Review article
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Systemic Administration of Escin for Post-Traumatic or Post-Operative Soft Tissue Edema: A Systematic Review of Randomized Clinical Trials

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Abstract

Background. Treatment of post-traumatic and post-operative soft tissue edema is especially relevant due to the high incidence of these conditions. They have a profound effect on patients´ quality of life and recovery process, as edema contributes to microcirculation impairment, pain exacerbation, fibrosis development, and limitation of motion. Escin, a promising treatment for edema, is a naturally derived compound with anti-edematous, angio- and endothelioprotective, anti-inflammatory, analgesic, and other effects.

The aim of the review — to summarize the clinical trial data on the efficacy and safety of systemically administered escin medications in the treatment of post-traumatic or post-operative soft tissue edema.

Methods. The review was conducted following the PRISMA-2020, ROBIS, and AMSTAR-2 guidelines and included clinical trials (CTs) that met the PICO(S) criteria. The search was carried out on January 8, 2025 in the PubMed, eLIBRARY, SciELO, Cochrane Library databases, and in the US, EU, and UK clinical trial registers. Qualitative evidence synthesis was performed in a narrative approach with confidence assessment by the GRADE-CERQual method. Risk of bias in individual CT was assessed using the RoB 2 tool.

Results. The review included three open-label, randomized, parallel-group CTs devoted to the anti-edematous effect of escin for managing post-operative edema in chronic venous disease (1 CT, n = 87), trauma-related skin flap transplantation (1 CT, n = 90), and surgical treatment for blunt limb trauma (1 CT, n = 102). In all trials reviewed, systemic administration of escin was effective in correcting local edema, did not significantly differ from comparison groups in terms of safety and tolerability, and had a positive effect on several pathogenetic laboratory markers of edema. All included CTs raised some concerns regarding the overall risk of bias, mainly due to the absence of blinding and randomization protection. The outcome reporting and publication bias for the evidence synthesis was deemed low.

Conclusions. The review has shown that systemic (oral or parenteral) administration of escin in the acute post-traumatic and post-operative periods effectively reduced the severity of edema (moderate confidence by GRADE-CERQual) and was well-tolerated. The incidence of adverse events did not significantly differ from the negative control, the active comparator (mannitol) (moderate confidence by GRADE-CERQual). The findings of this review may find further application as a basis for novel, more advanced approaches to the drug correction of edema of various etiologies.

Keywords: escin, escinate, edema, anti-edematous therapy, systematic review, clinical trials.

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Эсцин для системного введения при посттравматическом или постоперационном отеке мягких тканей: систематический обзор рандомизированных клинических исследований

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Реферат

Актуальность. Актуальность лечения посттравматического и послеоперационного отека мягких тканей обусловлена высокой частотой возникновения этих состояний, а также их значительным влиянием на качество жизни пациентов и процесс восстановления, что обусловлено нарушением микроциркуляции, усилением болевого синдрома, профибротическим действием и ограничением подвижности под влиянием этого патологического процесса. Перспективным представляется применение эсцина — соединения природного происхождения, обладающего противоотечным, ангио- и эндотелиопротективным, противовоспалительным, анальгезирующим и другими эффектами.

Цель обзора — анализ и синтез данных клинических исследований (КИ) об эффективности и безопасности препаратов эсцина для системного применения при посттравматическом или постоперационном отеке мягких тканей.

Материал и методы. Обзор проводили в соответствии с рекомендациями PRISMA-2020, ROBIS и AMSTAR-2. В обзор включали КИ, соответствовавшие критериям по системе PICO(S). Поиск источников проводили 08 января 2025 г. по базам научных публикаций PubMed, eLIBRARY, SciELO, Кохрейновской библиотеки, регистрам клинических исследований США, Евросоюза и Великобритании. Качественный синтез доказательств осуществляли в нарративном подходе с оценкой уверенности по системе GRADE-CERQual. Риск смещения результатов отдельных КИ оценивали с использованием инструмента RoB 2.

Результаты. В обзор вошли три открытых рандомизированных КИ с дизайном параллельных групп, посвященных оценке противоотечного эффекта эсцина при постоперационном отеке на фоне хронического заболевания вен (1 КИ, n = 87), трансплантации кожного лоскута по поводу травмы (1 КИ, n = 90) и хирургического лечения тупой травмы конечности (1 КИ, n = 102). Во всех рассмотренных КИ системное введение эсцина было эффективно для коррекции локального отека, значимо не отличалось от групп сравнения по безопасности и переносимости, а также оказывало положительное влияние на уровни некоторых патогенетических лабораторных маркеров отека. Во всех включенных КИ были найдены основания для некоторых опасений в отношении общего риска смещения эффекта, связанного, главным образом, с отсутствием ослепления и защиты процесса рандомизации. Риск смещения, связанного с выборочными публикацией и/или сообщением результатов, в рамках проведенного синтеза был оценен как низкий.

Заключение. Проведенный обзор показал, что системное (пероральное или парентеральное) введение эсцина в острый период после травм и оперативных вмешательств эффективно уменьшало выраженность отека (умеренная уверенность по GRADE-CERQual), хорошо переносилось и по частоте возникновения нежелательных явлений не отличалось от минус-контроля, от препарата сравнения (маннитола) (умеренная уверенность по GRADE-CERQual). Результаты обзора могут найти дальнейшее применение при обосновании новых, более совершенных подходов к проведению медикаментозной коррекции отеков различной этиологии.

Ключевые слова: эсцин, эсцинат, отек, противоотечная терапия, систематический обзор, клинические исследования.

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INTRODUCTION

Edema is a typical pathological process characterized by excessive accumulation of extracellular tissue fluid in the interstitial and/or intracellular space. Edema of varying localization and severity is common across a wide range of diseases, including chronic diseases of the cardiovascular system, kidneys, and liver; acute conditions accompanied by pronounced organ failure; inflammatory processes; endocrine and water-electrolyte imbalances; as well as trauma and postoperative states [1, 2]. The prevalence of soft tissue edema due to the injury or disruption of integrity during invasive procedures, including those performed in the context of trauma management, varies widely depending on the severity and location of the primary injury and may reach 60-75% [3, 4, 5, 6].

Regardless of its origin, edema develops as a result of the disruption of the physiological balance between the blood pressure and the tissues the blood supplies, as well as increased permeability of the capillary endothelial barrier. These changes lead to fluid being filtered into the interstitial space at a rate exceeding its reabsorption by the vascular system, resulting in fluid retention in the tissues. The presence of edema worsens the initial causes and contributing factors by exerting mechanical compression on affected structures, provoking or intensifying pain, impairing tissue perfusion and metabolic processes, and ultimately leading to tissue dysfunction, forming a vicious cycle [1, 2].

To manage edema of various origins and types, both non-pharmacological methods – such as the widely used RICE protocol (R – rest; I – ice; C – compression; E – elevation) – and pharmacological agents may be employed. These include diuretics, anti-inflammatory, antiallergic, vasoconstrictive drugs, venotonics, angioprotectors, and agents for pathogenetic therapy of the underlying disease [7, 8]. Management of post-traumatic, perioperative, and post-operative edema aims to facilitate tissue and/or bone fragment reduction (in case of fractures), restore tissue trophism, reduce pain, improve overall patient condition, accelerate functional rehabilitation, and prevent potential complications [6, 8, 9, 10].

Escin is a mixture of triterpene saponin glycosides obtained from the seeds of the horse chestnut (*Aesculus hippocastanum L.*), with β-escin being the predominant and biologically active component. *In vitro* and *in vivo* studies have shown a wide range of pharmacological effects for escin drugs (including sodium and lysine salts), such as anti-edematous, angio- and endothelioprotective, anti-inflammatory, analgesic, and antioxidant activities [11, 12]. The most relevant mechanisms of escin's anti-edematous action include direct inhibition of protein and mucopolysaccharide hydrolysis, preventing an increase in the oncotic pressure of interstitial fluid; steroid-like anti-inflammatory activity; antagonism to histamine and bradykinin; induction of endogenous antioxidant factors; correction of endothelial function; inhibition of endothelial cell apoptosis; and prevention of pathological cellular adhesion in the microcirculatory bed [11, 12, 13, 14].

Individual clinical trials (CTs) have demonstrated the efficacy of escin and total *Ae. hippocastanum*-based drugs as pharmacological agents for managing soft tissue edema of various etiologies. The most substantial evidence base exists for chronic venous disease (CVD) [15, 16, 17].

The aim of the systematic review – to summarize the clinical trial data on the efficacy and safety of systemically administered escin medications in the treatment of post-traumatic or post-operative soft tissue edema.

METHODS

The systematic review was conducted in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [18], as well as the ROBIS (Risk of Bias in Systematic Reviews) [19] and AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) [20] methodological quality and validity assessment tools. The PRISMA 2020 checklist with annotated review sections is provided in the supplementary materials. The objectives of the review, search strategies, inclusion and exclusion criteria, screening algorithms, source evaluation, qualitative synthesis, risk of bias assessment, certainty of evidence, and conflict resolution procedures were all defined prior to conducting the review and were not subject to change during its execution. The review protocol was not published or registered.

The review included CTs that met the criteria listed below, defined using the PICO(S) framework [21] (Table 1).

No restrictions were imposed regarding participants' age or gender, dosage forms of escin, or design features such as randomization, blinding, etc., beyond the specified criteria. CTs were excluded if they failed to meet any of the aforementioned criteria or belonged to one of the following categories:

1) synthetic research: narrative reviews, scoping reviews, umbrella reviews, systematic reviews, post-hoc analyses, meta-analyses, and clinical guidelines;

2) non-clinical studies;

3) materials with low levels of evidence: conference abstracts, case reports and case series, methodological guidelines, meeting protocols, press releases, etc.

The literature search was conducted on January 8, 2025, across the following databases: PubMed, eLIBRARY, SciELO, Cochrane Central Register of Controlled Trials, and clinical trial registries including ClinicalTrials.gov (USA)[1], EU Clinical Trial Register[2] and EU Clinical Trials Information System[3] (EU), and the UK Clinical Study Register[4] (UK). Working languages included English, Russian, and Spanish. No publication date restrictions were applied. Search queries are presented in Table 2.

Screening of sources, assessment of eligibility based on inclusion criteria, data extraction, and risk of bias assessment for the included CTs were performed independently by two review authors (V.A. Prikhodko, S.V. Okovityi) without the use of automation tools. All disagreements were resolved through discussion until consensus was reached, with the involvement

Table 1

Inclusion criteria for clinical studies

No.	Parameter	Inclusion criterion
1	**Population**	
1.1	State	Injuries of any localization, origin, nature, and severity OR prior surgical interventions of any localization, nature, and degree of invasiveness
2	**Intervention**	
2.1	Medication	Escin (in any form of salts or complexes)
2.2	Administration route	Systemic (oral or parenteral administration)
2.3	Treatment regimen	Monotherapy OR combination therapy (presence of a comparison arm without the inclusion of escin)
3	**Comparison**	Placebo OR basic/standard therapy OR any comparator drug OR combination therapy without the inclusion of escin
4	**Endpoints**	Any relevant to post-traumatic edema OR any relevant to post-operative edema
5	**Study design**	
5.1	Type	Prospective
5.2	Intervention	Interventional
5.3	Control	Controlled

[1] National Library of Medicine. ClinicalTrials.gov. Available at: https://www.clinicaltrials.gov/

[2] The European Union Clinical Trials Register. Available at: https://www.clinicaltrialsregister.eu/ctr-search/search

[3] The European Union (EU) and European Economic Area (EEA) register of clinical trials for human medicines. Available at: https://euclinicaltrials.eu/search-for-clinical-trials/

[4] The United Kingdom Clinical Study Registry. Available at: https://www.isrctn.com/

Table 2

Search queries

Database	Search query
PubMed	(escin* OR aescin*) AND (clinical trial)
eLIBRARY	What to search for: (escin* OR escins* OR escinate*) AND (clinical trial) (in Russian) Where to search: in the title; in the abstract; in the keywords Publication type: journal articles; conference materials; reports Parameters: search with morphological variations included
SciELO	(escina OR aescina OR escinato OR aescinato OR escin OR aescin OR escinate OR aescinate) AND type: research-article
Cochrane Central Register of Controlled Trials	Title Abstract Keyword: escin OR aescin OR escine OR aescine OR escina OR aescina OR escins OR aescins OR escinas OR aescinas OR escinate OR aescinate OR escinato OR aescinato [include word variations] Content type: trials Language: English, Russian, Spanish
ClinicalTrials.gov	Intervention/treatment: escin OR aescin OR escine OR aescine OR escina OR aescina OR escins OR aescins OR escinas OR aescinas OR escinate OR aescinate OR escinato OR aescinato
EU Clinical Trial Register	escin OR aescin OR escine OR aescine OR escina OR aescina OR escins OR aescins OR escinas OR aescinas OR escinate OR aescinate OR escinato OR aescinato Results status: trials with results
EU Clinical Trials Information System	escin*, aescin*, escine*, aescine*, escina*, aescina*, escins*, aescins*, escinas*, aescinas*, escinate*, aescinate*, escinato*, aescinato*
UK Clinical Study Register	Interventions: escin or aescin or escins or aescins or escinate or aescinate Study status: completed

of an independent consultant in cases where disagreement persisted. Decisions on trial inclusion were made in two sequential stages: (1) screening of the title and abstract; and (2) full-text assessment (for sources potentially meeting inclusion criteria based on the initial screening). For all included CTs, all available data on participants, efficacy, and/or safety of the intervention were extracted from the original sources, presented by the authors, including supplementary materials, without any quantitative transformation.

The qualitative synthesis of evidence and the investigation of data heterogeneity were conducted using a narrative approach [22], summarizing data from all included CTs according to group-specific inclusion criteria based on the PICO(S) framework, and presented in textual, tabular, and graphical formats. The confidence in the body of evidence was assessed using the GRADE-CERQual system, which evaluates sources based on four criteria: (1) methodological limitations; (2) coherence; (3) adequacy of data; and (4) relevance [23]. Key findings from the synthesis were summarized in a Summary of Qualitative Findings (SoQF) table [24].

The risk of bias in individual CTs included in the review was assessed using the RoB 2 (Risk of Bias) tool [25], as all studies were randomized and interventional. For non-randomized studies, the review protocol specified the use of the ROBINS-I scale [26]. The RoB 2 tool allows assessment of bias risk across five domains: (1) randomization process; (2) deviations from intended interventions; (3) missing endpoints' data; (4) assessment of the endpoints; and (5) selection of the reported result.

The risk of bias related to selective publication and/or selective outcome reporting was assessed by comparing the list of endpoints in the trial protocol with those reported in the corresponding publication. If the protocol was not available, the endpoints listed in the methods and results sections of the publication were compared.

RESULTS

A total of 237 publications were identified through the search process, and the screening and evaluation procedures are illustrated in the PRISMA diagram [18] (Figure 1).

Following the screening process, three clinical trials [27, 28, 29] that met all inclusion criteria were selected; their general characteristics are presented in Table 3.

All included trials were conducted in the People's Republic of China, were comparative in nature, had a parallel-group design (two trials with a single intervention group [27, 28], and one trial with two intervention groups [29]), were randomized, and did not implement blinding at any level. One trial included patients with post-operative edema associated with CVD [27]; another involved patients who had undergone skin flap transplantation due to trauma [28]; and the third included patients with limb trauma-related edema following surgical intervention [29].

Potentially relevant trials excluded after full-text assessment, along with the reasons for exclusion, are presented in Table 4.

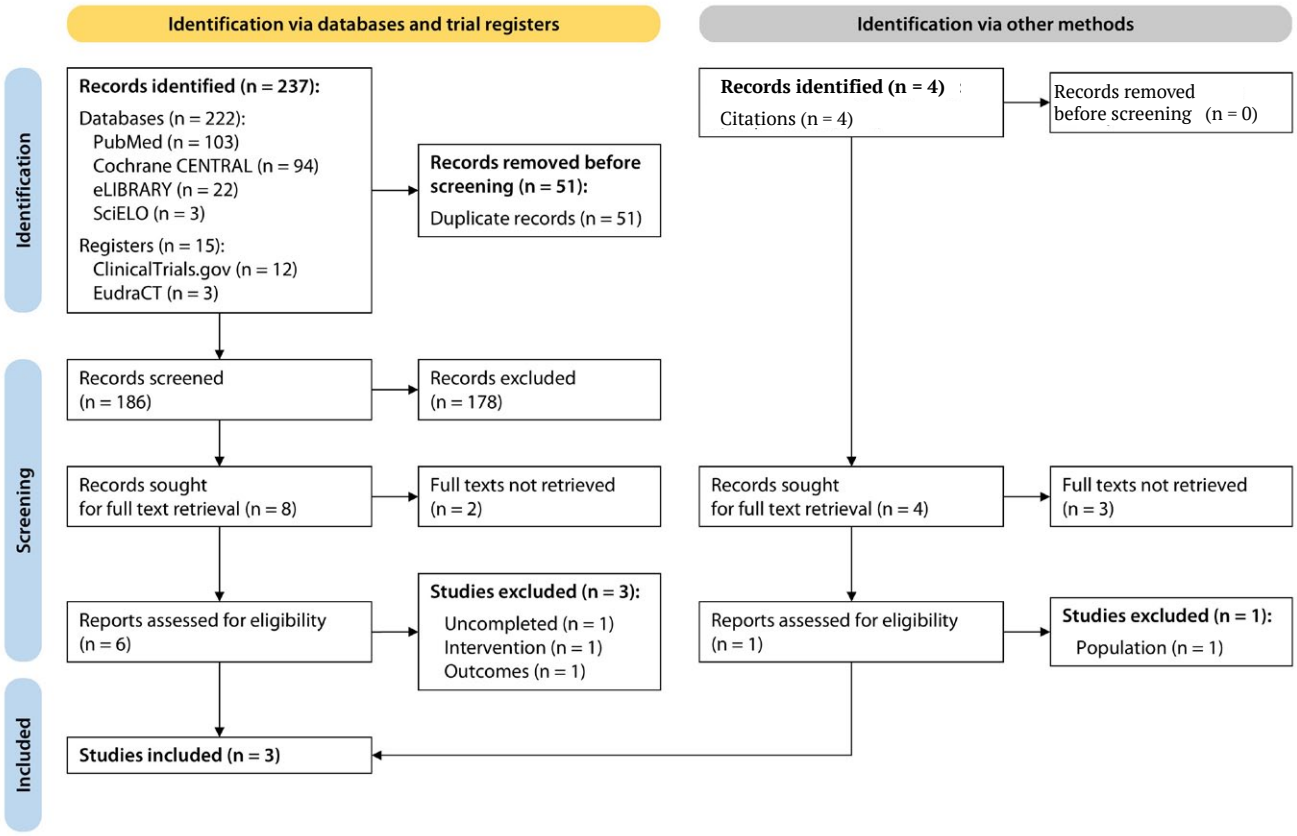

Figure 1. PRISMA flow diagram

Table 3

General characteristics of clinical studies included in the review

First author and year of publication	n	Country	Number of centers	Design of groups	Number of groups	Randomization	Blinding	Reference
Yang X., 2024	87	PRC	1	PG	2	Yes	No	[27]
Wei L., 2018	90	PRC	1	PG	2	Yes	No	[28]
Wang B., 2016	102	PRC	1	PG	3	Yes	No	[29]

PRC – People's Republic of China, PG – parallel groups.

Table 4

Potentially relevant clinical studies excluded after full-text assessment

First author and year of publication	Reasons for exclusion	Reference
Singhai A., 2024	Not completed (planned study protocol)	[38]
Xie Q., 2009	Endpoints not meeting inclusion criteria (time to recovery of intestinal gas passage, time to return of bowel sounds, time to first bowel movement)	[39]
Dusková M., 1999	Intervention not meeting inclusion criteria (escin arm: escin + etamsylate; comparator arm: proteolytic enzymes)	[40]

CT 1. Clinical efficacy of sodium escinate administration following endovenous laser ablation for varicose veins (Yang X. et al., 2024) [27]

X. Yang et al. evaluated the effects of systemic administration of escin salt in patients with lower limb varicose veins who underwent endovenous laser ablation (EVLA). The parameters assessed included the severity of edema, pain syndrome, the course and symptoms of CVD, as well as the quality of life [27]. The study was supported by the International Scientific and Technological Cooperation Program under the Science and Technology Innovation Action Plan of Shanghai, the Fundamental Research Program of the 9th People's Hospital, Shanghai Jiao Tong University School of Medicine, and the pharmaceutical company Shandong Luye Pharmaceutical Co., Ltd. (Luye Pharma Group) – the manufacturer of escin-based drugs Oukai® and Maitongna® (PRC). The authors declared no actual or potential conflicts of interest.

The CT included 90 adult patients, of whom 43 (49.4%), 20 (23.0%), 18 (20.7%), and 6 (6.9%) were classified as C2, C3, C4, and C5 clinical classes, respectively, according to the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification of CVD. The mean age of the participants was 59.9±10.7 years; among them, 54 (62.1%) were men and 33 (37.9%) were women. The baseline characteristics of the participants, common to all three included CTs, are presented in Table 5. Exclusion criteria included a history of previous surgical treatment for CVD; bilateral procedures performed during a single session; use of venoactive and/or diuretic drugs within the previous month; edema caused by other conditions, including those of the lymphatic system; stenosis and/or occlusion of deep veins; arterial disease (ankle-brachial index less than 0.9); prior experience with and/or inability to wear compression stockings; allergic reactions to escin salts or a history of escin intolerance.

Table 5

Patient characteristics at baseline

Patient characteristics at baseline	Clinical trial						
	Yang X., 2024 [27]		Wei L., 2018 [28]		Wang B., 2016 [29]		
	Escin group	Control group	Escin group	Control group	Escin group	Mannitol group	Escin + mannitol group
Number of participants	42	45	45	45	34	34	34
Age, years (men±SD)	58.5±12.1	61.1±9.3	9.3±2.7	9.1±2.8	45.3±7.6	46.8±7.3	45.8±6.3

End of Table 5

Patient characteristics at baseline

Patient characteristics at baseline	Clinical trial						
	Yang X., 2024 [27]		Wei L., 2018 [28]		Wang B., 2016 [29]		
	Escin group	Control group	Escin group	Control group	Escin group	Mannitol group	Escin + mannitol group
Male, n (%)	24 (57.1)	30 (66.7)	23 (51.1)	26 (57.8)	24 (70.6)	18 (52.9)	19 (55.9)
Etiology of edema	Post-operative (EVLA ± sclerotherapy ± phlebectomy for varicose veins of the lower limbs)		Post-traumatic + post-operative (pedicled skin flap transplantation for limb injury)		Post-traumatic + post-operative (surgical intervention for blunt trauma of the upper limb)		

SD – standard deviation, EVLA – endovenous laser ablation.

Participants were randomized using a block randomization method in a 1:1 ratio into two parallel groups: A) intervention group; B) negative control group. There were no statistically significant differences between the groups in terms of gender distribution, mean age, body mass index, tobacco and alcohol consumption, presence of comorbidities (including *diabetes mellitus*, arterial hypertension, and other cardiovascular diseases), as well as the location and severity of the underlying condition, as assessed by clinical scales, questionnaires, and instrumental diagnostic methods.

All patients underwent EVLA and ligation of the great saphenous vein under regional anesthesia. At the discretion of the surgeons, some patients additionally received sclerotherapy and/or phlebectomy. No pharmacological prophylaxis of deep vein thrombosis or wound infection was administered. All patients wore class II compression stockings throughout the entire study period. Participants in Group A additionally received escin salt (60 mg) orally twice daily for 20 days, starting on the day of the EVLA procedure. Patients in Group B did not receive any pharmacological therapy. The parameters of the intervention protocol in the described CT are presented in Table 6.

The assessment of the intervention's efficacy and tolerability was carried out over three visits: at 10±5, 21±3, and 30±5 days postoperatively. The primary endpoint was defined as the change in calf circumference (cm) on day 21, reflecting the resolution of local edema. Secondary endpoints included changes in ankle circumference (cm) on days 10, 21, and 30; pain intensity assessed by the Visual Analog Scale (VAS, score); clinical severity of chronic venous disease assessed by the Venous Clinical Severity Score (VCSS, score); and quality of life measured by the Aberdeen Varicose Vein Questionnaire (AVVQ, score). The time points and study endpoints are illustrated in Figure 2.

The full analysis set (FAS) included 87 patients who completed the study program, of whom 74 fully adhered to the treatment protocol (per protocol set, PPS). Among FAS participants receiving escin, a significantly lower absolute calf circumference was observed compared to the control group on days 10 and 21 of treatment (Day 10: 37.49±2.75 vs 38.98±2.87 cm, $p = 0.018$; Day 21: 36.93±2.64 vs 38.31±2.60 cm, $p = 0.019$). In addition, the increase in calf circumference relative to baseline was significantly smaller in the escin group at all time points (Day 10: 1.04±0.35 vs 2.39±1.15 cm; Day 21: 0.48±0.42 vs 1.73±1.00 cm; Day 30: 0.18±0.64 vs 0.82±0.96 cm; $p<0.001$ for all comparisons). The between-group differences were -1.44±0.18 cm (95% CI: -1.80, -1.07), -1.26±0.17 cm (95% CI: -1.59, -0.93), and -0.54±0.17 cm (95% CI: -0.88, -0.20) at the respective time points.

The mean ankle circumference was significantly lower in the escin group on day 10 (23.8±1.98 cm vs 24.85±1.66 cm, $p = 0.023$), with no difference observed between groups on days 21 and 30. A significantly smaller increase in this parameter was recorded in the escin group

Table 6

Characteristics of intervention protocols in the included studies

Parameter	Clinical trial						
	Yang X., 2024 [27]		Wei L., 2018 [28]		Wang B., 2016 [29]		
	Escin group	Control group	Escin group	Control group	Escin group	Mannitol group	Escin + mannitol group
Intervention	sodium escinate	no	sodium escinate	no	sodium escinate	mannitol	sodium escinate + mannitol
Administration route	orally	–	IV drip	–	IV drip	IV drip	IV drip
Dose per administration, mg	60	–	0.2 mg/kg, not exceeding 20 mg per day	–	20	25	10 + 25
Frequency of administration, times per day	2	–	1	–	1	2	1
Daily dose, mg	120	–	0.2 mg/kg, not exceeding 20 mg per day	–	20	50	10 + 25
Duration of therapy, days	20		7		7		
Baseline therapy	Non-pharmacological (compression stockings, class II)		Pharmacological (analgesics, antibacterial agents, nutritional support, fluid and electrolyte balance regulators)		No		

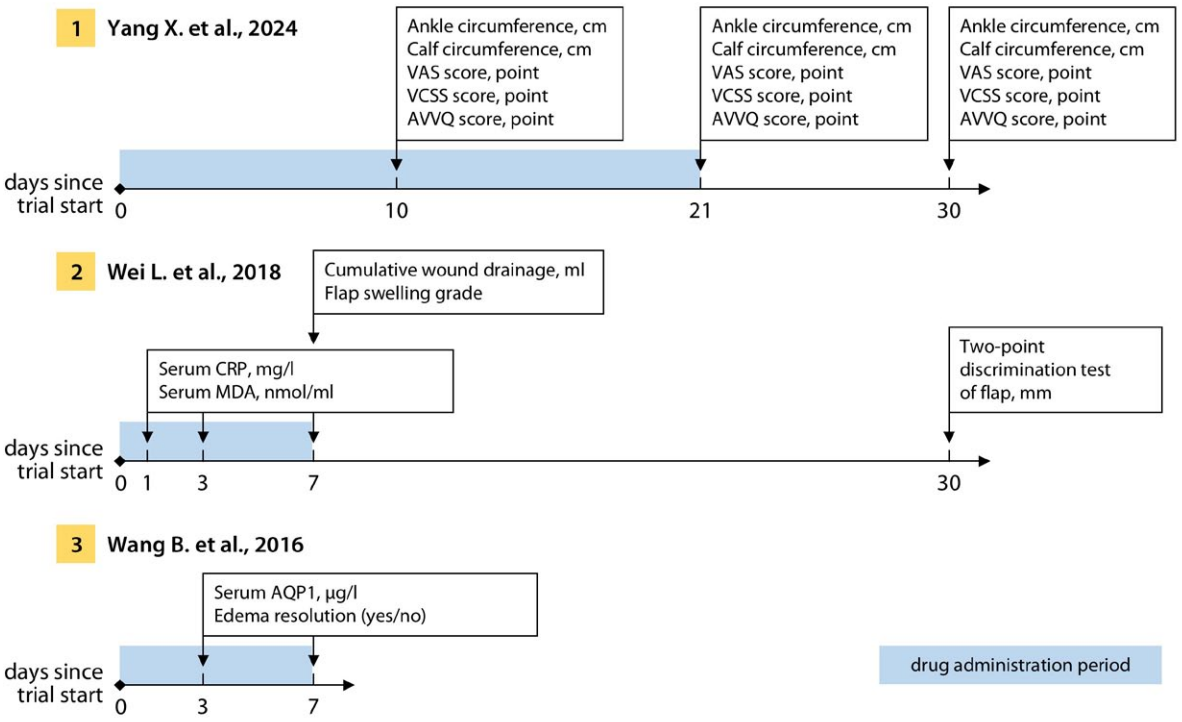

Figure 2. Time points and endpoints of the trials included in the review

at the first two time points (Day 10: 1.37±0.52 vs 2.36±0.93 cm, p<0.001; Day 21: 0.58±0.60 vs 1.14±0.88 cm, p = 0.002). Escin administration resulted in a significant reduction in ankle circumference by -1.00±0.17 cm (95% CI: -1.34, -0.66) and -0.57±0.17 cm (95% CI: -0.91, -0.22) compared to the control group on days 10 and 21, respectively.

The intensity of pain according to VAS, the overall severity of CVD by VCSS, and the quality of life as assessed by AVVQ did not differ significantly between the groups throughout the study period in the FAS analysis. For the PPS, a significantly lower pain intensity was observed on day 21 in the escin group compared to those not receiving drug therapy (0.508±0.794 vs 0.953±0.916, p = 0.047). The mean group scores for VCSS and AVVQ did not differ significantly between the groups, regardless of patient adherence to the protocol.

The overall frequency of adverse events (AEs) was 16.7% (n = 7) in the escin group and 11.1% (n = 5) in the control group, with no significant difference between them. None of the AEs were considered serious. The AEs included dyspeptic symptoms (n = 5; 2 patients discontinued the drug), chest discomfort (n = 2), skin reactions (n = 4), and hypersensitivity reactions (n = 1). The frequency of AEs did not differ significantly between the two groups. The results of the assessment of the intervention tolerability in the included trials are presented in Table 7.

Thus, in the study conducted by X. Yang et al., escin (60 mg orally twice a day for 20 days) in combination with the use of compression stockings effectively reduced the severity of lower limb edema and pain (in patients with high adherence to the protocol), had no impact on the overall course of the disease or quality of life in patients with CVD who underwent EVLA with optional sclerotherapy and/or phlebectomy [27].

Table 7

Incidence of adverse events in the included studies, number of patients (%)

Adverse event	Clinical trial						
	Yang X., 2024 [35]		Wei L., 2018 [36]		Wang B., 2016 [37]		
	Escin group	Control group	Escin group	Control group	Escin group	Mannitol group	Escin + mannitol group
All AEs	7 (16.7)	5 (11.1)	1 (2.2)	0	6 (17.7)	8 (23.5)	2 (5.9)
Dyspeptic symptoms, nausea, diarrhea	5*		0	0	N/A		
Chest discomfort, palpitations	2	0	0	0	N/A		
Skin reactions, blisters	4	0	N/A		3	2	1
Hypersensitivity reactions	1	0	0	0	1	1	0
Injection site reactions	N/A		1	0	N/A		
Dizziness	N/A		0	0	N/A		
Liver function disorders	N/A		0	0	N/A		
Kidney function disorders	N/A		0	0	0	4	0
Electrolyte imbalances	N/A		0	0	0	2	0
Dysuria, changes in urination frequency	N/A		0	0	N/A		
Phlebitis	N/A		N/A		2	0	1

* Data from the original source without group stratification.
N/A – no data available.

CT 2. Sodium escinate injection for skin flap transplantation of hand or foot in children (L. Wei et al., 2018) [28]

L. Wei et al. assessed the impact of parenteral administration of escin on the resolution of edema and exudation, serum marker levels (C-reactive protein (CRP), malondialdehyde (MDA)), and the recovery of sensory function following skin flap transplantation for the treatment of traumatic limb injuries in children. The authors did not disclose funding sources but stated that there were no apparent or potential conflicts of interest [28].

CRP is one of the so-called acute-phase proteins, widely used as laboratory markers of inflammation of any etiology, demonstrating high sensitivity and a rapid response to the development of the inflammatory process. Recent data suggest that CRP may play a role as a mediator of endothelial dysfunction, impairing normal endothelial reactivity and contributing to increased permeability of capillary walls [30]. MDA is the primary product of the peroxidative degradation of unsaturated lipids, reflecting the intensity of oxidative stress and oxidative damage to biomolecules and cellular structures. MDA and neoantigens formed from modified proteins possess pro-inflammatory activity by inducing corresponding cytokines and activating cellular immune response reactions [31].

The CT included 90 children aged 5 to 14 years (49 (54.4%) boys, 41 (45.6%) girls) with injuries to the upper (62 (68.9%)) or lower limbs (28 (31.1%)). All of them underwent pedicled skin flap transplantation as part of their treatment for the sustained injury, with the majority (75 (83.3%)) receiving it as part of emergency medical care. Baseline characteristics of the participants common to the three included trials are presented in Table 5. Exclusion criteria included the use of diuretics within 1 week and/or steroids within 1 month before the start of the CT; the presence of heart disease, previous heart surgery, kidney damage and/or renal failure, liver failure, HIV infection, coagulation disorders, electrolyte imbalance, or hemodynamic instability.

Patients were randomized into two parallel groups: A) intervention group (escin), and B) negative control group. The groups did not differ significantly in terms of gender ratio, mean age, time and circumstances of injury, injury location and severity, surgical protocols and operative features, or baseline serum concentrations of CRP and MDA. All children received baseline therapy, which included analgesics, antibiotics, nutritional support, and medications for water-electrolyte balance regulation. Participants assigned to Group A additionally received escin salt (0.2 mg/kg, not exceeding 20 mg) via intravenous infusion once daily for 7 days, starting on the day of transplantation. The parameters of the intervention protocol in the described CT are presented in Table 6.

The evaluation of the drug's efficacy and tolerability was performed on days 1, 3, 7, and 30 of the study. Venous blood serum levels of CRP (mg/l) and MDA (nmol/ml) were measured on days 1, 3, and 7. The total volume of wound exudate obtained via drainage (ml) and the degree of skin flap edema (on a scale from 0 to 3) were assessed on day 7. Thirty days after the start of the CT, recovery of sensory function in the transplanted area was evaluated using the two-point discrimination test by determining the minimal distance between two stimulation points perceived by the patient (mm). The timeline and endpoints of the CT are presented in Figure 2.

All 90 participants completed the study protocol and were included in the analytical sample. Serum CRP and MDA levels were significantly lower in the escin group compared to the control group at all time points, according to Student's t-test (CRP: t1 = 3.272, t3 = 8.597, t7 = 8.003, $p<0.05$ for all; MDA: t1 = 9.569, t3 = 10.046, t7 = 7.420, $p<0.05$ for all). The volume of wound exudate on day 7 after the start of therapy was significantly lower in the escin group compared to the control group (58.11±20.51 vs 72.25±22.70 ml, $p = 0.005$). Patients receiving escin also showed significantly more frequent cases of less severe local edema compared to those receiving standard therapy alone (absolute frequency of edema grades 0/I/II/III: 7/25/13/0 and 2/20/22/1 in the two groups, respectively, $p = 0.013$). One month after the start of the CT, the results of the two-point discrimination test also differed significantly: the minimal discernible distance was 7.46±3.74 mm in the escin group and 9.73±3.68 mm in the control group ($p = 0.004$).

In the experimental therapy group, one case of local irritation and pain during escin infusion was reported as an AE; the symptoms resolved spontaneously after reducing the infusion rate. The overall incidence of AEs did not differ

significantly between the two groups. The results of the tolerability assessment of the interventions in the included CTs are presented in Table 7.

Thus, in the study conducted by L. Wei et al., escin (0.2 mg/kg administered once daily via intravenous infusion for 7 days), when included in the pharmacological treatment regimen for post-traumatic limb injury and skin flap transplantation in children, significantly reduced serum levels of CRP and MDA, decreased the severity of edema and exudation in the affected area, and contributed to improved sensory function recovery of the flap in the long-term period [28].

CT 3. Clinical effects of joint application of β-sodium escinate and mannitol in treating early swelling after upper limb trauma surgery (B. Wang et al., 2016) [29]

B. Wang et al. evaluated the effects of escin as monotherapy and in combination with mannitol on the severity of local edema and serum levels of aquaporin-1 (AQP1), a marker of vascular wall permeability, in patients undergoing surgical procedures on the upper limb for blunt trauma. The authors did not disclose funding sources and did not report the presence or absence of any conflicts of interest [29].

AQP1 is a transmembrane protein responsible for water transport across cell membranes along the osmotic gradient and also participates in non-selective ion transport via a mechanism dependent on cyclic guanosine monophosphate. In adults, the highest levels of AQP1 expression are found in endothelial cells across nearly all anatomical locations, as well as in kidney structures, the choroid plexus of the brain, intrahepatic bile ducts, the gallbladder, and other regions of the gastrointestinal tract [32]. Induction of AQP1 and other aquaporins has been shown to be positively associated with the severity of edema in conditions such as chronic congestive heart failure, liver cirrhosis, chronic kidney disease, and other pathologies [33].

The study was conducted with the participation of 102 adult patients who underwent surgical treatment for upper limb trauma sustained no more than 8 hours prior to enrollment. Baseline characteristics of the participants, common to the three included CTs, are presented in Table 3. Patients were excluded if they had edema associated with severe damage to the nervous system and/or blood vessels, burns, venous and/or lymphatic obstruction, neoplastic processes, or comorbidities involving the heart, kidneys, or brain.

Participants were randomized into three groups (n = 34 in each): A) intervention group (escin monotherapy); B) active control group; and C) combination therapy group. The mean ages were 45.3±7.6, 46.8±7.3, and 45.8±6.3 years, and the mean time from injury to enrollment was 5.6±1.1, 5.4±1.5, and 5.8±1.3 hours in groups A, B, and C, respectively. In group A – 18 (52.9%) patients, in group B – 15 (44.1%) patients, and in group C – 17 (50.0%) patients had grade II edema; the remaining participants in each group presented with grade III edema. The groups did not differ significantly in terms of gender distribution, mean age, time from injury, or edema severity (graded I to III).

Patients in group A received escin sodium salt (20 mg) administered once daily via intravenous infusion. Participants in group B received the comparator drug – mannitol, an osmotic diuretic – administered as a 20% solution (125 ml; 25 mg) via intravenous infusion twice daily (every 12 hours). Patients in group C received combination therapy with half the daily doses of each drug: escin (10 mg) administered once daily via intravenous infusion plus 20% mannitol (125 ml; 25 mg) administered once daily via intravenous infusion. The intervention protocol parameters for this CT are presented in Table 6.

The efficacy and tolerability of the interventions were assessed by measuring serum concentrations of AQP1 (μg/l) on days 3 and 7 of treatment, as well as the time to complete resolution of edema. Therapy was considered effective if the edema resolved in less than 3 days, partially effective if it resolved in 4 to 7 days, and ineffective if it took more than 7 days. Overall efficacy was calculated as the proportion of patients with a complete or partial response relative to the total number of patients (%). The timeline and endpoints of the CT are presented in Figure 2.

The mean time to resolution of edema in the affected area was 6.38±1.37, 6.61±1.63, and 4.16±1.72 days in the escin, mannitol, and combination therapy groups, respectively; the combination treatment had a significantly greater effect ($p = 0.027$). The treatment was effective in reducing edema in 79.4%, 70.6%, and 94.1%

of patients in the three groups, respectively; a significantly higher efficacy was also observed for combination therapy (p = 0.042). At the start of the treatment, there were no significant differences in serum AQP1 levels between the groups. During the study, this level remained unchanged in the mannitol group, but significantly decreased in the escin and combination groups (escin: baseline – 16.54±3.06 μg/l, day 3 – 11.34±2.52 μg/l, day 7 – 7.28±1.23 μg/l (p<0.05); escin + mannitol: baseline – 17.24±3.26 μg/l, day 3 – 11.36±2.85 μg/l, day 7 – 7.31±1.52 μg/l (p<0.05)). There were no statistically significant differences in AQP1 levels between the groups.

In the escin group, AEs were observed with an overall frequency of 17.65%, including the appearance of blisters on the skin (n = 3), phlebitis (n = 2), and allergic reactions (n = 1). In the mannitol group, the overall frequency of AEs was 23.53%; these included kidney dysfunction (n = 4), blisters on the skin (n = 2), electrolyte imbalances (n = 2), and allergic reactions (n = 1). In the combination therapy group, AEs occurred at a frequency of 5.88% and were represented by phlebitis and skin blisters (n = 1 each). The overall frequency of AEs did not differ significantly between the patient groups. The results of the assessment of intervention tolerability in the included CTs are presented in Table 7.

Thus, in the study by B. Wang et al., escin (20 mg intravenously, once a day for 7 days) facilitated edema resolution, showing no significant difference compared to mannitol (25 mg intravenously, twice a day for 7 days). The combined administration of half-doses of escin and mannitol (10 mg + 25 mg intravenously, once a day for 7 days) significantly enhanced the overall anti-edematous effect of the components. Escin and its combination with mannitol significantly reduced serum concentrations of the AQP1 marker, which was not observed with mannitol monotherapy [29].

Risk of bias assessment

According to the RoB 2 system algorithms, all CTs included in the review raised concerns regarding the overall risk of bias (Figure 3). All CTs had a moderate risk of bias related to randomization, as none of them used allocation concealment as a measure to protect the randomization process. The risk of bias related to deviations from the intervention protocol was assessed as moderate for the CT by X. Yang et al., based on the reported significant impact of low adherence to the protocol on one of the endpoints, as well as the absence of pharmacological therapy in the negative control group. For this same CT, the risk of bias related to missing endpoint data was also assessed as moderate due to the absence of relevant data for more than 10% of participants [27]. All included CTs raised concerns regarding the risk related to endpoint assessment, due to the lack of blinding of both participants and medical staff. The risk of bias related to the selective reporting of results was assessed as low in all cases.

The risk of bias related to the selective publication and/or reporting of results was low in the conducted synthesis: all three CTs included in the review reported the results of all endpoints stated in the methods section of the respective publications.

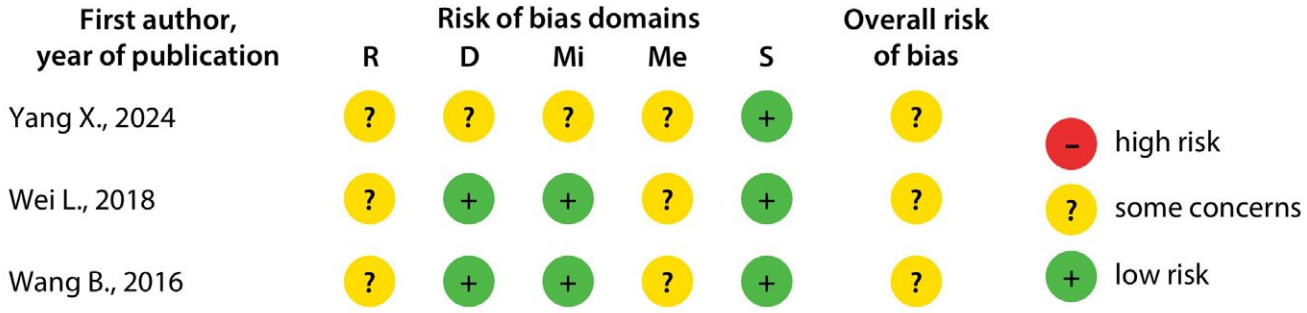

Figure 3. Risk of bias assessment for the included clinical trials according to the RoB 2 tool: R – bias related to randomization; D – bias related to deviations from the intervention protocol; Mi – bias related to missing endpoint data; Me – bias related to endpoint assessment; S – bias related to the selective reporting of results

DISCUSSION

The anti-edematous effect of escin may be associated with its influence on several pathogenic mechanisms common to edema of various origins, including inflammation, oxidative stress, lipid peroxidation, and dysfunction of transmembrane water channels. This was reflected in changes in relevant laboratory markers observed in participants receiving escin in the included CTs.

The results of three randomized CTs identified during the literature search allow for a reasonable degree of confidence in concluding that systemic administration of escin medications may be effective in reducing localized edema in patients following trauma or surgical interventions, including cases involving surgical management of injuries. Moreover, systemic use of escin during the acute post-traumatic or postoperative period was shown to be safe in the reviewed trials and was well tolerated, with no significant differences compared to placebo or the comparator drug (mannitol).

The findings of our systematic review are consistent with those reported by other authors. For instance, in a literature review by L. Gallelli, data were presented supporting the anti-edematous, anti-inflammatory, and venotonic effects of escin, as well as its ability to reduce the severity of ischemic-hypoxic injury to endothelial cells and restore physiological permeability of microcapillary walls [12]. Y. Yang et al. summarized the results of a broad range of preclinical studies demonstrating escin's efficacy in cases of brain and pulmonary edema, as well as in inflammatory diseases of various localizations accompanied by edema [34]. A reduction in circulating levels of MDA [35] and CRP [36] following the administration of escin or escin-containing combinations has also been previously observed in animal studies. Additionally, C. Chen et al. reported that escin suppressed the *in vitro* hyperexpression of AQP1 by endothelial cells [37].

The relatively high degree of uncertainty in the qualitative assessment presented above is attributable, first, to the small overall sample size of the included CTs (n = 3) and their participants (n = 279); second, to the high degree of heterogeneity among the trials; and third, to the substantial risk of bias in the observed effects, primarily resulting from suboptimal methodological aspects of the analyzed studies. The included trials exhibited considerable heterogeneity in terms of patient population characteristics (treatment indications), intervention protocols (route of administration, dosage, duration of treatment), endpoints and their assessment methods, as well as the statistical approaches used for analysis.

A more precise and quantitative assessment of the efficacy and safety of systemic escin administration for specific indications or groups of indications may become possible through CTs with greater statistical power and a design closely aligned with the gold standard (double-blind, placebo-controlled CTs). The key findings of this review and the authors' level of confidence in them are summarized in the SoQF table, developed in accordance with the GRADE-CERQual guidance [24] (Table 8). The results of this review may serve as a basis for developing improved approaches to the pharmacological management of edema of various etiologies.

Limitations

This review has several limitations that may affect the potential evidentiary value of its findings. The search strategy did not include fixed-dose escin combinations or compound medications, including herbal extracts containing escin, as the composition of such combinations is not always fully characterized, making it difficult to attribute observed effects to a specific component. The search was limited to the languages in which at least one of the review authors was sufficiently proficient, and no translation tools were used to access potentially relevant sources in other languages. Furthermore, the search was conducted exclusively in open-access databases and registries, which may have limited the identification of additional potentially relevant sources. The qualitative synthesis of evidence was conducted using a narrative textual approach without the use of advanced methodologies, primarily due to the small sample size and substantial heterogeneity of the included studies.

Table 8

Summary of the review results using the GRADE-CERQual method

Review result	Supporting trials	Methodological limitations	Coherence	Adequacy	Relevance	Confidence in the result	Justification of the assessment
Systemic (oral or parenteral) administration of escin effectively reduced the severity of edema in the acute period following trauma and surgical interventions	[27, 28, 29]	Moderate methodological limitations: three CTs with moderate methodological limitations (open design, lack of protection in the randomization process)	No concerns regarding coherence: three CTs with a high degree of coherence in primary data and synthesis results	Moderate concerns regarding adequacy: one CT with no concerns, two CTs with moderate concerns regarding adequacy (non-transparent presentation of the results of statistical analysis).	No concerns regarding relevance: three CTs with a high degree of relevance	Moderate confidence	Moderate methodological limitations and concerns regarding adequacy, no concerns regarding coherence and relevance
Systemic (oral or parenteral) administration of escin in the acute period following trauma and surgical interventions was well-tolerated and did not differ from the negative control or the comparator drug (mannitol) in terms of the frequency of adverse events	[27, 28, 29]	Moderate methodological limitations: three CTs with moderate methodological limitations (open design, lack of protection in the randomization process)	No concerns regarding coherence: three CTs with a high degree of coherence in primary data and synthesis results	Moderate concerns regarding adequacy: two CTs with no concerns, one CT with moderate concerns regarding adequacy (insufficient volume and depth of information)	No concerns regarding relevance: three CTs with a high degree of relevance	Moderate confidence	Moderate methodological limitations and concerns regarding adequacy, no concerns regarding coherence and relevance

CONCLUSIONS

During this systematic review of 237 sources, three randomized clinical trials were identified that evaluated the efficacy and safety of systemically administered escin medications for post-traumatic or post-operative edema. In these trials, orally or intravenously administered escin was effective in reducing the severity of localized edema in patients following endovenous laser ablation for varicose veins of the lower limbs (one trial), as well as in patients with limb injuries followed by surgical treatment (two trials). Escin administration was associated with normalization of serum levels of certain markers of inflammation, oxidative stress, and increased endothelial barrier permeability. Escin medications were well tolerated in all trials. Thus, systemic administration of escin may be effective and safe for managing post-traumatic and post-operative edema; however, confirmation of this hypothesis requires further evidence.

DISCLAIMERS

Author contribution

Prikhodko V.A. — source search and screening, literature data review, drafting the manuscript, figure preparation.

Okovityi S.V. — study concept and methodology, source search and screening, literature data review, editing the manuscript.

All authors have read and approved the final version of the manuscript of the article. All authors agree to bear responsibility for all aspects of the study to ensure proper consideration and resolution of all possible issues related to the correctness and reliability of any part of the work.

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