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Old and new applications of non-anticoagulant heparin

Giuseppe Cassinelli and Annamaria Naggi*

Istituto di Ricerche Chimiche e Biochimiche G Ronzoni, Milan, Italy

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ABSTRACT

The aim of this chapter is to provide an overview of non-anticoagulant effects of heparins and their potential use in new therapeutic applications. Heparin and heparin derivatives have been tested in inflammatory, pulmonary and reproductive diseases, in cardiovascular, nephro- and neuro-tissue protection and repair, but also as agents against angiogenesis, atheroschlerosis, metastasis, protozoa and viruses. Targeting and inhibition of specific mediators involved in the inflammatory process, promoting some of the above mentioned pathologies, are reported along with recent studies of heparin conjugates and oral delivery systems. Some reports from the institute of the authors, such as those devoted to glycol-split heparins are also included. Among the members and derivatives of this class, several are undergoing clinical trials as antimetastatic and antimalarial agents and for the treatment of labour pain and severe hereditary anaemia. Other heparins, whose therapeutic targets are non-anticoagulant such as nephropathies, retinopathies and cystic fibrosis are also under investigation.

1. Introduction

This chapter is an overview of the subject starting from the early landmark achievements, and includes papers, extended articles, reviews and books. Heparin and LMWHs are widely used for the prevention and treatment of thrombotic events by inhibiting antithrombin III (AT) and factor Xa through a specific oligosaccharide binding sequence (ATBR) present in only one third of unfractionated heparin chains as has been well-documented in two recent reviews [1,2]. Heparin, the most negatively charged biopolymer has an average of four negative charges for each disaccharide unit, can interact with a wide range of proteins, with interactions that exhibit a range of specificities [3] and induce several associated biological activities. These involve plasma or tissue proteins such as heparin cofactor II (HCII), tissue factor plasminogen inhibitor (TFPI), lipoproteinlipase, growth factors and heparanase. Interestingly, when a heparin ATIII-no-affinity fraction was added to normal plasma containing heparin, a marked increase in anti-factor Xa activity was observed, presumably due to the displacement of heparin with affinity for ATIII from binding plasma proteins [4].

2. Heparin and low molecular weight heparins (LMWH)

2.1. Anti-inflammatory, cardiovascular and tissue protection activities

The early reports of the beneficial effects of heparin in inflammation were attributed to the heparin binding and inhibition of chemokines, complement, growth and angiogenic factors, as reviewed recently [1,5,6,7]. Heparin can also bind to adhesion mediators expressed during inflammation, such as selectins, integrins and their receptors [8,9]. Tissue protection and repair were observed after heparin was inhaled to treat hot smoke inhalation injury in human fire survivors [5]. Topical, ophthalmic and parenteral formulations were also used to treat burns and lesions [10]. In low doses, heparin showed activity in several experimental models of inflammation as well as in the treatment of human chronic pulmonary diseases, by inhalation, or topically in allergic rhinitis [5]. Under various experimental and clinical conditions, such as oedema formation and pulmonary hypertension, heparin reduces leucocyte recruitment at the site of injury or inflammation stimuli, down-regulating cytokines, TNF-α, endotoxins and inhibiting human leukocyte elastase (HLE), as well as heparanase [5]. In response to vascular injuries, excessive repair by artery smooth muscle cells (SMC) can induce vascular disorders such as restenosis and hypoxy-pulmonary hypertension. SMC proliferation was inhibited by heparin in tissue culture and in rat, and rabbit injury models

* Corresponding author at: Istituto di Ricerche Chimiche e Biochimiche G. Ronzoni, Milan, Italy
E-mail address: naggi@ronzoni.it (A. Naggi).

[12]. A recent systematic review with meta-analysis showed the beneficial effects of heparin treatment in asthmatic patients [13]. In normal subjects, heparin can inhibit reactive oxygen species (ROS) generation [14], supporting the observed cardiovascular protective effects, and also increases nitric oxide bioavailability through the release of vessel immobilized myeloperoxidase [15]. The role of neutrophil elastase, a highly aggressive endopeptidase, seems to be crucial and is provoked by imbalances of natural inhibitors leading to degradation of connective and tissue components as observed in emphysema, cystic fibrosis, rheumatoid arthritis, psoriasis, perodontitis, mucopolysaccharidosis, wound healing and tumour invasion. Elastase can be inhibited "*in vitro*" by heparin and derivatives [16–18] as well as in emphysema experimental models [19].

2.2. Heparanase inhibition: implication in various pathologies

Heparin can also inhibit the endo-β-D (1-4) glucuronidase, heparanase [20,21] that through cleavage of HS chains of heparan sulfate proteoglycans affects their functions, the integrity and functional state of the extracellular matrix (ECM) and basement membrane of vessel walls. Owing to the ubiquitous presence and multiple roles of HS, such as growth factor storage and activity, cytokines, chemokines and heparanase degrading activity, it is involved in several pathological conditions including inflammation, amyloidosis, diabetic and glomerular nephropathies, cancer metastasis and angiogenesis. Overexpression and enhanced local activity of heparanase were observed particularly in atherosclerosis [22], type 2 diabetes [23], inflammatory bowel disease [24], in synovial fluid from rheumatoid arthritis patients [25], as well as in kidneys from both diabetic nephropathic and glomerular disease patients [26]. The first clinical trial of low dose heparin (in combination) dates back to the 1960s, followed in 1971 by long term high dose heparin in chronic glomerular nephritis [26]. The use of heparin and glycosaminoglycans as potential anti-complement agents in renal dysfunctions has been hypothesized [27].

2.3. Anticancer activity of heparin and LMWHs

The inhibitory activity of heparin on the growth of transplanted tumour tissues was first reported in 1930 [28]. Heparin and LMWHs have shown "*in vivo*" inhibitory activity in several experimental models. Their anti-metastatic activity seems to be based mainly on interference with the spreading of tumour cells in the blood and inhibition of angiogenesis, selectins as well as heparanase [29] and tissue factor (TF) over-expressed during inflammation and in the presence of aggressive cancers [30]. A recent report indicated an additional chemo-sensitizing activity of heparin through inhibition of P-glycoprotein- mediated multidrug resistance [31]. The results of "*in vitro*", "*in vivo*" studies and clinical trials have been reviewed [29,32–34]. Retrospective evaluation of early clinical trials indicated that heparin can provide survival benefits to cancer patients compared to other anti-thrombotics [32]. The inhibition of clots associated with tumour tissues, by heparin and LMWHs can increase accessibility of anticancer drugs and the efficacy of chemotherapy, but also induces drug resistance in some cases [35,36]. LMWHs are considered by current clinical guidelines to be the drug of choice for antithrombotic treatment in cancer patients. Adjunct therapy in small cell lung cancer patients with or without Bemiparin compared to chemo-radiation showed increased response rates and median survival times [37]. Comparable results were obtained with Dalteparin combined with chemotherapy in non-small cell lung cancer patients when compared with chemotherapy alone [38]. Other positive effects were observed in terminal cancer patients treated with Nadroparin or Dalteparin, as well as with Enoxaparin combined with chemotherapy in pancreatic cancer patients [29]. An updated systematic review and meta-analysis of randomized trials on survival of cancer patients treated with LMWHs has been reported [39]. A retrospective study on small cell lung cancer patients treated with heparin showed overall beneficial effects even when using different commercial heparin preparations [38]. Their intrinsic heterogeneity, despite their comparable anticoagulant activity, was probably one of the major factors behind some irreproducible or conflicting results. In this context the seminal report of J. Folkman *et al.* "Angiogenesis inhibition and tumour regression caused by heparin or a heparin fragments in the presence of cortisone" [40]. Following a preliminary selection from commercial heparins for their anti-angiogenic activity, the most active heparin found was "Panheprin" from Abbot that was discontinued soon after. Difficulties in reproducing the results using different commercial heparins interrupted this line of research [42]. Beneficial effects observed in anecdotal and clinical trials are reported in Table 1.

Table 1
Heparin: anecdotal* and clinical trials

Target	References
Acute respiratory distress syndrome*	[5,42]
Allergic rhinitis	[43]
Antimalaric[a]	[44]
Antiphospholipid syndrome	[45]
Asthma and bronchial constriction	[5,13]
Cardioversion of atrial fibrillation	[46]
Cardiopathies	[47]
Chronic obstructive pulmonary diseases	[5]
Cystic fibrosis	[18,48]
Glomerulonephritis	[26]
Hyperlipemias	[49]
Inflammatory bowel diseases	[5,29,50]
Mucolytic agent (Inhaled)	[51]
Nervous system protection by radiation	[52]
Rheumatoid arthritis	[5,53]
Severe sepsis	[54]
Tissue repair and wound healing	[5]
Vasoprotection	[55]

[a] Heparin, inhibiting and reversing cytoadherence and rosetting of *Plasmodium falciparium* infected erythrocytes "in vitro". Tested from 1967 in severe malaria clinical trials, after some overall promising outcomes, were discontinued due to severe intracranial bleeding [44]

2.4. Other experimentally investigated activities

After an early report [56] on the "*in vitro*" inhibition of *Herpes simplex* virus, in the mid-1980s, the potential for heparin and sulfated polysaccharides, to inhibit HIV *in vitro* [57], were investigated. Other reports showed the broad spectrum of "*in vitro*" activity of heparin on a variety of RNA and DNA viruses [58,59]. As for other therapeutic applications, anticoagulant activity limited doses, poor pharmacokinetics and the poor oral absorption of heparin were the major drawbacks to further developments. Heparin can exert neuroprotective effects in some models of neurodegenerative diseases inhibiting apoptotic processes [60]. Table 2 shows some other "*in vitro*" and "*in vivo*" activities of heparin that have been investigated.

2.5. LMWHs, ultra LMWHs and related oligosaccharides as nephro- and neuroprotective agents

Experimental and clinical studies in patients with proteinuric glomerulonephritis showed benefit by oral treatment with sulodexide, a mixture of LMW heparin and dermatan sulfate in a

Table 2
Heparin activity investigated "*in vitro*" and "*in vivo*"

Target	References
Allergic encephalomyelitis	[5]
Auto-immuno diseases	[61]
Anti-complement	[29,62,63]
Anti-atherosclerosis	[64]
Diabetic nephropathies	[26,65]
Emphysema	[66,67]
Iron-restricted anemia	[68]
Neuroprotection	[60]
Osteogenesis	[69]
Periodontal diseases	[70]

Table 3
Other clinical and experimental activities of LMWHs

Target	Compound	References
Asthma[a]	IVX0142 (Sulfate disaccharide) inhaled	[79]
Cystic fibrosis[b]		[80]
Emphysema[b]	Fraxiparine	[81]
Hematopoiesi[c]		[82]
Obstetrics[c,e]	Dalteparin	[83]
Retinal angiogenesis[c]	Suloparoid[d]	[84]
Ulcerative colitis[c]	LMWHs	[9]

[a] Anecdotal trial; [b] experimental models; [c] clinical trials; [d] LMW heparan sulfate; [e] shorter human labor.

4:1 weight ratio [26]. Clinical trials of parental LMHWs and oral sulodexide in diabetic nephropathic patients were also reported and their beneficial effects correlated principally with their inhibition of heparanase and oxidative renal insult [71]. In the early 1990s, clinical trials showed that "Ateroid" (present in the Italian market until 2014 as oral and parental formulations), a mixture of glycosaminoglycans (GAGs) similar to Sulodexide, may have improved the cognitive function of patients with various degenerative conditions correlated to amyloid diseases, such as Alzheimer's (AD), Parkinson's (PD) diseases and transmissible spongiform encephalopathy (TSE) [60]. In 1998 some heparin oligosaccharides were found able to cross the blood-brain barrier and inhibit β-amyloid precursor protein secretion [72]. Enoxaparin was also found to be active in an AD murine model [73]. Enoxaparin and Dalteparin inhibited experimental amyloidosis in clinically relevant doses [74]. To avoid anticoagulant effects, a mixture of oligosaccharides, named C3 or Neuroparin, prepared by γ-irradiation of high molecular weight heparin, showed neuroprotective effects in AD experimental models, also by the oral route [60].

2.6. Other investigated activities of LMWHs

Following randomized applications in vitreoretinal surgery [75] LMWHs have been used alone [76] or in combination with 5-fluoro-uracil [77], to mitigate the high risk of post-operative vitreoretinopathies, with significant improvement. As recently reviewed [78] in other clinical trials there was no statistical difference in the primary outcome, showing a narrow spectrum of experimental activity compared to heparin. In another recent review with meta-analysis, heparin and derivatives showed positive effects in cataract surgery [13]. LMWHs compared with heparin, showed more benefit as nephro- and neuroprotective agents. Other activities are listed in Table 3.

3. Chemical derivatives of heparin and LMWHs

The majority of biochemical, pharmacological and clinical investigations of heparins reported here, have employed heparin preparations manufactured as anticoagulants that can induce, in other therapeutic applications, side effects such as bleeding. This drove the investigation into the properties of heparin chains with no-affinity for AT and of chemically modified heparin with reduced anticoagulant activity. More selective approaches have been considered for both heparin fractions, with reduced AT affinity and anticoagulant activity, as well as rationally designed heparin derivatives targeting more specific interacting proteins. Comparison of the peculiar heparin sequences with libraries of amino acid sequences of heparin binding proteins may allow the prediction and identification of more specific interactions and new leads [85,86].

3.1. Sulfation degree modifications

Although the highly sulfated sequences of heparin show protein high-affinity binding, some of the sulfated groups can be compatible, but are not necessary for certain interactions. Selective desulfation can avoid or reduce heparin anticoagulant activity, by removing essential sulfated groups from the antithrombin binding region (ATBR) and induce selectivity among different protein targets. Similar results can be achieved by introducing sulfated groups in un-natural positions inducing conformational changes to impair ATIII binding.

Early chemical modifications included selective O-acylation in 1947 and N-desulfation in 1958 [87]. N-desulfated heparin, named "heparamine", showed reduced anticoagulant activity, experimental beneficial effects in preventing hepatic and renal damage by ischemia and reperfusion, as well as in inhibiting angiogenesis and experimental metastatic gastric cancer [88]. Structural modifications and structural activity relationship studies were mainly targeted towards inflammation [5], angiogenesis, cardiovascular and pulmonary diseases [11], metastasis [89] as well as Alzheimer's disease [90] and cerebral malaria [91]. The last two reports demonstrated the activity of N-desulfated-N-acetylated heparin (named heparide) and LMWHs. These and some N-acyl analogues showed beneficial effects in inflammation myocardial ischemic and reperfusion injury [5], inhibitory activity of angiogenesis and metastasis [89] in a broad spectrum of experimental models. An oversulfated LMWH preparation was found beneficial in an iron restricted anaemia model through inhibition of the peptide hormone Hepcidin [68]. Various types of derivatives, chemical processes, some biological interactions and activities are reported in dedicated reviews [87,89,92,93]. While the early structurally defined heparin binding to AT and thrombin supported the search of new anticoagulants and antithrombotics, only a few of the heparin interactions with the multitude of proteins involved, for example in inflammation [5], angiogenesis, metastasis and cancer [94] as well as atherosclerosis (LDL) [95] have been fully investigated to date. Owing to the intrinsic heterogeneity of heparin, which is sometimes increased by side reactions resulting from the difficulties of chemical handling and lack of selectivity, gave rise up to the 1990s to the development of a few leads and approved drugs. To our knowledge, Hirudoid, an oversulfated heparin is still on the market as a local vasoprotective formulation [93]. An O-butanoyl heparin derivative was found active in lung cancer experimental models [96]. Clinical trials of 2-O, 3-O desulfated heparin (ODSH), in combination with chemotherapy, showed benefits in untreated metastatic pancreatic cancer patients [97]. In the early 1990s another ODSH formulation was developed for the treatment of chronic obstructive pulmonary disease, but discontinued in 1994 [5].

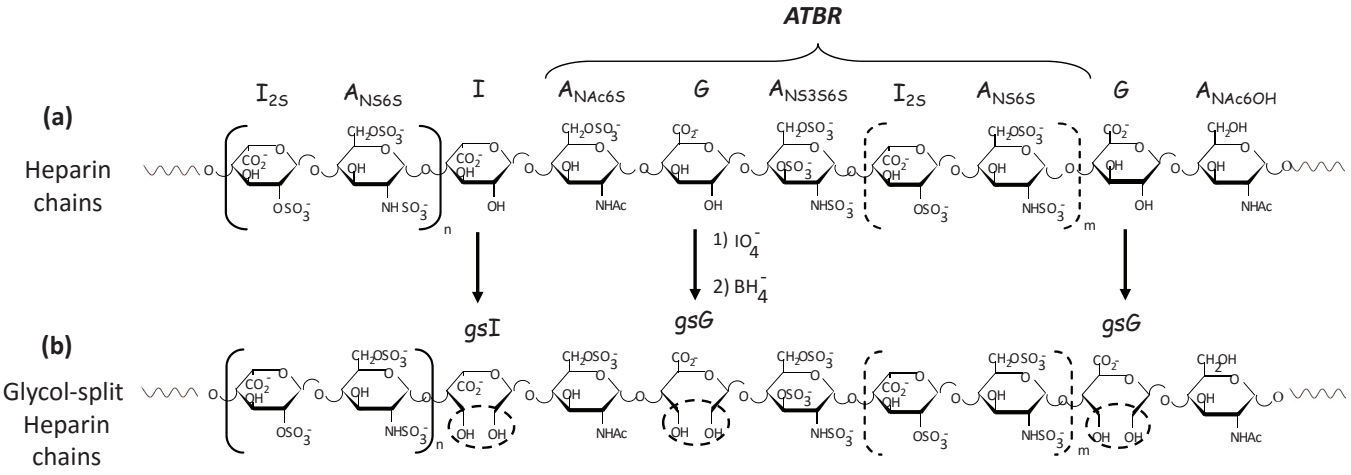

Fig. 1. Simplified formula of representative ATBR- containing chain of porcine mucosal heparin (a) and the corresponding gs derivative (b) obtained by periodate oxidation/ borohydride reduction. I = Iduronic acid, A= Glucosamine, G = glucuronic acid, gs = glicol-split, ATBR = antithrombin binding region.

3.2. Glycol-split heparins (gs-heparins)

Periodate oxidation has been applied to obtain non-anticoagulant heparins without impairing other biological activities and inducing reduced side reactions, i.e. depolymerization, and preserves both the pattern and degree of sulfation [98,99]. Periodate can selectively oxidize adjacent carbons bearing unsubstituted hydroxyl and /or amino groups [100], leading, in heparins, to the splitting of C(2)-C(3) bonds of un-sulfated uronic acids including the glucuronic acid, within the ATBR, essential for high anticoagulant activity [101]. Subsequent borohydride reduction leads to the "glycol-split" (gs) derivatives, also named reduced oxyheparins (ROHs), as shown in Fig. 1 Under well-controlled conditions, the first intermediate oxy-heparin and final gs-heparin samples, that preserved the original Mws, were fully-characterized in terms of their chemical-physical properties and "*in vivo*" anti-lipemic activity, as well as residual anticoagulant activity in 1986 [99]. The increase of chain flexibility, induced by gs-residues and the ability to maintain the principal biological interactions of heparin has led in the last thirty years to a number of active gs-heparins differing in size and extent of glycol-splitting, shown in Table 4.

Among the gs-heparins under development, only SST0001 (N-desulfated-N-acetyl gs-heparin) shows a size comparable to that of high molecular weight heparin. This inhibits heparanase, angiogenesis, downregulates FGF-2, HGF, MMP9 and PDGF abrogating PDGF receptor tyrosine phosphorylation. The heparanase role in radiation-enhanced invasiveness of pancreatic carcinoma is abolished by SST001 "*in vivo*" [102]. The SST0001 inhibition of heparanase mediated signaling overcame the resistance in Lapatinib resistant brain metastatic breast cancer cells [103]. An additional heparanase mediated pathway inhibited by SST0001 "*in vitro*" is the stimulation of chondrogenesis up-regulated by heparanase in human ectopic cartilage and possibly involved in hereditary multiple exostoses, a pediatric skeletal disorder characterized by benign cartilaginous tumours [104]. SST0001 was found effective in several tumour xenografts of hematologic (myeloma) [105] and solid (sarcoma) malignancies [106, 107]. Roneparstat has been tested in a Phase I trial for advanced myelomas and patients are being enrolled for a Phase II trial.

All the other gs-heparins including those in clinical trials show low or very low Mw. Vasoflux, obtained by glycol splitting of a LMWH, afforded anticoagulant activity independent of AT and HCII [108]. Addition of Vasoflux to streptokinase and Aspirin in a randomized clinical trial for prevention of acute myocardial infarction, did not improve the response compared to heparin [109].

M402, a gs-LMWH, inhibits heparanase, growth factors involved in angiogenesis, other pathways and metastasis in orthoptic murine carcinoma models [110]. Since June 2005, Nocuparanib has been a candidate in Phase II clinical trial for metastatic pancreatic cancer in combination with chemotherapy. Clinical trials of DF01 (Tafoxiparin) for the prevention and treatment of protracted labour are ongoing [111]. DFX -232 and Sevuparin, as inhibitors of red cell aggregation, known as rosetting, arising from "*Plasmodium falciparium*" infection, are under clinical trial as anti-malarials and for prevention of vascular occlusion by sickle red cells in severe hereditary anaemia [112].

3.3. Heparin oligosaccharides

The biosynthetic structural heterogeneity of heparin chains, further enhanced by chemical treatments during manufacture and purification, make their sequence analysis very difficult. To prepare a library of pure oligosaccharides from natural heparin is another very challenging task. Nevertheless hundreds of oligosaccharide have been isolated over the years, mainly by enzymatic or nitrous acid partial depolymerization, and tested for a broad range of biological activities and protein interactions. Through a recent rational approach, active oligosaccharides from hexa- up to dodecasaccharides have been chemo-enzymatically prepared starting from the structural homogeneous bacterial polysaccharide K5 [129] using recombinant versions of the heparin biosynthesis enzymes [130].

4. Heparin conjugates and orally delivery systems

An oxy-heparin preparation, (from heparin periodate oxidation) was linked through the newly formed aldehyde groups to polystyrene to provide the conjugate NAC-HCPS, inhibiting angiogenesis and metastasis in experimental models [131], the same activity shown by a conjugate of Fraxiparin (LH17), through a diaminoethylene bridge with taurocholate [132]. Other conjugates have been designed as delivery systems for anticancer drugs, such as Doxorubicin [133]. An orally active 6-O-desulfated Nadroparin conjugate with deoxycholate (6ODS-LHbD) was found to inhibit angiogenesis and bone destructive arthritis in experimental models [134]. Ignoring anecdotal reports, orally active heparin formulations have been the aim of formulation scientists and clinicians for some time. A variety of approaches have been summarized recently [135]. To mention one instance, N-[8-(2-hydroxyl benzoyl)amino]caprilate (SNAC) was selected as an oral enhancing delivery agent for heparin.

Table 4
Gs-heparins interactions and biological activities

Code/ name		Target/inhibition	References
gs-heparin			
	ROH	antilipemic[a]	[99]
	Astenose	Adjuvant in cardiovascular intervention [c]	[113]
	ROH	Heparanase antiangiogenesis inhibitor[b]	[114]
	ROH	P selectin inhibitor	[115]
	LAC-HP	antimetastatic[b]	[116]
	ROH	Integrin-melanoma cell binding inhibitor[a]	[117]
	ROH	Antianemic as hepicdine inhibitor[b]	[118]
	ROH	Antinflammation- human elastase inhibitors[a]	[118]
gs-LMWH			
	ORG 31733	HIV-1 and HIV-2 inhibitor[a]	[120]
	SR 80258	Allergic airway response inhibitor[b]	[121]
	Vasoflux	Anticoagulant independent from AT activity, coadjuvant in myocardial infarction therapy[d]	[108,109]
	NAC from Tinzaparin	Antimetastatic[b]	[122]
	gs-LMWH	antimalarial, parasite adhesion, inhibitor[b]	[44]
	DF01 - Tafoxiparin	Labor pain attenuation[d]	[111]
	M-402 Nocuparanib	Metastasis and multiple pathway inhibitor[d]	[110]
	DFX 232- Sevuparin	Antimalarial, distrupting "*Plasmodium falciparium*" rosettes[d]	[112]]-
		Preventive activity of vasoocclusion in sickle severe hereditary anemia [d]	
	S-NACH	Anticancer increasing tumor chemo-responsiveness[c]	[35]
gs-ULMWH			
	RO-Fondaparinux	Antinflammation[b]	[123]
Undersulfated RO			
	ST1514"	Antinflammatory - heparanase inhibitor[b]	[124]
		Antiangiogenic, as FGF-2 and VEGF inhibitors[b]	[125,126]
N-acylated gs-heparins			
	N-succinyl gs-LMWHs	Syncitium inhibitors	127
	SST0001-Roneparstat	Inhibitor of metastasis, angiogenesis, heparanase[d]	98
		P-selectins, multiple pathway inhibitor[b]	128

[a] "*In vitro*", [b] "*in vivo*", [c] preclinical, [d] clinical studies.

The efficacy of two liquid formulations in a thromboprophylaxis Phase III clinical trial, in comparison with standard s.c. LMWH therapy, did not show significant benefits [136].

5. Conclusion

Up-dating the non-anticoagulant activities of heparins has not been an easy task considering the number of reports disclosing their new roles in signaling and pathways involved in a variety of pathologies. In competition with chemo-enzymatic approaches, natural heparins, may improve their chances. The manufacture of pharmaceutical grade heparin has been optimized for anticoagulant efficacy which mainly represents the principal side effect for other applications. Given the heterogeneity of raw heparin chains, it is probable that sequences and chains better involved in other applications may be lost but, also selected in processing natural heparins. In the future, selection based on size or lack of AT-binding, followed by compositional and structural characterization would provide more useful and rational preparations preserving particular sequences, for new non-anticoagulant leads and applications.

Conflict of interest statement

The authors declare no competing financial interest.

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References

[1] Casu B, Naggi A, Torri G. Revisiting the structure of heparin. Carbohydr. Res. 2015;403:60-68
[2] Barrowcliffe TW, History of heparin. In Lever R, Mulloy B, Page CP editor Heparin A century of progress. Berlin-Heidelberg Spring Verlag; 2012 p3-22
[3] Capila I, Linhardt RJ. Heparin–protein interactions. Angew. Chem. Int. Ed. 2002;41(3): 390-412.
[4] Young E, Hirsh J. Contribution of red blood cells to the saturable mechanism of heparin clearance. Thromb. and Haemost. 1990; 64(4):559-563.
[5] Lever R, Page CP. Non-anticoagulant effects of heparin: an overview. In Lever R Mulloy B, Page CP. editor Heparin-A Century of Progress. Springer Berlin Heidelberg 2012 p. 281-305.
[6] Shute J. Glycosaminoglycan and chemokine/growth factor interactions. Lever R, Mulloy B, Page CP. editor Heparin-A Century of Progress. Springer Berlin Heidelberg 2012 p. 307-324.
[7] Chiodelli P, Bugatti A, Urbinati C, Rusnati M. Heparin/Heparan Sulfate Proteoglycans Glycomic Interactome in Angiogenesis: Biological Implications and Therapeutical Use. Molecules 2015; 20(4):6342-6388.
[8] Borsig L. Selectins facilitate carcinoma metastasis and heparin can prevent them. Physiol. 2004;19(1):6-21.
[9] Fritzsche J, Alban S, Ludwig RJ, Rubant S, Boehncke WH, Bendas G. et al. The influence of various structural parameters of semisynthetic sulfated polysaccharides on the P-selectin inhibitory capacity. Biochem. Pharmacol. 2006;72(4):474-485.
[10] Oremus M, Hanson MD, Whitlock R, Young E, Archer C, Dal Cin A. et al. A systematic review of heparin to treat burn injury. J. Burn Care Res. 2007;28(6): 794-804.
[11] Mousa SA, Heparin and low molecular weight heparin in thrombosis and inflammation: emerging link. In Care HG, Linhardt RJ, Hales CA. Editors, Chemistry and biology of heparin and heparan sulfate. 2005 pp. 571-582 Elsevier Ltd Oxford.
[12] Garg HG, Mrabat H, Yu L. Hales CA,. Li B, Moore CN,. Linhardt RJ. et al. Antiproliferative effects of O-acyl-low-molecular-weight heparin derivatives on bovine pulmonary artery smooth muscle cells. Glycoconj. J. 2011; 28(6):419-426.
[13] Mousavi S, Moradi M, Khorshidahmad T, Motamedi M, Anti-Inflammatory Effects of Heparin and Its Derivatives: A Systematic Review. Adv. in Pharm. Sci. 2015;507-151

[14] Grant D, Long WF, Mackintosh G, Williamson FB. The antioxidant activity of heparins. Biochem. Soc. Trans. 1996;24(2): 194S-194S.

[15] Baldus S,. Rudolph V, Roiss M, Ito WD, Rudolph TK, Eiserich JP. et al. Heparins increase endothelial nitric oxide bioavailability by liberating vessel-immobilized myeloperoxidase Circulation 2006; 113(15): 1871-1878.

[16] Baici A, Diczházi C, Neszmélyi A, Móczár E, Hornebeck W. Inhibition of the human leukocyte endopeptidases elastase and cathepsin G and of porcine pancreatic elastase by N-oleoyl derivatives of heparin. Biochem Pharmacol. 1993;46(9):1545-1549.

[17] Brown RA, Lever R, Jones N, Page CP. Effects of heparin and related molecules upon neutrophil aggregation and elastase release in vitro. Br J. Pharmacol. 2003;139(4):845-853.

[18] Veraldi N, Hughes AJ, Rudd TR, Thomas HB, Hadfield L, Yates EA. et al. Heparin derivatives for the targeting of multiple activities in the inflammatory response. Carbohydr. Polym. 2015;117:400-407.

[19] Redini F, Tixier JM, Petitou M, Choay J, Robert L, Hornebeck W. Inhibition of leucocyte elastase by heparin and its derivatives. Biochem. J 1988;252:515-519.

[20] Nakajima M, Irimura T, Nicolson GL. Heparanases and tumor metastasis. J. Cell. Biochem. 1988;36(2):57-167.

[21] Vlodavsky I, Ilan N, Naggi A, Casu B. Heparanase: structure biological functions and inhibition by heparin-derived mimetics of heparan sulfate. Curr. Pharm. Design. 2007;13(20):2057-2073.

[22] Vlodavsky I, Blich M, Li JP, Sanderson RD, Ilan N. Involvement of heparanase in atherosclerosis and other vessel wall pathologies. Matrix Biol 2013; 32(5):241-251.

[23] Shafat I, Ilan N, Zoabi S, Vlodavsky I, Nakhoul F. Heparanase levels are elevated in the urine and plasma of type 2 diabetes patients and associate with blood glucose levels. PLoS One 2011; 6 (2):e7312.

[24] Waterman M, Ben-Izhak O, Eliakim R, Groisman G, Vlodavsky I. Ilan N. Heparanase upregulation by colonic epithelium in inflammatory bowel disease. Mod. Pathol. 2007;20(1): 8-14.

[25] Li RW, Freeman C, Yu D, Hindmarsh EJ, Tymms KE, Parish CR, Smith PN. Dramatic regulation of heparanase activity and angiogenesis gene expression in synovium from patients with rheumatoid arthritis. Arthritis Rheum 2008;58(6):1590-1600.

[26] Gambaro G, Kong NC. Glycosaminoglycan treatment in glomerulonephritis? An interesting option to investigate. J Nephrol. 2010;23(3):244-252.

[27] Zaferani A, Talsma D, Richter MK, Daha M, Navis GJ, van den Born J. et al. Heparin/heparan sulphate interactions with complement-a possible target for reduction of renal function loss?. Nephrol Dial Transplant 2014; 29(3):515-522.

[28] Goerner A, The influence of anticlotting agents on transplantation and growth of tumor tissue. J Lab Clin Med 1931;16(4):369-372.

[29] Ludwig RJ. Therapeutic use of heparin beyond anticoagulation. Curr Drug Discov Technol 2009;6(4):281-289.

[30] Pfankuchen DB, Stölting DP, Schlesinger M, Royer HD, Bendas G. Low molecular weight heparin tinzaparin antagonizes cisplatin resistance of ovarian cancer cells. Biochem. Pharmacol. 2015;97(2):47-157.

[31] Angelini A, Di Febbo C, Ciofani G, Di Nisio M, Baccante G, Di Ilio C, et al. Inhibition of P-glycoprotein-mediated multidrug resistance by unfractionated heparin: a new potential chemosensitizer for cancer therapy. Cancer Biol Ther 2005;4(3):313-317.

[32] Smorenburg SM, Van Noorden CJ. The complex effects of heparins on cancer progression and metastasis in experimental studies. Pharmacol. Rev. 2015;3(1):93-106.

[33] L Borsig L. Antimetastatic activities of heparins and modified heparins. Experimental evidence. Thromb. Res. 2010;125:S66-S71.

[34] Noble S. Heparins and cancer survival: where do we stand? Thromb. Res. 2014;133:S133-S138.

[35] Phillips PG, Yalcin M, Cui H, Abdel-Nabi H, Sajjad M, Mousa SA. et al. Increased tumor uptake of chemotherapeutics and improved chemoresponse by novel non-anticoagulant low molecular weight heparin. Anticancer Res: 2011;31(2):411-419.

[36] Pan Y,. Li X, Duan J, Yuan L. Fan S, Fan J, Li X, Enoxaparin Sensitizes Human Non-Small-Cell Lung Carcinomas to Gefitinib by Inhibiting DOCK1 Expression Vimentin Phosphorylation and Akt Activation. Mol. Pharmacol. 2015;87(3):378-390.

[37] Lecumberri R, Vivanco GL, Font A, Billalabeitia EG, Gúrpide A, Codina J. et al. Adjuvant therapy with bemiparin in patients with limited-stage small cell lung cancer: results from the ABEL study. Thromb. Res. 2013;132(6):666-670.

[38] Lebeau B, Baud M, Masanes MJ, Febvre M, Mokhtari T, et al. Optimization of small-cell lung cancer chemotherapy with heparin: a comprehensive retrospective study of 239 patients treated in a single specialized center, Chemotherapy 2011,57:253-258.

[39] Sanford D, Naidu A, Alizadeh N, Lazo-Langner A. The effect of low molecular weight heparin on survival in cancer patients: an updated systematic review and meta-analysis of randomized trials. J. Thromb. Haemost.2014;12(7):076-1085.

[40] Folkman J, Langer R, Linhardt RJ, Haudenschild C, Taylor S. Angiogenesis inhibition and tumor regression caused by heparin or a heparin fragment in the presence of cortisone. Science 1983;221(4612):719-725.

[41] Folkman J. Tumor angiogenesis. In Klein G .and Weinhouse S. Editors Adv. Cancer Res. Academic Press New York 1985;43(1):75-203.

[42] MacLaren R, Stringer KA. Emerging role of anticoagulants and fibrinolytics in the treatment of acute respiratory distress syndrome. Pharmacother. 2007;27(6):860-873.

[43] C Vancheri C, Mastruzzo C, Armato F, Tomaselli V, Magrì S, Pistorio MP. et al. Intranasal heparin reduces eosinophil recruitment after nasal allergen challenge in patients with allergic rhinitis. J Allergy Clin. Immunol. 2001;108(5):703-708.

[44] Vogt AM. Pettersson F, Moll K, Jonsson C, Normark J, Ribacke U, et al. Release of sequestered malaria parasites upon injection of a glycosaminoglycan. PLoS Pathog. 2006;2(9):e100.

[45] Kutteh WH. Antiphospholipid antibody–associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am. J. Obstet. Gynecol. 1996;174(5):1584-1589.

[46] Hoppensteadt D, Fareed J, Klein AL, Jasper SE, Apperson-Hansen C, Lieber EA. et al. Comparison of anticoagulant and anti-inflammatory responses using enoxaparin versus unfractionated heparin for transesophageal echocardiography-guided cardioversion of atrial fibrillation. Am J Cardiol 2008;102(7):842-846.

[47] S. Baldus V, Rudolph M, Roiss WD, Ito TK, Rudolph JP. Eiserich. et al. Heparins increase endothelial nitric oxide bioavailability by liberating vessel-immobilized myeloperoxidase. Circulation 2006;113(15):871-1878.

[48] Downey DG, Bell SC. Elborn J.S. Neutrophils in cystic fibrosis. Thorax 2009;64(1):81-88.

[49] Rubinstein A, Gibson JC, Paterniti Jr JR,. Kakis G, Little A, Ginsberg HN. et al. Effect of heparin-induced lipolysis on the distribution of apolipoprotein e among lipoprotein subclasses. Studies with patients deficient in hepatic triglyceride lipase and lipoprotein lipase. J. of Clin. Invest.1985;75(2):710.

[50] Gaffney P, O'Leary J, Doyle C, Gaffney A, Hogan J, Smew F. et al. Response to heparin in patients with ulcerative colitis. The Lancet 1991;337(8735):238-239.

[51] King M, Rubin BK, Pharmacological approaches to discovery and development of new mucolytic agents. Adv Drug Deliv Rev 2002;54(11):1475-1490.

[52] Glantz MJ, Burger PC, Friedman AH, Radtke RA, Massey EW, Schold SC. Treatment of radiation-induced nervous system injury with heparin and warfarin. Neurology 1994;44(11):2020-2020.

[53] Gaffney A, Gaffney P. Rheumatoid arthritis and heparin. Br. J. Rheumatol. 1996;35(8):808-809.

[54] Davidson BL, Geerts WH. Lensing AW. Low-dose heparin for severe sepsis. N Eng J Med. 2002;347(13):036-1037.

[55] C Vec hio C, Frisinghelli A. Topically applied heparins for the treatment of vascular disorders. Clin. Drug Invest. 2008;28(10): 603-614.

[56] Nehmas AJ, Kibrick S. Inhibitory effect of heparin on herpes simplex virus. J. Bacteriol. 1964;87(5):1060-1066.

[57] Rider CC, The potential for heparin and its derivatives in the therapy and prevention of HIV-1 infection. Glycoconj J 1997;14(5):639-642.

[58] Shukla D, Liu J, Blaiklock P, Shworak NW, Bai X, Esko J, Det al. A novel role for 3-O-sulfated heparan sulfate in herpes simplex virus 1 entry. Cell 1999;99(1):13-22.

[59] Liu J, Shriver Z, Pope RM. Thorp S, Duncan MB, Sasisekharan R. et al. Characterization of a heparan sulfate octasaccharide that binds to herpes simplex virus type 1 glycoprotein D. J Biol Chem. 2002;277(36):33456-33467.

[60] Dudas B, Semeniken K, Glycosaminoglycans and neuroprotection. In Heparin - Lever R, Mulloy B, Page CP, editor Heparin A century of progress. Berlin-Heidelberg Spring Verlag; 2012 pp. 325-343

[61] Lider O, Baharav E, Mekori Y.A, Miller T, Naparstek Y, Vlodavsky I. Suppression of experimental autoimmune diseases and prolongation of allograft survival by treatment of animals with low doses of heparins, J. Clin. Invest, 83 (1989) 752-756

[62] Ecker EE,. Gross P. Anticomplementary power of heparin. J Infect Dis. 1929;250-253.

[63] Cofrancsco E, Radaelli F, Pogliani E, Amici N, Torri G, Casu B. Correlation of sulfate content and degree of carboxylation of heparin and related glycosaminoglycans with anticomplement activity. Relationships to the anticoagulant and platelet-aggregating activities. Thromb Res 1979;14(1):179-187.

[64] Engelberg H. Endogenous heparin activity deficiency: the 'Missing Link'in atherogenesis? Atherosclerosis 2001;159(2): 253-260.

[65] Striker LJ, Peten EP, Elliot SJ, Doi T, Striker GE. Mesangial cell turnover: effect of heparin and peptide growth factors. Lab Invest 1991;64(4):446.

[66] Rao NV, Kennedy TP, Rao G, Ky N, Hoidal JR. Sulfated polysaccharides prevent human leukocyte elastase-induced acute lung injury and emphysema in hamsters. Am Rev Resp Dis 1990;142(2):407-412.

[67] Spencer JL, Stone PJ, Nugent MA. New insights into the inhibition of human neutrophil elastase by heparin. Biochemistry 2006;45(30):9104-9120.

[68] Poli M, Girelli D, Campostrini N, Maccarinelli F, Finazzi D, Arosio P. et al. Heparin: a potent inhibitor of hepcidin expression in vitro and in vivo. Blood 2011;117(3):997-1004.

[69] Zhao B, Katagiri T, Toyoda H, Takada T, Yanai T, Fukuda T. et al. Heparin potentiates the in vivo ectopic bone formation induced by bone morphogenetic protein-2. J Biol Chem 2006;281(32):23246-23253.

[70] Götte M. Periodontal diseases and glycosaminoglycans. FASEB J 2003;17.6: 575-591.

[71] Lewis EJ, Xu X. Abnormal Glomerular Permeability Characteristics in Diabetic Nephropathy Implications for the therapeutic use of low–molecular weight heparin. Diabetes Care 2008;31(2):S202-S207.

[72] Leveugle B, Ding W, Laurence F, Dehouck MP, Scanameo A, Cecchelli R. et al. Heparin oligosaccharides that pass the blood-brain barrier inhibit β-amyloid pre-

cursor protein secretion and heparin binding to β-amyloid peptide. J Neurochem 1998;70(2):736-744.
[73] Bergamaschini L, Rossi E, Storini C, Pizzimenti S, Distaso M, Perego C. et al. Peripheral treatment with enoxaparin a low molecular weight heparin reduces plaques and β-amyloid accumulation in a mouse model of Alzheimer's disease. J Neurosci. 2004;24(17):4181-4186.
[74] Zhu H, Yu J, Kindy MS. Inhibition of amyloidosis using low-molecular-weight heparins. Mol Med 2001;7(8):7-22.
[75] Blumenkranz MS, Hartzer MK, Iverson D. An overview of potential applications of heparin in vitreoretinal surgery. Retina 1992;12(3):S71-S74.
[76] Kumar A, Nainiwal S, Sreenivas B. Intravitreal low molecular weight heparin in PVR surgery. Indian J Ophthalmol 2003;51(1):67.
[77] Asaria RH, Kon CH, Bunce C, Charteris DG, Wong D, Khaw PT. et al. Adjuvant 5-fluorouracil and heparin prevents proliferative vitreoretinopathy: results from a randomized double-blind controlled clinical trial. Ophthalmol 2001;108(7): 1179-1183.
[78] Khan M, Brady C, Kaiser R. Clinical management of proliferative vitreoretinopathy: an update. Retina 2015;35(2):165-175.
[79] Duong M, Cockcroft D, Boulet LP, Ahmed T, Iverson H. Atkinson D.C.et al. The effect of IVX-0142 a heparin-derived hypersulfated disaccharide on the allergic airway responses in asthma. Allergy 2008;63(9):195-1201.
[80] Cadène M, Boudier C, de Marcillac GD, Bieth JG. Influence of Low Molecular Mass Heparin on the Kinetics of Neutrophil Elastase Inhibition by Mucus Proteinase Inhibitor J Biol Chem 1995;270(22):3204-13209.
[81] Lafuma C, Frisdal E, Harf A, Robert L, Hornebeck W. Prevention of leucocyte elastase-induced emphysema in mice by heparin fragments. Eur Respir J 1991;4(8):1004-1009.
[82] Or R, Elad S, Shpilberg O, Eldor A, Low molecular weight heparin stimulates megakaryocytopoiesis in bone marrow transplantation patients. Am J.Hematol 1996;53(1):46-48.
[83] Mulloy B, Hogwood J, Gray E. Assays and reference materials for current and future applications of heparins. Biologicals 2010;38(4):459-466.
[84] Benelli U, Bocci G, Danesi R, Lepri A, Bernardini N, Bianchi F. et al. The heparan sulfate suleparoide inhibits rat corneal angiogenesis and in vitro neovascularization. Exp Eye Res 1998;67(2):133-142.
[85] Cardin AD, Weintraub HJ. Molecular modeling of protein-glycosaminoglycan interactions. Arteriosclerosis 1989; 9:21-32
[86] Mulloy B, Linhardt RJ, Order out of complexity - protein structures that interact with heparin. Curr Opin Struct Biol 2001; 11:623-628
[87] Fernández C, Hattan CM, Kerns RJ. Semi-synthetic heparin derivatives: chemical modifications of heparin beyond chain length sulfate substitution pattern and N-sulfo/N-acetyl groups. Carbohydr Res 2006;341(10):253-1265.
[88] Chen J, L. Fan J, Chen MX. Dong Y, Gu JZ. Effect of non-anticoagulant N-desulfated heparin on basic fibroblast growth factor expression angiogenesis and metastasis of gastric carcinoma in vitro and in vivo. Gastroenterol Res Prac 2012; 2012:1-6.
[89] Roy S, Lai H, Zouaoui R, Duffner J, Zhou H, Venkataraman G. et al. Bioactivity screening of partially desulfated low-molecular-weight heparins: a structure/activity relationship study. Glycobiol 2011;21(9):1194-1205.
[90] Patey SJ,. Edwards EA, Yates EA, Turnbull JE. Heparin derivatives as inhibitors of BACE-1 the Alzheimer's β-secretase with reduced activity against factor Xa and other proteases. J Med Chem 2006;49(20):6129-6132.
[91] Skidmore M, Dumax-Vorzet AF, Guimond SE, Rudd TR, Edwards EA, Yates EA. et al. Disruption of rosetting in Plasmodium falciparum malaria with chemically modified heparin and low molecular weight derivatives possessing reduced anticoagulant and other serine protease inhibition activities. J Med Chem 2008;51(5):1453-1458.
[92] Casu B, Lindahl U, Structure and biological interactions of heparin and heparan sulfate. Adv Carbohydr Chem Biochem 2000; 57: 159-206.
[93] Coombe DR, Kett WC. Heparin mimetics. In Lever R, Mulloy B, Page CP, editor Heparin A century of progress. Berlin-Heidelberg Spring Verlag; 2012 p. 361-383.
[94] Shriver Z, Capila I, Venkataraman G, Sasisekharan R. Heparin and heparan sulfate: analyzing structure and microheterogeneity. In Lever R, Mulloy B, Page CP. editor Heparin A century of progress. Berlin-Heidelberg Spring Verlag; 2012 p. 159-176).
[95] Gigli M, Consonni A, Ghiselli G, Rizzo V, Naggi A,. Torri G. Heparin binding to human plasma low-density lipoproteins: dependence on heparin sulfation degree and chain length. Biochemistry 1992;31(26):5996-6003.
[96] Yu L, Garg HG, Li B, Linhardt RJ, Hales CA.. Antitumor effect of butanoylated heparin with low anticoagulant activity on lung cancer growth in mice and rats. Cur. Cancer Drug Tar. 2010;10(2):229-241.
[97] Sigal DMSG, Rosen PJ, Cohen SJ, Lee P, Nguyen T, Borad MJ. et al. Association of 2-O 3-O desulfated heparin (ODSH) plus combination gemcitabine (G)/nab-paclitaxel (A) with preliminary benefit in untreated metastatic pancreatic cancer. J Clin Oncol 2013; 31(34):abst 2318.
[98] Naggi A, Casu B, Perez M, Torri G, Cassinelli G, Penco S. et al. Modulation of the heparanase-inhibiting activity of heparin through selective desulfation graded N-acetylation and glycol splitting. J Biol Chem 2005;280(13):12103-12113.
[99] Casu B, Diamantini G, Fedeli G, Mantovani M, Oreste P, Pescador R. et al. Retention of antilipemic activity by periodate-oxidized non-anticoagulant heparins. Arzneim.-Forsch.1986;36(4):637-642.
[100] Perlin AS. Glycol-cleavage oxidation. Adv Carbohydr Chem Biochem. 2006;60: 183-250.
[101] Islam T, Butler M, Sikkander SA, Toida T,. Linhardt RJ. Further evidence that periodate cleavage of heparin occurs primarily through the antithrombin binding site. Carbohydr Res 2002;337(21):2239-2243.
[102] Meirovitz A, Hermano E, Lerner I, Zcharia E, Pisano C, Peretz T. et al. Role of heparanase in radiation-enhanced invasiveness of pancreatic carcinoma. Cancer Res 2011;71(7):2772-2780.
[103] Zhang L, Ngo JA, Wetzel MD, Marchetti D. Heparanase mediates a novel mechanism in lapatinib-resistant brain metastatic breast cancer. Neoplasia 2015;17(1):101-113.
[104] Huegel J, Enomoto-Iwamoto M, Sgariglia F, Koyama E, Pacifici M. Heparanase stimulates shondrogenesis and is up-regulated in human ectopic cartilage: A mechanism possibly involved in hereditary multiple exostoses. Am J Pathol 2015;185(6): 1676-1685.
[105] Ritchie JP, Ramani V.C, Ren Y, Naggi A, Torri G, Casu B, Yang Y. SST0001 a chemically modified heparin inhibits myeloma growth and angiogenesis via disruption of the heparanase/syndecan-1 axis. Clin Cancer Res 2011;17(6) :382-1393.
[106] Shafat I, Ben-Arush MW, Issakov J, Meller I, Naroditsky I, Tortoreto M. et al. Preclinical and clinical significance of heparanase in Ewing's sarcoma. J Cell Mol Med 2011;15(9): 1857-1864.
[107] Cassinelli G, Lanzi C, Tortoreto M, Cominetti D, Petrangolini G, Favini E. et al. Antitumor efficacy of the heparanase inhibitor SST0001 alone and in combination with antiangiogenic agents in the treatment of human pediatric sarcoma models. Biochem Pharmacol 2013;85(10):424-1432.
[108] Weitz JI, Young E, Johnston M, Stafford AR, Fredenburgh JC, Hirsh J. Vasoflux a new anticoagulant with a novel mechanism of action. Circulation 1999;99(5):682-689.
[109] Peters RJ, Spickler W, Théroux P, White H, Gibson M, Molhoek PG, Weaver W.D. Randomized comparison of a novel anticoagulant vasoflux and heparin as adjunctive therapy to streptokinase for acute myocardial infarction: Results of the VITAL study (Vasoflux International Trial for Acute Myocardial Infarction Lysis). Am Heart J 2001;142(2):237-243.
[110] Zhou H, Roy S, Cochran E, Zouaoui R, Chu CL, Duffner J, Kishimoto TK. M402 a novel heparan sulfate mimetic targets multiple pathways implicated in tumor progression and metastasis. PLoS One 2011;6(6): e21106.
[111] Ekman-Ordeberg Hellgren M, Åkerud A, Andersson E, Dubicke A, Sennström M. et al. Low molecular weight heparin stimulates myometrial contractility and cervical remodeling in vitro. Acta Obstet Gyn Scan 2009;88(9):984-989.
[112] Leitgeb AM, Blomqvist K, Cho-Ngwa F, Samje M, Nde P, Titanji V. et al. Low anticoagulant heparin disrupts Plasmodium falciparum rosettes in fresh clinical isolates. The Am. J. Trop. Med. Hyg. 2011;84(3):390-396.
[113] Sobel M, Bird KE, Tyler-Cross R, Marques D, Toma N, Conrad HE, Harris RB. Heparins designed to specifically inhibit platelet interactions with von Willebrand factor. Circulation 1996;93(5):992-999.
[114] Lapierre F, Holme K, Lam L, Tressler R, JWee J, Tyrrell DJ. et al. Chemical modifications of heparin that diminish its anticoagulant but preserve its heparanase-inhibitory angiostatic anti-tumor and anti-metastatic properties. Glycobiol 1996;6(3):355-366.
[115] .Wei M, Tai G, Gao Y, Li N, Huang B, Zhou Y, Zeng X, Modified heparin inhibits P-selectin-mediated cell adhesion of human colon carcinoma cells to immobilized platelets under dynamic flow conditions, J Biol Chem 279 (2004). 29202-29210.
[116] Yoshitomi Y, Nakanishi Y, Kusano H, Munesue S, Oguri K, Tatematsu M. et al. Inhibition of experimental lung metastases of Lewis lung carcinoma cells by chemically modified heparin with reduced anticoagulant activity. Cancer Lett 2004;207(2):165-174.
[117] Schlesinger M, Naggi A, Torri G, Zeisig R, Alexander M, Bendas G. et al. Blocking of integrin-mediated human MV3 melanoma cell binding by commercial and modified heparins. Int J Clin Pharmacol Ther 2010;48(7):448.
[118] Poli M, Asperti M, Ruzzenenti P, Regoni M, Arosio P. Hepcidin antagonists for potential treatments of disorders with hepcidin excess. Front Pharmacol 2014;5:86
[119] Gao Y, Li N, Fei R, Chen Z, Zheng S, Zeng X, P-Selectin-mediated acute inflammation can be blocked by chemically modified heparin, RO-heparin. Mol Cells, 19 (2005) 350-355.
[120] Baba M, De Clercq E, Schols D, Pauwels R, Snoeck R, Van Boeckel C. et al. Novel sulfated polysaccharides: dissociation of anti-human immunodeficiency virus activity from antithrombin activity. J Infect Dis1990;161(2):208-213.
[121] Campo C, Molinari JF. Ungo J. Ahmed T. Molecular-weight-dependent effects of nonanticoagulant heparins on allergic airway responses. J Appl Physiol 1999;86(2):549-557.
[122] Kragh M,. Binderup L, Vig Hjarnaa PJ, Bramm E, Johansen KB. et al. Non-anticoagulant heparin inhibits metastasis but not primary tumor growth. Oncol Rep 2005;14(1):99-104.
[123] Frank RD, Holscher T, Schabbauer G, Tencati M, Pawlinski R, Weitz JI. et al. Non-anticoagulant synthetic pentasaccharide reduces inflammation in a murine model of kidney ischemia-reperfusion injury. Thromb Haemost 2006;96(6):802-806.
[124] Edovitsky E, Lerner I, Zcharia E, Peretz T, Vlodavsky I, Elkin M. Role of endothelial heparanase in delayed-type hypersensitivity. Blood 2006;107(9):3609-3616.
[125] Casu B, Guerrini M, Guglieri S, Naggi A, Perez M, Torri G. et al. Undersulfated and glycol-split heparins endowed with antiangiogenic activity. J Med Chem 2004;47(4) 838-848.

[126] Pisano C, Aulicino C, Vesci L, Casu B, Naggi A, Torri G. et al. Undersulfated low-molecular-weight glycol-split heparin as an antiangiogenic VEGF antagonist. Glycobiol 2005;15(2):1C-6C.
[127] Lopalco L, Ciccomascolo F, Lanza P, Zoppetti G, Caramazza I, Leoni F. et al. Anti-HIV type 1 properties of chemically modified heparins with diminished anticoagulant activity. AIDS Res. Hum Retroviruses 1994;10(7):87-793.
[128] Hostettler N, Naggi A, Torri G, Ishai-Michaeli R, Casu B, Vlodavsky I. et al. P-selectin-and heparanase-dependent antimetastatic activity of non-anticoagulant heparins. FASEB J;2007;21(13):3562-3572.
[129] Casu B, Grazioli G, Razi N, Guerrini M, Naggi A, Torri G. et al. Heparin-like compounds prepared by chemical modification of capsular polysaccharide from E. coli K5. Carbohydr Res 1994;263(2): 271-284.
[130] Liu J, Linhardt RJ. Chemoenzymatic synthesis of heparan sulfate and heparin. Nat Prod Rep 2014.
[131] Ono K, Ishihara M, Ishikawa K, Ozeki Y, Sato M, Maehara T. et al. Periodate-treated non-anticoagulant heparin-carrying polystyrene (NAC-HCPS) affects angiogenesis and inhibits subcutaneous induced tumour growth and metastasis to the lung. Br J Cancer 2002;86(11):1803-1812.
[132] Chung SW, Lee M, Bae S.M, Park J, Jeon OC, Lee HS. et al. Potentiation of anti-angiogenic activity of heparin by blocking the ATIII-interacting pentasaccharide unit and increasing net anionic charge. Biomaterials 2012;33(35):9070-9079.
[133] She W, Li N. Luo K, Guo C, Wang G. Geng Y. et al. Dendronized heparin-doxorubicin conjugate based nanoparticle as pH-responsive drug delivery system for cancer therapy. Biomaterials 2013;34(9):2252-2264.
[134] Hwang S,R. Seo D,H. Al-Hilal T,A. Jeon O,C. Kang J,H. Kim S. Het al. Orally active desulfated low molecular weight heparin and deoxycholic acid conjugate 6ODS-LHbD suppresses neovascularization and bone destruction in arthritis. J Controll. Release 2012;163(3):374-384.
[135] Paliwal R, Paliwal SR, Agrawal GP, Vyas SP. Recent advances in search of oral heparin therapeutics. Med Res Rev 2012;32(2):388-409.
[136] Arbit E, Goldberg M, Gomez-Orellana I, Majuru S, Oral heparin: status review. Thromb J 2006;4(1):6.