EBP1 and 70S6K phosphorylation, as well as HCC cell chemoresistance [89]. Similarly, miR-451a-modified hUCMSC-derived exosomes enhance apoptosis, reduce resistance to paclitaxel, and regulate the cell cycle in HCC. Studies suggest that miR-451a from hUCMSC-derived exosomes inhibit the progression of EMT by downregulating Disintegrin and Metallopeptidase 10 (ADAM10), functioning as a suppressor of HCC [90].

6 MSC secretome-mediated modulation of target signaling pathways for HCC treatment

MSC secretomes have emerged as promising therapeutic agents in HCC due to their ability to regulate key oncogenic signaling pathways [91]. Various studies highlight their role in suppressing HCC proliferation by modulating pathways such as NF-κB, Wnt/β-catenin, Notch1, STAT3, and TGF-β [92]. These pathways are crucial in tumor progression, immune evasion, and therapeutic resistance, making MSC-derived factors valuable in targeting HCC at multiple levels. MSC secretomes exhibit direct and indirect tumor-suppressive effects by influencing cytokine release, such as anti-tumor cytokines, angiogenesis, apoptosis induction, and immune modulation [93]. Mechanisms of action of MSC secretome in HCC are integral to exploring its therapeutic potential, as shown in Table 1. It summarizes the role of key signaling pathways in HCC, highlighting how MSC secretomes influence these pathways through the delivery of miRNAs, cytokines, and regulatory proteins. By modulating STAT3, NF-κB, and MAPK/ERK pathways, MSC secretomes can suppress tumor progression, reduce inflammation, and enhance apoptosis, as evidenced by various research studies.

Shiota et al. (2017) have shown that the MSC secretome can suppress HCC cell proliferation by regulating signaling pathways, including NF-κB, Wnt/β-catenin, Notch1, Stat3, and TGF-β [77]. Qiao et al. (2008) demonstrate that the conditioned media from human mesenchymal stem cells inhibit the proliferation of hepatoma and breast cancer cells, likely by downregulating specific factors of NF-κB signaling pathways and other related mechanisms [99]. Also, a recent investigation revealed that conditioned media from ADMSCs significantly inhibit the HCC cell proliferation and induction of programmed cell death. Studies also noted that treatment with ADMSCs resulted in the increased expression of tumor suppressor genes such as p53 and the decreased

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Table 1 Mechanisms of action of mesenchymal stem cells and its secretome in hepatocellular carcinoma

Signaling pathway	Role in HCC	MSC secretome's influence	Mechanisms of action	References
Wnt/β-Catenin	Promotes cell proliferation, migration, and survival; linked to tumor growth and poor prognosis.	MSC-derived exosomes can carry miRNAs that promote β-catenin degradation and reduce its nuclear activity.	Modulation through miRNAs such as miR-145 and miR-34a that downregulate Wnt pathway components.	[88]
TGF-β	It acts as a tumor suppressor in early HCC but promotes EMT and metastasis in later stages.	MSC secretome factors can counterbalance TGF-β's tumor-promoting effects, potentially restoring its suppressive role.	Includes cytokines and miRNAs that modulate TGF-β signaling, inhibiting EMT and enhancing anti-tumor immune response.	[94]
STAT3	Drives cell proliferation, angiogenesis, immune suppression, and chemoresistance.	MSC-derived EVs with miRNAs such as miR-124 and anti-inflammatory cytokines reduce STAT3 activity, promoting apoptosis.	Direct inhibition of STAT3 phosphorylation and transcriptional activity.	[95]
NF-κB	Regulates inflammatory responses and supports cell survival, contributing to chronic liver inflammation and HCC progression.	MSC secretome carries miRNAs (e.g., miR-146a) that can downregulate NF-κB signaling, reducing inflammation.	Inhibition of cytokine production and interference with NF-κB activation pathways.	[96]
PI3K/AKT	Promotes cell growth, survival, and metabolic activity in HCC	MSC-derived exosomes transfer miR-21 and miR-199a to modulate PI3K/AKT activity, potentially reducing chemoresistance.	Regulation through the modulation of PTEN and other signaling inhibitors.	[97]
MAPK/ERK	Associated with cell differentiation and proliferation; implicated in tumor growth and progression.	Factors from the MSC secretome can modulate MAPK/ERK pathways to promote apoptosis in HCC cells.	MSC-derived exosomes containing regulatory proteins inhibit ERK signaling.	[98]

expression of oncogenes like c-Myc and CTNNB1 [23]. These findings suggest that MSC-derived factors can influence pathways associated with β-catenin degradation and help suppress tumor growth [73]. ELISA and Western blot analysis revealed that MSCs secrete Dkk-1, inhibiting Wnt pathway factors like bcl-2 and β-catenin, leading to HepG2 cell apoptosis. Animal studies also confirmed that MSC secretomes suppress tumor growth in a dose-dependent manner, highlighting their therapeutic potential [100].

The Notch1 signaling pathway is a highly conserved pathway essential for regulating cell differentiation, tissue organization, and morphogenesis [101]. Emerging evidence indicates that this pathway is often dysregulated in various cancers and can function as either an oncogene or a tumor suppressor, depending on the cellular situation [102]. Recent studies have demonstrated that MSC secretome effectively inhibits HepG2 cell growth through the downregulation of Notch1 signaling. Furthermore, research indicates that novel curcumin derivative (NCD) amplifies the antitumor effects of MSC secretome by suppressing Notch1-regulated gene expression. These findings suggest that targeting the Notch1 pathway with MSCs and NCD could serve as a promising therapeutic strategy for HCC [103].

Also, the STAT3 pathway's critical transcription factor is frequently activated in HCC, playing a pivotal role in tumor progression and survival [104]. It drives carcinogenesis

by regulating genes that regulate cell proliferation, apoptosis inhibition, and angiogenesis. Frequent activation of STAT3 contributes to tumor aggressiveness, therapeutic resistance, and the modulation of the tumor microenvironment, making it a key target for HCC therapies [105, 106]. The MSC secretome modulates the TME in HCC, including the regulation of cytokines that influence STAT3 activation. Recent studies have shown that MSC-derived factors can help inhibit aberrant STAT3 signaling in tumor cells, promoting apoptosis and reducing tumor progression [107]. Certain anti-inflammatory cytokines released by MSCs have been reported to downregulate STAT3 activity, offering potential therapeutic benefits in HCC treatment [20]. Additionally, MSCs can enhance anti-tumor immunity by modulating immune responses through the release of specific cytokines, which can counteract the pro-tumorigenic effects of STAT3 activation in HCC [108]. This paracrine signaling effect positions MSCs as a promising tool for targeting STAT3 signaling and improving therapeutic outcomes in HCC [109].

Additionally, TGF-β signaling plays an important role in maintaining liver function and promoting tissue repair while also regulating cell proliferation and apoptosis. In HCC, it inhibits cell proliferation in the early stages but promotes EMT and metastasis in advanced stages [110]. Additionally, TGF-β influences the tumor microenvironment by regulating MMP expression and immune evasion. MSC-derived factors can counteract TGF-β's pro-tumor effects, restoring its tumor-suppressive function [111]. However, a recent study indicates that TGF-β can also exert anti-tumor effects under certain conditions by enhancing the immune response against tumors [94]. Targeting TGF-β signaling could, therefore, help restore its tumor-suppressive functions [112]. While TGF-β is often associated with tumor promotion, MSCs secrete other factors that can counteract its effects on cancer cells, potentially reestablishing its function as a tumor suppressor by augmenting immune responses against neoplasms [113]. Sohrabi et al. (2022) and Ferreira et al. (2018) emphasize that certain factors within the secretome can enhance immune responses and inhibit tumor growth by counteracting the immunosuppressive effects of TGF-β, thus restoring its tumor-inhibiting function. Altogether, these studies indicate that TGF-β signaling has a complex role in liver health and disease, affecting processes like cell proliferation, differentiation, and immune response within the TME [114, 115].

7 Potential therapeutic roles of MSCs and their secretome in HCC

Genetic modification of MSCs represents a promising strategy to enhance their anti-tumor properties [115]. A study demonstrated that genetically engineered MSCs can deliver therapeutic agents directly to HCC cells, utilizing their natural homing ability to target tumor sites effectively. This method not only enhances the local concentration of anti-tumor agents but also minimizes systemic toxicity, making it a compelling strategy for HCC treatment [85]. Exosomes derived from MSCs, which are extracellular vesicles of nanosize, are being explored for their therapeutic potential [116]. Research has shown that exosomes enriched with specific microRNAs can inhibit HCC cell proliferation and induce apoptosis. Adipose tissue-derived MSCs have demonstrated the ability to enhance radiotherapy's effectiveness on HCC cells by altering the expression of the TGF-β pathway [117].

Targeting specific signalling pathways influenced by the MSC secretome may offer new therapeutic strategies. TGF-β is recognized as an important factor in the development of

HCC and the development of fibrosis [26]. A study highlighted that MSC-derived factors could inhibit TGF-β1-induced EMT, a critical process in cancer metastasis. The STAT3 pathway is another target influenced by the MSC secretome. Evidence suggests that inhibiting STAT3 signaling can reduce tumor growth and enhance apoptosis in HCC cells. Studies have found that AT-MSCs can downregulate STAT3 expression, thereby enhancing the therapeutic efficacy of combined treatments like radiotherapy on HCC cells [118]. Despite the promising advantages of MSCs and their secretome in the management of HCC, they encompass a wide range of bioactive factors that facilitate tissue repair, regeneration, and the modulation of immune responses [119]. It is also defined as the aggregation of soluble proteins, nucleic acids, lipids, and EVs secreted by MSCs, which can exert significant biological effects on target cells [120].

In myocardial infarction, MSC secretomes have demonstrated the ability to enhance cardiac function by reducing myocardial apoptosis and promoting angiogenesis, possibly through the activation of growth factors within the secretome, such as insulin-like growth factor (IGF) and VEGF, which contribute to these effects [121]. MSC secretomes may help in neuronal differentiation and protection against ischemic damage [122], which depicts their diverse role. However, the secretome can inhibit T-cell activation and clonal expansion, thereby reducing the severity of autoimmune responses. This is particularly relevant in conditions like systemic lupus erythematosus (SLE), where MSC-derived factors have been demonstrated to reduce symptoms by influencing T-cell differentiation [118]. Also, the capacity of MSC secretomes to stimulate angiogenesis is important for effective tissue repair. Factors like FGF and VEGF found in the MSC secretome stimulate the proliferation and migration of endothelial cells, leading to the formation of additional blood vessels [121].

Among various sources of MSCs for prospective HCC therapy, UC-MSCs are observed to be a viable and potentially superior alternative to BM-MSCs. UC-MSCs possess a more primitive phenotype, higher proliferative capacity, and lower senescence rates compared to BM-MSCs [123]. These characteristics allow UC-MSCs to maintain their stemness and therapeutic functionality over prolonged culture periods, which is essential for secretomes for clinical use. Furthermore, UC-MSCs are more resistant to oxidative stress and hypoxic conditions, which enhances their viability and activity in the tumor microenvironment commonly observed in HCC [59].

In addition to their proliferative advantage, UC-MSCs have a more significant immunomodulatory profile than BM-MSCs. They secrete higher concentrations of immunosuppressive factors such as IL-10, TGF-β, and indoleamine 2,3-dioxygenase, which reduce pro-inflammatory responses and enhance immunological tolerance by regulating T cell activity and macrophage polarization [124]. Moreover, the UC-MSC secretome contains a distinct composition of anti-fibrotic and anti-tumor microRNAs and proteins that target key signaling pathways implicated in HCC progression, including Wnt/β-catenin, PI3K/Akt, and TGF-β/Smad [125]. These molecular characteristics not only support hepatocyte survival and tissue regeneration but also suppress tumor growth and metastasis. Given the possibility of isolating via non-invasive procedures, less ethical issues, and constant therapeutic output, UC-MSCs are an excellent cell source for the development of sophisticated, cell-free regenerative treatments for HCC. The MSC secretomes role has been the focus of a comprehensive investigation on wound healing.

Table 2 Therapeutic targets of mesenchymal stem cells and its secretome in hepatocellular carcinoma

Therapeutic targets	MSC secretome component	Mechanism of action	Potential benefits	Challenges	References
Genetically engineered MSCs	TRAIL-expressing exosomes	Induce targeted apoptosis in HCC cells through death receptor activation.	Selective induction of cancer cell death with minimal side effects.	Stability and targeted delivery in in vivo model.	[129]
Exosome-mediated Drug Delivery	Exosomes loaded with doxorubicin	Facilitates targeted chemotherapy delivery, enhancing drug cytotoxicity in HCC cells.	Reduces systemic toxicity and improves drug concentration at the tumor site.	Optimization of drug loading and release mechanisms.	[130]
miRNA-Enriched Exosome Therapy	miR-122, miR-199a	Sensitize HCC cells to sorafenib and inhibit growth through mTOR pathway downregulation.	Overcomes drug resistance and enhances the efficacy of chemotherapies	Potential risk of off-target effects and miRNA degradation.	[131]
Immune Modulation	Cytokines (e.g., IL-10, IFN-γ) and growth factors	Modulates immune response, enhancing T cell and NK cell activity and inhibiting immune evasion.	Boosts anti-tumor immune response and reduces tumor immune suppression	Potential immune overactivation and balancing anti-tumor vs. pro-tumor responses.	[132]
Anti-angiogenesis	VEGF inhibitors in MSC secretome	Suppresses VEGF signaling, reducing tumor vascularization and growth.	limits blood supply to the tumor, impairing nutrient access and metastasis potential.	Avoidance of compensatory angiogenesis pathways.	[133]
Liver Regeneration	HGF and FGF in MSC secretome	Stimulates regeneration of healthy liver tissue while targeting tumor growth	Supports post-treatment liver recovery and reduces risk of recurrence.	Risk of inadvertently promoting tumorigenic pathways.	[134]

MSC-CM has been demonstrated to enhance wound healing by promoting re-epithelialization, granulation tissue formation, and collagen deposition [126].

While MSC-derived secretomes have therapeutic potential, they also exhibit a dual role in cancer, which is context dependent and the therapeutic targets of MSC secretome in HCC, is shown in Table 2, which highlights therapeutic strategies using MSC secretomes in HCC, including gene-modified MSCs, exosome-mediated drug delivery, miRNA-enriched exosome therapy, immune modulation, anti-angiogenesis, and liver regeneration support. Each approach offers benefits like targeted therapy, reduced cellular toxicity, and enhanced immune response, though challenges such as stability, off-target effects, and balancing immune activity remain, further elucidating their complex role. TME and MSC secretomes can either inhibit or promote tumor growth depending upon the activation or deactivation of different cancer specific signaling pathways [127]. As research progresses towards understanding the precise mechanisms involved and optimizing production methods, MSC secretomes may pave the way for innovative cell-free therapies that harness the regenerative capabilities inherent in stem cell biology [128].

8 Challenges and future perspectives in MSC-based therapy for HCC

Large-scale clinical studies, improved delivery systems, and regulatory standardization of MSC-derived secretome products are to be the primary areas of future research [135]. Furthermore, bioengineered exosomes loaded with chemotherapeutic agents or siRNAs offer an exciting platform for targeted therapy, reducing systemic toxicity and improving HCC outcomes [136]. Promoting upon this, the clinical translation of MSC-derived secretome-based therapies requires standardization of manufacturing protocols, including the source of MSCs, culture conditions, and methods of secretome isolation and purification [137]. This standardization is essential to ensure batch-to-batch consistency, reproducibility, and regulatory compliance for clinical-grade secretome-based products.

Additionally, advancements in nanotechnology have enabled the engineering of EVs, particularly exosomes, as targeted drug-delivery vehicles [138]. By functionalizing the surface of exosomes with ligands that bind to receptors overexpressed in HCC cells, or by incorporating tumor-homing peptides, these vesicles can achieve selective delivery to tumor sites. Encapsulation of siRNAs, miRNAs, or small-molecule drugs within exosomes not only protects the therapeutic cargo from enzymatic degradation but also facilitates endocytosis-mediated uptake by cancer cells. This targeted approach has the potential to enhance intracellular drug bioavailability, bypass multidrug resistance mechanisms, and minimize off-target effects in healthy tissues [139]. Future research should focus on optimizing the loading efficiency, stability, and biodistribution of bioengineered exosomes, as well as conducting rigorous preclinical and clinical evaluations to support their therapeutic application in HCC. However, there are still safety concerns because one recent study has revealed that MSCs might unintentionally encourage tumor growth by improving the TME through pathways like Wnt/β-catenin and MAPK [133]. Before MSCs were used in the healthcare sector, the regulatory bodies placed more importance on high standards of research outcomes to ensure the quality and functional efficacy.

Moreover, MSCs frequently discover the difficulty of targeting HCC sites, so enhancing homing efficiency is still a concern to address. A greater understanding of the hazards is necessary because the delivery of MSCs has a risk of thromboinflammatory reactions, which can result in problems, including pulmonary embolism [132]. Ultimately, the shortage of long-term monitoring and efficacy in current research emphasizes the necessity of extensive longitudinal studies to assess potential negative effects over time. Future directions for MSC-based therapies for HCC depend on developing innovative methods to improve their therapeutic efficacy and safety. The MSC secretome is an exciting new therapeutic alternative for liver diseases as an acellular regenerative or reparative treatment. Almost every postnatal tissue, including the umbilical cord, bone marrow, and adipose tissue, has MSCs [36, 140]. Personalized therapy procedures that modify the MSC therapy profile and tumor type are also expected to improve results. Assessing the efficacy of MSC therapies while they go from the experimental to the clinical stages will also require developing a strong regulatory system. Additionally, the exact mechanism of action, potency, long-term efficacy, and safety of administering MSCs and its secretome in patients with HCC need to be validated further. MSCs and its secretome therapy are a new approach as they possess flexible differentiation potential and the ability to release cytokines and chemokines that enhance angiogenesis and aid in cell division and proliferation. In general, these developments have great potential for developing MSC-based therapies for HCC in the future [141].

9 Conclusion

This review summarises the pivotal roles of MSCs and their secretome in HCC. The nature of MSCs, characterized by their ability to both inhibit and promote tumor growth depending on the disease stage, presents significant challenges and opportunities for further validation of their therapeutic interventions in HCC. Since in the majority of advanced HCC cases, therapeutic options are limited due to underlying chronic liver cirrhosis and poor response to chemotherapy, advances in MSC engineering and secretome-based therapies promise to overcome drug resistance and enhance clinical outcomes in HCC. However, the specific mechanism of action by which MSCs, their secretome, and their paracrine factors exert their trophic and therapeutic effects in HCC still needs extensive research. Key signaling pathways, including Wnt/β-catenin, TGF-β, STAT3, and NF-κB, mediate these interactions, highlighting the complexity of MSC contributions to HCC dynamics. Further long-term clinical trials are warranted, with specific notes on route of administration, nature of transplanted cells, and HCC stage and association with other comorbidities, which might offer critical direction for clinicians and researchers in pursuit of the further translation of such therapies. Ultimately, integrating molecular insights with therapeutic perspectives, this review aims to provide a comprehensive understanding of the multifaceted roles of MSCs in HCC.

Author contributions
AB, AKD and AKR designed the study and conceptualized the work. JJ, RAT, and AM collected the datasets, performed all the data analysis and wide-ranging aspects of the manuscript preparation, and designed the pictorial representations. JJ, RAT, and AB designed the images and tables. AKR, AB, and AKD critically reviewed the draft manuscript and provided critical suggestions on the data analyses. All authors have read and approved the final manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
NA.

Consent for publication
All authors have read and approved the final version of the manuscript. All authors have given consent for publication of this review article.

Competing interests
The authors declare no competing interests.

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