Supplementary Material

Supplementary Table S1. Structure–activity relationship summary of PSS.

Structural Parameter	Observed Trend	Affected Activity	Proposed Mechanism	Key Ref.
↑ Molecular weight	↑ Activity	Anticoagulation	Minimal chain length required for ternary complex formation with AT-III and serine protease	[103,105]
↓ Molecular weight (FP-6k)	Antithrombosis retained; ↓ Bleeding risk	Antithrombosis / Safety	Decoupling of antithrombotic activity from full anticoagulant ternary complex	[96,103]
Oligosaccharide fractions	Activity lost	Anticoagulation	Chain length insufficient for bridging AT-III and protease	[106]
Oligosaccharide fractions	Activity retained or enhanced	FGF/FGFR activation	Smaller fragments may preferentially engage FGF/FGFR without forming AT-III complex	[106]
↓ M/G ratio (↑ G content)	↑ Activity	Anticoagulation	G-rich blocks adopt a rigid conformation that is associated with stronger anticoagulant activity	[9,96]
↓ M/G ratio (↑ G	↑ Bleeding risk	Safety profile	Associated with stronger anticoagulant	[9,96]

Structural Parameter	Observed Trend	Affected Activity	Proposed Mechanism	Key Ref.
content)			activity; precise conformational mechanism remains to be fully elucidated	
↑ G content (PGGS derivative)	↑ Activity	Anti-atrial fibrosis	Enhanced inhibition of TGF-β1/Smad pathway	[122]
↑ Sulfation degree	↑ Activity (threshold-dependent)	Anticoagulation	Increased charge density enhances electrostatic protein interactions	[9,106]
Excessive sulfation	Non-specific binding, potential toxicity	Safety profile	Excess charge density may disrupt physiological interactions	[9]
High M/G ratio; high Mw	↑ Activity	Anti-selectin (anti-metastasis)	Larger, M-rich chains present optimal spatial sulfate arrangement for selectin binding	[130,131]
M/G ~7:3; Mw ~9 kDa; DS 9–13%	Optimal risk–benefit	Overall clinical profile	Balanced modulation of anticoagulant potency and bleeding risk	[9,96]

Abbreviations: AT-III, antithrombin III; DS, degree of sulfation; FGF, fibroblast growth factor; FGFR, FGF receptor; G, guluronic acid; M, mannuronic acid; Mw, weight-average molecular weight; PGGS, polyguluronic acid sulfate derivative; SAR, structure–activity relationship.