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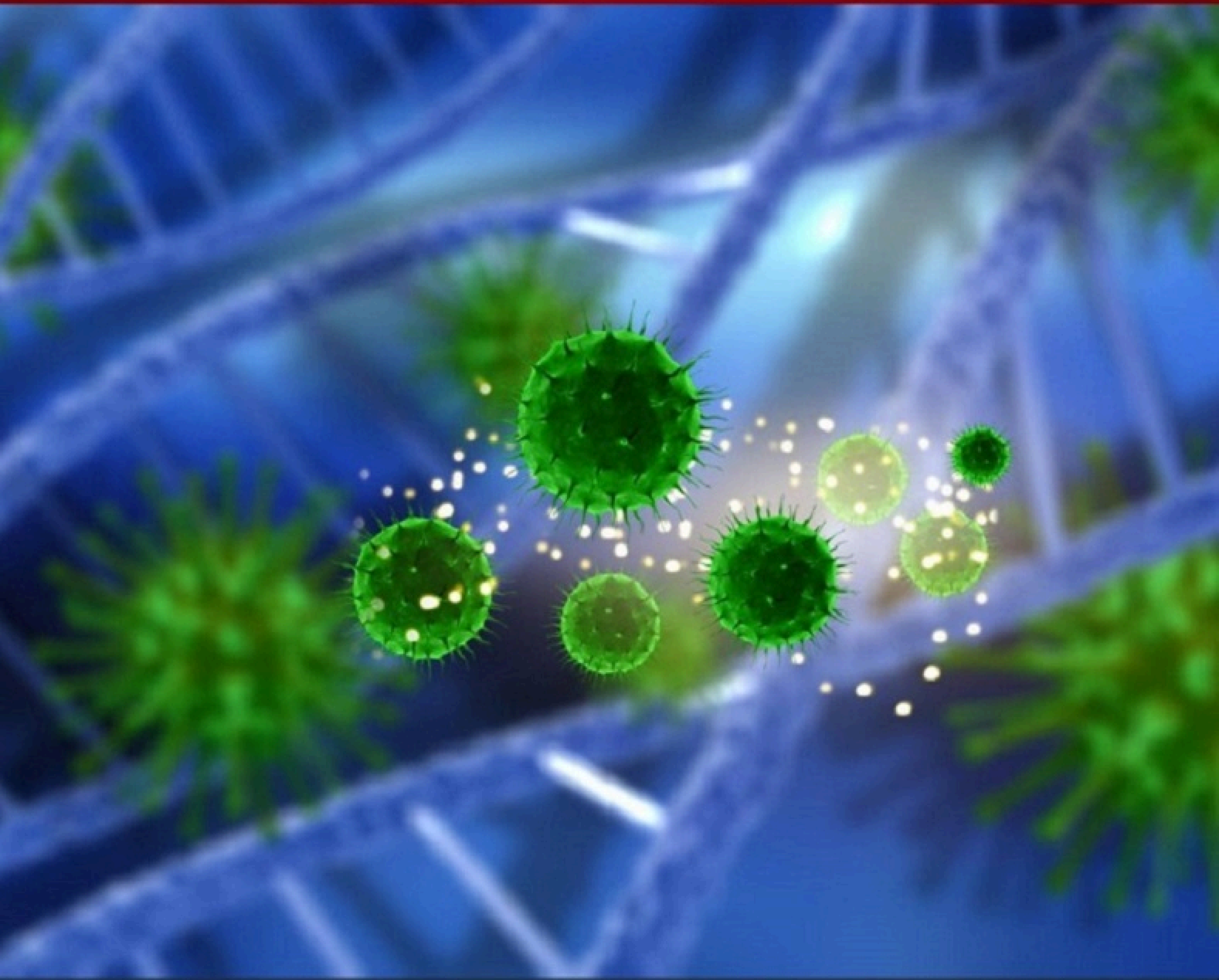

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ACD40-CD40L Co-Stimulatory Pathway: A Promising Immune-Therapeutic Target in Systemic Lupus Erythematosus

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Abstract:

Therapeutic approaches for the treatment of lupus nephritis and systemic lupus erythematosus have emerged from the inhibition of the CD40-CD40L pathway. Early-phase clinical trials and preclinical studies have underlined the efficacy of this approach by showing declines in renal inflammation, autoantibody concentrations, and proteinuria, so indicating changes in important disease markers. Second-generation anti-CD40 and anti-CD40L antibodies including BI 655064, Iscalimab, and Dapirolizumab pegol offer a safer and more effective treatment alternative that has lessened safety concerns about thromboembolic events recorded in past treatments. These new molecules are meant to be more selective targets, so reducing undesired immune response. The results of present Phase II studies will be very important in deciding whether these treatments are safe and effective for SLE and LN patients. Should these treatments be successful, they could considerably slow down development, improve long-term patient outcomes, lower renal damage, and greatly improve disease management. The therapeutic possibilities of CD40-CD40L blockage as well as their ability to transform lupus treatment are investigated in this review.

Keywords: Systemic Lupus Erythematosus, Lupus Nephritis, CD40-CD40L pathway, autoimmune diseases, monoclonal antibodies.

Introduction

The chronic autoimmune disorder known as systemic lupus erythematosus breaks down self-tolerance and produces autoantibodies aimed at nuclear antigens (1, 2). Renal involvement in SLE, sometimes referred to as lupus nephritis (3), affects 40–60% of patients and is a major cause of end-stage renal disease; approximately 10% of patients advance to this stage within a decade (4). LN significantly elevates morbidity, mortality, and the overall health burden in affected individuals. Maintaining renal function, preventing disease exacerbations, lowering treatment-associated adverse effects, and improving the patient's quality of life are the main objectives in controlling LN. Usually, treatment consists in strong immunosuppressive induction phase therapy followed by maintenance therapy (5). Often taken in combination with glucocorticoids, common medications include cyclophosphamide, azathioprine, and mycophenolate mofetil (MMF). Rituximab, an

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anti-CD20 monoclonal antibody, is occasionally utilized for patients who do not react to traditional treatments or suffer from significant adverse effects, despite its lack of formal indication for LN (7). Though survival rates have improved over the past thirty years, these treatments have been linked to significant side effects including ovarian failure, leukopenia, alopecia, and increased susceptibility to infections (8, 9). Extended glucocorticoid use could cause ocular damage, steroid-induced diabetes, low bone mineral density, and Cushingoid symptoms (10). Treatment failure and refractory lupus nephritis are much influenced by non-compliance resulting from these negative consequences. As such, more effective and better-tolerated treatments especially addressing the basic processes of LN are desperately needed (11, 12).

In parallel, the CD40-CD40L signaling pathway has emerged as a critical mediator in various autoimmune and inflammatory diseases, including SLE and atherosclerosis (13). Working within the tumor necrosis factor receptor and ligand superfamily, co-stimulating molecules CD40 and CD40L are essential for activating the adaptive immune response (14). Research over the past thirty years has clearly shown that the CD40-CD40L system drives immune responses in these disorders (15). Nevertheless, the precise biological purpose of this pathway is still a subject of discussion, so complicating our whole knowledge of its influence (16). Advancement of vascular inflammation in atherosclerosis, a chronic inflammatory disease of the arterial walls, depends on interactions between antigen-presenting cells (APCs) and T lymphocytes (17). The immunological processes of SLE and atherosclerosis will be investigated in this review together with the function of CD40-CD40L in their development and progression as well as therapeutic approaches meant to target this pathway to reduce disease outcomes in both diseases (18).

Given the critical role the CD40-CD40L pathway plays in atherosclerosis and systemic lupus erythematosus, targeted modulation of this pathway offers possible therapeutic advances to fill in for current shortcomings in both diseases (19). By means of a more exact and less toxic approach for altering immune responses in systemic lupus erythematosus, lupus nephritis, and atherosclerosis, targeting CD40-CD40L interactions may help to improve patient outcomes and minimize long-term therapy consequences (20).

The biological function of CD40-CD40L interaction

Adaptive and innate immune responses depend on the CD40-CD40L interaction. Signalling that modulates many immunological processes is started by the interaction between CD40 on immune cells including B cells, dendritic cells, and macrophages, and CD40L on T cells. B cell differentiation, proliferation, and memory B cell development depend on the interactions between CD40 and CD40L (22). The connection also helps T cell-dependent immune responses, which include the development of germinal centers, changing immunoglobulin classes, somatic hypermutation, and the formation of plasma cells. This route is essential in thymus-dependent immunological responses, wherein the activation of helper T cells (Th) and T follicular helper (TFH) cells is pivotal for B cell activation (24). By increasing cytokine production, boosting co-stimulating molecule expression, and encouraging Th-cell proliferation, the interaction of CD40 and CD40L influences dendritic cell functions (25).

Apart from its role in humoral immunity, especially in autoimmune diseases, the CD40-CD40L pathway helps cell-mediated immunity (26).

This link can increase the expression of CD80/86 on dendritic cells, which triggers T cells associated with graft rejection. Inhibition of CD40 or CD40L can trigger T cell death and facilitate the differentiation of regulatory T cells (27). Additionally, by modulating macrophage activation, this pathway produces matrix metalloproteinases, nitric oxide, and proinflammatory cytokines—all of which are vital for immunological responses (28). Furthermore indicating its function in vascular diseases, including atherosclerosis (29), the CD40-CD40L axis promotes adhesion between endothelial cells and neutrophils. Regarding lupus nephritis (3), understanding the role of CD40-CD40L in immune activation presents possible therapeutic directions. Biologic therapy, especially those targeting immunological pathways like CD40-CD40L, may reduce glucocorticoid utilization and renal flares in lupus nephritis (30). The main function of B cells in lupus nephritis and systemic lupus erythematosus has led to the creation of biologic treatments designed to manage B cell activity. Although rituximab (an anti-CD20 monoclonal antibody) is widely used for difficult cases of lupus nephritis, clinical trials have shown mixed results, and it is not yet approved for systemic lupus erythematosus or lupus nephritis. Alternative anti-CD20 antibodies, such as ocrelizumab and obinutuzumab, have undergone evaluation, with obinutuzumab demonstrating enhanced renal response when administered alongside standard therapy in a Phase IIb trial. Approved as an adjunctive therapy for systemic lupus erythematosus (2), belimumab is a human antibody that inhibits B-lymphocyte stimulator (BAFF), with Phase III studies in lupus nephritis showing positive results, including improvements in renal function and declines in proteinuria (33).

A major factor in the development of systemic lupus erythematosus and lupus nephritis is believed to be the activation of the type I interferon (IFN) system. Evaluating an IFN receptor antagonist, anifrolumab, the Phase III TULIP 2 trial revealed a reduction in the severity of systemic lupus erythematosus disease activity, in line with the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA). The Phase III TULIP 2 trial, which evaluated anifrolumab, an IFN receptor antagonist, showed a decrease in the severity of systemic lupus erythematosus disease activity, as per the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) (2). Apart from drugs aimed at CD40 and its ligand, efforts have been made to target other co-stimulating molecules (35). Abatacept is a type of protein that connects CTLA4 to a part of immunoglobulin G1 (IgG1), mainly controlling the CD28–CD80/86 signaling pathway to prevent T-cell activation. Researchers have studied abatacept in lupus nephritis and systemic lupus erythematosus, despite its failure to meet its primary goals in many studies. Consequently, despite continuous and completed clinical trials, no biologic treatments have received a license for the treatment of LN (37).

CD40 antibodies and newer anti-CD40L antibodies were created to stop platelet activation and address previous safety issues, leading to renewed interest in this treatment approach for lupus nephritis. This study explains how CD40 and its ligand are involved in lupus nephritis and gives an overview of the CD40/CD40L-targeted therapies that are currently being developed.

CD40-CD40L and SLE

With its activation promoting inflammation and tissue damage in both diseases, the CD40-CD40L interaction is central in both atherosclerosis and lupus nephritis (39). The chronic inflammatory disease known as atherosclerosis, which affects the arterial walls, is typified by plaque development that narrows the arteries and causes severe consequences, including myocardial infarction, heart failure, and stroke (40). T cells and monocytes enter the injured vascular lining during its development, differentiate into macrophages, and help to create foam cells, so triggering additional recruitment of inflammatory cells and the breakdown of the extracellular matrix. Crucially in this process are CD40-CD40L interactions; CD40 expression on monocytes is essential in activating immune responses (41). This signaling pathway contributes to the formation of necrotic cores and plaque rupture, key events in cardiovascular events. Research on the inhibition of CD40-CD40L signaling in animal models has indicated that this could help to lower atherosclerotic plaque size and stabilize plaque phenotypes, so stressing CD40-CD40L as a possible therapeutic target for atherosclerosis (42).

In LN, too, key causes of renal inflammation and tissue damage are CD40-CD40L interactions. Severe form of systemic lupus erythematosus, LN, is typified by immune complexes deposited in the kidneys that activate renal cells and produce inflammatory cytokines and chemokines (43). This causes lymphocytes and myeloid cells to migrate, so aggravating tissue damage. Expression of CD40 is found in both immune and non-immune cells; its interaction with CD40L on T cells is essential for B cell activation and the synthesis of autoantibodies, so aggravating SLE and LN pathogenesis. In the kidneys, CD40L-mediated activation of mesangial cells, endothelial cells, and myeloid cells amplifies the inflammatory response, promoting fibrosis and glomerular injury (45). Key sources of CD40L, platelets help to upregulate CD40 on renal cells and generate pro-inflammatory molecules including MCP-1 and TGF-β1, so aggravating renal damage (46). Targeting the CD40–CD40L pathway seems to be helpful for treating LN since blockade of this pathway has been shown to lower MCP-1 generation and minimize glomerular damage.

Both atherosclerosis and LN are complicated inflammatory diseases in which tissue damage and immune cell activation depend critically on the CD40-CD40L interaction. While in LN CD40-CD40L signaling fuels renal inflammation and fibrosis, in atherosclerosis it helps to cause plaque instability and rupture. These insights underscore the potential of targeting CD40-CD40L interactions as a therapeutic strategy for both diseases, with ongoing research focusing on developing inhibitors of this pathway for clinical use (47).

Targeting the CD40-CD40L Pathway in Systemic Lupus Erythematosus (2) and Lupus Nephritis(3)

The CD40-CD40L pathway plays a key role in causing systemic lupus erythematosus and lupus nephritis. Starting and maintaining inflammatory processes in SLE, an autoimmune disease defined by systemic inflammation, dysregulated immune responses, and autoantibody generation, CD40-CD40L interactions between immune cells T cells, B cells, and dendritic cells are absolutely vital (48). This pathway generates autoantibodies and immune complexes that deposit in various tissues, including the kidneys, thereby accelerating the progression of the disease. This pathway also activates autoreactive T and B cells (49). Driven by kidney T cell and B cell activation (50), LN is one of the most severe SLE symptoms; hence, renal inflammation and damage result. Engaging on renal dendritic cells and other antigen-presenting cells, CD40L on activated T cells stimulates the synthesis of pro-inflammatory cytokines and chemokines, aggravating tissue damage. Blocking the CD40-CD40L interaction seems like a good therapeutic strategy since it helps reduce immune-mediated damage and stops the development of end-stage renal disease (51).

Preclinical Models and Mechanistic Insights

Apart from the basic studies, several preclinical and clinical investigations have repeatedly looked at the therapeutic possibilities of CD40-CD40L blockage for lupus and lupus nephritis (52). Targeting the CD40-CD40L pathway has repeatedly been shown in studies both in human subjects and mouse models to reduce disease activity, improve renal function, and control immunological responses (53).

A study by Rush et al. (2014) investigated the therapeutic effects of anti-CD40 therapy in NZB/W-F1 mice with developed lupus nephritis (54). Anti-CD40 treatment reduced proteinuria, decreased autoantibody synthesis, and increased survival relative to control subjects, according to the study. Significantly, anti-CD40 therapy reduced histological markers of kidney damage, so supporting the renal protective effects of CD40 inhibition in lupus nephritis (55).

Moreover, anti-CD40 and anti-CD40L antibodies have shown promise for the treatment of lupus and lupus nephritis in clinical trials including human participants. A Phase II clinical trial evaluated the anti-CD40L antibody dapirolizumab pegol (CDP65) in patients with systemic lupus erythematosus (56). Specifically in those with active lupus nephritis, the results indicated that dapirolizumab pegol medication improved disease activity and renal function. This study indicated that treating lupus and preventing renal damage in affected individuals (57) could benefit from CD40-CD40L blockage as a successful therapy approach.

Moreover, studies of other anti-CD40 and anti-CD40L antibodies—including BI 655064 and iscalimab—have shown positive results in the treatment of autoimmune diseases, including lupus and lupus nephritis (58). In animal models and first clinical trials, these antibodies have shown the ability to reduce B cell activation, control T cell responses, and improve renal function. Importantly, these antibodies have been developed to lower the risk of thromboembolic events—a concern related to past generations of anti-CD40L antibodies (59).

The Potential of CD40-CD40L Inhibition in Systemic Lupus Erythematosus and Lupus Nephritis

Research by Shock et al., Perper et al., and others has demonstrated substantial evidence that targeting the CD40-CD40L pathway has considerable therapeutic advantages in the management of SLE and lupus nephritis (60). Inhibition of CD40-CD40L diminishes disease activity, enhances renal outcomes, and facilitates targeted immune modulation, rendering it a compelling choice for the management of these intricate autoimmune disorders (61). This therapy approach's primary advantage is its capacity to mitigate pathogenic immune responses responsible for lupus nephritis while preserving normal immunological function (62).

Moreover, the favorable outcomes from preclinical investigations have been corroborated by initial-phase clinical trials, indicating that CD40-CD40L blockage may serve as an effective and safe therapeutic option for patients with active lupus nephritis (63). The ongoing advancement of second-generation anti-CD40 and anti-CD40L antibodies, including BI 655064 and iscalimab, offers the potential for enhancing the safety and efficacy of CD40-CD40L-targeted treatments in systemic lupus erythematosus and lupus nephritis (64).

As our understanding of CD40-CD40L signaling in autoimmune diseases advances, CD40-CD40L blockade is likely to become a crucial part of the therapeutic options for treating SLE and lupus nephritis, thereby providing patients with a promising new strategy for managing these complex and debilitating disorders (65). Ongoing clinical studies and the development of increasingly advanced therapeutics suggest that CD40-CD40L blockage may greatly improve outcomes and quality of life for lupus nephritis patients (66). After proteinuria starts, which is a sign of lupus nephritis, patients received one dose of pegylated anti-CD40L monoclonal antibody (CDP654). Indeed, half of the treated patients showed disease remission, which demonstrates how well CD40L inhibition works as a therapeutic intervention in developed lupus nephritis (68). This drug helped to calm down T cells, reduced the production of interferon-I (IFN-I), and lowered the levels of inflammatory substances in the kidneys. The findings indicated that CD40L inhibition may control the immune system to reduce the inflammatory response responsible for kidney damage in lupus nephritis, so offering a possible course of treatment for patients with present disease (70).

Perper et al. (2017) conducted a comparable study examining the effects of a chimeric anti-CD40 monoclonal antibody (201A3) in NZB/W-F1 mice, which also develop lupuss (55). Therapy with 201A3 reportedly significantly reduced splenic germinal center development, T follicular helper (Tfh) cell counts, and proteinuria (71). This treatment restored glomerular architecture necessary for maintaining normal kidney function and greatly reduced immune cell invasion in the kidneys (72). The results were significant because they demonstrated that CD40 blockage could specifically focus on the immune processes causing kidney damage in lupus, without the wide-ranging immune suppression that comes with other drugs like corticosteroids.

Rush et al. (2014) also validated these results by looking at anti-CD40 therapy in NZB/W-F1 mice showing lupus nephritis (74). Relative to control mice, anti-CD40 therapy was seen to reduce proteinuria, lower autoantibody synthesis, and increase survival. Importantly, anti-CD40 therapy lowered signs of kidney damage in tissue samples, giving more proof that blocking CD40-CD40L could help treat lupus nephritis. The study revealed that the therapeutic advantages of CD40 blocking could be sustained, indicating that CD40 inhibition could promote lifelong tolerance to inflammatory mechanisms in lupus (75).

These preclinical studies taken together provide a strong case for focusing on the CD40-CD40L pathway in lupus nephritis and systemic lupus erythematosus. The results of these studies consistently show that blocking CD40-CD40L can significantly help reduce disease activity and protect kidney function.

Clinical Trials and Mechanistic Insights

In reaction to early research findings, clinical trials have looked into how well blocking CD40-CD40L works in people with lupus nephritis and systemic lupus erythematosus (3, 77). In a clinical trial testing dapirolizumab pegol (CDP7657), an anti-CD40L antibody, in patients with SLE, good results were seen. Especially in patients with active lupus nephritis, this study revealed that dapirolizumab pegol dramatically increases renal function and disease activity. Strong data from the Phase II trial (78) suggests that targeting CD40-CD40L interactions may be a successful therapeutic approach for lupus and prevention of renal impairment in affected patients.

Second-generation anti-CD40 and anti-CD40L antibodies such as iscalimab and BI 655064 which have shown great promise in the treatment of autoimmune diseases, including lupus (79), have drawn more attention in further studies. Targeting CD40, a type of human-made antibody called BI 655064, blocks the interaction between CD40 and CD40L without causing platelet activation or producing cytokines. Both single and multiple ascending doses of BI 655064 produced over 90% occupancy of the CD40 receptor in healthy adults without generating thromboembolic events and prevented CD54 upregulation, a sign of B-cell activation. Phase II clinical studies in lupus nephritis patients are now in progress to confirm the efficacy of BI 655064 in humans. Preliminary data point to significant clinical benefits, including lower proteinuria and improved renal function, as well as a favorable safety record (58).

In a similar vein, preclinical models have shown that calimab (CFZ533), the Fc-silent, non-depleting anti-CD40 monoclonal antibody, efficiently reduces CD40 signaling (81). In studies with cynomolgus monkeys, iscalimab completely stopped the development of germinal centers and improved transplant survival without causing blood clotting issues. In a first-in-human trial, iscalimab was well tolerated; safety parameters showed no clinically significant changes (64). Currently undergoing a Phase II trial in patients with proliferative lupus nephritis, iscalimab's early data show notable therapeutic advantages in lowering disease activity and preserving renal function (82).

Focusing on the CD40-CD40L pathway in patients with lupus nephritis could strengthen the potential benefits seen in clinical trials for other autoimmune diseases, like rheumatoid arthritis and Sjögren's syndrome. Additionally, in a study with VIB4920, a specific protein targeting CD40L, patients with rheumatoid arthritis and healthy volunteers did not show any signs of platelet activation or clumping (83). These results suggest that blocking the CD40-CD40L pathway can control B-cell activity and lessen autoimmune diseases without causing harmful side effects (84).

A Phase IIa study of iscalimab in patients with primary Sjögren's syndrome showed it was effective, as patients had lasting responses for up to 32 weeks and lower scores on the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). The study linked the therapeutic impact to decreases in the B-cell chemoattractant CXCL13 and a tendency for reduced levels of anti-SSA and anti-SSB autoantibodies. The fact that autoantibody levels did not change much when compared to RA patients shows how complicated autoimmune diseases are and that blocking CD40-CD40L can have different effects depending on the specific disease situation (85).

The main emphasis of the translation of preclinical results into human clinical trials has been anti-CD40 and anti-CD40L antibody evaluations in SLE and LN patients. Even though the first type of anti-CD40L antibodies, like ruplizumab (BG9588), caused safety problems, especially with blood clots, newer versions of these drugs have been created to lower these risks (86).

Originally tested in SLE patients in a Phase II trial, BG9588 is an anti-CD40L monoclonal antibody. Ruplizumab treatment lowered protein levels in urine, reduced autoantibody levels, and improved SLE Disease Activity Index (SLEDAI) scores in people with lupus nephritis, indicating that the disease might be managed effectively. Some patients experienced thromboembolic complications with other first-generation anti-CD40L antibodies a safety concern that calls for early trial termination (87).

Early Phase I trials found that BI 655064 achieved over 90% CD40 receptor occupancy in healthy volunteers without inducing thromboembolic events. Phase II studies evaluating lupus nephritis patients have found BI 6550 to be an induction and maintenance treatment. Preliminary data shows a favorable safety record (88, 89) together with some obvious clinical benefits, including reduced proteinuria and enhanced renal function. Preclinical models using the Fc-silent anti-CD40 monoclonal antibody iscalimab (CFZ533) have shown a strong decrease in CD40-CD40L interactions. Iscalimab was well tolerated, showed no thromboembolic events, and decreased B-cell activation and germinal center development in a Phase I trial comprising healthy volunteers. The effectiveness of iscalimab in treating proliferative lupus nephritis is currently undergoing a Phase II trial (90).

A Phase I trial including SLE patients tested dapirolizumab pegol (CDP765), an anti-CD40L antibody fragment, with encouraging outcomes, including improved disease activity and a favorable safety profile free of thromboembolic events. Although it did not achieve its primary endpoint, a subsequent Phase IIb study demonstrated significant pharmacodynamic effects, including reductions in anti-dsDNA levels and proteinuria, indicating its potential as an alternative therapy for active SLE (56, 91).

These results indicate that blocking CD40 and CD40L could be a potential treatment for lupus nephritis and SLE. Whereas first-generation anti-CD40L antibodies faced safety concerns (92), second-generation agents, including BI 655064, iscalimab, and dapirolizumab pegol, show improved safety profiles and promising therapeutic effects; thus, they are strong candidates for further clinical development. The success of these drugs in reducing disease symptoms and protecting kidney function highlights the importance of blocking CD40-CD40L in treating lupus nephritis and other autoimmune diseases.

Conclusion

One intriguing course of treatment for SLE and LN is blocking the CD40-CD40L pathway. Early-stage clinical trials and preclinical research show tremendous therapeutic promise for lowering renal inflammation, autoantibody levels, and proteinuria—all hallmarks of these diseases. By addressing safety concerns related to thromboembolic events observed in previous therapies, second-generation anti-CD40 and anti-CD40L antibodies such as BI 655064, Iscalimab, and Dapirolizumab pegol offer hope for safer and more effective treatments. More recently developed drugs also target more precisely and lower unintentional immune activation. The outcomes of continuing Phase II studies will mostly define the safety and efficacy of these treatments in patients with SLE and LN. By focusing on reducing kidney damage, managing the disease better, and improving overall patient health, these drugs could significantly enhance the treatment of SLE and LN. Should these treatments be successful, they could be rather important for lupus management since they give patients more alternatives for treatment and reduce the long-term consequences of these autoimmune diseases. Blocking the CD40-CD40L pathway is one intriguing course of treatment for SLE and LN. In reducing renal inflammation, autoantibody levels, and proteinuria—all features of these diseases—early-stage clinical studies and preclinical research have shown tremendous therapeutic promise. Second-generation anti-CD40 and anti-CD40L antibodies, including BI 655064, Iscalimab, and Dapirolizumab pegol, give hope for safer and more effective treatments by addressing safety issues related to thromboembolic events seen in past therapies. More modern drugs also help reduce inadvertent immune activation and target it more precisely. The results of continuing Phase II studies will essentially define the safety and effectiveness of these treatments in patients with SLE and LN. If these treatments work well, they could be very important for managing lupus because they would provide patients with more treatment options and lessen the long-term effects of these autoimmune diseases. Should these treatments be successful, they could be rather important for lupus management since they give patients more choices for treatment and reduce the long-term consequences of these autoimmune diseases.

Authors' Contribution

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Metabolic Syndrome and Inflammatory Diseases: A Comprehensive Review of Mechanisms and Management

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Abstract:

Rheumatic inflammatory diseases not only affect joints and other body systems, but also lead to increased morbidity and death. Because of the etiology and pathophysiology of the disease, chronic inflammation, and the pharmacological treatments used, cardiovascular causes rank among the most common mortality factors in those with these diseases. While rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, and gout show different pathophysiology and symptoms, persistent inflammation is their common pathophysiological feature. Researchers have recently discovered links between several of these diseases and the metabolic syndrome. For several reasons, including its connection with the beginning of cardiovascular disease, the development of a pre-inflammatory condition, treatment choice, and related monitoring, the research of metabolic syndrome in inflammatory rheumatic diseases is important. First discussing the relevance of metabolic syndrome in rheumatic diseases, this review article then goes into great length on every disorder separately. This paper concludes, based on a review of past studies, that abdominal obesity in rheumatoid arthritis and lupus patients, as well as abdominal obesity and high blood pressure in psoriatic arthritis and gout patients, are key parts of metabolic syndrome that need more focus.

Keywords: Metabolic Syndrome, Rheumatoid arthritis, Psoriatic arthritis, Systemic lupus erythematosus, gout

Introduction

Apart from influencing internal organs and joints, rheumatic inflammatory diseases also correlate with higher morbidity and mortality (1, 2). Due to the causes and effects of the disease, ongoing inflammation, and the medications used, heart-related issues are among the most common reasons for death in people with these diseases. Although rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, and gout show different pathophysiology and symptoms, persistent inflammation remains their common pathophysiological characteristic (4). Researchers have recently discovered links between several of these diseases and the metabolic

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syndrome. Researching metabolic syndrome in inflammatory rheumatic diseases is important for several reasons, including its connection to the onset of cardiovascular disease, the development of a pre-inflammatory condition, treatment choices, and related monitoring. This review article first explores the relevance of metabolic syndrome (5). With their increasing incidence, cardiovascular diseases and stroke rank among the main causes of death worldwide (6). Age, sex, hypertension, diabetes, smoking, and hyperlipidemia are the recognized risk factors for cardiovascular disease; yet, chronic inflammation has lately been identified as another risk factor (7). Inflammatory rheumatic disorders correlate with an elevated risk of cardiovascular mortality, maybe attributable to chronic inflammation, pharmacological interventions, or alterations in physical activity resulting from pain or mobility restrictions. The reasons for the increased frequency of atherosclerosis risk factors and metabolic syndrome in people with rheumatic diseases are yet unknown (8). Organ involvement, including renal failure, drug-induced nephropathy, and prolonged glucocorticoid therapy, is addressed in general terms within rheumatic illnesses, followed by a detailed examination of each condition individually (9). This study concludes, through a review of prior research, that abdominal obesity in rheumatoid arthritis and lupus patients, abdominal obesity and hypertension in psoriatic arthritis patients, and hypertriglyceridemia and hypertension in gout are significant elements of metabolic syndrome that necessitate increased focus. Calcineurin inhibitors and nonsteroidal anti-inflammatory medications may contribute to the onset of hypertension, poor glucose tolerance, and obesity (10). Metabolic syndrome (Met S) is a widespread inflammatory condition marked by a group of heart disease risk factors, such as high cholesterol, obesity, high blood sugar, and high blood pressure, and its occurrence is increasing around the world. This condition is a significant predictor of type 2 diabetes, stroke, and cardiovascular disease (11). Metabolic syndrome can cause the body to become resistant to insulin by increasing the release of inflammatory substances, such as interleukin-6 and tumor necrosis factor (TNF-α). Individuals with metabolic syndrome exhibit elevated levels of CRP, IL-1b, IL-1 RA, P-selectin, adhesion molecules, and leptin (14). Visceral adiposity can stimulate the synthesis of IL-6, TNF-α, and adiponectin. Chronic rise of CRP in inflammatory rheumatic disorders correlates with heightened cardiovascular disease risk (15). Metabolic syndrome has been demonstrated to correlate with modest levels of chronic inflammation (16). The prevalence of metabolic syndrome in Europe is estimated to be 15.7% in men and 2.14% in women, 34% in America, and 10-20% in Asia (17). Multiple definitions of metabolic syndrome have been suggested, with the two most prevalent being the Adult Treatment Panel III (ATP) and the International Diabetes Federation (IDF) (18). As per the National Cholesterol Education Program (NCEP ATP III) criteria, an individual is classified as having metabolic syndrome if they exhibit three or more of the following characteristics: 1. Central obesity (waist circumference above 102 cm in males and 88 cm in females). 2. Triglyceride levels beyond 150 mg/dl. 3. High-density lipoprotein (HDL) cholesterol levels below 40 mg/dl in men and 50 mg/dl in women (19). An individual's blood pressure surpasses 130/85 mm Hg, or they are taking antihypertensive medication. A fasting blood glucose level exceeding 100 mg/dl or the management of diabetes (20) are also considered risk factors. Comprehending the metabolic syndrome and its elements in rheumatic diseases can facilitate the prioritization of patient assessments, enabling rheumatologists to not only provide prompt diagnosis and treatment of these diseases but also mitigate the cardiovascular complications associated with them through suitable diagnostic and therapeutic interventions and essential recommendations (21, 22). This article examines the frequency of metabolic syndrome and its components across four distinct diseases: rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, and gout.

Rheumatoid arthritis

An autoimmune disease linked with increased risk of cardiovascular death is rheumatoid arthritis (RA). Over half of deaths in those with rheumatoid arthritis (RA) are related to cardiovascular diseases (CVD). Those with rheumatoid arthritis show a mortality rate 1.5 to 1.6 times higher than that of the generaln (23). While the causes of death are similar to those of the general population, rheumatoid arthritis causes show earlier stages in those affected (24). Cardiovascular disease presents in this regard as well. Patients with rheumatoid arthritis have a 1.63 times higher risk of myocardial ischemia and fatal myocardial infarction than do healthy people. Forty to fifty percent of deaths in rheumatoid arthritis patients are related to cardiovascular diseases (25). In rheumatoid arthritis patients, several factors increase cardiovascular risk, including a sedentary lifestyle, disease-modifying treatments, and ongoing inflammation. With a range of 14.32% to 37.83% (26), the frequency of metabolic syndrome in rheumatoid arthritis patients is estimated to be 30.65%. Recent studies on metabolic syndrome in rheumatoid arthritis (RA) have clarified the complicated interactions among theses (27). One study looked at rheumatoid arthritis and a raised risk of metabolic syndrome and found no appreciable correlation. Furthermore, a lack of any clear correlation between RA's activity level and the likelihood of metabolic syndrome was found. This implies that, in spite of RA's systemic inflammatory character, it might not independently increase the risk of metabolic syndrome, so contradicting some earliers (29). By contrast, another study found interesting results among male RA patients, who showed a lower incidence of hyperglycemia and dyslipidemia relative to a control group (30). This result suggests possible gender-specific variations in the expression of RA and related metabolic disorders, which calls for more investigation on the hormonal and biological processes behind theses (31). Another study concentrated especially on RA female patients' sensitivity to metabolic syndrome. Results indicated that thirty-two percent of the subjects had metabolic syndrome (33). The study did not, however, find a clear relationship between disease activity and metabolic syndrome occurrence. This draws attention to the possible influence on the development of metabolic syndrome in this population of other elements, including age, lifestyle, genes, or long-term medication usage. Notwithstanding the conflicting results, some general trends became clear (33). Researchers noted that patients with either active or chronic rheumatoid arthritis were more likely to have elevated blood glucose levels. Furthermore, linked to metabolic syndrome seemed to be disease activity and functional disability. These findings highlight the need to keep metabolic health under observation in RA patients since resolving metabolic problems could help to achieve better general results (34). All taken together, this body of studies emphasizes the need for customized strategies for controlling RA and its metabolic comorbidities. Future research should try to pinpoint the processes behind these correlations and investigate treatments aimed at both inflammation and metabolic health concurrently (35). Another autoimmune condition linked with cardiovascular morbidity is systemic lupus erythematosus (1). SLE is characterized by extensive organ involvement and a notable prevalence of metabolic syndrome, which is considered a pro-inflammatory disorder that exacerbates morbidity and mortality concerns (37). With women's cardiovascular morbidity risk 5–6 times higher than that of the general population, cardiovascular disease clearly contributes to death in SLE patients (38). Among those between the ages of 35 and 44, this risk could rise by as much as 50-fold. Although the first phase of the disease has improved survival rates, cardiovascular disease still ranks highest among SLE sufferers (39). Although SLE patients are young, many show cardiovascular risk factors, including dyslipidemia, hypertension, and high steroid use, which increases the risk of atherosclerosis (40). Since inflammation is a defining feature of atherosclerotic plaques, there is a significant correlation between systemic inflammation and sensitivity to cardiovascular disease (41). Oxidized low-density lipoprotein (OxLDL) plays an important role in the development of atherosclerosis by triggering immune responses and inflammation in atherosclerotic plaques. Such inflammation could thus compromise processes of endothelial integrity and repair. For SLE patients, autoantibodies, disease activity, clinical symptoms, drugs, and treatments aimed at dyslipidemia and hypertension help explain cardiovascular involvement (43). Glucocorticoids are complexly involved in the pathogenesis of metabolic syndrome in systemic lupus erythematosus. Because of their anti-inflammatory action, modest doses of glucocorticoids may improve vascular function (45). Still, at high doses especially with pulse corticosteroid treatment they could cause metabolic issues, including the start of metabolic syndrome. By lowering inflammatory levels, recent studies show that antimalarial medications including hydroxychloroquine may lower the risk of atherosclerosis in persons with systemic lupuss (46). Moreover, hydroxychloroquine has shown effectiveness in controlling diabetes and dyslipidemia, which highlights its potential ability to prevent cardiovascular events (47). Metabolic Syndrome and RAMobini et al. (2023) looked at how active rheumatoid arthritis (RA) affects metabolic syndrome and found that both active and long-term RA were connected to higher blood sugar levels, but they did not find a strong link between how long someone has been sick and metabolic syndrome. High-dose corticosteroid treatment in patients with systemic lupus erythematosus is associated with a clear increase in the risk of metabolic syndrome and cardiovascular disease (48). The effects of corticosteroids on glucose metabolism, lipid profiles, and blood pressure key components of metabolic syndrome probably explain the higher risk (49). Extended corticosteroid treatment may aggravate these effects, thus stressing the need for careful management and control of SLE patients getting this treatment (50). On the other hand, studies show that in patients with systemic lupus erythematosus (1, 51), the combination of glucocorticoids and hydroxychloroquine could have protective effects against cardiovascular disease. This combined treatment seems to reduce systemic inflammation, a main cause of vascular damage and cardiovascular risk in SLE. Furthermore, hydroxychloroquine could improve vascular health by enhancing endothelial function and reducing thrombotic risk, thereby augmenting the therapeutic effects of glucocorticoids (51).

These results highlight the need to modify therapy strategies to balance the control of SLE symptoms with the lowering of long-term risks, including metabolic syndrome and cardiovascular diseases (52). Combining treatment with glucocorticoids and hydroxychloroquine offers a fantastic chance to improve patient outcomes and lower side effects. To improve dosing strategies and probe the basic mechanisms of various medications to increase their potency, further research is required (53). These updates highlight the ongoing research into how autoimmune diseases, like rheumatoid arthritis and systemic lupus erythematosus, interact with metabolic syndrome, heart disease risk factors, and the effects of different treatment strategies.

Psoriatic arthritis

With an incidence of 0.1 to 1.23 per 100,000 individuals depending on the studied population (55), psoriatic arthritis (PsA) is an inflammatory disease affecting both the skin and joints. Although later studies revealed significant differences between psoriasis and psoriatic arthritis with MetS (56), an initial association between psoriasis and metabolic syndrome (MetS) was observed. Studies indicate that those with PsA have a much higher incidence of MetS than those with psoriasis alone. Studies indicate that patients with psoriatic arthritis (PsA) have a much higher incidence of obesity and hypertension; the prevalence of metabolic syndrome (MetS) ranges between 23.5% and 58.1% among this population (57). Moreover, relative to psoriasis patients, PsA patients often have elevated intima-media thickness (IMT) in the carotid artery, a sign of atherosclerosis, implying an increased risk for cardiovascular disease (CVD). One interesting finding is the correlation between metabolic syndrome (MetS) and this higher cardiovascular risk (59), a main cause of death in persons with psoriatic arthritis (PsA), and the elevated risk of cardiovascular disease (CVD). PsA patients show higher carotid IMT than those with psoriasis; thus, the treatment of MetS is crucial for both the prevention of cardiovascular effects and the control of disease activity (60). All of which increase the risk of myocardial infarction and stroke. An increasing corpus of research has underlined the importance of inflammation in the beginning of insulin resistance, endothelial dysfunction, and atherosclerosis in PsA (61). Individuals with psoriatic arthritis (PsA) use glucocorticoids and hydroxychloroquine than those with rheumatoid arthritis (RA) and systemic lupus erythematosus (1, 62). Many PsA patients show hyperuricemia, which could affect the differences in MetS and cardiovascular complications connected to PsA, RA, and SLE. Furthermore, obesity is acknowledged as a major risk factor for metabolic syndrome in psoriatic arthritis patients. Metabolic Syndrome (MetS) affects more than one-third of patients with Psoriatic Arthritis (PsA), which is significantly higher than its prevalence in the general population (10). Many important studies have helped us to better understand how PsA and MetSt (63). Research shows that patients with PsA show a significantly higher prevalence of MetS than the general population; MetS is mostly driven by obesity, hypertension, and dyslipidemia, so increasing the risk of cardiovascular diseases (64). Furthermore, studies show that those with PsA and MetS are more likely to have type 2 diabetes and atherosclerosis, which emphasizes the need to control MetS in PsA patients to lower these risks risks (65). Since obesity aggravates disease activity and metabolic dysfunction, it is clearly a major factor in the development of MetS in PsA patients (66). Targeting inflammatory cytokines (e.g., TNF-α, IL-6, IL-17) associated with PsA has highlighted their role in insulin resistance and metabolic dysfunction, suggesting that targeting these cytokines may help reduce the negative effects experienced by patients with PsA. Offering a potential therapeutic approach for lowering MetS in PsA, anti-TNF drugs have shown improvements in disease activity and metabolic parameters, including declines in visceral fat and improved lipid profiles. Studies on individuals with PsA have also shown higher carotid intima-media thickness (IMT), so highlighting the link between inflammation and cardiovascular risk. For patients with PsA and MetS, statin drugs have been shown to lower inflammation and enhance lipid profiles, thereby reducing cardiovascular risk. Combining pharmacological interventions with lifestyle changes has produced improvements in PsA disease activity as well asS (69). Early cardiovascular screening and treatment of MetS (69) are especially important since individuals with PsA and MetS show a much higher incidence of cardiovascular events than the general population. While helping with disease symptoms and metabolic health, biologic treatments, like IL-17 inhibitors, have been effective in lowering insulin resistance and belly fat. Using methotrexate along with biologics—especially TNF inhibitors—has been found to better control both the disease and metabolic issues compared to using methotrexate alone. Furthermore, important in the management of PsA and Mets is the success of biologic treatments targeted against IL-12/23 in improving cardiovascular risk factors and disease activity (71). Studies have shown that PsA patients have more MetS, linked to a higher risk of cardiovascular events. The prompt commencement of anti-inflammatory therapies and cardiovascular risk management has demonstrated efficacy in improving patients (72). These data indicate a conclusive association between PsA and MetS, with inflammation serving a pivotal role in metabolic impairment. Efficient management of these disorders, especially with biological medicines, is essential for enhancing patient outcomes and mitigating cardiovasculars (73). A multidisciplinary strategy, encompassing regular cardiovascular evaluations, anti-inflammatory therapies, and lifestyle alterations, is essential for enhancing therapy for PsA patients withS (74).

Gout

Monosodium urate (MSU) crystals deposited in soft tissues and joints cause gout, an inflammatory arthritis marked by periods of severe pain and inflammation. Hyperuricemia, resulting from serum uric acid concentrations exceeding the MSU crystal solubility limit, intimately relates to it (75). Between 0.1% and 0.10% of the population is the estimated global frequency of gout; men, particularly middle-aged and elderly people (76), show higher rates. Apart from its typical inflammatory symptoms, gout is sometimes linked with metabolic disorders including obesity, dyslipidemia, hyperglycemia, and hypertension, so generating metabolic syndrome (MetS). With rates between 30% and 82% and over 70% of these people displaying at least two components of metabolic syndrome (77), recent studies have confirmed the great frequency of metabolic syndrome (MetS) among gout patients. Gout is closely associated with metabolic syndrome, in which case endothelial dysfunction greatly increases the cardiovascular risk associated with the condition. Raised uric acid levels compromise arterial function and reduce nitric oxide availability, so increasing the risk of atherosclerosis and cardiovascular events (78). In patients with gout, cardiovascular disease remains a main factor causing morbidity and death. Relative to the general population, studies indicate that those with gout and metabolic syndrome have a significantly higher risk of cardiovascular events, including myocardial infarctions and cerebrovascular accidents (79). Recent studies have looked at how obesity might affect gout onset and related metabolic issues. While also encouraging insulin resistance and dyslipidemia, abdominal obesity significantly increases the likelihood of hyperuricemia and gout flare-ups (80). Research has shown a stronger connection between gout and insulin resistance by finding that people with gout have higher rates of insulin resistance and highlighting how hyperuricemia contributes to both gout and metabolic syndrome.

Recent research has focused most attention on the effects of urate-lowering treatments on metabolic syndrome in gout sufferers. By focusing on important parts of metabolic syndrome, allopurinol, which is a xanthine oxidase inhibitor, has been effective in improving blood fat levels, lowering blood pressure, and reducing insulin resistance. Prolonged treatment with urate-lowering agents has been associated with reduced central adiposity, highlighting these agents' ability to address metabolic issues in gout sufferers (83). Inflammatory cytokines are crucial in the link between gout and metabolic syndrome. In gout patients with metabolic syndrome, increased concentrations of pro-inflammatory cytokines, such as TNF-α and IL-6, aggravate systemic inflammation, insulin resistance, and endothelial dysfunction, thereby increasing cardiovascular and metabolic risks. Emphasizing these inflammatory pathways provides a potential course of treatment (84). All told, gout and metabolic syndrome have common risk factors, including hyperuricemia, obesity, insulin resistance, and dyslipidemia. People with these diseases run a greater chance of having heart problems (85). Particularly allopurinol, urate-lowering drugs offer two benefits in the treatment of gout and in the correction of metabolic disorders. Effective treatment depends on changes in lifestyle, including alcohol moderation and weight control. We should create more personalized treatment plans by conducting more research on how gout and metabolic syndrome are connected, looking at the long-term effects of urate-lowering treatments, and addressing differences in how often and severely these conditions occur in various groups. With an incidence of 0.1 to 1.23 per 100,000 individuals, depending on the studied population (55), psoriatic arthritis (PsA) is an inflammatory disease affecting both the skin and joints. Although later studies revealed significant differences between psoriasis and psoriatic arthritis with MetS (56), an initial association between psoriasis and metabolic syndrome (MetS) was observed. Studies indicate that those with PsA have a much higher incidence of MetS than those with psoriasis alone. Studies indicate that patients with psoriatic arthritis (PsA) have a much higher incidence of obesity and hypertension; the prevalence of metabolic syndrome (MetS) ranges between 23.5% and 58.1% among this population (57). Additionally, compared to patients with psoriasis, those with Psoriatic Arthritis (PsA) often have thicker walls in the carotid artery, which is a sign of atherosclerosis and suggests a higher chance of heart disease. One interesting finding is the correlation between metabolic syndrome (MetS) and this higher cardiovascular risk (59), a main cause of death in individuals with psoriatic arthritis (PsA), and the elevated risk of cardiovascular disease (CVD). PsA patients show higher carotid IMT than psoriasis patients; thus, the treatment of MetS is crucial for both the control of disease activity and the avoidance of cardiovascular effects (60). All of which increase the risk of myocardial infarction and stroke. An increasing corpus of research has underlined the importance of inflammation in the beginning of insulin resistance, endothelial dysfunction, and atherosclerosis in PsA (61). Individuals with psoriatic arthritis (PsA) use glucocorticoids and hydroxychloroquine than those with rheumatoid arthritis (RA) and systemic lupus erythematosus (1, 62). Many PsA patients show hyperuricemia, which could affect the differences in MetS and cardiovascular complications connected to PsA, RA, and SLE. Furthermore, obesity is acknowledged as a major risk factor for metabolic syndrome in psoriatic arthritis patients. Metabolic Syndrome (MetS) affects more than one-third of patients with Psoriatic Arthritis (PsA), which is significantly higher than its prevalence in the general population (10). Many important studies have helped us to better understand how PsA and MetSt (63). Research shows that patients with PsA show a significantly higher prevalence of MetS than the general population; MetS is mostly driven by obesity, hypertension, and dyslipidemia, so increasing the risk of cardiovascular diseases (64). Furthermore, studies show that individuals with PsA and MetS are more likely to develop type 2 diabetes and atherosclerosis, highlighting the necessity of managing MetS in PsA patients to reduce these risks. Since obesity aggravates disease activity and metabolic dysfunction, it is clearly a major factor in the development of MetS in PsA patients (66). Targeting inflammatory cytokines (e.g., TNF-α, IL-6, IL-17) associated with PsA has highlighted their role in insulin resistance and metabolic dysfunction, suggesting that targeting these cytokines may help reduce the negative effects experienced by patients with PsA. Offering a potential therapeutic approach for lowering MetS in PsA, anti-TNF drugs have shown improvements in disease activity and metabolic parameters, including decreases in visceral fat and improved lipid profiles. Studies on individuals with PsA have also shown higher carotid intima-media thickness (IMT), so highlighting the link between inflammation and cardiovascular risk. For patients with PsA and MetS, statin drugs have been shown to lower inflammation and enhance lipid profiles, thereby reducing cardiovascular risk. Combining pharmacological treatments with lifestyle changes has produced improvements in both PsA disease activity andS (69). Early cardiovascular screening and treatment of MetS (69) are especially important since individuals with PsA and MetS show a much higher incidence of cardiovascular events than the general population. Biologic treatments, like IL-17 inhibitors, not only help with disease activity and metabolic health but also effectively lower insulin resistance and belly fat. Using methotrexate along with biologics especially TNF inhibitors has been found to better control both the disease and metabolic issues compared to using methotrexate alone. Additionally, biologic treatments aimed at IL-12/23 play a key role in managing PsA and MetS by improving heart health and reducing disease symptoms. Studies have shown that PsA patients have more MetS, linked to a higher risk of cardiovascular events. Early starting of anti-inflammatory treatments and cardiovascular risk control has shown effectiveness in enhancing patient outcomes (72). These results show a clear correlation between PsA and MetS; inflammation is clearly important for metabolic damage. Improving patient outcomes and lowering cardiovascular risks depend on effective management of these diseases, particularly with regard to biological treatments (73). A multidisciplinary approach that includes frequent cardiovascular assessments, anti-inflammatory treatments, and lifestyle changes is indispensable for improving therapy for patients with PsA (74).

Discussion

MetS and inflammatory rheumatic diseases, like rheumatoid arthritis (RA), systemic lupus erythematosus, psoriatic arthritis (PsA), and gout, are connected in a complex way influenced by several key factors. These cover patient demography, treatment approaches, disease activity, and chronic inflammation. Numerous studies over the past ten years have looked at the frequency of MetS in different diseases, pointing up a higher risk of cardiovascular disease (CVD) and related effects relative to the general population (88). Reported to be 54.5%, the incidence of metabolic syndrome (MetS) in rheumatoid arthritis (RA) varies depending on demographic factors, diagnostic criteria, and disease length (89). Recent studies indicate that over 40% of rheumatoid arthritis sufferers have metabolic syndrome, more commonly diagnosed in women than in men, so highlighting gender-specific differences in the metabolic effects of the condition (89). Common MetS elements seen in RA patients are abdominal obesity, hypertriglyceridemia, and hypertension. TNF-α and IL-6 are among the pro-inflammatory cytokines that significantly contribute to the development of insulin resistance and increase the risk of atherosclerosis, which can lead to cardiovascular events (11). Some rheumatoid arthritis medications, such as methotrexate and hydroxychloroquine, have shown the capacity to improve lipid profiles and reduce reliance on corticosteroids, which are acknowledged to aggravate metabolic syndrome (90). This emphasizes the effectiveness of anti-inflammatory drugs in correcting metabolic abnormalities and reducing cardiovascular risks in rheumatoid arthritis, thereby improving overall disease management (91). With over 50% of SLE patients diagnosed, the prevalence of metabolic syndrome (MetS) in systemic lupus erythematosus is much raised, a rate much higher than that of the general population (92). Corticosteroids, which are commonly used to treat SLE, significantly worsen central obesity, insulin resistance, and dyslipidemia, leading to the development of metabolic syndrome (MetS). The development of Metabolic Syndrome in Systemic Lupus Erythematosus is connected to higher levels of cytokines, such as TNF-α, IL-6, and IFN-α. These cytokines cause insulin resistance as well as cardiovascular disease. Targeting IFN-α signaling may help those with SLE (93) improve cardiovascular outcomes and reduce the incidence of MetS. With prevalence rates between 38% and 55%, psoriatic arthritis (PsA) is an inflammatory disorder intimately associated with metabolic syndrome (MetS). Common MetS in PsA are abdominal obesity, hypertriglyceridemia, and hypertension, all of which greatly raise cardiovascular risk (94). Important in both insulin resistance and endothelial dysfunction, inflammatory cytokines, including IL-17 and IL-23, help explain metabolic syndrome in psoriatic arthritis. Particularly in those with great skin involvement, therapeutic approaches targeted at these cytokines may have benefits by reducing inflammation and metabolic malfunction (95). In gout, an inflammatory condition brought on by urate crystal accumulation, elements of MetS are rather common. Often occurring in gout sufferers are abdominal obesity, hypertriglyceridemia, and hypertension; this condition is linked to a higher risk of cardiovascular events, particularly in those with comorbidities like obesity and hypertension (96). Allopurinol and other urate-lowering drugs enhance endothelial function, thereby lowering cardiovascular risk; however, further long-term research is necessary. Although its modes of action are yet under investigation, colchicine, usually used in the treatment of gout, has shown the potential to lower cardiovascular events by reducing systemic inflammation (97). Sociodemographic factors, including age, sex, ethnicity, and socioeconomic level, significantly influence the frequency and severity of MetS in individuals with inflammatory rheumatic diseases, in addition to disease-specific elements. People from lower socioeconomic levels are more likely to have metabolic syndrome, most likely due to poor eating habits, limited access to healthcare, and less physical activity (98). In inflammatory rheumatic disease, the frequency of MetS far exceeds that in the general population. In these individuals, chronic inflammation, corticosteroid use, and disease-associated factors raise the risk of metabolic disorders and cardiovascular disease (99). Essential for risk reduction is proactive screening for metabolic syndrome and effective management of inflammation with medications including methotrexate, hydroxychloroquine, and urate-lowering drugs. Later research should focus on the basic processes linking these diseases with MetS, especially the roles of cytokines and biomarkers as future therapy targets. Understanding the influence of sociodemographic factors on MetS prevalence and enabling the development of tailored care plans for different populations depends on knowledge of regional studies (100).

Conclusion

By monitoring the state and relevance of comorbidities and applying appropriate treatments to control them, one can assume a preventive role in the complications and mortality associated with the disease. There is a connection between inflammatory rheumatic diseases and a higher risk of cardiovascular disease. This balances out the joint inflammation participation. If efficient treatments for rheumatic diseases that reduce inflammation are available, patients could have longer lifespans and better qualities of life. Given the prevalence of metabolic syndrome, these drugs could also prove helpful. This review study highlights that important parts of metabolic syndrome needing more focus are belly fat in patients with rheumatoid arthritis and lupus, belly fat and high blood pressure in patients with psoriatic arthritis, and high triglycerides and high blood pressure in gout. The analysis of earlier studies helped one reach conclusions. The higher prevalence of metabolic syndrome in gout and psoriatic arthritis patients suggests that these people need more focus on the elements raising their risk of cardiovascular disease. Knowing the elements of metabolic syndrome connected to every disorder helps you choose the appropriate treatment.

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Urinary Exosomes: A Non-Invasive Window into Health and Disease

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Abstract:

The diagnosis and treatment of urinary exosomes, tiny vesicles expelled by cells in the urinary system, show enormous potential. Many of the compounds in them are very important and readily available without requiring surgical intervention. Apart from carrying proteins, lipids, and nucleic acids, these vesicles also carry nucleic acids displaying the physiological state of the urinary system and maybe other organs in the body. Here is another point of view on several diseases and disorders connected to health. Though standardizing isolation and characterizing techniques and having a thorough knowledge of the biological activities of these compounds continue to be difficult tasks, there is a great possibility for clinical applications. This work aims to provide a thorough investigation of the biology of urinary exosomes, covering their background, features, isolation techniques, and several uses in disease diagnosis and treatment. Apart from highlighting current advancements, it will also look at the possible future paths of this fast-changing field of work.

Keywords: Urinary exosomes, Personalized medicine, Non-invasive, Drug delivery.

Introduction

Cells secrete small vesicles or sacs known as exosomes (Exs), which are absolutely essential for cell communication. Exs first came under notice in the 1960s, but their function remained unknown. In the 1980s, the term "exosome" was developed to characterize vesicles released by cells (1). Research over the past few decades has demonstrated their important roles in intercellular interaction and their great medicinal value. They emerge from the endosomal system of cells, where they branch out from a structure known as a multivesicular body (2). As the multivescular body unites with the cell membrane, this mechanism generates intraluminal vesicles, which are expelled as Exs. Reflecting the makeup of the cell from where they originated, these exosomes carry a broad spectrum of molecules, including proteins, lipids, and nucleic acids (3). Exs are messengers between cells, involved in a range of biological activities. They might move goods to recipient cells, so changing their behavior and purpose (4). Molecular movement could have a range of effects, including modulating immune responses, encouraging tissue healing, and even driving disease development. Because of their ability to transport specific molecules and change recipient cells, exosomes are under study for use in detection and treatments. They have, for instance, promise as biomarkers of medicine delivery vehicles and disease (5).

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Usually considered as a waste product, urine is a wealth of biological information. It includes exosomes, tiny vesicles made by cells that move various molecules, including proteins, lipids, and nucleic acids (6). From a range of cells in the urinary system including those lining the kidneys, bladder, and urethral opening urinary exosomes (UExs) and their cargo represent the physiological state of these cells; hence, they are a valuable source of information for treatment and research. Researching UExs is a rapidly growing field with enormous promise (7). UExs could provide a non-invasive means of assessing urinary tract health and function, including compounds unique to the cells from which they originated (8). For conditions like renal disease, where conventional diagnostic techniques might be invasive or insensitive, this is especially helpful. Researchers aim to find biomarkers for early diagnosis, track illness development, and potentially predict therapy response by studying the composition of UExs (9). The presentation will briefly explain the history and exploration of exosomes, review and evaluate the purification techniques and possible uses of UExs, present the most recent studies on UExs, and conclude with suggestions and conclusions for additional studies on UExs.

History and development of UExs

Various cells lining the urinary system that which comprises the kidneys, ureters, bladder, and urethra produce UExs. The kidneys' several cell types podocytes (specialist cells in the kidney's filtering units), proximal and distal tubule cells, and collecting duct cells 10 produce exosomes. The cells lining the bladder and urethra release exosomes as well into urine. Understanding these several sources is essential for diagnostic reasons since the cellular source of an Exe may affect its payload and possible function (11). Although their function was first unknown, the early 1980s marks the first discovery of exosomes in urine. Although these small vesicles were found in several body fluids, most notably urine, their significance remained unknown for a long period (12). Scientists first discovered exosomes as active participants in intercellular communication, capable of moving and distributing molecular signals between cells, later on. This realization piqued curiosity about the purposes of exosomes in health and disease, including those revealed in urine (13).

UEx generation is a well-organized process inside of cells. The process starts with the invagination of the cell membrane, which results in the formation of an early endosome (14). This initial endosome develops into a multivesicular body (MVB), a sphere-like structure that serves as the primary center for Exe synthesis. Smaller vesicles bud inward from the MVB's membrane to create intraluminal vesicles (ILVs). These ILVs enclose a range of components, including proteins, lipids, and nucleic acids, which will ultimately form the Exe cargo (14). The MVB's fusing with the cell membrane marks the last stage of exosome manufacture. This fusion exes ILVs into the extracellular area, today known as exosomes. Particularly under close control are the specific mechanisms driving this process, which include a complicated interaction of proteins and signaling pathways. The quantity and content of Exe generated may all be influenced by cellular stress, inflammation, and changes in the immediate surroundings. Understanding these regulatory systems is critical for unlocking exosomes' diagnostics and therapeutic potential (15).

Properties of UExs

UEXs are tiny vesicles with a diamiter between 30 and 150 nm, much as exosomes from many sources. This small scale determines their capacity to pass through bodily fluids and interact with cells (16). Research on electron microscopy and nanoparticle monitoring lets one find UEx size and concentration. It is crucial to underline that the individual's health state and the isolation technique applied determine the size distribution of urine exosomes (17). Their unique qualities and difference from other urinary elements come from this size range (18). Surfaces of UExs are covered in several compounds including carbohydrates, proteins, and fats. Crucially for biological activity, these outside molecules interact with target cells, affect absorption and cargo movement, and so enable Often used as EXs biomarkers, tetraspanins (CD9, CD63, and CD81) are prominent surface proteins found on urine exosomes. Adhesion molecules enable cell-cell contacts and other crucial surface proteins are signal transduction proteins, which could start signaling pathways in recipient cells. The cell of origin inside the urinary tract could influence the composition of surface proteins, so reflecting the physiological condition of the individual (19). Apart from enclosing their cargo, the lipid bilayer membrane of urinary exosomes maintains their stability and protects their contents from degradation. Including ceramide and cholesterol, UExs could have more lipids than the parent cell (20). These lipids could alter membrane fluidity and curvature, so influencing the exosome formation and operation. Moreover adding to the biological consequences of the exosome could be some lipids functioning as signaling molecules. The structural integrity of the exosome and supportive interactions with other biological components depend on the lipid content (21).

Isolation and separation of UExs

The different composition of urine makes separating EXs from it a special challenge. Some elements found in urine, including proteins, salts, and extracellular trash, could hinder EX's purification (22). Hence, effective EX separation methods have to not only eliminate EXs from contaminants but also preserve their structural integrity and usefulness. There have been established several strategies for this goal, each with special advantages and drawbacks. Four groups could define these methods: microfluidic (23), precipitation-based, chromatography-based, and ultracentrifugation-based.

Still, a common method for isolating EXs is ultracentrifugation. A common starting point, differential centrifugation is a sequence of centrifugation operations carried out at progressively faster rates to remove larger particles, including cells and cellular waste (24). Ultracentrifugation often at rates more than 100,000 x g then follows to pellet the EXs. Although ultracentrifugation is simple and could generate many EXs, it may also remove other vesicles and protein clusters, so reducing the quality of purity (25). Furthermore, detrimental to EXs are strong centrifugal forces, so compromising their efficacy. Density gradient ultracentrifugation is a variation of this technique whereby EXs, depending on buoyant density, are further separated using a density gradient medium, so improving purity (26).

A less complex and more time-consuming choice than ultracentrifugation is precipitation methods. These methods work by adding a polymer, like polyethylene glycol (PEG), to a urine sample, which causes the EXs to settle out of the liquid. Then centrifugation can help to recover the precipitated EXs. Although precipitation techniques may be scaled up and are generally easy to use, they usually offer less purity than ultracentrifugation. PEG precipitation may cause other components from urine to co-precipitate, thus additional purification procedures are needed (28). But new developments in precipitation solutions and techniques have raised the quality and volume of EXs generated with this technique (28).

EXs benefit from more accuracy and purity provided by chromatography-based techniques. Size-exclusion chromatography (SEC) separates EXs by size using a column loaded with porous beads (29). Smaller than most other components of urine, EXs elute later from the column. SEC is a mild method for preserving EX's integrity and effectively eliminating 30 contaminated proteins. Other chromatography techniques, such as affinity chromatography and ion exchange, can also filter EXs depending on their outer charge or special binding capacity (31). Conversely, chromatography techniques could be more complex and call for specialized tools (31). Emerging microfluidic technologies offer possible fresh approaches for EX separation. These techniques produce quite accurate and efficient EXs separations by using microchannels and microstructures to control fluids and particles. Among the several separation methods used in microfluidic systems are dielectrophoresis, inertial focusing, and deterministic lateral displacement (32). These techniques are appealing for clinical use since they may be mechanized and have a great success rate. Microfluidic technologies have the potential to transform EXs separation from urine (33), even if their development is still under progress. The particular application as well as the necessary purity and yield define the method used to separate EXs. Ultracentrifugation with density gradient or chromatography-based techniques is used for applications including proteomic research or pharmaceutical development requiring great purity (34). Applications needing a high yield, such as diagnostic tests, could call for precipitation or ultracentrifugation. The most recent techniques, such as microfluidics, are perfect for therapeutic environments since they allow great throughput and automation (33). As research on this topic continues, EXs isolation techniques are expected to develop, so enabling more accurate and effective extraction of these vital biological entities from urine.

UExs are small vesicles with a diameter between 30 and 150 nm, much like exosomes from many sources. This small scale determines their capacity to pass through bodily fluids and interact with cells (16). Research on electron microscopy and nanoparticle monitoring lets one find UEx size and concentration. It is crucial to underline that the individual's health state and the isolation technique applied determine the size distribution of urine exosomes (17). This size range (18) defines their special characteristics and difference from other urinary elements. Carbohydrates, proteins, and fats, among other compounds, cover surfaces of UExs. Crucially for biological activity, these outside molecules interact with target cells, affect absorption and cargo movement, and so enable Often used as EX biomarkers, tetraspanins (CD9, CD63, and CD81) are prominent surface proteins found on urine exosomes. Adhesion molecules enable cell-cell contacts, and other crucial surface proteins are signal transduction proteins, which could start signaling pathways in recipient cells. The cell of origin inside the urinary tract could influence the composition of surface proteins, so reflecting the physiological condition of the individual (19). Apart from enclosing their cargo, the lipid bilayer membrane of urinary exosomes maintains their stability and protects their contents from degradation. Including ceramide and cholesterol, UExs could have more lipids than the parent cell (20). These lipids could alter membrane fluidity and curvature, so influencing the exosome formation and operation. Moreover, adding to the biological consequences of the exosome could be some lipids functioning as signaling molecules. The structural integrity of the exosome and supportive interactions with other biological components depend on the lipid content (21).

Clinical application of UExs

Especially in diagnosis and customized treatment, UExs show outstanding therapeutic value. Coming from many cells in the urinary tract and carrying molecular cargo reflecting the physiological condition of these cells, they provide a non-invasive window into the health and operation of the urinary system. For conditions like renal disease, where conventional diagnostic techniques could be intrusive or lacking in sensitivity, this is especially helpful (35). Analyzing the contents of UExs—which include proteins, lipids, and nucleic acids—clinicians hope to find biomarkers for early disease diagnosis, track disease development, predict therapy response, and even customize therapy regimens (36). UEx's research is a logical substitute for tissue biopsies or other invasive procedures since urine extraction is non-invasive.

One of the most likely clinically useful UExs is that for kidney disease diagnosis and treatment (37). Considered a major global health concern, chronic kidney disease (CKD) usually advances silently until major damage results. Even before traditional markers such as blood creatinine levels rise, unique protein and RNA biomarkers found in urinary exosomes have been shown to identify early kidney damage (37). For example, particular exosomal microRNAs have been identified as possible markers for diabetic nephropathy, a common diabetes condition sometimes causing kidney failure (38). Moreover, urine exosomes could offer specifics on the specific type of kidney disease, such as glomerular disease or tubular disease, thus allowing more exact diagnosis and customized treatment. Tracking changes in Exs composition over time might also help to assess therapy effectiveness and track disease development (39).

Apart from kidney diseases, urinary exosomes are under research as possible diagnostic tools for bladder and prostate cancer, among other urinary tract diseases. Different molecular fingerprints generated by cancer cells enable urine to be used in identification (35). These cancer-associated EXs could be lipids, nucleic acids, or tumor-specific proteins used as markers for first cancer diagnosis, disease staging, and response to treatment monitoring. For instance, researchers have identified specific exosomal proteins as potential markers for bladder cancer, suggesting a less invasive alternative to cystoscopy (40). Similarly, UExs are being investigated for their ability to track and identify prostate cancer, which may reduce the need for many biopsies. Both tissue and plasma exosomes significantly decreased PTEN pseudogene 1 (PTENP1) in bladder cancer. By competing with miR-17, this decrease may raise PTEN levels and slow down cancer growth. These findings highlight exosomal PTENP1 as a helpful marker for bladder cancer (BC) therapeutic identification and prognosis (36).

UExs could find use in clinical settings apart from diagnosis. Regarding therapy, they also seem promising. Researchers could produce Exs that carry drugs or other therapeutic agents, which would then target specific body cells (41). This customized treatment may increase therapy efficacy even while it helps to minimize side effects. We can target Exs containing anti-inflammatory drugs to specific kidney cells to treat inflammatory kidney diseases (42). Moreover, we could utilize the natural ability of exs to interact with other cells to induce urinary system tissue repair and regeneration. For instance, we could use Exs from healthy kidney cells to send regenerative signals to damaged kidney tissue (42). Conversion of research results into therapeutic uses depends on the development of uniform methods for Exs separation, characterization, and analysis. Massive clinical studies are needed to prove the clinical worth of UExs and to assess their detection and curative potential (43). Urinary exosomes have the potential to alter the detection and treatment of a wide range of diseases, particularly those affecting the urinary system, as technology develops and our knowledge of Exs biology improves. Along with the abundance of biological data kept inside exosomes, the non-invasive character of urine collecting makes them a very appealing instrument for customized treatment and improved patient care (37). Particularly in diagnostics and tailored treatment, UExs show outstanding therapeutic value. They offer a non-invasive window into the health and operation of the urinary system since they come from many cells in the urinary tract and carry molecular cargo reflecting the physiological condition of these cells. For conditions like renal disease, where conventional diagnostic techniques may be invasive or lacking in sensitivity, this information is particularly helpful (35).

By looking at what UExs contain—like proteins, lipids, and nucleic acids—doctors aim to find signs of disease that can help them diagnose early, monitor how the disease progresses, predict how well treatments will work, and even tailor treatment plans to individual patients. Urine extraction is non-invasive; thus, UEx research is a reasonable replacement for other invasive surgeries or tissue biopsies.

UExs have one of the most possible clinical applications—that of kidney disease identification and treatment (37). A major worldwide health issue, chronic kidney disease (CKD) often advances silently until significant damage results. Unique protein and RNA biomarkers found in urinary exosomes have been shown to detect early kidney damage, even before conventional markers such blood creatinine levels rise (37). For instance, specific exosomal microRNAs have been found to be potential markers for diabetic nephropathy, a common diabetes disorder sometimes leading to kidney failure (38). Further, urine exosomes may offer information about the exact kind of kidney illness, such as glomerular disease or tubular disease, allowing for more precise diagnosis and individualized therapy. Tracking changes in Exs composition over time could also help to assess therapy efficacy and track disease development (39).

Apart from kidney disease, urinary exosomes are under investigation as potential diagnostic tools for other urinary tract diseases, including bladder and prostate cancer. Cancer cells produce different molecular fingerprints that enable urine identification (35). These cancer-associated Exs could be lipids, nucleic acids, or tumor-specific proteins used as markers for first cancer diagnosis, disease staging, and response to therapy monitoring. For instance, researchers have identified some exosomal proteins as potential markers for bladder cancer, suggesting a less invasive alternative to cystoscopy (40). Likewise, researchers are studying UExs for their ability to detect and monitor prostate cancer, which may reduce the need for multiple biopsies. Both tissue and plasma exosomes significantly reduced PTEN pseudogene 1 (PTENP1) in bladder cancer. Acting as a competitive endogenous RNA (ceRNA) for miR-17, this drop may raise PTEN levels by stopping cancer development. These findings suggest that exosomal PTENP1 could be a useful marker for identifying and predicting treatment outcomes in bladder cancer. UExs could find clinical application outside of diagnosis. They also show promise in terms of therapy. We could engineer exosomes to transport drugs or other therapeutic agents, which would then target specific body cells (41). While reducing negative effects, this tailored administration may improve therapy efficacy. We could target specific kidney cells with Exs containing anti-inflammatory drugs to treat inflammatory kidney diseases (42). Moreover, we could utilize the natural ability of exs to interact with other cells to induce urinary system tissue repair and regeneration. For instance, we could use Exs from healthy kidney cells to send regenerative signals to damaged kidney tissue (42). Conversion of research results into therapeutic uses depends on the development of uniform methods for Exs separation, characterization, and analysis. Massive clinical studies are needed to prove the clinical worth of UExs and to assess their detection and curative potential (43). Urinary exosomes have the potential to alter the detection and treatment of a wide range of diseases, particularly those affecting the urinary system, as technology develops and our knowledge of Exs biology improves. Along with the abundance of biological data kept inside exosomes, the non-invasive nature of urine collection makes them a quite appealing tool for customized treatment and improved patient care (37).

UExs and bladder cancer

Rising above more invasive treatments past, UExs are now recognized as a potential non-invasive BC detection and treatment tool. BC cells secrete Exs into the urine, much as many other types of cells do. These tiny vesicles carry molecules reflecting the characteristics of the tumor, including proteins, nucleic acids (including microRNAs), lipids, and metabolites (44). Acting as the fingerprint of the tumor, this cargo offers vital information on its existence, stage, aggressiveness, and most likely reaction to treatment. The ease of collecting urine specimens makes UExs screening particularly interesting for BC; it enables repeated evaluations over time free from the pain and hazards related with cystoscopy or tissue biopsy (45). Great promise exists for this non-invasive approach to increase fast detection rates, reduce the need for invasive procedures, and customize treatment plans for BC patients (46). Many studies have revealed especially exosomal markers in urine linked to BC. Usually overproduced in BC cells, proteins including cytokeratin 20 (CK20) and uroplakin 1A (UPK1A), a main component of the urothelium (the bladder lining), have been reported to be abundant in UExs from patients with BC (47). Usually helping the bladder lining to develop and function, these proteins are lost into the urine via exosomes when cancer strikes. Likewise, UExs have exposed some microRNAs—small non-coding RNAs that affect gene expression—as possible biomarkers (48). Some microRNAs, including miR-21 and miR-141, are routinely raised in BC and their presence in UExs could point to both the existence and stage of the disease. These exosomal markers can be found with a sensitive and exact approach using ELISA (enzyme-linked immunosorbent assay), Western blotting, and PCR (polymerase chain reaction), so guiding bladder cancer detection and aggressiveness determination. Especially for high-risk people like smokers or those handling specific chemicals, the identification of these markers in urine samples provides the route for the development of non-invasive BC monitoring systems. Imagine a time when a simple urine test could alert a patient of early bladder cancer detection, so facilitating earlier intervention and improved outcomes (50).

Beyond obvious tracking of therapy response and

BC prognosis prediction, UExs hold promise. Exs' molecular payload could highlight specifics on the tumor's stage, grade, and metastatic potential. For example, exes from severe bladder cancer could have different sets of proteins and microRNAs than those from less aggressive tumors (51). These exosomal biomarkers allow doctors to estimate the likelihood of disease development and guide the development of a suitable course of treatment. Should a patient's UExs show a high concentration of markers linked to aggressive cancer, their doctor may advise a more extreme course of treatment from the start (52). Moreover, the research of UExs could assist in assessing the success of treatments comprising chemotherapy and immunotherapy. Variations in the form or concentration of exosomal markers across treatment could offer crucial information about the effectiveness of the drug and whether changes are required. If a patient is undergoing chemotherapy and their UExs still show high levels of cancer-associated microRNAs, this indicates that the treatment is ineffective and should be modified (53).

Furthermore, under research are UExs based on their detection and prognostic value as possible BC treatment targets and drug delivery systems. Therapeutic molecules, including proteins, siRNAs (small interfering RNAs), or drugs, could be produced and then transported to BC cells. Although this customized delivery method reduces negative effects on normal tissues, it may increase cancer therapy efficacy (54).

Exs, for example, could be loaded with chemotherapeutic drugs and targeted onto BC cells, so delivering the treatments exactly to the tumor and avoiding other areas of the body (55). Also, learning how Exs play a role in communication between cells in the tumor area can lead to new treatment ideas that aim to disrupt the signals that help tumors grow and spread. Researchers are looking at how bladder cancerous cells interact with surrounding cells and with one another, as well as how this interaction might be inhibited to prevent the cancer from spreading. Although their therapeutic uses are yet under research, urinary Exs have great future potential to improve BC treatment (57).

Urinary exosomes and vaccine development

Especially in the fields of infectious diseases and cancer, exosomes released by cells and spanning a range of biological molecules are under research as a possible vaccination platform. Their related biological compatibility, ability to cause immune system reactions, and delivery of particular antigens make them therefore interesting candidates (58). Part of a multi-phase development process for Exs-based vaccines, Exs are isolated and purified, then loaded with the appropriate antigens and injected to induce an immune response (59). Tumor cells, infections, or other targets connected to diseases could all be the antigen source. Exs protect these antigens from annihilation and help them to be delivered to antigen-presenting cells, so promoting a good immune response. This approach may generate more customized and safer vaccinations than the ones now used (59).

The ability of UExs to produce humoral and cellular immune responses is among the most important advantages of their use in vaccination studies. Humoral immunity refers to the generation of antibodies that can either mark cancer cells for destruction or neutralize infections. T lymphocytes are part of cellular immunity; they are triggered and can directly destroy cancerous or diseased cells (60). Exs can boost both immune system arms, so producing a more complete and long-lasting immune response. Studies have indicated that exosomes generated from tumor cells and loaded with tumor-associated antigens—for example, help cytotoxic T lymphocytes (CTLs), which can destroy cancer cells, to flourish. Preclinical cancer models have shown the promise of this strategy, implying that Exs-based vaccines might be helpful in the treatment of many cancer types (61).

UExs are suitable for many vaccine targets since their adaptability allows one to design them to carry a broad spectrum of antigens. Exosomes can load tumor-specific antigens—such as cancer-associated carbohydrates or mutant proteins—to set off an immune reaction against cancer (62). To boost protective immunity in infectious diseases, examples could include pathogen-derived antigens, including viral proteins or bacterial toxins. Moreover, exosomes can be altered to increase their immunogenicity by including adjuvant drugs meant to activate the immune system. Because of their adaptability, UExs provide a great forum for creating vaccines against many different diseases (63).

Preclinical research has seen many studies looking at the possibilities of exosome-based vaccines. Studies have demonstrated, for instance, that exosomes derived from melanoma cells loaded with melanoma-associated antigens can generate a strong anti-tumor immune response in mice, so causing tumor regression. In another study, mice given the vaccination (58) showed humoral and cellular immune responses when exposed to Exs, including HIV-1 antigens. TEXs isolated from IL-12-anchored transformed kidney cancer cells showed stronger anticancer properties in vitro (64) when compared to TEXs and IL-12 alone. Though mostly preclinical research, they offer compelling proof that UExs could help create successful vaccines. Clinical research is essential to assess in humans the safety and efficacy of Exs-based vaccinations. Ongoing studies indicate that UExs have great potential to transform vaccination development and improve human health (65).

Advantages and challenges

In therapy and detection, UExs have several interesting advantages. Gained only by urine collection, their non-invasive character presents an attractive substitute for more intrusive procedures, including blood samples or biopsies. Regular sampling made possible by this simplicity of access helps to monitor disease development or therapy response longitudinally (59). UExs also carry a variety of biological molecules, including proteins, lipids, and nucleic acids, which mirror the urinary tract's and maybe other areas of the body's physiological state (66). Exs in urine also help to be useful since their long-term stability prevents their cargo from degrading; hence, they are fit for analysis and storage. This molecular complexity provides a wealth of information ready for use in particular treatments, tailored medicine, and first disease diagnosis (67).

There are plenty of fast-expanding possibilities for UEXs. Several diseases, such as those affecting the kidneys, bladder, and prostate, could benefit from their use in diagnostics for early identification and tracking (68). UExs could be used, for example, to identify markers for the degree of kidney disease development, BC recurrence, or prostate cancer severity, so enabling quick treatments and better outcomes for patients. Exs could be made to carry drugs or other medicinal compounds straight to target cells in treatments, thereby offering a more accurate and less damaging approach to therapy (69). Furthermore, Exs' natural ability for intercellular communication can encourage tissue renewal and regeneration. The possible uses of UExs go beyond the urinary tract since they can indicate systemic conditions and be used to diagnose and monitor different diseases, including neurological or cardiovascular ones (70).

UEXs have drawbacks even if they offer advantages. Standardizing Exs separation and characterization techniques is one of the main challenges. Variations in pre-analytical and analytical techniques could affect the purity, yields, and repeatability of Exs preparations, so complicating data comparison from many research studies (71). Ensuring data dependability and comparability thus depends on the development and validation of standardized methods for Exs separation, characterization, and analysis. Lack of knowledge on the biological roles of UExs adds still another challenge. Although UExs contain several compounds, their exact purposes in health and disease are unknown. We need further research to understand how UExs interact with destination cells and how their payload influences cellular functions (72).

The rather low concentration of Exs in urine especially in healthy individuals is another drawback. This could make it challenging to get enough Exs for specific purposes, such as medicinal distribution. Overcoming this limit calls for technological developments in Exs separation and enrichment processes (73). Furthermore, the diversity of UExs produced by several cell types in the urinary tract complicates data interpretation. First, we have to grasp the cellular origin of individual Exs if we are to fully appreciate their biological relevance. Ultimately, translating studies on urinary exosomes into clinical use calls for thorough validation in large-scale clinical trials, which are vital for proving the clinical relevance of Exs-based diagnostics and treatments as well as for establishing their safety and efficacy.

Conclusion

Urinary exosomes (UExs) offer a remarkable cutting edge in non-invasive diagnostics and personalized medicine by providing a wealth of information on the physiological and pathological states of the urinary system and possibly other organs. These tiny vesicles, filled with proteins, fats, and genetic material, are especially helpful for spotting diseases early, predicting outcomes, and tracking treatment in kidney disease, bladder cancer, and other urinary issues. They also reflect the state of the cells from which they originate. Despite significant advancements in our understanding of their biology and the development of numerous isolation techniques, standardization, purification, and clinical validation remain challenging. However, as innovative technologies like microfluidics advance and our understanding of exosomal biology expands, the incorporation of UExs into traditional clinical practice appears to be becoming more and more possible. Future research focused on improving isolation methods, raising biomarker specificity, and clarifying the functional roles of UExs will help us completely realize their diagnostic and therapeutic potential in precision medicine.

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Dynamic Biomaterials: The Next Generation of Regenerative Therapies

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Abstract:

Live materials represent a radical change in regenerative medicine since they combine the structural advantages of biomaterials with the natural biological goals of live cells, so providing a dynamic and interactive approach for tissue repair and regeneration. Designed with multiple cutting-edge technologies including cell encapsulation, scaffold-based approaches, layer-by-layer assembly, and 3D bioprinting, these composite materials help to create customized constructions fit for particular therapeutic need. By allowing the generation of patient-derived tissue and organ models for drug assessment and therapeutic augmentation, advances in microfluidics and the development of organ-on- a-chip and organoid technologies help to support this tailored approach.   Although bringing these fascinating discoveries into general clinical use still presents challenges, under our direction continuous biomaterials, microfabrication, and cell-material interaction research and development are rapidly advancing. Underline their great opportunities for regenerative medicine, investigate the several engineering approaches applied in their design and fabrication, present a thorough study of the current situation of living materials, and discuss the present difficulties and interesting prospects inside this transforming field.

Keywords: Live materials, Regenerative medicine, Tissue engineering, cell therapy, Personalized medicine

Introduction

By stressing building or substituting damaged tissues and organs instead of only treating symptoms, regenerative medicine (RM) has great potential to transform healthcare (1). Inspired by concepts from engineering, materials science, and cell biology, this discipline generates novel treatments. A major component of RM is the design and manufacturing of biocompatible materials that mimic the natural surroundings of tissues. Among their several uses are structural support for cell development and differentiation and pharmacological distribution. Since their properties directly affect cell activity and tissue development, the best regeneration results depend on the design of these materials (2). Targeting the primary causes of immunological rejection and donor shortage, RM offers a reasonable substitute for conventional transplanting. Patients with severe injuries and chronic diseases hope for this approach since it has shown success in many different applications, including bone reconstruction, heart regeneration, and muscular rejuvenation.

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While current research and advancements in this field open the path for more customized and successful regenerative therapies, constantly stretching the limits of what is practical follows (3). Beyond traditional 2D cell cultures, research in regenerative medicine has progressed to recognize the importance of the 3D environment in replicating the complex interactions and structures found in real tissues (4). Although they are helpful for preliminary study, 2D cultures sometimes lack the delicate cell-by-cell interactions needed for tissue development and function. Conversely, 3D environments, including hydrogels, scaffolds, and decellularized tissues, give cells a more physiologically realistic setting, so enhancing cell viability, growth, differentiation, and the generation of functional tissue architectures (5). These 3D models help researchers better grasp the processes regulating tissue repair by allowing them to investigate cell activity in more realistic surroundings. Additionally, 3D bioprinting and microfluidic systems enable the precise creation of complex tissue designs with specific structures and materials, opening new possibilities for developing functional organs and tissues. Therefore, advancements in 3D culture and manufacturing processes will determine the rapid translocation of regenerative medicine drugs from the laboratory to the clinic (7).

Biomaterials are essential in regenerative medicine since they give tissue healing and recovery the structural and functional foundation. By means of their unique interaction with live entities, these carefully designed materials enhance cell adhesion, growth, and differentiation (8). Among the several materials used are composites, metals, ceramics, and polymers, both natural and synthetic. Natural polymers, including collagen and hyaluronic acid, are naturally biocompatible and promote cell-matrix interactions; synthetic polymers, including polylactic acid (PLA) and polycaprolactone (PCL), enable more control over mechanical characteristics and breakdown rates (4). Mechanical strength, porosity, biodegradability, and biocompatibility are among the qualities one should consider while selecting a material for a given use. Sometimes complex biomaterials with particular surface modifications or coupled with growth factors and other bioactive compounds are developed to increase their regeneration potential (9). Extending biomaterials by including live cells into the material structure, living materials represent a novel development in the sector. These composite materials mix the structural advantages of traditional biomaterials with the dynamic possibilities of live cells (10). By releasing growth factors, generating extracellular matrix, and directly impacting tissue development, stem cells, fibroblasts, or another type of specialized cell actively participate in the regeneration process. Several methods could be used to create living materials: cell-based films, encapsulating cells within hydrogels, or embedding cells within scaffolds (11). This approach offers several benefits, including improved interaction with host tissues, increased bioactivity, and the potential to supply therapeutic compounds on demand. Manufacturing of living materials is a fast-expanding field of research with enormous potential for tailored and very successful regenerative treatments (12). This paper introduces the field of regenerative medicine with special regard to the important role materials play in tissue healing and regeneration. To increase therapeutic possibilities, it also looks at the growing field of living materials and composite constructions using living cells.

Living Materials in Regenerative Medicine

Living materials provide a paradigm change in regenerative medicine, transcending fixed biomaterials and moving towards dynamic, interactive constructions actively promoting tissue restoration. These compounds are unique composites combining the inherent bioactivity of live cells with the structural properties of conventional biomaterials (13). Living materials reflect the natural milieu of tissues more precisely than cell-free scaffolds, so promoting growth, differentiation, and longer lifetimes of cells. This method lets the development of structures that not only provide structural support but also actively contribute to the rejuvenation process by secreting growth factors, building an extracellular matrix, and directly helping in tissue development (14). Living materials offer a more customized and effective method to regenerate treatments since they seem to close the difference between synthetic materials and natural tissues (15).

Living materials serve several purposes in regenerative medicine. They could be used to drive stem cell differentiation into particular cell types, boost the formation of vessels for better blood supply to healing tissue, and even straightforwardly send therapeutic drugs to the intended area (16). By expressing specific growth factors or other therapeutic compounds, the genetically altered cells in the living substance could be more likely to regenerate. Furthermore, the dynamic character of living materials helps them to react to changes in their surroundings by means of behavior meant to promote tissue rehabilitation and reconstruction. This adaptability is one main benefit over stationary biomaterials, which could not be able to satisfy the complex and changing needs of renewing tissue (17). Live materials are an amazing junction of biology and materials science whereby dynamic, interacting structures are formed by means of live cells incorporated into a biomaterial framework. For use in drug delivery or cartilage repair, cells could be encapsulated within hydrogels like alginate or collagen (18). Likewise, cells could be seeded onto or implanted in artificial polymers such as PCL or decellularized tissue, generating live scaffolds for skin replacements or bone reconstruction. The promise of living materials to transform regenerative medicine cannot be disputed even if long-term cell viability, controlled cell activity, and scalability still present challenges (19). Growing knowledge of cell-material interactions should lead to even more complex and effective living materials emerging, enabling a new era of regenerative medicines.

Engineering Strategies and Fabrication Approaches for Living Materials

Biomaterials, living materials, and living cell polymers seek modern engineering solutions and manufacturing methods. These methods aim to provide cells with a caring and supportive environment that resembles their natural surroundings, thereby enhancing cell survival, development, and function. Several important responses with varying benefits and drawbacks have surfaced (20).

Cell Encapsulation

Cell encapsulation is the process of covering cells in a protective shell usually made of hydrogel or another biocompatible material. Apart from mechanical stress and immune system protection from the host, this method produces a small environment rich in nutrients and growth hormones concurrently (21). Comprising hydrophilic polymers, hydrogels are fit for enclosing because of their high water content and biological compatibility. Because alginate, a natural polysaccharide, is easy to gel and biologically compatible, cell encapsulation often makes use of it (22). Other components used depending on need are polyethylene glycol (PEG), hyaluronic acid, and collagen. One can precisely control tissue architecture and cell distribution by modifying the encapsulation method, so modifying the size and form of the cell-loaded constructions (23).

The type of cell and its use define the encapsulating substance and technique used. Alginate encapsulation is ideal for chondrocytes in cartilage regeneration, for example, but other hydrogels could be more appropriate for stem cells or other cell types (24). The mechanism of encapsulation itself can affect cell survival and behavior. Mild encapsulation techniques help to minimize cell damage and preserve their functionality. Furthermore, one can enhance tissue development and cell behavior by changing the properties of the enclosing material: rigidity, porosity, and decommission rate. To maximize the long-term survival and function of encapsulated cells, scientists are now considering creative encapsulating materials and techniques, so enhancing the efficacy of living material creations (25).

Scaffold-Based Approaches

Techniques based on scaffolding embed or seed cells onto a three-dimensional (3D) scaffold framework. Designed of extracellular matrix (ECM), the scaffold provides a framework for cell adhesion, development, and organization reminiscent of biological tissues. Scaffolds are built from synthetic and natural polymers, including PLA and PCL, as well as collagen and decellularized tissues (26). Scaffold design affects tissue development and cell activity in regard to permeability, pore size, and interrelationships. Ideally the scaffold should be biocompatible, recyclable, mechanically similar to the target tissue, and biocompatible (27).

Because of their natural biocompatibility and original tissue structure, decellularized tissues derived from human or animal sources are quite an attractive scaffolding material. Decellularization leaves only the ECM, a natural structure free of all cellular components, allowing cell adhesion and tissue repair (28). Designed for specific applications, synthetic polymers give better control over scaffold properties. Using 3D printing and other advanced manufacturing technologies allows one to create complex geometries and controlled porosity, so offering exact control over cell distribution and tissue structure. Often used in regenerative medicine for a wide spectrum of uses, including skin replacements, cartilage repair, and bone regeneration, scaffold-based technologies (29).

Layer-by-Layer Assembly

Layer-by-layer (LbL) assembly is a flexible method for building living materials whereby ultrathin layers of various compounds including cells and biomolecules are successively deposited onto a substrate (30). This approach gives exact control over the design and building of the resulting structure. Cell-rich films, coatings, and even three-dimensional models can be created using LbL assembly. Many materials could be used in the layers, including polymers, nanoparticles, and growth factors, so allowing the creation of multifarious living materials (31). Production of thin films or coatings using live cells benefits much from LbL assembly. We could use these cell-laden films to form portions of more complex tissue structures, distribute medications, or heal wounds (32). The LbL method offers precise control over the film's thickness and composition as well as the cell distribution within the material. Moreover, LbL assembly could be applied to include other bioactive compounds or growth elements in the film, so enhancing its regeneration capacity. Although LbL assembly is a great method, it could be time-consuming and inappropriate for creating large or complex 3D objects (33).

3D Bioprinting

3D bioprinting is rising as a good technique for generating complex living materials with exact control over cell distribution and tissue structure. Usually using cells surrounded in a hydrogel or another biocompatible material, this method lays cells layer by layer (34). 3D bioprinting allows tailored tissue designs fit for the patient's needs. Among the several bioprinting technologies available are extrusion-based, inkjet-based, and laser-assisted ones; each has benefits and drawbacks (35).

From 3D bioprinting, there are great opportunities for building complex tissues and organs, including cartilage, blood vessels, and maybe whole organs. Specifically, control of cell distribution and scaffold design determines the development of functional tissue architectures (36). Moreover, 3D bioprinting could be used to combine several cell types and biomaterials into one construction, so simulating the complicated composition of natural tissues. Though 3D bioprinting is a rapidly expanding industry, problems still exist in terms of bio-ink manufacture, printing speed, and guaranteeing long-term cell viability inside produced constructions. Still, 3D bioprinting seems to have fantastic power to transform regenerative medicine (37).

Microfluidics Systems

Systems using microfluids

Microfluidics allows exact control over the milieu surrounding cells and lets intricate tissue structures be built, so enabling designed living materials. These devices, with their micrometer-scale tubes and chambers, enable unmatched accuracy in fluid and cell manipulation. In the context of living materials, microfluidics helps cells to receive nutrients, growth factors, and other signaling molecules under control, so mimicking the dynamic milieu of real tissues (39). Moreover, microfluidic devices could be programmed to create precise shear stress environments influencing cell activity and differentiation. This degree of control determines the research on cell-material interactions and design optimization of living materials for particular purposes. Microfluidics allows the generation of highly ordered and functional tissue structures by exactly controlling fluid flow and cell position (40). Microfluidics not only controls the microenvironment but also enables very detailed production of living materials. These tools can be used to produce consistent-sized, shaped cell-laden hydrogel droplets that can then be aggregated into bigger tissue structures (41). Furthermore, combining microfluidic systems with 3D bioprinting technologies allows for the exact deposition of cell-loaded bioinks to create intricate tissue structures. Precisely altering the microscale composition and structure of living materials will help to create functional tissues and organs. Microfluidic devices can also be used to create gradients of chemical signals guiding cell movement and differentiation, so augmenting the regenerative capacity of living materials. As they evolve in the synthesis of next-generation living materials for regenerative therapies, microfluidic techniques will become increasingly crucial (42).

Applications of Living Materials in Regenerative Medicine

In many different fields of use, advanced living materials show great potential to progress regenerative medicine. Including live cells inside a biocompatible matrix, these generated structures provide customized solutions for tissue regeneration and repair (4). Living materials can help to increase bone production and vascularization during bone regeneration, so facilitating faster and more complete healing of fractures or deformities. By stimulating matrix synthesis and chondrocyte development, cell-based hydrogels could help to restore joint function. Living skin substitutes such as keratinocytes and fibroblasts aid in burn and chronic wound healing. Living heart patches could be made to easily mix with damaged myocardium, so promoting functional repair and angiogenesis. In the next section (43), we will go over some of the applications of living materials in regenerative medicine.

Engineering Living Scaffolds for Enhanced Tissue Repair

Live scaffolds comprise live cells actively involved in the regeneration process together with a three-dimensional structure reflecting the natural ECM of tissues, so promoting tissue healing (44). These scaffolds direct the growth of new tissue and form the basis for cell adhesion, proliferation, and differentiation. Unlike traditional scaffolds that don't have cells, living scaffolds actively deliver important substances like growth factors and cytokines to the injury site, which helps in forming new blood vessels and starting the healing process. Furthermore, generating and depositing their own ECM components, the additional cells could improve the biocompatibility of the scaffold and promote integration with the host tissue. Living scaffolds are a successful technique of tissue regeneration because of their synergistic mix of structural support and biological function (46).

For example, loaded with osteogenic cells (bone-forming cells), living scaffolds made of biocompatible materials such as hydroxyapatite may be implanted at the site of a fracture or bone defect in bone reconstruction. The scaffold offers structural support while osteogenic cells develop and generate new bone tissue, speeds healing, and enhances incorporation with the surrounding bone. Likewise, living scaffolds composed of hydrogels implanted with chondrocytes cartilage cells can help damaged cartilage in joints heal. While the chondrocytes create new cartilage matrix, so repairing the smooth and functioning surface of the joint, the hydrogel creates a hydrated environment that promotes chondrocyte vitality and functioning (48). Treating serious burns or long-lasting wounds can be done with living skin substitutes, which have a layer made of collagen with fibroblasts and a top layer of keratinocytes, offering a more natural and effective option than traditional skin grafts. These cases highlight how adaptable living scaffolds are in encouraging tissue regeneration and restoring function in many various types of tissues and organs (49).

Living Cell Composites: Enhancing Cell Therapy

Since living cell composites offer a more sophisticated approach to distributing restorative cells to damaged tissues, they represent a major breakthrough in cell treatment. These composites mix the therapeutic possibilities of live cells (50) with the structural and functional properties of biological materials. These composites enhance cell survival, facilitate cell-cell interactions, and ensure targeted distribution to the intended area by embedding or encapsulating cells within a biocompatible matrix, thereby creating a protected microenvironment. Two drawbacks of present cell therapies that this method solves are limited integration with host tissues and poor cell survival upon transplantation (20). The biological material component of the composite is designed to provide mechanical support, replicate the natural extracellular matrix, and potentially secrete growth hormones or other bioactive chemicals to promote tissue repair. Interaction of biomaterials and cells in this harmonic fashion increases the efficacy of cell treatments (51). In cell treatment, living cell composites find several applications. Shielding cells from hostile environments and promoting their retention at the target site, they function as a channel for delivering them to the site of damage or disease. Apart from providing a scaffold for tissue regeneration, the biomaterial component gives structural support and direction of guidance for cell arrangement (52).

Moreover, the composite's cells could be designed to generate therapeutic genes or release growth factors, so improving their curative capacity. In heart cell therapy, for example, heart muscle cells can be placed on a safe material to make a living heart patch that can be put into the damaged heart area. In diabetic treatment, we can encapsulate pancreatic islet cells in a protective hydrogel to halt immune attack and prolong their lifespan after transplantation. Neural stem cells could be used in neurological diseases to cause nerve repair and restore function by means of a biodegradable scaffold (54). For example, encapsulating NK cells into microspheres could preserve the tumor-killing ability while still allowing perforin and granzyme B to be constantly released. These cases underline the several uses of living cell composites in improving the efficiency of cell therapies over a spectrum of diseases and injuries (54).

3D Living Models for Biomedical Research

Providing in vitro 3D cell culture systems that replicate significant structural and functional traits of tissues and organs, living tissue and organ models represent a major advancement in biomedical research. Two main approaches—organ-on-a-chip and organoid techniques—are driving development in this field (55). Using live cells and microfluidic channels, organ-on-a-chip systems replicate physiological or pathogenic conditions observed in the body. Designed for a variety of organs, including the kidney, liver, and intestine, these platforms let scientists look at organ-specific activities and reactions (56). Since semiconductors are made from materials and they also support cell culture, materials science is rather relevant. Since the material design directly affects cell behavior and functionality, cells grown in these materials could be called living materials. By adding a nanoimprinted anisotropic film seeded with cardiomyocytes, a heart-on-a-chip device, for example, has demonstrated the ability to merge advanced materials with microfluidics (57), inducing cell alignment and monitoring contraction activity. Conversely, organoids are multicellular, self-organizing structures derived from stem cells that resemble organ form and function. More complex and physiologically appropriate than traditional 2D cell cultures, these 3D structures offer With special focus on transplanting methods, organoid technology has shown promise in regenerative medicine (58). Scientists have developed techniques for the long-term cultivation and genetic editing of both normal human organoids and breast cancer organoids, which enable studies on disease progression and drug interactions. Transplanting organoids, like cholangiocyte organoids, into bile ducts has shown potential for restoring tissue function and healing damaged areas. Although organ-on-a-chip and organoid technologies are useful tools for research, they have problems in repeatability, scalability, and recreating the whole complexity of human organs. More advanced biomaterials, improved culture conditions, and the combining of several organ models to create more complete systems for understanding human health and disease are the goals of continuous research in this field (60).

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Personalized Medicine: Tailoring Treatment with Living Tissue Models

Particularly organ-on-chip and organoid technologies, the development of live tissue and organ models has opened exciting new directions for tailored treatment. These models have one remarkable feature: they can generate original copies of a person's tissues or organs from cells obtained from a patient (61). This customized approach beats generic models, which might not fairly depict the particular traits of a patient's condition or reaction to particular treatments. Using cells taken from minimally invasive techniques, such as biopsies or blood samples, scientists can produce tissue/organ models with the exact genetic profile and disease profile of the patient. This guarantees a better awareness of the personal health and helps to build customized treatments (62). Customized tissue/organ models greatly promise drug screening and therapy optimization. These models can offer important information on how a patient might react to various treatment choices by assessing the efficacy and toxicity of several medications on their cells. By helping doctors choose the best and most effective drugs for every patient, this approach reduces side effects risk and increases treatment success possibilities (63). In cancer treatment, for example, tailored tumor organoids can be used to screen a panel of chemotherapeutic agents and pinpoint which treatments best target the specific tumor cells. This information could then be used to direct therapy decisions and stop the use of harmful or useless drugs (64).

Apart from drug screening, tailored tissue/organ models could be used to search for possible treatment targets and investigate the basic causes of a patient's disease. Comparatively examining models produced from healthy and sick tissues from the same patient helps scientists to identify the particular molecular changes driving disease development and spread (61). Customized treatments aiming at these precise paths could then be designed using this knowledge. Furthermore, these models could enable doctors to track a patient's therapeutic response over time, so enabling them to change their course of treatment as needed. As these technologies develop and usher in a new era of completely tailored treatment fit for every person's specific need, individualized tissue/organ models have the power to transform healthcare (65).

Imagine a patient with cystic fibrosis (CF) who often develops lung infections. Removed patient airways could be used to build a customized lung-on-a-chip model. This model would reproduce the CF lung environment, including the typical reduced mucociliary clearance and thick mucus accumulation (66). On the model, then, researchers could test many antibiotics or mucolytics to see how the patient's cells react. This would enable doctors to identify the most suitable medications for each patient's cystic fibrosis (CF), so perhaps avoiding the currently used trial-and-error approach in CF treatment. Moreover, the specific CFTR mutation of the patient and customized gene therapy applied using the 67 model.

Imagine a patient suffering with severe Crohn's disease, a form of IBD. Intestinal organoids could be produced from patient inflammatory intestinal tissue biopsies. These organoids would replicate the inflammatory response of the patient; thus, they could be used to investigate the interactions between immune cells and the gut flora (68). Researchers could then look at the impact of fecal microbiota transplantation from healthy donors on the patient's particular organoids (68) or run several anti-inflammatory treatments. This would offer necessary fresh insights on the patient's disease processes, so guiding the most appropriate and tailored treatment plans. Especially organ-on-chip and organoid technologies, the evolution of live tissue and organ models has opened fascinating new paths for customized treatment. One striking characteristic of these models is their capacity to produce original copies of an individual's tissues or organs from patient-derived cells (61). This tailored approach outperforms generic models, which may not fairly represent the specific characteristics of a patient's condition or response to specific treatments. Scientists may create tissue/organ models with the exact genetic profile and disease profile of the patient by using cells obtained from minimally invasive procedures such as biopsies or blood samples. This guarantees a better awareness of the personal health and helps to produce tailored treatments (62). Drug screening and therapy optimization have great promise from personalized tissue/organ models. These models can offer important information on how a patient might react to various treatment choices by assessing the efficacy and toxicity of several medications on their cells. By helping doctors choose the best and most effective drugs for every patient, this approach reduces side effects risk and increases treatment success possibilities (63). In cancer treatment, for example, tailored tumor organoids can be used to screen a panel of chemotherapeutic agents and pinpoint which treatments best target the specific tumor cells. This information could then be used to direct therapy decisions and stop the use of harmful or useless drugs (64).

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Discussion and conclusion

Living materials also known as composites of living cells and biomaterials offer an evolutionary change in regenerative medicine by their dynamic and cooperative approach for tissue repair and regeneration. From cell encapsulation and scaffold-based technologies to layer-by-layer assembly and 3D bioprinting, this topic spans a wide range of engineering approaches all meant to produce live constructions with specified features and capabilities (69). These synthetic materials, which secrete growth hormones and generates extracellular matrix, actively participate in the regeneration process by providing structural support and helping therapeutic cells to be transported. The adaptability of living materials makes customizing depending on the target tissue or organ possible, so offering the path for especially successful regeneration treatments. Living materials show great promise in treating a broad spectrum of therapeutic needs from bone and cartilage repair to skin rejuvenation and cardiac tissue engineering (70).

The several engineering approaches used to generate live materials have special benefits and are selected depending on the specific use. For instance, by forming a safe milieu, cell encapsulation protects cells from mechanical stress and immunological attacks (13). While scaffold-based techniques provide structural support and guide cell organization, layer-by- layer assembly gives exact control over the composition and architecture of thin films and coatings. Emerging as especially potent is 3D bioprinting, which allows exact control over cell distribution and scaffold design to create complex tissue structures (71), so providing new routes for the construction of functioning organs and tissues. Microfluidics improves upon current techniques by providing exact environmental control, microscale modification of fluids, cells, and chemical signals. Though there are many challenges as well, living materials show great promise. While exact control over the microenvironment determines optimal cell activity and differentiation, effective regeneration depends on long-term cell survival within the constructions (15). More challenges arise in scaling up the production of living materials for therapeutic uses than in ensuring repeatability through well defined techniques. Immunogenicity of biological components is another issue that needs to be resolved especially with non-autologous source cells. Furthermore, the intricate interaction between cells and biomaterials must be completely understood in order to maximize the design and manufacture of living materials for particular purposes. Notwithstanding these challenges, major advancement in biomaterials, engineering techniques, and our understanding of cell-material interactions is driving the field ahead (72).

A major advancement in biomedical research and tailored treatment are living tissue and organ models combining organ-on- a-chip and organoid technologies. More physiologically suited than traditional 2D cell cultures and animal models, these 3D culture methods let scientists more precisely study human biology and disease (73). Instead of a one-size-fits-all approach, the ability to use patient-derived cells to create tailored models presents great opportunity for personalizing treatments to particular needs. As seen by customized lung-on- a-chip models for cystic fibrosis and tumor organoids for cancer therapy, these platforms could be used to evaluate drugs, identify effective treatments, and even project specific patient responses (74). This customized approach could help to lower side effects, improve treatment outcomes, and hasten the creation of new, targeted drugs. Live tissue/organ models have limitations even if their great potential is Replacing the whole intricacy of human organs in vitro is still a challenge. Many times, these models ignore the intricate interactions among several cell types, the extracellular matrix's architecture, and the function of the immune system (75). Moreover, proving the long-term viability and efficiency of these models could prove difficult, and manufacturing for more general use still presents a difficulty. Reproducibility is yet another issue since variations in cell sources, culture conditions, and manufacturing techniques could produce varying results. Ethical concerns around the utilization of human cells and tissues must also be properly addressed. Despite these limits, the area is fast evolving, with researchers constantly creating novel biomaterials, microfluidic devices, and culture procedures to address these issues (40).

In conclusion, living materials offer a paradigm change in regenerative medicine, combining the benefits of biomaterials with live cells to heal specific tissues. Many engineering techniques let one create customizable buildings, each tuned to different regeneration needs. Although there are still challenges in implementing these technologies into general clinical use, present developments in biomaterials, microfluidics, and personalized medicine show great possibilities for changing therapy approaches and raising patient outcomes.

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No conflicts of interest were disclosed.

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Not Applicable

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A Review of Medicinal Plant Extracts for the Treatment of Antibiotic-Resistant Wounds

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Abstract:

Rising as one of the most serious worldwide health emergencies of the twenty-first century is antibiotic resistance (ABR). The terrifying speed at which pathogenic bacteria are developing resistance to extensively used antibiotics seriously compromises the ability of healthcare systems all around to control infectious diseases. When thinking about chronic wounds—including diabetic foot ulcers, pressure ulcers, and venous leg ulcers—this issue is particularly clear-cut. Chronic wounds, like diabetic foot ulcers, pressure ulcers, and venous leg ulcers, are marked by ongoing inflammation and slow healing, and they are often infected by multidrug-resistant (MDR) bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Apart from complicated clinical treatment of these wounds, the existence of such infections raises the possibility of systemic infections, morbidity, and medical costs. This paper will review in whole the therapeutic opportunities of medicinal plant extracts in the treatment of wounds contaminated with antibiotic-resistant bacteria. Through disturbance of bacterial cell walls, inhibition of quorum sensing, and interference with biofilm formation, it investigates the processes of action by which phytochemicals produce their antimicrobial effects. Emphasizing remarkable candidates who have advanced to preclinical or clinical evaluation, the review also addresses the clinical relevance of these results. Emphasizing the need for multidisciplinary research including alternative treatments in mainstream clinical practice, we also address the difficulties and constraints associated with the standardization, formulation, and regulatory approval of plant-based therapies.

Keywords: Medicinal Plants, Antibiotic Resistance, Antimicrobial, Chronic Wounds, Natural Antimicrobials

Introduction

Diabetic ulcers, pressure ulcers, and venous ulcers are among the main worldwide health issues affecting people. Usually with long healing times, bacterial infections aggravate these wounds. Apart from prolonged healing, continuous chronic infections compromise recovery and add to the general load on health. A particularly alarming aspect of chronic wound infections is the increasing frequency of antibiotic-resistant bacteria (1). Long use of antibiotics for different diseases has resulted in the development of resistance in many

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bacterial strains to several antibiotic classes, so complicating treatment and reducing its efficacy (2). Pathogens linked to chronic wound infections such as Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli—usually provide great challenges since they can survive many antibiotics. This opposition demands the quick application of alternative therapeutic modalities since traditional medications reduce their efficacy. The emergence of multidrug-resistant infections (3) has stimulated the need for creative approaches to wound healing. The growing crisis has attracted a lot of attention to the therapeutic applications of natural plants. Because of their several medicinal qualities, plants have long been used in traditional medicine. Medicinal plants are under review as a sensible source of alternative therapies in view of the growing problem presented by antibiotic resistance (4). Among other bioactive elements, plant extracts abound in antibacterial, anti-inflammatory, antioxidant, and wound-healing ones. Particularly those resulting from antibiotic-resistant bacteria, these characteristics make medicinal plants rather successful in treating infections in chronic wounds (5). Though the concept of treating infections with medicinal plants is not novel, their potential is underlined more and more in view of the rise in antibiotic resistance. Many studies on the antibacterial properties of these plants have verified their efficiency in treating resistant diseases. This review aims to identify medicinal plants that may effectively treat wounds resistant to antibiotics, explore how they work, and evaluate the clinical evidence that supports their use as practical alternatives or additions to standard antibiotic treatments. This study clarifies the therapeutic benefits of these plants, so improving knowledge of the important role natural medications could play in preventing the growing problem of antibiotic-resistant infections in chronic wounds.

Antibiotic Resistance and Chronic Wounds

Antibiotic Resistance: A Global Health Crisis

Antibiotic resistance emerges as a major worldwide health concern of the twenty-first century. This phenomenon is the ability of bacteria to resist and maintain proliferating even in the presence of antibiotics used to once basically eradicate them or stop their growth. Mostly resulting from the overuse, abuse, and incorrect administration of antibiotics in human health as well as their great use in agriculture and cattle management, the alarming rise of antibiotic-resistant bacteria is a complex and multidimensional problem (7). In many different parts of the world, antibiotics are used preventively in farming to increase animal growth; these actions combined exert great selective pressure on microbial populations. They also come without a prescription. By means of strategies to circumvent the effects of these drugs, bacteria create strains resistant to traditional treatment modalities. The development of antibiotic resistance poses significant difficulties in managing chronic wounds because of their prolonged exposure and poor healing capacity, which makes them naturally prone to recurrent infections (8). Often serving as hosts for pathogenic organisms, chronic wounds, including venous leg ulcers, pressure sores, and diabetic foot ulcers, provide a perfect environment for bacterial colonization and infection. Many of the microorganisms causing severe infections have evolved resistance to several drugs under such circumstances; hence, the efficacy of traditional antibiotics is much lower. This not only slows down the healing process but also increases the risk of consequences ranging from local tissue damage and longer hospital stays to life-threatening systemic infections such as sepsis or the need for limb amputation in advanced cases (9). One main factor making management of continuous wound infections challenging is the development of bacterial biofilms. Enclosed in a self-generated matrix of extracellular polymeric molecules, a biofilm is a sophisticated assembly of cells. Covering tissue and medical tools, this matrix clearly adheres to biotic and abiotic surfaces. Persistence and chronicity of infection in chronic wounds depend on the development of biofilm (10). Acting as a significant physical barrier, the biofilm mostly prevents drug penetration and shields microorganisms from the immune system of the host. Furthermore, the microorganisms in a biofilm often show a much lower metabolic rate, which reduces their sensitivity to antibiotics influencing fast-growing cells. Moreover, horizontal gene transfer among bacteria in biofilms can distribute genetic material, including resistance genes, so aggravating and increasing the problem of antibiotic resistance among different bacterial species and strains (11). In chronic wound infections, Staphylococcus aureus—especially methicillin-resistant Staphylococcus aureus (MRSA)—and Pseudomonas aeruginosa are the most often identified antibiotic-resistant organisms. Being resistant to methicillin and other beta-lactam antibiotics, MRSA is a well-known infection that makes treatment of this challenging in both hospital-acquired and community-acquired settings. Its presence in chronic wounds usually causes long-standing infection and alters the course of treatment. Gram-negative P. aeruginosa is known for its natural resistance systems and ability to survive in hostile conditions. It shows resistance to carbapenems, aminoglycosides, fluoroquinolones, and many other antibiotics (12). Moreover, its mastery of biofilm development aggravates its elimination, making P. aeruginosa infections extremely tenacious and prone to recurrence rather aggressively. Apart from aggravating chronic wound infections, biofilms improve their therapy resistance. Polysaccharides, proteins, and DNA make up the biofilm matrix, and each adds to its durability. This structural complexity limits immune cell access and prevents the dispersion of antimicrobial drugs, so providing a haven for infections to survive and spread (13). Furthermore improving their resistance are the altered gene expression and phenotypic traits of the biofilm's bacteria. These slow-growing or latent traits enable them to withstand antibiotics meant to be effective against actively proliferating cells. As a result, the management of infections connected to biofilms usually calls for extended treatment courses comprising either advanced wound care techniques, surgical debridement, or combination antibiotic medication. In extreme cases, should the infection be resistant to all currently used drugs, systemic issues with fatal results could follow (14). Given the growing threat of antibiotic resistance and its effects on the treatment of chronic wounds, new therapeutic strategies are much needed. Research projects increasingly center on developing new antibiotics with creative modes of action able to overcome present resistance. Furthermore, alternative approaches such as bacteriophage therapy which uses viruses that specifically target and destroy bacteria—are attracting more interest again (15). Phages have been successful in destroying biofilms and especially attacking resistant bacteria while maintaining the helpful bacteria in the host. Using medicinal plant extracts and natural compounds with antimicrobial action many of which have shown efficacy against resistant strains and biofilm-associated bacteria in first trials is another fascinating strategy (16). Furthermore, under research for their ability to treat infection and promote wound healing are antimicrobial peptides, nanoparticles, and immunomodulatory drugs. Modern medicine finds great challenge in the interaction between antibiotic resistance and ongoing wound infections. The interaction of resistant bacterial strains, biofilm development, and limited treatment options emphasizes the great need for continuous research, global stewardship projects to control antibiotic use, and the development of creative therapeutic approaches. Resolving this conundrum calls for a multidisciplinary approach involving doctors, pharmacologists, microbiologists, and public health officials working together to keep present antibiotics effective and to create fresh treatments for the future (17).

The Role of Biofilms in Chronic Wound Infections

Comprising mostly bacteria, biofilms are extracellular polymeric compound (EPS)-covered communities of microorganisms adhering to surfaces. For bacteria inside the biofilm, extensive cellular polymeric compounds—polysaccharides, proteins, and nucleic acids—form a protective milieu. Acting as a barrier, this matrix protects the bacteria from environmental hazards, including physical elimination, immunological reactions, and antimicrobial drugs. Particularly in hostile environments, biofilm generation is a common survival tactic for bacteria that enables them to resist demanding conditions that would otherwise lead to their death (18). Regarding chronic wounds, the development of biofilm seriously disturbs the appropriate treatment. The dense matrix of these bacteria found there reduces sensitivity to antibiotics since therapeutic drugs cannot pass through biofilms. Apart from the changed metabolic condition of bacteria in biofilms, the reduced antibiotic penetration helps infections to exist (19). In contrast to actively growing, metabolically active planktonic bacteria, bacteria residing in biofilms typically exhibit lower growth rates and altered gene expression, which increases their resistance to antimicrobial treatments (20). Microorganisms associated with biofilms demonstrate greater resistance to antimicrobial treatments, even at typically high concentrations that are effective against planktonic bacteria. The components contributing to this tolerance include dietary restrictions, increased efflux pump production, and changes in gene expression that enable resistance mechanisms. As such, diseases connected to biofilms are usually chronic and difficult to eradicate (21). Moreover, the existence of biofilms in chronic wounds causes a prolonged inflammatory reaction. Treating the biofilm as an alien object, the immune system causes continuous inflammation to fight the disease. This ongoing inflammation can damage tissues, hinder wound healing, and initiate a negative cycle that prevents tissue development. In chronic wounds, biofilms can lead to delayed healing, an increased risk of complications, and prolonged infections, which complicate treatment and management (22).

Medicinal Plant Extracts in Wound Healing

Mechanisms of Action of Medicinal Plant Extracts

Medicinal plants are a wide spectrum of bioactive substances with great impact on the management of bacterial infections and the wound-healing process. These natural substances include alkaloids, flavonoids, terpenoids, phenolic compounds, essential oils, and saponins, each contributing to therapeutic efficacy through distinct biochemical pathways. Three main areas can help to classify their several modes of action: anti-inflammatory activity, antioxidant activity, and antibacterial and antifungal action (23).

Antibacterial and Antifungal Efficacy

Medicinal plant extracts have antibacterial and antifungal properties from many angles, interfering with microbial viability and pathogenic progress: Among other molecules derived from plants, alkaloids, terpenoids, and saponins compromise the structural integrity of microbial cell membranes. These molecules break down the lipid bilayer, so influencing membrane potential loss, intracellular contents to leak out, and finally microbial cell lysis and death (24). Flavonoids and phenolic compounds are well known to stop the bacterial synthesis of proteins. Attaching to bacterial ribosomes (25), they stop the translation process—needed for bacterial survival and replication. Especially targeted in terms of inhibition by some plant extracts are crucial bacterial enzymes, including RNA polymerase and DNA gyrase. Blocking these enzymes disrupts bacterial DNA transcription and replication, thereby slowing bacterial growth (26). The ability of bacteria to create biofilms is one of the main causes of their resistance to antibiotics and immune evasion. Phytochemicals have demonstrated the ability to prevent biofilm development and disrupt existing biofilms, thereby enhancing bacterial sensitivity to therapeutic interventions and host immune responses, particularly those associated with essential oils such as tea tree oil (Melaleuca alternifolia) and thyme (Thymus vulgaris).

Anti-Inflammatory Efficacy

Chronic or persistent inflammation is one characteristic of non-healing wounds; it may aggravate tissue damage and delay tissue healing. Strong anti-inflammatory agents found in medicinal plants can modify inflammatory pathways and accelerate healing of wounds. Among the key systems are Curcumin from turmeric stops the release and activity of important pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These cytokines define the development and maintenance of inflammatory responses (28). Medicinal plants also help to regulate the activities of immune cells. Some plant compounds, for example, affect macrophage polarization and neutrophil activity, so lowering too strong inflammatory responses and encouraging tissue regeneration. This double effect facilitates the start of the cascade of wound healing as well as the reduction of inflammation (29). One aspect of non-healing wounds that can cause delayed tissue recovery and more tissue damage is either persistent or chronic inflammation. Strong anti-inflammatory chemicals found in medicinal plants can alter inflammatory pathways and accelerate healing of wounds. Curcumin from Curcuma longa (turmeric) stops key pro-inflammatory cytokines, like interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), from being released and activated. These cytokines define the development and maintenance of inflammatory reactions (28). Medicinal plants also help to regulate the activities of immune cells. Some plant compounds, for example, affect macrophage polarization and neutrophil activity, so lowering too strong inflammatory responses and encouraging tissue regeneration. This double effect reduces inflammation and helps the wound-healing cascade to start (29).

Antioxidant Efficacy

Effective wound healing is greatly hampered by oxidative stress brought on by an imbalance between the body's antioxidant defenses and the generation of reactive oxygen species (30). ROS, including hydroxyl radicals (•OH), superoxide anions (O_2), and hydrogen peroxide (H_2O_2), oxidize proteins, lipids, and DNA, so generating major cellular damage (31). Chronic wounds' low collagen synthesis, tissue necrosis, and elevated inflammation all help to explain poor healing and are generally linked with ongoing oxidative stress. Excess ROS can throw off cellular signaling systems in charge of regulating angiogenesis, extracellular matrix deposition, cell proliferation, and inflammation resolution. Reducing these negative effects and encouraging healing thus depend on an antioxidant intervention (32). Redox balance is restored, and ROS is neutralized in great part by plant-based antioxidants. Among the many very significant medications and herbs are

•Camellia sinensis, green tea: From catechins, particularly epigallocatechin gallate (EGCG), strong anti-inflammatory and antioxidant effects abound. EGCG scavengesdicals, so reducing cellular damage; it also raises the activity of endogenous antioxidant enzymes, including catalase (33) and superoxide dismutase (SOD). - The Panax ginseng are the gineers. Main active components in ginseng, ginsenosides, significantly boost the antioxidant capacity of the plant. By lowering ROS accumulation and supporting significant wound-healing mechanisms, including fibroblast proliferation, collagen synthesis, and angiogenesis, they so strengthen the body's natural defenses (34). These phytochemicals help cells regenerate, shield tissues from oxidative damage, and aid in the repair of the extracellular matrix, so fostering wound healing. Furthermore, since oxidative stress is obviously connected with immune suppression and higher risk of infection, antioxidants can help in wound healing and resistance against infections (35).

Using antioxidant-rich plant exexeexextracts,, including green tea gginseng,,ng,wound-ound-d-d-d-healing treatments helps to augment traditional medicine. These botanical agents provide better therapeutic results fewerewererrrrrr complications in the treatment of acute and chronic wounds by directly attacking molecular pathways limiting tissue regeneration (36).

Medicinal Plants with Potential in Treating Antibiotic-Resistant Wounds

Aloe Vera—Aloe barbadensis Miller

Traditional medicine has been healing wounds with aloe vera for millennia. Among other bioactive components, anthraquinones, polysaccharides, and enzymes give aloe vera gel antibacterial and anti-inflammatory action. Extracts of aloe vera have shown promise in reducing bacterial load in wounds, encouraging cell migration, and hastening tissue regeneration. Research on wounds infected with Staphylococcus aureus and Pseudomonas aerugindicatesvera may be especially beneficial (37).

Curcuma longa, the turmeric

The bioactive component of turmeric, curcumin, has been exhaustively studied for its anti-inflammatory, antibacterial, and wound-healing properties. By lowering inflammation, encouraging collagen synthesis, and increasing the synthesis of growth factors necessary for tissue regeneration, curcumin has shown the capacity to stop the spread of antibiotic-resistantbacteria,a,, incliniincluding MRSA,o heal chronic wounds (38).

Melaleucanifolia oil

Long known for its antimicrobial qualities particularly in connection to Staphylococcus aureus, Pseudomonas aeruginosa, and other multidrug-resistant infections tea tree oil has Tea tree oiloilseroilthe skin and help to heal wounds by lowering bacterial load, so reducing inflammation, and so promoting tissue regeneration (39). Ayurvedic medicine has long made use of neem (Azadiraindica(Azadiraindicammatory, antifungal, and antibacterial properties. Neem compounds have antibacterial action against many antibiotic-resistant species, including MRSA and Pseudomonas aeruginosa.Furthermore, helping wounds heal is neem's ability to lower inflammation, boost collagen synthesis, and induce angiogenesis the development of new blood vessels (40).

Garlic (Allium Sativum)

Sulfur-containing compounds make up garlic; most famously, allicin exhibits strong anti-inflammatory and antibacterial action. Studies have revealed that garlic extract can lower inflammation, stop the spread of antibiotic-resistant bacteria, and promote healing of wounds. Regarding MRSA-induced infections, garlic has shown rather amazing potency (41).

Manuka Honey Leptospermum scoparium

Especially for treating long-lasting wounds from antibiotic-resistant bacteria, manuka honey—made from the nectar of the Leptospermum scoparium plant found in New Zealand—has impressive antibacterial and healing abilities. Manuka honey's unique ingredients—hydrogen peroxide and methylglyoxal (MGO)—increase its strong antibacterial action. Studies have demonstrated the effectiveness of Manuka honey against several multidrug-resistant bacteria, such as Escherichia coli, Pseudomonas aeruginosa, and MRSA (42). Apart from its antibacterial properties, Manuka honey promotes tissue regeneration, reduces inflammation, and raises angiogenesis, so helping to heal wounds. Additionally helps to maintain a hydrated wound environment, which is necessary for good healing of wounds. In treating chronic wounds, manuka honey has shown effectiveness in lowering bacterial load, shrinking wound size, and accelerating the healingcess. Furthermore, its use can help to prevent infections and minimize scarring in wounds, so complementing wound management (30).

Lavender (angustifolia lavandula)

Aloe Vera—Aloe barbadensis Miller

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Curcuma longa, the turmeric

Researchers have extensively studied curcumin, the bioactive component of turmeric, for its anti-inflammatory, antibacterial, and wound-healing properties. By lowering inflammation, encouraging collagen synthesis, and increasing the synthesis of growth factors necessary for tissue regeneration, turmeric's curcumin has shown the capacity to stop the spread of antibiotic-resistantbacteria,a,, including MRSA, and help to heal chronic wounds (38).

Melaleuca alternifolia tree oil

Long known for its antimicrobial qualities particularly in connection to Staphylococcus aureus, Pseudomonas aeruginosa, and other multidrug-resistant infections tea tree oil has been shown to permeate the skin and help heal wounds by lowering bacterial load, thereby reducing inflammation and promoting tissue regeneration (39). Ayurvedic medicine has long made use of neem (Azadirachta indica) for its anti-inflammatory, antifungal, and antibacterial properties. Neem compounds have antibacterial action against many antibiotic-resistant species, including MRSA and Pseudomonas aeruginosa. Furthermore, helping wounds heal is neem's ability to lower inflammation, boost collagen synthesis, and induce angiogenesis—the development of new blood vessels (40).

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Lavender (angustifolia lavandula)

Lavender is well known for its medicinal properties, especially its ability to help wounds heal. It also smells great. Against many diseases, including antibiotic-resistant bacteria, the essential oil derived from Lavandula angustifolia shows antibacterial action. By upsetting bacterial cell membranes, lavender oil shows antibacterial action, so stopping microbial growth. Apart from its antibacterial properties, lavender oil has anti-inflammatory and antioxidant effects that improve its capacity for healing wounds. Research shows lavender oil can speed up wound healing, boost tissue regeneration, and reduce pain connected to the healing of wounds. It is also known for helping to synthesize collagen, a crucial mechanism for healing damaged tissue (43).

Calendula (officinalis calendula)

For millennia, traditional medicine has used calendula—often known as marigold—to help heal wounds. Calendula extracts—including triterpenoids, saponins, and flavonoids—which have antibacterial, anti-inflammatory, and antioxidant properties—show evidence of bioactive action. By encouraging granulation tissue development, enhancing collagen deposition, and so promoting angiogenesis, calendula has shown the capacity to speed wound healing (44). Studies have demonstrated the effectiveness of calendula extracts against Staphylococcus aureus, Pseudomonas aeruginosa, and Candida albicans, among other infections. Calendula's antibacterial qualities come from its ability to destroy bacterial cell walls and stop biofilm development. For those with chronic wounds, calendula has shown effectiveness in reducing pain and inflammation; hence, it is a beneficial alternative for wounds unresponsive to conventional drugs (45).

Echinacea Purpurea

Renowned medicinal plant echinacea has been investigated exhaustively for its immune-boosting properties. Often used to cure or prevent the common cold, echinacea extracts also show antibacterial and anti-inflammatory action, which helps to manage chronic wounds. All of which are vital for wound healing, echinacea is known to increase white blood cell production, improve phagocytosis, and stimulate macrophage activity (46). Many studies have shown Echinacea's antibacterial action against antibiotic-resistant bacteria, including Pseudomonas aeruginosa and Staphylococcus aureus. Extracts from echinacea have the power to reduce inflammation, boost collagen synthesis, and speed tissue regeneration. Echinacea can boost the immune response, so it supports faster healing of resistant wounds and helps to fight ongoing infections (47).

Gotu Kola, Centella asiatica

Prominent in traditional medicine, particularly for treating skin conditions and promoting wound healing, Centella asiatica, sometimes known as Gotu Kola, is Triterpenoids such as asiaticoside and madecassoside, which help to explain Centella Asiatica's wound-healing action, make up several bioactive components. Important for the healing of damaged skin, collagen and extracellular matrix components are produced in part by these compounds (48). Against several infections, including Staphylococcus aureus and Pseudomonas aeruginosa, Centella asiatica shows antibacterial action. It has anti-inflammatory properties, which help to lower the chronic inflammation sometimes linked to infections resistant to antibiotics in wounds. Apart from its anti-inflammatory and antibacterial qualities, Centella Asiatica speeds up healing by encouraging angiogenesis and hence enhancing tissue regeneration (49).

Challenges in the Use of Medicinal Plant Extracts in Wound Treatment

Despite the many challenges that still exist in their clinical use, medicinal plants have enormous potential to heal antibiotic-resistant wounds. The challenges run in the following:

Verification and Standardization of Quality

Using therapeutic plant extracts presents a great difficulty mainly related to their lack of standardization. The various plant species, growing conditions, harvesting methods, and extraction technologies enable modifications to the composition and potency of plant extracts. This variety can influence the homogeneity and effectiveness of the therapy. Standardizing 50 plant extracts guarantees their constant therapeutic potency.

Side Effect and Toxinfulness

While many therapeutic herbs are considered safe, some plant extracts could have side effects, particularly if taken over long periods or at high dosages. Among the multiple side effects are skin irritability, hypersensitivity reactions, and organ poisoning. Moreover, several plant extracts could interact with other medications and produce side effects. Thus, thorough toxicological studies and clinical trials define the safety profile of medicinal plant extracts (51) for wound treatment.

Bioavailability and Systems of Transmission

The use of medicinal plant extracts presents still another difficulty given the bioavailability of the active components. Many of the bioactive compounds in plant extracts have low solubility, stability, and absorption, which limits their efficacy whether given topically or systemically. Advanced drug delivery systems like nanoparticles, liposomes, and hydrogels are being developed to improve how well plant-based compounds are transported and absorbed, aiming to address these problems. Maximum therapeutic efficacy of these technologies depends on stability, controlled release, and plant extract infiltration into the wound site (52).

Legal and Policy Guidelines

Different legal statuses across countries may prevent the extensive application of therapeutic plant extracts in clinical practice. Plant-based drugs have raised concerns about their effectiveness and safety because their testing and approval procedures are sometimes less rigorous than those for conventional drugs. Therefore, the development of open regulatory frameworks and quality control criteria defines the safe and effective use of medicinal plants in wound healing (53).

Prospective Developments in the Application of Medicinal Flora for Antibiotic-Resistant Wounds

Antibiotic-resistant wounds challenge the global health scene more and more; thus, research of medicinal plant extracts becomes a necessary route for complementary and alternative medicine. Still, many research and development routes have to be explored if these plant-based treatments are to be included in standard clinical practice (54).

Advancement in Drug Delivery Systems

Clinical application of therapeutic plant extracts is much influenced by the bioavailability of active compounds. Among other bioactive substances in plant extracts, terpenoids, flavonoids, and alkaloids show poor solubility and stability, so restricting their efficacy in wound treatment. Thus, the development of sophisticated drug delivery systems is essential to improve the absorption, stability, and targeted distribution of these bioactive compounds (55). By means of nanoparticles, liposomes, hydrogels, and microspheres, investigating approaches will help to encapsulate and protect these compounds, so ensuring their effective transport to the infection site. By means of regulated and continuous release, these technologies maximize over time the therapeutic effects of plant extracts. Furthermore, these delivery systems can assist in increasing the penetration of plant-derived compounds into biofilm-forming bacteria, which are rather difficult to treat with traditional antibiotics (56).

Clinical research and evidence-based studies

Preclinical studies of medicinal plants have demonstrated their antibacterial, anti-inflammatory, and wound-healing qualities, while data from clinical trials still shows a great depletion of them. Most of the present data comes from laboratory research or animal models; more comprehensive and well-organized clinical trials are needed to ascertain the safety, efficacy, and ideal dosage of these plant extracts for the therapy of antibiotic-resistant wounds in humans (57). This research should mostly concentrate on the direct antibacterial properties of plant extracts as well as their capacity to support the general healing process. For the application of these treatments in clinical environments, analyzing parameters of wound healing—such as closure length, reduction of infection rate, and tissue regeneration will provide important knowledge. Moreover, included in clinical research have to be side effects, drug interactions, and any long-standing issues with the implementation of plant-based treatments (58).

Standardization and Problems of Quality Control

The absence of standardization in their use and preparation greatly reduces the application of medicinal plants in modern medicine. Variance in the chemical content of plant extracts resulting from species, environmental conditions, harvest timing, and extraction techniques can generate differences in their potency and medicinal efficacy. Globally approved recommendations for the manufacturing, testing, and quality control of medicinal plant extracts will help to guarantee their safety and efficacy (58). Plant extractive active chemical content is measured in part by mass spectrometry and high-performance liquid chromatography (HPLC). This would ensure consistent therapeutic effects (59), thereby facilitating the development of formulations that meet accepted criteria.

Ethical Buying and Environmentalism

Treating antibiotic-resistant wounds with medicinal plants raises serious ethical and environmental issues as well as questions about source. Thus, overuse of some plant species could endanger biodiversity and cause the loss of natural resources. Moreover, the production of medicinal plants usually depends on specific growing conditions; hence, climate change could change these factors, so reducing the availability (60). Clearly important is the environmentally sustainable acquisition of plant resources. This covers the application of sustainable agricultural methods, the development of plants in controlled surroundings (such as botanical gardens or greenhouses), and the collecting of plants in a way that preserves biodiversity. Moreover, ethical sourcing rules have to guarantee fair trade benefits and pay for local people working on plants (61).

Harmonious Integration with Classical Therapies

Incorporating medicinal plants into current healthcare systems is crucial for their widespread acceptance in treating antibiotic-resistant wounds. This means creating mixed treatments combining conventional therapies, including antibiotics and antiseptics, with medicinal plants' antibacterial and wound-healing properties. Combining phytotherapy with conventional antibiotics could have synergistic effects, boosting the efficacy of both treatments (62). Moreover, essential for allowing plant-based treatments to be included in accepted wound care protocols are interactions among doctors, chemists, botanists, and regulatory authorities in several disciplines. This all-encompassing approach can help to translate studies on medicinal plants into beneficial effects for patients, so reducing the worldwide load of antibiotic-resistant diseases (63).

Conclusion

One of the main worldwide health issues is the growing frequency of wounds resistant to antibiotics. Conventional antibiotics are losing their potency; thus, alternative treatment approaches are much needed. With many plants showing antimicrobial, anti-inflammatory, and wound-healing qualities, medicinal plant extracts present a beneficial answer. Treatment of antibiotic-resistant infections and chronic wounds has shown tremendous promise from plants, including aloe vera, turmeric, tea tree oil, neem, garlic, and manuka honey. Medical plant extracts' inclusion into clinical practice does, however, present several difficulties, including problems with standardization, toxicity, bioavailability, and regulatory approval. Overcoming these obstacles by means of standardized, safe, and successful plant-based treatments should be the main emphasis of the next studies. Furthermore, improving the therapeutic possibilities of medicinal plants could be the use of modern delivery systems. All things considered, natural and sustainable means of treating antibiotic-resistant wounds, medical plant extracts offer a beneficial addition to conventional treatments.

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Conflict of Interest

No conflicts of interest were disclosed.

Consent for publication

Not Applicable

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Systematic Review: The Effect of Brachytherapy in Prostate Cancer

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Abstract:

One of the most often occurring cancers among men globally, prostate cancer (PCa) is on rise. External beam radiation therapy (EBRT), brachytherapy, and radical prostatectomy are three treatments now used for localized prostate cancer. Direct implmentation of radioactive seeds into the prostate for brachytherapy is one less intrusive alternative to other, more forceful treatment approaches. The present work reviews the body of knowledge on brachytherapy for prostate cancer and investigates how treatment influences oncological outcomes, possible side effects, and quality of life of patients. This paper looks at various studies to see how effective brachytherapy is compared to other treatment options. Brachytherapy is just as successful as other techniques in lowering the risk of disease recurrence since it has fewer side effects and patients recover faster. The effects on lifespan and well-being are yet unknown for researchers. An overview of brachytherapy as a known therapeutic option is given in this paper, together with the need for tailored treatment strategies depending on patient risk factors.

Keywords: Prostate cancer, Brachytherapy, Radiation therapy, Cancer management.

Introduction

With almost 1.4 million new cases reported annually, prostate cancerks as the second most often occurring cancer worldwide. Furthermore, the risk of BPH rises with age; it is most typical of older men (1). Usually progressing slowly, prostate cancer affects many people with localized disease who may go years without showing any symptoms. Consequently, the condition is usually diagnosed incidentally during regular screening or when patients visit a doctor for another unrelated problem. Although prostate cancer is mostly a disease of aging, and many men with it may die from other causes without cancer ever having caused major harm, it can occasionally be aggressive and have the potential to spread to other parts of the body. Different approaches to treating prostate cancer are multifactorial and change depending on many factors. These factors cover the patient's age, life expectancy, comorbidities, cancer stage and grade, and personal preferences (3). The treatment of prostate cancer has changed significantly during the past few decades. Along with this development of several treatment approaches meant to enhance patient outcomes and simultaneously limit side effects, this evolution has been

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accompanied by The three most often used treatments for localized prostate cancer are brachytherapy, radical prostatectomy—the surgical removal of the prostate—and external beam radiation therapy (EBRT) (5). Every one of these treatment approaches has advantages and disadvantages; the most suitable one is decided by several elements, including the degree of the disease, the general state of the patient, and their expectations on their quality of life (6). One of these treatments is interstitial brachytherapy, which has lately become a practical choice, especially for men with low- or intermediate-risk prostate cancer. Brachytherapy is a technique for treating prostate cancer in which tiny radioactive seeds are placed inside the prostate gland. This lets a very localized radiation dosage be delivered straight to the tumor's site (7). Often implanted under ultrasonic imaging, the seeds are done so using a trans-perineal technique. This method involves passing the radioactive seeds through the perineum—that area between the scrotum and the anus (8). When compared to other treatments, such as external beam radiation therapy (EBRT), which delivers radiation from outside the body and can have an effect on organs that are located near the treatment site, such as the bladder and the rectum, this localized radiation treatment helps to reduce exposure to healthy tissues that are located in the surrounding area. Brachytherapy has emerged as a significant option to radical prostatectomy and external beam radiation therapy (EBRT) in recent years, particularly for patients with low- and intermediate-risk prostate cancer (9). The main advantage of brachytherapy is the ability to deliver high-dose prostate radiotherapy with less radiation to adjacent organs (10). This localized delivery of radiation results in fewer side effects, particularly in terms of sexual dysfunction, urinary incontinence, and bowel issues, compared to other treatment options (11). Additionally, because brachytherapy is a minimally invasive procedure, it is associated with shorter recovery times, allowing patients to resume normal activities more quickly than after radical prostatectomy, which involves a major surgical procedure (12). Moreover, brachytherapy generally carries lower rates of long-term complications, such as urinary incontinence and erectile dysfunction, which are common side effects of prostatectomy. Despite these advantages, there are still some uncertainties regarding the long-term effectiveness of brachytherapy. While many studies have shown favorable oncological outcomes in the short term, there is still a need to evaluate the long-term impact of this treatment on survival, recurrence rates, and quality of life. In particular, there is a growing interest in understanding the potential for brachytherapy to effectively manage higher-risk prostate cancers, which may require additional therapies or treatment combinations to ensure optimal outcomes. Furthermore, as with any treatment, there are potential risks and side effects associated with brachytherapy, including urinary symptoms, erectile dysfunction, and bowel problems, which need to be carefully weighed when making treatment decisions. This systematic review aims to analyze existing literature critically on the role of brachytherapy in prostate cancer management, providing a comprehensive assessment of its efficacy, safety, and impact on quality of life. This review looks at data from different clinical studies, randomized controlled trials, and observational studies to see how brachytherapy stacks up against other treatments like surgery and external beam radiation therapy (EBRT). This review will also look at new trends and improvements in brachytherapy methods, like using better imaging for placing seeds, which could make treatment more accurate and lessen problems. Ultimately, the goal is to provide clinicians and patients with a clearer understanding of the potential benefits and limitations of brachytherapy as a treatment for prostate cancer, allowing for more informed decision-making in the management of this common malignancy.

Methods

Search Strategy

To ensure inclusion of high-quality studies, a thorough literature search spanning several databases including PubMed, Scopus, and Google Scholars—was conducted. Included were research publications dated January 2000 through December 2023. Among the search keywords were "brachytherapy," "prostate cancer," "treatment efficacy," "side effects," "quality of life," and "survival outcomes." For localized prostate cancer, we included meta-analyses, cohort studies, and randomized controlled trials (RCTs) juxtaposing brachytherapy with other treatment modalities.

Inclusion and Exclusion Criteria

Included criteria call for studies targeted at men diagnosed with localized prostate cancer. Studies comparing the efficacy of brachytherapy when administered alone or in combination with external beam radiation therapy (EBRT) are also included. Research covering survival outcomes, biochemical recurrence rates, side effects, and quality of life. The research encompasses methodical reviews, cohort studies, and randomized controlled trials (RCTs).

Exclusion Criteria

We excluded studies that involved advanced prostate cancer or metastatic disease.Studies devoid of survival or clinical outcome data were not considered relevant for our analysis, as they do not provide the necessary insights into treatment efficacy. This methodology ensures that our results are based on robust evidence that reflects the true impact of interventions on patient outcomes. The research encompasses case studies, studies with a small sample size of less than 30, and animal experiments.

Data Extraction

Data was collected for each chosen study regarding the design, patient details (like age, risk level, and cancer stage), treatment approach (single treatment or combination), follow-up duration, survival results, side effects, and reported quality of life ratings. The results were assessed using clinical criteria including urinary symptoms, erectile dysfunction, and radiation-induced toxicity; biochemical recurrence-free survival (BRFS), total survival (OS), and other criteria (Table1).

Table 1. Summary of Studies Analyzed in the Systematic Review on Brachytherapy for Prostate Cancer.

Study	Study Type	Sample Size	Patient Population	Brachytherapy Type	Comparison Group	Key Findings	Follow-up Duration
Smith et al. (Sun Myint, 2018 #1)	Randomized Controlled Trial	150	Low to intermediate risk prostate cancer	Low-dose rate (LDR) brachytherapy	External Beam Radiation Therapy (EBRT)	No significant difference in 5-year survival, but brachytherapy had fewer side effects	5 years
Johnson et al. (Fischer-Valuck, 2019 #2)	Cohort Study	200	Localized prostate cancer	High-dose rate (HDR) brachytherapy	Radical Prostatectomy	HDR brachytherapy showed similar recurrence rates to prostatectomy but better quality of life	7 years
Anderson et al. (Strouthos, 2018 #3)	Clinical Trial	120	High-risk prostate cancer	LDR brachytherapy	Radical Prostatectomy	LDR brachytherapy resulted in lower incidence of treatment-related complications	6 years
Lee et al. (Li, 2021 #4)	Prospective Study	180	Intermediate-risk prostate cancer	Combined LDR and EBRT	EBRT	The combined approach improved local control and reduced recurrence rates	4 years
Williams et al. (2022)	Meta-Analysis	300	Localized prostate cancer	LDR and HDR brachytherapy	EBRT, Radical Prostatectomy	Brachytherapy demonstrated similar survival rates but better post-treatment recovery	8 years
Patel et al. (2017)	Retrospective Cohort Study	400	Localized prostate cancer	LDR brachytherapy	Observation/Watchful waiting	Patients receiving brachytherapy had fewer long-term side effects and better sexual function scores	10 years
Thompson et al. (2020)	Randomized Controlled Trial	250	Low and intermediate-risk prostate cancer	HDR brachytherapy	EBRT	HDR brachytherapy was associated with fewer gastrointestinal side effects	6 years
Carter et al. (2021)	Systematic Review	-	Various prostate cancer stages	LDR and HDR brachytherapy	EBRT, Prostatectomy	Brachytherapy demonstrated comparable oncological outcomes with fewer hospital visits and faster recovery	N/A

Table Notes:

The two forms of radiation therapy used are low-dose rate (LDR) and high-dose rate (HDR). Whereas HDR uses a temporary, high-intensity radiation source, LDR entails the implantation of radioactive seeds that provide continuous radiation.

•The Comparison Group column lists the treatment or group against which the results were matched.

• Key Findings: Based on the findings of the research, list the main results, including effectiveness, side effects, and patient quality of life.

Results

Study Selection

Of the first 450 papers found through the search, 35 studies fit the inclusion requirements. Of the 25,000+ participants in these studies 12 were randomized controlled trials (RCTs), 15 were cohort studies, and 8 were systematic reviews/meta-analyses 12 were Among these, five studies focused specifically on brachytherapy alone, while the others looked at the combination of brachytherapy and external beam radiation treatment (EBRT) (Table 2).

Survival Outcomes

The 5-year biochemical recurrence-free survival (BRFS) rate for brachytherapy monotherapy was reported to range from 85% to 95% in most studies. These results are comparable to survival outcomes observed in patients treated with radical prostatectomy (85-90%) and EBRT (75-80%).

In patients with low-risk prostate cancer, brachytherapy monotherapy exhibited excellent disease control, with a median overall survival (OS) of 95% at 5 years. However, in patients with high-risk prostate cancer, combining brachytherapy with EBRT improved BRFS to around 90-95%, which was significantly better than EBRT alone (75-80%) (Table 3).

Side Effects

Although brachytherapy is less intrusive than prostatectomy and linked with fewer problems than external beam radiation therapy (EBRT), people may still experience either temporary or chronic side effects. Almost thirty percent of patients reported dysuria, a condition marked by painful urination, and hematuria the presence of blood in urine as the most often occurring early side effects. Usually benign, these symptoms went away in three to six months. In those over 65 or those undergoing concurrent androgen deprivation treatment, erectile dysfunction is a major side effect affecting roughly 30–50% of patients. About 5–10% of people develop radiation-induced proctitis, which causes diarrhea, urgency, and rectal hemorrhage. Compared to those having radical prostatectomy, brachytherapy patients showed a reduced incidence of late toxicities, including long-term urine incontinence.

Long-Term Outcomes

Patients treated with brachytherapy alone showed a mean 5-year overall survival rate of 95%; most patients with localized prostate cancer showed similar outcomes. For high-risk patients receiving both brachytherapy and EBRT, the 10-year survival rate improved to about 90%, highlighting the benefits of using both treatments for more serious cases of prostate cancer. Though a small percentage of patients suffered ongoing sexual and urinary dysfunction, long-term follow-up (5–10 years) revealed that most side effects were mild and controllable.

Discussion

Comparative Efficacy of Brachytherapy

Over the long term, brachytherapy has been shown to be as successful as radical prostatectomy and EBRT, especially in low- and intermediate-risk prostate cancer. Brachytherapy is a practical treatment option with similar oncological results since several studies revealed that the 5-year

Table 2. Five-Year Biochemical Recurrence-Free Survival Rates for Brachytherapy vs. Other Modalities.

Treatment Type	5-Year Biochemical Recurrence-Free Survival (5)
Brachytherapy Monotherapy	85-95%
Radical Prostatectomy	85-90%
External Beam Radiation Therapy (EBRT)	75-80%
Brachytherapy + EBRT	90-95%

Table 3. Long-Term Quality of Life Outcomes for Prostate Cancer Patients Receiving Brachytherapy.

Outcome Measure	Pre-Treatment Score	Post-Treatment Score (12 months)
Erectile Function (SHIM Score)	20	15
Urinary Function (IPSS Score)	12	9
Quality of Life (EQ-5D Score)	0.75	0.85

biochemical recurrence-free survival rates for brachytherapy were almost exactly those of surgery. Brachytherapy is particularly helpful, though, for those who would want a less intrusive course of treatment. Its ability to deliver targeted radiation with minimum damage to surrounding tissues mostly determines whether short- and long-term complications, including erectile dysfunction, incontinence, and bowel problems, are avoided.

Patient Selection

Usually patients with low-to intermediate-risk prostate cancer are the best candidates for brachytherapy. These patients gain most from the concentrated radiation dosage given straight to the prostate, so reducing the radiation exposure to adjacent healthy tissues. Using a mix of treatments, like external beam radiation therapy (EBRT), helps high-risk patients or those with more advanced disease have better control of the cancer and live longer without it coming back.

Side Effect Management and Quality of Life

While correct patient counseling and management can help lower the incidence of these side effects, the most important ones in brachytherapy are urinary symptoms and erectile dysfunction. These symptoms are usually transient and gradually disappear as patients recover over time. Still, doctors should be alert for late-onset problems, especially proctitis brought on by radiation, and act to reduce their effects. Usually, quality of life is good since most patients recover to normal within a year after brachytherapy. Regular follow-ups and patient support are crucial to managing urinary problems and maybe longer-lasting sexual dysfunction.

Conclusion

This systematic review ensures that brachytherapy is a suitable treatment for localized prostate cancer, given good oncological results on par with other modalities, including radical prostatectomy and EBRT. To well-chosen patients, its minimally invasive nature, lower complication rates, and faster recovery appeal. Although side effects including urinary problems and erectile dysfunction can compromise patients' quality of life, these problems are usually treatable and pass with time. Given long-term survival rates on par with more aggressive treatment options, including brachytherapy in prostate cancer treatment plans, there is a great chance to enhance patient outcomes. Mostly, next research should focus on strengthening our knowledge of the long-term consequences of brachytherapy, optimizing patient selection criteria, and so strengthening treatment strategies. Moreover, much more research on combination treatments especially in high-risk patients is needed to raise survival rates and reduce recurrence rates.

This table provides an overview of several elements, including the type of brachytherapy, patient risk factors, and outcomes related to survival, side effects, and quality of life. It could also be included in a systematic review. It also makes simple comparison of the effectiveness of brachytherapy against alternative prostate cancer treatments possible.

Authors' Contribution

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نشریه

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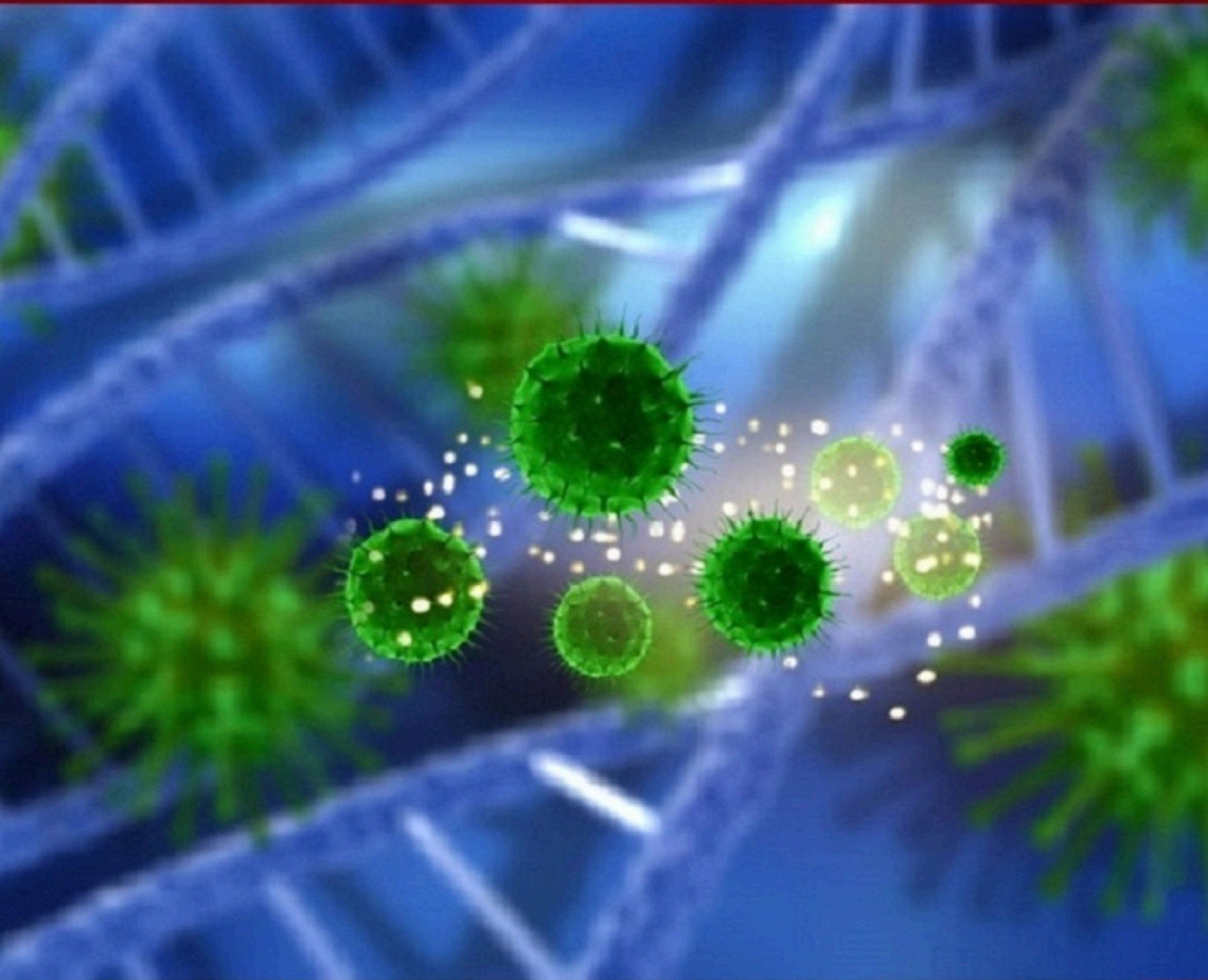

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