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Review

Surface Engineering of a Bioartificial Membrane for Its Application in Bioengineering Devices

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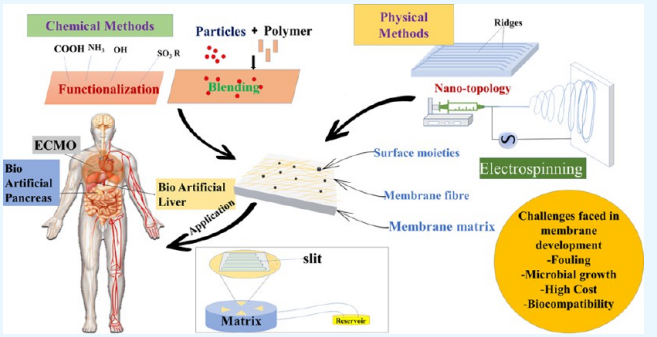
ABSTRACT: Membrane technology is playing a crucial role in cutting-edge innovations in the biomedical field. One such innovation is the surface engineering of a membrane for enhanced longevity, efficient separation, and better throughput. Hence, surface engineering is widely used while developing membranes for its use in bioartificial organ development, separation processes, extracorporeal devices, etc. Chemical-based surface modifications are usually performed by functional group/biomolecule grafting, surface moiety modification, and altercation of hydrophilic and hydrophobic properties. Further, creation of micro/nanogrooves, pillars, channel networks, and other topologies is achieved to modify physio-mechanical processes. These surface modifications facilitate improved cellular attachment, directional migration, and communication among the neighboring cells and enhanced diffusional transport of nutrients, gases, and waste across the membrane. These modifications, apart from improving functional efficiency, also help in overcoming fouling issues, biofilm formation, and infection incidences. Multiple strategies are adopted, like lysozyme enzymatic action, topographical modifications, nanomaterial coating, and antibiotic/antibacterial agent doping in the membrane to counter the challenges of biofilm formation, fouling challenges, and microbial invasion. Therefore, in the current review, we have comprehensibly discussed different types of membranes, their fabrication and surface modifications, antifouling/antibacterial strategies, and their applications in bioengineering. Thus, this review would benefit bioengineers and membrane scientists who aim to improve membranes for applications in tissue engineering, bioseparation, extra corporeal membrane devices, wound healing, and others.



1. INTRODUCTION

Membranes are a crucial part of man-made or natural macro−micro systems, used in separation processes, directly or indirectly affecting human life. They are the critical component of several optimally functioning instruments and processes used in the chemical and biomedical fields, for instance, a biological cell where membranes house different cellular contents and cell organelles to achieve a defined microenvironment; bioseparation units in biochemical plants where a membrane is required for separation processes; artificial organs like several extracorporeal membrane devices (ECMDs) for replacing/augmenting the performance of existing organs; sensors and purification systems where membrane act as a barrier between two fluidic systems; drug delivery vehicles where membranes act as a reservoir for controlled and sustained delivery of drugs, etc.[1,2] Membranes have been traditionally designed and fabricated through several synthetic polymers and polymer composites for separation and filtration applications.

With the introduction of the field of bioengineering, researchers borrowed membrane science technologies to apply them in several areas of bioengineering. They redesigned these traditional membranes while preserving their goodness of mechanical properties and processability and incorporated the additional characteristics of biocompatibility and biodegradability, providing a natural microenvironment to cells as any biopolymer. These membranes later got popularized as bioartificial membranes (BAMs).[3] The BAMs prepared for different applications require specific, tailored parameters such as porosity, material, thickness, thermal stability, chemical reactivity, biocompatibility, antifouling, antibacterial properties, etc., for their proper functioning.[4−6]

The applications of BAM technology range from organ-on-chip devices to blood purification systems to cell culture, single-cell analysis, high-throughput drug screening, drug delivery systems, tissue engineering, wound healing, bioartifi-

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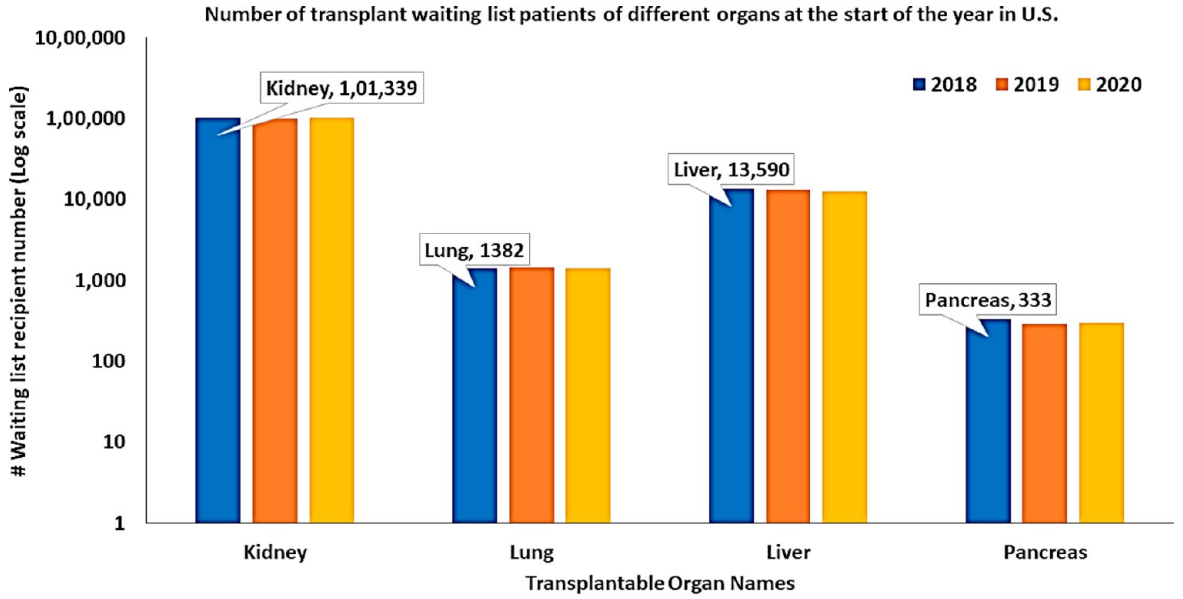

Figure 1. Graphical representation of the number of patients on the waiting list for transplantation for the years of 2018, 2019, and 2020 in the US for the organs kidney, lung, liver, and pancreas. Data collected from HRSA (Health Resources and Services Administration), Scientific Registry of Transplant Recipient, U.S. Department of Health & Human Services.[13]

cial organ (BAO) development and others.[6] For instance, chronic kidney disease (CKD) patients rely on dialysis using membrane technology to compensate for the reduced function of their own kidney.[7] Researchers have investigated different designs on silicone-based nanoporous membranes to simulate a kidney system where separation and biological function was restored.[8] Additionally, BAMs have been used in extracorporeal membrane oxygenators (ECMOs).[5] Further, BAMs also act as an excellent scaffolding system for tissue engineering and regenerative medicine applications.[9] They have been explored to develop an artificial pancreas and liver for the release of insulin and toxin removal, respectively.[2,10] However, the major challenge manifests when BAM is used in tissue engineering is to maintain and fabricate the 3D architecture of the organ, which spatially houses the different cell types to achieve the desired function.[11] For instance, Salerno et al. proposed the fabrication of a 3D vascularized structure of the liver from hollow fiber membranes (HFMs) of polycaprolactone (PCL). Thereafter, they solved this challenge of spatial localization of cells by trapping the hepatocyte cells on the external surface of the HFMs and housed the endothelial cells on the inner surface of the fiber lumen.[12] Moreover, from the Figure 1, it can be observed that the requirement of transplantable organs like the kidney, liver, lungs, and pancreas is quite high due to donor scarcity. Hence, the number of wait-listed candidates has remained similar in the past few years. In this critical scenario, BAMs can serve as a potential scaffolding device to develop transplantable organs/tissues to meet the growing demand. The success of BAMs is highly dependent on several factors such as the need, the design parameters, and scalable fabrication processes.

In the last few decades, several technologies have been developed that can efficiently fabricate BAMs with different material types with varying properties. Electrospinning and spin jets have emerged as two of the major methods for the design and fabrication of BAMs used in tissue engineering.[14,15] These methods generate a micro/nanofibrous, porous membrane of biomaterials that mimics the fibrous nature of natural collagen of the extracellular matrix (ECM). Hence, they suitably provide a microenvironment for cells during any tissue regeneration.[16,17] For instance, researchers have used the rotary spin jet method to form a membrane scaffold of PCL for the regeneration of critical bone defects in rats. The scaffold supported new bone formation, after 60 days of implanting membrane scaffold in rats.[18] Kumar et al. also explored the electrospun nanofibrous PCL−gel membrane to design a cell culture insert device wherein they cultured HaCaT cells to develop an epidermal layer of skin tissue. These free-standing membranes facilitated the formation of tight junctions in the developed skin tissue.[19] Similarly, Sakai et al. showed the application of a sol−gel method to develop the aminopropyl−silicate membrane for development of an artificial pancreas.[20]

The solid microporous polymeric membranes fabricated by the aforementioned techniques use synthetic polymers such as poly(vinylidene fluoride) (PVDF), poly(lactic acid) (PLA), polycaprolactone, polymethyl methacrylate (PMMA), etc.; ceramics materials like silica, titania, and zirconia; and biodegradable polymers such as collagen, chitosan, alginate, etc.[21,22] These material-based BAMs provide an opportunity to be tailored for properties like thermomechanical stability, chemical resistance, biocompatibility, hemocompatibility, porosity, shear resistance, fouling, biofilm formation, etc., that are essential to withstand different stresses and perform the designated functions in biomedical devices.[23] For instance, biocompatibility, porosity, antifouling, and antibacterial properties are very essential properties when BAMs are explored for tissue engineering applications, whereas surface properties, pore size, chemical reactivity, and hemo-compatibility of BAMs are essential when explored in filtration/separation processes.[24] Although there is a plethora of literature that describes the BAMs in different applications, there has been limited effort to consolidate the knowledge of the design and fabrication of BAMs to have the requisite surface properties needed to achieve different bioengineering applications.

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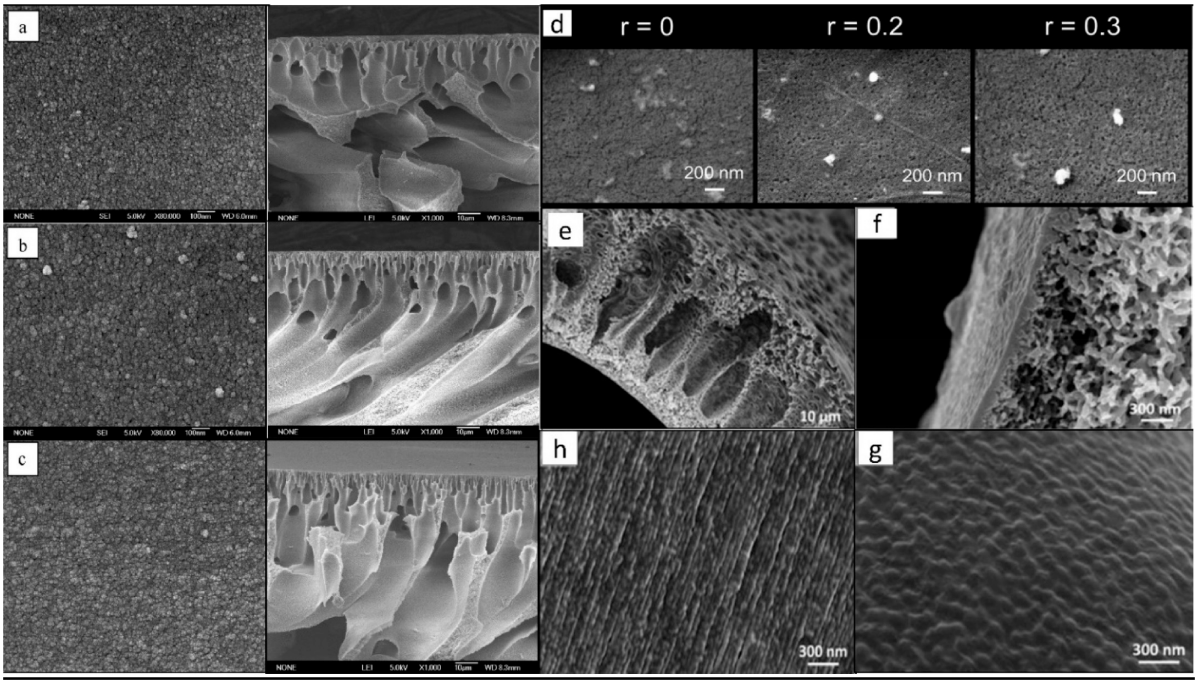

Figure 2. (a–c) SEM images of the surface (left side) and cross section (right side) of different concentrations of PAN-*b*-PEG. Reprinted with permission from reference 25. Copyright 2011, Journal of Membrane Science, Elsevier. (d) SEM images of the surface of a pristine PSF membrane after a fouling test using gas with an injection rate r = 0, 0.2, and 0.3. Reprinted with the permission from reference 125. Open Access, 2021, Science of the Total Environment, Elsevier. (e, f) Cross-sectional SEM image of microgel uncoated and coated PES/PVP HF membrane. (g, h) Surface SEM image of microgel coated and uncoated PES/PVP HF membrane, respectively. Reprinted with permission from reference 180. Open Access Advanced Biosystems, Copyright 1999–2022, John Wiley & Sons, Inc.

In this review, we have discussed the chemical composition of different bioartificial membranes, their fabrication techniques, major challenges faced by membrane-like fouling, and their wide range of applications that have been explored in the last 10 years' time. Based on different materials, chemical composition, and functions, different types of BAMs are thoroughly analyzed and discussed in the application section. We have also concluded with a future scope and challenges in BAMs for revolutionizing bioengineering applications. This review will provide a good insight for bioengineers and membrane scientists to apply BAMs to solve challenging issues in healthcare and medicine.

2. PHYSICAL AND CHEMICAL CHARACTERISTICS OF BIOARTIFICIAL MEMBRANES

2.1. Chemical Properties of Bioartificial Membranes.

The membranes were initially developed for separation applications in chemical/biochemical industries. So, their performance was being gauged by their ability to process a large quantity of feed and selectively separate specific components from the feed. For an efficient separation, the membrane should be mechanically stable, heat and fouling resistant, chemically inert, and heat resistant. These properties of membranes are directly dependent on the physio-mechanical and -chemical characteristics of the material used in developing the membrane. Conventionally, ceramic and polymeric materials were chosen for membrane fabrication. However, polymeric membranes are generally preferred as they are economically viable, possess good chemical resistance, and offer greater mechanical strength along with flexibility but with a disadvantage of reduced fouling resistance compared to the ceramic membranes.[25]

Polymer membranes used in biomedical applications derived from either natural polymers, that include cellulose, chitosan, alginate, starch, dextran, etc., or the typical synthetic polymers like polysulfone (PSU), polycarbonate (PC), polypropylene (PP), poly(lactic acid), poly(vinylidene fluoride) (PVDF), polyether-sulfone (PES), polyether ether ketone (PEEK), polyacrylonitrile (PAN), polymethyl methacrylate (PMMA), polytetrafluoroethylene (PTFE), polyphenyl sulfone (PPSU), poly(vinyl alcohol) (PVA), etc.[26] Most of the synthetic polymers were being avoided in the beginning because of challenges with compatibility. Also, the synthetic polymeric membrane's hydrophobicity needs to be taken care of before it can be used as a BAM. In one of the methods, the synthesis of a copolymer, polyacrylonitrile-*block*-polyethylene glycol (PAN-*b*-PEG), has been demonstrated by Chen et al. through immersion precipitation and the phase inversion method. X-ray photoelectronic spectroscopy (XPS) and contact angle studies showed that PAN-*b*-PEG copolymer membranes had achieved hydrophilicity on incorporation of polyethylene glycol (PEG). It resulted in reduced BSA absorption by 45% and increased fouling resistance by seven times as compared to the unmodified PAN membrane.[27] In Figure 2(a–c), the changes in the membrane surface structure can be observed with the changes in the concentration of PAN-*b*-PEG, hence proving successful copolymer formation. Often, the synthesis of copolymers with hydrophilicity is difficult to achieve with certain polymers. In such cases, blending of polymers is an alternate method to increase hydrophilicity. Jin et al. proposed that blending hydrophilic macromolecules with a synthetic polymer membrane matrix can improve the hydrophilicity of the surface and can also increase fouling resistance.[28] The effect of antifouling properties can be observed in Figure 2(d)

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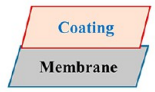
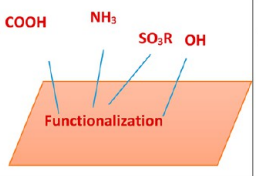
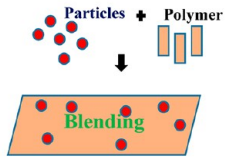
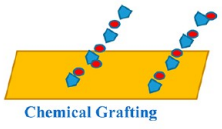
Table 1. Explaining Different Strategies of Chemical Modification of the Membrane Surface

Surface Modification	Merits	Demerits	Example
	Versatile, easily reproducible with cost-effectiveness	Aggregation and depletion of coated particles with time. Long term stability of the performance[151]	Surface modification of polyamide based thin membrane by coating with polydopamine and reduced silver to give antimicrobial property.
	Ease of fabrication is high, cost-efficient	Permeability improved with appropriate functionalization, less dispersion.	Functionalization of polysulfone membrane with SiO2 improved the hydrophobicity. Permeability improved almost 16 folds with the modification.[32]
	Permeable, replicability, environmental-friendly, cost-effective	Ease of fabrication is less, particle aggregation.	Graphene oxide and Ag nanocomposites were blended with polyether sulfone blended membrane. Permeability can be improved such that BSA permeability flux increased to 120 kg/m^{2}h on blending 0.2%wt rGO/Ag[54] Carboxylated polyetherimide and polyacrylonitrile were blended to form a BAM. Hydrophilicity, permeability and protein adsorption improved. Water flux increased to 324.1ml/m^{2}h mm Hg at 70/30 PAN/CPEI blend from 155.8m L/m^{2}h for PAN membrane.[31]
	Improves the adsorption resistance, permeability and integrity of the polymer.	Chances of agglomeration, and permanent damage to the surface hence causing less efficient functionality	Poly ethylene glycol was grafted on polysulfone membrane for the application of haemodialysis. It has shown 72% reduction in BSA adsorption in compared to traditional polysulfone membrane[55].

where the foulant resistance to different gas injection rates on the PSF membrane can be observed, and the structural difference due to the microgel coating can be observed in Figure 2(e−h). Surface architecture plays a crucial role in the adhesion of foulant because it directly affects the hydrophobicity of the surface. Similar approaches can be found in the work of Li et al., where his group synthesized a PVDF−poly(*p*-phenylene terepthalamide) blend to increase the hydrophilicity of the membrane with increased polar poly(*p*-phenylene terephthalamide) content.[29]

Synthetic polymer membranes upon contact with blood, platelet adhesion, and coagulation pathways are activated, which starts confining the use of freshly prepared membranes in biomedical devices.[30] Therefore, increased hydrophilicity in synthetic polymer membranes is desirable in achieving hemocompatibility. Yin et al. for the first time reported the synthesis of a PES-based composite membrane in which PU is chosen as a potential candidate in accordance with the Hansen solubility coefficient value that determines the blending ability of two polymers; closer values of two polymers suggest stronger blending miscibility. This has been achieved by blending the triblock polymer of PEG−PU−PEG and CA−PU−CA with PES as the base matrix. Integration of polyethylene glycol (PEG) and citric acid (CA) in the composite membrane has a significant improvement on the fouling resistance and anticoagulant property of the membrane, respectively.[31−33] Senthikumar et al. investigated another approach to solve the challenges of hemocompatibility by decorating the PAN surface with a hydrophilic moiety, namely, polyetherimide (PEI). The PAN surface was treated with dry CO_2 to develop carboxylated PEI (CPEI), which has improved the surface wettability, hydrophilicity, and surface charge. The strong intermolecular bonding between PAN and CPEI in the blend system has led to enhanced compatibility and homogeneity at a molecular scale, which was evident from ATR-FTIR (attenuated total reflectance-Fourier transform infrared spectroscopy) and DSC (differential scanning calorimetry) characterization of the modified membrane. This membrane has showed significant separation efficiency in uremic toxin, urea, creatinine, and cytochrome C tests. AFM (atomic force microscopy) analysis revealed that the integrating CPEI in a pure PAN has led to significant smoothening of large nodules present on the pure PAN, which happened due to polymer aggregation on the surface. The presence of polar moieties like ether, imide, and carboxylic groups competes effectively with the water molecules through hydrogen bonding, and the Van der Waal's interaction explains the lowering of reduced protein adsorption and platelet adhesion.[34] The different types of chemical modifications and their advantages are collated in a tabular form at the end of this section in Table 1.

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The nanomaterials have also been explored recently to modify the surface properties of synthetic membranes. Different types of nanomaterials, such as SiO_2,[35] TiO_2,[36] ZrO_2[37,38] (Figure 3), carbon nanotubes (CNT),[39] and graphene oxide (GO),[40] have been used as additives to different polymeric materials, such as cellulose acetate (CAc), PVDF, PA, PEI, and sulfone polymer, to achieve the desired functional properties.[41] Among inorganic nanomaterials, GO is one of the most appealing nanomaterials because of the presence of hydroxyl, epoxy, carbonyl, and carboxyl reactive species that provide high solubility in polar solvent with good colloidal properties, low toxicity, and a large surface area which can be useful for further modification. Modi et al. reported GO-doped PES HFM (GP-HFM), favoring hemocompatibility and biocompatibility. An amount of 0.5 wt % GO was sonicated in *N*-methyl pyrrolidone (NMP) solvent, which followed the treatment of 1 wt % PES into GO-NMP solution. It resulted in the successful development of GP-HFM. The doping of GO into HFM was confirmed by ATR-FTIR spectroscopy. The water contact angle of GP-HFM was observed to be reduced compared to a a pristine HFM because of the presence of hydroxyl groups on GO nanosheets. This modified membrane showed a higher reduction ratio for urea, creatinine, and phosphorus compared to commercial Hemoflow F6 in a simulated blood sample. SEM and confocal images of GP-HFMs reveal higher accumulation of cells. It was observed that the human embryonic cells (HEK-239) showed better attachment, growth, and proliferation on the outer surface of the GP-HFM than pure-HFM (p-HFM) and hence proved to be a promising hemocompatible and biocompatible material for biomedical applications.[42]

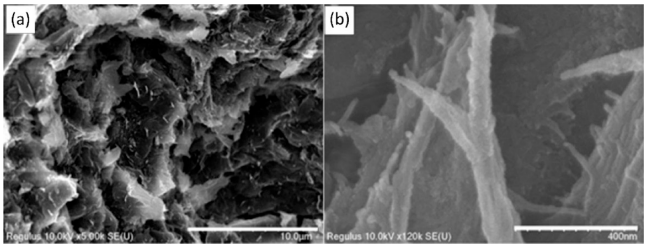

Figure 3. SEM images of a GO/PNF/CNF-ZrO_2 hybrid nanofibrous membrane at (a) 10 μm and (b) 400 nm magnification. Reprinted with permission from reference 36. Copyright 2022, Chemical Engineering Journal, Elsevier.

Another versatile polymeric material for membrane fabrication is PVDF for its chemical and thermal stability, high mechanical strength, and resistance to radiation,[43] but lower surface energy renders it poor wettability; therefore, on treating with aqueous solution, the PVDF membrane is likely to adsorb hydrophobic proteins and organic foulants, thereby affecting its permeability and separation performance. Li et al. carboxylated nanodiamonds (CNDs) by thermal oxidation and then incorporated CNDs into PVDF membranes by the phase inversion method. TEM (transmission electron microscopy) showed that the CNDs had minimized aggregation and better dispersity compared with the raw nanodiamonds. Experimental characterizations, such as SEM (scanning electron microscopy), AFM, and water contact angle analysis, were carried out to compare the results with other pristine PVDF membranes, and it was observed that CND-blended membranes had larger surface pores, thus demonstrating higher water permeability and lesser roughness on the surface. Moreover, the irreversible fouling ratio to the total fouling ratio (R_{ir}/R_t) dropped from 85% for the pure PVDF membrane to 21% for the CND-blended membrane.[44,45]

Many of these synthetic polymers are either avoided for use in biomedical applications or modified through biological/chemical means to tailor their surfaces to be suitable for bioengineering applications. At the same time, natural polymers, although being promising for developing membranes for bioengineering, suffer from poor mechanical and manufacturing processability. Therefore, they are being blended or used in conjunction with synthetic polymers. Polysaccharide-based natural polymers are widely preferred over protein-based polymers due to their high mechanical strength and availability.[46]

Collagen is the most resourceful protein polymer in animals; however, its poor thermostability and mechanical strength confine its application in scaffold development. However, introducing cross-linkers and their derivatives can improve collagen's property without affecting its triple helical structure. Du et al. have shown the cross-linking collagen using a natural cross-linker, chitosan, followed by the addition of a bioactive cross-linker, alginate dialdehyde, which has led to improved fiber formation along with thermal stability, indicating its enhanced mechanical strength.[47]

CAc is an excellent candidate for membrane-based systems because of its biodegradability. In a study conducted by Yang et al., it was found that the CAc membrane is prone to fouling because of adsorption of protein molecules into the valleys of the rough surface of the membrane surface.[48] When the membrane is blended with graphene oxide and a metal organic framework (HKUST-1) using the phase inversion method, it was found that water flux is higher in HKUST-1@GO blended in CAc than normally blended CAc with GO.[49] Guo et al. reported a novel cellulose acetate membrane decorated with dopamine designed by chlorination of cellulose acetate by tosyl chloride followed by its substitution by dopamine (CAc-DA). The CAc-DA flat membrane was developed by a nonsolvent-induced phase separation method using PVP. SEM images of the membrane have revealed increased pore size because of dopamine incorporation. Also, dopamine integration has led to a sharp increase in hydrophilicity, thus improving the surface free energy of the CAc-DA membrane.[50] Zwitterion molecules in cellulose acetate have been reported to raise the hydrophilicity of the membrane.

A study by Gu et al. involved the fabrication of an antifouling PS membrane by the nonsolvent phase separation method with PEG followed by layer-by-layer assembly of polyethylenimine with lignosulfonate (LS), a derivative of a natural polysaccharide, lignin. The presence of hydroxyl, sulfonate, and phenolic groups on LS and the positive charge on polyethylenimine create a promising building block with an enhanced hydrophilic surface that adsorbs water molecules and forms a hydration layer and, therefore, repels the hydrophobic foulant adsorption, making it an excellent antifouling substrate for microfiltration, ultrafiltration, and nanofiltration application.[51]

Chitin, being the most abundant polysaccharide polymer, is famous for its biodegradability and antifouling property in addition to good film and fiber forming property, making it usable in a wide range of applications. Elizalde et al. prepared a blend membrane of PVDF/chitin by a phase inversion technique using *N*,*N*-dimethylacetamide (DMAc) and lithium

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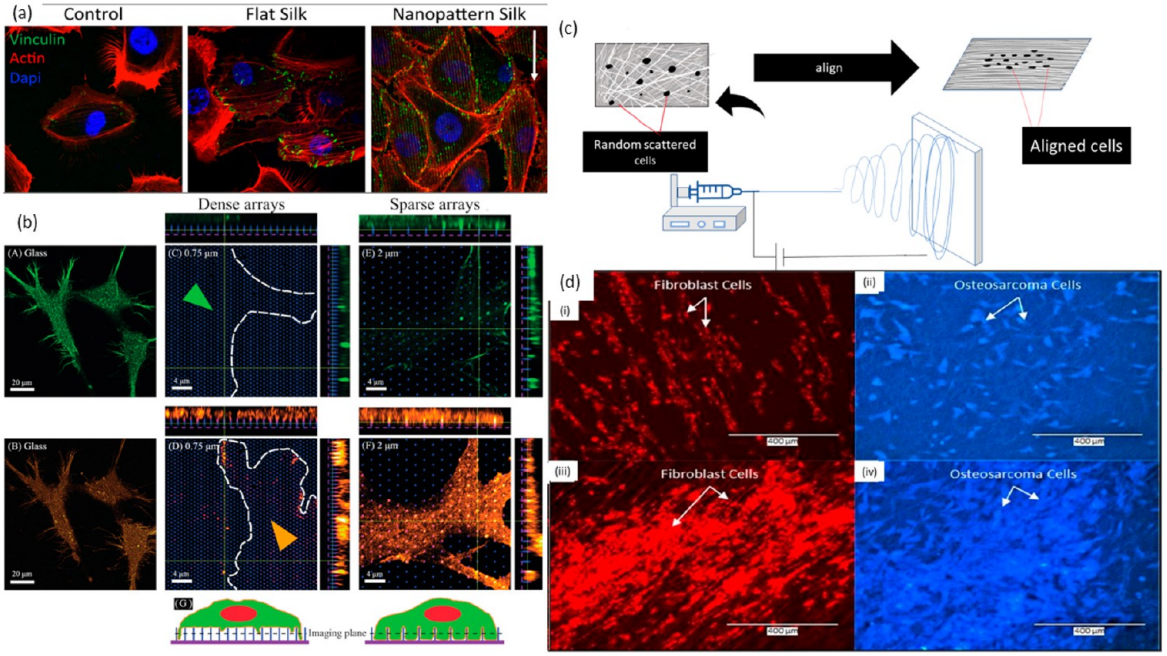

Figure 4. (a) Immunofluorescence stained HCLE cells cultured on TCP, flat silk, and nanopatterned silk films. Reprinted with permission from reference 60. Copyright 2017, Open Access, Investigative Ophthalmology and Visual Science, ARVO journals. (b) Nanopillar influence on cell motility and adhesion on a glass substrate. Reprinted with permission from reference 64. Copyright Open Access Nano Micro Small, Wiley Online Library, 1999−2022 John Wiley & Sons, Inc. (c) Schematic of electrospun membrane formation of aligned and nonaligned surfaces. (d) (i, iii) Show that cells in response to aligned electrospun fibers tend to align parallelly, unlike (ii, iv) which show cells grown on random electrospun fibers. Reprinted with permission from reference 106. Copyright 2022, Open Access, Nanobiomedicine, SAGE journals.

chloride as cosolvent.[52] In another study conducted by Xie et al., it was found that PVDF membranes blended with chitin membranes increase the performance of water permeability and fouling resistance. When the blend was kept in a coagulation bath using ethanoic acid (HAc), it was observed that the concentration of HAc directly affects the chitin content on the surface of the blend membrane and increases water permeability and hydrophilicity, thus increasing fouling resistance.[53]

2.2. Physical Properties of Bioartificial Membranes. *2.2.1. Need for Micro- and Nanoscale Physical Features in Bioartificial Membranes.* Advances in the field of materials science show that micro- and nanostructures, patterns, and other specialized topographies on the surface of a membrane are essential for its applicability in tissue engineering. Separate confinement zones are often linked to cellular adhesion, aggregation, and movement in biological systems. Hence, topological features such as grooves, ridges, and pillars are incorporated into the surface of BAMs in the in vitro study of cell adhesion and migration.

It has been observed that animal cells respond to specific micro- or nanotopographies and surface chemistry.[56] Systems with special micropatterned features are observed to encourage and control cell adsorption,[57] cell adhesion,[58] and micro-transduction.[59] The cytoskeletal proteins such as actin and microtubule positively interact and are influenced by the nanotopology, resulting in cell morphology and mobility modifications. Nanotopological features such as the nano-ridges, grooves, and gratings are essentially highly aligned structures and provide optimal conditions for studying cell alignment, cell elongation, and also cell mobility. Wheatley et al. investigated the T-cell activation, mobility, and signaling in response to this specific nanotopology.[60] Mammalian cells' response to the surface chemistry of a membrane they are cultured on has been extensively studied and discussed to show that cells can develop differential morphological and physiological characteristics in response to specific topological features but constant surface chemistry, pointing toward the sole effect of topology on the cellular behavior irrespective of the effect of surface chemistry. It was established through osteoblast response on the PMMA/polystyrene-based thin-film blends.[61] Also, to further understand the relationship between the cell morphology modifications and the contributing gene expressions, in a study in human corneal tissue engineering, nanoridges were printed on the silk films by soft lithography (Figure 4a). An RNA sequencing study was performed following the study of cytoskeletal structures corresponding to mobility.[62] The native biological systems also have separate zones of confinement that help in the organization, adhesion, alignment, and motility. Thus, the micro-/nanotopographies are fabricated to mimic the inherent biological system, such as the extracellular matrix of a particular tissue or the epithelial and endothelial barriers that provide essential cues for characteristic cell behavior, cell differentiation, and cell migration leading to tissue regeneration.[63] Cellular orientation and morphology can be controlled and intentionally modified by oriented surface topologies such as nanogrooves, especially important in epithelial cell and neuronal cell differentiation, including aligned cell-body/axon orientation and an increased axonal outgrowth[64] (Figure 4c,d). In another study, nano-patterns, specifically gratings imprinted on PDMS and PMMA with the help of soft lithography, produced smooth muscle cell morphology change by elongation, and alignment parallel to the grating axis was observed.[65] It was due to the polarization of the microtubule organization centers inside the cell in response to the gratings.

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Table 2. Description of Unique Nano- and Microtopologies with Their Fabrication Techniques

Fabrication Technique	Membrane Composition	Nanotopological Feature	Biological and Biomedical Advantage	Application	Ref
Phase Inversion Method (Spinneret)	Poly(ether sulfone), Polytetrafluoroethylene, PSF, PVDF, Polystyrene, Polypyrrole	Hollow fibers and Nanofiber Membranes (Tubular)	Improves cell attachment, and the curvature of the membrane upregulates the differentiation and functions of renal tubular cells, hepatocytes, and Caco-2 cells.	Used for hollow fiber membrane bioreactors, especially for hepatocyte culture ultrafiltration devices.	79−82
Sol−Gel/Solution Casting	PVDF, Polyamide, Aminopropyl-silicate	Microporous Surface	Provides specific and controllable membrane porosity and surface functionalization.	Fabrication of membrane for immuno-isolation and controlled drug delivery.	20, 83
Ion Track or Electrochemical or Acid Etching	PET, PC, PVDF	Roughness, Nanoneedle, Basement Membrane Mimicking Nanotexture	Induces specific gene expressions, metabolic pathway mobilization such as Rho GTPase, and nuclear membrane morphology differentiation.	Cancer cell isolation devices and bactericidal surfaces for tissue engineering.	84−87
Spin Coating		Micrometric Patterned Porous Surface	Improves cell attachment, angiogenesis, osteo-integration, and bactericidal properties.	Allows surface modifications purposed for various biomedical applications.	88−90
Extreme UV Interference Lithography	Polystyrene, Poly(isopropylacrylamide)	Microgrooves, Microwells, Porous Membranes	Enables protein adsorption and cell adhesion and allows cell alignment and spreading. Improves neurite outgrowth and separates neuritis with the help of alternate smooth and porous structures. Enables macrophage activation. Controlled cross-linking increases the elastic modulus and drives cell morphology by mechanical cues.	Space-time-controlled networks can be used as sensors for single-cell analysis.	91−96
Soft Lithographic Techniques, Microcontact Printing, Replica Printing	PS, PDMS, Silk Fiber Membrane	Parallel Ridges, Nanogrooves and Nanopillars, Unordered Patterns	Desired changes in the cell morphology, improved adhesion and directed gene expression, and cell alignment. Cell differentiation and self-renewal. Heterogeneous cell culture.	Structured substrate for cell culture. Biochemical assays and medical diagnostic kits.	97−99
Nanoimprint Lithography or Photolithography	PMMA, PBMA, PE, PS, PCL	Patterns, Nanopillars, Complex Hierarchical Structures, Line-Patterned Substrates Imprinted	Increased mechanical strength of the BAM. Noticeable cell alignment and elongation. Inhibition of cell spreading. Myogenic differentiation.	Biomimetic surface structures are fabricated by imprinting. Substrates can be patterns specifically imprinted.	100−103
Atomic Layer Deposition		Roughness, Wettability	Antibacterial surfaces, osteoinduction, inhibits platelet adhesion.	Membrane fuel cells, intravascular stents, alkaline exchange membranes, antibio-fouling membranes, and intracellular delivery systems.	104,105
Electrospinning	Gelatin, PVDF, Chitosan, PSF, PVP, PCL, PAN/PMMA, Polystyrene, PVA, PLA	Aligned Nanofibers, Beaded Nanofibers	Orientation of cells, multicell culture by random and aligned fiber patterns, and osteoinduction.	Organ-on-a-chip, barrier and interface models.	106−108
Polymer Demixing	PLA/PS, PCL, Polystyrene/Polybromostyrene	Nanoislands, Regular Nanopatterned Surface	Intracellular signaling, mechano-transduction, osteogenic differentiation of stem cells, and topographical fidelity.	Support structure for cell culture.	109−111

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Other nanotopological features such as the nanopillars and nanoislands introduce a new dimension to the membrane and provide definite zones of confinement to the cells. They are generally seen to assist the cells in adsorbing or adhering to the surface of the membrane and restrict cell spreading. Migration across a surface with nanopillars imprinted on the surface requires the cells to overcome their membrane bending stiffness and thereby is energetically expensive, leading to increased cell adhesion and adsorption on such a surface. These unique nanotopological features were designed in varied concentrations in a study by[66] to understand the phenomenon in great detail (Figure 4b). It was observed that the distance between the adjacent nanopillars also affects the cell adhesion mechanism. It was discovered in this study that the presence of dense and sparse nanopillars corresponds to cells in a suspended state and conformal state. The cells adopt a different strategy to adhere to the surface as it serves to be energetically efficient.

Nanotopographical features have also shown evidence to induce differentiation of stem cells in a specific desired line of lineage. Khattak et al. studied the effects of nanoisland-like topographical features fabricated on the PCL/PMMA-based thin film on the mesenchymal stem cells cultured to understand the phenomenon further and discovered that the surface's topography positively affects the differentiation into the osteogenic lineage.[67] In the following study, a combination of nanopillars and nanogrooves were fabricated on the membrane surface and successfully observed that the murine stem cells positively responded to the differential topography by generating a heterogeneous cluster of cells. At the same time, the human stem cells did not differentiate with the same enthusiasm. This further muddled the general hypothesis of nanotopology, affecting the differentiation of stem cells. Chemical surface modifications, signaling, and growth factors may be needed to supplement the nanotopography to bring about similar results.[68]

The surface stiffness has also been observed to provide the requisite mechanical stimulus to encourage the differentiation of stem cells to form a specific cell type. It was possible to culture polymeric cell types by utilizing the differential mechanical properties of different polymers and polymer composites to fabricate the support platform.[69,70] These advances have made possible the predictability of cellular responses to characteristic nanotopographical features.

Topologically significant surfaces are developed in various other applications such as separation technology, membrane bioreactors, sensors, and bactericidal surfaces. Physical surface modifications were mimicked for various biomedical and biotechnological research advancements through extensive study of the relationship between topological characteristics and cell or substrate−cell interactions.

2.2.2. Different Physical Methods of Fabrication of BAMs. Scientists and engineers have developed and modified micro- and nanofabrication techniques in recent years to enable researchers to study and exploit the in vivo conditions in an in vitro system to address several scientific and engineering queries. These fabrication techniques primarily mimic the morphological, topographical, and mechanical properties of natural membranes to design the BAMs. The membranes' specific pore size and porosity are essential to ensure optimal cell proliferation, as confirmed by a study conducted in wound healing applications.[71] In another study, an organ-on-chip device was fabricated with a PDMS-based porous membrane as the support layer for cell culturing. A PDMS porous membrane with measured pores and porosity was developed using a microelectromechanical system. Characteristic markers for cell culture such as cell proliferation, transmigration, tight junction formation, and barrier integrity were observed on the membrane.[72] Porosity in the cell culture support layer ensures space for the cell mass to occupy and the continuous supply of nutrition and waste removal. The mechanical strength of the membrane support is important for ensuring its stability and durability, but it also has an effect on cell proliferation and stem cell lineage decisions. Cartilage is one of the trickiest tissues to be cultured in vitro; however, composite membranes of silk fibroin−collagen type II showed promise due to their specific tensile and creep behavior.[73]

The fabricating techniques for developing a membrane with the desired structural and functional patterns are based on additive manufacturing such as 3D printing, sol−gel, layer-by-layer deposition, replica printing; stamping techniques such as soft lithography techniques and imprint lithography; coating techniques such as spin coating, atomic layer deposition, and etching; and fibers such as phase inversion and electrospinning (depicted in Table 2). Electrospinning techniques are one of the most common methodologies used for the development of BAMs because it provides the biomimicking bionano-niche environment for the growth of the cells. Electrospun membranes of chitosan and silk fibroin with extrafibrillar and intrafibrillar nanohydroxyapatite depositions provided an ideal microenvironment for the stem cells to differentiate into osteogenic lineage.[74] In a later study, the hierarchical and dynamic structure of the natural ECM was mimicked by using multiscale or micronanofibers for the fabrication of the membrane. Electrospun membranes are considered as 2D structures and thus are generally incapable of mimicking the infiltration characteristics of a native tissue, but this modification proved to be an improvement, noticed through the enhanced infiltration and proliferation of the cells.[75] Electrospinning not only allows for multiscale fibers but also possesses the ability to print different fibers in a coaxial fashion. Controlling the alignment of the sheath and core of the membrane allowed for the replication of cartilage tissue[76] (Figure 4c,d). Most of the common techniques used for the development of the membrane support for cell culture depend on the irregularities of the fiber or layer deposition, but in the case of a rapid prototyping process, the native microenvironment can be mimicked. Thickness, layer-by-layer composition and design, and porosity can be predetermined and fabricated. A PLA-based membrane with chitosan and sodium alginate was fabricated by Ilhan et al. to develop an in vitro tissue engineered tympanic membrane.[77] The 3D-printed patch served as an ideal platform for the cells to develop the requisite characteristics. 3D-printed microfluidic systems also allowed for the in situ observation of morphological and physiological changes in the cells in response to the nanotopological features of the membrane. This technique allowed for precise ordered nanotopographical feature printing on the membranes.[78]

Moreover, gradient cross-linking of the polymers, organized or unorganized differential patterning, or adsorbed compounds are also significant modifications adopted for membranes to be better suited in the biomedical field.

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3. FOULING: A CHALLENGE OF BIOARTIFICIAL MEMBRANES

3.1. Definition of Fouling. Fouling is one of the challenges before developing sustainable membrane technology. Fouling refers to an accumulation of foreign particles which hinder the performance and longevity of the membrane. The problem of membrane fouling can be addressed via two major ways: one is the removal of fouling agents from the surface of a membrane, and the other is the prevention of fouling agents being adsorbed on the surface of the membrane in the first place.[112]

Fouling is caused by one or more physical, chemical, or biological factors. When a membrane is subjected to mechanical stresses for a long period of time, there are possibilities of surface corrosion with time. The extent of corrosion is dependent on the type of membrane and nature of the fluid interacting with it. Liu et al. have demonstrated that surface roughness on the PVDF membrane is the potential site of corrosion, and it triggers the erosion process.[113] Membranes made up of certain polymers are more likely to undergo withering/corrosion in an ionic solution like blood, while ceramic and silicon membranes are quite inert to any ionic solution.[114,115] The debris created during erosion is accumulated on the surface of the membrane and results in fouling. Often, when the fluid is a chemically reactive species, it tends to react with the membrane surface, forming byproducts that result in fouling. The other crucial factor that causes fouling of membranes is microbial biofilm formation. Microbes attack the membrane surface and accumulate over the period of time and develop a biofilm, which reduces the life span of the membrane as well as the permeability flux of the membrane. Apart from that, the excessive flocculants, made up of surfactants or different types of biomolecules, are deposited on the surface of the membrane, causing a reduction in the permeability flux. Contamination is another big challenge in the membrane technology domain, which is a direct outcome of biofilm formation or aggregate formation on the membrane surface.[116] The prolonged exposure to corroding agents, contaminants, or flocculants results in a film formation leading to biofouling. Ayyavvo et al. extensively reviewed various foulants and their diminution by surface modification of the membrane, improvising the quality and functions of the membrane.[117] The film is generally composed of flocculants or microbial biomass or chemical particles of pesticides, etc.[118]

Membrane fouling happens traditionally through three modes of action, namely, pore blocking, pore constriction, and cake formation.[119] Further, depending on the origin and nature of fouling agents, foulants are categorized as biological, colloidal, scaling, and organic.[120] The factors that determine the nature of fouling on a membrane are the dimensions of the solute particles, the porosity of the membrane, the microarchitecture of the membrane surface, the surface chemistry defining its hydrophilicity or hydrophobicity, and the interaction between the solute and the membrane itself.[121] The variations in the magnitude of these factors result in different types of challenges associated with the membrane performance. Among these challenges, pore blocking is the biggest challenge that affects the performance of the membrane.[122] Biofilm formation and removal of cake that originate from fouling also degrade the filtration performance of the membrane. These problems can be addressed by the proper choice of materials for membrane fabrication, designing optimal operational conditions (which includes flow rate, temperature, and pressure), developing micro-/nanoarchitecture, and tailoring surface chemistry that independently or in combination affects the membrane permeability.[123,124]

3.2. Different Categories of Fouling. *3.2.1. Particulate Fouling.* Particulate fouling refers to the buildup of colloid particles on the membrane surface. Usually, biofluid colloids are made up of carbohydrates, protein, lipids, and many other inorganic salts. These colloidal particles bind to the pore wall of the membrane through a two-stage process. In the beginning, the colloids start to clog the pores of a membrane which reduces the permeability of the pores and thus reduces the efficacy of the membrane. In the second phase, the accumulated colloids start forming layers on the surface of a membrane, creating a cake-like structure. This reduces the lumen/pore diameter, resulting in increased hydraulic resistance and causing strong concentration polarization, which is not good for the longevity of a membrane.[125]

3.2.2. Chemical Fouling. Chemical fouling is caused by agents that are primarily organic or inorganic in nature. When biomolecules such as carbohydrates, proteins, and lipids which are soluble in the solvent are getting coagulated in the pores, it leads to organic fouling. In practice, most of the dissolved organic matter and microbial cell mass cause organic fouling. Further, the inorganic salts such as sulfate, carbonate, calcium, magnesium, etc., having low solubility or having the tendency to make a supersaturated solution are accumulated in the pores of the membrane and cause crystallization or particulate fouling.[126] Figure 2d demonstrates the antifouling rate of the pristine PSF membrane with different injection rates of gas. This figure shows a demonstration of successful resistance of a fouling test.

3.2.3. Biological Fouling. Biological fouling is caused by the microbial attack on the membrane's surface and then subsequent adhesion, accumulation, and growth of that micro-organism (MO) on the membrane surface. Due to the metabolism of the adhered MO, different biomolecules tend to form aggregates and flocs, which causes biofilm formation, ultimately causing biofouling.[127] Mainly fungi, bacteria, algae, and protozoa attack the membrane surface. The process of biofouling gets initiated when a film of polysaccharides, proteins, or humus is adsorbed on the surface of the membrane, which is also called conditioning film formation. Then the MO cells adhere to the surface of the membrane using this film as their primary attaching site. After adhering to the surface, the microbes start producing extracellular polymeric substances (EPSs) and soluble microbial products (SMPs), which strengthen the attachment to the surface and help in proliferation of the microbes.[128] Then the mature cells detach from the film matrix and affect another part of the membrane, and this cycle keeps on rotating. The attachment and detachment of biofilms to the surface depend on different factors such as rate of erosion due to turbulence, predator gazing which is caused by predatory MOs eating a chunk of the biofilm, and abrasion which is due to the collision of large colloidal particles with the biofilm chunks present on the membrane. It is observed that different parameters such as hydrophobicity, zeta potential, overall pH of the solution, and surface roughness play an important role in harboring biofoulants on the membrane surface.[129−131] Moreover, total direct cell count, quantification of ATP, biofilm formation rate, and assimilable organic carbon content are some of the popular parameters that are currently used in sensing of biofouling.

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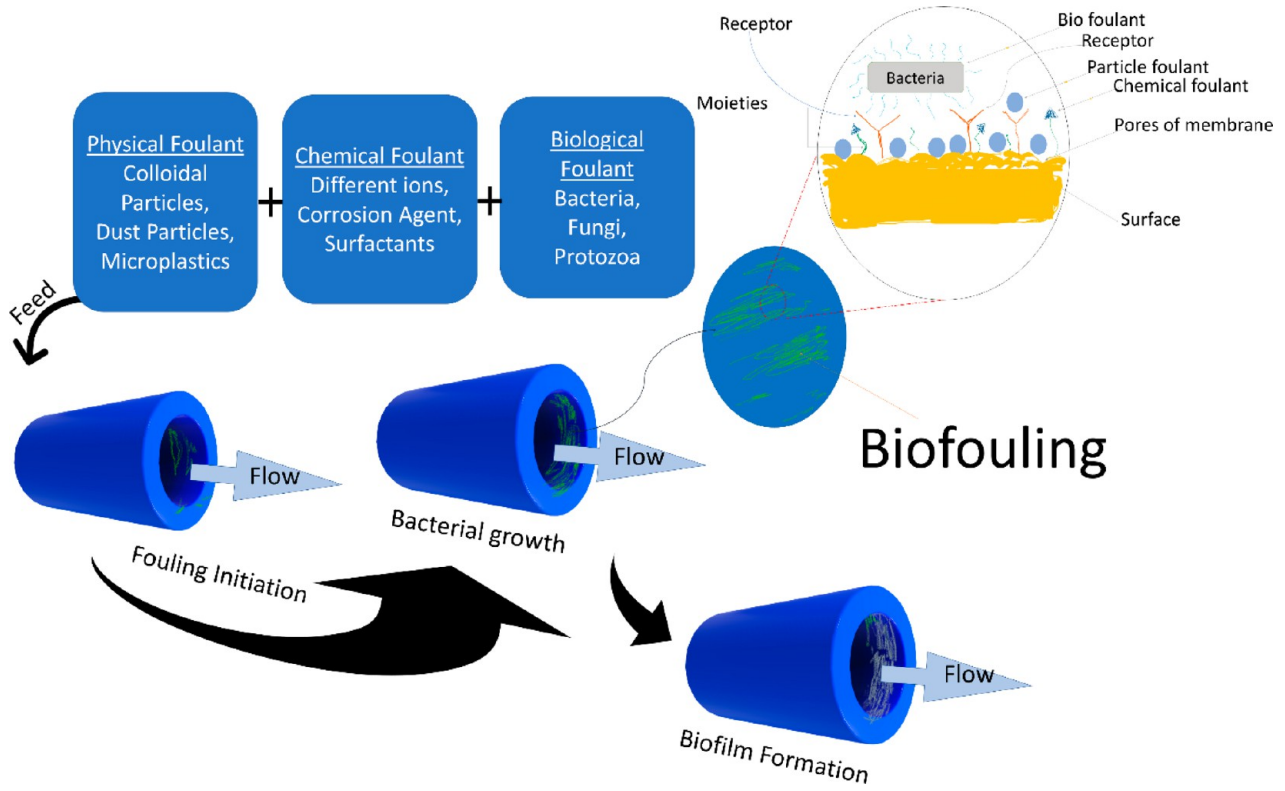

Figure 5. Schematic of different stages and causes of biofilm formation in a tube.

However, despite these parameters, scientists are facing challenges in early sensing of the biofilm formation and subsequent biofouling. This can be observed mostly at the site of transplantation for extracorporeal devices like oxygenators, etc.[132] (Figure 5).

3.3. Different Antifouling Strategies. Fouling of the membrane reduces the efficacy and the life span of a membrane. Therefore, it becomes a necessity to assess the quality, origin, causes, type of fouling, and intended application of the membrane before introducing antifouling strategies. Antifouling strategies are adopted to counter and mitigate the fouling processes[133−135] (Figure 6).

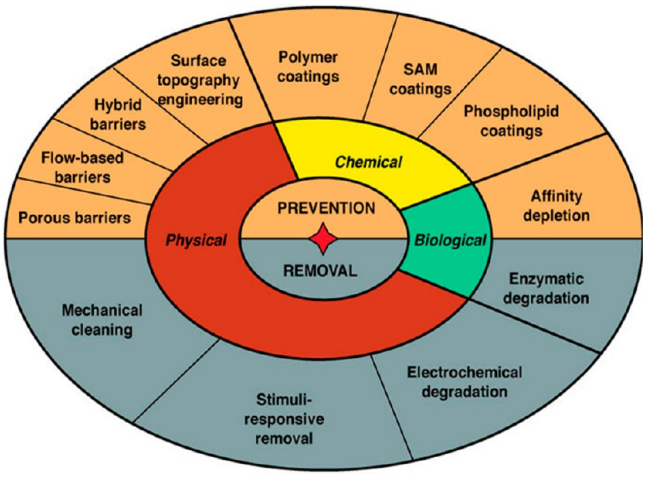

Figure 6. Overview of the antifouling strategies. Reprinted with permission from reference 119. Copyright 2022, Open Access APL Materials, AIP Publishing.

Antifouling strategies can be divided into three major categories: first, the conventional, i.e., physio-mechanical, approach; second, chemical approaches; and finally, biological approaches.[136,137] Based on the mode of action of the antifouling strategies, they can be divided into active or passive mode. The active antifouling approach includes on the surface and off the surface approaches, whereas passive fouling can be categorized into fouling release and fouling resistance. These categorizations of antifouling approaches help to determine the most suitable approach in the least amount of time. Also, it helps researchers to find solutions for each challenge in an innovative way.[138] The different types of antifouling strategies are comprehensively discussed in a tabular format in Table 3.

3.4. Efficacy of Antifouling Strategies. With the improvement and innovation of different antifouling strategies, it has become the need of the hour to distinguish and quantify the efficacy of different techniques. For that reason, it is crucial to determine the efficiency of an antifouling process, the materials used in that process, and the side effect of that process.[139,140] To effectively measure the effectiveness and efficacy of the antifouling strategies, traditionally, there are three different ways: The first is estimating the quantity of the adsorbed material on the membrane surface by exploring the initial and final weight of the membrane. The second method is to explore the longevity, stress-bearing capacity, or the physical feature of the surface of the membrane, and the third method is implementing sensors on the surface to detect the growth of the foulant material.[141,142] Generally, the first method is an affordable and easy technique to implement; however, it does not provide enough information regarding the foulant. Although the other two methods are expensive methods, they provide accurate information regarding the

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Table 3. Advantages and Disadvantages of Different Applications of Various Antifouling Strategies[a]

Strategy	Advantage	Disadvantage
Nitric-oxide-releasing materials to induce oxidative stress and initiate cell lysis	Synthetic NO donor supplements the natural sources	Highly instable, and because of that the usage requires special attention
Peptide modification of the surfaces to inhibit bacterial adhesion	Resistance to a large spectrum of protein molecules also can be modified according to the surface structure for effective performance	Costly process
Hydrophilic polymers to inhibit protein adsorption	Polyethylene glycol or PEG is used which is considered to be safe	Oxidative damage, low surface densities limit the life span
Immobilization of PEG to anchor it with the surface	Less susceptible to hydrolytic degradation than free PEG	Availability of suitable surfaces is less
Zwitterionic polymers to incorporate the super hydrophilic mechanism of action	Functional life span is long. Ligand immobilization	Costly and mostly unavailable for commercial production
Hydrophobic polymers to inhibit protein adsorption	Many hydrophobic polymers are available for commercial production	Toxicity
Lotus effect is a physical microtexturing process that mimics the action of a lotus leaf which can self-clean	Micropatterned texture increases the effectiveness of the hydrophobic mechanism of antifouling and antiadsorbent functions	Realistically not scalable
Shark-skin patterns to inhibit the growth of cells or junk on the body by using a chemical agent	Micropatterning increases the surface area to make space for the chemical agent to effect more in a moving surface	Realistically not scalable

[a]Reprinted with permission from reference 132. Copyright 2022 Open Access, Biomaterials Research, BMC.

fouling on the membrane surface.[73] When a novel polymer has been designed, it needs to have an optimized porosity along with the biocompatibility, but the special effort should be put into the building of the functional transport properties which directly control the employability of the membrane.[143] It is very important to understand the relation between antifouling strategies and the life span and efficiency of a membrane.

4. ANTIMICROBIAL PROPERTY

Another major challenge faced by many membrane experts is the colonization of the surface of a membrane by well-organized microbial communities. The biofilms harboring the microbial communities present serious threats to public health when found on medical devices, tissue-engineered products, or membrane-based devices.[144] The hydrophobic polymeric membranes are susceptible to bacterial adsorption and release bacterial exopolysaccharides that deposit on the surface and pores of the membranes, leading to a sharp decline in the permeation flux.[145] The complex biofilm matrix formed helps micro-organisms to protect themselves from environmental stresses, UV radiation, pH variation, and osmotic shock.[146,147] Conventional cleaning or normal antifouling modification may not help to eliminate bacterial growth, and therefore, a highly modified membrane having antibacterial properties is necessary to address this issue. Several strategies to prevent biofilm formation are adopted, which include coating surfaces with antimicrobial peptides (AMPs) or biocidal substances like polyquaternary amines.[148] These modified membranes have increased hydrophilicity which helps to resist fouling to a greater extent.[149,150] Traditionally antibiotics and enzymes are used in the cleaning of the membrane surfaces, by flowing antibiotic-based[151−153] solution through the channels or adding enzymatic solution[154,155] to the membrane surface. Antibiotics such as cyclodextrin, rifampin, etc. and enzymes such as α-amylase and lysozyme are tested for the purpose of membrane surface cleaning, hence inhibiting microbial growth. Different types of antimicrobial strategies which include the use of antibiotics, enzymes, nanoparticles, etc. are listed below in Table 4. The various other methods studied to fabricate antibacterial membranes are surface coating of antibacterial polymers, surface immobilization, and blending of inorganic nanomaterials and biocides of metal ions.[156]

Some renewable, biodegradable, and biocompatible polymers have been exploited from natural sources as a promising and pervasive tool for antibacterial activity. Cellulose is the most abundant natural polymer that has been explored for the fabrication of membranes. However, cellulose lacks antibacterial properties. Therefore, many bacteria-resistant substances like chitosan, zinc oxide nanoparticles, quaternary ammonium, GO, and benzalkonium chloride are amalgamated with cellulose to impart it antibacterial properties. Li et al. have developed surface amination of regenerated cellulose by functionalizing ammonium persulfate (APS), 3-aminopropyl triethoxysilane (APTES), 3-aminopropyl dimethylmethoxysilane (APDMS), and *N*-[3(trimethoxysilyl)propyl] ethylenediamine (TMSPED), in which TMSPED has three methoxy groups with the highest number of amino groups. They have been proven to exert a maximum bacteria killing ratio.[54]

Silver nanoparticle (AgNPs) have strong antimicrobial property and can be functionalized into membranes to impart antibacterial property against Gram-positive and Gram-negative bacteria. Yang et al. observed in their study that immobilization of silver nanoparticles on the surface of the polysulfone membrane surface via the polydopamine deposition method helps to increase the antifouling effect of the membrane. AgNP-blended membranes were characterized by XPS, SEM, AFM, and water contact angle measurements, and the results demonstrated promising antibacterial properties.[157] In another study, graphene oxide incorporated with Ag nanoparticles imparts antibacterial property to the membrane due to the good dispersion properties of GO. Vatanpour et al. successfully fabricated novel polyether sulfone (PES) by embedding GO, of which the hydrophilicity of the membrane is increased leading to decreased fouling Ag nanoparticles as a result of the resulting membrane, while Ag nanoparticles induce antibacterial property. The structural characteristics of the membranes were investigated using SEM, water contact angle, and overall porosity.

Polyethylene glycol (PEG) is known to be a nontoxic, mobile polymer and resists adherence of foulants through grafting, blending into membranes, or block copolymerization. Pan et al. found that if a PVDF membrane is doped with SiO_2 then the hydroxyl groups present in SiO_2−PVDF nanocomposite membranes increase the surface area, thus hindering the hydrophobic interaction between the contaminants and the

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Table 4. Different Antimicrobial Strategies for Bioartificial Membranes

Strategy	Materials Used	Mechanism	Merit	Demerit	Ref
Antibiotics	Nitrofurazone, Gentamicin, Norfloxacin, Vancomycin, Rifampin	Cell wall disintegration, DNA dissociation, pore formation, inhibition of crucial enzymes for development	Easy to use and most employed technique as an antimicrobial technique	Causes bacterial resistance formation, hence developing super bacteria, also a very costly process	151−153
Antimicrobial peptides	Abaecin, Indolicidin, Pyrrhocoricin, Nisin	Membrane lysing, inhibition of DNAK protein for replication, pore formation on the cell wall, inhibition of protein folding	Being a contact-based inhibition, it works better in comparison to antibiotic-based approaches	Loss of activity, nonspecific binding, altered peptide orientations, inadequate spreading	138,148,159−161
Bacteriophages	*S. epidermidis* bacteriophage 456	Lytic and lysogenic life cycles help these viruses to protrude the microbes cell wall or to cleave the DNA	Very specific mode of action. Quantitative and visual analysis of crystalline biofilm shows promising results. Does not promote bacterial resistance like antibiotics and nontoxic to mammalian cells	Unstable under extreme conditions. Despite overall good results, it is considered mostly in the early stage of development	162,163
Material doping	Graphene oxide, carbon nanotubes, SiO_2	Structural damage to the cell membrane and expels all the intracellular content; also employs oxidative stress and interruption to the transmembrane electron transfer chain	Easy to fabricate and use	Uncertainty regarding the long-term antibacterial efficacy and safety	54,164
Nanoparticles	ZnO, Ag, Au, TiO_2, etc.	Binds to the cell membrane and forms a pore; interferes with DNA and RNA stability	Easy to use and materials usually do not show any side effects	Cost is very high and difficult to scale up and has questionable standards for safety	37,38,41,165,166
Topography	Pyramids, ridges, surface roughness	Alters the behavior of the surface, affecting the overall binding efficacy of the microbes	Very effective as any chemical agents are not used	Difficult to scale up	123,167
Enzymatic disruption	Hydrolytic enzymes (substilin, DNase, α-amylase, lysozyme, etc.)	Pore formation, DNA/RNA destabilization, protein folding inhibition, etc.	Same efficacy as the antibiotics, but it does not cause bacterial resistance	Difficult to scale up	154,155,168

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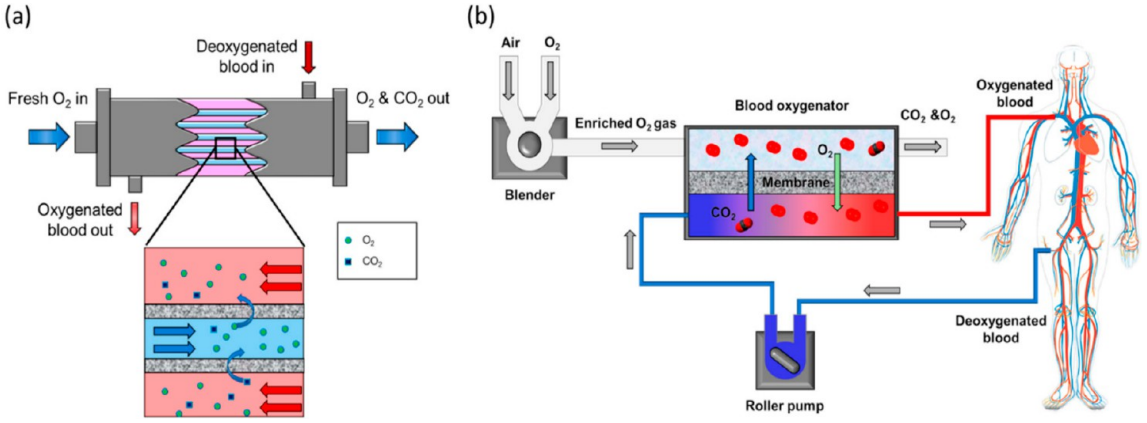

Figure 7. (a) Schematic of a hollow fiber based artificial lung. (b) Schematic of an extracorporeal membrane oxygenation device. Reprinted with permission from reference 6. Copyright 2021 Open Access, Membrane, MDPI.

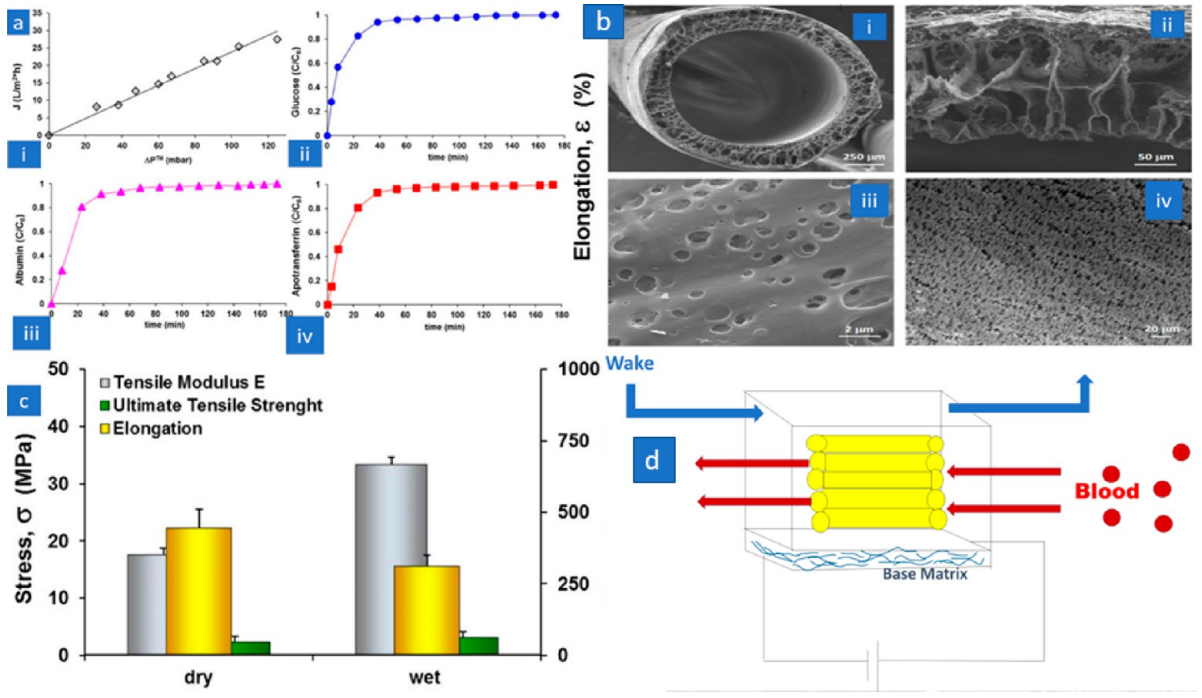

Figure 8. (a) (i) Hydraulic permeance of water in PCL HFM. Different transmembrane pressure in the presence of various solutes at different concentrations of (ii) glucose, (iii) albumin, and (iv) apotransferrin. (b) SEM images of PCL HF at different magnification. (c) Tensile strength in dry and wet conditions of PCL HFM. (d) Schematic of a bioartificial kidney. (a,b,d) Adapted with permission from reference 12. Copyright, 2021, Open Access, Membranes, MDPI.

membrane. Incorporation of Ag in the SiO_2−PVDF membrane exhibits antibacterial property as well. Further, the smoothening of the rough surface of the PVDF membrane also demonstrated the same result, when the membrane was characterized using XRD, SEM, FTIR-AFR, XPS, and AFM analysis.[158] BSA is used as a standard foulant to analyze the fouling resistance, while antibacterial activity was evaluated using three strains, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *E. coli* bacteria.[54] Another method to impose antibacterial activity to the membrane surface is through an electron beam immobilization method to functionalize bioactive compounds. Reinhardt and co-workers have prepared a PES membrane with a newly discovered peptide sequence called IL-KKA and covalently immobilized it on the membrane by using electron beam irradiation. The membrane was characterized using XPS, SEM, and water contact angle measurements, and the results demonstrated promising results against *B. subtilis*.[159]

The functionalization of relevant targeted proteins or amino acids on the membrane surface with useful and accurate functions forms a stable conjugated polymeric membrane that allows the fabrication of modified nanoparticles for a broad spectrum of applications.[160] The amalgamation of membrane-based technology and nanotechnology is also an emerging technology for the development of innovative membrane-based biomedical devices and improves the quality of living.

5. APPLICATION

5.1. Bioartificial Organ. The need for life support systems such as hemodialysis (HD), artificial lungs, or ECMO devices (Figure 7) is gradually increasing due to the emergence of several diseases, like acute or chronic renal failure and critical

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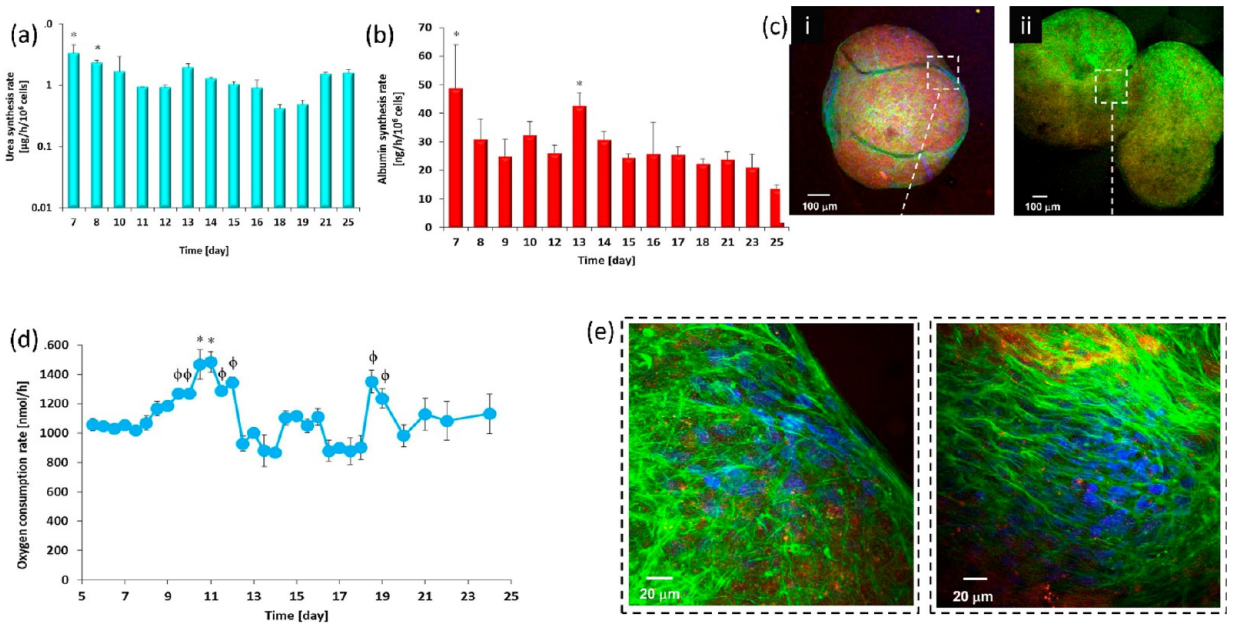

Figure 9. Primary human hepatocyte cells. (a) Urea synthesis rate of microtissue spheroids. (b) Albumin secretion rate. (c,e) CLSM image of microtissues at day 18. (d) Water consumption rate. Reproduced from ref 177 with permission from Colloids and Surfaces B: Biointerfaces, Elsevier. Copyright Elsevier, 2017.

operation procedures such as open bypass surgery, etc., which render quality of life to the patients. HD machines employ fundamental mechanics of fluid flow like adsorption, diffusion osmosis, etc., to separate uremic salts from the bloodstream by providing a counter-current stream of dialysate and blood over the surface of the semipermeable membrane.[169,170] The efficiency of separation of a HD system directly depends on the material type that is used as the membrane, as it also dictates the longevity of the membrane as well. Generally, the majority of the materials that are used in HD devices is naturally derived polymers like cellulose and synthetic polymers such as PSf, PES, PAN, PVDF, etc, out of which PS is the most widely accepted because of its high thermal stability, mechanical strength, and chemical resistance along with appreciable biocompatibility.[55,171] However, each membrane has its own limitations: a cellulose-based membrane is less expensive than a synthetic polymer, but it triggers activation of the complementary system due to the presence of hydroxyl groups; on the other hand, the synthetic membrane is costly to develop.

It has been reported that blending hydroxyapatite with a PSf membrane develops a hydrophilic−hydrophobic balance that has significantly improved the functionality of the blend membrane, and the absence of shear stress has improved the anticoagulant activity of the membrane. Thus, HA-loaded PSf membranes serve as one of the best candidates for HD application.[172] Moreover, human collagen IV, a constituent of ECM on mixing with L-3,4-dihydroxyphenylalanine (L-DOPA), can be employed as a coating on the customized HFM in order to improve the biocompatibility and separation performance which is evident from proliferation studies of human embryonic kidney cells-293 (HEK-239).[173] HFMs are used in this experiment to anchor the living cells and act as a matrix. Modi et al. and his group doped graphene oxide (GO) in HFMs to create a new type of HFM-based BAK device.[174] It is reported to have increased coagulation time and decreased hemolysis, demonstrating improved separation efficiency which was almost 3 times better than the existing commercial membranes used in a dialyzer. In another instance, Salerno et al. proposed fabrication of a 3D vascularized structure of the liver from hollow fiber membranes (HFMs) of polycaprolactone (PCL). Thereafter, they solved the challenge of spatial localization of cells by trapping the hepatocyte cells on the external surface of the HFMs and housed the endothelial cells on the inner surface of the fiber lumen.[12] Also, in the experiments, it was observed that the ammonium production increased with time before it hit a plateau, which is an important marker for the survival of the cells (Figure 8a,c,d). Artificial kidneys is one of the important areas of organ development. The principal mechanism is based on osmosis or diffusive forces. Figure 8b shows a schematic of an artificial waste removal system from blood which is synonymous to kidney functioning. At every aspect of membrane-based organ development, HFMs are being utilized because of their unique functioning. HFMs are holding great promise in the area of artificial-membrane-based organ development, and the artificial liver shown below is just one example of the success stories.

Similar to bioartificial kidneys, another modern membrane-based system that is being employed in saving lives is the bioartificial pancreas (BAP). A biodegradable hydrogel, poly(organophosphazene), as an ECM matrix carrying α-amino-ω-methyl-poly(ethylene glycol) (AMPEG) with L-isoleucine ethyl ester side groups that are injectable, thermosensitive, and biodegradable, has been developed by Park et al.. The hydrogels have been illustrated to be efficient to support cellular viability and prolonged insulin secretion when rat islets were entrapped in the gel. This hydrogel could be a potential tool for diabetic research and could be a foundation to create synthetic ECM for the development of an artificial pancreas.[10] Starting from tissue engineering to scaffold formation, artificial organ platform development, extracorporeal devices, drug delivery systems, ECM preparation, wound healing, and cell transportation for therapeutical use, all of the phenomena are directly dependent on some sort of barrier-

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based membrane, which will allow selective molecules and stop unwanted particles from getting in the way. For these applications, 3D bioprinting, decellularization, recellularization, and electrospinning methods are used. Electrospun fibers especially have shown great promise for the development of membranes, as they help to produce membranes with controllable pore sizes, which allows selective permeation of cells.[175]

5.2. Membrane Bioreactors. Membrane bioreactors have been introduced to tissue engineering as they provide a surface for the cells to adhere to and provide a constant, replenishable media supply. These reactors also provide the cells' optimal temperature, pH, and stress for their growth and proliferation. Though the membrane bioreactors seem ideal for all tissue engineering approaches, their applicability is often limited by the insufficient and nonuniform mixing of the media. They were observed by Wang et al. in a study conducted to understand the effects of pore morphologies and transport inefficiency in the case of bone tissue engineering. In this study, the example of a membrane prepared by electrospinning was considered, where the pore morphology depended entirely on the process parameters, electrospinning rate, and duration.[176] In later studies, efforts have been made to improve the reactor's design and operational parameters. Dual-chambered bioreactors developed by Javier Navarro et al. allowed for better transport mechanisms owing to the dual action of convection and diffusion patterns. Two different cell populations were developed on the two sides of the membrane and successfully paved the way for the development of skin tissue in vitro, which consists of multiple morphologically distinct layers of cells of a similar lineage.[177] This approach might also be helpful in the development of interface tissue engineering. Another approach to improve the function of the membrane reactor would be to change the overall morphology of the membrane to increase the surface area available for cell adhesion, a uniform microenvironment, and optimal mixing. Hollow fiber membranes fabricated by electrospinning have shown the potential to achieve these improvements. Ahmed et al. were able to develop a functional liver microtissue in the bioreactor.[178] In Figure 9, the survivability of the hepatocyte cells is projected through the estimation of urea and albumin synthesis and oxygen consumption rate. Also, the cellular images can be visualized in Figure 9e. PCL/HF-based membranes allowed for the liver tissue to be vascularised and retained functionality for 18 days.[179] Regenerative medicine and cell therapies often require in vitro scaffold-free tissue constructs, which is a challenge as they lose their structural stability in the free form. A hollow fiber membrane bioreactor was developed by Djeljadini et al. which allowed reversible adhesion of the cells to the membrane triggered by temperature, thereby meeting the demand for scaffold-free tissue constructs.[180] Membrane bioreactors have immense potential in tissue engineering and organoid development.

5.3. Microfluidics in Biomedical Applications. Drug discovery and development on average is a very tedious, lengthy, and cost-intensive process. Thus, the need for developing an accessible, fast, scalable, and affordable technology for drug development arose. Microfluidic device design can be easily tuned to mimic the in vivo environments, in a miniaturized spatiotemporally controlled manner, and used to develop working models of human organs, also known as organ on chips. An important aspect of these microfluidic devices is the bioartificial membranes used to provide a mechanical support layer for the cell culture, control the fluid transfusions in the microfluidic device, and separate the different tissue compartments. For instance, a polycarbonate membrane was incorporated in a microfluidic device for the development of renal tubules. With matrigel and microchannels serving as a substituent for ECM and extracapillary vessels, respectively, cultured cells behaved as an in vitro microseparation device.[181] Similarly, disease models have also been developed on chip wherein successful drug testing has been carried out.[182]

Microfluidic devices have found their applicability in carrying out biochemical reactions or as a concentrator to extract rare substances and by screening, evaluating, and studying drugs' interactions, as a point of a carefully controlled diagnostic device, and helping in understanding different fluid dynamics models and development of microvasculature models. These serve as platforms for cell culture, micromolecule synthesis[183] (PCR), and related studies, as they provide a large surface area to volume ratio, which is appropriate for cell attachments, continuous and laminar fluid flow allowing replenishment of nutrients and excretion of wastes, and controllable temperature and shear stresses.

Using these advantages, microfluidic devices are currently being employed in BAO development as well. In one project, researchers have demonstrated that sandwiching porous membranes made up of collagen fiber in between two PDMS blocks can actually help the hepatocyte cells to grow. It actually increases the secretion of urea which acts as a marker in this process.[184] Microfluidic organ-on-chip devices are playing a critical role in the development of the bioartificial organs. The usage of hollow fiber and nanofiber membranes is overcoming the challenges of the vasculature of the organs.[185] A similar approach can be seen in the area of bioartificial pancreas development. Researchers are trying to develop pancreatic organoids for insulin production via mass producing the pancreatic cells.[186] In one instance, PEG was used to create a biocompatible membrane system in order to separate and microencapsulate islet cells.[187]

Recent advances in the field generally focus on bringing microfluidics into mainstream application in drug development. One important milestone was the development of a combinatorial model for high-throughput drug screening against organoids and tumor organoids developed in situ in numerous controlled environments and pathological cases. Schuster et al. developed a device using photolithography with a bottom chamber layer where cells were cultured within the hydrogel or matrigel and a fluid flow layer or channel layer through which media and drugs are passed through the channels with a software-based programmable flow of media and drugs in a time-specific manner, high throughput screening of varied drugs, along with cells from different sources cultured to form organoids.[188] Advances in controlled fluid flow such as droplet microfluidics devices have been made to enable simultaneous encapsulation of the drugs within liposomes and screened against tumor organoids and pathological cases in a concise period.[189]

5.4. Single-Cell Analysis. Cellular heterogenicity exists within both healthy and diseased tissue, resulting in varied identifiable properties of the cells such as differential size, shape, and function. It often also presents different surface markers on the different cell types and exhibits unique responses toward drugs.[190] Cellular heterogenicity is a useful parameter for the early detection of cancer and many other

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genetic diseases. Earlier, fluorescence imaging and automatic microscopy of the cells that are nonadherent on the surface were the most common choices for assessing cellular heterogenicity.[190] Microfluidic devices for single-cell analysis are fabricated based on principles of concentrators or dividing the sample into numerous individual droplets on surface platforms, using pneumatic valves or optical/acoustic stimulation, etc.[191] Thin microporous PDMS membranes with controlled pore geometries and sizes (<35 μm) were fabricated using micropillars in a microfluidic molding tool. These free-standing membranes allowed the localization of single cells on the membrane and were efficient in cell tracking, controlled cell trapping, and analysis of the functional properties of the individual cells.[182] Drug resistance and esterase activity experimentation on HeLa cells with a detailed detection of single cell deaths in a time-dependent manner along with caspase-3 detection using florescence was also facilitated by the microporous membrane system.[182]

6. FUTURE TRENDS AND CHALLENGES

The market size of the medical membrane is estimated to be 2.93 billion USD in the year of 2022. This market is expected to grow with an astounding CAGR of 10.15% from 2023 to 2030, reaching a total market size of 6.83 billion USD.[192] Currently, it is observed that medical membranes are primarily employed in artificial kidney and lung devices. However, other applications like the development of artificial organs like the liver and pancreas, tissue engineering, and drug delivery patches are gaining momentum and being explored widely. This is because BAMs serve as important scaffolding systems that are suitable for housing cells, biomolecules, and drugs without being affected due to mass transfer limitations unlike 3D scaffolds. For instance, Roy et al. demonstrated that the BAMs to culture kidney cells develop an implantable kidney device which performs the dual function of bioseparation and kidney hormone release to compensate for the biological function of the kidney.[8] Currently, efforts have been directed to develop BAMs with designs that can create a fully functional construct of tissue for implant application using tissue engineering approaches. To meet the demand of an artificial pancreas, BAMs have been deployed in a smart material matrix membrane that releases insulin in response to the glucose concentration. Figure 10 clearly shows the current trend of the Scopus published documents. New materials and designs are constantly being explored to develop BAMs for the above applications.

For the successful implementation of these applications, microfabrication/polymer processing techniques like 3D bioprinting, decellularization, recellularization, electrospinning, etc. are used to develop membranes with controllable pore sizes, surface texture and chemistry, and physio-mechanical properties.[175] Thus, it is clear that the future trend in the field of membrane technology is heading toward precision-based membrane fabrication, where membranes will be formed according to the needs of the problem, having attributes necessary for its functioning. The holy grail of BAM technology is to create membranes that can completely mimic the 3D structure with appropriate vascularization for the development of bio organs for implant applications.

The challenge that arises in bio organ development is due to the interplay of different biological factors and parameters such as compatibility, thermal stability, chemical degradation rate, surface properties, compartmentalization of the units, etc.[193]

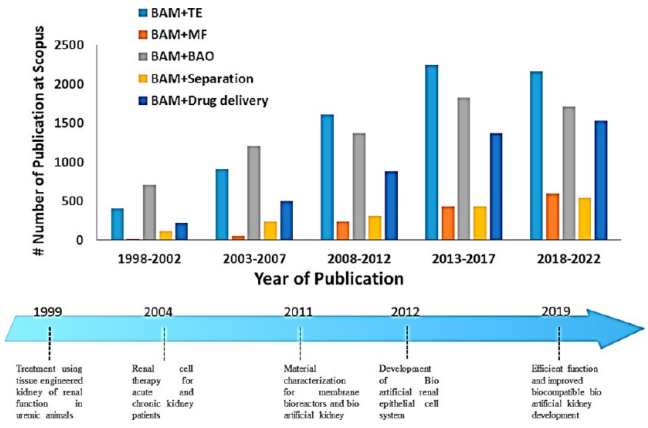

Figure 10. Timeline for bioartificial kidney development. Graphical representation of published documents at Scopus from 1998 to 2022 with the keywords bioartificial membrane (BAM), tissue engineering (TE), bioartificial organ (BAO), microfluidics (MF), separation and drug delivery.

Although membrane technology is thriving in the 21st century for its wide range of applications, it still suffers from several limitations. In fact, one of the major challenges faced by membrane science researchers is the selection and processing of materials to develop membranes. Owing to a plethora of materials like polymers, ceramics, and composites for fabricating membranes, selecting a specific material suitable for a specific purpose is a difficult challenge in the absence of a database. To overcome this challenge, it is important to understand the required physical, chemical, and biological properties of the membrane as per the need and development of a database of materials for effective screening of materials based on properties.[194,195] Physical properties such as mechanical strength, shear stability, thermal stability, elasticity, porosity, etc. play a major role in the proper functioning and life span of the membrane. However, scalable fabrication of membranes with the above properties is a huge challenge. The major fabrication processes are borrowed from either the electronic industry or traditional chemical industries. The manufacturing process borrowed from the electronic industry requires a huge investment and is limited primarily to metals/semiconductors, although their precision is great. The manufacturing processes of traditional chemical/polymer industries are unable to precisely control the pore size and porosity.[196] Moreover, they lack the ability to process polymers at different length scales at the same time which is critical for the development of BAMs. Nevertheless, few technologies have managed to develop a multiscale architecture of the developed BAMs, including electrospinning and others. However, these techniques are still struggling to produce BAMs at a commercial scale, although they have demonstrated their capabilities at the lab scale.[185,197−200]

The surface adsorption property of BAMs is primarily due to the enhanced surface area offered by nanotopologies on BAMs. However, these nanotopologies offer additional surface area for unwanted adsorption, making the BAMs vulnerable to the problem of fouling. As a result of fouling, there is an increased chance of a decrease in porosity affecting the permeability and microbial contaminations leading to the growth of biofilms and generating a toxic microenvironment unsuitable for cellular growth and proliferation. Thus, increased surface area due nanotexturing may have beneficial effects on utilizing BAMs for

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organ/tissue development, but the same enhanced surface area may be detrimental due to fouling and microbial contamination. Hence, researchers face the challenge of optimizing the surface topologies to enhance cellular growth without being affected by fouling and microbial contamination problems.

The chemical composition of the membrane decides biocompatibility; because of the high rejection rate, it is very difficult to build a membrane that has very high hemocompatibility and also prevents or reduces the hemolysis. Membranes can be tailored as per our need; different parameters such as permeability, stability, and compatibility can be tailored by using biologically originated molecules. Apart from that, membrane technology faces different types of challenges as well. Functional challenges include immune rejection, construct vascularization, construct innervation, etc., and these problems can only be observed when an artificial organ part is being transplanted; however, these problems will still be present if a fully functional BAO is being transplanted in the body. The technique behind rapid vascularization is not fully understood yet, and those membranes are still struggling to sense a neuronal stimulus.

There are a lot of scopes present in the domain of functionality of bioartificial membranes. However, functional and component challenges are not the only ones, as strategic challenges also limit the pace of the development of the bioartificial membranes. Upscaling is still a huge issue in this field, along with quality management issues and costs that are associated with it. So far, the costs of aid devices are so high that most of the population in the relatively poorer section of society is not able to afford it. Regulatory processes take time to approve any product; however, if any bypass route can be developed then the development process of these types of technologies will increase.

7. CONCLUSION

An increased demand in various sectors of the biomedical field led to the emergence of artificial membrane technology. To cater to the varying requirements in the field ranging from bioartificial organ development to separation processes, different types of membranes have been developed by simply tailoring the surface of the membrane by both chemical and physical modifications. Directed modifications improve specific functional characteristics and also counter the common drawbacks of the membranes. In recent years, researchers have turned to combining hollow fiber membranes with other different surface-active materials to develop unique membranes with greater separation potential. Carbon nanotubes are another cutting-edge innovation that was amalgamated with hollow fiber membranes to create a biocompatible platform for bioartificial organ development.[193,201] Separation technology is a domain where the requirement of a unique innovative membrane is very high. Fouling is one of the major challenges for researchers to manage in the field of membrane technology, so fouling-resistant membranes will find utility in industry, academic research, and clinical applications and is required for scale up and implementation, although there are a lot of physio-chemical, biological, and strategic challenges that need to be met before implementation of these technologies into society.

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Notes

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ACRONYMS

ECMDs Extracorporeal membrane devices
BAMs Bioartificial membranes
BAOs Bioartificial organs
CKD Chronic kidney disease
ECMO Extracorporeal membrane oxygenator
HFMs Hollow fiber membranes
CNT Carbon nanotubes
PCL Polycaprolactone
ECM Extracellular matrix
PVDF Poly(vinylidene fluoride)
PLA Poly(lactic acid)
PCL Polycaprolactone
PMMA Polymethyl methacrylate
PSU Polysulfone
PC Polycarbonate
PP Polypropylene
PLA Poly(lactic acid)
PES Polyether-sulfone
PEEK Polyether ether ketone
PAN Polyacrylonitrile
PTFE Polytetrafluoroethylene
PPSU Polyphenyl sulfone

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PVA Poly(vinyl alcohol)
PEG Polyethylene glycol
APTES Aminopropyl triethoxysilane
APDMS 3-Aminopropyl dimethylmethoxysilane
TMSPED *N*-[3-(Trimethoxysilyl)propyl] ethylenediamine
CAc Cellulose acetate
HAc Ethanoic acid
DMAc *N*,*N*-Dimethylacetamide
XPS X-ray photoelectronic spectroscopy
ATR-FTIR Attenuated total reflectance-Fourier transform infrared spectroscopy
DSC Differential scanning calorimeter
AFM Atomic force microscopy

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