Carbohydrate Polymers 295 (2022) 119818

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Review

Heparin: An old drug for new clinical applications

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ARTICLE INFO

Keywords:
Heparin
Preparation
Non-anticoagulant bioactivity
Clinical application

ABSTRACT

Heparin, an old but first-line anticoagulant, has been used over a century. It is a heterogeneous, linear, highly sulfated, anionic glycosaminoglycan with a broad distribution in relative molecular weight and charge density. These structural properties allow heparin to selectively interact with multiple proteins, leading to heparin's various pharmacological functions, such as anticoagulant, anti-viral, anti-tumor and anti-inflammatory activities. Clinical data suggest that unfractionated heparin or low molecule weight heparin could decrease mortality in COVID-19 patients with sepsis-induced hypercoagulation through the anticoagulant, anti-viral and anti-inflammatory activities of these drugs. Thus, the non-anticoagulant activity of heparin has again aroused attention. This review highlights recent advances in the preparation of heparin-derived drugs and clinical research on its non-anticoagulant properties over the past decade, to further the development and utilization of these important drugs.

1. Introduction

At present, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains globally prevalent and has become the most significant global public health crisis after the influenza pandemic of 1918 (Hippensteel, LaRiviere, Colbert, Langouet-Astrie, & Schmidt, 2020). A remarkable clinical feature of pandemic COVID-19 disease is respiratory failure followed by infection with SARS-CoV-2. Severe cases of COVID-19 with higher risks of death, are often accompanied microcirculation dysfunction combined with thrombotic microangiopathy, especially in elderly, diabetic, and hypertensive patients, and those with other cardiovascular diseases (Karim, Islam, Rafiq, & Laher, 2021; Kollias et al., 2020). Research hypotheses, retrospective cohort studies, and clinical data have suggested that unfractioned heparin (UFH) or low molecule weight heparin (LMWH) could decrease mortality in critically ill COVID-19 patients through not only their anticoagulant but also anti-viral and anti-inflammatory activities (Dutch & Thrombosis, 2021; Ennemoser et al., 2022; Hippensteel et al., 2020; Kow, Ramachandram, & Hasan, 2022; Lindahl & Li, 2020b; Seffer, Cottam, Forni, & Kielstein, 2020; Shi

Abbreviations: Aβ, beta-amyloid; ACE, angiotensin-converting enzyme; AD, Alzheimer's disease; AT, antithrombin; ATR, angiotensin receptor; BACE1, beta-site amyloid precursor protein cleaving enzyme 1; BBB, blood-brain barrier; CAT, cancer-associated thrombosis; cGMP, current good manufacturing practice; CHO, Chinese hamster ovary cells; CHs, circulating histones; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DENV, dengue virus; DN, diabetic nephropathy; FDA, the US Food and Drug Administration; FGFs, fibroblast growth factors; GAG, glycosaminoglycan; GBM, glomerular basement membrane; GlcA, glucuronic acid; GlcN, glucosamine; HBP, heparin-binding protein; HCC, hepatoma carcinoma; HMGB1, high mobility group box 1 protein; HP, heparin; HPV16, human papilloma virus 16; HIT, heparin-induced thrombocytopenia; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IFNγ, interferon-γ; IdoA, iduronic acid; IL-6, interleukin-1; ISTH, the International Society for Thrombosis and Hemostasis; LD, Lyme disease; LMWH, low-molecular weight heparin; LPS, lipopolysaccharide; MODS, multiple organ dysfunction syndrome; MW, molecular weight; NF-κB, nuclear factor κB; NFTs, intracellular neurofibrillary tangles; pRBCs, *Plasmodium*-infected red blood cells; RAGE, advanced glycation end products; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCLC, limited-stage small-cell lung cancer; Sp, spike protein; VEGF, vascular endothelial growth factor; UFH, unfractionated heparin; ULMWH, ultralow molecular weight heparin; VTE, venous thrombus embolism.

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https://doi.org/10.1016/j.carbpol.2022.119818
Received 28 April 2022; Received in revised form 26 June 2022; Accepted 28 June 2022
Available online 3 July 2022

et al., 2020; Thachil, 2020). These results give rise to new attention to the non-anticoagulant activities of HP, which will contribute to the development of new therapeutic approaches of other diseases.

Heparin (HP), discovered by Jay McLean and William Henry Howell in 1916, is the oldest and currently most widely used anticoagulant drug worldwide (Hao, Xu, Yu, & Zhang, 2019). As an anticoagulant and antithrombotic drug, HP has been in clinical use for >80 years since it is approved in 1935. HP is obtained from animal tissues, particularly from pig intestinal mucosa and bovine lung. It is a heterogeneous linear glycosaminoglycan (GAG) with high sulfate substitution. The backbone of HP is mainly composed of a repeating sulfated (S) disaccharide unit of 1,4 linked α-L-iduronic (IdoA) or β-D-glucuronic acid (GlcA), and α-D-glucosamine (GlcN), while a trisulfated disaccharide GlcNS6S (1 → 4) IdoA2S is HP's major repeating unit (Fig. 1A). The polydispersity and structural variations allow HP to selectively interact with multiple proteins. Among these HP-binding proteins, the classic case is the serine protease inhibitor antithrombin-III (AT), which results in HP's anticoagulant activity. AT specifically recognizes a rare pentasaccharide unit GlcNAc/S6S → GlcA→GlcNS3S6S → IdoA2S → GlcNS6S in HP chains (Fig. 1B) that activates a conformational change in AT and accelerates the flexibility of its reactive loop. As a result, AT's binding affinity for thrombin and other coagulation cascade proteases is greatly enhanced. Additionally, HP can simultaneously inhibit thrombin generation and thrombin activity in the bloodstream (Hao, Xu, et al., 2019).

In addition to AT, a number of biologically relevant, HP-protein interactions have been investigated, accelerating the discovery of many additional pharmacological activities for HP, including anti-viral, anti-tumor, anti-inflammatory, anti-hypolipidemic, and anti-angiogenesis activities (Alaez-Verson, Lantero, & Fernandez-Busquets, 2017; Hao, Xu, et al., 2019; Lever & Page, 2002; Lindahl, 2000; Shi, Sheng, & Chi, 2021; Torri & Naggi, 2016; Folkman, Langer, Linhardt, Haudenschild, & Taylor, 1983). In this review, the advances in the preparation methods of HP are described and the updated clinical research on its non-anticoagulant are highlighted (Fig. 2).

2. HP preparation method

According to molecular weight distribution, three forms of HP are approved by the US Food and Drug Administration (FDA): unfractionated heparin (UFH, average molecular weight (MW_{avg}) 15,000 to 19,000 Da) for *intravenous* administration; several types of low molecular weight heparin (LMWH, MW_{avg} 3500–6000 Da) for *subcutaneous* administration; and ultralow molecular weight heparin (ULMWH, MW_{avg} < 2000 Da) for *subcutaneous* administration (Qiao et al., 2020).

UFH, the first-generation HP product, is extracted and isolated from animal tissues, especially from porcine intestinal mucosa or bovine lung. Commercial LMWH and ULMWH are originally prepared by depolymerization of UFH with chemical or enzymatic methods (Baytas & Linhardt, 2020). Typical industrial processes for UFH preparation can be divided into five steps (Baytas & Linhardt, 2020; van der Meer, Kellenbach, & van den Bos, 2017) including collection materials, digestion, and release of HP, capture and recovery of HP, purification of HP, and finally isolation and drying. Due to the animal origins of UFH and the limitations of extraction and preparation methods, it is not possible to make a pure HP without the presence of other GAG impurities (*i.e.*, dermatan sulfate, chondroitin sulfate, and heparan sulfate). Also, viruses, prions, and HP-binding growth factors are usually found in animal extracts, which are hard to ignore and needed to be carefully concerned in animal-derived HP (Baytas & Linhardt, 2020). Further, UFH has a high MW_{avg} with complex pharmacokinetic, biophysical, and biological properties, which limits its therapeutic application. For example, UFH shows a 1–6 % incidence of heparin-induced thrombocytopenia (HIT), a life-threatening complication (Liu & Linhardt, 2014).

Compared to UFH, LMWH has several advantages, including higher bioavailability, longer half-lives, lower doses and longer duration of action, and less binding to other proteins, reducing its serious side effects. LMWH is obtained from the partial depolymerization of UFH by chemical or enzymatic methods. The mechanism for the depolymerization of UFH mainly includes peroxidative cleavage, nitrous acid cleavage, and β-elimination. Several commercial LMWHs, with different chemical properties, are produced by these methods, such as Bemiparin, Certoparin, Dalteparin, Enoxaparin, Nadroparin, Parnaparin, Reviparin, and Tinzaparin (Hao, Sun, Wang, Zhang, & Wang, 2019; Qiu et al., 2021). The subtle structural differences and MW_{avg} distribution of these LMWH are shown in Table 1. For example, Dalteparin, Reviparin, Nadroparin, and Certoparin have the same reducing end characteristics with presence of 2,5-anhydro-D-mannose, which are produced by nitrous acid depolymerization. The non-reducing end characteristics of Enoxaparin and Tinzaparin is presence of 4,5 unsaturated uronic acid, which are obtained by β-elimination with alkaline or enzymatic depolymerization.

New approaches combining physical methods with chemoenzymatic methods have been developed in recent years to solve problems of chemical and enzymatic preparation of LMWH, including high cost, chemical by-products, and low yields. For example, titanium oxide is a solid, non-toxic catalyst to produce hydroxyl radicals, which is used in the photodepolymerization of UFH. It can be easily removed by centrifugation or filtration after the photochemical reaction takes place,

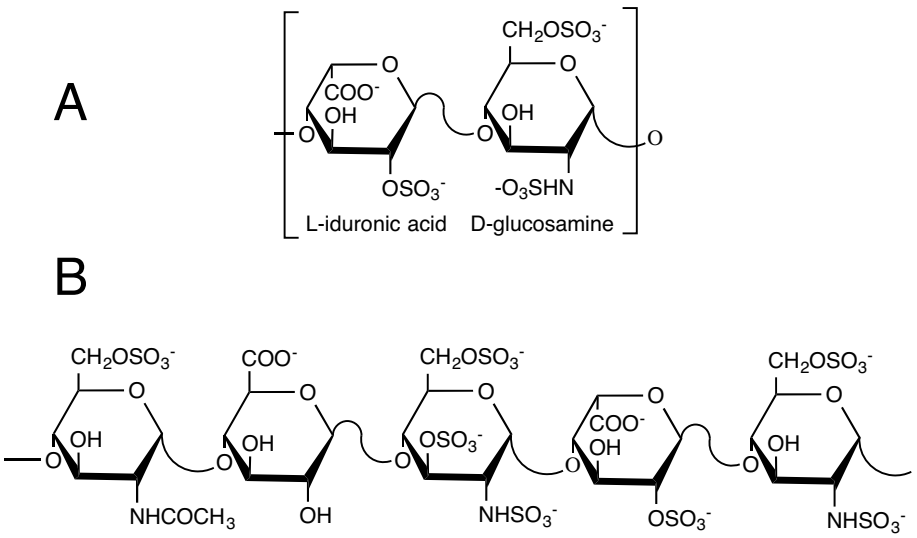

Fig. 1. A) The structure of the major repeating disaccharide of heparin and B) the major heparin pentasaccharide sequence in pig intestinal heparin.

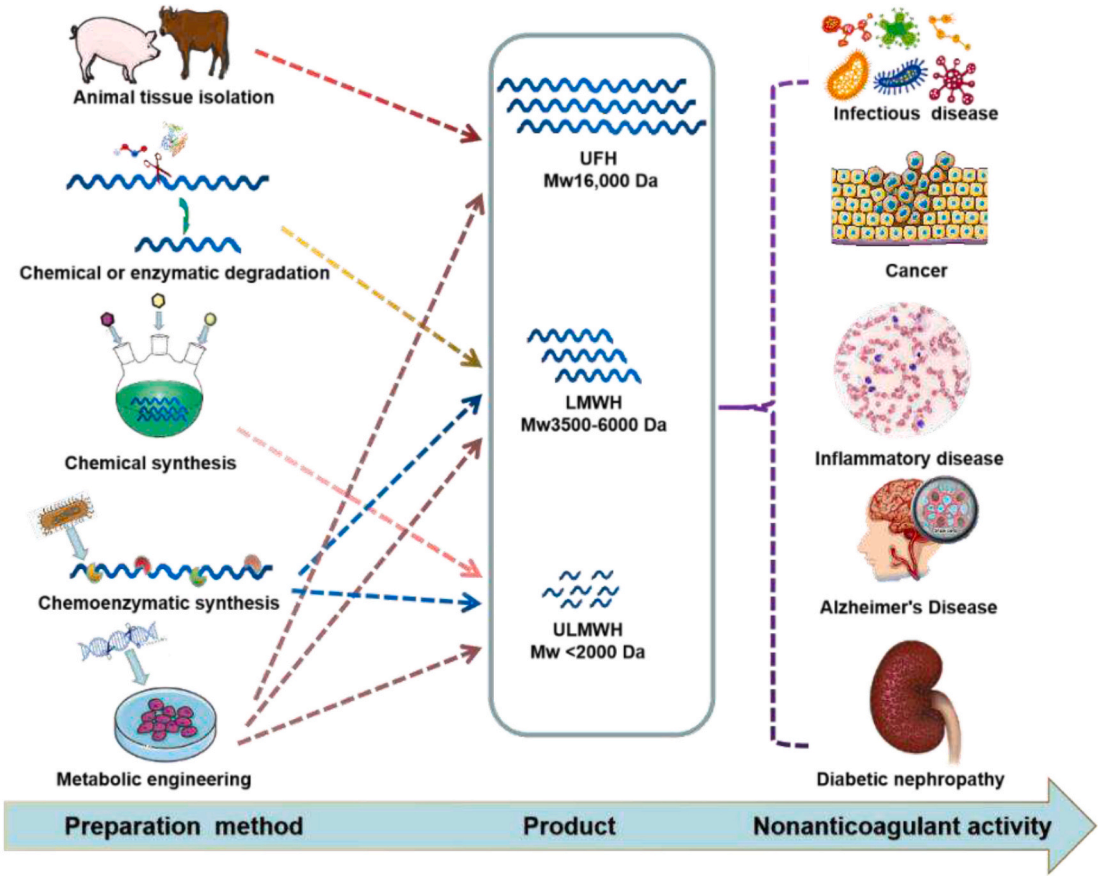

Fig. 2. Major methods for preparing heparin and its mimetics.

Table 1
Preparation methods and structural characteristics of LMWH (Hao, Sun, et al., 2019).

LMWH	Reducing end (RE) or non-reducing end (NRE) characteristics	Preparation methods	MW (Da)
Dalteparin	RE 2,5-anhydro-D-mannose	Nitrous acid depolymerization	6000
Reviparin	RE 2,5-anhydro-D-mannose	Nitrous acid depolymerization	4400
Nadroparin	RE 2,5-anhydro-D-mannose	Nitrous acid depolymerization	4300
Certoparin	RE 2,5-anhydro-D-mannose	Isoamyl nitrite depolymerization	5400
Enoxaparin	NRE 4,5 unsaturated uronic acid	Benzylation followed by alkaline depolymerization	4500
Bemiparin	NRE 2-*O*-sulfo-4,5 unsaturated uronic acid	Alkaline depolymerization	3600
Tinzaparin	NRE 4,5 unsaturated uronic acid	Enzymatic depolymerization	6500
Parnaparin	2-N,6-O-disulfo-D-glucosamine residue	Oxidative depolymerization	5000

resulting a highly pure LMWH (Higashi et al., 2012). Zhi et al. invented a new method of LMWH preparation, named as sono-Fenton, by combining physical ultrasonic treatment with a chemical Fenton reaction (Zhi et al., 2019), which is an effective method to rapidly obtain LMWH with significantly higher anticoagulant activity than UFH and other LMWH. H_2O_2/ascorbic acid free radical reaction combined with ultrasonic treatment is also used to preparing LMWH (Shen et al., 2019). Recently, LMWH is prepared through chemoenzymatic synthesis (Baytas et al., 2021). These mild and environmentally friendly process is being applied to the large-scale preparation of LMWH to meet industrial applications.

ULMWH, the latest generation of HP, are synthetic oligosaccharides, including five to ten saccharide units. Fondaparinux (Arixtra, MW 1508 Da), the only clinically approved ULMWH in 2003, is a pentasaccharide specially binding to the AT-binding domain as a selective inhibitor of FXa (Ding, Prasad, Bai, & Wang, 2017; Linhardt & Liu, 2012). Compared to UFH and LWMH, ULMWH have higher structural consistency and better quality control and exhibits the lowest bleeding side-effects. However, ULMWH is still a small percentage of clinical HP products, primarily due to its high cost (Alaez-Verson et al., 2017). When preparing synthetic ULMWHs, multiple challenges are unavoidable, such as cumbersome steps in chemical synthesis of oligosaccharides, difficulty in purification and low synthetic yields. Over the past decades, several groups have accomplished challenging and innovative work to synthesize fondaparinux by reducing the reaction steps and increasing the yield of glycan products (Baytas & Linhardt, 2020). Improvement strategies based on one-pot glycosylation method are developed to synthesis of fondaparinux, leading to high stereoselectivity, simple purification, and high synthetic efficiency (Dey, Lo, & Wong, 2020; Ding et al., 2017; Jin et al., 2019). The yields of ULMWH can be further improved by avoiding protection/deprotection steps through chemoenzymatic synthesis (Xu et al., 2011).

HP, the most widely used anticoagulant worldwide, is an animal-sourced product which still has potential risks of adulteration and contamination. The contamination crisis in 2008 push forward to provide HP of non-animal origin, which can be produced under current good manufacturing practice (cGMP) conditions (Kishimoto et al., 2008; Liu, Zhang, & Linhardt, 2009). Up to now, several strategies have been attempted to produce a bioengineered HP, such as microbial production, mammalian cell production, and chemo-enzymatic modification (Baytas

& Linhardt, 2020; Fu, Suflita, & Linhardt, 2016; Liu & Linhardt, 2014; Xu et al., 2011; Zhang et al., 2008). The recombinant HP biosynthetic enzymes including glycosyltransferases and sulfotransferases are successful expressed, which make chemoenzymatic synthesis of UFH, LMWH and ULMWH possible. The utility of enzymes as catalysts results from their higher stereoselectivity and regioselectivity compared to chemical synthesis, as the latter needs protecting group manipulations in glycosylation reactions. Chemoenzymatic synthesis is an efficient, mild, and environmentally friendly method for preparing HP, LMWH and ULMWH, which overcomes many of the challenges encountered in chemical synthesis (Baytas & Linhardt, 2020). An alternate strategy to prepare commercial HP is metabolically engineering by using Chinese hamster ovary cells (CHO) or *Escherichia coli* as manufacturing plant, since several enzymes required for the synthesis of HP can be expressed and controlled (Baik et al., 2012; Datta, Li, et al., 2013; Datta, Linhardt, & Sharfstein, 2013; Leyh, Taylor, & Markham, 1988). Moreover, CRISPR/Cas 9 technology can regulate the expression of the enzymes involved in the HP biosynthetic pathway by an efficient genome editing method (Cress et al., 2015). Thus, if the remaining HP biosynthetic enzymes can be actively expressed, it might be possible to produce the large-scale metabolically engineered HP. This would represent an important milestone work towards bioengineering HP with mammalian cells (Oduah, Linhardt, & Sharfstein, 2016).

3. Non-anticoagulant activities of HP in clinical applications

Based on its anticoagulant activity, HP is mainly used in clinical practice to prevent deep vein thrombosis, and pulmonary embolism. Additionally, the hypolipidemic effect of HP has long been reported (Lever, Smith, & Hurley, 1953; Pinter, Csergo, & Karady, 1957). Hyperlipidemia is a common metabolic disorder, which is a significant contributor to atherosclerosis, and acute pancreatitis risk (Hernandez et al., 2021). Growing evidence indicates HP and insulin can activate lipoprotein lipase, thereby reducing plasma triglyceride levels. It seems to be a safe, effective, and inexpensive treatment for hypertriglyceridemia-associated acute pancreatitis (Altinkaya & Aktas, 2021; Guo, Li, Zhang, & He, 2019; Joury et al., 2020). Extensive literature is available on the anticoagulant and hypolipidemic activities of HP. This review mainly focuses on the updated non-anticoagulant activities of HP and its derivatives its therapeutic activities in infectious disease, cancer, inflammatory disease, Alzheimer's disease (AD) and diabetic nephropathy (DN). A summary of several clinical applications of HP and its derivatives based on non-anticoagulant activities is shown in Table 2.

3.1. Heparin in infectious diseases

Infectious diseases remain a major health problem worldwide (Linder, Soehnlein, & Akesson, 2010), since new pathogens and virus variants are constantly emerging, due to the change of environment and climate. The first step in pathogen infection is to overcome a sophisticated defense which protecting their host targets (Kamhi, Joo, Dordick, & Linhardt, 2013). One significant connection between pathogens and host is heparan sulfate (HS), which is structurally similar to HP but with relative low degree of sulfation and IdoA content. Unlike HP, which is an exclusive product of mast cells, HS can be isolated from almost all animal cells and participates in a variety of physiological functions such as cell recognition, adhesion, signal transduction as well as in host-pathogen interactions. Many publications, including several reviews, demonstrate that several viruses, bacteria, and fungi infect the host firstly by binding HS on the host cell surface, receiving pathogens adhesion and invasion (Boyle et al., 2017; Chen et al., 2020; Clausen et al., 2020; Conzelmann et al., 2020; Fisher & Linder, 2017; Kamhi et al., 2013; Pomin, 2017; Shi et al., 2021; Skidmore et al., 2015; Wu et al., 2019). HP, a mimetic of HS, is a competitive inhibitor blocking the binding between the pathogen protein and HS on the host cell surface, suggesting its potential for clinical application in the treatment or prevention of infectious diseases. Of particular interest is the potential application of HP in COVID-19 treatment, as well as for other viruses, bacteria or parasites.

3.1.1. Heparin in COVID-19

Today, the antiviral activity of HP is being intensively studied for its role in the COVID-19, especially in patients suffering severe infections

Table 2
The summary of clinical application of heparin and its derivatives based on non-anticoagulant activities.

Disease area	Related diseases	Heparin-binding protein	Possible mechanisms	References
Infectious diseases	SARS-CoV-2, HSV, DENV, HPV16, HIV, Influenza virus, Zika virus, Adenovirus, *Mycobacterium tuberculosis*, Malaria, Lyme disease	Spike (Sp) glycoprotein, main protease, envelope protein, EGFR, HBP, Borrelia GAGs protein	1) Blocking pathogens adhesion and invasion by binding pathogens proteins; 2) Inhibiting pathogens replication; 3) Reducing of the formation of thrombosis by anticoagulant activity; and 4) Attenuating cytokines storm by anti-inflammatory activity.	(Clausen et al., 2020; Ennemoser et al., 2022; Jin et al., 2020; Lai, Goh, & Lee, 2020; Li, Zhang, Pang, & Li, 2022; Lin et al., 2020; Shi et al., 2021)
Cancer	Lung, colon, breast, hepatoma carcinoma, pancreatic, cervical, melanoma	Integrin, selectin, heparanase, galectin, VEGF, FGF, VEGF, CXCL12-CXCR4 axis	1) Inhibiting tumor cell proliferation, migration, invasion, and metastasis; 2) Preventing thrombosis, inhibiting inflammation and angiogenesis; 3) Preventing cancer relapse by inhibiting cancer stem cells; and 4) Enhancing the chemosensitivity of tumor cells.	(Atallah, Khachfe, Berro, & Assi, 2020; Chhabra et al., 2022; Du et al., 2019; Kaur, Deb, Diwan, & Saini, 2021; Ma et al., 2020)
Inflammatory diseases	Inflammatory bowel disease, bronchial asthma, arthritis, ulcerative colitis, pancreatitis, sepsis	Heparanase, selectin, HMGB1, CHs, IFNγ, IL-6	1) Inhibiting the activation and function of neutrophils; 2) Inhibiting the proliferation of vascular smooth muscle cells; 3) Blocking the expression of inflammatory factors; and 4) Suppressing inflammation by anticoagulant activity.	(Fu, Yu, Wang, Ma, & Li, 2022; Litov et al., 2021; Seffer et al., 2020)
Neurodegenerative diseases	Alzheimer's disease	Aβ, BACE1, Tau	1) Reducing inflammation; 2) Decreasing Aβ plaques by reducing Aβ production and accelerating its clearance; 3) Blocking bacterial and viral invasion; 4) Inhibiting tau phosphorylation; and 5) Reducing neurotoxicity.	(Mycroft-West et al., 2021; Stopschinski et al., 2020; Zhao et al., 2020)
Diabetic complications	Diabetic nephropathy	Heparanase, RAGE	1) Reducing inflammation; and 2) Maintaining the integrity of the glomerular basement membrane.	(Bignamini, Chebil, Gambaro, & Matuska, 2021; Myint et al., 2006)

associated with thrombotic events and organ damage (Qiu et al., 2021). At present, there are several benefits HP has demonstrated in patients with COVID-19 (Fig. 3) based on clinical data and experimental results.

Coagulopathy in COVID-19 infection is associated with high mortality (N. Tang, Li, Wang, & Sun, 2020). Accumulated evidence has suggested that treatment with LMWH or UFH could reduce mortality in critically ill COVID-19 patients, depending on its anticoagulant activity (Dutch & Thrombosis, 2021; Kyriakoulis et al., 2022; Poli et al., 2022; Tang et al., 2020; van Haren et al., 2022). The first evidence of the utility of HP as an anticoagulant in COVID-19 was posited by a retrospective report on 449 COVID-19 patients from Wuhan, China, where prophylaxis in medical patients was relatively uncommon due to a low incidence of venous thrombus embolism (VTE) (Zhai et al., 2019). In a nationwide cohort study of 4297 COVID-19 patients in the United States, when comparing the absence of anticoagulant with the administration of HP as prophylactic anticoagulant within the first 24 h, a relative risk reduction was observed (Rentsch et al., 2021). A multicenter, retrospective, observational study on COVID-19 patients in Italy showed that HP use was independently associated with reduction of mortality rates especially in patients older than 59 years of age (Poli et al., 2022). These clinical data provide strong real-world evidence to support guidelines recommending the use of prophylactic anticoagulant as initial treatment COVID-19 patients on hospital admission. Now, the International Society for Thrombosis and Hemostasis (ISTH) have guidance on detecting and treating coagulopathy in COVID-19 patients by using LMWH as early as possible for prophylactic anticoagulant to prevent thrombosis and organ damage (Thachil et al., 2020).

In addition to the anticoagulant activity of HP, the direct antiviral activity of HP is also of interest based on its binding to SARS-CoV-2 proteins, preventing viral adhesion and replication. SARS-CoV-2 enters a host cell by binding the angiotensin-converting enzyme 2 (ACE2) receptor on the respiratory epithelial cell through its surface-anchored trimeric spike (Sp) glycoprotein. It is noteworthy that HS acts as a co-receptor, promoting Sp-ACE2 interaction by interacting with its receptor-binding domain (RBD). HP and its analogues can be used as a bait receptor to bind this Sp protein, inhibit the binding of the virus to HS, and, thus, reduce virus attachment (Clausen et al., 2020; Mycroft-West, Su, et al., 2020; Zhang et al., 2020). A library of HP analogs and size-defined fragments have been prepared and used to probe the structural domain of this interaction. Results showed that binding of the RBD is more strongly dependent on the presence of 2*S* or 6*S* groups than on *N*S groups. A hexasaccharide is the minimum size required for secondary structural changes to be induced in the RBD (Mycroft-West, Su, et al., 2020). Next, SARS-CoV-2 replicates in host cells depending on its main protease (M(pro), also called 3CLpro) which cuts the viral precursor polyproteins. M-pro is another major target for antiviral drug design (Jin et al., 2020). A recent study showed that HP could strongly bind M-pro with a dissociation constants K_D of 17 and 32 μM at 25 and 35 °C, respectively. Also, HP inhibits the proteolytic activity of M-pro with an inhibition constant K_i of 7 nM and a half maximal inhibitory concentration (IC_{50}) of 8 ± 3 nM. This finding suggests that HP inhibits SARS-CoV-2 infection by blocking the viral replication (Li et al., 2022). It is worthwhile considering the rapid development of HP and its derivatives as first-line antiviral agents against SARS-CoV-2 and other members of the *Coronaviridae* (Mycroft-West, Su, et al., 2020).

Another noteworthy point is that HP has beneficial effects on inflammation associated with COVID-19. Studies found that "cytokine storm syndrome" usually occurred in patients with severe COVID-19, associated with severe lung tissue damage and disseminated intravascular coagulation (DIC) events. This event is triggered by the activation of interleukin 6 (IL-6), leading to a deadly systemic inflammatory disorder and life-threatening for COVID-19 patients (Contini, Enrica Gallenga, Neri, Maritati, & Conti, 2020). HP can bind several inflammatory cytokines reducing their level, inhibiting the activity of many adhesion molecules and heparanase, decreasing the adhesion and penetration of inflammatory cells into tissues, and promoting the release of nitric oxide by various pathways (Crijns, Vanheule, & Proost, 2020; Qiu et al., 2021). It has been reported that HP can directly dampen the pro-inflammatory transcription factor nuclear factor κB (NF-κB) signaling pathway in lipopolysaccharide (LPS) stimulated human endothelial cells and human monocytes (Li, Li, Shi, Yu, & Ma, 2020). This signaling pathway has been also involved in the pathogenesis of SARS-CoV, which caused the 2003 severe acute respiratory syndrome (SARS) epidemic (Kanzawa et al., 2006). Notably, a retrospective clinical study showed that LMWH could significantly decrease IL-6 level in COVID-19 patients' plasma, which is a key trigger in the "cytokine storm" associated with the severe symptoms of this disease (Shi et al., 2020). Recently, some hypotheses suggested that HP, as an anti-inflammatory reagent, has a potential use in treatment of COVID-19 associated myocarditis (Yu, 2022). Sun et al. observed that a heparin-binding protein (HBP), also known as cationic antimicrobial protein with a molecular weight of 37 kDa, increased in critically ill COVID-19 patients following disease aggravation. The correlation of HBP with COVID-19 deterioration suggests its pivotal role in systemic inflammatory response in patients with severe COVID-19 and highlights HBP as a disease indicator and a potential therapeutic target in COVID-19 disease (Xue et al., 2021).

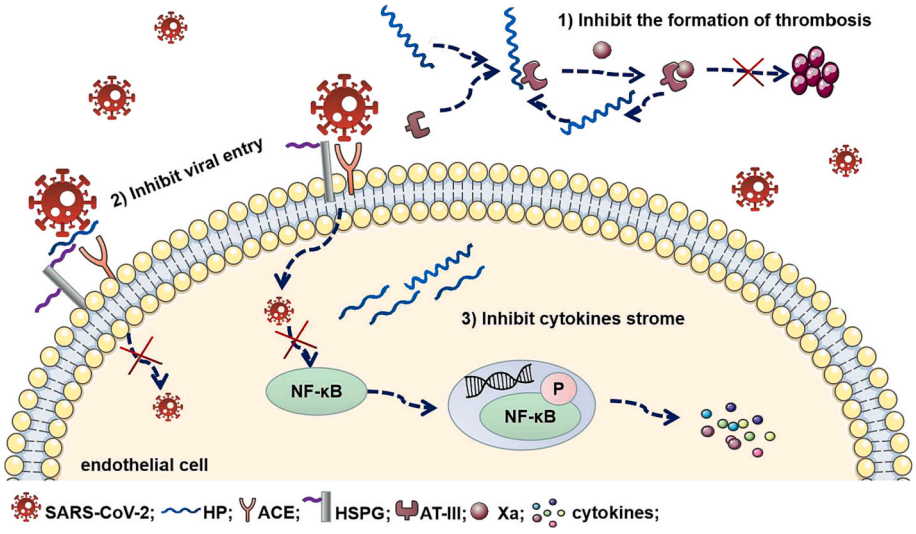

Fig. 3. Major approaches for heparin and its mimetics for treatment of COVID 19: 1) inhibition of the formation of thrombosis; 2) inhibition of viral entry; 3) inhibition cytokines storm.

In brief, HP has beneficial effects to patients with COVID-19 in multiple ways. The appropriate dose, time point of administration and the length of administration need to be further explored. It is suggested that a higher dose in some individuals with high body mass index are important to consider rather than the prophylactic dose used in most patients (Thachil, 2020).

3.1.2. Heparin in other infectious diseases

In addition to COVID-19, which is currently the focus of active research, HP and its derivatives have been also shown to inhibit host adhesion and invasion of various viruses, such as herpes simplex virus (HSV) (Copeland et al., 2008), dengue virus (DENV) (Lin et al., 2002), human papillomavirus 16 (HPV16) (Angeletti, 2017), human immunodeficiency virus (HIV) (Nassar, Browne, Chen, & Klibanov, 2012; Plochmann et al., 2012; Urbinati et al., 2021), influenza virus (Skidmore et al., 2015) and Zika virus (Ghezzi et al., 2017; Kim et al., 2019; Kim et al., 2017). Additionally, HP has a direct effect on viruses or bacteria. For example, HP can reduce iron levels in human macrophages and then inhibit *Mycobacterium tuberculosis* bacterial replication (Abreu, Essler, Loy, Quinn, & Giri, 2018). Ghezzi et al. found that HP can partially inhibit Zika virus replication, prevent Zika virus-induced cell necrosis and apoptosis, while showing no toxicity to uninfected cells (Ghezzi et al., 2017). HP may also protect infected cells from toxicity effects and cell death by the activation of cell survival signaling pathways. HP has an ability to protect non-infected human cells from programmed cell death (Hills et al., 2006).

Malaria is still a common infectious epidemic in tropical and subtropical regions of the world, causing of high morbidity and mortality. It is caused by infection with plasmodium parasites, usually transmitted through mosquito bites (Karnad et al., 2018; Marques et al., 2014). HP has antimalarial activity and can specifically bind *Plasmodium*-infected red blood cells (pRBCs) without binding non-infected erythrocytes (Leitgeb et al., 2011; Marques et al., 2014) and to circumsporozoites binding to the liver (Sinnis et al., 2007). Furthermore, based on its antimalarial activity, nanomedical applications of HP have been developed, such as those designed to deliver relevant drugs to the mosquito stages of malaria parasites (Alaez-Verson et al., 2017). Lyme disease (LD) is caused by the infection of spirochete *Borrelia burgdorferi sensu lato* (Bbsl). Once Bbsl is transmitted to human cells, it spreads to multiple organs and triggers a series of inflammatory reactions, leading to arthritis, carditis and neuroborreliosis (Steere et al., 2016). The binding recognition of Bbsl and GAGs on cell membrane is part of the initiation of LD. A non-anticoagulant product of HP named as NACH could block Bbsl attachment to mammalian cells and upregulate antibody immune responses to prevent LD (Lin et al., 2020).

Given that many bacteria or viruses bind to HP, it is possible to exploit such strategies to capture bacteria and viruses and remove them from the circulation by an extracorporeal medical device. The Seraph® 100 Microbind® Affinity Blood Filter is an extracorporeal hemoperfusion device, which core component is consisting of polyethylene beads with immobilized HP bound to it. This device has been approved for reducing and removing of pathogens from the bloodstream either as a single agent or as an auxiliary medical device to conventional anti-infective agents (Axelsson et al., 2010). This extracorporeal device can reduce viral load, for example, up to 87 % for Zika virus and 62 % for adenovirus in preclinical tests. Furthermore, SARS CoV-2 can also be reduced by the Seraph® 100 device *in vitro*. This application maybe considered as a possible adjutant therapy for seriously ill patients with COVID-19 (Seffer et al., 2020).

3.2. Heparin in cancer

The link between cancer and thrombosis could date back to 1865 when Armand Trousseau firstly described superficial thrombophlebitis as a precursor of mysterious visceral malignancy (Goubran, Burnouf, Radosevic, & El-Ekiaby, 2013). VTE is the most common thromboembolic complication of cancer-associated thrombosis (CAT). LMWH as anticoagulants have been used as a standard treatment for CAT for decades (Cosmi, 2020; Smorenburg & Van Noorden, 2001). Several reviews and meta-analysis data have concluded that besides cancer-related CAT, HP or its derivatives can directly impact the tumor biology in multiple ways such as tumor cell signaling, inflammation, angiogenesis, and metastasis through multiple mechanisms. Many growth factors, adhesions, chemokines, and enzymes are involved in these processes, such as heparanase, P-/L-selectin, and CXC chemokine ligand (CXCL)12-CXC chemokine receptor (CXCR)4 (Bobek & Kovarik, 2004; Bochenek, Puskulluoglu, & Krzemieniecki, 2013; Cheng et al., 2017; Falanga & Piccioli, 2005; Ma et al., 2020; Morla, 2019; Mousa & Petersen, 2009; Presta et al., 2003; Zacharski & Loynes, 2003). HP interaction with these mediators, ultimately triggers a cascade of biochemical responses and then affects tumor growth and invasion (Coombe & Gandhi, 2019; Du et al., 2019; Shi et al., 2021).

Heparanase is an endoglycosidase that can cleave HS or HP chains of proteoglycans and has been demonstrated as a valid drug target for cancer for several years. It is highly expressed in many malignant tumors, which is closely related to the occurrence and development of tumors and a poor prognosis (Coombe & Gandhi, 2019; Kaur et al., 2021; Lindahl & Li, 2020a). Many sulfated sugar molecules, including HP and its mimetics, have been identified to selectively inhibit heparanase expression (Lanzi, Zaffaroni, & Cassinelli, 2017; Ma et al., 2020). In addition to heparanase, fibroblast growth factors (FGFs) and vascular endothelial growth factor (VEGF) are also essential mediators of tumor angiogenesis and have been identified as attractive cancer targets (Kilarski & Bikfalvi, 2007). HP and its mimetics can bind FGF or VEGF and inhibit tumor angiogenesis, suggesting use as a viable therapeutic strategy for cancer treatment (Ellis & Hicklin, 2008; Rusnati & Presta, 2007). Furthermore, Duckworth et al. found that some chemically modified HP derivatives with non-anticoagulant activity could bind galectin 3 and block galectin 3 mediated cancer cell-endothelial adhesion and angiogenesis, without cytotoxicity. Galectin 3 is a metastasis promoter and is highly expressed in a variety of cancer patients. These 2- or 6-de-*O*-sulfated, *N*-acetylated HP derivatives can be used as potent galectin 3 inhibitors and have substantial potential applications in the development of anti-metastasis or anti-cancer drugs (Duckworth et al., 2015).

Now, over 50 clinical trials clinical trials are focused on the use of HP and HP-like molecules in oncology drug development (Atallah et al., 2020). However, despite promising experimental results, clinical trial results were unfavorable. In two randomized phase III lung cancer trials (RASTEN), the LMWH-adherent subgroup did not show statistically improved survival (Ek et al., 2018; Gezelius et al., 2019). These results were contradictory to another meta-analysis study of lung cancer in 2016, which showed that by administration of HP or LMWH as principal thromboprophylaxis, lung cancer patients without indication for anticoagulants have a distinct survival benefit, especially in limited-stage small-cell lung cancer (SCLC) (Yu, Lv, Zhang, Lan, & Dai, 2016). Another disappointingly negative result was the failure of the non-anticoagulant HP derivative necuparanib in Phase II pancreatic cancer trials (O'Reilly et al., 2017) despite good preclinical indicators (Mulloy, 2019).

PI-88, a HP mimetic, failed to meet the primary disease-free survival endpoint in a Phase III clinical trials for hepatoma carcinoma (HCC). Furthermore, PI-88 led to some common adverse effects related to bleeding, including thrombosis and thrombocytopenia (Atallah et al., 2020). Another promising HP mimetic is PG545, belonging to a second-generation version of PI-88 (Chhabra et al., 2022). Like other HP mimetics, PG545 interferes with several angiogenic factors (for example, VEGF and FGF) and inhibits heparanase expression, leading to immunomodulatory and antiangiogenic activity. In a Phase I study, PG545 showed a tolerable safety data and acceptable pharmacokinetic (PK) properties and gave evidence of stimulating immune cell and controlling disease progression in advanced solid tumors (Dredge et al., 2018). Now,

it is currently in Phase II clinical trials in combination with nivolumab (Clinical Trials.gov Identifier: NCT05061017) (Chhabra et al., 2022).

Above all, although plentiful studies indicate that HP and its derivatives are beneficial in the treatment of cancer, there is a need for an improved understanding of the underlying mechanisms (Ma et al., 2020), the development of HP mimetics with anti-tumor activity but having reduced anticoagulant activity, and the optimization of dosing (Mohamed & Coombe, 2017). More clinical studies on the anti-cancer effects of HP and its derivatives or the combination therapy of these with chemotherapy are needed in the future (Gezelius et al., 2018).

3.3. Heparin in inflammatory disease

Besides the anticoagulant properties of HP, it has also been recognized to have anti-inflammatory effects. Several reviews have summarized the anti-inflammatory properties of HP and its mimetics, which are mainly related to their interaction with various proteins such as complement system proteins, selectins and chemokines. These proteins have different functions to facilitate inflammation (Casu, Naggi, & Torri, 2010; Linhardt & Toida, 2004; Mousavi, Moradi, Khorshidahmad, & Motamedi, 2015; Poterucha, Libby, & Goldhaber, 2017; Severin et al., 2012; Yan et al., 2017; Young, 2008). Here, the application of HP and its derivatives in inflammatory diseases is discussed. Poterucha et al. systematically elaborated that HP exerted anti-inflammatory effects in multiple ways. HP can inhibit the activation and function of neutrophils and inhibit the proliferation of vascular smooth muscle cells (Gilotti et al., 2014). In addition, HP can interact with vascular endothelial cells to block the expression of inflammatory mediators involved in initiating and driving the activation of the innate immune system. Finally, HP suppresses inflammation through its anticoagulant activity (Poterucha et al., 2017). Multiples studies have shown that HP and its mimetics benefits patients with arthritis (Qi, Zhang, & Wang, 2016), inflammatory bowel disease (Baumgart, 2010; Malhotra, Bhasin, Shafiq, & Pandhi, 2004), bronchial asthma (Abdelaty & Abd-Elsalam, 2007; Bendstrup & Jensen, 2000; Ghonim et al., 2018; Shastri, Peterson, & Patel, 2017; Shute, Puxeddu, & Calzetta, 2018) and pancreatitis (Cai, Wang, Wang, Zheng, & Hu, 2020; Ceranowicz et al., 2008; Granell et al., 2003). CB-01-05-MMX (LMW HP MMX), is a novel oral Parnaparin sodium being developed for the potential treatment of ulcerative colitis. In a phase I and a phase IIb trial, CB-01-05-MMX showed an acceptable safety index without bleeding side-effect in patients with left-sided ulcerative colitis (Baumgart, 2010). The typical symptoms of asthma and chronic obstructive pulmonary disease (COPD) include chronic bronchial airway inflammatory response and mucus hypersecretion which lead to airflow blockage and breathing-related problems. Inhaled HP is a potential effective additional treatment in COPD and asthma that patients will benefit from anti-inflammatory and mucolytic effects of HP (Fath et al., 1998; Shute et al., 2018). In a retrospective analysis of 80 patients with high triglyceride acute pancreatitis, the effect of LMWH calcium combined with insulin was evaluated. Results showed that this combination drug therapy significantly regulated immune system function, improved hemorheology and coagulation function, which are clinically helpful to improve patient health (Cai et al., 2020).

Sepsis is defined as life-threatening organ dysfunction by a disordered host response to infection, which is usually triggered by Gram-negative bacteria. Today sepsis requires intensive attention due to its high mortality (Chen, 2021). HP interacts with numbers of pro-inflammatory factors and participates in procoagulant cascades to prevent inflammation and coagulopathy which are associated with sepsis (Derhaschnig et al., 2003; Li & Ma, 2017; Poterucha et al., 2017). For example, high mobility group box 1 protein (HMGB1) is a nuclear non-histone DNA-binding protein and can mediate inflammatory responses. The pro-inflammatory activity of recombinant HMGB1 is based on the formation of complexes with other mediators, such as LPS (Li, Ling, et al., 2015), which as a microbial product is involved in systemic inflammation syndrome in sepsis. One recent study indicated that HP could interfere HMGB1-LPS interaction and inhibit degradation activity of macrophage heparanase, resulting a significant anti-inflammatory effect in sepsis (Tang et al., 2021). Circulating histones (CHs), are a group of positively charged nucleoproteins, belonging to damage-associated molecules. CHs play a key role in sepsis by mediating inflammation response, organ injury and death by toll-like receptors or inflammatory signaling pathway (Allam, Kumar, Darisipudi, & Anders, 2014; Ibanez-Cabellos et al., 2018). Growing evidence has further suggested that HP and selectively desulfated HP could effectively bind to positively charged histones and attenuate histone induced inflammatory action (Hogwood, Pitchford, Mulloy, Page, & Gray, 2020; Wang et al., 2020). The selectively desulfated HP, with reduced anticoagulant activities, retains a high degree of effectiveness as an anti-histone agent. For example, an anti-thrombin affinity depleted heparin (AADH) without anticoagulant activity is purified from clinical grade HP, which can directly bound to histones and attenuate histone-mediated cytotoxicity *in vitro* and reduce mortality from sterile inflammation and sepsis in mouse models without increasing the risk of bleeding (Wildhagen et al., 2014). Moreover, oligosaccharides of HP or HS released by heparinase from the glycocalyx in sepsis might impact patient cognitive functions (Zhang et al., 2019). A therapeutic dose of UFH could protect glycocalyx from shedding by inhibiting inflammation in a septic shock model (Yini, Heng, Xin, & Xiaochun, 2015). LMWH is one standard supportive therapy for sepsis (X. Li & Ma, 2017). The efficacy and safety of LMWH in adult septic patients was explored by meta-analysis in 2021. Evidence indicated LMWH could improve multiple organ dysfunction syndrome (MODS) and reduce 28-day mortality rate of septic patients (Li, Liu, et al., 2021). Recently, a systematic review and meta-analysis of clinical efficacy of UFH in sepsis was undertaken in 2022. The 28-day mortality was relatively reduced by 16 % in the UFH group, without significant bleeding complications, which indicates the safety of UFH. Compared with LMWH, the role of UFH in sepsis is much more than just anticoagulation. It can interfere with NF-κB activation, inhibit chemokines and monocytes migration, enhance endothelial barrier function and angiopoietin axis (Fu et al., 2022).

The anti-inflammatory effect of HP is independent of its anticoagulant activity. Furthermore, the bleeding side effect associated with anticoagulation of HP can be an inherent drawback for it to act as an anti-inflammatory agent. Therefore, modification of HP to reduce or remove anticoagulant activity is an attractive strategy to improve its therapeutic potential in inflammatory disease (Li, Wan, et al., 2021).

3.4. Heparin in Alzheimer's disease

AD as a neurodegenerative disease is the leading cause of dementia and cognitive disorder with high morbidity and mortality in the elderly. The pathogenesis of AD is very complex and the progress of it is slow and irreversible, seriously impacting the lives of the elderly. Of note, two typical symptoms of AD widely recognized are the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs) within the brain. Due to the complex pathogenesis of AD, the current research and development of new drugs for AD is still full of challenges and difficulties, with little success. Snow and Wight in 1989 first hypothesized that heparin sulfate proteoglycans (HSPGs) are involved in initiating AD pathogenesis (Snow, Cummings, & Lake, 2021), which has been proven over the last decades. Now, evidence indicates that HSPGs play key roles in AD pathogenesis by leading to the formation of plaques and tangles, also helping bacteria and viruses entering cells. New studies suggest HP and related oligosaccharides as promising agents because of their multiple effects on the AD pathogenesis, such as decreasing amyloid peptide production and accelerating its clearance, inhibiting tau phosphorylation, and reducing inflammation (Bergamaschini, Rossi, Vergani, & De Simoni, 2009; Ma et al., 2007) (Fig. 4).

Enoxaparin has been reported to lower beta-amyloid (Aβ) plaque deposition and improve cognitive function in AD transgenic mice (Timmer et al., 2010) by decreasing amyloid precursor protein (APP)

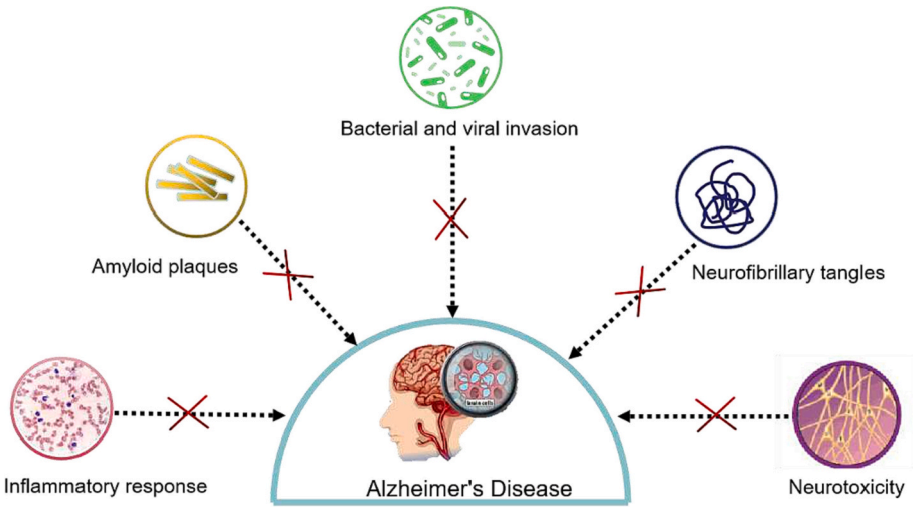

Fig. 4. The possible roles of heparin and its mimetics involved in Alzheimer's disease. 1) Reducing inflammation; 2) decreasing amyloid plaques by reducing amyloid peptide production and accelerating its clearance; 3) blocking bacterial and viral invasion; 4) inhibiting tau phosphorylation; and 5) reducing neurotoxicity.

processing *via* both α- and β-secretase pathways and Aβ production (Cui et al., 2011). In another AD murine model, Enoxaparin significantly reduced the number and the area of Aβ deposits and the total Aβ cortical concentration by reducing Aβ load, cytotoxicity and proinflammatory activity (Bergamaschini et al., 2004). Sain et al. suggested that long-term use of LMWH may delay the progression of cognitive impairment in AD patients, since it can directly reduce Aβ content in the blood and inhibit Aβ accumulation in the brain, and indirectly prevent complement activation (Sain, Kovacic, Radic, Ljutic, & Jelicic, 2012). It was found that HP oligosaccharides could pass the blood-brain barrier (BBB) and have neuroprotective capacity in AD experimental models by inhibit Aβ precursor protein secretion and HP binding to Aβ (Leveugle et al., 1998). In addition, the primary neuronal β-secretase, beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) is another key AD drug target. It is a rate-limiting enzyme to produce Aβ. The amyloidogenic APP are sequential proteolytic by BACE-1 and γ-secretase to produce series of Aβ peptides (Mycroft-West, Devlin, et al., 2020). Previous studies showed that HP could promote BACE1 cleavage in neuroblastoma cells and directly inhibit BACE1 activity *in vitro* by high-affinity binding of HP to the BACE1 zymogen (Beckman, Holsinger, & Small, 2006). Porcine intestinal mucosal HP, after modified at the principal positions with *O*-sulfo and *N*-sulfo/-acetyl groups could inhibit BACE-1 activities and attenuate cathepsin-D and renin activities, two other structurally related aspartyl proteases (Patey, Edwards, Yates, & Turnbull, 2006). Similarly, with in other diseases, the deployment of HP in AD treatment is largely limited by its considerable anticoagulant activity (Mycroft-West et al., 2019). An alternative approach is the acquisition of new HP analogues from marine sources, which could inhibit BACE1 without anticoagulant activity. Mycroft-West et al. successively isolated three marine-derived HS-containing GAG extracts from *Portunus pelagicus*, *Sardina pilchardus* and *Litopenaeus vannamei*, which could inhibit BACE1 activity and display a more favorable therapeutic effect *in vitro* compared with pharmaceutical HP (Mycroft-West et al., 2019; Mycroft-West et al., 2021; Mycroft-West, Devlin, et al., 2020). Tau aggregation is a key factor to cause neurodegeneration in AD and related tauopathies. HSPGs on the cell surface mediate the cellular uptake of tau aggregates, and these interactions can be interfered by HP. HP and HP oligosaccharides competitively inhibit cellular tau aggregates uptake and decrease tau-induced cell toxicity (Zhao et al., 2020). Recently, a HP-like oligosaccharide SN7–13 with similar pentasaccharide units was generated, which could bind to tau protein and block its cellular uptake and inhibit cellular tau aggregate. These activity data are similar to standard porcine HP, but without anticoagulant activity. This synthetic HP oligosaccharide may have potential application in the development of agents to treat tauopathy (Weiss, Niecestro, & Raz, 2007).

3.5. *Heparin in diabetic nephropathy*

Diabetic nephropathy (DN) is a major microvascular complication in diabetic patients and an important cause of morbidity and mortality. Clinical reports indicated that sulodexide, a low molecular weight GAGs, can significantly diminish proteinuria in DN patients, even when these patients are receiving either an ACE inhibitor or angiotensin receptor (ATR) antagonist (Stopschinski et al., 2020), which indicates sulodexide has a renal protection effect (Li, Xing, et al., 2015). One hypothesis is that sulodexide as a heparanase inhibitor, prevents degradation of HS on glomerular capillary wall and, thus, restores ionic permselectivity of glomerular basement membrane (GBM). Two clinical trials are currently being conducted to investigate whether sulodexide has renal protection in DN (Lewis & Xu, 2008). The chemical and anatomic remodeling is induced by exogenous GAGs in renal tissues (Abaterusso & Gambaro, 2006). Of note, HP or LMWH can inhibit inflammatory responses in diabetic glomeruli (Abbadi et al., 2020; Wang, Ren, Wang, & Hascall, 2014). In a rat model of diabetes mellitus-induced glomerulosclerosis, by daily administration of a modified HP with low anticoagulant activity, the glomerular and tubular matrix accumulation is prevented, the expression of transforming growth factor beta TGF-β1 and albuminuria also decrease. These results indicate GAG therapy has potential for the prevention of diabetic glomerulosclerosis by inhibiting TGF-β1 overexpression (Ceol et al., 2000). One effective therapy of development of DN drugs is directed towards the identification of the key molecular target. Studies found that the degree of kidney injury was proportional to advanced glycation end products (RAGE) gene content. LMWH can bind RAGE and act as an antagonist to RAGE, and then significantly prevent albuminuria, increase glomerular cell number and mesangial expansion in a dose-dependent manner, suggesting RAGE antagonists as a useful remedy in the treatment of DN (Myint et al., 2006).

4. Conclusion and future perspectives

As a first-line anticoagulant, HP has been used for >100 years. Even with a wave of new anticoagulants (Montoya & Gajra, 2012), HP as a very viable drug, has shown new and unexpected therapeutic effects in several other diseases besides as an anticoagulant (Alaez-Verson et al., 2017), such as in cancer, infectious disease, inflammatory related disease, and AD (Cassinelli, Torri, & Naggi, 2020). These activities are closely related to the high electronegativity and structural diversity of HP, which make it bind multiple disease-related proteins, selectin,

inflammatory factors, and proteases, and then act as key modulators during cell adhesion, migration, proliferation, and differentiation. During novel Coronavirus treatment, a disease that is still prevalent worldwide, the direct antiviral activity and anti-inflammatory activity of HP have again gained attention. At present, several preclinical and clinical studies on non-anticoagulant HP are ongoing. However, several limiting factors and challenges need to be carefully considered in these clinical trials. First, the strong anticoagulant activity of HP accompanied by side effects hinders the development and utilization of HP as non-anticoagulant drugs, such as bleeding and thrombocytopenia, osteoporosis, skin lesions, alopecia and the elevation of hepatic enzymes (Onishi, St Ange, Dordick, & Linhardt, 2016). Second, the complicated mechanism of HP involved in cancer, AD and other diseases requires further elucidation. The dosage and duration of administration, standard and reasonable study protocols, and the exact dose-response relationship need to be investigated for effectively designing clinical therapy by HP and its derivatives (Ripsman et al., 2020). Third, due to the chemical properties and sources of HP, the safety, quality stability, bioavailability, administration methods, and interactions with other drugs of HP and its derivatives should be fully considered before its clinical application. Fourth, since heparin is a generic drug, there is limited financial incentive to expand its use in other applications. It is noteworthy that new structurally HP and its derivatives are constantly emerging with the fast developments of synthesis, biotechnology, and metabolic engineering (Baytas & Linhardt, 2020). The strategies for creating “designer” HP and its mimics with novel therapeutic potentials will undoubtedly be achieved in the future.

CRediT authorship contribution statement

Peipei Wang: Writing – original draft. **Lianli Chi:** Writing – review & editing. **Zhenqing Zhang:** Writing – review & editing. **Hongmei Zhao:** Writing – review & editing. **Fuming Zhang:** Writing – review & editing. **Robert J. Linhardt:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgement

This work was supported by the project was Supported by Open Projects Fund of Shandong Key Laboratory of Carbohydrate Chemistry and Glycobiology, Shandong University (2021CCG03) and GlycoMIP a National Science Foundation Materials Innovation Platform funded through Cooperative Agreement DMR-1933525.

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