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Review article

Exosomes as novel tools for renal cell carcinoma therapy, diagnosis, and prognosis

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ABSTRACT

Background: Renal Cell Carcinoma (RCC) stands as a formidable challenge within the field of oncology, despite considerable research endeavors. The advanced stages of this malignancy present formidable barriers to effective treatment and management.
Objective: This review aims to explore the potential of exosomes in addressing the diagnostic and therapeutic challenges associated with RCC. Specifically, it investigates the role of exosomes as biomarkers and therapeutic vehicles in the context of RCC management.
Methods: For this review article, a comprehensive literature search was conducted using databases such as PubMed, employing relevant keywords to identify research articles pertinent to the objectives of the review. Initially, 200 articles were identified, which underwent screening to remove duplicates and assess relevance based on titles and abstracts, followed by a detailed examination of full texts. From the selected articles, relevant data were extracted and synthesized to address the review's objectives. The conclusions were drawn based on a thorough analysis of the findings. The quality was ensured through independent review and resolution of discrepancies among multiple reviewers.
Results: Exosomes demonstrate potential as diagnostic tools for early detection, prognosis, and treatment monitoring in RCC. Their ability to deliver various therapeutic agents, such as small interfering RNAs, lncRNAs, chemotherapeutic drugs, and immune-stimulating agents, allows for a personalized approach to RCC management. By leveraging exosome-based technologies, precision and efficacy in treatment strategies can be significantly enhanced.
Conclusion: Despite the promising advancements enabled by exosomes in the management of RCC, further research is necessary to refine exosome-based technologies and validate their efficacy,

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safety, and long-term benefits through rigorous clinical trials. Embracing exosomes as integral components of RCC diagnosis and treatment represents a significant step towards improving patient outcomes and addressing the persistent challenges posed by this malignancy in the field of oncology.

1. Introduction

Cancer remains to be serious global health burden, despite the decades of ongoing efforts to fight against this disease. The phenomenon can manifest itself in a multitude of diverse forms, exerting distinct impacts on individuals in varying manners. Cancer arises when cells within the human body undergo uncontrolled proliferation, leading to the formation of tumors that possess the capacity to metastasize to other organs within the organism. Various factors can increase your risk of developing cancer, including genetic background, exposure to certain chemicals or substances, and lifestyle factors like smoking or poor diet. Early detection of cancer is imperative since cancer treatments are extremely effective at the early stages of the disease. Therefore, regular check-ups and consulting with physicians in the case of any unusual symptoms would help to reduce the mortality rates of cancer [1].

Renal cell carcinoma (RCC) is a type of kidney cancer that could be developed in the cells lining the tubules of the kidney. The symptoms of RCC can vary from person to person but may include blood in the urine, lower back pain, fatigue, and fever. The most prevalent form of kidney cancer in adults is RCC, which is usually diagnosed through imaging tests and biopsies. The causes of RCC are not yet fully understood, but there are several known risk factors, such as smoking, overweight, high blood pressure, and a history of kidney cancer in the family. Treatment for RCC may involve surgery, targeted drug therapy, immunotherapy, and radiation therapy depending on the stage and location of the cancer. Overall, early detection and treatment of RCC are important for improving the chances of successful treatment and long-term survival. RCC can be difficult to detect in its early stages. This is partly due to the unspecific symptoms of RCC, which often do not appear until the disease has progressed to a later stage. As a result, there is an imminent need to find new and more accurate methods of RCC diagnoses [2]. Developing new diagnostic methods for RCC is critical for several reasons. Firstly, detecting the disease in its earliest stages can improve patient outcomes, as early treatment can be more effective in the control of cancer. Secondly, accurate diagnosis is essential for determining the most appropriate treatment options, as different subtypes of RCC may respond differently to various therapies. Thirdly, non-invasive diagnostic techniques can reduce the need for more invasive and potentially uncomfortable procedures, which can also be costly. Additionally, the identification of specific exosomes associated with RCC could have significant implications for cancer research and treatment as a whole. By understanding the unique properties of these exosomes, new targeted therapies that are more efficient and less harmful to healthy cells might be created. One promising approach that researchers have been recently exploring is the use of exosomes. These are small vesicular structures that are secreted by various cell types. Exosomes could contain numerous molecules, including microRNAs that can provide important information about the cellular processes. Scientists have discovered that RCC cells release specific types of exosomes, which contain biomolecules that are associated with cancer development and progress [3].

The auspicious potential of exosomes extends to the domain of RCC (Renal Cell Carcinoma) treatment, evoking considerable interest among researchers due to the prospect of unleashing targeted therapies with unparalleled precision. These incredible vesicles have shown their capability to transport bioactive molecules directly to cancer cells, which opens up an exciting possibility for drug delivery. By engineering exosomes to bear therapeutic agents, researchers aim to optimize the effectiveness of anticancer treatments while minimizing their collateral damage. In parallel, researchers have become fascinated by the potential of exosomes derived from immune cells as an immunotherapeutic approach. This shows promise in triggering a strong immune response against RCC.

Overall, the development of more accurate diagnostic and therapeutic methods for RCC is of great significance. Exosomes' potential role in this process is an exciting and rapidly evolving area of research that has the potential to transform how we detect and treat RCC and other types of cancer. By continuing to investigate the potential of exosomes and other innovative diagnostic and therapeutic methods, there is a hopeful outlook for making significant progress in the battle against cancer.

2. Methodology

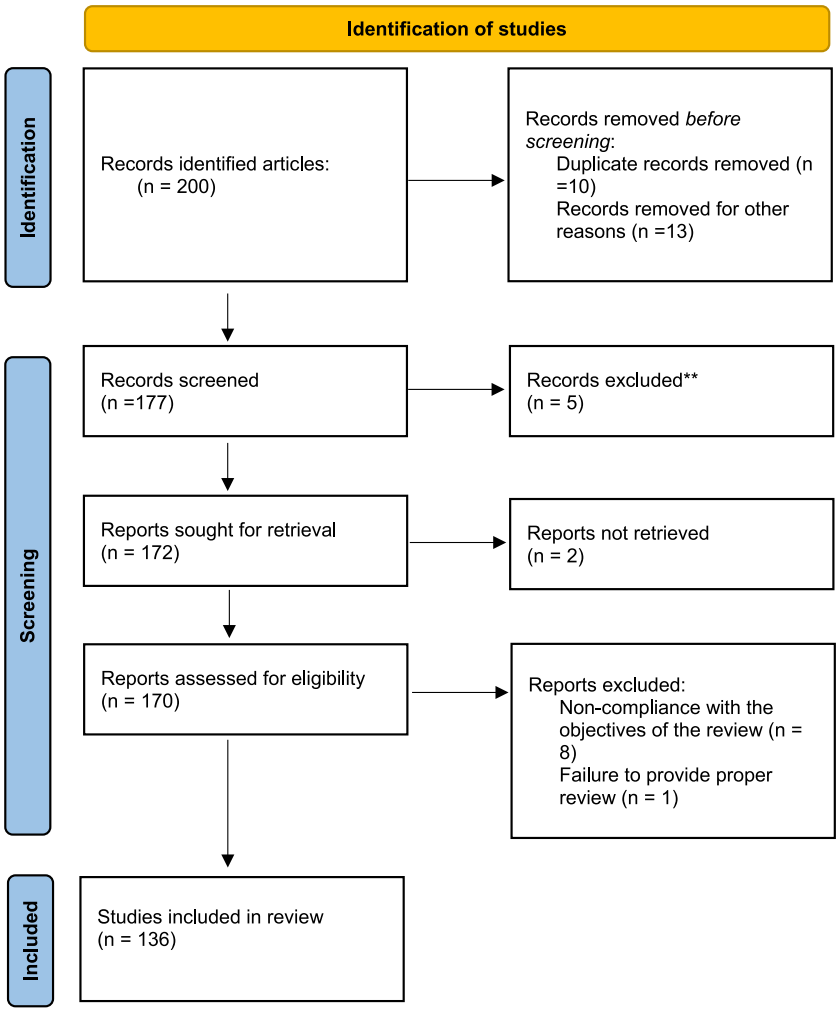
Commencing with a comprehensive literature search across prominent electronic databases such as PubMed, and targeted perusal of academic journals, the endeavor was underpinned by a judicious application of predefined inclusion and exclusion criteria tailored to ensure the relevance and pertinence of the identified articles to the focal subject matter. Through this exhaustive process, a corpus of 200 articles was initially identified. Subsequent to the initial identification, a stringent screening process ensued, involving a meticulous examination of article titles and abstracts to ascertain alignment with the predetermined criteria. This discerning assessment led to the exclusion of 64 articles, refining the pool to 136 potentially relevant studies for further scrutiny. The shortlisted articles underwent thorough full-text assessments, wherein critical appraisal of content and methodology was conducted. Essential parameters such as study design, methodology employed, key findings, and conclusions were systematically extracted and structured for subsequent analysis and synthesis. Integral to ensuring methodological robustness, a comprehensive quality assessment was conducted to gauge the methodological rigor and validity of the included studies. Leveraging established quality assessment tools or criteria pertinent to the nature of the articles under review, this appraisal further fortified the scholarly integrity of the synthesis. The next phase entailed a meticulous examination of the extracted data, aimed at identifying prevailing themes, emerging trends, and discernible gaps within the literature landscape. This iterative process of analysis and interpretation culminated in the development of

coherent narratives underpinned by scholarly rigor and contextual relevance. Moreover, adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines underscored the transparency and methodological robustness of the review process. A meticulously crafted PRISMA flowchart (Table 1) delineated the trajectory of article selection, screening, inclusion, and exclusion, thus ensuring clarity and transparency in the review pathway. Subsequent to the synthesis of findings, the narrative underwent rigorous peer review, incorporating feedback from peers and mentors to enhance clarity, coherence, and scholarly integrity.

3. Exosomes biology and applications

Exosomes have triggered a significant shift in how we perceive intercellular communication in the scientific community. Initially, these microscopic vesicles were believed to be a waste disposal mechanism used by cells. However, researchers soon discovered that exosomes, diminutive extracellular vesicles discharged by cellular entities, serve as conveyors of intercellular information and partake in a myriad of biological phenomena, notably within the field of oncology [4,5]. Exosomes are critical components of cell-to-cell communication, releasing signaling molecules, nucleic acids, and proteins that transmit biological information to other cells. Exosomes have been discovered to be released by a variety of different cell types, including immune cells, neurons, and cancer cells. Exosomes are essential in maintaining normal cellular functions, and their release and uptake have been linked to the emergence of diseases like cancer, cardiovascular diseases, and neurodegenerative disorders [6]. Exosomes could be used to create novel diagnostic and therapeutic methods for a variety of diseases. Exosomes can be isolated from bodily fluids, such as blood and urine, and their molecular content could be analyzed to provide valuable information about the state of the cells that released them. As a result, exosome-based liquid biopsy techniques for cancer diagnosis and monitoring and exosome-based drug delivery systems for targeted

Table 1
PRISMA flow chart of the study.



therapy approaches have been developed. Their importance in maintaining normal cellular function and their role in the development of various diseases have fueled scientific interest. The full diagnostic and therapeutic potential of exosomes may be unlocked with further research [7]. The proteins found in exosomes include tetraspanins, which are integral membrane proteins that play a crucial role in the formation and release of exosomes. Perhaps among the most intriguing aspects of exosomes is their content of nucleic acids, including RNA and DNA. Various RNA molecule types can be found in exosomes; for example, mRNA, miRNA, and small non-coding RNA molecules, which can regulate gene expression and cellular function [8]. The presence of RNA molecules in exosomes has made them an attractive target to develop liquid biopsy approaches for the detection and monitoring of cancer. The diverse range of lipids, nucleic acids, and proteins of exosomes, make them a valuable tool for studying cellular processes and developing new diagnostic and therapeutic approaches [6,7,9]. The structure of the exosome is schematically shown in Fig. 1.

MicroRNAs are non-coding RNA molecules of small size that govern gene expression by targeting specific messenger RNAs (mRNAs), leading to mRNA degradation or translational inhibition. Encapsulated within exosomes, miRNAs are released by donor cells and internalized by recipient cells, thereby modulating gene expression and influencing cellular functions. Similarly, long non-coding RNAs, a distinct class of non-coding RNA molecules with considerable length, also find packaging into exosomes. By partaking in diverse cellular processes, such as epigenetic regulation, transcriptional control, and post-transcriptional regulation, exosomal lncRNAs are involved in a range of physiological and pathological phenomena. Acting as signaling molecules, they exert regulatory effects on cellular responses and have been linked to the pathogenesis of various diseases, including cancer, neurodegenerative disorders, and cardiovascular conditions. Exosomal cargo is not limited to nucleic acids; these vesicles also encapsulate an assortment of proteins, which can vary depending on the cell type, cellular conditions, and disease state. These proteins encompass membrane proteins, cytoplasmic proteins, signaling molecules, and enzymes, among others. Their presence within exosomes is reflective of the cellular origin of these vesicles and is pivotal in mediating their functional interactions with recipient cells. By modulating cell signaling pathways, facilitating cell-to-cell communication, and participating in immune responses, exosomal proteins significantly contribute to the biological effects of exosomes [8,10,11].

Tracing exosomes is important to understand their role in RCC and other diseases. One of the primary functions of exosomes is to transport molecular cargo, containing nucleic acids, lipids, and proteins, among cells (Fig. 2). This transfer of molecules can lead to changes in cellular behavior and can have a significant impact on the recipient cell's phenotype. For example, exosomes released by immune cells can transfer signaling molecules to other immune cells, modulating the immune response. Exosomes also play a significant part in removing unwanted cellular components, such as misfolded proteins or damaged organelles, by transferring them to other cells for degradation. This process, known as exosomal-mediated autophagy, is essential for maintaining cellular homeostasis. In addition to their essential physiological functions, exosomes also play a crucial part in the pathogenesis of illnesses, including cancer [10,12]. Cancer cells release exosomes containing oncogenic proteins and nucleic acids that can promote tumor growth and metastasis. Exosomes can also participate in immune evasion by inhibiting the activity of immune cells [13–15]. Secretion and transfer of exosomes are schematically shown in Fig. 3.

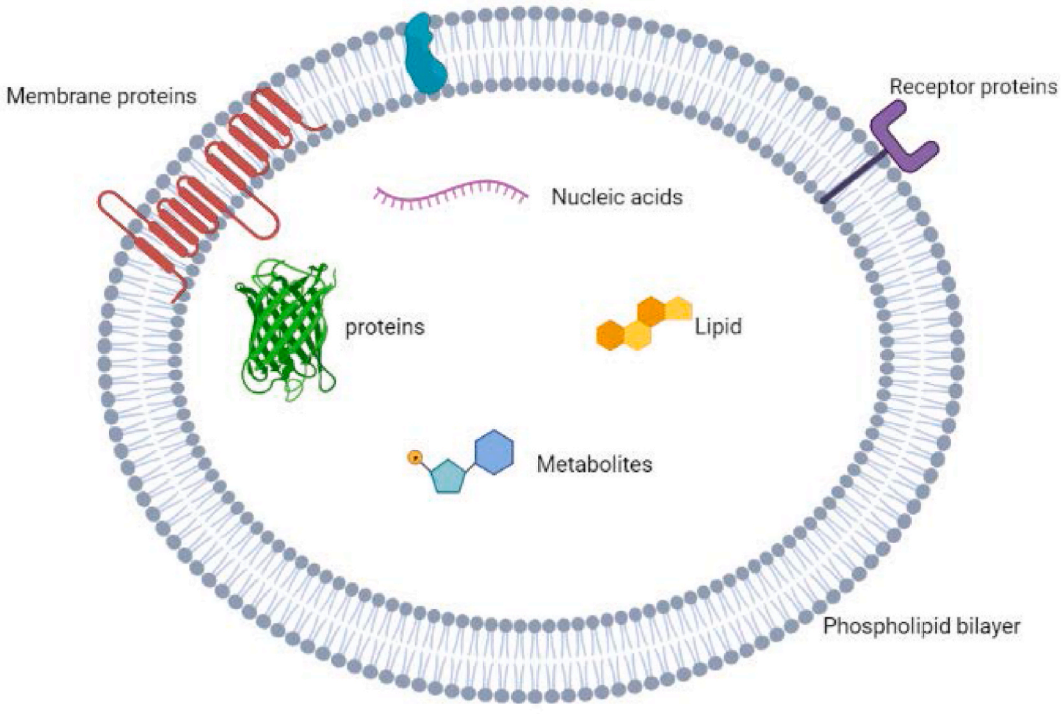


Fig. 1. The structure and content of exosome.

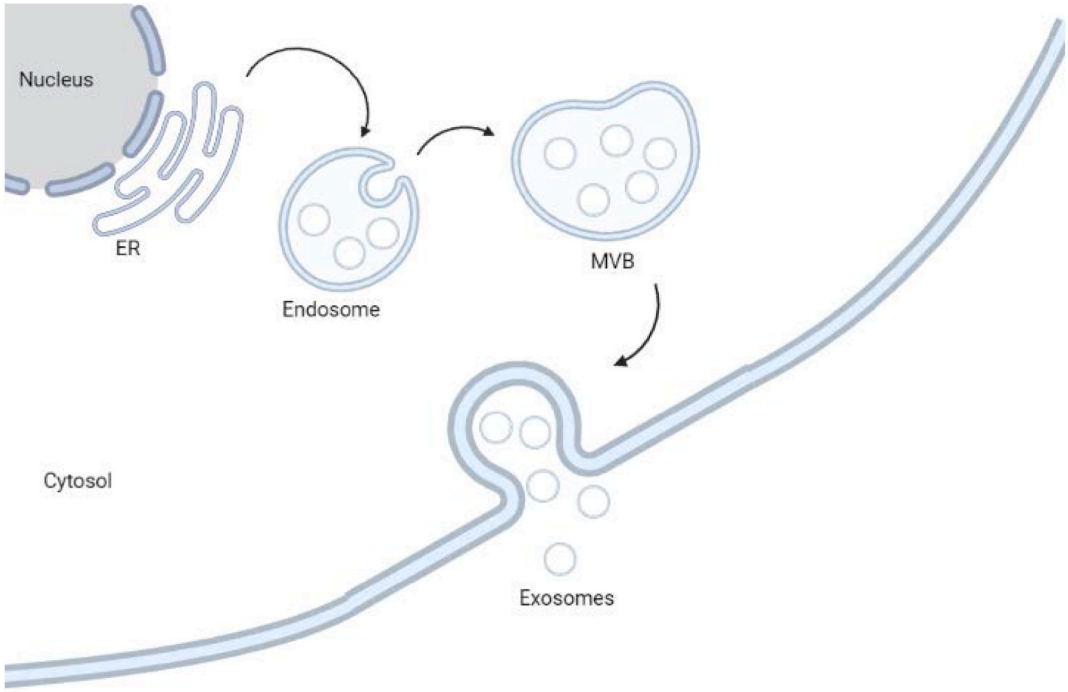


Fig. 2. Secretion of exosomes.

A variety of techniques, including fluorescence microscopy, electron microscopy, and flow cytometry, provide researchers with valuable insights into the behavior and function of exosomes [16]. Fluorescence microscopy involves the labeling of exosomes with fluorescent dyes, allowing for real-time visualization of their movement and interactions with other cells. This technique is particularly useful for studying the dynamic behavior of exosomes and their particular function in cellular communication [17]. Electron microscopy provides high-resolution imaging of exosomes, allowing researchers to observe their size, shape, and structure in detail. This

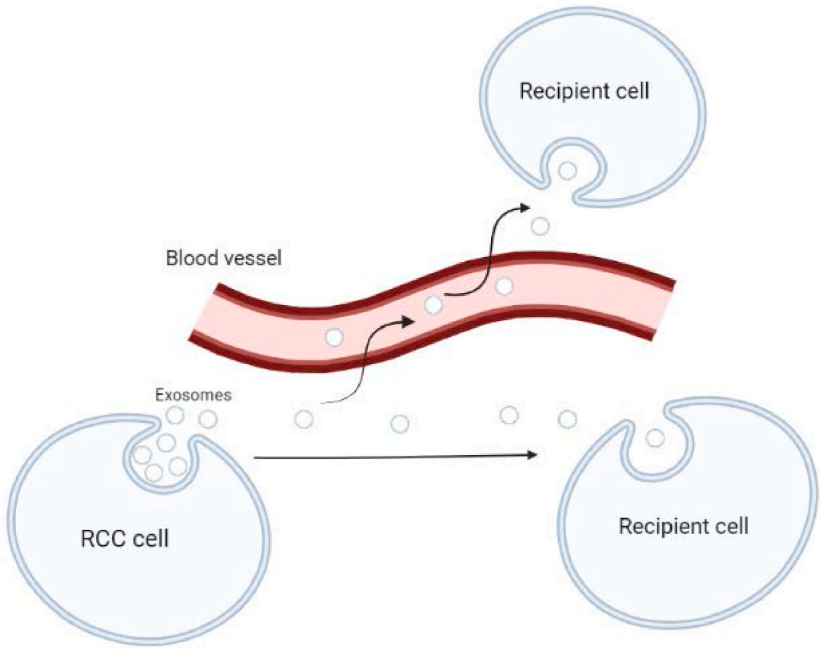


Fig. 3. The transfer of exosomes from RCC cells to other cells with the possibility of transfer through blood vessels.

technique is especially useful for studying the physical characteristics of exosomes and their interactions with other cellular components [18]. Flow cytometry is another technique that enables researchers to analyze exosomes according to their size and quantity. This technique is particularly useful for quantifying exosomes in a sample and for identifying specific markers on their surfaces [19]. By using these techniques, researchers can gain a better understanding of the mechanisms by which exosomes contribute to the development and progression of diseases such as RCC. This information can then be used to develop new diagnostic and therapeutic approaches that specifically target exosomes' function in the disease process.

Overall, research into exosomes has provided significant insight into cellular communication and disease pathogenesis. Their diverse functions and ability to transfer molecular cargo between cells make them a promising target to develop novel diagnostic and therapeutic strategies against diseases.

4. Molecules mechanism of exosomes in RCC

Exosomes exert a pivotal influence on the progression of RCC through intricate molecular mechanisms. These nanosized extracellular vesicles facilitate intercellular communication by transporting bioactive cargo, including proteins, lipids, and nucleic acids, thus modulating various aspects of tumor biology within the renal microenvironment [20–22]. Exosomes derived from RCC cells play a crucial role in promoting angiogenesis, a hallmark of tumor progression, by delivering pro-angiogenic factors to endothelial cells. This facilitates the formation of new blood vessels, thereby supporting tumor growth and metastasis [21,23,24]. On the other hand, exosomes participate in immune regulation by modulating the activity of immune cells within the tumor milieu. Specifically, RCC-derived exosomes have been shown to induce apoptosis of T cells, inhibit the cytotoxic function of natural killer cells, and foster the expansion of immunosuppressive cell subsets such as regulatory T cells and myeloid-derived suppressor cells. Thereby, they create an immunosuppressive microenvironment, which is conducive to tumor growth [22,25–28]. Moreover, exosomes contribute to the metastatic cascade in RCC by orchestrating processes such as epithelial-mesenchymal transition (EMT) in tumor cells and preparing pre-metastatic niches in distant organs. Through the transfer of molecular cargo, exosomes enhance the migratory and invasive capacities of tumor cells, which facilitate their dissemination to secondary sites [27–30]. Furthermore, exosomes are implicated in mediating resistance to conventional chemotherapy and targeted therapies in RCC. By shuttling drug efflux pumps, anti-apoptotic proteins, and pro-survival factors to recipient cells, exosomes confer resistance traits upon tumor cells, thereby promoting treatment evasion and disease recurrence [21,26,28]. Understanding the intricate molecular mechanisms underlying exosome-mediated regulation of RCC progression holds significant implications for the development of targeted therapeutic strategies aimed at disrupting intercellular communication networks and impeding tumor advancement.

5. RCC diagnosis & treatment

RCC is a complex disease that poses significant diagnostic and therapeutic challenges. It is critical to develop new and effective diagnostic approaches to ensure early detection and prompt intervention. Current diagnostic methods for RCC have limitations and may not provide reliable results in all cases [11]. However, researchers are exploring innovative approaches to improve the accuracy of RCC diagnosis, such as utilizing liquid biopsy and AI-powered analyses [31]. Standardization of diagnostic methods and criteria is also necessary to ensure consistent and accurate diagnosis for RCC. Utilization of multiple diagnostic approaches may also be necessary to improve the sensitivity and specificity of diagnostic methods [32]. In addition to augmentation of accuracy for RCC diagnosis, it is also important to develop personalized treatment options based on the individual characteristics of each patient's tumor. This can involve analyzing the genetic mutations present in the tumor and tailoring treatments to target those specific mutations [33]. Additionally, the use of immunotherapy, which harnesses the body's immune system to fight cancer, has shown promise in RCC treatment [34].

Exosomes are microscopic particles that are released by cells, and scientists have been studying them in RCC. Early detection is pivotal for the effective treatment of RCC, and exosomes have shown promise as potential biomarkers for its diagnosis and prognosis. Research has shown that exosomes from RCC cells can be found in the blood and urine of patients with RCC, and they carry unique molecular signatures that can differentiate them from exosomes produced by normal kidney cells. This means that exosomes could be beneficial to detect the presence of RCC [35]. For instance, Campbell et al. have found that a specific protein called caveolin-1 in exosomes from the blood of patients with RCC was associated with a higher risk of tumor recurrence and worse survival [36]. Similarly, Kurahashi et al. have discovered that the levels of certain microRNAs in exosomes from the urine of RCC patients were significantly different from those found in healthy individuals, indicating their potential as biomarkers [37]. Hosseinikhah and colleagues have also stated that exosomes can be used as effective therapeutic carriers by studying the effect of exosomes on tumor growth [38]. Ivanova et al. have demonstrated that miRNA-146a and miRNA-126 can be applied for the immunotherapy of RCC. They have investigated the exosomes' function in the treatment of RCC [39]. While exosomes hold promise as RCC diagnostic biomarkers, additional studies are required to determine their clinical usefulness and develop standardized methods for their detection and measurement.

In conclusion, improved RCC diagnosis is essential for improved patient outcomes and increased chances of successful treatment. Ongoing research is required to develop novel and effective diagnostic tools and approaches that can accurately detect RCC at the earliest stage. Additionally, the development of personalized treatment options based on the individual characteristics of tumors can further increase the chances of successful treatment.

5.1. Exosomal miRNAs in RCC diagnosis

Recent studies suggested that exosomal miRNAs could act as biomarkers for RCC diagnosis and prognosis. Further research is necessary to fully comprehend the complex role of miRNAs in RCC and develop effective exosomal miRNA-based diagnostic tools. Since exosomal miRNAs play a significant role in RCC pathogenesis, they could be potentially used as biomarkers for diagnosis and prognosis. Recent studies have also shown that exosomal miRNAs could serve as conceivable biomarkers for the detection and prognosis of RCC. For example, serum exosomal miR-1233 has been discovered to be noticeably upregulated in RCC patients and could differentiate RCC from healthy controls with great sensitivity and specificity [40]. Similarly, the expression of exosomal miR-146b-5p and miR-99a-5p was discovered to be significantly correlated with RCC patient survival and could serve as prognostic markers for RCC [41]. Moreover, the analysis of urinary exosomal miRNAs could provide a non-invasive and practical method for RCC detection and monitoring. According to studies, urinary exosomal miR-10a-5p and miR-30a-5p were significantly upregulated in RCC patients and could differentiate RCC from healthy controls with high accuracy [42]. Another study has demonstrated that urinary exosomal miR-122-5p could serve as an attainable biomarker for the early detection of RCC [43].

Other studies showed that a panel of exosomal miRNAs (miR-378, miR-451a, miR-16, and miR-106b) can act as a diagnostic method for RCC with high accuracy. Research has shown that these exosomal miRNAs were significantly upregulated in RCC patients compared to healthy controls [44–47]. Other studies have suggested that using some exosomal miRNAs such as miR-23a-3p, miR-210-3p, and miR-222-3p can create a suitable diagnostic panel for RCC. Studies have shown that the use of this panel can have good diagnostic accuracy [48–50]. One study in 2021 concluded that the integrated analysis of exosomal miRNAs and proteins can provide valuable diagnostic biomarkers for RCC. The panel of miRNAs, including miR-192, miR-let-7c, and miR-122, showed promising diagnostic accuracy and highlighted potential molecular mechanisms underlying RCC [51]. It has also been concluded that the panel of exosomal miRNAs, including miR-210, miR-1238, miR-141, and miR-200a, could serve as promising diagnostic biomarkers for RCC. Further validation studies with larger cohorts are warranted to confirm these findings and evaluate the clinical utility of exosomal miRNAs in RCC diagnosis [40,52–54].

It could be deduced that exosomal miRNAs are of significant implications in RCC diagnosis and prognosis. Further research in this field could lead to novel diagnostic strategies for RCC management.

5.2. Exosomal miRNAs for RCC treatment

Exosomal miRNAs have been demonstrated to have potential as therapeutic targets for cancer treatment, including RCC. By targeting specific miRNAs in exosomes, it may be possible to modulate their function and influence tumor growth and metastasis. One approach is to use exosomes as transporters for miRNA-based therapies. This involves the engineering of exosomes to express specific miRNAs that can target oncogenes or tumor suppressor genes, depending on the specific cancer type and context [55]. Another approach is to use exosomes to enhance the efficacy of existing cancer treatments, like chemotherapy or immunotherapy. Exosomes can be isolated from cells that are sensitive to these treatments and be used to deliver miRNAs to cancer cells that are resistant to therapy. This may help to sensitize these cells to the treatment and improve overall treatment outcomes [56].

Exosomes can act as therapeutic agents or as targets for developing new drugs. By delivering specific miRNAs to cancer cells or inhibiting the expression of specific miRNAs, there is a chance to modulate gene expression and thereby alter cancer cell behavior. For

Table 2
Exosomal miRNAs proposed for use in RCC diagnosis and treatment.

Exosomal miRNAs	Biomarkers for RCC diagnosis	Therapeutic targets	Expression in RCC	Function	Ref
miR-1233	☒	☐	Downregulated	Tumor suppressor	[61]
miR-146b-5p	☒	☐	Downregulated	Tumor suppressor	[62]
miR-99a-5p	☒	☐	Downregulated	Tumor suppressor	[63]
miR-10a-5p	☒	☐	Downregulated	Regulation of Signaling Pathways	[64]
miR-30a-5p	☒	☐	Downregulated	Suppression of Metastasis and Invasion	[65]
miR-122-5p	☒	☐	Downregulated	Tumor suppressor	[43]
miR-378	☒	☐	Downregulated	Tumor suppressor	[44]
miR-451a	☒	☐	Downregulated	Angiogenesis Inhibition	[66]
miR-16	☒	☐	Downregulated	Regulation of cell cycle	[67]
miR-106b	☒	☐	Upregulated	Tumor Promotion	[68]
miR-23a-3p	☒	☐	Upregulated	Angiogenesis Regulation	[69]
miR-210-3p	☒	☐	Upregulated	Promotion of cell Proliferation	[70]
miR-222-3p	☒	☐	Upregulated	Inhibition of Apoptosis	[50]
miR-192	☒	☐	Downregulated	Regulation of Apoptosis	[71]
miR-let-7c	☒	☐	Downregulated	Tumor suppressor	[72]
miR-122	☒	☐	Downregulated	Tumor suppressor	[43]
miR-210	☒	☐	Upregulated	Angiogenesis promotion	[43]
miR-1238	☒	☐	Downregulated	Tumor suppressor	[73]
miR-141	☒	☐	Downregulated	Tumor suppressor	[74]
miR-200a	☒	☐	Downregulated	Modulation of cell Invasion and Metastasis	[75]
miR-34a	☐	☒	Downregulated	inhibit cancer cell growth	[76]
miR-210	☐	☒	Upregulated	Chemoresistance and Radioresistance	[77]

example, some research has indicated that exosomal miRNAs can sensitize cancer cells to chemotherapy by downregulating drug-resistance genes. In addition, it has been shown that exosomal miRNAs modulate the immune response, which may help to overcome immune evasion by cancer cells. Exosomal miRNAs may also have applications in targeted drug delivery. By engineering exosomes to carry therapeutic miRNAs, there is a chance to achieve targeted delivery of these molecules to cancer cells. This strategy may increase the effectiveness of cancer treatment while reducing side effects [57].

There is ongoing research to identify specific miRNAs that can be utilized for RCC treatment. One of the potential candidates is the miR-34a, which has been demonstrated to have tumor suppressor activity in RCC cells, miR-34a has emerged as a promising therapeutic candidate for RCC treatment. It is a tumor-suppressive microRNA that plays a crucial role in regulating key pathways involved in tumor growth, invasion, and metastasis. Downregulation of miR-34a is frequently observed in RCC, contributing to tumor progression and resistance to therapy. Restoring the expression of miR-34a has shown potential therapeutic benefits in preclinical studies and holds promise for clinical applications [58]. Another potential candidate is miR-210, which is overexpressed in RCC and has been demonstrated to promote angiogenesis and tumor growth. By targeting these specific miRNAs using various methods, including miRNA mimics or inhibitors, researchers aim to develop novel therapeutic approaches against RCC. miR-210 is a microRNA that has garnered significant attention in the context of renal cell carcinoma (RCC) treatment. It is considered a master regulator of hypoxia-inducible factor (HIF) signaling and is frequently upregulated in RCC [59]. Additional research is needed to fully understand the mechanisms of action and potential side effects of these treatments. In 2022, Hirofumi Yoshino et al. stated that microRNA-1 derived from exosomes can have tumor suppressor function for RCC cells [60]. The possibility of using all the miRNAs mentioned in the diagnosis and treatment of RCC is summarized in Table 2.

Overall, the use of exosomal miRNAs in cancer treatment is a promising area of research that may lead to the development of new and more effective therapies for renal cell carcinoma and other types of cancer.

5.3. Exosomal lncRNAs and RCC

Exosomal long non-coding RNAs (lncRNAs) play crucial roles in RCC. In the context of RCC, dysregulated exosomal lncRNAs have been identified in both tumor tissues and the corresponding exosomes. The transfer of these aberrant lncRNAs from tumor cells to recipient cells via exosomes holds significance for multiple cellular processes, one prominent area of investigation concerning exosomal lncRNAs in RCC pertains to their potential utility as non-invasive biomarkers for early detection and diagnosis. By scrutinizing exosomes present in readily accessible body fluids like blood and urine, researchers seek to unveil specific lncRNA signatures that bear relevance to RCC onset and progression [78]. Notwithstanding the potential promises offered by exosomal lncRNAs in RCC research, it is imperative to acknowledge that the field remains in its infancy. Comprehensive investigations are warranted to fully elucidate the functional significance of specific lncRNAs and their contributions to RCC biology. Furthermore, the clinical utility of exosomal lncRNAs as viable biomarkers and therapeutic targets necessitates rigorous exploration and subsequent clinical trials.

In previous years, there has been increasing research interest in understanding the functions of various exosomal lncRNAs in RCC [78]. One of the most thoroughly investigated exosomal lncRNAs in RCC is HOTTIP, which is upregulated in RCC and has been connected to increased cell proliferation, migration, and invasion. Research has indicated that inhibition of HOTTIP could be a potential strategy for RCC treatment [79]. Another exosomal lncRNA that has been linked to RCC is MALAT1, which is also overexpressed in RCC and is known to promote cell growth and invasion. Inhibition of MALAT1 has been demonstrated to reduce RCC cell proliferation and induce apoptosis [80]. Other exosomal lncRNAs that were discovered to be potential biomarkers or therapeutic targets in RCC include lncRNA-ATB [81], HULC [82], and H19 [83]. These lncRNAs have been discovered to be upregulated in RCC and it could lead to tumor progression and metastasis. LeQu et al. stated in their review in 2016, the existence of an ncRNA called lncARSR in exosomes isolated from RCC cells can make these cells resistant to Sunitinib, which is a drug used in the therapy of RCC, and it caused problems with treatment [84]. Therefore, if it manages to somehow prevent the function of this lncRNA, an important step can be taken toward the treatment of RCC disease. The possibility of using all the lncRNAs mentioned in the diagnosis and treatment of RCC is summarized in Table 3.

Overall, the emerging evidence suggests that exosomal lncRNAs are key players in the development and progression of RCC, and targeting these molecules could offer promising new avenues for the treatment and diagnosis of this disease. However, further studies are needed to fully understand the complex regulatory mechanisms of exosomal lncRNAs in RCC and to identify the most effective ways to target them for therapeutic benefit [78]. Aside from the mentioned exosomal lncRNAs, there are several other exosomal lncRNAs have been recognized as potential biomarkers or therapeutic targets in RCC. It's worth noting that exosomal lncRNAs are just one piece of the puzzle and when it comes to RCC many other genetic and molecular factors could lead to the development and

Table 3
Exosomal lncRNAs proposed for use in RCC diagnosis and treatment.

Exosomal lncRNAs	biomarkers for RCC diagnosis	therapeutic targets	Expression in RCC	Function	Ref
HOTTIP	☐	☒	Upregulated	tumor progression	[79]
MALAT1	☒	☐	Upregulated	cancer development and progression	[80]
LncRNA-ATB	☐	☒	Upregulated	tumor progression and metastasis	[81]
HULC	☐	☒	Upregulated	tumor progression and metastasis	[82]
H19	☐	☒	Upregulated	tumor progression and metastasis	[83]
lncARSR	☐	☒	Upregulated	Drug-resistant	[84]

progression of the disease. Nonetheless, the growing body of research on exosomal lncRNAs in RCC is providing important insights into the molecular mechanisms underlying the disease and is opening up exciting new possibilities for treatment.

5.4. Exosomal proteins and RCC

Exosomal proteins have been studied as potential diagnostic, prognostic, and therapeutic agents of RCC. CD105 is a protein that is expressed on the surface of endothelial cells and has been demonstrated to be upregulated in renal cancer. Exosomal CD105 has been proposed as a possible RCC diagnostic biomarker [85]. TIMP-1 (tissue inhibitor of metalloproteinases-1) is another protein that participates in the regulation of extracellular matrix remodeling and is often upregulated in cancer. Exosomal TIMP-1 has been proposed as a possible prognostic and diagnostic biomarker for RCC [86]. Annexin A3 is a protein that participates in cell signaling and is often upregulated in cancer. Exosomal Annexin A3 has been proposed as a possible prognostic and diagnostic biomarker for RCC [87]. The identification of these and other exosomal proteins in RCC could result in the development of more effective diagnostic and therapeutic methods. However, further research is needed to fully understand the roles of these proteins in renal cancer progression and to develop targeted therapies that can effectively disrupt their function in cancer cells.

In the context of RCC treatment, exosomal proteins hold promise for several applications, including targeted drug delivery, immune modulation, and biomarker discovery. Exosomes derived from normal cells can carry tumor suppressor proteins, such as p53 [88], PTEN [89], and VHL [90]. These proteins play important roles in regulating cell growth, apoptosis, and angiogenesis. Delivering exosomes loaded with tumor suppressor proteins to RCC cells may help restore normal cellular functions and inhibit tumor growth. Exosomes can also be engineered to carry immune-modulating proteins that enhance the anti-tumor immune responses. For example, exosomes can be loaded with cytokines like interleukin-2 (IL-2) or immune checkpoint inhibitors like programmed cell death protein 1 (PD-1) antibodies. These exosomes can then be used to activate and enhance the activity of immune cells, such as T cells and natural killer cells, to target RCC cells [91,92]. Heat shock proteins, such as HSP70 [93] and HSP90 [94], are known to play important roles in cellular stress response and protein folding. Exosomes derived from heat-stressed cells can contain increased levels of HSPs. These HSP-enriched exosomes can have potential therapeutic effects by inducing anti-tumor immune responses and enhancing the presentation of tumor antigens to immune cells [95]. Exosomal proteins derived from RCC cells can carry oncogenic proteins or signaling molecules that contribute to tumor progression. Understanding the specific cargo of these exosomes may provide insights into the mechanisms of RCC development and identify potential therapeutic targets [96]. The possibility of using all the proteins mentioned in the diagnosis and treatment of RCC is summarized in Table 4.

It is important to note that while exosomal proteins hold promise for RCC treatment, their use as therapeutic agents is still in the early stages of research and development. Further studies are needed to optimize the cargo loading, delivery methods, and safety profiles of exosomes for effective RCC treatment. Clinical trials and preclinical studies are ongoing to explore the therapeutic potential of exosomes in various cancers, including RCC [97]. Overall, exosomal proteins have great potential as RCC treatment targets and as biomarkers for RCC diagnosis, prognosis, and treatment monitoring. However, more research is needed to fully understand the biology of exosomes and to develop effective strategies for their clinical use.

6. Exosome and personalized medicine for RCC

Exosomes contain various potential biomarkers that can be tracked and studied to understand the origins of different types of renal diseases, especially RCC. Since RCC patients do not show early symptoms, it is crucial to use the biomarkers for a reliable diagnosis. These biomarkers also can help in using specific treatments for each type of RCC patient. Therefore, studying the exosome contents of RCC patients is an important step toward personalized medicine.

Wwith the advent of personalized medicine, expanding consideration has been paid to accomplishing accurate diagnosis and the targeted treatment of different diseases [99]. The practice of tailoring medical care to each patient's unique characteristics is referred to as "personalized medicine." This includes the ability to divide people into subpopulations based on their resistance to a specific disease or treatment response [100,101]. In the past few years, numerous studies have been carried out with the aim of diagnosis and treatment of various types of cancer to achieve a personalized medicine approach. In the following, we present examples of information and materials that exosomes carry in patients with RCC, which could lead to their use in personalized medicine.

Table 4
Exosomal proteins proposed for use in RCC diagnosis and treatment.

Exosomal proteins	biomarkers for RCC diagnosis	therapeutic targets	Expression in RCC	Function	Ref
CD105	☒	☐	Upregulated	Angiogenesis	[85]
TIMP-1	☒	☐	Upregulated	Regulation of extracellular matrix	[86]
Annexin A3	☒	☐	Upregulated	Cell signaling	[87]
p53	☒	☒	Downregulated	Tumor suppressor	[88]
PTEN	☒	☒	Downregulated	Tumor suppressor	[89]
VHL	☒	☒	Downregulated	Tumor suppressor	[90]
IL-2	☒	☒	Downregulated	Immunomodulation	[91]
PD-1	☒	☒	Downregulated	Programmed cell death	[91,92]
HSP70	☐	☒	Downregulated	cellular stress response and protein folding	[98]
HSP90	☐	☒	Downregulated	cellular stress response and protein folding	[94]

Circulating microRNAs (present outside of the cells in the blood and other body fluids) are often found in communication with exosomes and mostly with RNA-binding proteins (Ago, HDL, etc.). The majority of the ideal features for biomarkers are present in microRNAs. They are specific to the concerned pathology, provide a solid sign of the disease before clinical symptoms show up, and show sensitivity to changes in the body or pathology. Therefore, they can predict the prognosis of a wide range of cancer patients. For example, in clear-cell-RCC miR-187 has been found down-regulated, resulting in poor patient survival [102]. Another example is miR-183, which promotes renal cell carcinoma's proliferation and metastasis. Exosomes released by human renal cancer stem cells raise miR-183 expression, which is also increased in blood and tissue samples of RCC patients [99]. Another study demonstrated that IFN-gamma production and activation of Tcytotoxic lymphocytes may be enhanced by exosomes derived from genetically altered RCC cells. According to a different study, a higher level of miR-15a slows down the expression of B-cell translation gene 2. ccRCC cell invasion, migration, and proliferation are all accelerated as a result. Therefore inhibition of this miR could be incorporated as a therapeutic strategy in the future. Exosomes derived from RCC cells, according to one study, can aid in the increase of lung metastases and tumor growth. Suppressing the MALAT-1 transcription factor may have the potential to decrease the malignant behavior of cells [103]. Through liquid biopsies, microRNAs can be extracted from a variety of bodily fluids, at a lower cost and faster than non-liquid samples. This looks like a significant step toward achieving personalized medicine [102].

It has been claimed that exosomes contain a higher concentration of particular proteins than the entire cell that produced them. For instance, the Tamm-Horsfall protein's large polymeric fibers typically cover urinary exosomes. Consequently, they wouldn't be able to connect to cell surfaces unless the polymeric network is dissolved locally. As a result, they may aid in comprehending how renal disease might be brought on by mutations in the Tamm-Horsfall protein [104]. Currently, natural exosomes are applied in primary clinical trials. For example, there are studies that the human bone marrow-derived MSC exosomes are loaded with TRAIL and used for the treatment of renal cancer *in vitro* [105]. According to the findings of a different study, exosomes derived from specific tumor cells can be home to their parent tumor cell type. Doxil, a sphere containing the cancer treatment doxorubicin (D-HT1080 exo), was engineered to be carried by tumor-derived exosomes (HT1080 exosomes). This survey showed significant suppression of tumor growth. They also engineered D-Hela exo and D-Exo to investigate the cellular uptake efficiency of Doxil. It has been indicated that the HT1080 tumor cell types absorbed the D-HT1080 exo at a significantly higher rate than the other engineered exosomes [106]. For some organs, including the liver, heart, lungs, brain, kidneys, bone, and skin, the regenerative potential of exosomes was pre-clinically demonstrated. This is a crucial therapeutic tool for personalized medicine. Since exosomes carry along the hallmarks of disease, exosome-based personalized medicine opens up additional opportunities for customizing treatment and diagnosis [107].

In conclusion, the integration of exosome research with personalized medicine approaches holds great potential in revolutionizing RCC patient care. The non-invasive nature of exosomal biomarkers and their capacity to reveal the tumor's molecular landscape offers unprecedented opportunities for precise diagnosis, prognosis, and treatment selection. As the field continues to evolve, exosome-based personalized medicine may ultimately pave the way for improved therapeutic outcomes and enhanced quality of life for RCC patients.

7. Exosomes and RCC drug delivery

Exosomes can deliver therapeutic genes/cargo specifically to the recipient cells due to their lipid bilayer membrane, which protects internal contents. Additionally, because of their nano-scale, exosomes can easily pass across biological membranes [108–110]. Exosomes transport therapeutic agents directly to target organs across a variety of biological barriers. For instance, exosomes derived from macrophages have delivered protein-like molecules across the blood-brain barrier [111]. There are two methods to load exosomes with drugs. Exogenous loading is the loading of exosomes by therapeutic agents following their isolation. This can be done via a variety of techniques, including incubation, electroporation, and sonication [112]. Additionally, to prevent off-target effects exosomes can be directed towards their target through specific ligands, which has been done previously for several tumors [113]. The development of novel therapeutic or diagnostic biomarkers is necessary since RCC is a frequent urological malignancy with a high mortality rate and the propensity to metastasize due to inadequate early-stage diagnosis and treatment resistance [114]. Due to the RCC's resistance to standard treatments like radiation or chemotherapy [115], metastatic RCC treatment remains challenging. Even though surgery is the primary curative treatment for patients with localized RCC, their survival is poor (having a 10 % chance of a 5-year survival rate). The most common clinical implications for the ccRCC treatments are VEGF, Raf Kinase, and mammalian target of rapamycin (mTOR) inhibitors [116,117]. The mTOR signaling pathway is compromised in more than 50 % of ccRCC patients [118]. Therefore, one strategy may be the exosomal encapsulation of drugs/siRNA targeting these pathways for specific delivery of therapeutics to the target tissue. So, exosomes have emerged as promising vehicles for drug delivery in RCC treatment. These small extracellular vesicles possess several desirable characteristics that make them attractive for therapeutic applications. Exosomes can be isolated from various cell sources, including MSCs, and can be loaded with miRNAs or other therapeutic cargo. Exosomes offer several advantages as drug delivery vehicles for RCC treatment. Firstly, exosomes have inherent tumor-targeting properties, allowing for specific delivery to RCC cells [119–121]. Additionally, they exhibit natural stability and biocompatibility, minimizing the risk of immunogenicity or adverse effects. Furthermore, exosomes can protect their cargo from degradation and enhance its delivery to target cells. However, despite these advancements, challenges remain in the clinical translation of exosomal drug delivery for RCC treatment. Optimizing methods for large-scale exosome production, improving cargo loading efficiency, enhancing targeting specificity, and ensuring controlled and sustained release of therapeutic cargo are areas that require further investigation. Furthermore, rigorous evaluation of the safety, efficacy, and pharmacokinetics of exosome-based therapies through well-designed clinical trials is necessary to establish their clinical utility. Understanding the bio-distribution, immunogenicity, and long-term effects of exosomes in patients with RCC will be critical for their successful integration into clinical practice. In 2021, Jacob W. Greenberg and colleagues also stated that ketoconazole can be delivered to RCC cells using exosomes [122]. This study has mentioned the ability of exosomes in drug delivery when drug molecules

can be attached to exosomes as adjuvants to target the desired cells. Mesenchymal stem cell exosomes (MSC-Exo) are useful for immune system modulation. Additionally, MSCs have a significant impact on the tumor microenvironment, particularly due to their anti-tumor effects [123]. However, still, the MSC-Exo role in ccRCC remains unknown. To determine whether exosomal miRNA can be used as potential noninvasive biomarkers for ccRCC treatment, Daoyuan Li et al., demonstrated that MSC-exosomes slow the progression of ccRCC through a T-cell immune response. MSC-Exo was injected into an orthotopic ccRCC mouse model and then the tumor metastasis was evaluated along with the dendritic cells, NK cells, and $CD8^+$ T cell counts. It was found that MSC-Exo therapy dramatically reduced tumor growth and spread while enhancing the immune response *in vivo*. The obtained results showed that MSC-Exo enhanced the sensitivity of ccRcc cells to NK cells. Moreover, their experimental results demonstrated that MSC-Exo could transport miR-182, targeting VEGFA against ccRCC [124]. Together, miR-182 inhibits VEGFA expression in MSC-Exo and stimulates T-cell's immune responses, which prevents the growth of ccRCC. These results revealed that the MSC-Exo containing miR-182 can stimulate T-cell activation and proliferation. Given that NK T cells are tumor cell killers, the sensitivity of ccRCC cells to NK cells suggests that the tumorigenicity was reduced [125].

In conclusion, exosomes hold great promise as carriers in RCC treatment. Their ability to efficiently deliver therapeutic cargo to RCC cells, their tumor-targeting properties, and their potential for combination therapies make them valuable tools in the fight against RCC. Continued research, rigorous preclinical and clinical investigations, and optimization of exosome-based therapies will pave the way for improved treatment strategies and better outcomes for RCC patients. The advantages of using exosomes as a therapeutic carrier are shown in Fig. 4.

8. Exosomes and new vaccines against RCC

As RCC is one of the most immune-sensitive human malignancies, several immunotherapeutic strategies have been implemented to boost antitumor immunity, including the administration of cytokines and tumor and dendritic cell-based vaccines [126]. However, the response rate of the administered cytokines and existing tumor vaccines was unsatisfactory [127]. As a result, there is an urgent need for the development of new therapeutic approaches for RCC therapy. The characteristics of an ideal tumor vaccine are the activation of tumor antigen-specific cytotoxic T-lymphocytes (CTL) and the improvement of the Th1-related cellular immune response while reducing the Th2-related humoral immune response. However, one of the limitations is the absence of an antigen delivery method that continues to hinder efficacy [128]. Tumor-derived exosomes have met all requirements for antigen presentation and successfully overcome the drawbacks of conventional vaccines. Tumor rejection antigens and tetraspanins, HSP70-80, MHC-I molecules, and LAMP1 are all enriched in them. They also simultaneously trigger cancer immunity and MHC-I-restricted T-cell responses [129–131]. On the other hand, tumor-derived exosomes express some immunosuppressive molecules, which lower their immunogenicity. Therefore, exosome-based immunotherapy needs to be modified to improve therapeutic efficacy. Since cancer cells have abundant

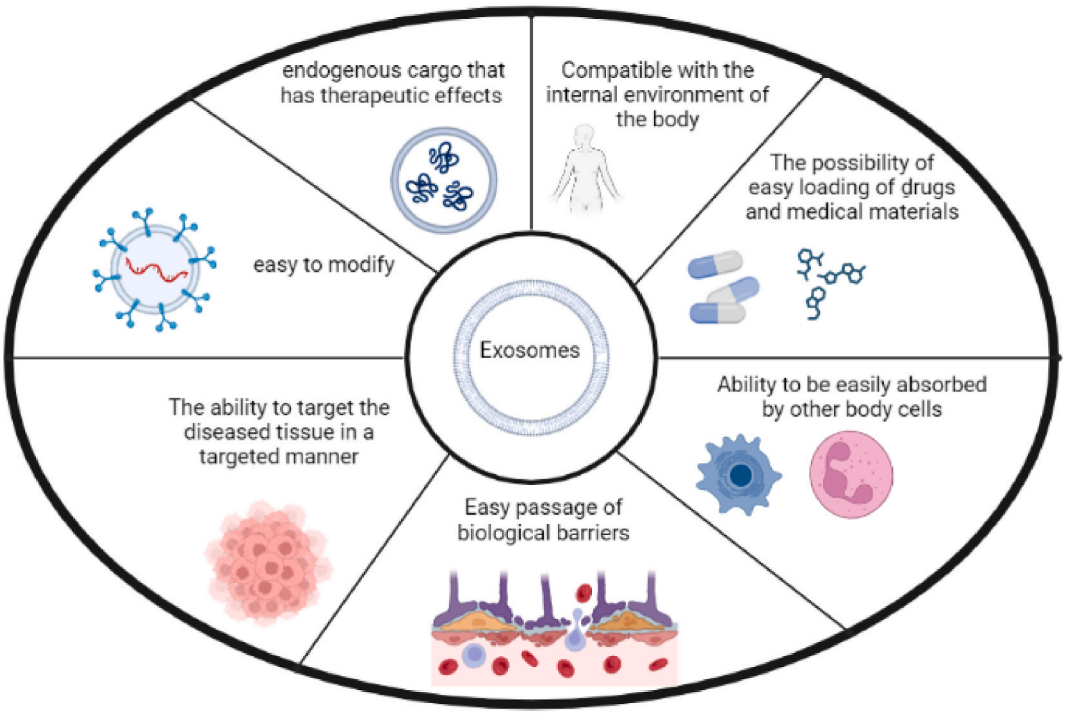


Fig. 4. Advantages of exosome as the therapeutic carrier.

RCC-associated antigen G250 [132], they can be used as a vaccine in renal carcinoma therapy. Antigen-presenting cells (APCs) and phagocytic cells both produce the important cytokine interleukin 12 (IL-12), which is critical for the stimulation of cellular immunity [133,134]. This proposed a potential approach for an exosome-based vaccination against RCC. The cytotoxic ability of NK and cytotoxic T cells can be stimulated by IL-12, which augments the level of Jak-STAT signaling intermediates in tumor and immune effector cells [135]. This change promotes the Th0 differentiation to Th1 and substantially stimulates IFN production. In a study, to develop a renal cancer exosome-based vaccine, exosomes expressing G250 were required. They investigated whether IL-12 tethering to RCCs exosomes could increase their immunogenicity and the generation of certain anticancer responses [136]. They discovered that IL-12-anchored RCC- derived exosomes carried GPI-IL-12 and G250, which dramatically increased their immunogenicity and effectively induced CTL. They induced an immune response directed toward the antigen, leading to more pronounced cytotoxic effects *in vitro* [136]. Thus, by transfecting the tumor cells with fusion genes from which they originated, cytokines can be effectively attached to exosomes via GPI anchor and functionally delivered at the local level. Exosomes derived from renal carcinoma were found to differ in their cytotoxic effects to RC-2, T24, and SW480, demonstrating their capacity to elicit an immune response specific to an antigen.

In conclusion, exosomes hold promise as a novel approach for the development of vaccines against RCC. Their unique properties, immunomodulatory capabilities, and ability to target tumor-specific antigens make them attractive candidates for enhancing anti-tumor immune responses. Continued research and clinical investigations will help unlock the full potential of exosome-based vaccines in RCC treatment, potentially leading to improved outcomes and better management of this challenging disease.

9. Conclusion

Exosomes have emerged as a highly fascinating discovery in the field of medical research. They have captured the attention of scientists and researchers alike. Nano-scale vesicles hold great potential in unraveling the inner workings of our cells, and researchers are now delving into their application for diagnosing and treating diseases like RCC. A significant advantage of using exosomes is that they can be easily found in fluids like blood, urine, and saliva. This means that doctors could potentially detect RCC with a simple urine test, which would be much less invasive than current diagnostic methods. Another exciting possibility is the use of exosomes to deliver drugs directly to cancer cells. Exosomes are great at targeting specific cells, and they can protect their cargo from being destroyed before it reaches its destination. This could make treatments more effective and reduce side effects. Of course, there are still some obstacles to overcome. Exosomes are pretty diverse, which can make them difficult to study and standardize. And we still have much to learn about how they work and interact with the body. But overall, exosomes have a lot of potential to improve how we diagnose and treat RCC. One of the most thrilling features of using exosomes in RCC research is their potential for biomarker discovery. Since exosomes are derived from cells, they can provide valuable information about the state of those cells. Researchers can look for a particular protein or nucleic acid in exosomes that are unique to RCC cells, which could lead to more accurate and earlier detection of the disease. The clinical relevance of exosomes in the context of RCC is underscored by their potential as biomarkers for various facets of disease management, including diagnosis, prognosis, and treatment response assessment. Exosomes, as carriers of molecular cargo, are reflective of the tumor's genetic and phenotypic traits. They also offer valuable insights into the intricate dynamics of RCC pathogenesis and progression.

However, as with any new technology, there are still some restrictions and difficulties to get past. As exosome research represents a nascent domain of investigation, a plethora of knowledge gaps persist, signifying a limited comprehension of their underlying intricacies and mechanisms. We still need to better understand how exosomes interact with the body and other cells, and how we can effectively manipulate them for diagnostic and therapeutic purposes. Another challenge is that exosomes are very small and can be challenging to isolate and purify. This can make it challenging to isolate a large amount of them for research, and there is still much work to be done in developing standard protocols and techniques for exosome isolation and analysis. Despite these challenges, the potential benefits of utilizing exosomes in RCC diagnosis and treatment are significant, and researchers are continuing to make strides in this area. As our understanding of exosomes and their function in disease grows, we may see even more exciting developments in the field in the coming years. Exosomes and the contents carried by these vesicles, especially lncRNAs, play a significant role in the formation, survival, and expansion of RCC cells. Several research has indicated that exosomal miRNAs can be utilized as non-invasive diagnostic and prognostic markers for RCC, providing a potential alternative to invasive imaging tests and biopsies. Exosomes also hold great potential as a treatment method for RCC. Therapeutic molecules can be delivered using them, such as siRNAs, to tumor cells, and can also be utilized to stimulate an immune response against cancer cells. While more study is required to fully comprehend the mechanisms by which exosomes contribute to RCC and to develop effective therapies based on these vesicles, the potential for exosomes in the diagnosis and treatment of RCC is exciting and promising. Overall, utilizing exosomes in RCC represents a growing research field that may ultimately lead to better results for patients with this disease. By harnessing the power of exosomes, researchers and clinicians can possibly develop new and innovative approaches to the diagnosis and treatment of RCC, ultimately improving patient outcomes and quality of life.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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