REVIEW

Small Extracellular Vesicles in Alcohol Use Disorders: A Scoping Review

Малые внеклеточные везикулы при расстройствах, вызванных употреблением алкоголя: обзор предметного поля

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Review

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ABSTRACT

BACKGROUND: Alcohol consumption is one of the most significant global public health challenges. The pathophysiology of alcohol use disorder remains only partially elucidated, and direct biomarkers for this disorder have yet to be identified. Some studies have investigated the profiles of small extracellular vesicles (sEVs) in different bodily fluids. However, the findings across these studies are heterogeneous, and the methodological quality of these studies has not been systematically assessed.

AIM: To summarize the results of studies examining the sEVs' profiles in alcohol use disorders.

METHODS: The review included original research articles that explored the sEVs' profiles in alcohol use disorders. The MEDLINE (for studies published up to November 2025) and Scopus (for studies published up to January 10, 2026) were searched. The analysis of the included studies was conducted using a descriptive evidence synthesis approach based on the categories of lipid profile, protein profile, and signaling molecules. The methodological quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS) adapted for extracellular vesicle research.

RESULTS: Ten studies were included. All studies employed a cross-sectional design, were conducted in small cohorts, and included patients with acute and chronic alcohol intoxication, as well as those with alcohol use disorder. Significant differences in the sEVs' profiles were identified in individuals with alcohol use disorders compared to healthy controls. These differences encompassed modifications in lipid and protein profiles, decreased expression of hsa-miR-144-5p, hsa-miR-182-5p, hsa-miR-142-5p, hsa-miR-7-5p, hsa-miR-15b-5p, and hsa-circ-0004771, an increased expression of miR-30a-5p and miR-194-5p, as well as alterations in inflammatory response parameters. The majority of these differences were related to the regulation of inflammation.

CONCLUSION: In alcohol use disorders, sEVs differ in lipid and protein profiles as well as in microRNA expression. New studies are needed to investigate the impact of sEVs on the regulation of systemic inflammation in alcohol use disorders using a prospective design with repeated measurements of specific sEV characteristics.

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АННОТАЦИЯ

ВВЕДЕНИЕ: Употребление алкоголя — одна из наиболее значимых глобальных проблем здравоохранения. Патофизиология синдрома зависимости от алкоголя изучена лишь частично, прямые биомаркеры данного расстройства не определены. В ряде исследований применительно к синдрому зависимости от алкоголя изучался состав малых внеклеточных везикул (мВВ) в различных биологических средах. Однако результаты этих исследований неоднородны, а методологическое качество работ систематически не оценивалось.

ЦЕЛЬ: Обобщить результаты исследований состава мВВ при расстройствах, вызванных употреблением алкоголя.

МЕТОДЫ: В обзор включали оригинальные исследования, в которых изучался состав мВВ при расстройствах, связанных с употреблением алкоголя. Поиск осуществлялся в MEDLINE (работы, опубликованные до ноября 2025 г.) и Scopus (работы, опубликованные до 10 января 2026 г.). Анализ вошедших в обзор работ выполнен с использованием метода описательного синтеза по категориям «липидный состав», «белковый состав» и «сигнальные молекулы» мВВ. Методологическое качество исследований оценивали с применением «Шкалы оценки качества Ньюкасл–Оттава» (NOS), модифицированной для исследований внеклеточных везикул.

РЕЗУЛЬТАТЫ: В обзор включено 10 исследований. Все исследования имели поперечный дизайн, были проведены на небольших выборках и включали пациентов с острой и хронической интоксикацией, а также с синдромом зависимости. Выявлены значимые отличия состава мВВ при расстройствах, вызванных употреблением алкоголя, по сравнению со здоровыми добровольцами: модификации липидного и белкового состава, более низкая экспрессия hsa-miR-144-5p, hsa-miR-182-5p, hsa-miR-142-5p, hsa-miR-7-5p, hsa-miR-15b-5p и hsa-circ-0004771, более высокая экспрессия miR-30a-5p и miR-194-5p, а также отличия параметров воспалительного ответа. Большинство обнаруженных отличий ассоциированы с регуляцией воспаления.

ЗАКЛЮЧЕНИЕ: При расстройствах, связанных с употреблением алкоголя, мВВ отличаются по составу липидов, белков и экспрессии микроРНК. Необходимы новые исследования влияния мВВ на регуляцию системного воспаления при синдроме зависимости от алкоголя с проспективным дизайном и повторными измерениями специфичных характеристик мВВ.

Keywords: *alcohol dependence syndrome; small extracellular vesicles; exosomes; microRNA*
Ключевые слова: *расстройства, вызванные употреблением алкоголя; малые внеклеточные везикулы; экзосомы; микроРНК*

INTRODUCTION

According to data from the World Health Organization's (WHO) "Global status report on alcohol and health and treatment of substance use disorders" (2024), alcohol-related conditions (including dependence and harmful alcohol use) were responsible for 2.6 million deaths worldwide and accounted for 27% of all fatalities among individuals under 39 years of age in 2019[1].

In the International Classification of Diseases, 10th Revision (ICD-10), alcohol use disorders encompass a wide spectrum of conditions ranging from acute intoxication to late-onset psychotic disorders[2]. The primary nosological entity in this category is alcohol use disorders, while other disorders (except those due to acute alcohol intoxication and harmful use) develop in patients suffering from alcohol use disorders [1].

WHO data from 2019 indicated that 2.5 billion individuals over the age of 15 had consumed alcoholic beverages worldwide[1]. In Russia, 1.1 million assessments of alcohol intoxication identified 475,000 cases (42%) [2]. Alcohol use disorder is a chronic, progressive mental disorder with a worldwide prevalence of 111 million individuals

1 Global status report on alcohol and health and treatment of substance use disorders / World Health Organization. 2024. Available at: https://www.who.int/publications/i/item/9789240096745?ysclid=mo1iceo9lx145543746

2 Chapter V. Mental and behavioural disorders (F00-F99) / ICD-10 Version:2019. Available at: https://icd.who.int/browse10/2019/en#/F10.6

in 2021 [3]. In Russia in 2023, the number of cases exceeded 1.13 million cases (776.5 per 100,000 population), whereas harmful alcohol use was reported in 174,000 individuals (119.4 cases per 100,000 population) [2].

Despite significant advances in medical and biomedical sciences, the pathophysiological mechanisms underlying the development and progression of alcohol use disorders have not been fully elucidated. Currently, no direct biomarkers are available for diagnosing this condition or identifying at-risk groups [4]. Although research on non-coding RNAs (particularly microRNAs) is a rapidly advancing field in the search for potential biomarkers, the results obtained thus far have shown limited reproducibility and are still far from clinical application [5]. Existing therapeutic approaches have limited efficacy and are primarily targeted at alleviating individual symptoms rather than addressing key pathogenic mechanisms [6, 7]. This highlights the need for new approaches to investigate the pathophysiology of alcohol use disorders.

In this context, small extracellular vesicles (sEVs) warrant special attention. These are biogenic, membrane-bound vesicles ranging in size from 100–200 nm that are secreted by all cell types and belong to the broader category of extracellular vesicles [8]. sEVs exhibit several unique properties, including the ability to cross the blood-brain barrier and express proteins characteristic of their parent cells [8]. These characteristics suggest that sEVs are a potential source of information about the status of individual brain cell populations. Consequently, they are promising biomarkers for mental disorders (including alcohol use disorders), as well as a potential platform for developing new therapeutic agents and targeted drug delivery strategies [9].

The growing interest in exploring the role of sEVs in mental disorders is reflected in reviews published in 2025, which summarized findings from studies involving patients with depression and bipolar disorder [10] and schizophrenia [11]. Studies have shown that different components of sEVs, along with their physical characteristics, have diagnostic and prognostic potential for both mood disorders and schizophrenia [10, 11]. Reviews published in the past five years that have analyzed changes in extracellular vesicles in the context of alcohol consumption emphasize their involvement in neuroinflammation and disturbances in blood-brain barrier integrity [12, 13], neurodegeneration [14, 15], fetal alcohol syndrome [16], and alcohol-related liver disease [17, 18], as well as the pathogenesis of psychoactive substance dependence more broadly [14, 19]. However, all existing reviews are descriptive and include the results obtained in cell cultures [20] and animal studies [21], which limits the ability to draw definitive conclusions regarding clinical studies in humans.

This review aimed to summarize the results of studies examining the sEVs' profiles in alcohol use disorders.

METHODS

Protocol and registration

The review was conducted in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [22]. The study protocol was not registered publicly.

Eligibility criteria

Inclusion criteria:

- the publication presents the results of an original study in which an analysis of sEVs was conducted;
- the studied disorders included acute alcohol intoxication, chronic alcohol intoxication, and alcohol dependence syndrome. These disorders were selected because they were the most common alcohol use disorders and due to the need to compare the changes occurring with both short-term and long-term alcohol consumption;
- the studies were conducted in humans.

Exclusion criteria were as follows:

- review-type publications, non-peer-reviewed publications;
- preclinical studies (i.e., experiments conducted solely on cell cultures or animal models);
- studies that did not include a group of patients for whom alcohol was the primary exposure factor;
- studies focused on other alcohol related disorders (e.g., alcohol-related liver disease); and
- studies for which the full text was unavailable.

No language restrictions were imposed.

Information sources

A search was conducted in the electronic databases MEDLINE (accessed via PubMed) and Scopus without restrictions on publication date. The search in MEDLINE was performed on November 15, 2025, and the search in Scopus on January 10, 2026.

Search strategy

The search was performed using the keywords and MeSH terms "extracellular vesicles", "exosomes", "microvesicles" combined with "alcohol", "ethanol", "binge drinking". The keywords were chosen to cover the most commonly used terms for extracellular vesicles and to maximize search coverage. The reference lists of the included studies and narrative reviews not included in the analysis were screened for studies meeting the eligibility criteria. The search query is shown in Appendix 1 in the Supplementary.

Selection process

The sources were selected in two stages. At first, two authors (E.K. and E.S.) independently selected studies for the review by screening titles and abstracts. Discrepancies were resolved through discussion with a third author (V.S.). In the second stage, full-text articles were assessed for eligibility, again by two independent authors (E.K. and E.S.). Any disagreements at this stage were resolved in a similar manner, with the involvement of a third author (V.S.). Agreement was reached in 95% of cases.

Data charting process

Data extraction was performed by one author (M.G.) and independently verified by another author (V.S.). Information for each included study was entered into a standardized table according to the study protocol.

Data items

The following data were extracted for analysis: the author, year of publication, country, study design, condition studied, sampling method, patient characteristics, source of extracellular vesicles, type of vesicles, method of confirming the vesicle origin, method of vesicle isolation, isolation of individual vesicle fractions, and results of the study.

Critical assessment of sources

The quality and risk of bias (RoB) in the included non-randomized studies in this review were assessed using the Newcastle–Ottawa Scale (NOS)[3] in a version adapted for extracellular vesicle testing [10]. The scale was used without translation into Russian. The adapted version includes evaluations in three categories: study group selection, group comparability, and methodology and assessment of the outcome of interest.

This modified scale differs substantially from the original NOS in two respects:

1) the studies that reported adjusted results for differences in extracellular vesicle yield between groups using a validated method were awarded one star in the comparability category;
2) studies that reported adherence to the Minimal Information for Studies of Extracellular Vesicles (MISEV) guidelines [8, 23] were awarded one star in the "methodology" category.

The quality of studies was classified as low (0–4 stars), moderate (5–6 stars), or high (7–8 stars).

The assessment was conducted by two authors (M.G., V.S.) independent of each other. The discrepancies were resolved by discussing until reaching an agreement.

Synthesis of results

Data extracted from the included studies were tabulated. The included studies were analyzed using a descriptive synthesis approach based on the key characteristics of sEVs studied, i.e., lipid profile, protein profile, and signaling molecules.

RESULTS

Selection of sources of evidence

The search yielded 1,431 publications of which 330 duplicates were removed prior to screening. Titles and abstracts of 1,101 publications were screened, resulting in the exclusion of 1,049 articles due to non-compliance with the inclusion criteria (see Table S2 in the Supplementary). At the second screening stage, 52 full-text articles were assessed for eligibility, of which 42 were excluded for various reasons. Ten publications were included in the review (see Table S3 in the Supplementary). A flowchart of the literature selection procedure is shown in Figure 1.

Characteristics of sources of evidence

All studies were published between 2018 and 2025, i.e., following the publication of the first guidelines of the International Society for Extracellular Vesicles [23]. The geographical distribution of the studies was Spain (4 studies) [24–27], the USA (4 studies) [28–31], and China (2 studies) [32, 33].

All studies had a cross-sectional design [24–33]. In four of the studies, patients with alcohol use disorder were compared

[3] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: https://ohri.ca/en/who-we-are/core-facilities-and-platforms/ottawa-methods-centre/newcastle-ottawa-scale

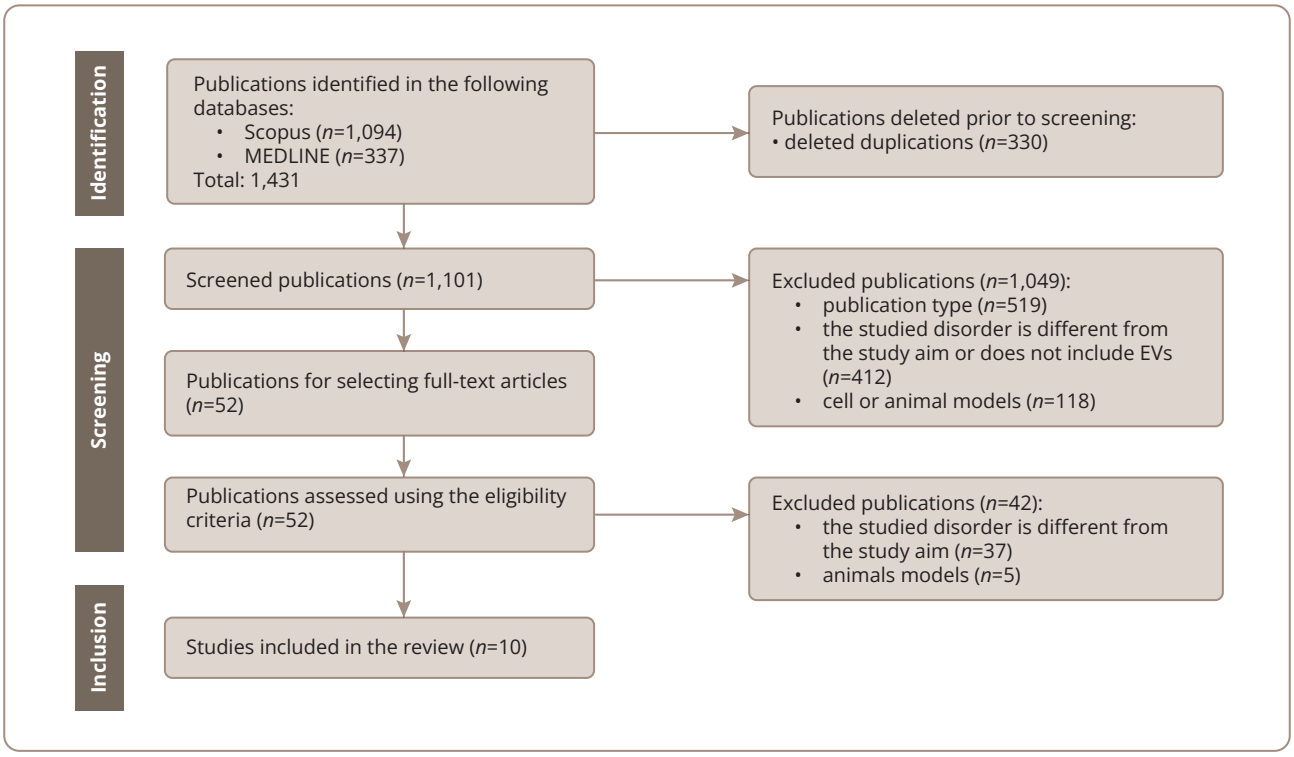

Figure 1. PRISMA flow diagram of the literature search and selection process.

Note: EVs — extracellular vesicles.

Source: Severtsev et al., 2026.

with a control group of healthy volunteers [24, 25, 32, 33]. In three of these, the diagnosis was established according to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) either the 4th [32] or 5th edition (DSM-IV and/or DSM-5) [24, 25]; in one study, the diagnostic criteria were not reported [33]. Three studies were based on a single cohort recruited in Cameroon (Africa) [34]. The participants were allocated into six groups: (1) HIV-negative, non-users of alcohol or tobacco; (2) HIV-negative, smokers but non-users of alcohol; (3) HIV-negative, alcohol users but non-smokers; (4) HIV-positive, non-users of alcohol or tobacco; (5) HIV-positive, smokers but non-users of alcohol; and (6) HIV-positive, alcohol users but non-smokers [29–31]. In two studies, patients in a state of acute alcohol intoxication of moderate or severe degree participated, with the control group comprising volunteers matched by sex and age [26, 27]. Both of these studies were conducted on blood samples from the same population. In one study, an adolescent population, enrolled as part of the Adolescent and Young Adult Twin Study (AYATS, R01MH101518 [35]), was evaluated. Participants were divided into control and primary groups based on the results of the Alcohol Use Disorders Identification Test (AUDIT) [28]. Table 1 shows the inclusion criteria and patient characteristics. Extended data on the inclusion criteria and group characteristics are provided in Table S3 in the Supplementary.

Study quality assessment

Thirty percent of the 10 studies evaluated using the NOS were rated as moderate quality [24–26] and 70% as low quality [27–33]. All studies received zero points in the "Representativeness" and "Sample size" sections because they were conducted on small samples, and the sample sizes were never justified. In three studies, inclusion in the study group was based solely on self-report, and in one study, the sampling method was not described, resulting in a loss of one point in the "Case definition" category [29–31, 33]. Six studies did not mention adjustments for the vesicle release, resulting in the loss of additional points [27–29, 31–33]. Comparability by sex and age was lacking in three studies [29–31]. Although all studies employed validated methods for vesicle isolation and confirmed the presence of exosomal markers, only one study [30] specifically reported adherence to the MISEV guidelines [23]; all the other studies lost one point in the "Methodology" section. Detailed assessments for each study are provided in Table S4 (in the Supplementary).

Table 1. Inclusion criteria and main patient characteristics

First author, year	Country	Study design	Characteristics of the study group
Martín-Urdiales et al., 2025 [24]	Spain	Cross-sectional	7 male subjects; mean age 43 years; AUD based on the DSM-5 criteria.
Wang et al., 2024 [33]	China	Cross-sectional	35 male subjects; 45.83±11.83 years; daily alcohol consumption.
Yakovlev et al., 2024 [28]	USA	Cross-sectional	24 participants (5 twin pairs (*n*=10) and 14 non-twins) with a mean age of 19.7±1.5 years; 66.7% were male and 33.3% female; mean AUDIT-C score 8.0±1.0.
Perpiñá-Clérigues et al., 2024 [25]	Spain	Cross-sectional	11 participants (54.5% male, 45.5% female) with a median age of 47.83 years for males and 40 years for females; AUD based on the DSM-5 criteria.
Perpiñá-Clérigues et al., 2023 [26]	Spain	Cross-sectional	18 patients (50% male, 50% female) with mean ages of 19.67±0.34 years for males and 19.89±0.50 years for females diagnosed with acute alcohol intoxication, defined by both clinical and laboratory criteria (blood alcohol concentration >1 g/L).
Liu et al., 2021 [32]	China	Cross-sectional	6 patients (5 males, 1 female) with a mean age of 45.50±6.070 years; AD based on the DSM-IV criteria; a history of alcohol consumption for a week prior to admission.
Ibáñez et al., 2020 [27]	Spain	Cross-sectional	18 patients (50% male, 50% female) with mean ages of 20.67±1.36 years for males and 19.88±1.50 years for females, who met the clinical and laboratory criteria for acute alcohol intoxication (blood alcohol concentration >1 g/L).
Kodidela et al., 2020 [30]	USA	Cross-sectional	23 subjects were allocated to 6 groups. Age range: 25–60 years. Inclusion criteria: • for HIV-positive subjects: a CD4 count of 200–500 cells/μL; • for smokers: a smoking history of less than 20 pack-years (a pack-year is defined as smoking at least 1 pack per day for 1 year); • for alcohol consumers: consumption of 7–14 alcohol units per week for men and 4–7 units per week for women.
Kodidela et al., 2020 [29]	USA	Cross-sectional	27 subjects allocated to 6 groups. Age range: 25–60 years. Inclusion criteria: • for HIV-positive subjects: a CD4 count of 200–500 cells/μL; • for smokers: a smoking history of less than 20 pack-years (a pack-year is defined as smoking at least 1 pack per day for 1 year); • for alcohol consumers: consumption of 7–14 alcohol units per week for men and 4–7 units per week for women.
Kodidela et al., 2018 [31]	USA	Cross-sectional	39 subjects allocated to 6 groups. Age range: 25–60 years. Inclusion criteria: • for HIV-positive subjects: a CD4 count of 200–500 cells/μL; • for smokers: a smoking history of less than 20 pack-years (a pack-year is defined as smoking at least 1 pack per day for 1 year); • for alcohol consumers: consumption of 7–14 alcohol units per week for men and 4–7 units per week for women.

Note: AD — alcohol dependence; AUD — alcohol use disorder; AUDIT-C — Alcohol Use Disorders Identification Test – Consumption).

Extracellular vesicle profiles in alcohol use disorder and their possible association with pathogenesis

Sources and methods of vesicle isolation

In eight of the studies, extracellular vesicles were isolated from plasma [25–31, 33], in one study from serum [32], and in another study from urine [24]. In all studies, the isolated vesicles were confirmed to carry exosomal markers. In seven out of ten studies, vesicle isolation was conducted using polyethylene glycol (PEG) precipitation [25–27, 29–32], using ultracentrifugation in two studies [24, 33], and chromatography in another study [28]. Only one study analyzed neuronal and astrocytic vesicle fractions [28]; in the rest of the studies, the total pool of isolated sEVs was analyzed. A summary of the study results is provided in Table 2.

Lipid profile differences

Three studies conducted by the same research group specifically investigated differences in the lipid composition of sEVs [24–26]. Using mass spectrometry-based lipidomics, these studies demonstrated increased levels of fatty acids and glycerophospholipids alongside reduced levels of sphingolipids in urinary sEVs from men with alcohol dependence compared to healthy individuals. In particular, the level of behenic acid (fatty acid 22:0) was higher in both urine and blood samples in men with alcohol use disorders [24, 25]. Sex-related lipid profile differences were identified. The lipid profile differed not only between healthy individuals and subjects with alcohol dependence but also between males and females with alcohol dependence, and even between healthy male and female subjects.

Table 2. Key results of the included studies

First author, year	Method of isolation	EVs sources	Method of EVs presence confirmation	Results
Martín-Urdiales et al., 2025 [24]	UCF	Urine	TEM, NTA, WB	Male subjects with alcohol use disorder exhibited higher levels of lipid subclasses such as fatty acids (FA), HexCer_AP and SM including those with saturated acyl chains and very long-chain FAs.
Wang et al., 2024 [33]	UCF	Plasma	TEM, NTA, WB	The main group showed differential expression of microRNAs hsa-miR-144-5p, hsa-miR-182-5p, hsa-miR-142-5p, hsa-miR-7-5p, and hsa-miR-15b-5p.
Yakovlev et al., 2024 [28]	SEC, immunoprecipitation	Plasma	TEM, NTA, WB	miRNA-30a-5p, miR-194-5p, miR-339-3p expression was higher in the main group.
Perpiñá-Clérigues et al., 2024 [25]	PEG	Plasma	TEM, NTA, WB	Female patients with AUD exhibited higher levels of lipid subclasses LPC and PC (as well as phospholipases and acyltransferases). Male patients with AUD had lower levels of Cer and SM lipid subclasses (which include enzymes such as sphingomyelinases, sphingomyelin phosphodiesterase, and sphingomyelin synthase). A bioinformatic analysis identified sex-specific variations in EVs lipids that appear to play a role in vesicle fusion.
Perpiñá-Clérigues et al., 2023 [26]	PEG	Plasma	TEM, NTA, WB	Adolescent females showed a higher enrichment of specific lipid subclasses in their EVs compared to male subjects. Similar sex-dependent differences in EVs lipid profiles were more pronounced in wild-type (WT) mice compared with TLR4-knockout (TLR4-KO) mice.
Liu et al., 2021 [32]	PEG	Serum	TEM, NTA, WB	AUC for hsa-circ-0004771 in patients with AD was 0.874.
Ibáñez et al., 2020 [27]	PEG	Plasma	TEM, NTA, WB	In EVs isolated from plasma of adolescent females and female mice under conditions of alcohol intoxication displayed lower levels of anti-inflammatory microRNAs (miR-146a-5p, miR-21-5p, miR-182-5p) compared to their male counterparts.
Kodidela et al., 2020 [30]	PEG	Plasma	TEM, TRPS, WB	The level of the GFAP was higher in plasma-derived EVs from HIV-infected patients.
Kodidela et al., 2020 [29]	PEG in duplicate	Plasma	TEM, DLS, WB	Hemopexin, fibulin-1, alpha-2-macroglobulin, and properdin demonstrated differential expression among the study groups.
Kodidela et al., 2018 [31]	PEG	Plasma	TEM, DLS, WB	In HIV-infected alcohol consumers, the plasma IL-8 levels were higher compared to HIV-infected non-alcohol consumers. The level of IL-1 receptor antagonist (IL-1ra) was significantly higher in the exosomes of HIV-negative alcohol users compared to their HIV-positive counterparts. Furthermore, IL-10 levels were higher in exosomes relative to the corresponding plasma levels in all study groups, except for HIV-infected non-alcohol users.

Note: AD — alcohol dependence; AP — alkylphospholipids; AUC — area under the curve; Cer — ceramides; DLS — dynamic light scattering; EVs — extracellular vesicles; Ex — exosomes; FA — fatty acids; GFAP — glial fibrillary acidic protein; HexCer — hexosylceramides; IL — interleukin; IL-1ra — interleukin-1 receptor antagonist; LPC — lysophosphatidylcholine; miRNA — microRNA; NTA — nanoparticle tracking analysis; PEG — polyethylene glycol; PC — phosphatidylcholine; SEC — size-exclusion chromatography; SM — sphingomyelin; TEM — transmission electron microscopy; TLR4-KO — Toll-like receptor 4 knockout; TRPS — tunable resistive pulse sensing; UCF — ultracentrifugation; WB — western blot; WT — wild-type.

Potential specific markers of dependence have been proposed: phosphatidylcholine 16:0_16:1 for women and phosphatidylinositol 34:1 for men [25]. The bioinformatic analysis showed that the observed changes were associated with disturbances in lipid signaling processes, cell membrane remodeling, and vesicle biogenesis [25].

Another study showed that the lipid profile with respect to glycerophosphoinositols, glycerophosphates, glycerophosphocholines, fatty acids, and their complex esters in young individuals with alcohol intoxication were different in males and females. This finding was further validated using a murine model [26]. Experiments in murine models revealed that differences in the lipid profile of sEVs during alcohol intoxication were less pronounced in TLR4 knockout mice, suggesting that these lipid changes are associated with the activation of proinflammatory signaling cascades [26].

Protein profile differences

In two studies, differences in the protein profiles of sEVs were identified in patients with heavy alcohol use compared to healthy controls and HIV-infected subjects [29, 30]. The concentration of glial fibrillary acidic protein (GFAP) in sEVs was higher in alcohol users compared with healthy individuals and smokers, but did not differ from that in HIV-positive heavy alcohol users [30].

Proteomic analysis revealed differential expression of several proteins among the groups, these findings were subsequently validated using Western blotting. It was demonstrated that the expression of alpha-2-macroglobulin was lower in alcohol users compared with healthy subjects, while properdin levels were lower in HIV-positive heavy alcohol users than in HIV-positive nondrinkers [29].

Bioinformatic analysis in this study further indicated that the proteins differentiating HIV-positive heavy alcohol users from HIV-negative subjects are involved in immune response and lipid binding, whereas proteins distinguishing HIV-positive from HIV-negative heavy alcohol users are associated with the activation of the complement system and serine protease activity [29].

Differences in the signaling molecules expression

In four studies, differences in the microRNA content carried by sEVs were demonstrated [27, 28, 32, 33]. Differences in cytokines were found in one study [31]. In one study, patients with alcohol use disorders exhibited decreased expression of the following microRNAs: hsa-miR-144-5p, hsa-miR-182-5p, hsa-miR-142-5p, hsa-miR-7-5p, and hsa-miR-15b-5p. The expression was evaluated using sequencing techniques and polymerase chain reaction (PCR) testing. The ROC curve analysis yielded area under the curve (AUC) values ranging from 0.723 to 0.950, underscoring the diagnostic potential of these markers [33]. Based on the results of the bioinformatic analysis, the authors also hypothesized the presence of a regulatory network formed by circulating microRNAs and hippocampal mRNAs that may be involved in the pathogenesis of the disorder [33]. In another study, the expression of the circular RNA hsa-circ-0004771 was significantly lower in patients with alcohol dependence (this finding was validated via PCR testing). ROC analysis demonstrated an AUC of 0.874, and expression levels correlated with the severity of alcohol dependence as assessed by questionnaires [32]. The bioinformatic analysis further suggested that the differentially expressed circular RNAs might be associated with the regulation of neuronal projection, axonal regeneration, and immune cell regulation [32].

Additionally, a study of neuronal sEVs in young individuals with heavy alcohol use revealed that the expression of miR-30a-5p and miR-194-5p (determined by DNA sequencing and PCR testing) was significantly higher compared with their peers not using alcohol [28]. The bioinformatic analysis showed that, collectively, these microRNAs may interact with 44 genes associated with alcohol dependence based on whole-genome sequencing [28].

During alcohol intoxication, the expression of miR-146a-5p, miR-21-5p, and miR-182-5p in plasma-derived sEVs in young women and female mice was lower than in their male counterparts [27]. In the same study, using a murine model of alcohol intoxication, the expression of these microRNAs in the cerebral cortex was also lower in female mice compared to male mice, while the expression of their target genes — Traf6, Stat3, and Camk2a — was higher [27]. The authors also showed that in TLR-4 knockout mice, these differences were less pronounced [27]. Based on these results and the bioinformatic analysis, the authors concluded that alcohol-induced neuroinflammation is present even with short-term intoxication [27].

Studies of cytokine levels in HIV-infected heavy alcohol users showed that their plasma IL-8 levels were higher compared to HIV-infected non-alcohol users [31]. Among alcohol users, regardless of their HIV status, IL-10 was detectable exclusively in sEVs and completely absent in whole plasma samples, whereas the levels of IL-1 and monocyte chemoattractant protein-1 (MCP-1) were higher in plasma samples [31]. In addition, the concentration of IL-1ra was lower in HIV-positive heavy alcohol users compared to HIV-negative alcohol users [31].

DISCUSSION

In this review, we summarized the results from 10 original studies. Overall, the analysis indicates that alterations in the composition of sEVs in alcohol use disorders reflect the involvement of these vesicles in inflammatory signaling pathways. Specifically, differences in the protein profiles include a higher expression of GFAP and lower alpha-2-macroglobulin levels. Lipids such as phosphatidylcholines and phosphatidylinositols have been proposed as potential sex-specific markers for female and male individuals, respectively. Sex-dependent differences in the composition

of glycerophosphoinositols, glycerophosphates, and glycerophosphocholines during alcohol intoxication were also found; these alterations were associated with TLR4 activity. Moreover, differences in the regulatory RNA content of sEVs were identified, including lower expression of hsa-miR-144-5p, hsa-miR-182-5p, hsa-miR-142-5p, hsa-miR-7-5p, hsa-miR-15b-5p, and hsa-circ-0004771, along with higher expression of miR-30a-5p and miR-194-5p. In addition, differences in interleukin concentrations were found both within sEVs and in whole plasma when comparing healthy individuals with individuals with alcohol dependence. Functional bioinformatic analyses and animal model experiments demonstrated that most of the reported differences are linked to the regulation of inflammation.

The main limitation in generalizing the current studies is the heterogeneity of the populations examined. First, the studied conditions ranged from acute alcohol intoxication, heavy alcohol use, to established dependence syndrome, making direct comparison of results problematic. Second, all studies had a cross-sectional design. This heterogeneity precludes assessment of the stability of the described changes and establishing causality. However, two studies included experimental validation in a murine model, which supports a causal relationship. Third, the studies included small sample sizes of subjects of a single race and ethnicity, with some overlap across different studies. This substantially reduces the generalizability of the results. Fourth, although the approaches for isolating and characterizing sEVs generally complied with the MISEV guidelines [8, 23], almost every study employed different analytical methods for evaluating the sEVs characteristics of interest, which cannot be directly compared. Fifth, nine out of the 10 studies analyzed the total pool of plasma vesicles — even though these vesicles originate from most organs and tissues — thereby significantly limiting the interpretability of the results. Sixth, all isolation methods used, especially PEG precipitation, are associated with the co-precipitation of non-targeted plasma components alongside the sEVs. This could also affect the results [36].

It should be noted that some relevant studies may have been missed for several reasons. First, the formulated search query could have been insufficiently sensitive. Second, the review did not include studies investigating other alcohol use disorders, e.g., alcohol-related liver disease, although it has been demonstrated that at least half of the patients with alcohol use disorders have concomitant liver diseases [37].

The evaluation of sEVs in mental disorders is a rapidly developing area, and the vesicles are considered promising targets for developing biomarkers and novel therapeutic approaches [10, 11, 19]. Published narrative reviews generally emphasize the role of alcohol in the activation of neuroinflammation and the damage to the brain and other target organs via immune-mediated mechanisms [14, 17, 18]. Changes in sEVs lipid profile in patients with alcohol dependence syndrome are an interesting and promising area for future research. Given that sEVs, like all membrane-bound structures, primarily consist of a lipid bilayer, and the production and release of exosomes are related to sphingomyelinase activity [38, 39], the lipid profile can provide important information about the parent cell. Ibáñez et al. previously demonstrated, in animal models and cell cultures, that ethanol increases cholesterol uptake by activating mitochondria-associated membranes of the endoplasmic reticulum, increases cholesterol esterification, and enhances sphingomyelinase activity in microglia [40]. Furthermore, alcohol disrupts overall lipid metabolism, potentially leading to global alterations in signaling processes mediated by various lipid sEVs [41].

Lipid profile changes may indicate both changes in sEVs production and redistribution of individual vesicle fractions, e.g., associated with impairment of the blood-brain barrier [42]. Studies in small cohorts demonstrated that the concentration of astrocytic GFAP-containing sEVs is elevated in the first month after a stroke [43], while the concentration of astrocytic vesicles containing the glutamate/aspartate transporter (GLAST-1) is associated with stroke severity [44]. These data may indirectly indicate the severity of brain damage. Similar differences were identified in a study by Kodidela et al. [30] in alcohol users, regardless of their HIV status. Alpha-2-macroglobulin, which is less common in sEVs of alcohol users, as was demonstrated in the proteomic analysis, is a well-known serum marker of liver fibrosis [45]. As a proteinase inhibitor, it participates in many signaling cascades and, particularly, has anti-inflammatory activity by binding cytokines and interacting with complement proteins [46]. Japanese researchers used proteomic analysis of serum-derived sEVs and demonstrated that an increased level of alpha-2-macroglobulin may predict stroke occurrence over the subsequent eight years [47]. Properdin, which is less common in HIV-positive alcohol users compared to non-alcohol consumers, is a pro-inflammatory regulator of the

complement system in immune cells [48]. Interestingly, in the proteomic analysis of plasma sEVs in patients with cannabinoid dependence, a higher expression of properdin was observed [49]. However, it has not been fully elucidated whether these proteins are located inside the vesicles or on their surface (in a "protein coating") or are artifacts that are produced during release and can therefore be detected in plasma [50].

Differences in cytokine content between sEVs and plasma have been identified by some researchers, including Kodidela et al. [31], highlighting an important direction for future research into the sEVs composition and the role of the protein corona. A 2020 meta-analysis showed that cytokine concentrations may change at different stages of the alcohol use disorder but consistently differ from those in healthy populations [51].

Hsa-circ-0004771, which has been proposed as a potential biomarker of alcohol use disorder [32], also demonstrates diagnostic potential as a marker of colorectal cancer [52], which somewhat reduces the potential significance of this finding for real-world diagnostics. It is noteworthy that miR-30a-5p and miR-194-5p, the expression of which is increased in young individuals with heavy alcohol use, regulate the activity of genes associated with alcohol dependence [28]. This reinforces the concept of epigenetic regulation in polygenic diseases [53]. However, the causal relationship between these events remains unclear. The possible functional interactions between circulating microRNAs and hippocampal mRNAs shed light on potential communication mechanisms between the brain and the body. Nonetheless, the methodology of the study, specifically the bioinformatic analysis, does not allow for definitive conclusions regarding the existence of such a network in alcohol dependence [33].

The role of Toll-like receptor 4 (TLR4) in the pathogenesis of alcohol-associated diseases is widely discussed, with experimental findings being summarized in numerous review articles [54–56]. Two studies demonstrated that TLR4 contributes to differences in vesicle composition and also influences the intensity of the inflammatory response in alcohol use disorders [26, 27].

Since all included studies were published after 2018, it can be concluded that this line of research is relatively new and holds significant potential for further development. A key area for future investigation appears to be the regulation of sEVs biogenesis and the packaging of signaling molecules (nucleic acids, cytokines) into these vesicles via inflammatory signaling pathways, particularly through TLR4. The findings reported in cross-sectional studies not only preclude establishing causal relationships but also do not permit conclusions regarding the stability of specific sEVs characteristics within the study population. Therefore, studies with a prospective design and serial measurements of targeted vesicle characteristics are required. In addition, the current body of literature predominantly focuses on circulating sEVs in general. However, given that dependence is primarily a mental disorder, particular attention should be paid to specific sEVs fractions derived from neurons and glial cells.

It is critically important to use more rigorous participant selection methods and conduct analyses that take into account the disease stage. The alcohol use disorder is characterized by dynamic changes in the patient's condition, at least during intoxication, withdrawal, and abstinence, which may significantly influence the parameters being evaluated.

CONCLUSION

The findings of this scoping review indicate that sEVs represent a promising platform for studying the pathophysiology of alcohol use disorders and identifying relevant biomarkers. Most of the studies included in the review identified differences in the composition of sEVs in individuals with alcohol use disorders compared to healthy volunteers. These differences involve sex-dependent alterations in lipid profiles, as well as variations in microRNA expression related to the regulation of inflammation. However, the studies reviewed are highly heterogeneous in methodology and predominantly of low quality, which means that the results cannot be extrapolated to the population level. New studies with larger sample sizes, prospective study designs, and repeated measurements of specific sEVs characteristics are needed to validate the relevance of these findings.

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Supplementary data

Supplementary material to this article can be found in the online version by doi:
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Table S2: 10.17816/CP15803-146105
Table S3: 10.17816/CP15803-146106
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