Research Article

A Systematic Review of the Role Played by Aquaporins in the Etiology of Rheumatoid Arthritis

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ABSTRACT

Background: Aquaporins (AQPs) are integral membrane proteins that are essential for preserving the equilibrium of water. These proteins also regulate cell volume and cell migration as well as apoptosis that relates to various inflammatory diseases like Rheumatoid Arthritis (RA). **Materials and Methods:** From Scopus and Web of Science databases, recent report depicting the role of AQPs on RA pathophysiology between 2018-2023 were used to search related articles using specific keywords and parentheses to understand the current scenario of AQPs during RA pathogenesis as per PRISMA guidelines. **Results:** A total of 83 articles were retrieved initially, and after using automation tools, the number of reports came down to 20. In the subsequent steps, articles were further excluded based upon open access availability, relevant abstract, text, title, case study and related information related to this work. Finally, 5 articles were retrieved from which data was extracted for summarising this finding. Our results showed that AQPs are up-regulated in the synovium and cartilage of people with RA, and that AQP1 may be responsible for joint-swelling and synovial inflammation. It also stimulates anti-apoptotic proteins like Bcl2, Bax, and caspase 3, which leads to synovial hyperplasia. Moreover, β-catenin and NF-κβ signaling pathways are stimulated and over-expressed in the presence of AQPs, which also promote the disease severity. **Conclusion:** In summary, this study reports that the overexpression of AQPs stimulates several intracellular signaling pathways crucial for RA development and opens a new avenue for therapeutic approaches for future RA drug development.

Keywords: Aquaporins, Inflammation, Rheumatoid arthritis, Synovial fibroblasts.

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INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disease that involves joint-swelling, formation of pannus, and gradual destruction of the bone joints. It results in chronic proliferative synovitis, cartilage damage, motor impairment, and gradual deterioration of quality of life. Recent research has shown that the activity of Synovial Fibroblasts (SFs) or Rheumatoid Arthritis-Specific synovial Fibroblasts (RASFs) in the RA synovium is one of the key factors contributing to the disease's progression. In RA, the hypercellularity of the synovial membrane cause the infiltration of immune cells, like macrophages and the fibroblast like cells leading to prolonged inflammation inside the rheumatoid joint in hypoxic conditions.[1] The innate immune response, together with cellular signalling systems, mobilizes the SFs in the RA synovium, leading to the development of their aggressive and invasive characteristics.[2] These effects eventually cause inflammation and a disturbance in cellular homeostasis, both of which may be seen in the swelling of cells and tissues when there is an excess of extracellular fluids.[3] Furthermore, cytokines and a number of other inflammatory players, such as chemokines, may alter a cell's sensitivity to homeostatic signals as well as the gate or channel access that is linked with them.[4]

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Mechanisms and mediators behind the onset of inflammation, which begins with alterations in cellular and tissue homeostasis, are worth investigation. Disease vulnerability arises when homeostasis is interrupted, such as under settings indicated by systemic or localized inflammation, and this phenomena is associated with abnormal ion transport.[5] In response to external stimuli, cells adjust their internal environment. Dysfunction of transmembrane fluid flow leads to a drastically modified physiology of the cell, as well as disruptions in homeostasis and aberrant ion transport, all of which elevate the vulnerability to disease.[5] Moreover, a variety of inflammatory signals, such as chemokines and cytokines, can modify gate or channel access or modify the sensitivity of tissues/cells to homeostatic signals in order to affect tissue/cell homeostasis.[6] Important proteins like Aquaporins (AQPs), which regulate water balance and volume fluctuations, are largely responsible for immune cells' ability to move, phagocytose, and absorb antigens and also facilitate communication between immune cells (via chemokines).[7] Thirteen isoforms of AQPs (intrinsic hydrophobic membrane channel proteins) allow for passive water transfer in response to the osmotic pressure that exists on both sides of the membrane.[8] These membrane porins are vital and significant tools for investigating their pathophysiological role because of their ability to control inflammation-related processes such as cell volume, migration, and apoptosis.[7,8]

A body of research has demonstrated that AQPs play a fundamental role in the development of RA. It was initially established by Mobasheri and Marples (2004) that AQP1 was expressed in healthy human synoviocytes and articular chondrocytes.[9] The production of AQP1 mRNA and protein in articular chondrocytes and synoviocytes subsequently supports AQP1-mediated water transport throughout the synovial vasculature.[10] In particular, hydrarthrosis and joint swelling linked to synovial inflammation in RA patients may be pathologically influenced by the up-regulated AQP1 in inflammatory synovial tissues.[10,11] Another study by Nagahara *et al*., AQP9 was linked to the etiology of hydrarthrosis and synovitis and was found to be highly expressed in the synovial tissues of Osteoarthritis (OA) and RA patients.[12] According to a recent study, articular chondrocytes of Adjuvant-Induced Arthritis (AIA) rats exhibited over activation of AQP4, and the degree of AIA was positively linked with higher levels of AQP4 protein in cartilage, indicating the role of AQP4 overexpression in RA pathogenesis.[13] Additionally, through the activation of p38 Mitogen-Activated Protein Kinase (MAPK), AQP4 has been connected to chondrocyte apoptosis induced by Interleukin 1 beta (IL1ß).[14] These studies revealed that AQPs' crucial role in joint swelling in RA pathogenesis. However, the main mechanisms of AQP in RA pathogenesis are still unclear.

As far as we are aware, there have been no systematic reviews based on published research have looked into the role of AQPs in the occurrence of RA. Thus, this systematic review paper summarises the role of AQPs in the pathophysiology of RA and discusses how AQPs may be used as a therapeutic target to treat the disease condition.

MATERIALS AND METHODS

This is a systematic review and, in this study, two international databases Scopus and Web of science were methodically checked up using various keywords. The findings were reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[15]

Search strategy

A mix of similar keywords was employed in two databases, Web of Science and Scopus, in order to find associated papers from November 13, 2022, up to March 22, 2023, using the appropriate terms and Boolean operators. The Medical Subject Heading (MeSH) recommended terms as well as additional relevant terms were combined to create the list of keywords. The following was the Scopus search query that was used: Aquaporin AND (synovial OR synovium OR synoviocytes AND synovitis) AND Expression AND Rheumatoid AND Arthritis. The Web of Science database was also searched using the same set of keywords.

Study selection and screening

All retrieved articles were put into Microsoft Excel software (Version 2303), where duplicate articles were initially identified and eliminated before being screened for relevancy. Subsequently, the articles underwent a screening process based on their title and abstract, with any unrelated articles being removed. Subsequently, the whole texts of the associated publications underwent screening to determine which ones satisfied the inclusion requirements. The relevant data were then examined and the necessary information was collected (Figure 1).

Inclusion and exclusion criteria

Full-text English-language articles that have been indexed in the specified databases as of March 2023 (from 2018

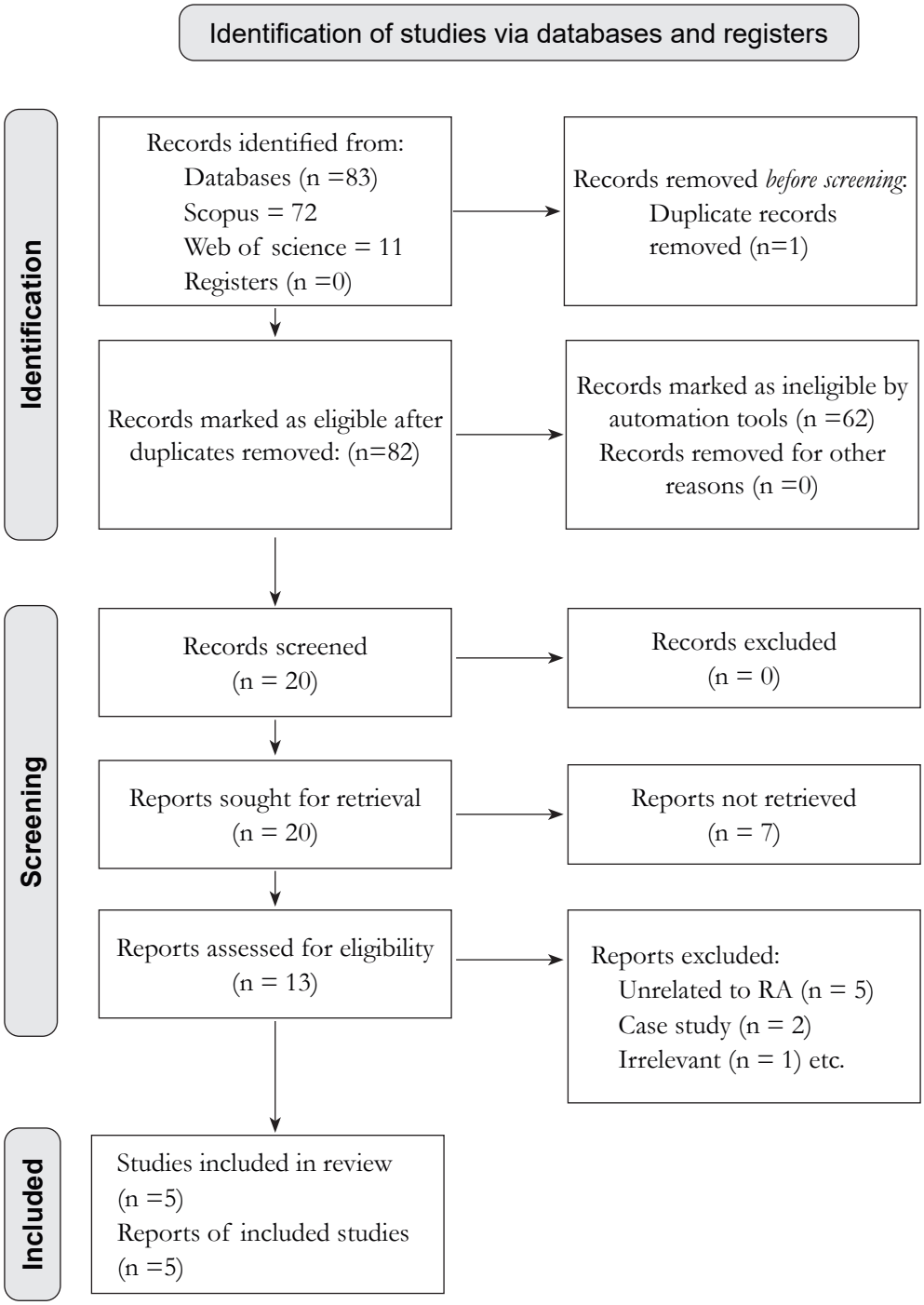

Figure 1: Diagram showing the steps involved in choosing studies using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

to 2023) were searched from mentioned databases and the study includes all empirical investigations that describe the regulation and function of aquaporin in RA patients. The following publications were eliminated: case reports, case series studies, editorials, letters to the editor, editorials, review articles, commentary, and clinical trials. Finally, the extracted data were further analyzed in result section.

RESULTS

Study Selection

The whole PRISMA guidelines mentioned in Figure 1. First, we obtained a total of 83 primary studies after scanning the relevant databases. Out of these, 72 studies were retrieved from Scopus database and 11 studies were from Web of Science database. Then, in excel software, 1 article was removed due to duplication and rest 82 studies were found to be unique. The following phase involved utilizing an automation program to exclude 62 papers in total based on the year, document type, and language. Twenty manuscripts were still evaluated for eligibility after that, and seven were rejected due to open access. Then data from 13 articles were retrieved for eligibility from which again 8 papers were excluded on the basis of (unrelated to RA, case study and irrelevant). In the final section, the review contained 5 articles.

Summary of the studies

Tables 1 and 2 summarize the study features of the five papers. These studies were published from 2018-2023. From the five articles, 3 articles were based on animal model-based study (Table 1) and rest were *in vitro* studies (Table 2). Study conducted by Cai *et al.* (2018) had reported that Acetazolamide (AZ), inhibits AQP1-mediated water permeability in a variety of cell types.[16] Additionally, investigations showed that AZ might decrease tumour metastasis and angiogenesis and directly inhibited the expression of the AQP1 protein. The anti-proliferative and anti-inflammatory effects of AZ on RA Fibroblast-Like Synoviocytes (RA-FLS) *in vitro* have been shown to reduce AQP1 mRNA expression in cultured FLS, along with the growth of RA-FLS and the amounts of TNF-α and IL-1β in the supernatant fluid. For analyzing the molecular mechanisms of AQP1 and NF-ϰβ, Western blot assays were carried out with the help of the synovial tissues acquired from the ankle joints of the AIA rat models (Table 1). It was seen that AZ and aspirin-treated rats had a lowered level of AQP1 protein expression than those deprived of the drug treatment. Additionally, rats with AIA have higher levels of IϰBα phosphorylation and degradation than normal rats but treatment with AZ successfully restrained these processes in contrast to AIA rats.[16] Thus, this study experimentally proved that the inhibiting AQP1 may be a useful treatment strategy for RA.

Table 1: Summary of the animal-model based studies in the systematic review.

Study	Cai *et al*., 2018	Mu *et al*., 2020	Mu *et al*., 2021
Experimental animals	Sprague-Dawley Rats (male).	Sprague-Dawley Rats (male).	Sprague-Dawley Rats (male).
Induction of RA	Complete Freund's Adjuvant (CFA) induced model.	Collagen-Induced Arthritis (CIA) model.	Collagen-Induced Arthritis (CIA) model.
Duration of experiment	28 days	36 days	36 days
Molecular detection	Real-time quantitative Polymerase Chain Reaction (Q-PCR) and Western blot assays in the synovial tissues that were taken from the AIA rat models' knee joints.	Immunohistochemistry (IHC) and a Western blot test methods were employed to assess the expression of β-catenin and AQP1 in the synovium. Small interfering RNA (siRNA) and Transfection study was also performed.	To examine AZ's potential anti-arthritic benefits on rat CIA, paw edema, arthritis index, histological evaluations, and blood serum levels of TNF-α, IL-1β, and Collagen type II (Col II) antibodies were examined. Immunohistochemistry (IHC) and Western blot test were utilised to assess AQP1 and β-catenin expression in the synovium.
Targets	AQP1, IκBα.	AQP1, β-catenin.	AQP1, IL-1β, TNF-α.
Key highlights	Compared to normal rats, AIA animals had greater levels of AQP1 expression and IκBα degradation; however, AZ therapy significantly suppressed both processes. The synovial tissues of AIA	AQP1 and β-catenin protein were found in significantly higher concentrations in the synovial tissues of CIA rats. Correlation analysis of the IHC results revealed a substantial relationship between the	Administration with AZ to CIA rats lessened ankle joint pathology, ameliorated the paw edema, lowered the arthritis index, and decreased TNF-α, IL-11β, and Col II antibody levels in the serum.

	rats exhibited considerably increased amounts of NF-κβ p65 protein compared to normal rats.	synovial β-catenin expression and the synovial AQP1 expression in CIA rats. By using AQP1 siRNA, the number of invasive and migrating cells was significantly decreased. Furthermore, it was noted that AQP1 siRNA might inhibit β-catenin signalling in CIA FLS.	In CIA rats, AZ significantly reduced the Wnt/β-catenin pathway and induced synovial apoptosis by increasing the apoptosis index in CIA synovial tissues.

Another study conducted by Mu *et al.* (2020) stated that the increased expression of synovial AQP1 activates β-catenin signalling, which may be crucial in the aetiology of RA and amplifies the abnormal behaviours of RAFLS.[17] Immunohistochemistry (IHC) assay results showed that β-catenin and AQP1 were primarily localized in the synovial cytoplasm and synovial membrane of the cell, respectively and compared to normal rats; CIA rats' synovial tissues contained much higher levels of β-catenin protein and AQP1 than usual (Table 1). Comparing the treated and untreated CIA-FLS groups, AQP1 siRNA transfection resulted in a significant decrease in AQP1 protein levels, but Negative Control (NC) siRNA group had no effect on AQP1 expression. Moreover, it was observed that in the AQP1 siRNA group, the protein level of AQP1 was 15% lower than in the NC siRNA group. While NC siRNA had no impact on CIA FLS migration or invasion, AQP1 siRNA significantly decreased the number of migrating and invasive cells as compared to the CIA FLS group. LiC1, an activating factor of β -catenin, blocked AQP1 siRNA's inhibitory effect on CIA FLS migration and invasion, suggesting that β-catenin signalling may be implicated in the AQP1 siRNA-induced suppression of CIA FLS migration and invasion. Accordingly, this data implies that β-catenin signalling could play a role in AQP1's pathogenic function in the rat CIA model.[17] In RA, synovial hyperplasia and invasive pannus development can eventually cause cartilage and subchondral bone invasion, leading to joint degeneration and disability.[18,19] Therefore, preventing synoviocyte growth and triggering their death can be a promising strategy for treating RA by suppressing synovial hyperplasia.[20] Thus, inhibition of AQPs in RA synovium could be therapeutic approach to combat the RA pathogenesis. In a recent study Mu *et al.* (2021) also reported that Acetazolamide (AZ), an inhibitor of AQP1, showed strong anti-RA effects by blocking the Wnt/β-catenin pathway and causing synovial apoptosis in the CIA rat model.[21] Moreover, it was found that administering AZ to CIA rats might lower the arthritis index, and decreased serum Collagen type II (Col II) antibody, TNF-α, and IL-11β levels. Moreover, treatment of AZ to CIA rats decreased the elevated level of the protein Bcl-2, and simultaneously increased the apoptotic proteins like Bax and caspase 3 levels. These ultimately brought Bcl-2/Bax ratios back to normal, indicated that the treatment with AZ to CIA rats might induce the apoptosis index in CIA synovial tissues (Table 1). Given that AQP1 is essential for the growth and migration of different tumour cells, Mu *et al.* (2021) came to the conclusion that AZ, an AQP1 inhibitor, would have an effects on the growth and apoptosis of synovial cells in CIA rats.[21]

A study conducted by Ji *et al.* (2021) reported that by increasing the amounts of electrolytes and promoting water-flow through $Na^+K^+2Cl^-$ Co-transporter1 (NKCC1) and AQP1, RA-FLS produces cellular swelling that ultimately results in cytotoxic edema.[22] Stimulated by IL-6, RA-FLS were observed to express more NKCC1 activity and to be susceptible to hypertonic stimulation (Table 2). Moreover, in contrast to Human normal Synovial tissues (HFLS) and osteoarthritis Fibroblast-Like Synoviocytes (OA-FLS), RA-FLS showed elevated NKCC1 and AQP-1 membrane expression in response to IL-6 stimulation, whereas HFLS and OA-FLS's did not respond differently to IL-6 stimulation. According to Ji *et al.* (2021) phosphorylation of Oxidative Stress-Responsive kinase (OSR)-1 may be restored through IL-6's increased hypertonic sensitivity and osmotic regulation.[22] Their study indicated that RA-FLS had a high potential for RVI (Regulatory Volume Increase) due to the convergence of NKCC1 and AQP-1 regulation in response to proinflammatory cytokines present in synovial fluid of RA patients, particularly IL-6.[22] Additionally, previously Mu *et al.* (2020) reported that severe arthritis developed in mice with collagen-induced arthritis when AQP1 was elevated and by limiting the growth, invasion and migration of CIA cultured-FLS, AQP1 siRNA was able to regulate this severity which suggests a potential link between AQP1 and the biological activity of RA-FLS.[17]

Table 2: Summary of the cell line-based studies in the systematic review.

Study	Ji *et al*., 2021	Zhou *et al*., 2021
Participants	Human FLS isolated from HFLS, RA-FLS, and OA-FLS.	RA-FLS (MH7A cells).
Method	Synovial fluid was collected from patients suffering from RA and OA into separate groups respectively and screened for synovial IL-6 levels. Quantitative RT-PCR, immunostaining, and Western blot was carried out for observation of the results from the collected synovial fluids from both the group of the patient.	A lentivirus was transfected into RA FLS (MH7A) culture and it was divided into four groups respectively depending upon the mediator. Green fluorescence protein labelling and the western blot assay were used for validation. Analysis of the cell cycle and invasion by migrating cells were also done.
Duration of experiment	48 hr.	24 to 48 hr.
Targets	NKCC1 and AQP1.	AQP1 and β-catenin.
Result	RA-FLS stimulated by IL-6 were sensitive to hypertonic stimulation along with increased expression of NKCC1 activity. IL-6 stimulated membranous expression of NKCC1 and AQP1 AQP-1 showed increased expression in RA and was expressed in FLS. RA-FLS displayed increased NKCC1 and AQP-1 membrane expression. However, HFLS and OA-FLS's did not respond differently to IL-6 stimulation. In the presence of IL-6, OSR-1 protein production enhanced.	AQP1 overexpression caused TNF-α stimulated MH7A cell proliferation. AQP1 silencing resulted in a striking decrease in cell proliferation. TNF α activates MH7A cells, and overexpression of AQP1 reduces the number of cells in the G0/G1 phase and increases the number in the S phase, hastening the G0/G1 phase to S phase transition. AQP1 silencing boosted G0/G1 phase population while decreasing S phase population, leading to G0/G1 phase arrest. Apoptosis rate significantly increased in the LV-SHAQP1 group where the AQP1 gene was silenced through shRNA. While pro-apoptotic proteins Bax and cleaved caspase 3 were reduced in quantity, anti-apoptotic protein Bcl-2 was elevated by AQP1 upregulation. Amplification of AQP1 significantly increased the TNF-stimulated MH7A cells' migration index. AQP1 overexpression resulted in increased F-actin expression, aberrant fibre shape and arrangement, and the development of pseudopodia.

The *in vitro* model of TNF-α stimulated RA-FLS has been widely employed to investigate the pathophysiology of RA and to assess possibilities for RA treatments. A recent study by Zhou *et al.* (2021) has demonstrated the effects of AQP1 overexpression or silencing mediated by lentiviruses on TNF-stimulated RA-FLS (MH7A) migration, invasion, apoptosis, and proliferation (Table 2).[23] According to their experimental setup a lentivirus was transfected into RA FLS (MH7A) culture and it was divided into four groups respectively depending upon the mediator. Green fluorescent protein labelling and the Western blot assay were used for validation to make sure the culture had been effectively transfected with the desired gene. Depending on the results four cell groups were considered including a control group (non-transfected MH7A), LV-AQP1-NC group (transfection was done without AQP1 gene; experimental control group), LV-AQP1 group (transfected with AQP1 gene), LV-shRNA-AQP1 group (AQP1 gene was silenced through ShRNA).[23] Cell cycle study revealed that AQP1 overexpression accelerates the transition from G0/G1 phase to S phase by decreasing the G0/G1 phase population and increasing the S phase population after 24 to 48 hours of TNF-α (10 μg/mL) stimulation. On the other hand, G0/G1 phase arrest resulted from AQP1 silencing, which increased G0/G1 phase population while lowering S phase population.[23] Furthermore, neither LV-AQP1 NC nor LV-shRNA NC transfection affected the cell cycle distribution or the cell proliferation rate in TNF-stimulated MH7A cells. Furthermore, it was noted that in the LV-SHAQP1 group, where the AQP1 gene was suppressed by shRNA, the apoptosis rate elevated noticeably. Furthermore, compared to the LV-AQP1 NC group, the Bcl-2/Bax protein ratio in the LV-AQP1 group was much higher, while in the LV-shAQP1 group it was significantly lower.[23] Finally, it was seen that when compared to the LV-AQP1 NC group, AQP1 overexpression greatly increased the migration index of TNF-stimulated MH7A cells; however, when compared to the LV-shRNA NC group, AQP1 silencing dramatically decreased the migration index.[23] F-actin expression, aberrant fibre shape and

arrangement, and the development of pseudopodia elevated in TNF-stimulated MH7A cells as a result of AQP1 overexpression, however, there were hardly any pseudopodia observed in the LV-shAQP1 group because of the poor F-actin expression.[23]

DISCUSSION

Previous research has shown that the aberrant proliferative ability of RA-FLS is caused by an increase in the population of S-phase cells, and that RA FLS may be prevented by inhibiting the transition of cells from the G0/G1 phase to the S phase.[24] It was well reported that the AQP1 has been shown to affect cell cycle progression and assist in maintaining the equilibrium between apoptosis and proliferation.[25] According to Zhou *et al.* (2021), the regulation of the stability of the mitochondrial membrane potential and the activity of mitochondria may be connected to the effects of AQP1 on the apoptosis of MH7A cells and they also showed TNF-α induced MH7A cells' apoptosis was decreased by AQP1 overexpression.[23] Moreover, several studies reported that the primary cause of the persistent thickening of the synovial membrane or synovial hyperplasia is the results of insufficient apoptosis of RA-FLS.[26,27] So, the treatment strategies for RA that aim to induce RA-FLS apoptosis and maintain the balance between apoptosis and proliferation of RA FLS could be beneficial.[20,28] In this context, suppression or inhibiting the AQP1 would be a potential treatment for RA.

CONCLUSION

Aquaporins are integral proteins responsible for forming pores in the biological membranes of cells and transport water. Aquaporins also have significant impact on inflammatory processes, cell migration, and proliferation. The expression of Aquaporins (AQP)-1 in rheumatoid synovium elevates the cell proliferation and develops fibroblast-like synovitis leading to hydrarthrosis and joint swelling connected to synovial inflammation. Aberrant expression of aquaporins also inhibits apoptosis, leading to synovial hyperplasia. Moreover, AQP1 stimulates the NF-κβ pathway along with enhancement in the aberrant behaviours of RA-FLS by activating β-catenin signalling pathways. All of these experimental information states that aquaporins mainly AQP1 is a crucial factor in the development of RA. Our analysis highlights the critical role that the aquaporins play in the pathophysiology of RA, and it indicates that in the future, RA patients may be able to receive novel therapeutic options by preventing the production of this protein.

AUTHOR'S CONTRIBUTIONS

SB conceptualized the idea behind this review manuscript. The original draft manuscript was prepared by DM and SK. DM, SK, PS and SKR contributed to the gathering of raw data, screening of articles for study selection, revised the manuscript. SB edited the final manuscript. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding this work.

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ABBREVIATIONS

AIA: Adjuvant-induced arthritis; **AQPs:** Aquaporins; **AZ:** Acetazolamide; **CFA:** Complete Freund's adjuvant; **CIA:** Collagen-induced arthritis; **Col II:** Collagen type II; **HFLS:** Human normal synovial tissues; **IHC:** Immunohistochemistry; **MAPK:** Mitogen-activated protein kinase; **NKCC1:** $Na^+K^+2Cl^-$ co-transporter1; **OA:** Osteoarthritis; **OA-FLS:** Osteoarthritis fibroblast-like synoviocytes; **OSR:** Oxidative stress-responsive kinase; **PRISMA:** Preferred reporting items for systematic Reviews and Meta analyses; **RA:** Rheumatoid arthritis; **RA-FLS:** Rheumatoid Arthritis fibroblast-like synoviocytes; **RASFs:** Rheumatoid arthritis-specific synovial fibroblasts; **SFs:** Synovial fibroblasts; **siRNA:** Small Interfering RNA.

SUMMARY

Aquaporins (AQPs) are crucial for maintaining the water's balance and for controlling cell migration and volume. According to recent studies, RA patients' synovial inflammation is strongly correlated with higher levels of the AQPs present in the synovium, which is

linked to hydrarthrosis and joint swelling. Thus, this review critically investigates the role of aquaporins in the pathogenesis of rheumatoid arthritis.

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