doi.org/10.36721/PJPS.2026.39.2.REG.14546.1

Clinical efficacy of sodium heptasaponin combined with diosmin in postoperative patients undergoing posterior open surgery for degenerative diseases of the spine: A retrospective study

Canglu Wu[1#], Feng Zhou[2#], Shitao Luo[3] and Wenxia Xiao[4*]
[1]Spinal Surgery, Zhoushan Guanghua Hospital, Zhoushan, Zhejiang, China
[2]Department of Pharmacy, Zhoushan Guanghua Hospital, Zhoushan, Zhejiang, China
[3]Department of Rehabilitation, Zhoushan Guanghua Hospital, Zhoushan, Zhejiang, China
[4]Department of Orthopedics, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

Abstract: **Background**: Degenerative diseases of the spine seriously affect the quality of life of patients and clinical treatment is currently facing certain challenges. **Objectives**: To analyze the clinical efficacy of sodium heptasaponin combined with diosmin in postoperative patients undergoing posterior open surgery for degenerative diseases of the spine (POSDDS). **Methods**: 160 patients with POSDDS from Zhoushan Guanghua Hospital between January 2024 and December 2024 were categorised into SA and SD groups, both groups were treated with sodium heptasaponin and the SD group was added with diosmin. The primary assessment was inflammatory indexes, immune indexes [immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM)], spinal function score (JOA), pain score (VAS) and clinical efficacy in both groups. Secondary outcomes included quality of life [(SF-36) score], complication and adverse reactions incidences. **Results**: After treatment, the indicators of both groups were remarkably difference with pre-treatment (P<0.05). The immune indicators, JOA score, clinical efficacy and SF-36 score in the SD group were significantly higher than SA group and inflammatory indicators, VAS score and the incidence of complications and adverse reactions were significantly lower than SA group (P<0.05). **Conclusion**: Sodium heptasaponin combined with diosmin can effectively optimize the inflammatory and immune indexes of POSDDS patients, elevate spinal function and quality of life, and reduce adverse events, thus deserving clinical promotion.

Keywords: Diosmin; Degenerative diseases of the spine; Immune indicators; Inflammatory indicators; Sodium heptasaponin;

Submitted on 05-05-2025 – Revised on 17-07-2025 – Accepted on 28-08-2025

INTRODUCTION

Degenerative diseases of the spine are a series of conditions caused by aging or degeneration of the spine and its surrounding tissues. The causes are complex, covering vertebral degeneration, intervertebral disc degeneration, synovial joint degeneration and ligament degeneration (Scarcia *et al.*, 2022). The disease is highly prevalent in middle-aged and elderly people, with the lumbar spine being the most common, the cervical spine the second most common and the thoracic spine relatively rare. With the degeneration of the spine, a series of morphological changes will occur, such as disc degeneration and narrowing, vertebral body edge degeneration and hyperplasia and small joint hyperplasia and hypertrophy. When the degeneration is further aggravated, it can lead to narrowing of the spinal canal and nerve root canal, hypertrophy and hyperplasia of the ligaments or even calcification, which in turn can cause many symptoms (X Zhao *et al.*, 2022). Common symptoms include localised pain in the spine, pain or numbness in the limbs, dyskinesia, intermittent claudication and changes in bowel and bladder function. Spinal degenerative diseases seriously affect the quality of life of patients, limiting their daily activities, reducing their ability to work and even requiring some patients to be bedridden for a long period of time, which imposes a heavy burden on the family and society (Ding *et al.*, 2022). Spinal degeneration itself is difficult to cure and the aim of treatment is mainly to reduce symptoms and slow down disease progression. Most patients can improve their symptoms and have less impact on their daily life after early and standardised treatment, but some patients have poor outcomes and may need repeated treatment (Huang *et al.*, 2023).

Posterior open surgery plays an important role in the treatment of degenerative spinal diseases. Its surgical principle is to directly reveal the posterior structures of the spine, including the diseased vertebral body, intervertebral discs, vertebral plates and small joints by making an incision in the back and cutting through the tissues layer by layer, so as to provide a clear vision for accurate diagnosis and treatment (Xu *et al.*, 2022). During surgery, the surgeon can directly remove the herniated disc tissue and relieve the compression on the nerves. For spinal fractures, the fracture site can be reset and fixed to restore the normal

**Corresponding author:* e-mail: xiao12qqx@hotmail.com
#The authors contributed equally therefore they are the co-first authors

sequence and stability of the spine. If part of the spinal structure, such as the vertebral plate and small joints, is removed during surgery, internal fixation devices, such as pedicle screws and connecting rods, can also be used to rebuild the stability of the spine and prevent deformity or further damage to the spine (L He *et al.*, 2022). Meanwhile, for nerve compression due to spinal canal stenosis and tumours, operations such as enlargement of the spinal canal and removal of tumours can be performed to create a more relaxed environment for the nerves and alleviate neurological symptoms (Ramanathan *et al.*, 2023). However, there are some disadvantages of posterior open surgery. As the surgery requires a large incision, it causes more trauma to the back muscles, soft tissues, etc., more intraoperative bleeding and relatively longer recovery time for the patient after surgery. Surgical risks are also relatively high and some complications may occur, such as nerve root injury, cerebrospinal fluid leakage due to dural injury, cauda equina injury, etc. and in severe cases, it may lead to haemorrhagic shock or even death due to injury of retroperitoneal large vessels (Ambrosio *et al.*, 2025).

Sodium heptasaponin is mainly derived from the dried mature seeds of Tianshi Chestnut, a plant in the family Hepatophyllaceae. Its chemical structure contains unique glycosidic and glycosyl parts and this structure confers a variety of efficacies, which are quite widely used in clinical practice (Wang *et al.*, 2023). In terms of mechanism of action, sodium heptasaponin is able to reduce vascular permeability and effectively counteracts exudation by inhibiting the disruption of tight junctions of vascular endothelial cells by inflammatory mediators. In the face of venous congestion, it reduces the leakage of intravascular fluid into the tissue interstitium, which in turn reduces tissue swelling and can significantly reduce the size of the swelling. For example, in patients with venous oedema of the lower limbs, a significant reduction in the circumference of the swollen limb can be observed with the use of sodium heptasaponin (Tucker *et al.*, 2022). It also has a reducing effect on the embolic volume after thrombosis and is effective in the prevention and treatment of venous oedema and tissue oedema. It also acts on vascular endothelial cell receptors, causing venous constriction by activating the relevant signalling pathways, which in turn increases venous return flow and effectively improves the symptoms of bruising (Savarino *et al.*, 2023). Because of this, it is commonly used in the treatment of venous reflux disorders and can effectively relieve the patient's limb swelling, pain, itching, fatigue and heaviness and other uncomfortable symptoms. In clinical practice, many patients with varicose veins of the lower limbs with impaired reflux were treated with sodium heptasaponin, the heaviness of the limbs was reduced and the endurance of activities was improved (Petkov *et al.*, 2025). In addition, sodium heptasaponin can enhance the elasticity of blood vessels and increase vascular tone. Its principle of action is to restore the strength and elasticity of venous blood vessels by inhibiting the action of proteolytic enzymes in the blood, so that the glycoprotein collagen fibres in the walls of venous blood vessels are not destroyed and the integrity of the blood vessel wall is maintained, thus restoring the strength and elasticity of the venous blood vessels. Based on this property, it is also used in the treatment of acute closed soft tissue injuries, such as sprains, compression injuries and ecchymosis in tendons, muscles and joints, which can accelerate the swelling and promote the repair of damaged tissues (Elshal and Hazem, 2022).

Diosmin belongs to the group of flavonoids obtained mainly from citrus plants. It has excellent vasoprotective and anti-inflammatory properties and is effective in the treatment of conditions related to venous insufficiency and lymphatic insufficiency. In patients with venous insufficiency, it can effectively alleviate venous oedema, reduce leg heaviness, pain, numbness, as well as soreness and discomfort when waking up in the morning and it also has a good improvement effect on soft tissue swelling (Huwait and Mobashir, 2022). In patients with thrombophlebitis and deep vein thrombosis syndrome, Diosmin can reduce limb swelling and relieve pain symptoms by promoting venous return (Rahman *et al.*, 2024). In the field of anus and intestines, when acute haemorrhoidal attack, patients often suffer from painful symptoms such as anal moisture, itching, pain or blood in stool due to varicose haemorrhoidal veins and Diosmin can enhance vascular tone and reduce vascular permeability, thus effectively alleviating the above mentioned discomforts and helping patients to alleviate their pain and restore their health (Mustafa *et al.*, 2022). Its mechanism of action is mainly to improve the function of the venous and lymphatic systems by increasing venous tone, decreasing vascular permeability and promoting lymphatic return. For impaired local blood circulation and lymphatic reflux and tissue oedema caused by surgical trauma, Diosmin can reduce postoperative tissue oedema by improving venous and lymphatic function and relieve patients' pain and other discomforts due to oedema (Gerges *et al.*, 2022).

Spinal degenerative diseases seriously affect the quality of life of patients and posterior open surgery is an important treatment but has some shortcomings. In view of the positive effects of sodium heptasaponin and diosmin in postoperative rehabilitation, such as promoting oedema subsidence, this study observed the clinical efficacy of sodium heptasaponin combined with diosmin in postoperative patients with postoperative open surgery for posterior spinal degenerative diseases (POSDDS), so as to further clarify the efficacy and safety of the combination of the two after the treatment and to improve the quality of life of the patients and to provide more therapeutic choices for the clinic.

MATERIALS AND METHODS

Study design

This is a systematic clinical retrospective study aimed at analysing the clinical efficacy of the combination of sodium heptasaponin and diosmin in the treatment of postoperative patients with POSDDS and further assessing its effect on the inflammatory and immune indices of the patients. Patients with POSDDS from Zhoushan Guanghua Hospital between January 2024 and December 2024 were selected and divided into SA group (treated with sodium heptasaponin) and SD group (treated with sodium heptasaponin combined with diosmin). A total of 170 patients' information was collected, 163 were included after exclusion and 3 were lost during the follow-up period, resulting in a final total of 160 cases analysed. To minimise bias, the following measures were taken in this study: (1) Strictly formulating the inclusion and exclusion criteria to ensure that the two groups of patients were comparable in terms of baseline information (e.g., age, gender and severity of disease). (2) Two independent researchers were arranged to extract and check the clinical data of the patients to ensure the accuracy and completeness of the data. (3) Statistical methods were used to correct for confounding factors that might affect the results in order to reduce their interference with the study results. In this study, the therapeutic effect of the two drugs on patients with POSDDS was analysed by comparison to provide a scientific basis for clinically relevant drug treatment options. The flow chart of this study is illustrated in fig. 1.

Inclusion and exclusion criteria

Inclusion criteria

(1) Patients who met the clinical diagnostic criteria for degenerative diseases of the spine (Kim *et al.*, 2022) and underwent posterior open surgery at our institution; (2) Age ≥55 years old; (3) 2 to 5 affected vertebral segments; (4) Patients with good compliance and willingness to cooperate with the treatment plan developed by the study; (5) The overall mental state of the patient is good, the patient is basically healthy and can truthfully express his/her complaints about the symptoms and answer the relevant questions of the medical staff; (6) Tolerant to the drugs involved in this study; (7) The patient and his/her family members are informed and agree to the study and sign the informed consent form.

Exclusion criteria

(1) Patients with lower extremity venous thrombosis, or with other vascular diseases; (2) Patients with continuous use of anticoagulant drugs such as heparin, low molecular heparin, or antiplatelet drugs in the last three months; (3) Malignant tumour of any site or type; (4) Patients with combined haemorrhagic coagulation dysfunction, or severe liver or renal function defects, severe cardiovascular disease or other more serious diseases; (5) Combined chronic infectious diseases; (6) Combined cerebral, cardiac, hepatic and renal functional abnormalities; (7) Patients who have been involved in clinical drug trials or clinical research; (8) Requesting cessation of treatment or automatic discharge for personal reasons; (9) Other conditions that, in the opinion of the study physician, should not be included; (10) Other circumstances affecting the indicators of follow-up observation.

Interventions

The surgery was performed by the same team of surgeons and the patient was placed in the prone position under general anaesthesia. The surgical area was disinfected and toweled and the patient was incised layer by layer through a posterior median incision (approximately 15 cm) to isolate the erector spinae muscle and expose the operative segment. X-ray fluoroscopy was used to locate and implant pedicle screws and to confirm fixation stability, followed by decompression of the spinal canal and the bilateral nerve root canals, excision of the diseased discs and treatment of the endplates and implantation of intervertebral fusion devices and fixation of the connecting rods. Intraoperative hemostasis was performed, dexamethasone was applied to the spinal canal to reduce oedema and a drain was placed to close the incision layer by layer. Dexamethasone (National Drug Code H20045100, Manufacturer: Zhejiang Xianju Pharmaceutical Co.).

Patients in both groups underwent routine treatment and care after surgery. During this period both groups were treated with sodium heptasaponin. Sodium hepatosaponin is the sodium salt of a triterpenoid saponin obtained from the dried mature seeds of Tenshi Chestnut, family Hepataceae, with anti-inflammatory and decongestive properties (Idris *et al.*, 2020). Sodium heptasaponin tablets (trade name: Ou Kai, State Pharmaceutical Standards H20051590, manufacturer: Shandong Green Leaf Pharmaceutical Co., Ltd.), 30 mg once, twice a day, once in the morning and once in the evening. A total of 4 weeks of treatment.

The SD group was treated with diosmin. Diosmin (trade name: GeTai, State Drug Permit H20058471, manufacturer: Nanjing Zhengda Tianqing Pharmaceutical Co., Ltd.), 0.45 g once, twice a day, once in the morning and once in the evening. A total of 4 weeks of treatment.

Diosmin is used in combination with hepcidium saponin because hepcidium saponin sodium mainly works through anti-inflammatory and improves microcirculation, whereas diosmin focuses on enhancing venous reflux and reducing oedema and the mechanisms of action of the two are different, so that their combined use can play a synergistic therapeutic effect in many aspects and studies have shown that similar drug combination programmes can improve the efficacy in the treatment of related diseases (Gwozdzinski *et al.*, 2023).

Observation indicators

Primary indicators

Inflammation indicators

Fasting peripheral venous blood was drawn from patients, centrifuged and kept refrigerated for testing and enzyme-linked immunosorbent assay (ELISA) was used to determine and calculate the levels of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8) and ultrasensitive C-reactive protein (hs-CRP) in the patient's serum samples (Bakhsh *et al.*, 2022).

The kits used were Human TNF-α ELISA kit (Item No.: ml077385, Shanghai Enzyme-linked Biotechnology Co., Ltd.), Human IL-6 ELISA kit (Item No.: ml027379, Shanghai Enzyme-linked Biotechnology Co., Ltd.), Human IL-8 ELISA kit (Item No.: ml103387, Shanghai Enzyme-linked Biotechnology Co., Ltd.) and Human hs-CRP ELISA kit (Item No.: ml106583, Shanghai Enzyme-linked Biotechnology Co., Ltd.).

Immunological indicators

Fasting venous blood was drawn from patients and immunoglobulin A (IgA), immunoglobulin G (IgG) and immunoglobulin M (IgM) levels were measured by a fully automated biochemical analyser (Beckman Coulter K.K., AU5800, National Instruments Note 20152401623) (Qian *et al.*, 2020).

Spinal function score

The degree of recovery of spinal function was evaluated using the Japanese Orthopaedic Association Assessment Treatment Score (JOA). The scale covered subjective symptoms, clinical signs, limb movements and bladder function respectively, with a maximum score of 29 and a minimum score of 0. The lower the score, the more obvious the dysfunction (Kato *et al.*, 2019).

Pain score

Comparison of pain levels between the two groups. Visual analogue scoring (VAS) was used for assessment, with a total score of 0-10 and higher scores indicated more severe pain (Zheng *et al.*, 2023).

Clinical efficacy

Compare the clinical efficacy of the two groups. Efficacy assessment criteria: obvious effect: JOA score increased by more than 15 scores, VAS score decreased by more than 7 scores, patients' subjective symptoms basically disappeared, clinical signs remarkably improved, pain basically disappeared and only occasional slight discomfort in specific cases. Effective: JOA scores improved by 5-15 scores, VAS scores decreased by 3-7 scores, patients' subjective symptoms were reduced, clinical signs improved, pain was markedly reduced and the extent to which daily activities were affected by pain was remarkably reduced. Ineffective: JOA score elevation is less than 5 scores, VAS score reduction is less than 3 scores, the patient's subjective symptoms and clinical signs have not markedly improved and the degree of pain has not changed remarkably, or even aggravated. Total effective rate = (obvious effect + effective) / total × 100%.

Secondary indicators

Quality of life

The Health Status Survey short form (SF-36 score) was used to compare the quality of life of the two groups of patients, including physiological function, physical function, somatic pain, general health, social function, emotional function and mental health. The total score was 100, with higher scores indicating better quality of life (de Beurs *et al.*, 2022).

Complications

The occurrence of complications in both groups was recorded, including shock, hypoxaemia, acidosis, venous thrombosis, necrotising small bowel colitis, intestinal flora dysbiosis and osteoporosis.

Adverse reactions

Record the occurrence of adverse reactions during treatment in both groups, including nausea/vomiting, hot flashes/sweating, headache, hepatic and renal impairment, rash, angioedema, coagulation dysfunction and so on.

Follow-up visits

This study was primarily scheduled for a 6-month post-treatment follow-up to assess the durability of the effects and to address any potential adverse reactions or problems. Follow-up visits included inflammatory indicators (e.g., TNF-α), immune indicators (e.g., IgA), assessment of clinical symptoms (e.g., spinal function, pain, etc.) and recording of adverse reactions and complications; for patients who were unable to attend outpatient follow-up visits in a timely manner, additional information was provided through telephone follow-up visits to ensure the completeness of follow-up data.

Sample size calculation

Power analysis was performed to calculate the sample size according to the G*Power 3.1.9.7 computer software to determine the sample size required to detect a statistically significant difference. Based on the primary outcome of clinical efficacy, taking into account an alpha level of 0.05 and 90% efficacy, we calculated that a sample size of 70 patients was required for each group. Considering the potential for uncertainty, a sample size of 80 cases per group was chosen for this study and we believe that the sample size of this study allows for reliable conclusions to be drawn.

Statistical analysis

SPSS 28.0 statistical software was used for data analysis. Lucidchart was used to draw flow charts. The data in this study were tested for normal distribution. Baseline characteristics were described as number of people and

variables (expressed as $\bar{x}$±s). Inflammatory indicators, immune indicators, JOA scores, VAS scores and SF-36 score results in the results are expressed as $\bar{x}$±s. Comparison between the two groups was tested using independent samples t-test. The clinical efficacy, incidence of complications and adverse effects in the results were expressed as proportions (%). Comparison between two groups was analysed using x^2 test. All statistical tests were two-sided and P<0.05 indicated a statistically significant difference.

RESULTS

Basic information

In this study, 160 patients with POSDDS between January 2024 and December 2024 were categorised into SA group (n=80) and SD group (n=80) based on different interventions, with the aim of exploring the differences in the efficacy of different interventions in postoperative patients with POSDDS. The baseline demographic and baseline characteristics in both groups are illustrated in table 1, which were statistically analysed using independent samples t-test (for continuous variables) and chi-square test (for categorical variables). This indicates that the two groups were well comparable before treatment and the confounding effects of demographic and clinical factors were effectively controlled in this study, with minimal impact on the analysis of the results, thus guaranteeing the reliability and accuracy of the subsequent efficacy evaluation.

Inflammation indicators

The results of the comparison of inflammatory indicators of both groups are displayed in table 2. Before treatment, no significantly different was found among the levels of TNF-α, IL-6, IL-8 and hs-CRP in both groups (P>0.05). After treatment, the levels of inflammatory indicators were significantly lower in both groups than pre-treatment and the SD group was significantly lower than the SA group (P<0.05). It indicated that the levels of inflammatory indicators were markedly reduced in both groups post-treatment and patients in the SD group showed better improvement.

Immune indicators

We analysed and compared the results of the immune indicators of both groups and the results are displayed in table 3. No remarkable difference was found in the immunological indexes of both groups at pre-treatment (P>0.05). After treatment, IgA, IgG and IgM levels were significantly higher in both groups than before treatment and significantly higher in the SD group than in the SA group (P<0.05). It indicates that the immune indexes of both groups improved remarkably after treatment and the improvement of immune function was more obvious in the SD group.

JOA score

The JOA score is an important quantitative index for assessing the neurological functional status of patients with spinal degenerative diseases and the level of its score reflects the degree of limb motor, sensory and bladder dysfunction. The JOA score results of both groups of patients are demonstrated in table 4. No significantly different was found among the JOA scores of both groups of patients pre-treatment (P>0.05). After treatment, the scores of patients in both groups were increased significantly (P<0.05). The score of patients in SD group significantly higher than the score of SA group (P<0.05). It shows that both treatments can improve the patients' limb motor function and the SD group has better improvement effect.

Pain scores

The VAS scores of both groups of patients are presented in table 5. Before treatment, no marked difference was found between the scores of both groups of patients compared to each other (P>0.05). After treatment, SD group had significantly lower scores than those in the SA group (P<0.05). It showed that the pain level of both groups was relieved after treatment and the pain relief of SD group patients was better.

Clinical efficacy

Combined with the treatment effect we analysed the clinical efficacy of both groups of patients and the results of the analysis are presented in table 6. The total efficacy rate of SD group patients was 90.00% (72/80) and SA group was 75.00% (60/80), with a marked difference in both groups (P<0.05). The results indicated that patients in SD group had better efficacy, suggesting that the clinical efficacy of the combined treatment was better.

Quality of life

The results of comparing the quality of life scores of the two groups of patients are demonstrated in table 7. No significantly different was found in SF-36 scores of both groups of patients in pre-treatment (P>0.05). After treatment, the SF-36 scores of patients in both groups were improved, the SF-36 scores in the SD group were significantly higher than those in the SA group and the difference was statistically significant (P<0.05). It indicates that the combination therapy in this study can effectively improve the quality of life of patients.

Complications

The occurrence of complications, including shock and hypoxaemia, in patients of both groups is demonstrated in table 8. No remarkable difference was observed among both groups when compared to the group of patients who developed complications such as shock (P>0.05). The total complication rate of patients in the SD group was 6.25% (5/80) significantly lower than the 16.25% (13/80) in the SA group (P<0.05).

Table 1: Patient demographics and baseline disease characteristics

Parameter	SA group (n=80)	SD group (n=80)	t/x^2	P
Age (year)	64.59±5.21	64.05±5.23	-0.654	0.514
Gender (male/female)	46/34	48/32	0.137	0.711
Height (cm)	159.24±4.86	159.39±5.15	0.189	0.850
Weight (kg)	65.11±5.05	65.61±5.21	0.616	0.539
Body mass index (kg/m^2)	23.03±1.85	22.91±1.90	-0.405	0.686
Surgical segment (n)	3.01±0.91	3.07±1.02	0.393	0.695
Surgical time (min)	240.71±53.32	240.35±43.38	-0.047	0.963
Intraoperative haemorrhage (mL)	254.17±24.60	253.50±31.36	-0.150	0.881
Blood transfusion (yes/no)	8/72	9/71	0.053	0.818
Surgical site (lumbar/other)	77/3	78/2	0.159	0.691
Smoking (yes/no)	20/60	21/59	0.026	0.871
Alcohol consumption (yes/no)	25/55	26/54	0.065	0.799
Hypertension (yes/no)	17/63	16/64	0.031	0.861
Diabetes (yes/no)	16/64	15/65	0.032	0.858
Ethnicity (Han Chinese/minority)	75/5	74/6	0.286	0.593
Occupation (Physical labour / mental labour)	45/35	46/34	0.042	0.838
Marital Status (Married/unmarried)	70/0	70/0	-	-
Educational Level (Below high school / high school and above)	37/43	36/44	0.020	0.887
Payment method (With medical insurance/no medical insurance)	58/22	59/21	0.076	0.783
Temperature (℃)	36.09±0.45	36.21±0.45	1.687	0.094
Respiration (breaths/min)	17.59±1.77	17.36±2.26	-0.717	0.475
Heart rate (beat/min)	74.89±5.47	74.52±6.11	-0.404	0.687
Systolic blood pressure (mmHg)	119.18±4.99	119.57±5.27	0.481	0.631
Diastolic blood pressure (mmHg)	75.45±4.27	75.51±5.17	0.080	0.936

Table 2: Comparisons of inflammation indicators ($\bar{x}$±s)

norm	time	SA group	SD group	t	P
TNF-α (μg/L)	Pre-treatment	28.07±4.50	27.87±3.92	-0.300	0.765
	Post-treatment	15.44±3.64*	10.18±2.05*	-11.262	<0.001
IL-6 (μg/L)	Pre-treatment	34.92±4.62	35.11±4.86	0.253	0.800
	Post-treatment	19.94±5.24*	10.62±4.63*	-11.921	<0.001
IL-8 (ng/mL)	Pre-treatment	65.04±7.63	65.16±9.84	0.086	0.931
	Post-treatment	41.75±9.11*	27.60±4.81*	-12.285	<0.001
hs-CRP (mg/L)	Pre-treatment	123.65±13.70	123.77±13.91	0.055	0.956
	Post-treatment	54.60±7.01*	31.74±4.27*	-24.910	<0.001

Note: "*" represents significantly different compared with pre-treatment, P<0.05.

Table 3: Immune indicators ($\bar{x}$±s, g/L)

norm	time	SA group	SD group	t	P
IgA	Pre-treatment	2.01±0.62	1.98±0.62	-0.306	0.760
	Post-treatment	3.37±1.03*	4.52±1.00*	7.165	<0.001
IgG	Pre-treatment	7.19±0.99	7.16±0.98	-0.193	0.848
	Post-treatment	9.39±1.63*	10.96±1.51*	6.320	<0.001
IgM	Pre-treatment	0.92±0.33	0.93±0.32	0.195	0.846
	Post-treatment	1.19±0.27*	1.54±0.20*	9.317	<0.001

Note: "*" represents significantly different compared with pre-treatment, P<0.05.

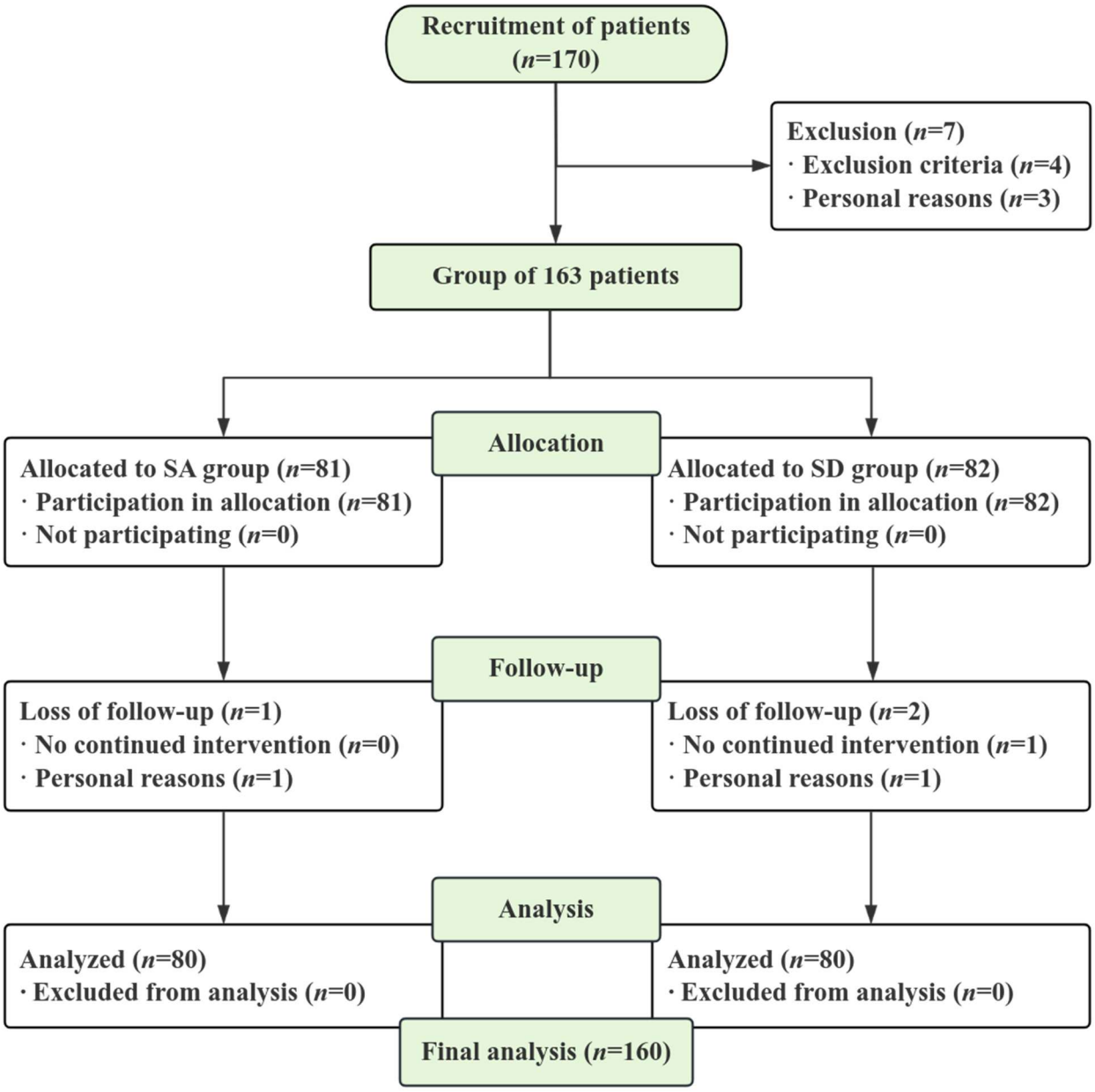

Fig.1: Flow chart

Table 4: JOA scores ($\bar{x}$±s, score)

	SA group	SD group	*t*	*P*
Pre-treatment	4.06±1.05	4.15±0.96	0.566	0.572
Post-treatment	17.82±1.95	23.84±1.75	20.550	<0.001
t	55.570	88.232		
P	<0.001	<0.001		

Table 5: VAS score ($\bar{x}$±s, score)

	SA group	SD group	*t*	*P*
Pre-treatment	7.43±1.04	7.61±0.97	1.132	0.259
Post-treatment	5.10±1.08	2.69±0.53	-17.918	<0.001
t	-13.900	-39.812		
P	<0.001	<0.001		

Table 6: Clinical efficacy analysis

Group	Obvious effect (*n*)	Effective (*n*)	Ineffective (*n*)	Total effective rate (*n*, %)
SA group	20	40	20	60 (75.00)
SD group	30	42	8	72 (90.00)
x^2		7.792		
P		<0.05		

Table 7: SF-36 scores ($\bar{x}$±s, score)

	SA group	SD group	*t*	*P*
Pre-treatment	83.49±2.83	83.89±2.57	0.936	0.351
Post-treatment	90.05±3.57	95.63±2.80	11.000	<0.001
t	12.880	27.628		
P	<0.001	<0.001		

Table 8: Complications [*n*(%)]

	SA group	SD group	x^2	*P*
Shock	1 (1.25)	0 (0.00)	1.005	0.316
Hypoxaemia	2 (2.50)	1 (1.25)	1.000	0.317
Acidosis	1 (1.25)	0 (0.00)	1.005	0.316
Venous thrombosis	1 (1.25)	0 (0.00)	1.005	0.316
Necrotising small bowel colitis	1 (1.25)	1 (1.25)	0.000	1.000
Respiratory tract infection	1 (1.25)	1 (1.25)	0.000	1.000
Heart failure	2 (2.50)	0 (0.00)	3.015	0.082
Intestinal dysbiosis	2 (2.50)	1 (1.25)	1.000	0.317
Osteoporosis	2 (2.50)	1 (1.25)	1.000	0.317
Total incidence	13 (16.25)	5 (6.25)	5.107	<0.05

Table 9: Adverse reactions [*n*(%)]

	SA group	SD group	x^2	*P*
Nausea/vomiting	2 (2.50)	1 (1.25)	1.000	0.317
Hot flashes/sweating	1 (1.25)	1 (1.25)	0.000	1.000
Headaches	2 (2.50)	1 (1.25)	1.000	0.317
Liver and kidney impairment	1 (1.25)	0 (0.00)	1.005	0.316
Rash	2 (2.50)	0 (0.00)	3.015	0.082
Angioedema	2 (2.50)	0 (0.00)	3.015	0.082
Coagulation disorders	1 (1.25)	0 (0.00)	1.005	0.316
Fatigue	1 (1.25)	1 (1.25)	0.000	1.000
Total incidence	12 (15.00)	4 (5.00)	5.556	<0.05

It indicates that the combined treatment can effectively reduce the incidence of complications.

Adverse reactions

We followed up the patients to observe the adverse reactions. Adverse reactions such as nausea/vomiting and other adverse reactions with varying degrees of severity occurred in patients of both groups during the treatment period as presented in table 9. No marked difference was found in the comparison of adverse reactions such as nausea/vomiting among both groups (P>0.05). The total incidence of adverse reactions in patients in the SA group was 15.00% (12/80), which was significantly higher than the 5.00% (4/80) in patients in the SD group (P<0.05), indicating that the therapeutic efficacy of the treatments used in patients in the SD group was better and safer.

DISCUSSION

In recent years, the incidence of degenerative diseases of the spine has risen significantly and has become an important public health problem affecting human health and quality of life (Morimoto *et al.*, 2023). The clinical manifestations of patients are diverse, such as neck, shoulder, back and leg pain, limb numbness and weakness, intermittent claudication and in severe cases, even urinary and faecal dysfunction, which greatly interferes with daily activities and work ability (Chu *et al.*, 2022). Posterior

open surgery is widely used in the clinic as a classical measure for the treatment of degenerative spinal diseases. The procedure is performed by making an incision in the posterior aspect of the spine to directly reveal the vertebral plates, articular processes, intervertebral discs and other structures in the diseased segment and the surgeon is able to operate accurately under direct vision (Amaral *et al.*, 2023). However, posterior open surgery also has certain limitations, such as greater surgical trauma and relatively longer postoperative recovery time Therefore, this study investigated the value of sodium heptasaponin combined with diosmin in the treatment of postoperative patients with POSDDS and the results showed that this combined regimen was superior to sodium heptasaponin alone in terms of improvement of inflammatory markers, immune function and clinical symptoms.

IL-6 is an inflammatory mediator involved in acute inflammation, IL-8 and TNF-α are common pro-inflammatory cytokines and hs-CRP is closely related to acute bacterial infections and all four of them are commonly used to reflect the severity of infectious diseases (Ren, 2024; Zwiri *et al.*, 2022). Higher levels of inflammatory factors indicate a more severe inflammatory response and the detection of changes in inflammatory markers can be a guide to assessing the condition of neonatal sepsis and the efficacy of treatment (Li *et al.*, 2020; Mahmoud *et al.*, 2025). IgA, IgG and IgM are all immunoglobulins, which are proteins produced by immune cells and are important components of the body's defence system. Newborns are susceptible to sepsis due to their immune insufficiency and immune function can help to observe the effectiveness of treatment and recovery of the children (Beudeker *et al.*, 2022). The findings of this study revealed that there were marked differences among the indicators of the both groups post-treatment versus pre-treatment. The inflammatory indexes of SD group were significantly lower than SA group and the immune indexes were significantly higher than SA group (P<0.05). It shows that the treatment of postoperative POSDDS patients with sodium heptasaponin combined with diosmin can effectively reduce the inflammatory indexes of the patients and improve the immune function. In terms of mechanism of action, sodium heptasaponin can induce the body to raise the plasma concentration of adrenocorticotropic hormone and cortisone, thus exerting anti-inflammatory and anti-exudative effects; it can also increase venous tone, improve blood circulation and microcirculation, protect the vascular wall and enhance the elasticity and tone of blood vessels (Gwozdzinski *et al.*, 2023). Diosmin is mainly used to enhance venous tone, improve microcirculation and promote lymphatic return (Mitra *et al.*, 2022). The two have complementary pathways of action and when used in combination they can intervene synergistically in a multidimensional manner from anti-inflammation, improvement of vascular function and promotion of fluid reflux.

The JOA score is a core index for quantitatively assessing the degree of neurological damage in patients with spinal degenerative diseases and the change of its score can intuitively reflect the severity of the disease and the efficacy of neurological recovery, which can provide an objective basis for the formulation of surgical plans and prognosis (Nishant *et al.*, 2024). The VAS score can visually quantify the degree of pain in patients to determine the effectiveness of therapeutic measures in relieving pain, which can help to adjust the treatment plan in time (Y He *et al.*, 2023). The outcomes of this study indicated that the VAS score of the SD group was significantly lower than the SA group and the JOA score and clinical efficacy were significantly higher than the SA group (P<0.05). It indicated that the combined treatment could alleviate the degree of pain and improve the patients' limb function with remarkable efficacy. Zhao *et al*. in their study of edaravone combined with sodium hesperidin in the treatment of elderly post-drainage patients with hypertensive cerebral haemorrhage reported a significant reduction in the level of inflammation and a remarkable improvement in the ability to perform life activities after treatment, which is consistent with the results reported in this study (M Zhao *et al.*, 2020). In a study by Cengiz *et al*. it was reported that sodium heptasaponin is mainly used for swelling due to cerebral oedema, trauma or surgery and is effective in relieving symptoms of venous reflux disorders, such as swelling and pain in the limbs, by decreasing the degree of tissue swelling through reducing vascular permeability (Cengiz *et al.*, 2024). Hassanein *et al*. study reported that diosmin is commonly used in the treatment of symptoms associated with venous lymphatic insufficiency, such as leg heaviness, pain and morning soreness and discomfort (Hassanein *et al.*, 2025). Both drugs have a palliative effect on pain symptoms though and the combination is more effective in providing relief.

The SF-36 score is a standardised tool for assessing an individual's health-related quality of life, with the level of the score directly reflecting the patient's comprehensive level of daily life, social activities and psychological status. This scoring system is widely used in studies such as chronic disease management and clinical efficacy evaluation to provide data support for assessing the impact of treatment options on patients' quality of life (Choate *et al.*, 2024). The outcomes revealed that after combined treatment, the SF-36 score of the SD group was significantly higher than that the SA group and the total incidence of complications and adverse reactions was significantly lower than the SA group (P<0.05). Tian *et al*. reported remarkable efficacy and reduced adverse effects after combination therapy in a study of compound sodium heptapodophyllosaponin gel combined with diosmin for the treatment of eyelid swelling after blepharoplasty, which was similar to the results of the present study (Tian and Shao, 2020). This study confirms that the combination of hepcidium saponin sodium and diosmin can improve

clinical efficacy and its clinical relevance is reflected in the following: on the one hand, it provides a new choice of anti-inflammatory drug for postoperative swelling reduction, especially suitable for patients who have poor response to a single drug; on the other hand, the combination regimen did not increase the adverse effects significantly and it has a high degree of clinical feasibility. In the future, this combination may be considered as a routine adjuvant treatment after POSDDS to accelerate the recovery and improve the quality of life of patients.

There are multiple limitations to this study and these limitations may have some impact on the reliability and persuasiveness of the findings. The retrospective design of this study is inherently flawed, as the study data were obtained from previous clinical records and patients were not randomly assigned to treatment regimens based on a strict study design, but rather were determined by clinicians based on the specific circumstances of the patients at the time, which may have led to uncontrollable differences in baseline information between the groups and thus introduced a selection bias. At the same time, retrospective studies rely on existing medical records, which may also interfere with the authenticity of the study results if there are incomplete or inaccurate records. This study could not completely exclude the influence of all potential confounding factors, for example, patients' lifestyle habits (e.g., smoking, alcohol consumption), adherence to postoperative rehabilitation training and comorbid medication use may affect the treatment outcome to a certain extent, but due to the nature of retrospective studies, these factors may not have been comprehensively and accurately documented and included in the analyses, which may adversely affect the rigour of the study conclusions. The short follow-up period of this study and the lack of long-term follow-up data, short-term follow-up can only reflect the immediate effects of the treatment, while the long-term efficacy (such as disease recurrence rate, the occurrence of long-term complications, etc.) and long-term safety (such as cumulative adverse effects of the drug) cannot be adequately assessed, which, to a certain extent, limits the value of the results of the study in guiding the clinical decision-making for long-term treatment. In addition, the relatively limited sample size and the failure to cover postoperative POSDDS patients with different conditions may lead to bias in the study results, affecting the extrapolation and reliability of the conclusions. Meanwhile, individual differences in patients' underlying conditions may also interfere with the generalisability of the study results. For this reason, it is advisable to further expand the sample size and extend the follow-up period to more comprehensively evaluate the efficacy and safety of sodium heptasaponin combined with diosmin in the treatment of postoperative POSDDS patients.

CONCLUSION

This study analysed the efficacy of sodium heptasaponin combined with diosmin in the treatment of postoperative patients with POSDDS, in order to provide a new reference basis for the treatment of this type of disease. The results showed that after the combined treatment, the patients' inflammatory indexes, immune indexes and quality of life were improved and the incidence of complications and adverse reactions was reduced, which provides a scientific basis for the clinical treatment of related diseases. However, the present study has a small sample size and a short follow-up period, failing to observe the long-term effectiveness of this method of treatment. Multi-centre, large-sample, high-quality clinical studies can be continued for verification in the later stage.

Acknowledgments
None

Author's contribution
Canglu Wu, Feng Zhou: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.
Shitao Luo: Participated in collecting, assessing and interpreting the data. Made significant contributions to data interpretation and manuscript preparation.
Wenxia Xiao: Provided substantial intellectual input during the drafting and revision of the manuscript.

Funding
None

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval
This study was approved by the Ethics Committee of the Zhoushan Guanghua Hospital, the ethical approval number is 2023-K-063.

Conflict of interest
The authors declare that they have no financial conflicts of interest.

Consent to participate
We secured a signed informed consent form from every participant.

REFERENCES

Amaral R, Pokorny G, Marcelino F, Moriguchi R, Pokorny J, Barreira I, Mizael W, Yozo M, Fragoso S and Pimenta L (2023). Lateral versus posterior approaches to treat degenerative lumbar pathologies-systematic review and meta-analysis of recent literature. *Eur. Spine J.,* **32**(5): 1655-1677.

Ambrosio L, Muthu S, Cho SK, Virk MS, Cabrera JP, Hsieh PC, Demetriades AK, Ćorluka S, Yoon ST and

Vadalà G (2025). Open versus minimally invasive spine surgery in the treatment of single-level degenerative lumbar spondylolisthesis: An ao spine global cross-sectional study. *Neurospine.,* **22**(1): 40-47.

Bakhsh A, Moyes D, Proctor G, Mannocci F and Niazi SA (2022). The impact of apical periodontitis, non-surgical root canal retreatment and periapical surgery on serum inflammatory biomarkers. *Int. Endod. J.,* **55**(9): 923-937.

Beudeker CR, Vijlbrief DC, van Montfrans JM, Rooijakkers SH and Flier Mvd (2022). Neonatal sepsis and transient immunodeficiency: Potential for novel immunoglobulin therapies? *Front. Immunol.,* **13**: 1016877.

Cengiz M, Peker Cengiz B, Teixeira Andrade A and Ayhanci A (2024). Protective Effect of Escin Against Kidney Injury: Histopathological and biochemical evaluations. *Current Issues Mol. Biol.,* **46**(12): 13471-13481.

Choate R, Holm KE, Sandhaus RA, Mannino DM and Strange C (2024). Characteristics associated with SF-36 in alpha-1 antitrypsin deficiency-associated COPD: A cross-sectional analysis. *BMC Pulm. Med.,* **24**(1): 138.

Chu P, Wang T, Zheng J, Xu C, Yan Y, Ma Q, Mengchen Y and Dasheng T (2022). Global and current research trends of unilateral biportal endoscopy/biportal endoscopic spinal surgery in the treatment of lumbar degenerative diseases: A bibliometric and visualization study. *Orthop. Surg.,* **14**(4): 635-643.

De Beurs E, Carlier I and van Hemert A (2022). Psychopathology and health-related quality of life as patient-reported treatment outcomes: Evaluation of concordance between the Brief Symptom Inventory (BSI) and the Short Form-36 (SF-36) in psychiatric outpatients. *Qual. Life Res.,* **31**(5): 1461-1471.

Ding J, Kong C, Li X, Sun X, Lu S and Zhao G (2022). Different degeneration patterns of paraspinal muscles in degenerative lumbar diseases: A MRI analysis of 154 patients. *Eur. Spine J.,* **31**(3): 764-773.

Elshal M and Hazem SH (2022). Escin suppresses immune cell infiltration and selectively modulates Nrf2/HO-1, TNF-α/JNK and IL-22/STAT3 signaling pathways in concanavalin A-induced autoimmune hepatitis in mice. *Inflammopharmacology,* **30**(6): 2317-2329.

Gerges SH, Wahdan SA, Elsherbiny DA and El-Demerdash E (2022). Pharmacology of diosmin, a citrus flavone glycoside: An updated review. *Eur. J. Drug Metab. Ph.,* **47**(1): 1-18.

Guan J, Liu T, Li W, Zhao H, Yang K, Li C, Feng N, Jiang G, Yang Y and Yu X (2022). Effects of posterior lumbar nonfusion surgery with isobar devices versus posterior lumbar interbody fusion surgery on clinical and radiological features in patients with lumbar degenerative diseases: A meta-analysis. *J. Orthop. Surg. Res.,* **17**(1): 116.

Gwozdzinski L, Bernasinska-Slomczewska J, Hikisz P, Wiktorowska-Owczarek A, Kowalczyk E and Pieniazek A (2023). The effect of diosmin, escin and bromelain on human endothelial cells derived from the umbilical vein and the varicose vein-A preliminary study. *Biomid.,* **11**(6): 1702.

Hassanein EHM, Althagafy HS, Baraka MA and Amin H (2025). Hepatoprotective effects of diosmin: A narrative review. *N-S Arch. Pharmacol.,* **398**(1): 279-295.

He L, Chen K, Chen C, Chang Q, Sun L, Zhang Y, Chang J and Feng H (2022). Comparison of percutaneous endoscopic and open posterior lumbar interbody fusion for the treatment of single-segmental lumbar degenerative diseases. *BMC Musculoskel. Dis.,* **23**(1): 329.

He Y, Lin Y, He X, Li C, Lu Q and He J (2023). The conservative management for improving Visual Analog Scale (VAS) pain scoring in greater trochanteric pain syndrome: A Bayesian analysis. *BMC Musculoskel. Dis.,* **24**(1): 423.

Huang W, Gong Z, Wang H, Zheng C, Chen Y, Xia X, Ma X and Jiang J (2023). Use of MRI-based vertebral bone quality score (VBQ) of S1 body in bone mineral density assessment for patients with lumbar degenerative diseases. *Eur. Spine J.,* **32**(5): 1553-1560.

Huwait E and Mobashir M (2022). Potential and therapeutic roles of diosmin in human diseases. *Biomid.,* **10**(5): 1076.

Idris S, Mishra A and Khushtar M (2020). Phytochemical, ethanomedicinal and pharmacological applications of escin from *Aesculus hippocastanum L*. towards future medicine. *J. Basic Clin. Physiol. Pharmacol.,* **31**(5): 20190115.

Kato S, Oshima Y, Matsubayashi Y, Taniguchi Y, Tanaka S and Takeshita K (2019). Minimum clinically important difference and patient acceptable symptom state of japanese orthopaedic association score in degenerative cervical myelopathy patients. *Spine,* **44**(10): 691-697.

Kim GU, Park WT, Chang MC and Lee GW (2022). Diagnostic technology for spine pathology. *Asian Spine J.,* **16**(5): 764-775.

Li T, Dong G, Zhang M, Xu Z, Hu Y, Xie B, Wang Y and Xu B (2020). Association of neutrophil-lymphocyte ratio and the presence of neonatal sepsis. *J. Immunol. Res.,* **2020**(1): 7650713.

Mahmoud I, Maryam AK, Ava A, Evan S, Gabriel S, Jill I, Nora RO, Heather OD, Linda G, Zoe F, Alan Mariño del P, Yvonne C and Adams BD (2025). The miRNA-9 isoform story in cancer: An oncomiR or tumor suppressor? *J. Can. Biomol. Therap.,* **2**(2): 13-36.

Mitra R, Nersesyan A, Pentland K, Melin MM, Levy RM and Ebong EE (2022). Diosmin and its glycocalyx restorative and anti-inflammatory effects on injured blood vessels. *FASEB J.,* **36**(12): e22630.

Morimoto T, Kobayashi T, Kakiuchi T, Esaki M, Tsukamoto M, Yoshihara T, Hirata H, Yabuki S and Mawatari M (2023). Gut-spine axis: A possible correlation between gut microbiota and spinal degenerative diseases. *Front. Microbiol.,* **14**: 1290858.

Mustafa S, Akbar M, Khan MA, Sunita K, Parveen S, Pawar JS, Massey S, Agarwal NR and Husain SA (2022). Plant metabolite diosmin as the therapeutic agent in human diseases. *CRPHAR,* **3**: 100122.

Nishant N, Agarwal VK, Garg P and Somashekarappa T (2024). Hindi translation and modification of modified JOA score for cervical myelopathy and its validation for the Indian population. *Indian Spine J.,* **7**(1): 28-41.

Petkov V, Tsibranska S, Manoylov I, Kechidzhieva L, Ilieva K, Bradyanova S, Ralchev N, Mihaylova N, Denkov N, Tchorbanov A and Tcholakova S (2025). ISCOM-type matrix from beta-escin and glycyrrhizin saponins. *Heliyon,* **11**(2): e41935.

Qian C, Zhou M, Cheng F, Lin X, Gong Y, Xie X, Li P, Li Z, Zhang P and Liu Z (2020). Development and multicenter performance evaluation of fully automated SARS-CoV-2 IgM and IgG immunoassays. *CCLM,* **58**(9): 1601-1607.

Rahman L, Talha Khalil A, Ahsan Shahid S, Shinwari Z K, Almarhoon ZM, Alalmaie A, Sharifi-Rad J and Calina D (2024). Diosmin: A promising phytochemical for functional foods, nutraceuticals and cancer therapy. *Food Sci. Nutr.,* **12**(9): 6070-6092.

Rajesh N, Moudgil-Joshi J and Kaliaperumal C (2022). Smoking and degenerative spinal disease: A systematic review. *Brain Spine,* **2**: 100916.

Ramanathan S, Rapp A, Perez Cruet M and Fahim DK (2023). Long-term reoperation rates after open versus minimally invasive spine surgery for degenerative lumbar disease: Five year follow-up of 2130 patients. *World Neurosurg.,* **171**: e126-e136.

Ren J (2024). Advances in Combination Therapy for Gastric Cancer: Integrating Targeted Agents and Immunotherapy. *Adv. Clin. Pharmacol. Ther.,* **1**(1): 1-15.

Savarino P, Colson E andré J and Gerbaux P (2023). Horse chestnut saponins-escins, isoescins, transescins and desacylescins. *Molecules,* **28**(5): 2087.

Scarcia L, Pileggi M, Camilli A, Romi A, Bartolo A, Giubbolini F, Valente I, Garignano G, D'Argento F, Pedicelli A and Alexandre AM (2022). Degenerative disc disease of the spine: From anatomy to pathophysiology and radiological appearance, with morphological and functional considerations. *J. Pers. Med.,* **12**(11): 1810.

Tian X and Shao F (2020). Clinical efficacy and safety of compound sodium aescinate gel combined with dioxin in treating postoperative eyelid swelling after blepharoplasty. *Chin. J. of Clinical Rational Drug Use,* **12**(3): 17-19.

Tucker IM, Burley A, Petkova RE, Hosking SL, RP Webster J, X Li P, Ma K, Doutch J, Penfoldoo J and Thomas RK (2022). Self-assembly in escin-nonionic surfactant mixtures: From micelles to vesicles. *J. Colloid Interface Sci.,* **626**: 305-313.

Wang Y, Han X, Wan X, Niu F and Zhou C (2023). β-Escin: An updated review of its analysis, pharmacology, pharmacokinetics and toxicity. *Am. J. Chinese Med.,* **51**(08): 2095-2120.

Xu W, Ran B, Zhao J, Luo W and Gu R (2022). Risk factors for failed back surgery syndrome following open posterior lumbar surgery for degenerative lumbar disease. *BMC Musculoskel. Dis.,* **23**(1): 1141.

Zhao M, Xu P, Zhao J and Yang Y (2020). Effects of edaravone combined with sodium aescinate on elderly patients with hypertensive intracerebral hemorrhage after drainage. *Acta Medicinae Sinica,* **35**(5): 64-68.

Zhao X, Ma H, Han H, Zhang L, Tian J, Lei B and Zhang Y (2022). Precision medicine strategies for spinal degenerative diseases: Injectable biomaterials with in situ repair and regeneration. *Mater. Today Bio.,* **16**: 100336.

Zheng SH, Chen XX, Chen Y, Wu ZC, Chen XQ and Li XL (2023). Antioxidant vitamins supplementation reduce endometriosis related pelvic pain in humans: A systematic review and meta-analysis. *Reprod. Biol. Endocrinol.,* **21**(1): 79.

Zwiri AM, Ahmad WMAW, Asif JA, Phaik KS, Husein A, Kassim NK and Ab-Ghani Z (2022). A randomized controlled trial evaluating the levels of the biomarkers hs-CRP, IL-6 and IL-8 in patients with temporomandibular disorder treated with LLLT, traditional conservative treatment and a combination of both. *Int. J. Env. Res. Pub. He.,* **19**(15): 8987.