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Alleviation of Oxidative Stress during Hemodialysis Sessions by Hemodialysis Membrane Innovation: A Multidisciplinary Perspective

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Abstract
Oxidative stress is prevalent in end-stage kidney disease patients receiving chronic hemodialysis and is associated with heavy cardiovascular disease burdens and increased mortality risks. Hemoincompatible hemodialysis membranes per se contribute to the activation of oxidative reactions and the generation of oxygen free radicals. Since the early 1990s, vitamin E-coated membranes have been extensively used in hemodialysis patients to reduce oxidative stress during hemodialysis sessions. However, the beneficial effects of vitamin E-coated membranes versus unmodified synthetic membranes on long-term patient-centered outcomes, such as survival, quality of life, and prevalence of cardiovascular diseases, remain controversial. Accordingly, novel antioxidant hemodialysis membranes were prepared to replace the use of vitamin E-coated membranes despite the translational research on these membranes unfortunately coming to a standstill. In this review, we first summarize the state-of-the-art on the use of vitamin E-coated membranes in hemodialysis patients to highlight their strengths and limitations. Then, we discuss the latest advances in fabricating antioxidant hemodialysis membranes and provide perspectives to bridge knowledge gaps between laboratorial investigations and clinical practice in fabricating antioxidant hemodialysis membranes.

Introduction

Hemodialysis is the most common modality of renal replacement therapy for patients with end-stage kidney disease (ESKD) worldwide [1, 2]. Hemodialysis membranes are major components of a hemodialysis session at the interface of the patient's blood and dialysate fluid for controlling solute exchange [3]. Although much progress has been made in the field of hemodialysis membrane manufacturing during the past half-century, patients receiving long-term hemodialysis still suffer from increased oxidative stress and chronic inflammation, which

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have been implicated in the pathogenesis of cardiovascular disease, anemia, and malnutrition [4]. In fact, the heavy cardiovascular disease burden and the increased mortality risk of hemodialysis patients are at least partially explained by severe oxidative stress seen in these patients [5]. Growing evidence has shown that oxidative stress is prevalent in hemodialysis patients owing to increased generation of reactive oxygen species (ROS) and impaired antioxidant defense mechanisms in these patients [5]. More importantly, hemoincompatible hemodialysis membranes per se contribute to the activation of oxidative reactions and the generation of oxygen-free radicals [4, 6]. Despite extensive improvements in hemodialysis membranes, multiple forms of ROS remain at increased levels and cannot be eliminated by high-flux polysulfone membranes [7]. During hemodialysis, the contact of blood with artificial hemodialysis membranes can significantly activate neutrophils to produce proteolytic enzymes and ROS in amounts that impair neighboring tissues/cells, evoke an inflammatory response, and cause subsequent lipid peroxidation [8]. It was therefore hypothesized that the type of dialyzer membrane may play a pivotal role in alleviating oxidative stress.

The lipophilic antioxidant radical scavenger vitamin E (α-tocopherol) has been used since the early 1990s as a blood surface modifier of cellulosic and synthetic polysulfone membranes with the ultimate goal of neutralizing harmful reactive species and endowing hemodialysis membranes with antioxidant bioactivity [9]. During the past 3 decades, the efficacy and safety of hemodialysis with vitamin E-coated membranes have been extensively studied in a large number of clinical studies [10]. However, the beneficial effects of these membranes versus unmodified synthetic membranes on long-term patient-centered outcomes, such as survival, quality of life, and prevalence of cardiovascular diseases, remain controversial [4]. Thus, the routine use of vitamin E-coated membranes in maintaining hemodialysis patients is not recommended by any clinical guideline.

On the hand, there has been much progress in the design and fabrication of novel antioxidant hemodialysis membranes (AHMs) aiming to reduce ROS generation during hemodialysis sessions [11]. The hemocompatibilities and antioxidant bioactivities of these novel membranes were well characterized in vitro. Nevertheless, subsequent translational research on these membranes unfortunately comes to a standstill. Obliviously, there are significant knowledge gaps between laboratory investigations and clinical practice in the development of AHMs. In this review, we aim to summarize the state-of-the-art on the use of vitamin E-coated membranes in hemodialysis patients, to discuss the latest advances in fabricating AHMs, and most importantly, to provide perspectives to bridge knowledge gaps between laboratorial investigations and clinical practice in this field.

Current State-of-the-Art on the Use of Commercial Vitamin E-Coated Membranes in Hemodialysis Patients

Vitamin E-Coated Membranes for ROS Scavenging and Inflammation Alleviation

Vitamin E is a lipophilic antioxidant and can be coated on hemodialysis membranes with a site-specific effect on ROS [4]. Yang et al. [12] found that a vitamin E-coated EE18 Excerbrane membrane (Terumo Co., Shibuyaku, Japan) per se reduced lipid peroxidation and protected erythrocytes from oxidative stress in dialysis patients. The use of the Excerbrane® membrane also resulted in a significant decrease in ROS formation by 50% in whole blood. In another prospective, controlled, observational cohort study, Kirmizis et al. [13] demonstrated that the vitamin E-coated Clirans® E hollow fiber dialyzer (Terumo Co., Shibuyaku, Japan) resulted in a significant increase in total antioxidant status and a decrease in thiobarbituric acid reactive substances and oxidant low-density lipoprotein (ox-LDL). Meanwhile, the vitamin E-coated membrane also displayed an anti-inflammatory effect, as evidenced by a significant decline in the pro-inflammatory cytokines C-reactive protein and interleukin-6 compared with baseline after the use of the vitamin E-coated membrane for 6 months. Similar results were also observed in 62 dialysis patients who received chronic hemodialysis with a vitamin E-coated polysulfone (PSF) membrane (Asahi Kasei Kuraray Medical Co. Ltd, Tokyo, Japan) for 6 months [14]. In another study enrolling 46 hemodialysis patients, the use of vitamin E-coated PSF membranes was found to lower levels of oxidative DNA damage (assessed by lower levels of oxidized DNA bases) than conventional PSF membranes after a 6-month follow-up, suggesting a protective effect of vitamin E-coated PSF membranes on genomic and DNA oxidative damage levels [15]. Accordingly, a meta-analysis showed that vitamin E-coated HMs were competent to decrease oxidative stress biomarkers such as thiobarbituric acid reactive substances and ox-LDL and pro-inflammatory cytokines such as C-reactive protein and interleukin-6 [16].

In summary, both cellulosic and synthetic membranes coated with vitamin E were found to suppress oxidative stress and chronic inflammation in dialysis patients.

However, no clinical trial has been conducted to compare the difference in the antioxidant and anti-inflammatory properties between the two kinds of hemodialyzers thus far. It is also noteworthy that there are no data showing the protective effect of vitamin E-coated hemodialysis membranes on patient-centered outcomes, including mortality and major cardiovascular events. Therefore, clinical trials with larger sample sizes and longer follow-up periods are required to determine whether the use of vitamin E-coated HMs is associated with improved long-term outcomes of dialysis patients.

Vitamin E-Coated Membranes for Anemia Management

Oxidative stress and chronic inflammation contribute to the pathogenesis of resistance to erythropoietin and anemia [17]. As discussed above, vitamin E-coated membranes can significantly scavenge ROS and improve total antioxidant status as well as red blood cell antioxidant status in dialysis patients [18]. Growing evidence also shows that vitamin E-coated membranes can prolong erythrocyte lifespan, reduce erythrocyte fragility, and alleviate erythrocyte deformability dysfunction during hemodialysis [19, 20]. Accordingly, several clinical studies have been conducted to investigate whether vitamin E-coated membranes could improve anemia in patients receiving long-term hemodialysis.

Panichi et al. [14] reported, in a crossover randomized study on 37 hemodialysis patients, that a vitamin E-coated polysulfone membrane (ViE, Asahi Kasei Kuraray Medical Co. Ltd, Japan) could remarkably decrease the erythropoietin resistance index from 9.17 to 8.8 and thus lead to a significant increase in hemoglobin level from 11.2 ± 0.3 to 11.9 ± 0.3 g/dL ($p < 0.05$). These findings are consistent with those from other reports by Mandolfo et al. [21] and Locatelli et al. [22] that vitamin E-coated HMs were associated with a reduced erythropoietin resistance index and erythropoietin requirement in Italian hemodialysis patients. In contrast, a multicenter prospective randomized controlled study conducted in a Japanese population found no significant difference in the overall relative erythropoiesis resistance index between vitamin E-coated dialyzers and conventional polysulfone dialyzers at 12 months, although a subsequent exploratory subgroup analysis demonstrated that vitamin E-coated dialyzers showed a better relative erythropoiesis resistance index in patients with higher baseline hemoglobin levels [23]. Likewise, another randomized controlled trial enrolling 260 prevalent hemodialysis patients also concluded that the use of vitamin E-coated membranes appears not to be associated with improvements in erythropoiesis-stimulating agent responsiveness [24]. Most recently, a meta-analysis concluded that the use of vitamin E-coated membranes could only lower erythropoietin resistance but could not improve total hemoglobin levels [10]. Taken together, the general impact of vitamin E-coated membranes on anemia control remains inconclusive. High-quality trials with hard clinical endpoints are thus required to fully clarify the clinical value of vitamin E-coated membranes for anemia management in ESKD patients.

Vitamin E-Coated Membranes for Heparin-Free Hemodialysis

In addition to antioxidant and anti-inflammatory effects, vitamin E-coated membranes might also be an alternative to conventional dialysis with systemic heparinization in patients at high risk of bleeding or those with heparin-induced thrombocytopenia. For instance, Huraib and colleagues found that membrane clotting and heparin requirements in the vitamin E-coated membrane group were less than those in the low-flux cellulose membrane group [25]. Likewise, a small prospective study also showed that vitamin E-coated membranes (ViE, Asahi Kasei Kuraray Medical Co. Ltd, Japan) contributed to reducing the administration dose of low-molecular-weight heparin (LMWH) in seven pediatric dialysis patients. The LMWH dose during the 1st week was 110 IU/kg ± 18 (defined as 100%); in the 2nd week, the dose was 77 IU/kg ± 12 (70%); in the 3rd week, the dose was 33 IU/kg ± 5 (30%); and in the 4th week, anticoagulation could even be stopped in 1 patient [26]. In another multicenter, randomized, crossover study, Islam et al. [27] enrolled 32 adult long-term hemodialysis patients from two French hemodialysis units to evaluate the noninferiority of vitamin E-coated versus heparin-coated dialyzers in 4-h heparin-free hemodialysis sessions. The primary outcome was the percentage of successful study periods, defined as no circuit-clotting event leading to premature interruption of any dialysis sessions. Their results showed that the percentage of success with vitamin E-coated dialyzers (25/32 study periods [78%]) was not inferior to that with heparin-coated dialyzers (26/32 study periods [81%]). Using visual inspection of dialyzer membrane status, the authors further observed less clotting with the vitamin E-coated dialyzer than with the heparin-coated dialyzer.

Notably, it remains essential to consider the place of vitamin E-coated membranes in the broader context of currently available heparin-free dialysis techniques, such as regional citrate anticoagulation (RCA) and predilution hemodiafiltration. Owing to its safety and efficacy, RCA has been widely adopted in clinical practice for both critically ill and hemodialysis patients at high risk of bleeding and filter clotting [28–30]. However, the utilization of RCA is not devoid of challenges. Its complex protocol requires constant monitoring and oversight by trained staff to avoid potential metabolic alkalosis and severe hypocalcemia, which may pose operational hurdles, particularly in resource-

constrained settings [31]. In contrast, vitamin E-coated membranes may provide a less complex alternative without a risk of homeostasis disturbance and could be more widely applied in various clinical settings.

Predilution hemodiafiltration is another feasible technique for heparin-free hemodialysis [32]. However, its effectiveness in anticoagulant-free hemodialysis sessions remains unsatisfactory. For instance, Krummel et al. [33] observed more premature clotting in predilution hemodiafiltration than in conventional heparin-free hemodialysis. Another study by Brunot et al. [32] also found no significant differences in the duration of the sessions and in dialyzer clotting between the predilution HDF group and the conventional hemodialysis group after propensity score matching. Accordingly, vitamin E-coated membranes remain a promising alternative to predilution hemodiafiltration for heparin-free dialysis due to their noninferiority to heparin-coated membranes. However, further exploration into the safety, efficacy, and mechanism of action of vitamin E-coated membranes in heparin-free dialysis sessions is of paramount importance.

Vitamin E-Coated Membranes for Critically Ill Patients with Acute Kidney Injury

The potential role of vitamin E-coated membranes in critically ill patients with acute kidney injury deserves particular attention. Despite a lack of clinical evidence, Hatanaka et al. [34] evaluated the efficacy of blood purification therapy with vitamin E-coated polysulfone membranes in a mouse model of lipopolysaccharide-induced systemic inflammation [35]. Their results indicated that the use of vitamin E-coated membranes led to an increased survival rate, reduced lung injury, and decreased infiltration of inflammatory cells compared to conventional polysulfone membranes, suggesting the potential applicability of vitamin E-coated membranes in treating severe systemic inflammation. However, large-scale clinical trials are needed to further validate the efficacy and safety of vitamin E-coated membranes in patients with acute kidney injury.

Vitamin E-Coated Membranes for Patients Receiving Hemodialysis with Ultrapure Dialysate or Extended Hemodialysis

The utility of vitamin E-coated membranes in patients receiving hemodialysis with on-line produced ultrapure dialysate or extended hemodialysis may offer another promising direction for future research. Ultrapure dialysate is reverse osmosis-treated water with minimal bacterial and endotoxin contamination (≥100 CFU/L, endotoxin LAL <0.03 EU/mL) [36]. Studies have shown that ultrapure dialysate can reduce markers of inflammation and oxidative stress, improve iron utilization, and enhance the erythropoietin response in chronic hemodialysis patients [37, 38]. Currently, there is a lack of research on the utility of vitamin E-coated membranes in hemodialysis patients receiving on-line produced ultrapure dialysate. We speculated that there is potential that these membranes could amplify the beneficial effects of ultrapure dialysate by further reducing oxidative stress and inflammation. Additionally, they may also mitigate the impact of contamination when ultrapure dialysate is compromised or does not meet standards.

Vitamin E-coated membranes have also recently been used for expanded hemodialysis [39]. In a small prospective study, Maduell et al. [40] found that the removal of medium-sized solutes, such as myoglobin, kappa-free immunoglobulin light chains, prolactin, and α1-microglobulin, in expanded hemodialysis with the vitamin E-coated membrane (Vie-18X, Asahi) was significantly higher than that in high-flux hemodialysis. Theoretically, hemodialysis patients may benefit from the greater removal of such medium-sized uremic toxins. However, the advantage of expanded hemodialysis with vitamin E-coated membranes in patient-centered outcomes against conventional high-flux dialysis warrants investigation in future large-scale, randomized controlled trials.

Barriers to Broad Clinical Adoption of Vitamin E-Coated Membranes

Despite these promising potentials, it is essential to note the obstacles to the broad clinical adoption of vitamin E-coated membranes. Currently, large-scale, randomized controlled trials to confirm their positive effect on patient-centered outcomes for dialysis patients, such as mortality and major cardiovascular events, are lacking [16]. In this regard, the broad use of vitamin E-coated dialysis membranes may be hindered by their higher cost than their uncoated counterparts, particularly in resource-limited settings. Additionally, discrepancies across different manufacturers pose challenges in establishing stringent standards and quality control systems to ensure expected survival benefits from all vitamin E-coated membranes made by different manufacturers. To address these obstacles, concerted efforts in scientific investigation and policy-making are needed from biomaterial scientists, industrialists, and nephrologists to fully utilize the potential benefits of vitamin E-coated membranes for chronic dialysis patients.

State-of-the-Art Laboratory Investigations of AHMs

Despite a lack of solid evidence of survival benefit by vitamin E-coated membranes in clinical hemodialysis, the development of novel AHMs has become a

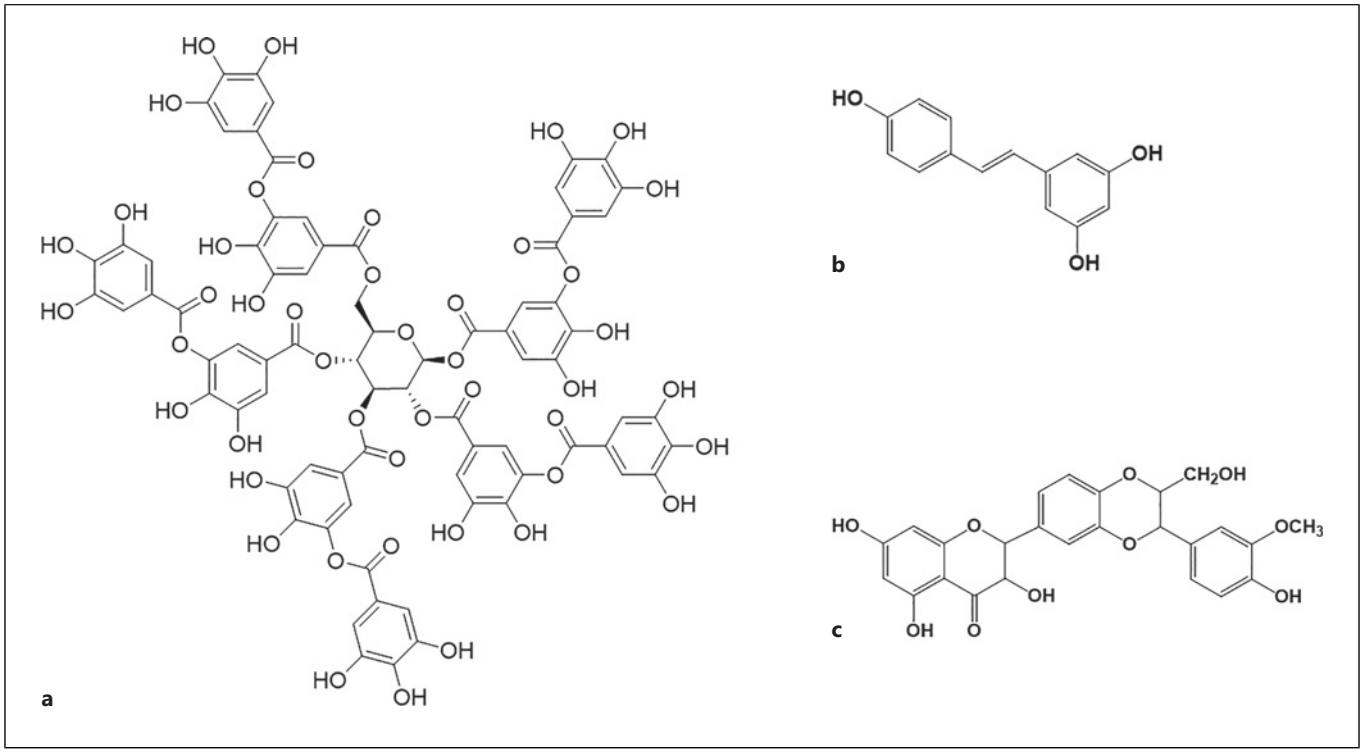

Fig. 1. Chemical structures of tannic acid (**a**), resveratrol (**b**), and silibinin (**c**).

major research topic in the field of membrane manufacturing during the past decade. Generally, various antioxidant molecules or enzymes, such as natural polyphenols, alpha-lipoic acid (ALA), and conjugated linoleic acid (CLA), have been used to modify polysulfone or polyethersulfone (PES) membranes to enhance their antioxidant capacities. In this section, we discuss the latest laboratory advances in fabricating novel AHMs.

Natural polyphenols are secondary metabolites of plants [41]. Most polyphenols share a typical structural characteristic with a common intermediate or a close precursor. First, they occur in conjugated forms, with one or more sugar residues linked to hydroxyl groups, but direct linkages of the sugar to an aromatic carbon also exist [41]. Linkage with other compounds, such as amines, carboxylic and organic acids, and lipids, was also common [42]. A large number of previous reviews have reported the multiple biological activities of polyphenols, such as antioxidant, anti-inflammatory, antiaging, cardioprotective, antitumor, and antimicrobial effects [42–44]. Accordingly, natural polyphenols, such as tannic acid (TA), resveratrol, and silibinin, have been widely used to modify hemodialysis membranes to suppress oxidative stress during hemodialysis sessions. Figure 1 further shows the chemical structures of TA, resveratrol, and silibinin.

TA-Modified Membranes

TA is a naturally occurring antioxidant polyphenol that is composed of a central glucose molecule derivatized at its hydroxyl groups with one or more galloyl residues [45]. Early in the 2010s, Gulcin and colleagues found that TA inhibited 97.7% lipid peroxidation of linoleic acid emulsion at 15 μg/mL concentration, with effective 2,2-Diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) scavenging, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate) ($ABTS^{\bullet+}$) scavenging, superoxide anion radical ($O_2\cdot^-$) scavenging, and hydrogen peroxide (·OH) scavenging [45]. The unique properties of TA come from its pinwheel structure, which makes its many phenol groups available for molecular interactions [46]. Recently, TA-based biomaterials have been widely used in multiple biomedical scenarios, such as tumor therapeutics, antimicrobial applications, and wound and bone tissue regeneration [47, 48]. Meanwhile, TA-based metal-phenolic nanozymes have also been incorporated into microspheres as promising hemoperfusion adsorbents for the alleviation

of oxidative stress during extracorporeal blood purification sessions [49, 50].

Currently, TA is the most commonly used modifier for the preparation of hemodialysis membranes with antioxidant properties. TA can be stably and easily fixed on PES membrane surfaces through a mussel-inspired strategy that is mediated by hydrophobic interactions and hydrogen bonding [51]. For instance, Chen et al. [52] successfully incorporated a TA coating onto a PES hollow fiber membrane and then introduced poly(2-ethyl-2-oxazoline) (PEtOx) brushes to the membrane surface through the Michael addition reaction between TA and PEtOx brushes. On the one hand, the TA/PEtOx-functionalized PES membrane could effectively eliminate ROS, increase serum antioxidant levels, inhibit lipid peroxide and glycation product generation, and attenuate H_2O_2-induced oxidative damage to cardiomyocytes and vascular endothelial cells. On the other hand, the functionalized membrane exhibited decreased protein adsorption, anaphylatoxin generation, and platelet adhesion compared with the pure PES membrane owing to the introduction of hemocompatible PEtOx brushes on membrane surfaces. In another work by the same research group, a heparin layer was further immobilized onto a TA/PEtOx-functionalized PES hollow fiber membrane to enhance its anticoagulant property. The results showed that the TA/PEtOx/heparin-functionalized PES membrane could effectively inhibit the activation of the coagulation cascade because it had a significantly longer activated partial thromboplastin time than the unmodified PES or TA/PEtOx-functionalized PES membrane [53]. Similarly, biocompatible poly(N-acryloyl morpholine) molecules could also be immobilized onto the TA-functionalized PES hollow fiber membrane through hydrogen-bonded layer-by-layer assembly technology [54]. Furthermore, the introduction of a TA layer on the PES membrane significantly contributed to an increase in hydrophilicity, pure water flux, and water-soluble uremic toxin clearance of TA-functionalized PES membranes [51, 55–57].

It should be noted that although most TA-functionalized hemodialysis membranes show excellent hemocompatibility, as evidenced by reduced plasma protein adsorption, platelet adhesion, and complement activation in in vitro studies [52, 56], the safety of such membranes has never been tested in in vivo animal experiments or clinical trials. A majority of researchers overlooked the effect of TA leakage from modified hemodialysis membranes, an inherent limitation of TA coating through a mussel-inspired strategy, on the structure and function of blood cells and proteins. In fact, the hemocompatibility and cytocompatibility of TA also depend on the concentration of TA in the blood. At a high concentration of 100 μg/mL, TA could significantly lead to crinkling and hemolysis of erythrocytes, changes in fibrinogen conformation and destruction of coagulation function [58]. In most cases, the concentration of TA used for membrane modification is as high as 2 mg/mL during the process of membrane manufacturing, making it very important to determine the amount of TA leak from TA-modified hemodialysis membranes in future works. Ultimately, a systemic efficacy and safety evaluation of the TA-modified hemodialysis membranes should be performed in in vivo animal experiments or clinical trials to accelerate their clinical applications.

Resveratrol-Blended Membrane

Resveratrol, a bioactive polyphenol secreted by at least 100 different plants, has a number of functional properties, including antioxidant, anti-inflammatory, platelet aggregation and activation inhibition, antiaging, and antidiabetic properties [59]. Qi et al. [60] first prepared a polysulfone/resveratrol blend membrane using an immersion precipitation phase inversion method. Their results showed that the resveratrol-modified polysulfone membrane had good removal effects on $DPPH^{\bullet}$, $ABTS^{\bullet+}$, O_2^-, OH, and H_2O_2 radicals, high inhibition of lipid peroxidation, and long-term high antioxidant stability (at least 60 days). The $DPPH^{\bullet}$, $ABTS^{\bullet+}$, O_2^-, OH, and H_2O_2 radical scavenging rates of the blended membrane were 79.98%, 98.52%, 44.89%, 57.55%, and 70.76%, respectively. In a simulated dialysis experiment, the resveratrol-modified polysulfone membrane removed 90.33% of urea, 89.50% of creatinine, 74.60% of lysozyme and maintained over 90.47% of bovine serum albumin. These encouraging results suggested that the resveratrol-modified polysulfone membrane is a potential alternative to commercial hemodialyzers for alleviating oxidative stress during hemodialysis sessions. However, the efficacy and safety of such a membrane should be further evaluated in in vivo animal experiments and clinical studies in the future.

Silibinin-Blended Membrane

Silibinin, the predominant and primary active ingredient in silymarin, was identified as the first member of a new family of natural compounds called flavonolignans in 1959 [61]. As with TA and resveratrol, silibinin can exert its antioxidant properties by directly scavenging free radicals such as hypochlorous acid, O_2^-, and H_2O_2 by inhibiting specific enzymes responsible for free radical production or by maintaining the optimal redox status of cells [61]. The antioxidant activity of silibinin has been extensively studied in various cell lines, animal models,

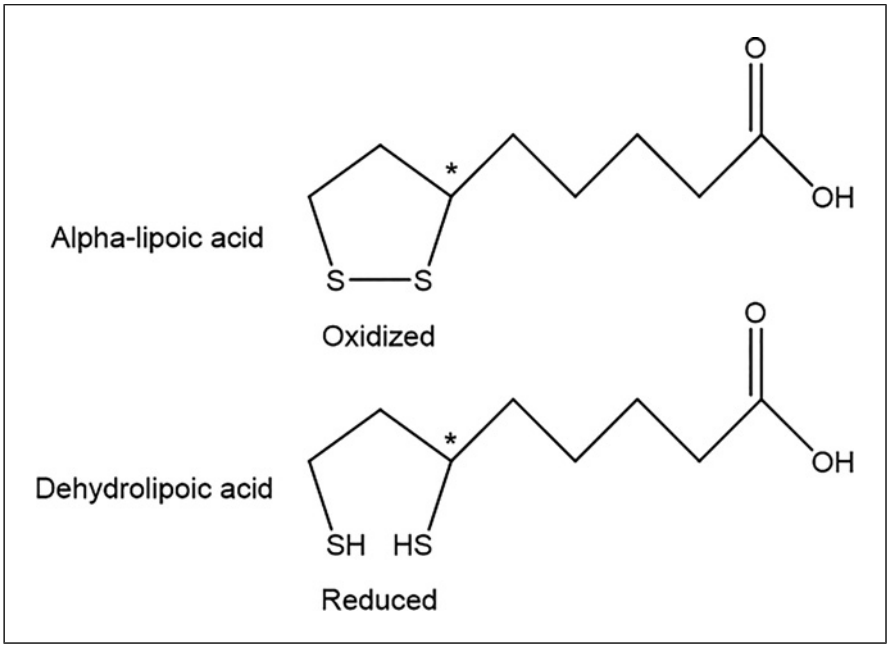

Fig. 2. Chemical structure of alpha-lipoic acid and dihydrolipoic acid.

and human beings thus far [62–64]. Accordingly, silibinin is a potential natural antioxidant for modifying hemodialysis membranes to suppress hemodialysis-induced oxidative stress.

Yang et al. [65] successfully prepared a polysulfone/silibinin blend membrane using an immersion precipitation phase inversion method. The results showed that the optimal polysulfone/silibinin blend membrane showed significantly higher DPPH$^{\bullet}$ and ABTS$^{\bullet+}$ free radical scavenging abilities than the unmodified polysulfone membrane, with high scavenging rates of 90.5 ± 1.7% and 99.7 ± 1.3% for DPPH$^{\bullet}$ and ABTS$^{\bullet+}$, respectively. Interestingly, the polysulfone/silibinin blend membrane could also maintain its antioxidant property for 90 days. In the simulation hemodialysis experiment, small (urea) and medium-sized molecules (lysozyme) were effectively removed (53.40% and 42.60%, respectively) by the polysulfone/silibinin blend membrane, while bovine serum albumin was well preserved (~93%). Therefore, the authors concluded that the polysulfone/silibinin blend membrane could alleviate oxidative stress in patients during each hemodialysis session and have potential hemodialysis applications in the future.

ALA-based AHMs

ALA, an organosulfur component produced from plants, animals, and humans, is a universal antioxidant that can act as a metal chelating agent, free radical scavenger, and regenerator of endogenous antioxidants (namely, glutathione and vitamins C and E) [66]. As shown in Figure 2, two reduced or oxidized thiol groups are present in the small molecule ALA. The oxidized form is known as ALA or simply lipoic acid, while the reduced form is noted as dihydrolipoic acid. ALA inactivates free radicals, and dihydrolipoic acid also interacts with ROS [66]. Unlike other antioxidants, ALA is conceived as a biological antioxidant in both water- and fat-soluble media [67]. In a recent multicenter, randomized, controlled study, Hamid and colleagues showed that ALA administration significantly improved anemia and erythropoietin resistance and reduced cardiovascular risk in diabetic patients on chronic hemodialysis [68]. However, the instability of ALA under light or heat and its short biological half-life of 30 min may restrict its clinical use [67].

Beyond its direct use as an oral agent, ALA can also be immobilized onto hemodialysis membranes to endow the membranes with antioxidant properties. In 2014, Mahlicli et al. [67] modified polysulfone hemodialysis membranes with ALA through an intermediate polyethyleneimine layer. Briefly, polyethyleneimine was first coated onto the surface of a negatively charged polysulfone/sulfonated polysulfone blend membrane through electrostatic attraction. Then, the ALA layer was further immobilized on the polyethyleneimine-functionalized membrane through the electrostatic interaction between ALA and polyethyleneimine. The results showed that ALA-modified polysulfone membranes not only reduced ROS generation

Table 1. Major membrane modification strategies to prepare antioxidant hemodialysis membranes in laboratorial settings

Author, year	Membrane substrate	Modifier	Modification method	Membrane modality
Chen et al. [52], 2022	Polyethersulfone	Tannic acid	Surface modification	Hollow fiber membrane
Chen et al. [53], 2021	Polyethersulfone	Tannic acid	Surface modification	Hollow fiber membrane
Zhang et al. [51], 2022	Polyethersulfone	Tannic acid	Surface modification	Flat membrane
Chen et al. [54], 2021	Polyethersulfone	Tannic acid	Surface modification	Hollow fiber membrane
Wei et al. [56], 2022	Polyethersulfone	Tannic acid and/or alpha-lipoic acid	Surface modification	Flat membrane
Mahlicli et al. [67], 2014	Polysulfone	Alpha-lipoic acid	Surface modification	Flat membrane
Kohlova et al. [69], 2020	Polysulfone	Vitamin E and/or alpha-lipoic acid	Blend modification	Flat membrane
Kung et al. [72], 2007	Polysulfone	Conjugated linoleic acid	Surface modification	Flat membrane
Qi et al. [60], 2021	Polysulfone	Resveratrol	Blend modification	Flat membrane
Yang et al. [65], 2019	Polysulfone	Silibinin	Blend modification	Flat membrane
Yasar Mahlicli et al. [76], 2015	Polysulfone	Superoxide dismutase and/or catalase	Surface modification	Flat membrane

in blood but also significantly improved the hemocompatibility of the resulting membranes, as evidenced by inhibited protein adsorption capacity, platelet adhesion, and activation and prolongation of clotting-activated partial thromboplastin time [67]. In addition, ALA can also collaborate with other antioxidants, such as TA and vitamin E, to prepare hemocompatible hemodialysis membranes with antioxidant properties via either surface modification or blend modification [56, 69, 70]. In conclusion, ALA-modified hemodialysis membranes could be alternative membranes for suppressing hemodialysis-induced oxidative stress and reducing the anticoagulant dose in extracorporeal circuits during hemodialysis sessions in the future.

CLA-based AHMs

CLA is a subgroup of conjugated polyunsaturated fatty acids that include 28 isomers with 18 carbons and 2 conjugated bonds [71]. Several studies collectively showed that CLA could not only scavenge-free radicals but also inhibit platelet aggregation and blood coagulation [72, 73]. Kung et al. [72] grafted a CLA-bonded polyacrylic acid layer onto the surface of polysulfone flat-sheet membranes to reduce ROS and blood coagulation during hemodialysis sessions. In brief, polyacrylic acid was first grafted onto polysulfone membranes through an ozone-induced treatment. Then, CLA was directly immobilized onto membrane surfaces by using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride EDC as a crosslinker. The results showed that the hypochlorous acid level for the CLA-grafted polysulfone membrane was 1.44 times that of the control (whole blood), while that for the unmodified polysulfone membrane was 6.19 times that of the control. Theoretically, the CLA-grafted polysulfone membrane might exert its antioxidant ability by directly reacting with free radicals to terminate the radical chain reaction or by chelating transition metals to suppress the initiation of radical formation. Meanwhile, the hemocompatibility of PSF membranes can also be improved by immobilizing CLA, as evidenced by a significant increase in the activated partial thromboplastin time of plasma after incubation with the CLA-grafted polysulfone membrane for 30 min. Of note, CLA grafting can also be used to modify other hemodialyzers, such as polyacrylonitrile and cellulose acetate membranes [74, 75].

Antioxidant Enzyme-Based AHMs

Beyond the use of antioxidant molecules as modifiers of hemodialysis membranes, bioactive antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), can also be used to generate AHMs for hemodialysis. In 2016, Yasar Mahlicli et al. [76] successfully coimmobilized SOD and CAT both covalently and ionically onto plasma-modified PEI-deposited polysulfone membranes. The results showed that both SOD/CAT-coated PSF membranes were capable of reducing the levels of ROS in blood and prolonging the activated partial thromboplastin time. In addition, both the adsorption of human plasma proteins and platelet activation on all modified membranes decreased significantly compared to the unmodified PSF membranes. Therefore, the authors concluded that SOD/CAT immobilization could become an attractive alternative for generating bioactive hemodialysis membranes that are capable of suppressing oxidative stress. Table 1 further summarizes the major membrane modification strategies to prepare AHMs in laboratory settings.

Knowledge Gaps between Laboratory Investigations and Clinical Practice in the Development of AHMs

Although there have been a number of advances in fabricating novel AHMs in laboratory settings, the therapeutic potential of these AHMs is almost speculative. Several knowledge gaps in laboratory investigations and clinical practice have significantly hindered the clinical translational research of these AHMs. First, since hollow fiber membranes are currently the preferred membrane modality for hemodialysis in clinical settings, researchers should further determine whether a surface modification strategy of conventional polysulfone or PES hemodialysis membranes by TA or other antioxidants will affect the inner diameter, wall thickness, and permeability of every single hollow fiber. Second, although most prepared AHMs showed significantly improved hemocompatibilities, as evidenced by decreased platelet adhesion and protein adsorption, their actual superiority against unmodified polysulfone or PES hemodialysis membranes should also be evaluated through in vivo animal models or clinical studies. Third, researchers should pay more attention to the evaluation of the antioxidant properties of these AHMs using clinical rather than laboratory biomarkers for oxidative stress in vivo because direct measurements of free radicals, such as $DPPH^{\bullet}$ and $ABTS^{\bullet+}$, are sometimes not available in real clinical practice. More importantly, well-designed high-quality clinical studies should be performed to investigate the effect of novel AHMs on patient-centered outcomes, especially long-term survival and quality of life. Accordingly, interdisciplinary collaboration between biomaterial scientists, industrialists, and nephrologists is urgently required to address these gaps.

Conclusion

In conclusion, clinical evidence suggests that the use of commercial vitamin E-coated membranes significantly reduces the generation of ROS, alleviates inflammation, and lowers erythropoietin resistance. Moreover, vitamin E-coated membranes could also be used in heparin-free hemodialysis sessions despite an unsatisfactory technique success rate of 78% in extracorporeal circuits. However, it should be noted that the beneficial effects of vitamin E-coated membranes versus unmodified synthetic membranes on long-term patient-centered outcomes, such as survival, quality of life, and prevalence of cardiovascular diseases, remain controversial. High-quality trials with hard clinical endpoints are thus required to fully clarify the clinical value of vitamin E-coated membranes in ESKD patients.

On the other hand, the development of novel AHMs has become a major research topic in the field of membrane manufacturing during the past decade. Natural polyphenols, such as TA, resveratrol, and silibinin, are currently the most widely used modifiers to enhance the antioxidant capacities of conventional polysulfone or PES membranes. Although the hemocompatibility, antioxidant activity, and permeability of each developed antioxidant membrane have been systemically evaluated using in vitro tests in laboratory settings, the clinical translational research of these membranes is stagnant owing to the knowledge gaps in laboratory investigations and clinical practice in this field. Therefore, we call for interdisciplinary collaboration between biomaterial scientists, industrialists, and nephrologists to accelerate the mass production and clinical evaluation of newly developed AHMs.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Yupei Li and Xinyao Luo drafted the manuscript, and Mei Yang and Baihai Su critically revised it and approved the final version.

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