Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Sulodexide

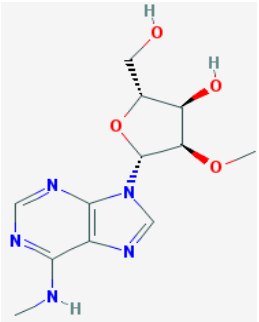
Evidence Summary

Anti-thrombotic agent with reduced risk for bleeding. Protects vasculature by regulating endothelial function and reducing inflammation. May protect against hypertension and atherosclerosis.

Neuroprotective Benefit: May help protect against vascular-related cognitive impairments by regulating vascular endothelial cell function.

Aging and related health concerns: Beneficial for vascular diseases due to lipid lowering, anti-oxidant, anti-hypertensive, and anti-inflammatory activities. May also benefit patients with early stage hypertensive kidney disease.

Safety: Well-tolerated, does not significantly alter normal hematological measures or increase the risk for bleeding. Mild gastrointestinal problems are possible.

Availability: Rx (Europe)	**Dose**: IV/IM 600 LSU 15-20 days then Oral 250 LSU (mg) 2x daily 30-40 days (repeat cycle as needed)	**Chemical formula:** $C_{12}H_{17}N_5O_4$ **MW**: 295.299 g/mol  Source: Pubchem
Half-life: 12 hours (IV) 18-25 hours (oral 50-100 mg)	**BBB**: Penetrant	
Clinical trials: Meta-analyses of RCTs indicate benefit for vascular diseases. RCTS for diabetic kidney disease have been mixed. A Phase 3 RCT (n=1056) failed to show benefit, but had potential methodological flaws.	**Observational studies**: A small study (n=93) suggests sulodexide use may lower dementia risk in patients with thrombotic diseases.	

What is it? Sulodexide is an extract from porcine intestinal mucosa that is a mixture of glycoaminoglycans comprised of 80% fast-moving (low molecular weight) heparin and 20% dermatan sulfate. Due to its low molecular weight it has a high bioavailability of 40-60% after oral administration and 90% after intramuscular administration [1]. It is an anti-thrombotic drug used to treat vascular diseases in patients at risk for thrombosis. Its anti-thrombotic activity stems from its ability to potentiate the activities of antithrombin III and heparin cofactor II [2]. Sulodexide also has endothelial protective, anti-inflammatory, and lipid lowering properties. It was developed in Italy over 30 years ago, and has been marketed extensively in Europe for vascular disease. Efforts to bring sulodexide to market in North America for the treatment of diabetes-associated kidney disease have been stalled due to a negative Phase 3 RCT.

Neuroprotective Benefit: May help protect against vascular-related cognitive impairments by regulating vascular endothelial cell function.

Types of evidence:

- 3 clinical trials (1 RCT for vascular dementia, 2 non-placebo-controlled studies for tinnitus and vertigo).
- 1 observational study

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Dementia prevention: Potential minor benefit/unclear

In a small prospective observational study, the incidence of Alzheimer's disease was assessed in patients over age 65 (n=93, average age 77) treated with different anticoagulants to prevent atherothrombotic disease for at least three years (average 6.5 years) [3]. Patients treated with sulodexide were compared to those treated with acenocoumarol, which is a derivative of coumarin and functions as a Vitamin K antagonist. The diagnosis of AD was based on neurological evaluation (using MMSE and GENCD), thus the measure is more of an assessment of cognitive impairment incidence than for AD per se. The overall relative incidence for AD was 2.02 for sulodexide and 4.86 for acenocoumarol, however, the breakdown by age suggests that the protection may be age-dependent or a sampling-size artifact. In patients age 70-79, the relative incidence was higher for sulodexide (3.31 vs 1.45). The oldest patients appeared to derive the most benefit from sulodexide, leading to lower relative incidence for 80-89-year-olds (1.18 vs 7.07) and 90-93-year-olds (0 vs 18.75). The difference may also reflect that the two populations had different pathology related to dementia risk, as sulodexide-treated patients had more vascular pathology, while acenocoumarol-treated patients had more cardiac pathology.

Human research to suggest benefits to patients with dementia:

Vascular dementia: Potential benefit/unclear

In a small RCT (VA.D.I.S.S), patients with vascular dementia (n=86, average age 75±5 years) were treated with sulodexide (50 mg BID orally) or pentoxifylline (400 mg TID orally) for 6 months [4]. Pentoxifylline is a non-selective phosphodiesterase inhibitor used to treat muscle pain, which has previously shown benefit in patients with vascular dementia, and to increase soluble Klotho levels in patients with diabetic kidney disease [5]. Both treatments reduced plasma fibrinogen levels and led to non-statistically significant improvements in MMSE scores (from 17.6 ± 0.4 to 20 ± 0.6 for sulodexide). Although both led

to minor improvements in the Gottfries-Bråne-Steen (GBS) Rating Scale for Dementia subscales (motor, intellectual, and emotional impairment), they were only statistically significant for sulodexide. The improvements were only slightly better for sulodexide, which may stem from this population having slightly worse scores at baseline, and not reflective of a true clinical benefit.

Due to sulodexide's endothelial protecting and anti-inflammatory effects, a beneficial effect for vascular dementia is highly plausible, but a larger placebo-controlled trial is needed to confirm benefit.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Sulodexide is hypothesized to offer protection against vascular dementia due to its ability to **regulate vascular endothelial cell function**, including the production of growth factors, and the expression of inflammatory factors [2]. A protective effect against Alzheimer's disease has also been anticipated due to its ability to **promote the release of tissue plasminogen activator (tPA**), which *in vitro* and rodent studies suggest may play a role in the clearance of Aβ [6; 7].

Two small non-placebo controlled clinical studies suggests that sulodexide may also offer benefits for people with tinnitus or vertigo. In 30 patients taking 250 LSU (25 mg BID) plus melatonin (3mg) for 80 days, 90% experienced significant improvements in a tone audiometry test, and reductions in the Tinnitus Handicap Inventory from 37±20 at baseline to 27±18 ($P<0.001$) to 21±19 ($P<0.001$) at 80 days [8].

In patients (n=90) with vascular vertigo and white matter lesions on MRI, treatment with sulodexide for 90 days (500 LSU for 45 days, then 250 LSU) led to a 60% reduction in anxiety ($p<0.0001$) and 30% reduction in motion sickness scores ($P<0.02$) [9]. However, it is not known whether the sulodexide had a beneficial (or negative) effect on the white matter lesions. The beneficial effects are expected to be related to improvements in vascular function, but the underlying molecular mechanisms have yet to be determined.

APOE4 interactions: Unknown

Aging and related health concerns: Beneficial for vascular diseases due to lipid lowering, anti-oxidant, anti-hypertensive, and anti-inflammatory activities. May also benefit patients with early stage hypertensive kidney disease.

Types of evidence:

- 4 meta-analyses (RCTs for sulodexide (n=8), diabetic nephropathy (n=2), thrombosis (n=3) and peripheral occlusive arterial disease (n=19 studies).
- 3 clinical trials (Phase 3 RCT for diabetic nephropathy (late stage), RCT for diabetic nephropathy (early stage), non-placebo-controlled study for chronic venous insufficiency)
- Several laboratory studies

Vascular disease: Benefit

Sulodexide is beneficial for vascular disease due to its anti-thrombotic, anti-inflammatory, hypolipidemic, and endothelial protecting properties.

Thromboembolism: In a meta-analysis of studies (n=4) with patients (n=1461) at risk for recurrent thromboembolism, sulodexide treatment for at least 6 months was associated with a significant reduction in recurrent venous thromboembolism [Risk ratio (RR): 0.51, 95 % Confidence Interval (CI) (0.35 to 0.74), P = 0.0004] and superficial vein thrombosis [RR: 0.41, 95% CI (0.22 to 0.76), P = 0.005] [10].

Arterial or venous disease: Beneficial effects are related to the **anti-atherosclerotic lipid-lowering activities** of sulodexide for arterial disease, and **anti-inflammatory activity** for venous disease. In a meta-analysis of 19 studies including patients with occlusive arterial disease, sulodexide treatment led to a 36% increase in pain-free walking distance compared to controls (P<0.001) and was effective in improving claudication (leg cramping) [11]. Sulodexide had a marked effect in lowering triglycerides (overall −28%, P = 0.0015), fibrinogen (−13%, P < 0.0001) and plasma and serum viscosities, and in increasing high-density-lipoprotein cholesterol (HLDL-c) (24.4%, P = 0.0007). In patients (n=11) with Stage 5 chronic venous disease, sulodexide reduced the serum pro-inflammatory mediator IL-6 (from 11.5±3.4 pg/mL to 10.1±2.3, P<0.005), and leukocyte-derived MMP-9 (6.50±3.48 ng/mL to 5.41±1.36, P<0.05), which is involved in vascular remodeling [12].

Mechanism:

Anti-inflammatory: Human vascular endothelial cells treated with serum from patients with cardiovascular disease leads to increases in the expression of pro-inflammatory mediators (IL-6, MCP-1,

ICAM-1), and accelerates cellular senescence [12; 13; 14; 15]. Pre-treatment with sulodexide *in vitro* **protects against the inflammation and senescence promoting factors** present in the patient serum [13; 14]. Sulodexide exerts similar protective effects *in vivo*, as serum from patients with vascular disease treated with sulodexide does not exert these damaging effects to the cultured endothelial cells [12; 15] . These protective effects are mediated, in part, by the reduction in AGE-related signaling (inhibiting activation of ERK/cPLA2/COX-2/PGE2), and preventing the downstream induction of the NF-kB signaling pathway [16].

Anti-oxidant: Sulodexide also acts on the endothelial cells to affect vascular relaxation, and in diabetic rats was shown to decrease the sensitivity of arteries to norepinephrine and produce higher relaxatory responses toward acetylcholine [17]. This was accompanied by an increase in the oxygen consumption rate and mitochondrial respiratory control ratio. Notably, the mitochondria of non-diabetic rats were not affected, which is consistent with antioxidant activity, in which the beneficial effects are related to the mitigation of oxidative stress relative to baseline level of stress.

Anti-angiogenic: Sulodexide can prevent aberrant vascular remodeling and neovascularization through inhibition of MMP-9 and VEGF [18; 19].

Glycocalyx remodeling: The glycocalyx serves as the interface between the blood and the vascular endothelium and is composed of a network of membrane bound carbohydrate-rich proteoglycans (sugar-modified proteins). It is damaged in the context of vascular disease. As a glycoaminogen, sulodexide has a similar structure to the glycocalyx, and could potentially provide precursors for glycocalyx repair [20]. In rats with carotid artery injury, sulodexide reduced glycocalyx damage-related expression of CD31 and ICAM-1 in endothelium, leukocyte counts, C-reactive protein, and atherosclerosis-related factors [20]. Additionally, **restoration of the endothelial glycocalyx** by sulodexide was found to reduce vascular permeability and decrease mortality in septic mice [21].

Hypertension: Sulodexide treatment has been shown to **lead to decreases in blood pressure**, with the greatest level of reduction experienced by people with hypertension and/or impaired renal function.

Sulodexide was found to result in a significant reduction in systolic [2.2 mmHg, 95% CI (0.3 to 4.1), P = 0.02] and diastolic blood pressure reduction [1.7 mmHg, 95% CI (0.6 to 2.9), P = 0.004] compared to control treatment in a meta-analysis of RCTs involving sulodexide [22]. Hypertensive patients experienced the largest reductions such that **higher baseline values were associated with larger reductions** in systolic (r^2=0.83, P < 0.001) and diastolic blood pressure (r^2=0.41, P = 0.02) after sulodexide treatment. These effects are thought to involve increased nitric oxide (NO) production and

non-osmotic sodium storage. The effect was also related to an improvement in kidney function, as measured by a reduction in albuminuria.

In a post-hoc analysis of results from the SUN-micro and SUN-macro trials for the use of sulodexide in patients with microalbuminuria or microalbuminuria, reductions in blood pressure were related to the baseline urine albumin-to-creatinine ratio (UACR) such that in people with elevated UACR >1000 mg/g, sulodexide lowered systolic blood pressure by 4.6 mmHg [95% CI (3.6 to 5.6); P < 0.001], but it had no effect on blood pressure in people with UACAR <300 mg/g. Benefits were attributed to an increase in endothelial layer volume [23].

Kidney disease: Potential benefit (for early stages)

Benefits seen in small clinical studies with respect to the effect of sulodexide on renal function prompted a Phase 3 RCT for patients with diabetic nephropathy. The negative Phase 3 trial has mitigated enthusiasm, but some experts believe that discounting sulodexide for use in kidney disease is premature due to caveats in the trial design such as patient selection, primary outcome measure, and drug sourcing [24; 25; 26]. Sulodexide may be more beneficial for patients with hypertensive than for diabetic kidney disease.

Hypertensive nephropathy: The potential benefit of sulodexide may be affected by the underlying etiology of the kidney disease. In a clinical study of 100 patients with different types of chronic kidney disease, **patients with hypertensive nephropathy had the greatest improvement in kidney function**, as measured by a decrease in proteinuria (73± 29%), whereas those with diabetic nephropathy experienced less benefit (57±39% reduction) [27]. The hypertensive patients were also the only ones to demonstrate a significant reduction in the enhanced glomerular filtration rate (eGFR), which is considered a more relevant marker of kidney function, and has been approved as clinical trial endpoint based on a National Kidney Foundation sponsored FDA workshop. It is important to note that traditional biomarkers for kidney disease generally lack sensitivity and predictive value, thus the surrogate endpoints used to measure kidney function may both influence trial results and lack clinical value [25]. It is still unclear whether albuminuria is a clinically reliable marker.

Diabetic nephropathy: Urinary TGF-β1 levels were used as an endpoint in an RCT (TCTR20140806001) of diabetic patients with kidney injury that were normoalbuminuric (early stage) (n=40) [28]. In this trial, sulodexide treatment prevented an increase in urinary TGF-β1, however, there is currently no evidence that this is relevant to long-term clinical efficacy.

In the Phase 3 RCT (n=1056), sulodexide treatment was not more effective than placebo in reducing albuminuria in patients with diabetic neuronopathy [29]. However, there are several caveats to this trial, as the patients has later stage (3-4) kidney disease than in previous trials, and were also taking anti-hypertensives (ACE inhibitors) at the maximum allowed dose, which may have masked potential benefits. The trial was sponsored by Keryx Biopharmaceudicals, and they manufactured their own formulation of sulodexide, whereas previous clinical trials (in Europe) used the original Vessel Due F formulation from Alfa Wassermann. The manufacturing process is complex; thus, it is unclear whether the two formulations had comparable bioavailability in patients.

Mechanism: Rodent models suggest that the renal protective effects of sulodexide stem from its antioxidant and Klotho promoting activities. Correspondingly, sulodexide would be expected to be most effective at **protecting against oxidative stress damage**, and not promoting regeneration. Consistent with this mechanism and the clinical trial results, sulodexide is only protective at early stages, and cannot repair external damage. In rats with (streptozotocin-induced) diabetic nephropathy, sulodexide treatment starting at early stages (weeks 0-24) was able to protect against renal cell loss and fibrosis, and was associated with a reduction in oxidative activity and normalization of Klotho levels [16]. In contrast, treatment starting in advanced disease (weeks 13-24) failed to provide renoprotection or promote Klotho. Similarly, sulodexide was also able to reduce proteinuria and protect against early but not late-stage radiation-induced nephropathy [30].

Safety: Well-tolerated, does not significantly alter normal hematological measures or increase the risk for bleeding. Mild gastrointestinal problems are possible.

Types of evidence:

- 2 meta-analyses (RCTS for thrombosis (n=3) and venous leg ulcers (n=4) and 1 systematic review (pharmacokinetic studies)
- 4 clinical trials (RCTs for Diabetic nephropathy and vascular dementia, non-placebo-controlled study for chronic venous insufficiency)
- Several laboratory studies

Sulodexide has been used by patients in Europe for over 30 years, and has been found to be largely well-tolerated, but can lead to transient mild gastrointestinal problems in some patients [4; 10]. No side effects or signs of intolerance were reported in trials for patients with chronic venous disease or tinnitus [8; 12]. Additionally, some patients in clinical trials developed allergic reactions to sulodexide, leading to

the developing of a skin rash and itching [10]. In a trial for vascular dementia, sulodexide did not lead to any abnormalities in routine hematological or hematochemical parameters [4]. The majority of clinical trials with sulodexide reported no significant adverse effects. The Phase 3 study for diabetic nephropathy reported no difference in severe adverse events compared to placebo, and none of these events were drug-related [29]. However, a Cochrane review examining the use of sulodexide in patients with venous ulcers found that it was unclear whether there was an increased risk for adverse events with sulodexide due to low quality of evidence [31]. Most notably, sulodexide use **does not appear to lead to the increased risk for bleeding** that is commonly seen with other anti-coagulants [1; 10].

According to Drugbank.com, there are 748 entries for potential drug interactions, which primarily consist of other anti-coagulant drugs which may increase the risk for bleeding.

Sources and dosing:

Sulodexide is sold under a variety of labels primarily in Italy, Spain, Eastern Europe, South America, and Asia. It was originally developed in Italy by Alfa Wasserman, and the Vessel Due F formulation has been most commonly associated with benefits in clinical trials. Sulodexide activity is expressed in terms of lipasemic-releasing units (LSU) because it results in the release of lipoprotein lipase (1 mg= 10 LSU).

The recommended dosing for patients at risk for thrombosis is 600 LSU intravenous or intramuscular for 15-20 days then oral 250 LSU (mg) 2x daily 30-40 days, with the cycle repeated at least twice a year, as needed.

Research underway:

Clinicaltrialsregister.eu lists two ongoing trials for sulodexide on investigating the effects of sulodexide on reversing endothelial glycocalyx damage in male patients with type 2 diabetes (2006-004043-35), and a Phase 3 trial for sulodexide in patients with chronic venous insufficiency (2016-000783-42).

According to Clincaltrials.gov, there is one active Phase 3 trial (NCT03370705) evaluating endothelial function in patients with peripheral occlusion artery disease treated with sulodexide. These Phase 3 trials are sponsored by Alfa Wassermann.

Search terms:

Pubmed, Google: Sulodexide + neurodegeneration, Alzheimer's disease, dementia, cogntive, aging, lifespan, cardiovascular, atherosclerosis, hypertension, diabetes, kidney, inflammation, klotho, meta-analysis, safety, pharmacokinetics

Websites visited for Sulodexide:

- Clinicaltrials.gov
- Clincaltrialsregister.eu
- Drugs.com
- PubChem
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- Mims.com

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