

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2022 January 15; 14(1): 1-368



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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

INDEXING/ABSTRACTING

The WJGO is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJGO as 3.393; IF without journal self cites: 3.333; 5-year IF: 3.519; Journal Citation Indicator: 0.5; Ranking: 163 among 242 journals in oncology; Quartile category: Q3; Ranking: 60 among 92 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO's CiteScore for 2020 is 3.3 and Scopus CiteScore rank 2020: Gastroenterology is 70/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xiang Li*; Editorial Office Director: *Ya-Juan Ma*.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

January 15, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Exosomes as potential diagnosis and treatment for liver cancer

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Author contributions: Wei XC and Liu LJ equally contributed to this manuscript; Wei XC designed the research, drafted and revised the paper; Liu LJ analyzed the data, drafted and revised the paper; Zhu F was responsible for the design, edit, and revision of the article and supervised the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: All authors do not have any conflicts of interest relevant to this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Supported by National Natural Science Foundation of China, No. 81971943 and No. 81772196; and the Medical Science Advancement Program (Clinical Medicine) of Wuhan University, No. TFLC 2018003.

Country/Territory of origin: China

Specialty type: Gastroenterology and hepatology

Provenance and peer review:

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Abstract

BACKGROUND

Liver cancer is the fourth most significant cause of cancer-related death. Lack of early diagnosis strategy and a scarcity of efficient therapy constitute the main reasons for its lethality. Exosomes, which contain various bioactive molecules, are characterized by high biocompatibility, low immunogenicity, and high transport efficiency. As a result, exosomes have become a research hotspot and present significant potential for cancer diagnosis biomarkers, biotherapeutics, therapy targets, drug carriers and therapeutic agents.

AIM

To explore the potential of exosomes in the diagnosis and treatment of liver cancer.

METHODS

We conducted a systematic literature search *via* PubMed and Web of Science. The following keywords were used: "exosomal biomarkers", "exosomal therapy", "exosomal therapy", and "liver cancer" or "HCC". The duplicate data were deleted by EndNote software. Literature search focused on full-texts and references of each article were carefully checked. One author (Xiao-Cui Wei) screened the literature that met the following inclusion criteria: (1) Detection of exosomes or their contents in clinical samples (body fluid or tissue); or (2) Exosomes served as drug carriers or therapeutic factors. Two authors (Xiao-Cui Wei and Li-Juan Liu) independently reviewed all retained literature and analyzed the information.

RESULTS

A total of 1295 studies were identified using the systematic literature search. Of these, 835 duplicate studies were removed. A further 402 irrelevant studies were excluded due to being irrelevant, including other diseases, review articles, the literature containing neither clinical samples nor animal experiments, exosome-independent studies, methods for detecting exosomes, or articles in Chinese. Finally, 58 published papers were retained and analyzed in the study. It showed a

Invited article; Externally peer reviewed.

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Received: March 22, 2021

Peer-review started: March 22, 2021

First decision: June 14, 2021

Revised: July 3, 2021

Accepted: September 8, 2021

Article in press: September 8, 2021

Published online: January 15, 2022

P-Reviewer: de Melo FF

S-Editor: Ma YJ

L-Editor: Kerr C

P-Editor: Yu HG



list of potential exosomal biomarkers that were upregulated in the blood samples of patients with liver cancer. Those downregulated in exosomes might serve as possible biotherapeutics. Some exosomes derived from cells in vitro were used for cytology or animal experiments to explore the mechanism of these exosome contents in disease. These contents might serve as potential targets for liver cancer. Additionally, we also discussed that exosomes serve as drug carriers or therapeutic factors.

CONCLUSION

Exosomes might serve as potential biomarkers or therapeutic biotargets in liver cancer and have the potential to act as drug carriers and self-treatment factors for liver cancer patients.

Key Words: Exosomes; Liver cancer; Biomarker; Treatment; Drug delivery system

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Core tip: We used a literature search to identify potential exosome diagnostic markers and novel therapeutic strategies for liver cancer. The latest literature was published in June 2021. Results were presented in tabular form, including 40 potential liver cancer biomarkers, 13 potential biotherapeutics, and 10 potential therapeutic targets for hepatocellular carcinoma. In addition, we also listed papers about exosomes as drug carriers and therapeutic factors.

Citation: Wei XC, Liu LJ, Zhu F. Exosomes as potential diagnosis and treatment for liver cancer. *World J Gastrointest Oncol* 2022; 14(1): 334-347

URL: <https://www.wjgnet.com/1948-5204/full/v14/i1/334.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v14.i1.334>

INTRODUCTION

Liver cancer is a common malignancy and the fourth leading cause of cancer death worldwide[1]. It is one of the most challenging cancers to treat. For patients with an early stage of liver cancer, surgical treatment is the standard of care. However, most patients with liver cancer are already in the advanced stage at the initial diagnosis, which results in a poor prognosis[2]. Currently, α -fetoprotein (AFP) is the most commonly used serum marker for liver cancer[3]. However, AFP has a sensitivity of 41%–64% and a specificity of 80%–94%, which is often missed diagnosis, especially in the early stages of liver cancer[4]. Therefore, it is vital to develop more sensitive and specific liver cancer biomarkers to improve patient survival.

Recent studies have shown that exosomes have potential as biomarkers for liver cancer[5]. Once considered cellular waste, exosomes are rich in bioactive molecules, such as proteins, lipids, and nucleic acids[6,7]. Almost all human cells can secrete exosomes. Tumor cells release more exosomes than normal cells, and the exosome contents of tumor cells are different from those of normal cells[8,9]. Additionally, the exosomal envelope protects proteins, nucleic acids, and other substances in exosomes from degradation by extramembrane enzymes[10]. The stability and abundance of exosome contents show the advantages of its unique liver cancer biomarkers.

Exosomes are widely involved in cell-to-cell communication. They can deliver their functional RNAs and proteins to recipient cells and affect their physiological functions [11]. Therefore, exosomes can also serve as drug delivery vehicles. Here, we summarize the potential of exosome contents in the diagnosis and treatment of liver cancer, provide new ideas for the diagnosis and treatment of liver cancer, and promote further research on the potential clinical applications of exosomes.

MATERIALS AND METHODS

Literature search

According to the conventional research methods of systematic review[12], a systematic literature search was conducted in PubMed and Web of Science using the following keywords: "exosomal biomarkers", "exosomal therapy", "exosomal therapy" and "liver cancer" or "HCC". The EndNote software was used to delete duplicate data[13]. The latest literature was published in June 2021. Literature search focused on full texts. Two reviewers independently screened the references of each article to remove the irrelevant studies according to our inclusion criteria. The inclusion criteria were as follows: (1) Detection of exosomes or their contents in clinical samples (body fluid or tissue); or (2) Exosomes served as drug carriers or therapeutic factors. Two authors (Xiao-Cui Wei and Li-Juan Liu) independently reviewed the full texts of all retained literature and analyzed the information.

Data extraction

The data collected from each study included the clinical sample, expression level, and application of exosomes divided into three major segments. The first part involved the exosomes isolated from the body fluid samples. The second part meant the data that were relevant to the detection of exosomal contents in the clinical tissue samples. The third part included the collection of data pertinent to the application of exosomes.

RESULTS

Literature selection

A total of 1295 studies were identified using the systematic literature search. After 835 duplicate studies were found and omitted, 460 were screened by two independent reviewers. A further 402 irrelevant studies were excluded, including review articles, other diseases, records containing neither clinical samples nor animal experiments, exosome-independent studies, methods for detecting exosome or articles in Chinese. Finally, 58 published papers were included in the study (Figure 1).

Exosomes are identified as potential biomarkers or potential biotherapeutics

In some literature, exosomes were isolated from liver cancer patients' blood samples. Then, the level of exosomal molecular contents was detected. Table 1[14-46] lists the potential biomarkers for liver cancer. In these studies, exosomal contents that were upregulated in blood exosomes might be potential exosomal biomarkers.

Table 2[22,35,39,47-56] includes potential biotherapeutics of exosomal contents for liver cancer. Those downregulated exosomal contents in blood liver cancer samples might serve as possible biotherapeutic drugs.

Exosomal contents are identified as potential therapeutic targets

The expression of exosomal contents was detected in liver cancer clinical tissue samples, and cytology or animal experiments were used to identify the role of exosomal contents. Upregulated exosomal contents might enhance hepatocellular carcinoma (HCC) progression, angiogenesis, and drug resistance, while downregulated exosomal contents might attenuate angiogenesis. In Table 3[57-66], all these abnormally expressed exosomal contents may become novel therapeutic targets for liver cancer.

Exosomes serve as drug carriers and therapeutic factors

Table 4[67-69] focuses on the carrier roles of exosomes in HCC. Drug-carrying exosomes were injected into tumor-prone mice to observe the effects of the drugs. These studies indicated that exosomes could serve as drug carriers that made cancer cells sensitive to antitumor drugs or enhanced their antitumor efficacy.

Table 5[70,71] shows the self-derived exosomes from dendritic cells as potential therapeutic factors. Data showed exosomes isolated from dendritic cells could inhibit tumor growth and improve the immune response. This indicated that exosomes serve as potential therapeutic factors.

Table 1 Potential biomarkers for liver cancer

Exosomal content	Sample	Expression	Isolation of exosomes	Content detection	Function	Ref.	Direction
HCC							
Proteins							
ANGPT2	Serum (<i>n</i> = 93)	Up	SBI	Immunoblotting and ELISA	Induces tumor angiogenesis	[14]	Potential targets
mRNAs							
hnRNPH1	Serum (<i>n</i> = 223)	Up	Total exosome isolation reagent (Thermo Fisher Scientific Co.)	qRT-PCR	Associated with the Child-Pugh classification, portal vein tumor emboli, lymph node metastasis, TNM stage, and OS	[15]	
LDH-C4	Serum (<i>n</i> = 212)	Up	exoRNeasy Serum/Plasma Midi Kit (Qiagen)	qRT-PCR	Related to treatments and recurrence prediction of HCC patients	[16]	
miRNAs							
miR-10b-5p	Serum (<i>n</i> = 37)	Up	Ultracentrifugation	qRT-PCR	Respectively, associated with early diagnosis and prognosis of HCC	[17]	
miR-1247-3p	Serum (<i>n</i> = 135)	Up	Ultracentrifugation	qRT-PCR	Shows a positive correlation with lung metastasis in HCC patients	[18]	Potential targets
miR-125b	Serum (<i>n</i> = 218)	Up	SBI	qRT-PCR	Discriminate HCC patients with a high risk of recurrence and poor prognosis	[19]	
miR-182	Serum and ascitic fluid	Up	exoRNeasy Serum/Plasma Midi Kit (Qiagen)	qRT-PCR	Up-regulated in NASH-induced liver cirrhosis with HCC compared to NASH-induced liver cirrhosis without HCC	[20]	
miR-21	Serum (<i>n</i> = 79)	Up	SBI	qRT-PCR	Related to TNM stage and other prognostic factors	[21]	
	Plasma (<i>n</i> = 150)	Up	SBI	qRT-PCR	Significantly higher in patients with HCC compared with cirrhotic patients and the control group	[22]	
	Serum (<i>n</i> = 90)	Up	Total Exosome Isolation Reagent (Invitrogen)	qRT-PCR	Positively correlated with cirrhosis and tumor stage	[23]	
	Serum (<i>n</i> = 95)	Up	Ultracentrifugation	qRT-PCR	Shows a positive correlation with survival in HCC patients	[24]	Potential targets
miR-215-5p	Serum (<i>n</i> = 37)	Up	Ultracentrifugation	qRT-PCR	Respectively, associated with early diagnosis and prognosis of HCC	[17]	
miR-224	Serum (<i>n</i> = 139)	Up	Total Exosome Isolation Kit	qRT-PCR	Related to tumor size and differentiate HCC patients from healthy controls	[25]	Potential targets
miR23-a/b	Serum (<i>n</i> = 50)	Up	Ultracentrifugation	qRT-PCR	A promising target for future treatment of HCC	[26]	Potential targets
miR-301a	Serum and ascitic fluid (<i>n</i> = 52)	Up	exoRNeasy Serum/Plasma Midi Kit (Qiagen)	qRT-PCR	Up-regulated in NASH-induced liver cirrhosis with HCC compared to NASH-induced liver cirrhosis without HCC	[20]	
miR-373	Serum and ascitic fluid (<i>n</i> = 52)	Up	exoRNeasy Serum/Plasma Midi Kit (Qiagen)	qRT-PCR	Up-regulated in NASH-induced liver cirrhosis with HCC compared to NASH-induced liver cirrhosis without HCC	[20]	
miR-4661-5p	Serum (<i>n</i> = 720)	Up	SBI	qRT-PCR	Associated with the prognosis of patients with HCC	[27]	

miR-638	Serum (<i>n</i> = Up 54)	Ultracentrifugation	qRT-PCR	Promising for surveillance of HCC recurrence	[28]	Potential targets
miR-665	Serum (<i>n</i> = Up 40)	SBI	qRT-PCR	Associated with tumor size, invasion, and clinical stage of HCC patients	[29]	Potential targets
miR-92a-3p	Plasma (<i>n</i> = Up 42)	Ultracentrifugation	qRT-PCR	Shows a positive correlation with metastasis in HCC patients	[30]	Potential targets
miR-92b	Serum (<i>n</i> = Up 121)	SBI	qRT-PCR	Prediction of posttransplant HCC early recurrence	[31]	
miR-93	Serum (<i>n</i> = Up 108)	Total Exosome Isolation Reagent (Invitrogen)	qRT-PCR	Correlated with stage, tumor size and predict patients' survival rate of HCC patients	[32]	Potential targets
miRNA-96	Plasma (<i>n</i> = Up 150)	SBI	qRT-PCR	Significantly higher in patients with HCC compared with cirrhotic patients and the control group	[22]	
lncRNAs						
lncRNA-ATB	Serum (<i>n</i> = Up 79)	SBI	qRT-PCR	Related to TNM stage and other prognostic factors	[21]	
DANCR	Serum (<i>n</i> = Up 183)	SBI	Digital droplet PCR (DDPCR)	Positively associated with HCV-HCC recurrence	[33]	
lncRNA FAL1	Serum (<i>n</i> = Up 60)	SBI	qRT-PCR	Play an oncogenic role in HCC	[34]	Potential targets
lnc-FAM72D-3	Serum (<i>n</i> = Up 180)	Ultracentrifugation	qRT-PCR	Functions as an oncogene in HCC	[35]	Potential targets
lncRNA Jpx	Plasma (<i>n</i> = Up 100)	SBI	qRT-PCR	Promising biomarkers for female patients with HCC	[36]	
LINC00161	Serum (<i>n</i> = Up 112)	Total Exosome Isolation Kit (Invitrogen)	qRT-PCR	A significant prediction of tumor growth and metastasis in HCC	[37]	
	Serum (<i>n</i> = Up ?)	-	qRT-PCR	Promote HCC tumorigenesis	[38]	Potential targets
lncRNA-RP11-583F2.2	Serum (<i>n</i> = Up 120)	exoRNeasy Serum/Plasma Midi Kit (Qiagen)	qRT-PCR	Up-regulated in the serum of hepatocellular carcinoma patients as compared with hepatitis C virus patients and normal good health control	[39]	
ENSG00000248932.1 ENST00000440688.1 ENST00000457302.2	Serum (<i>n</i> = Up 600)	SBI	qRT-PCR	Potential fingerprints for the tumorigenesis prediction	[40]	
circRNAs						
circ_0070396	Plasma (<i>n</i> = Up 273)	exoEasy Maxi Kit (QIAGEN)	qRT-PCR	Discriminate HCC individuals from patients with chronic hepatitis B and liver cirrhosis	[41]	
circAKT3	Serum (<i>n</i> = Up 224)	SBI	qRT-PCR	Associated with HCC recurrence and mortality	[42]	
circ-DB	Plasma (<i>n</i> = Up 40)	Ultracentrifugation	qRT-PCR	Promote the tumor growth	[43]	Potential targets
circPTGR1	Serum (<i>n</i> = Up 129)	SBI	qRT-PCR	Promote HCC progression	[44]	Potential targets
circUHRF1	Serum (<i>n</i> = Up 643)	SBI	qRT-PCR	Drive resistance to anti-PD1 immunotherapy	[45]	Potential targets
HB						
miRNAs						
miR-21	Serum (<i>n</i> = Up 64)	SBI	qRT-PCR	Significantly higher in patients with HB	[46]	

Up: Upregulated; SBI: Exo-Quick exosome precipitation solution; HCC: Hepatocellular carcinoma; HB: Hepatoblastoma; qRT-PCR: Quantitative reverse transcription polymerase chain reaction.

DISCUSSION

Liver cancer is a global disease with high morbidity and mortality[72]. Despite the continuous development of novel treatment options, the 5-year survival rate of liver cancer patients is still low because of the delayed diagnosis[73,74]. Scientists are still trying to find new markers for early diagnosis and individualized treatments.

Over the past decade, exosomes have received widespread attention. Many studies have found that the differential expression of exosome proteins and RNAs has diagnostic significance for various cancers. Previous studies have suggested that exosomes may serve as liquid biopsies to help diagnose malignancies such as breast, pancreatic and lung cancer, and glioblastoma[75-78]. Here, we listed exosomal contents that have been identified as possible biomarkers for liver cancer in recent years. We found multiple research reports about miR-21[21-24,46] and LINC00161[37,38]. There are five papers on exosomal miR-21. These studies indicate that expression level of miR-21 in serum exosomes of liver cancer patients is higher than that of healthy people, suggesting that it is the most likely marker for early liver cancer screening. Among the contents of liver cancer serum with downregulated exosomal expression, miR-122 has been reported most often. These studies suggest that miR-122 may be the most likely biotherapeutic drug for liver cancer[22,47].

In addition to serving as disease markers in patients' serum, exosomes are involved in the occurrence, development and prognosis of various cancers[79]. Bai *et al*[80] have shown that exosomes secreted by gastric cancer cells deliver miR-135b to tumor cells and promote angiogenesis by negatively regulating intracellular forkhead box O1. This study provides a potential target for antiangiogenic therapy. Huang and his collaborators demonstrated that colon cancer cells secrete Wnt4-rich exosomes delivered to normoxic cells to activate β -catenin signaling and enhance their metastatic behavior. They found that β -catenin inhibitors ICG-001 can inhibit this metastatic behavior, which provides a new target for treating metastatic colon cancer[81]. In this paper, we listed the previous studies on the mechanism of exosomal contents involved in the development of liver cancer. Therefore, developing drugs targeting these exosomal contents may be a potential therapy for liver cancer.

As drug carriers, exosomes have the characteristics of stability in circulation, good biocompatibility, low immunogenicity, and low toxicity[82,83]. Liang *et al*[84] have shown that exosomes loaded with 5-fluorouracil and miR-21 inhibitors can effectively improve cancer cell drug resistance and colon cancer treatment efficiency. Zhang and his group also found that HEK293T-cell-derived exosomes deliver exogenous si-c-Met to gastric cancer cells and enhance gastric cancer cell sensitivity to cisplatin[85]. In this paper, we reviewed recent studies on the therapeutic effect of exosomes as carriers in HCC.

In addition to being carriers, some researchers have reported the therapeutic effect of exosomes. As early as 1998, Zitvogel *et al*[86] found that dendritic-cell-derived exosomes (DEXs) could activate tumor-specific cytotoxic T lymphocyte response and inhibit tumor growth *in vivo*. DEXs have been used in several clinical trials. Researchers have processed DEXs derived from melanoma patients, loaded them with melanoma antigens, and observed an enhanced antimelanoma immunity after self-inoculation[87]. Another trial indicated that DEX therapy increases natural killer cells (NKs) lytic activity in patients with non-small cell lung cancer (NSCLC)[88]. Besse's group has conducted phase II clinical trials in NSCLC and confirmed the capacity of DEXs to boost the NK cell arm of antitumor immunity in patients with advanced NSCLC[89]. In addition to injecting DEXs, Dai and colleagues have found that the immunotherapy of colorectal cancer (CRC) with ascites-derived exosomes in combination with granulocyte-macrophage colony-stimulating factor can serve as a choice for immunotherapy of advanced CRC[90]. In liver cancer, however, there have been no such clinical trials.

Although exosomes present good application value, there are still problems with their clinical application. Firstly, the separation and purification of exosomes are complex. Secondly, the contents in exosomes are not unique. Thirdly, not all exosomes secreted by cells are suitable for use as carriers. Although there are currently small-scale clinical trials, the actual application of exosomes in the clinical diagnosis and treatment of liver cancer still needs more in-depth studies.

Table 2 Potential therapeutic drugs

Exosomal content	Sample	Expression	Isolation of exosomes	Content detection	Function	Ref.
HCC						
miRNAs						
miR-122	Serum (<i>n</i> = 75)	Down	SBI	qRT-PCR	Reflect the liver damage and residual liver function levels	[47]
	Plasma (<i>n</i> = 150)	Down	SBI	qRT-PCR	Significantly lower in patients with HCC compared with cirrhotic patients and the control group	[22]
miRNA-1298	Serum (<i>n</i> = 120)	Down	exoRNeasy Serum/Plasma MidiKit (Qiagen)	qRT-PCR	Down-regulated in patients of hepatocellular carcinoma compared with patients of hepatitis C virus and normal good health control	[39]
miR-320a	Serum (<i>n</i> = 209)	Down	SBI	qRT-PCR	Associated with lymph node metastasis, vein invasion, TNM stage, and survival of HCC patients	[48]
miR-320d	Serum (<i>n</i> = 150)	Down	Total Exosome Isolation Kit (Invitrogen)	qRT-PCR	Associated with clinicopathological parameters and prognosis of HCC patients	[49]
miR-638	Serum (<i>n</i> = 147)	Down	Total Exosome Isolation Kit (Invitrogen)	qRT-PCR	Influence liver carcinogenesis	[50]
miR-718	Serum (<i>n</i> = 59)	Down	Ultracentrifugation	qRT-PCR	Significantly different expression of HCC cases with recurrence after LT compared with those without recurrence	[51]
miR-744	Serum (<i>n</i> = 20)	Down	Ultracentrifugation	qRT-PCR	Facilitates the propagation and drug resistance of HCC cells	[52]
miR-9-3p	Serum (<i>n</i> = ?)	Down	Ultracentrifugation	qRT-PCR	A potential therapeutic target for HCC	[53]
lncRNAs						
lnc-EPC1-4	Serum (<i>n</i> = 180)	Down	Ultracentrifugation	qRT-PCR	Function as a tumor suppressor gene	[35]
SEN3-EIF4A1	Serum (<i>n</i> = 6)	Down	SBI	qRT-PCR	Block HCC progression	[54]
circRNAs						
circ-0051443	Plasma (<i>n</i> = 120)	Down	SBI	qRT-PCR	Suppress HCC progression	[55]
HB						
miRNAs						
miR-34s	Serum (<i>n</i> = 152)	Down	SBI	qRT-PCR	Significantly lower in patients with HB compared with the control group	[56]

Down: Downregulated; SBI: Exo-Quick exosome precipitation solution; HCC: Hepatocellular carcinoma; HB: Hepatoblastoma; qRT-PCR: Quantitative reverse transcription polymerase chain reaction.

CONCLUSION

Exosomes are composed of a lipid bilayer membrane structure, which has the advantages of rich content, high stability, ability to reflect the state of disease, and cellular communication. These features make them a research hotspot for liver cancer for potential biomarkers, biotherapeutics, therapeutic targets, drug carriers, and therapeutic factors.

Table 3 Potential therapeutic targets

Exosomal content	Sample	Expression	Content identification	Animal model (Yes/No)	Function	Ref.
HCC						
Proteins						
ENO1	Cancer cells-exosomes, tissue (<i>n</i> = 94)	Up	IHC staining	Y	Promotes HCC growth, metastasis, and further patient deterioration	[57]
miRNAs						
miR-125a/b	TAMs-exosomes Tissue (<i>n</i> = 6)	Down	qRT-PCR	N	A possible therapeutic target in HCC	[58]
miR-150-3p	Fibroblasts-exosomes, tissues (<i>n</i> = 82)	Down	qRT-PCR	N	Abrogate HCC migration and invasiveness	[59]
miR-32-5p	Bel/5-FU-exosomes, tissue (<i>n</i> = 72)	Up	qRT-PCR	Y	Induce multidrug resistance in HCC	[60]
miR-320a	Cancer cells-exosomes, tissue (<i>n</i> = 6)	Down	qRT-PCR	Y	Mediates HCC tumor progression	[61]
miR-3682-3p	Cancer cells-exosomes, tissue (<i>n</i> = 8)	Down	qRT-PCR	Y	Attenuate angiogenesis and provides novel potential targets for liver cancer therapy	[62]
miR-378b	Cancer cells-exosomes, tissue (<i>n</i> = 105)	Up	qRT-PCR	Y	Enhance HCC cell progression and angiogenesis	[63]
lncRNAs						
ASMTL-AS1	Cancer cells-exosomes, tissues (<i>n</i> = 70)	Up	qRT-PCR	Y	Aggravate the malignancy in residual HCC	[64]
PCED1B-AS1	Cancer cells-exosomes, tissues (<i>n</i> = 45)	Up	qRT-PCR	Y	Induce immunosuppression in HCC	[65]
circRNAs						
circRNA Cdr1as	Cancer cells-exosomes, tissues (<i>n</i> = 42)	Up	qRT-PCR	Y	Promote the progression of HCC by sponging miR-1270 to upregulate AFP level	[66]

IHC: Immunohistochemistry; TAMs: Tumor-associated macrophages; Up: Upregulated; Down: Downregulated; HCC: Hepatocellular carcinoma; HB: Hepatoblastoma; qRT-PCR: Quantitative reverse transcription polymerase chain reaction.

Table 4 As a carrier for drug treatment

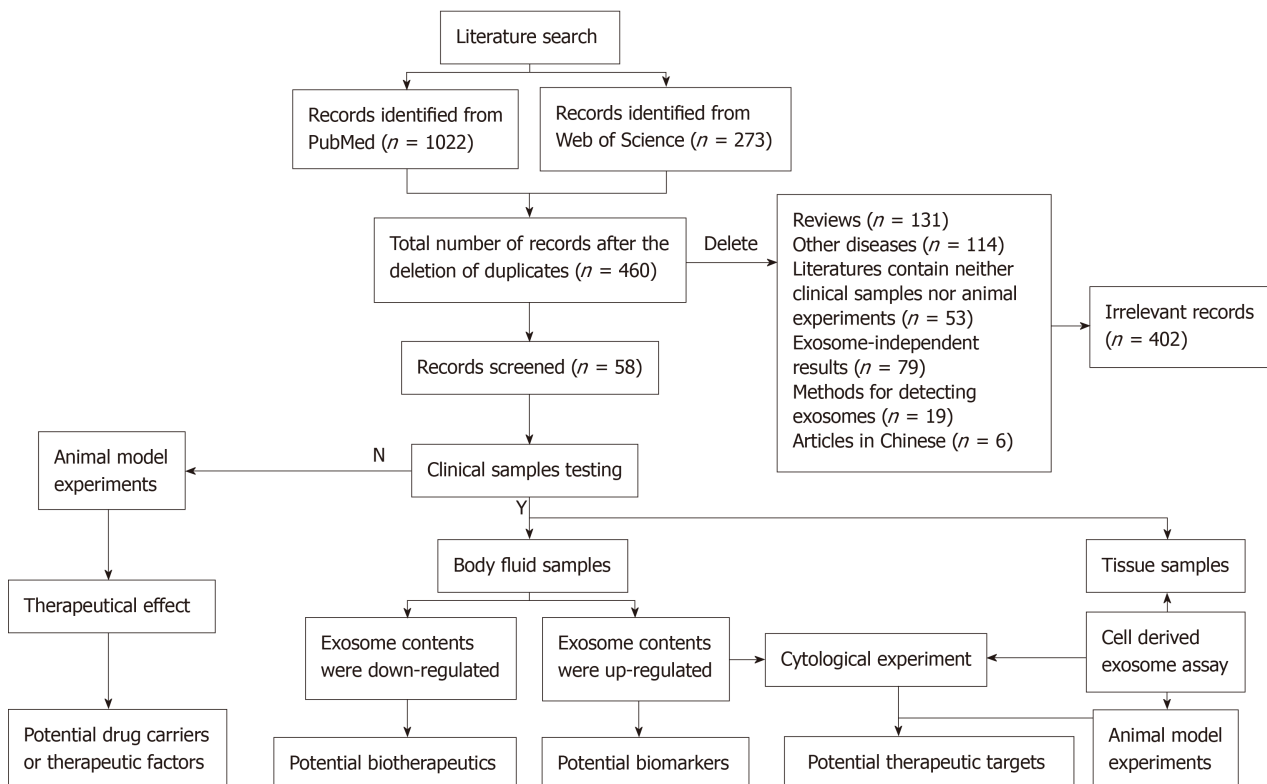
Drugs	Source of exosomes	Animal model (Yes/No)	Clinical sample (Yes/No)	Functions	Ref.
Norcantharidin	BMSCs-exosomes	Y	N	Induce cell cycle arrest, reduced tumor cell proliferation, increased apoptosis	[67]
siGRP78	BMSCs-exosomes	Y	N	Sensitize Sorafenib resistant cancer cells to Sorafenib	[68]
miR-214	hCEC-exosomes	N	Y (<i>n</i> = 6)	Enhances the anti-tumor efficacy of oxaliplatin and sorafenib on HCC cells	[69]

BMSCs: Bone marrow mesenchymal stem cell; hCEC: Human cerebral endothelial cell; HCC: Hepatocellular carcinoma.

Table 5 Exosomes from dendritic cells as potential therapeutic factors

Cargos	Source of exosomes	Animal model (Yes/No)	Clinical sample (Yes/No)	Functions	Ref.
Exosomes plus microwave ablation	DCs-exosomes	Y	N	Inhibit tumor growth and improve the immune microenvironment	[70]
Exosomes	DCs-exosomes	Y	N	Elicited strong antigen-specific immune responses and resulted in tumor growth retardation and prolonged survival rates in mice with ectopic	[71]

DCs: Dendritic cells.

**Figure 1** Flow diagram of the study search and selection in this review.

ARTICLE HIGHLIGHTS

Research background

Liver cancer is one of the most common malignant tumors with high morbidity and mortality because of lacking early diagnosis and treatment. Exosomes have been a newly discovered cellular communication tool with high biocompatibility, low immunogenicity, and high transport efficiency. They show great potential for cancer diagnosis and therapy.

Research motivation

This review aimed to consolidate the evidence on exosomes as biomarkers for the diagnosis and therapeutics for liver cancer in a systematic fashion.

Research objectives

The main result that the authors are concerned about is discovering the great potential of exosomes in the diagnosis and treatment of liver cancer.

Research methods

A systematic literature search was performed using PubMed and Web of Science. The latest literature was published in June 2021.

Research results

Fifty-eight studies were included in this systematic review. Blood-derived exosomes could be biomarkers or biotherapeutics. Cell-derived exosomes, which were used to explore underlying mechanisms of differentially expressed exosome contents in clinical tissue samples, might serve as potential therapeutic targets for liver cancer. Exosomes might also serve as drug carriers or therapeutic factors.

Research conclusions

Existing studies show that exosomes have great potential for clinical application as potential novel diagnostic and therapeutic markers of liver cancer.

Research perspectives

This present review might be helpful as a reference for clinical research on exosomes in liver cancer.

ACKNOWLEDGEMENTS

We are grateful to Wang Ying for her skillful statistical analysis guidance.

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