ISSN: 2754-494X

Journal of Dermatology Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Exosomes: Cutting-Edge Therapies for Autoimmune Dermatologic Diseases

Reyhaneh Yarmohammadi[1*], Kimia Didehvar[2*], Jose Carlos Rivas Ferreira[3], Saeideh Hatami[4], Dorsa Bahrami Zanjanbar[5,6], Najmeh Kamali[7**] and Naser Amini[8***]**

[1]Department of Pharmaceutical Sciences, School of Pharmacy and Health Professions, University of Maryland Eastern Shore, Princess Anne, MD 21853, USA

[2]School of Medicine, Iran University of Medical Sciences, Tehran, Iran

[3]Maternal Fetal Research Laboratory (LIMaF), Department of Gynecology and Obstetrics. School of Medicine. University of Conception, Chili

[4]Department of Tissue Engineering and Regenerative Medicine, Iran University of Medical Sciences, Tehran, Iran

[5]Pharmaceutical Science Research Center, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

[6]GI Pharmacology Interest Group (GPIG), Universal Scientific Education and Research Network (USERN), Tehran, Iran

[7]Dr. Kamali aesthetic office, Mashhad, Iran

[8]Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran

ABSTRACT

Exosomes are small extracellular vesicles with bioactive substances like proteins, lipids and RNAs which are involved in cell-to-cell communication. These vehicles have the capacity to influence major biological procedures such as immune signaling, inflammation and tissue repair hence they can serve as excellent therapeutic approaches. Exosomes may be utilized for delivery of directly into targeted cells and therefore minimizing side effects and increasing the differential effects of treatment. This review focuses on the mechanisms of action and its associated roles as exosomes are being crucial player in autoimmune mediated skin diseases and also used to develop new therapeutic options. Autoimmune diseases (AID) known when immune responses of targeted autoantigens cause a tissue destruction and significantly affecting the quality of life. The current medications often have shown an adverse reactions and limited efficacy in different patient populations. Exosome, macrovesicle, and apoptotic bodies are among the extracellular vesicles found in body fluids and human tissues including blood. They have the tendency to transport the bioactive materials such as membrane receptors or proteins that are specific cells and able to make them more popular, specifically in the field of dermatology. Extracellular exosome-like vesicles are majorly found in human's largest organ (as skin) that can regulate both normal and pathological conditions through numerous ways. Recently developed drugs are highly successful for treating certain problems in different pathological conditions involving synaptogenesis. These processes are included in immune signaling, inflammation, angiogenesis that are characterized by scleroderma, melanoma, and hair loss. Skin disorders could be able to encompass abnormal behaviors in skin that are majorly involved immune signaling pathways such as inflammation. These kinds of inherent properties as stability, biocompatibility and evasion from host immunity system shows exosomes as excellent candidates for therapeutics delivery. The aim of this review is to summarize the earlier and currently available literature on how effective exosome therapy is and its possible role for showing its mechanism of action when it deals with the common dermatological conditions. We therefore attempt to emphasize the novel role of exosomes in targeting autoimmune skin diseases and their potential to be used for clinical applications.

***Co-first author:**
Kimia Didehvar, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

****Co-corresponding author:**
N. Kamali, Dr. Kamali aesthetic office, Mashhad, Iran.

*****Corresponding authors:**
Reyhaneh Yarmohammadi, Department of Pharmaceutical Sciences, School of Pharmacy and Health Professions, University of Maryland Eastern Shore, Princess Anne, MD 21853, USA.

Naser Amini, Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran Postal Code: 3762265011, Iran.

Received: May 23, 2025; **Accepted:** June 02, 2025; **Published:** July 05, 2025

Keywords: Exosomes, Extracellular Vesicles, Autoimmune Diseases, Skin

Autoimmune Diseases: An Overview

Autoimmune diseases (AID) are the severe conditions in which an immune system unknowingly attacks body tissues that has led a chronic inflammation and its related damage of tissues [1]. These diseases have led to chronicity, and therefore causing a significant mortality globally due to the complex care they require for patients. It is worth noting that autoimmune diseases disproportionately affect women approximately 80% of the cases occur in females [2]. This gender underlies to evaluate the potential role of hormones, genes, and environmental elements in the development and progression of AID. The exact underlying causes of autoimmune diseases are still unknown. However, genetic predisposition and environmental factors have been suggested as possible triggers towards their onset. There are individuals whose genetic constitution makes them more likely to develop AID while others can develop these conditions after infections exposure to certain environmental factors such as chemicals or drugs [3].

Autoimmune Conditions Fall into Two Primary Groups:

Organ-Specific Autoimmune Diseases

Herein, immunity targets a specific organ. These include:

1. **Type 1 Diabetes Mellitus (T1DM):** The pancreas has its insulin-producing beta cells destroyed by the immune response.
2. **Multiple Sclerosis (MS):** Nerve fibers within the central nervous system are attacked by an immune response destroying their myelin sheath covering.
3. **Psoriasis:** This is an autoimmune disease where rapid skin cell turnover caused by an overactive immune system result in scaly patches on the skin.

Systemic Autoimmune Diseases

These involve simultaneous immune reactions against multiple organs/tissues. They include,

1. **Systemic Lupus Erythematosus (SLE):** Immunity begins attacking several body systems including skin, joints, kidneys, and brain.
2. **Sjögren's Syndrome (SS):** Usually characterized by dry eye and mouth due to the destruction of glands that produce tears/ saliva mainly by immunity.
3. **-Rheumatoid Arthritis (RA):** It occurs when immunity attacks joints resulting in inflammation pain, and joint destruction eventually [4-7].

The main objective of treating autoimmune diseases is minimizing inflammation and preventing tissue damage. Immunosuppressive drugs, which reduce the immune system's activity are frequently used. Nevertheless, these drugs may have severe side effects like increased susceptibility to infections, bleeding of the gastrointestinal tract, and cardiovascular ailments. Moreover, stem cell transplantation as a treatment can be effective but it is usually expensive and intricate.

Emerging Role of Exosomes

Today, new treatments in the field of regenerative medicine have been presented for skin diseases and exosomes can be helpful in prevention, diagnosis, and treatment in this field [8,9]. Exosomes refer to microscopic vesicles produced by cells that play a crucial role in intercellular communication by carrying proteins, lipids, and nucleic acids [10]. Their unique features have made them gain attention recently as potential therapeutic modalities including:

- Low Immunogenicity: do not potentiate immune response making them suitable for therapy.
- Biodegradability and Low Toxicity: are natural substances that can be metabolized by our bodies thereby reducing toxicity levels.

  -Encapsulation of Bioactive Molecules: This nanovesicle transportation modality can protect such molecules as proteins or RNA until they reach their target cells where they function optimally.
- Crossing the Blood-Brain Barrier (BBB): When exosomes cross BBB it's significant because BBB poses an important challenge when treating neurological autoimmune diseases [11-14].

Exosomes

In the microenvironment, cells communicate through different ways such as paracrine, juxtacrine, and autocrine signaling [15]. In the past decades, scientists have realized that cells upon secretion of soluble elements also manufacture exosomes which are molecules that interact with other cells around and far [16]. The concept behind producing exosomes was initially understood as a process for discarding waste inside a cell. However, it has been recognized that these components play significant roles in normal and pathological biological processes [17]. Exosomes belong to the extracellular vesicle family which is classified by size and origin. They are the smallest among these members whose production involves endocytosis. Numerous molecules and procedures participate in their synthesis, intracellular transit as well as secretion. These vesicles consist of many biological elements including proteins, nucleic acids, and lipids that are released into extracellular space before reaching target cells thereafter [18].

Discovery and Function of Exosomes

They the Johnstone group identified maturing mammalian reticulocytes selectively releasing transferrin receptors and other membrane-associated proteins into multivesicular body-derived circulating vesicles, and named as exosomes [19,20]. Initially, it was believed that these vehicles were emitted by a cell to counteract excrete waste products i.e., transport receptors. Consequently, the term "exosome" has been used to refer to one among several groups of secreted extracellular vehicles [20]. Different mammals can secrete exosomes when grown on in vitro system [21]. These organelles can also be found in plasma, amniotic fluid, joint fluid cerebrospinal fluid urine saliva milk from breasts, etc. even bile medical literature reveals.

The both biological or kinetic activity of the exosomes may be differed based on whether it is in its normal or in pathological state [22]. Likely, any other alterations in amount of cytosolic calcium in immune mediated mast cells has an influence to evaluate the rate of exosomal secretion under severe allergic reactions including those seen in human K562 cell line [23]. Exosomes are mostly different from other extracellular vesicles such as macrovesicles and apoptotic bodies which are then encompasses heterogeneous populations of vacuoles that appear under electron microscopy [24]. This process occurs through many pathways involving selective protein and lipid entry into endosomal membrane; inclusion of molecules into ILVs and sorting out ILVs. Some major pathways include ESCRT machinery located on MVB membrane cytosol which recognizes Membrane transport proteins, Golgi-trans network proteins, and cell surface proteins [25]. Other pathways operate independently from ESCRT machinery.

Normal biological activities and its connected pathology could be influenced by exosomes that may act as carriers taking specialized cargo to target cells. Intercellular communication is one crucial role played by these exosomes, while others include modulating immune responses or various cellular processes. Their diagnostic potential continues to unfold about cancer, neurodegenerative disorders; autoimmune diseases among other conditions [26].

Exosomes are also an integral part of cellular communication whereby the carrier of such key biological materials between different cells are then influencing several kinds of numerous physiological and pathological processes. These special features and functions are connected for making a promising hub for research achieved at developing new diagnostic tools and therapeutic strategies [24]. Other different forms forms of extracellular vehicles (EVs), including immune cells, red blood cells, platelets, cancer cells, stem cells, and others are able to secrete a wide range of small phospholipid bilayers known as extracellular vehicles (EVs) [27]. These biocarriers contain proteins, DNA, RNA, and lipids. They are also cataegorized on the basis of their size where the three main categories are knowns as exosomes, macrovesicles (MVs), and apoptotic bodies (ABs) [28].

Exosomes are vesicles recognized from endosomes that are released through the fusion of the multivesicular body (MVB) with the plasma membrane. In particulate size, these ranges are setlled as a range from 40-100 nm and have a most variability of biological molecules like DNA, mRNA, microRNA, other non-coding RNAs, cytoplasmic proteins, membrane proteins, and lipids. In relation to cytokinesis, the process is mainly involved for the budding and separation of vesicles from the cell membrane surface which is like the cleavage stage [28, 29].

Macrovesicles (MVs) arise from cells like endothelial cells, platelets as well as erythrocytes by demonstrating a mechanism like viral budding. This confers that these vehicles respond to certain signals. They could bind with nnexin V more actively and have integrated membranes rich in phosphatidylserine [30]. The content of MVs can change in response to cellular stimuli such as during pre-thrombotic conditions when platelets release larger macrovesicles containing factors that activate endothelial cells [31]. Apoptotic bodies (ABs) represent the largest type of extracellular vesicle which are shed off by dying apoptotic cells as fragments. The formation of ABs is activated by caspase-3 that induces ROCK1 protein leading to myosin light chain phosphorylation thus causing cell membrane fragmentation. They contain various proteins, DNA and miRNAs which help in cell communication as well as transmission of diseases [32].

Dermatology Exosomes

In human system the skin is well known to act as a physical, chemical barrier and immune barrier due to being the largest organ. The integumentary system is composed of three layers, epidermis, dermis, and subcutaneous tissue. The stratum corneum which is in the outermost layer of skin is the most important part of the skin barrier made up of keratinocytes, lipids, and desmosomes [33]. The second layer of the epidermis contains mainly keratinocytes in different stages of development together with melanocytes, Langerhans cells, and other cell types. Dermis, which is the third layer contains multiple lineages of fibroblast-producing growth factors as well as extracellular matrix proteins (ECMs). Lastly, hypodermis, also known as the subcutaneous layer, contains mesenchymal stem cells (MSCs), fat cells, and connective tissues (Figure 1) [34].

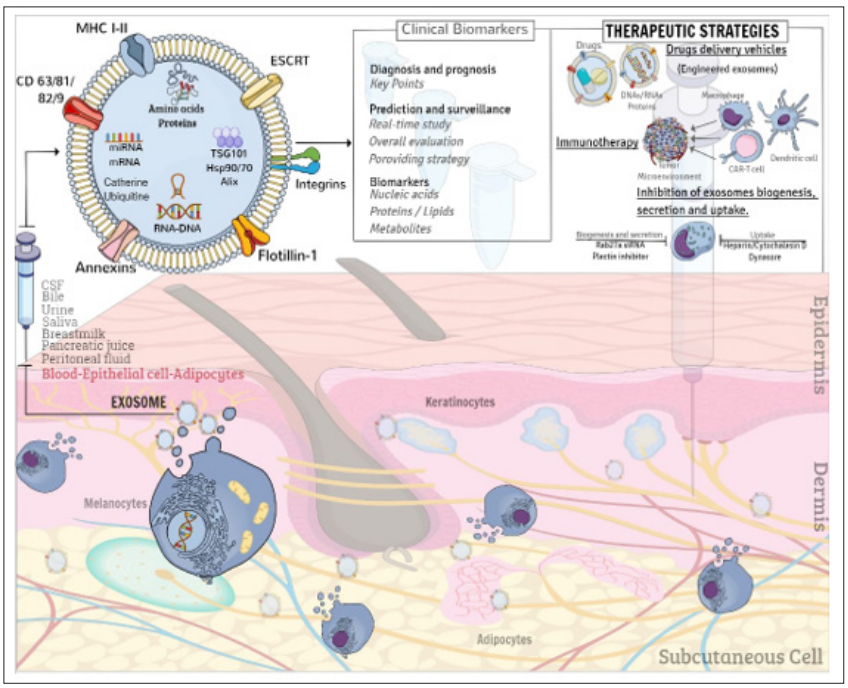

Figure 1: This figure illustrates the structure, their functions as well as therapeutic applications. Exosomes are illustrated in the middle of the drawing, and they have certain proteins that are on their surface (e.g., CD63, CD81) that transport biological molecules such as mRNA, miRNA, and proteins. Different types of cells including epithelial cells and adipocytes secrete them into fluids like blood, urine, or saliva.

Exosome's Role in Regulating Skin Pathology and Homeostasis
Skin excretion, digestion, and metabolism are among other responsible mechanism as it does aside from being a protective covering for human beings. In case of such injury's notices on the skin, its regenerative capacity can be compromised for leading to the conditions including chronic ulcers, and necrosis of skin flaps among others causing inflammation [35]. Exosomes also help to regulate various aspects connected with skin disease while contributing to their homeostasis hence their involvement in developing cell-free treatments for repairing and regenerating skin. During infections, exosomes can act as antigen-presenting vehicles carrying pathogen-derived proteins nucleic acids lipids carbohydrates [36].

Exosomes: Bioactive Substances Involved in Skin Biology
Their potential is immensely notified, as it can be used to induce the more probable vaccines and immune-based therapies. Exosomes can also present antigens and able to produce various immune responses that makes them a valuable candidate for vaccine delivery systems, while their immunomodulatory properties are also suggested as that they can be incorporated into treatment plans for different dermatopathies like psoriasis, onychomycosis, eczema, erythema, moles, and acne [37].

According to studies, exosomes from mouse keratinocytes stimulate the production of cytokines such as IL-6, IL-10, and IL-12 in dendritic cells thereby promoting their maturation process along with increasing their immune response capacity. These findings imply that skin-associated exosomes contribute to the regulation of cutaneous immunity by promoting tissue homeostasis while defending against pathogenic invaders [38].

Role of EVs (Exosomes) in Autoimmune Skin Diseases
Some studies have highlighted the key importance of extracellular vehicles (EVs) that is clinically linked to AD which is an inflammatory response caused by microbial infections with enhanced EV production which has recently become more common [39].

Recent discoveries indicate that CD3+HLA-DR+ circulating EVs may serve as markers for pathologic conditions involving T-cells like AD. Moreover, AD pathogenesis is alleviated by membrane vesicles (MVs) generated from Lactobacillus plantarum [40]. The crucial role in the pathogenesis of AD is played by MVs from Staphylococcus aureus that carry key microbial proteins and induce an inflammatory response in the host cells. Increased production of pro-inflammatory cytokines and chemokines, Th1-, Th2- and Th17-induced inflammatory changes, endothelial cell activation, and monocyte recruitment are all involved in this process. Several troubles with the release of microbial MVs have led to improved AD pathogenesis [41,42].

Also, EVs have therapeutic potential in contact hypersensitivity as they inhibit cytotoxic T-cells, T-helper cells as well as regulatory T-cells. Again, human adipose tissue mesenchymal stem-derived exosomes (ASC exosomes) can also modulate IgE and eosinophils thus ameliorating AD pathogenesis [43]. exosomes along with other EVs play significant roles in pathogenesis and possible treatment of multiple autoimmune and inflammatory skin diseases. Hence, there is an emergence as ideal candidates for new treatments targeting certain sites that can either manipulate immune responses or deliver therapeutic agents [44].

Exosomes in the Pathogenesis of Psoriasis
Psoriasis is a chronic inflammatory skin disease that is mainly characterized by dysregulation of the immune system. T cells and neutrophils are mainly involved, although their exact role remains unknown [45]. T cells are more tended to protect organisms against pathogens such as viruses or bacteria. However, in psoriasis, these T cells mistakenly attack healthy skin cells. CD4+ T cells are pivotal for correct immune responses during both host defense and inflammatory diseases [46]. Inflammation of psoriatic plaques is associated with increased numbers of neutrophils, NK cells, NKT cells, mast cells, macrophages, ILCs type 1 & 3, CD4 and CD8 T-cells [47].

Methods available for dealing with psoriasis include biological and systemic drugs as well as phototherapy among others. Topical treatments often involve glucocorticoids, vitamin D analogs, and phototherapy for mild psoriasis [48]. Systemic treatment options available include methotrexate, retinoids, or ciclosporin while biologics (monoclonal antibodies and receptor fusion proteins) are used in moderate to severe cases. The main objective of these treatments is to inhibit immune functions or slow down cell division by targeting cytokines like IL-23 [49].

The Pathogenesis of Psoriasis and the Role of Exosomes
Exosomes have been shown to play an important role in the pathogenesis of psoriasis including other inflammatory skin diseases such as autoimmune conditions [50]. Cutaneous keratinocytes play a crucial part in the pathogenesis of psoriasis through interactions involving both innate and adaptive immunity systems while interacting with the immune system complexly [51]. Keratinocytes initiate both innate and adaptive immune responses; however, they do not release most exosomes physiologically under normal conditions [52]. These exosomes are mainly activated through the NF-κB and MAPK pathways, which are mediated by psoriatic keratinocytes, resulting in overexpression of various cytokines including IL-6, IL-8, and TNF-α [53]. Consequently, these vesicles can be involved in the regulation of communication between immune cells that infiltrate the epidermal layer and keratinocytes during psoriasis [54].

Mechanisms of Exosome-Mediated Immune Modulation
Throughout several stages of inflammation leading to autoimmune diseases, exosomes regulate immune responses. Mast cells release exosomes containing phospholipase A2 which forms neo-lipid antigens recognized by CD1a-reactive T-cells leading to production of IL-22 and IL-17A. Psoriasis-derived T cells are more sensitive to phospholipase A2 than those from healthy people [55]. Thus, blocking phospholipase A2 may be a therapeutic option for patients with psoriasis because it could reduce lipid-specific CD1a-reactive T-cell-mediated inflammatory reactions [56].

MSC-Derived Exosomes in Psoriasis Treatment
Mesenchymal stromal cells (MSCs) secrete a range of extracellular vesicles such as exosomes known for their immunomodulatory properties. MSC-derived exosomes have demonstrated potential for relieving signs of psoriasis via modulating immunity. For example, topical application of MSC exosomes onto imiquimod-induced psoriatic mouse models showed a reduction in key pathogenic mediators IL-17 and IL-23 as well as terminal complement complex C5b9 [56,57]. Additionally, since these vesicles do not go beyond stratum corneum it means that their effects are limited within the outermost part of the skin [57].

The therapeutic effects of MSC exosomes are thought to be mediated through inhibition of complement activation. MSC exosomes carry CD59, a protein that regulates complement function and inhibits C5b-9 formation. This blocks IL-17 secretion by neutrophils which is an important cytokine involved in psoriasis. Also, these vesicles promote polarization of T-cells towards a regulatory phenotype (Tregs) as well as induce anti-inflammatory cytokines release [58].

The approach of MSC exosome-based therapies for psoriasis growth is analogous to other therapeutics. Firstly, there are preliminary stages requiring the preparation of characterized MSC exosomes with proven efficacy in pertinent preclinical animal models. Several issues that address concerns such as scalability and reproducibility must be taken into consideration for regulatory compliance during the making of such exosomes. Immortalized MSC lines may be used to produce a consistent supply of similar exosomes with minimum functional heterogeneity. Exosomes, especially those derived from MSCs, show promise in treating psoriasis by modulating immune responses and reducing inflammation. This has brought their potential as an effective treatment for chronic skin condition like psoriasis into focus due to their selective target of specific immune pathways and cytokines involved in the pathogenesis of this disease.

Exosomes in the Pathogenesis of Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that affects mostly women at a higher rate than men [59]. This malady involves multiple organs such as the skin, kidney, and central nervous system with significant morbidity and mortality associated with lupus nephritis [60]. The mechanism of SLE pathogenesis is not fully known but it has been proposed that it results from interplay between genetic predisposition, environmental stimuli, and immune dysfunction [61]. The disease is marked by alternating periods of relapse and remission posing management difficulties.

In SLE, B cell hyperactivity in the immune system results in the production of various autoantibodies [62]. These autoantibodies bind to nuclear antigens like dsDNA and ribonucleoproteins producing immune complexes that deposit in different tissues resulting in inflammation throughout the body. Traditional treatment regimens for mild SLE include NSAIDs and antimalarials [63]. However, severe cases are required for the administration of potent immunosuppressive drugs such as glucocorticoids, azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, and methotrexate [63]. Despite an effectiveness of these medications, it has numerous adverse effects hence there is a need to develop more specific or safer treatments. Recently developed knowledge on the genetic molecular cellular basis of autoimmune diseases has opened new frontiers for fresh therapeutic strategies which involve exosome use.

Exosomes are small membrane-enclosed vesicles involved in cell-to-cell communication and regulation of immunity. T-cell-derived exosomes have been reported to be over-expressed in individuals with SLE. These exosomes carry various proteins including protein phosphatases protein kinases and metabolic enzymes that facilitate the disease by enhancing the production of autoantibodies thereby causing an increase in the proportion of plasma B cells leading to an inflammatory state across many organs [64]. To target exosome or its cargo could therefore be a novel approach to treating SLE. Exosomes possess various characteristics that make them suitable for use in therapeutics; they are stable over long periods, easily preserved, protect their cargo from degradation, evade immune recognition, and can transverse biological barriers [65]. Henceforth, they can be expected to deliver therapeutic agents that can ameliorate symptoms and reduce tissue damage or minimize side effects of conventional treatments. Accordingly, patients' long-term prognosis and survival with SLE may be improved.

Potential Therapeutic Applications of Exosomes in SLE

Diagnostic Biomarkers

Exosomes hold promise as biomarkers for diagnosing SLE and monitoring disease activity. Studies have also indicated that certain miRNAs as well as proteins consists of inner exosomes and are reflective of pathological state hence serving possible non-invasive means for diagnosis [66].

Drug Delivery

The use of exosomes in carrying medicinal drugs directly to the required tissues is possible. This is due to the ability of such substances to penetrate through biological barriers without being detected by the immune system, which makes them a good choice for targeted delivery. For example, exosomes with anti-inflammatory drugs or genetic material can be used to possibly modulate immune responses and reduce inflammation in SLE [67].

Immune Regulation

There are indications that exosomes play some roles in immunity modulation. Treg cell-derived exosomes have immunosuppressive functionalities that could be exploited to counter hyperactive immune reactions witnessed during the SLE disease process. These exosomes transfer regulatory molecules to effector T cells lowering the body's inflammatory response and promoting immune tolerance [68, 69].

Exosome-based therapies have immensly recognzied for its propensate potential but face several major challenges. It is important that we understand how exactly these substances lead to SLE development. Moreover, it is important that there exist standardized protocols for the isolation of exosomes, characterizing them, and determining their function to ensure reproducibility and efficacy in clinical applications [70]. Therefore, more investigations are also needed to fully elucidate the role of exosomes in SLE and to come up with strong protocols for therapeutic uses.

In conclusion, the exploration of exosome nature within SLE scenario opens new frontiers in AD research. By exploiting specific properties of exosome technology, novel diagnosis systems and treatments for patients with SLE could potentially give better health outcomes improving their quality of life in future days to come ultimately leading to enhanced condition toward longevity.

Exosomes in Bullous Pemphigoid: Potential Therapeutic and Diagnostic Approaches

The disease of bullous pemphigoid (BP) is marked by the presence of autoantibodies against hemidesmosomal proteins, causing subepidermal blistering. BP pricks mainly elderly individuals and occurs as itchy blisters that are tense over inflamed or uninvolved skin [71]. The leading target proteins for such autoantibodies are structural ones like collagen XVII (BP180) or dystonin (BP230) [72]. The most applied therapy in BP is oral corticosteroids, although these drugs have significant adverse effects [73]. Recent

research has characterized exosomes found in BP blister fluids and revealed their pro-inflammatory role. These very small vesicles contain CD63, CD81 and CD9 markers. When keratinocytes Uptake them it initiates an inflammatory response through the release of cytokines and chemokines This suggests that exosomes might interact with molecules associated with autoantigens such as BP180 and BP230 during this period of bullous pemphigoid pathogenesis [74]. Exosomes shuttle antibodies implicated in the development of BP including anti-BP180 and anti-BP230 antibodies. Once inside a cell, these antibodies can activate immune responses [75]. Though unclear if exosome inflammation contributes to disease initiation; studies on its biology may provide new treatment approaches for bullous pemphigoid together with alternative diagnostic biomarkers. Therefore, understanding how exosomes function within the immune system could be highly beneficial for developing therapeutic strategies that improve patient outcomes.

Potential Treatment Methods Involving Exosomes

Exosome Inhibition
Targeting Exosomal Pathways: Specifically blocking the uptake or signaling pathways activated by exosomes through inhibitors could help reduce inflammatory response in BP. For example, inhibition of ERK1/2 and STAT3 pathways could decrease cytokine production resulting in neutrophil recruitment [76].

Exosome-based Therapeutics
Therapeutic Exosomes: Engineering exosomes to carry anti-inflammatory molecules or therapeutic agents could help modulate the immune response. These exosomes can be designed to deliver drugs or RNA molecules that inhibit the pathogenic effects of autoantibodies in BP [77].

Diagnostic Biomarkers
Exosomal Biomarkers: Identifying specific proteins or RNA molecules within BP-derived exosomes could serve as biomarkers for early diagnosis and monitoring of disease progression. This may eventually lead to more precise and timely treatments [76].

Combination Therapies
Combining Exosome Therapy with Existing Treatments: Exosome-based therapies combined with conventional remedies like corticosteroids or immunosuppressive agents and growth factors could help enhance treatment efficacy and minimize side effects [78]. This scenario may even allow for reduced corticosteroid dosages, thereby minimizing their adverse effects [79].

Conclusion and Perspectives
We have a lot to learn about the etiology of autoimmune diseases (AID); how to diagnose them effectively, what treatment methods to use or how they can be prevented completely. This means that it will be difficult to find an ideal biomarker or drug that will meet the ever-increasing demand for better therapies. For several decades now, researchers and doctors around the world have sought new ways of diagnosing, treating, and preventing AID.

Future Directions in Exosome Treatment of AID
Several important aspects need more research with regards to exosome therapy for autoimmune conditions:

- **Separation and Purification:** Developing efficient methods for isolation and purification of exosomes is pivotal [80].
- **Understanding Biogenesis and Targeting:** Understanding fully biogenesis as well as targeting mechanism in exosomes.
- **In Vivo Assessment:** Determining the efficiency including safety of exosome-based treatments by testing their influence on live organisms.
- **Clinical Applications:** The translation of findings from research into clinical applications used in treatment for AID sufferers. Despite many challenges faced by using these endogenous vesicles, there are great possibilities for using them as therapeutic agents thus representing a potentially new generation of advanced drug therapy in biomedicine. With further investigations on the biology and functions of exosomes unmasking characteristics of cell-based replacement therapies, they will most likely become popular clinical alternatives to autoimmune disease management [81].

Exosomes as Therapeutic and Diagnostic Tools
Through studying various autoimmune diseases characterized by exosomes we can optimize them as preventive/therapeutic tools against human diseases like cancer. In addition, this study will introduce novel biomarkers to select correct treatment modalities during disease diagnosis. Only a few decades ago it was found out that exosomes could function as stimulators immune response, potential biomarkers, or therapeutics against autoimmune disorders. Also now widely accepted is the fact that these vehicles play important roles during physiological processes besides pathological settings linked with these ailments [81].

There are several aspects that make exosomes promising candidates for disease therapy:

- **Isolation and Stability:** Exosomes can be collected from various body fluids and remain stable for prolonged time periods at -80°C (81).
- **Half-Life:** When in the body, exosomes have relatively long half-life [79, 80].
- **Bioactive Substance Protection:** Enzymatic degradation of bioactive substances is prevented by exosome encapsulation.
- **Modifiability:** Each patient can have his or her own type of exosome treatment.

The Immuno-Modulating Effects of Exosomes
Exosomes have been found to mediate immunomodulation directly or indirectly in some autoimmune diseases. This may be includeed as the modulation of immunity and as well as influence on different cellular or molecular processes. However, mechanisms behind these intricate processes are not yet completely known and both basic and applied research involving exosomes is still in its infancy.

Despite major obstacles in application aspects regarding the use of exosomes, their distinct features and possible applications within the biomedical field show great potential. Further investigations will expand their clinical utilities thereby making them potent therapeutic tools against AID. Thus, through doing comprehensive studies we will improve our understanding and employment of the particles leading to novel treatments with better outcomes among patients.

Declaration

Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial.

Funding source
None

Publisher's Note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed, or endorsed by the publisher.

References

1. Miao C, Wang X, Zhou W, Huang J (2021) The emerging roles of exosomes in autoimmune diseases, with special emphasis on microRNAs in exosomes, Pharmacological research 169: 105680.
2. Angum F, Khan T, Kaler J, Siddiqui L, Hussain A (2020) The prevalence of autoimmune disorders in women: a narrative review, Cureus 12.
3. Migliore L, Nicoli V, Stoccoro A (2021) Gender specific differences in disease susceptibility: the role of epigenetics, Biomedicines 9: 652.
4. Cobo Vuilleumier N, Gauthier BR, (2020) Time for a paradigm shift in treating type 1 diabetes mellitus: coupling inflammation to islet regeneration, Metabolism 104: 154137.
5. Leslie KA (2019) Signal Transducer and Activator of Transcription 6 (STAT6) as a Regulator of Pancreatic Beta Cell Health, University of Exeter (United Kingdom).
6. Fox RI (2012) Sjögren's syndrome: an immunological perspective, Oxford University Press New York 43-61.
7. Shrivastava AK, Pandey A (2013) Inflammation and rheumatoid arthritis, Journal of physiology and biochemistry 69: 335-347.
8. Seresht HB, Aghajanzadeh MS, Imani R, Haghbin Nazarpak M (2024) Structural relaxation in a Schiff base-crosslinked aldehyde modified xanthan gum/gelatin hydrogel: Experimental and numerical validation using linear poroelasticity model. Polymers for Advanced Technologies 35: e6402.
9. Karimmirza E, Manavizadeh N (2024) Fabrication of Wearable Flexible Triboelectric Nanogenerators Using E-Glass as a Skin Substitute in Skin-Contact Devices. Journal of Advanced Materials and Technologies 13: 40-62.
10. Jella KK, Nasti TH, Li Z, Malla SR, Buchwald ZS, et al. (2018) Exosomes, their biogenesis and role in inter-cellular communication, tumor microenvironment and cancer immunotherapy, Vaccines 6: 69.
11. Zhou S, Huang J, Zhang Y, Yu H, Wang X (2024) Exosomes in Action: Unraveling Their Role in Autoimmune Diseases and Exploring Potential Therapeutic Applications, Immune Network 24.
12. Raimondo S, Giavaresi G, Lorico A, Alessandro R (2019) Extracellular vesicles as biological shuttles for targeted therapies, international journal of molecular sciences 20: 1848.
13. Xia X, Wang Y, Huang Y, Zhang H, Lu H, (2019) Exosomal miRNAs in central nervous system diseases: biomarkers, pathological mediators, protective factors and therapeutic agents, Progress in neurobiology 183: 101694.
14. Xu Z, Xu Y, Zhang K, Liu Y, Liang Q, (2023) Plant-derived extracellular vesicles (PDEVs) in nanomedicine for human disease and therapeutic modalities, Journal of nanobiotechnology 21: 114.
15. Brücher BL, Jamall IS (2014) Cell-cell communication in the tumor microenvironment, carcinogenesis, and anticancer treatment, Cellular Physiology and Biochemistry 34: 213-243.
16. Corrado C, Raimondo S, Chiesi A, Ciccia F, De Leo G, et al. (2013) Exosomes as intercellular signaling organelles involved in health and disease: basic science and clinical applications, international journal of molecular sciences 14: 5338-5366.
17. Hessvik NP, Llorente A (2018) Current knowledge on exosome biogenesis and release, Cellular and Molecular Life Sciences 75: 193-208.
18. Di Bella MA (2022) Overview and update on extracellular vesicles: considerations on exosomes and their application in modern medicine, Biology 11: 804.
19. Lin J, Li J, Huang B, Liu J, Chen X, et al. (2015) Exosomes: novel biomarkers for clinical diagnosis, The scientific world journal 657086.
20. Nassar WF, Mostafa MAA (2014) Clinical impact of apparent structural and functional similarities between extracellular vesicles RNA (EVs RNA) and chronic RNA viruses. https://www.sciencepublishinggroup.com/article/10.11648/j.cb.20140205.11.
21. Mincheva Nilsson L, Baranov V, Nagaeva O, Dehlin E, (2016) Isolation and characterization of exosomes from cultures of tissue explants and cell lines, Current protocols in immunology 115: 1- 21.
22. Doyle LM (2019) Targeted Proteomics for Exosome Analysis and Its Application to Develop Blood Markers of Liver Drug-Metabolizing Enzymes, University of Kansas.
23. Savina A, Furlán M, Vidal M, Colombo MI (2003) Exosome release is regulated by a calcium-dependent mechanism in K562 cells, Journal of Biological Chemistry 278: 20083-20090.
24. Mastronikolis NS, Kyrodimos E, Spyropoulou D, Delides A, Giotakis E, et al. (2023) The role of exosomes in epithelial–to-mesenchymal transition and cell functional properties in head and neck cancer, Cancers 15: 2156.
25. Elkin SR, Lakoduk AM, Schmid SL (2016) Endocytic pathways and endosomal trafficking: a primer, Wiener Medizinische Wochenschrift 166: 196-204.
26. Hurley JH, Hanson PI (2010) Membrane budding and scission by the ESCRT machinery: it's all in the neck, Nature reviews Molecular cell biology 11: 556-566.
27. Kumar MA, Baba SK, Sadida HQ, Marzooqi SA, Jerobin J, et al. (2024) Extracellular vesicles as tools and targets in therapy for diseases, Signal transduction and targeted therapy 9: 27.
28. Kalluri R, LeBleu VS (2020) The biology, function, and biomedical applications of exosomes, Science 367: eaau6977.
29. Fais S, Logozzi M, Lugini L, Federici C, Azzarito T, et al. (2013) Exosomes: the ideal nanovectors for biodelivery, biological chemistry 394: 1-15.
30. Zarà M, Guidetti GF, Camera M, Canobbio I, Amadio P, et al. (2019) Biology and role of extracellular vesicles (EVs) in the pathogenesis of thrombosis, international journal of molecular sciences 20: 2840.
31. Lv Y, Tan J, Miao Y, Zhang Q (2019) The role of microvesicles and its active molecules in regulating cellular biology, Journal of Cellular and Molecular Medicine 23: 7894-7904.
32. Battistelli M, Falcieri E (2021) Apoptotic bodies: particular extracellular vesicles involved in intercellular communication, Advances in Medical Biochemistry, Genomics, Physiology, and Pathology 473-486.
33. Zhang C, Merana GR, Harris Tryon T, Scharschmidt TC (2022) Skin immunity: dissecting the complex biology of our body's outer barrier, Mucosal Immunology 15: 551-561.
34. Goodarzi P, Falahzadeh K, Nematizadeh M, Farazandeh P, Payab M, et al. (2018) Tissue engineered skin substitutes, Cell Biology and Translational Medicine, Volume 3: Stem Cells,

Bio-materials and Tissue Engineering 143-188.
35. Shi H, Wang M, Sun Y, Yang D, Xu W, et al. (2021) Exosomes: emerging cell-free based therapeutics in dermatologic diseases, Frontiers in Cell and Developmental Biology 9: 736022.
36. Tienda Vázquez MA, Hanel JM, Márquez Arteaga EM, Salgado Álvarez AP, Scheckhuber CQ, et al. (2023) Exosomes: a promising strategy for repair, regeneration and treatment of skin disorders, Cells 12: 1625.
37. Negahdaripour M, Vakili B, Nezafat N (2022) Exosome-based vaccines and their position in next generation vaccines, International Immunopharmacology 113: 109265.
38. Ha DH, Kim Hk, Lee J, Kwon HH, Park GH, et al. (2020) Mesenchymal stem/stromal cell-derived exosomes for immunomodulatory therapeutics and skin regeneration, Cells 9: 1157.
39. Xie J, Haesebrouck F, Van Hoecke L, Vandenbroucke RE (2023) Bacterial extracellular vesicles: an emerging avenue to tackle diseases, Trends in Microbiology 31: 1206-1224.
40. Oba R, Isomura M, Igarashi A, Nagata K (2019) Circulating CD3+ HLA-DR+ Extracellular Vesicles as a Marker for Th1/Tc1-Type Immune Responses, Journal of immunology research 6720819.
41. Salazar F, Brown GD (2018) Antifungal innate immunity: a perspective from the last 10 years, Journal of innate immunity 10: 373-397.
42. Khan AQ, Akhtar S, Prabhu KS, Zarif L, Khan R, et al. (2020) Exosomes: emerging diagnostic and therapeutic targets in cutaneous diseases, International Journal of Molecular Sciences 21: 9264.
43. Han Y, Yang J, Fang J, Zhou Y, Candi E, et al. (2022) The secretion profile of mesenchymal stem cells and potential applications in treating human diseases, Signal Transduction and Targeted Therapy 7: 92.
44. Hazrati A, Soudi S, Malekpour K, Mahmoudi M, Rahimi A, et al (2022) Immune cells-derived exosomes function as a double-edged sword: role in disease progression and their therapeutic applications, Biomarker Research 10: 30.
45. Bos J, De Rie M, Teunissen M, Piskin G (2005) Psoriasis: dysregulation of innate immunity, British Journal of Dermatology 152: 1098-1107.
46. Jesús Gil CD (2021) Role of CLA+ T lymphocytes in the mechanisms triggering psoriasis.
47. Sieminska I, Pieniawska M, Grzywa TM (2024) The Immunology of Psoriasis—Current Concepts in Pathogenesis, Clinical Reviews in Allergy & Immunology 1-28.
48. Afifi T, De Gannes G, Huang C, Zhou Y (2005) Topical therapies for psoriasis: evidence-based review, Canadian family physician 51: 519-525.
49. Mohd Noor AA, Azlan M, Mohd Redzwan N (2022) Orchestrated cytokines mediated by biologics in psoriasis and its mechanisms of action, Biomedicines 10: 498.
50. Wang WM, Wu C, Jin HZ (2019) Exosomes in chronic inflammatory skin diseases and skin tumors, Experimental dermatology 28: 213-218.
51. Wolfram S (2019) Cellular automaton fluids 1: Basic theory, Lattice Gas Methods for Partial Differential Equations, CRC Press 19-74.
52. Golan T, Sella T, O'Reilly EM, Katz MH, Epelbaum R, et al (2017) Overall survival and clinical characteristics of BRCA mutation carriers with stage I/II pancreatic cancer, British journal of cancer 116: 697-702.
53. Yang J, Li S, Su J, Yu X (2013) Continuous nonsingular terminal sliding mode control for systems with mismatched disturbances, Automatica 49: 2287-2291.
54. Lei Y, Yang K, Wang B, Sheng Y, Bird BW, et al. (2014) Response of inland lake dynamics over the Tibetan Plateau to climate change, Climatic Change 125: 281-290.
55. Kim ES, Chin BS, Kang CK, Kim NJ, Kang YM, et al. (2020) Clinical course and outcomes of patients with severe acute respiratory syndrome coronavirus 2 infection: a preliminary report of the first 28 patients from the Korean cohort study on COVID-19, Journal of Korean medical science 35.
56. Diotallevi F, Di Vincenzo M, Martina E, Radi G, Lariccia V, et al. (2022) Mesenchymal stem cells and psoriasis: systematic review, International Journal of Molecular Sciences 23: 15080.
57. Cevc G (2004) Lipid vesicles and other colloids as drug carriers on the skin, Advanced drug delivery reviews 56: 675-711.
58. Zhang B, Lai RC, Sim WK, Choo ABH, Lane EB, et al. (2021) Topical application of mesenchymal stem cell exosomes alleviates the imiquimod induced psoriasis-like inflammation, international journal of molecular sciences 22: 720.
59. Pons Estel GJ, Ugarte Gil MF, Alarcón GS (2017) Epidemiology of systemic lupus erythematosus, Expert review of clinical immunology 13: 799-814.
60. Hafeez MH, Safdar W, Arshad A, Talpur F, Ali Y, et al. (2023) Systemic Lupus Erythematosus and its major organ complications: a narrative review on available literature, Liaquat National Journal of Primary Care 5: 1-10.
61. Tsokos GC, Lo MS, Reis PC, Sullivan KE (2016) New insights into the immunopathogenesis of systemic lupus erythematosus, Nature Reviews Rheumatology 12: 716-730.
62. Ameer MA, Chaudhry H, Mushtaq J, Khan OS, Babar M, et al. (2022) An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management, Cureus 14.
63. Ruiz Irastorza G, Bertsias G (2020) Treating systemic lupus erythematosus in the 21st century: new drugs and new perspectives on old drugs, Rheumatology 59: 69-81.
64. Hao Y, Chen P, Zhang X, Shao Y, Xu Y, Qian W (2021) The effects of tumor-derived exosomes on T-cell function and efficacy of cancer immunotherapy, ImmunoMedicine 1: e1029.
65. Finbloom JA, Sousa F, Stevens MM, Desai TA (2020) Engineering the drug carrier biointerface to overcome biological barriers to drug delivery, Advanced drug delivery reviews 167: 89-108.
66. Yuan YG, Wang JL, Zhang YX, Li L, Reza AMMT, et al. (2023) Biogenesis, composition and potential therapeutic applications of mesenchymal stem cells derived exosomes in various diseases, International Journal of Nanomedicine 3177-3210.
67. Ha D, Yang N, Nadithe V (2016) Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: current perspectives and future challenges, Acta Pharmaceutica Sinica B 6: 287-296.
68. Gangadaran P, Madhyastha H, Madhyastha R, Rajendran RL, Nakajima Y, et al. (2023) The emerging role of exosomes in innate immunity, diagnosis and therapy, Frontiers in Immunology 13: 1085057.
69. Jin K, Parreau S, Warrington KJ, Koster MJ, Berry GJ, et al. (2022) Regulatory T cells in autoimmune vasculitis, Frontiers in immunology 13: 844300.
70. Kim HI, Park J, Zhu Y, Wang X, Han Y, et al. (2024) Recent advances in extracellular vesicles for therapeutic cargo delivery, Experimental & Molecular Medicine 56: 836-849.

71. Moro F, Fania L, Sinagra JLM, Salemme A, Di Zenzo G (2020) Bullous pemphigoid: trigger and predisposing factors, Biomolecules 10: 1432.
72. Goletz S, Zillikens D, Schmidt E (2017) Structural proteins of the dermal-epidermal junction targeted by autoantibodies in pemphigoid diseases, Experimental dermatology 26: 1154-1162.
73. Giudice A, Antonelli A, Chiarella E, Baudi F, Barni T, et al. (2020) The case of medication-related osteonecrosis of the jaw addressed from a pathogenic point of view. Innovative therapeutic strategies: Focus on the most recent discoveries on oral mesenchymal stem cell-derived exosomes, Pharmaceuticals 13: 423.
74. Fang H, Shao S, Jiang M, Dang E, Shen S, et al. (2018) Proinflammatory role of blister fluid-derived exosomes in bullous pemphigoid, The Journal of Pathology 245: 114-125.
75. Cole C, Borradori L, Amber KT (2022) Deciphering the contribution of BP230 autoantibodies in bullous pemphigoid, Antibodies 11: 44.
76. Genovese G, Di Zenzo G, Cozzani E, Berti E, Cugno M, et al. (2019) New insights into the pathogenesis of bullous pemphigoid: 2019 update, Frontiers in Immunology 10: 1506.
77. Afarideh M, Borucki R, Werth VP (2022) A review of the immunologic pathways involved in bullous pemphigoid and novel therapeutic targets, Journal of Clinical Medicine 11: 2856.
78. Sisakht MM, Rezaeinejad A, Didehvar K, Doust-Vaghe YK, Behrangi E, et al. (2025) Evaluation of topical adjuvant treatment of psoriasis with recombinant epidermal growth factor to control the e-regulation of EGFR: a clinical study. SN Comprehensive Clinical Medicine 7: 1.
79. Xu Z, Zeng S, Gong Z, Yan Y (2020) Exosome-based immunotherapy: a promising approach for cancer treatment, Molecular cancer 19: 1-16.
80. Chen J, Li P, Zhang T, Xu Z, Huang X, et al. (2022) Review on strategies and technologies for exosome isolation and purification, Frontiers in bioengineering and biotechnology 9: 811971.
81. Arenaccio C, Chiozzini C, Ferrantelli F, Leone P, Olivetta E, et al. (2019) Exosomes in therapy: engineering, pharmacokinetics and future applications, Current Drug Targets 20: 87-95.