*EJPMR, 2026, 13(3), 334-338* **Research Article** **Impact Factor: 8.158**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

**www.ejpmr.com**

**ISSN (O): 2394-3211**
**ISSN (P): 3051-2573**
**Coden USA: EJPMAG**

# EMERGING PHARMACOTHERAPIES: TARGETING OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN SJOGREN'S SYNDROME

**Srihari S.*, Kirubha D., Dhinakaran S., Vishal D., Prakash S., Balan P.**

The Erode College of Pharmacy, Erode, Tamil Nadu, India.

***Corresponding Author: Srihari S.**

The Erode College of Pharmacy, Erode, Tamil Nadu, India.

**DOI:** https://doi.org/10.5281/zenodo.18875055

**How to cite this Article:** Srihari S.*, Kirubha D., Dhinakaran S., Vishal D., Prakash S., Balan P. (2026). Emerging Pharmacotherapies: Targeting Oxidative Stress And Mitochondrial Dysfunction In Sjogren's Syndrome. European Journal of Pharmaceutical and Medical Research, 13(3), 334–338.



**Article Received on 04/02/2026** **Article Revised on 24/02/2026** **Article Published on 01/03/2026**

## ABSTRACT

Sjogren's syndrome is a chronic condition characterized by the immune system attacking the glands responsible for producing tears and saliva. Patients with Sjogren's syndrome commonly experience persistent dry mouth and dry eyes. Sjogren's syndrome does not just affect the gland that makes tears and saliva. It can encompass involvement of the joints, lungs, kidneys, nervous system, and hematologic system as well. This makes Sjogren's syndrome is different, we do not know how Sjogren's syndrome will progress in each person, with Sjogren's syndrome. Doctors are trying to make people feel better by dealing with the symptoms of mouth and dry eyes. They use medicine that helps the system to take care of other issues. Sjogren's syndrome is a disease. It is really tough to find something that works for every single person who has Sjogren's syndrome.Conventional treatment with artificial tears and saliva and topical anti- inflammatory agents remain the mainstays in the symptomatic treatment of Sjogren's syndrome. Our understanding of Sjögren's syndrome, particularly the role of B-cells dysregulation, BAFF overexpression, interferon signaling and co-stimulatory pathways, has led to the development of biologic agents and small molecules targeted therapies. Herein, we review the established and emerging pharmacologic treatments for Sjogren's syndrome, highlighting the efficacy, clinical indications, safety profiles, and future directions.

**KEYWORDS:** Sjogren's, autoimmune disease, biological therapy, dry eye, B-cell targeting.

## INTRODUCTION

The disease does not just affect the glands. It can also cause problems in parts of the body like the muscles, lungs, kidneys and nerves. This is because of the immune system is not working correctly.

Sjogren's syndrome is a disease that affects people in many ways. What we know about Sjogren's syndrome now tells us that the immune system is no working properly which is a part of problem. The immune system is like a defense system that's always on and this leads to the production of too many bad things like pro-inflammatory cytokines, autoantibodies and reactive oxygen species. This makes the glands in our body get damaged and die which makes the disease worse. The mitochondria in our cell are very important because they are affected by oxygen species and they also make reactive oxygen species. Sjogren's syndrome is a disease and understanding how the immune system and mitochondria work is crucial, to figuring out what happens in Sjogren's syndrome. Mitochondrial dysfunction in Sjogren's syndrome is a problem. It affects the way that the mitochondria are not able to make energy. This means that they do not make ATP, which is what gives our cell energy. The mitochondria in people with Sjogren's syndrome also do not move around. Change shape like they should. This can cause the mitochondria to release things that hurt our cells. Mitochondrial dysfunction, in Sjogren's syndrome is something that we need to learn more about so we can figure out how to make it better. The way we Sjogren's syndrome has changed a lot. We used to try to make the symptoms better but now we are trying to fix the problem with immune system. We still use treatment like steroids and special drugs that help with rheumatic disease, nowadays we are using new treatments that target specific part of immune system. These new treatments include proteins and small molecules that can

stop certain immune cells from working or reduce the amount of bad chemicals in the body. Understanding the interplay between immune mechanisms, oxidative stress, and mitochondrial dysfunction is crucial for the development of more effective and personalized therapeutic approaches in Sjogren's syndrome.

## SUBSTANTIATION OF OXIDATIVE STRESS IN SS

Several independent studies confirm elevated oxidative stress labels in SS cases

• Increased tube protein carbonyls and advanced oxidation protein products.
• Elevated TNF- α, myeloperoxidase(MPO), and Nitrotyrosine situations.
• Reduced glutathione(GSH) attention.
• Increased salivary 8-hydroxy- 2'-deoxyguanosine(8-OHdG) and propanoyl- lysine.
• dropped antioxidant enzyme expression(superoxide dismutase, catalase, glutathione peroxidase) in conjunctival epithelium inclusively, these findings support the bracket of SS as an oxidative stress – affiliated complaint.

## MITOCHONDRIAL DAMAGE IN SJÖGREN'S PATTERN

Whenever oxidative stress is intertwined in complaint, mitochondrial function becomes central to disquisition. Mitochondria are critical for oxygen metabolism and are the primary intracellular source of ROS. Mitochondrial dysfunction(MDF) has been intertwined in aging, cancer, diabetes, neurodegeneration, and inheritable oxidative stress diseases. Substantiation of Autoimmune-Affiliated Mitochondrial Damage.

Studies in SS cases have linked

•Antimitochondrialautoantibodies(AMA) targeting dihydrolipoamide acetyltransferases and α- ketoglutarate dehydrogenase.
•Antibodies act against pyruvate dehydrogenase complex(PDC- E2).
• Associations between AMA and liver pathology in primary SS.
• Increased expression of mitochondrial glutamic-oxaloacetic transaminase(m- GOT) relating with oxidative stress labels.

These mitochondrial targets are factors of the Krebs cycle, suggesting impairment of mitochondrial energy metabolism. While numerous studies proved autoimmune mitochondrial damage, smaller explicitly connected these findings with oxidative stress. still, arising substantiation explosively supports an intertwined pathogenic model.

## BRIDGING OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN SS CLINICAL MANAGEMENT

The relationship between seditious/ autoimmunediseases and mitochondrial dysfunction is well established. Mitochondrial abnormalities contribute to enhanced ROS product, metabolic dysregulation, and cell death. In autoimmune conditions similar as systemic lupus erythematosus, mitochondrial hyperpolarization and nitric oxide overproduction have been linked to abnormal vulnerable activation. analogous mechanisms may operate in SS.

In SS specifically.

• Oxidative damage to proteins and DNA has been proved.
• Autoimmune- mediated mitochondrial injury affects crucial metabolic pathways.
• Both oxidative stress and mitochondrial dysfunction appear connected.

farther mechanistic studies are needed to clarify their bidirectional relationship in SS pathogenesis.

## IMMUNOPATHOGENESIS AND THERAPEUTIC TARGETS

Many factors including genetic background, environmental exposure and immune dysfunction contribute to the development of Sjogren's syndrome. Disease characteristics include B-cell hyperactivity, with an emphasis on hypergammaglobulinemia, the production of autoantibodies and the presence of ectopic lymphoid structures in salivary glands. Elevated B-cell activating factor (BAFF) levels promote the survival and maturation of B cells and are implicated in autoimmune responses and lymphomagenesis. t-cell response considerably aggravates injury by providing cytokines and co-stimulatory signals. A type 1 IFN signature has been described in many patients and enhances inflammatory cascades. Finally, the salivary gland epithelial cells have a role in activation of the immune system by participating as antigen-presenting cells in perpetuating local inflammation. These findings have led to the development of B cell-, cytokine-, and co-stimulation-targeted therapies.

## THERAPEUTIC PRINCIPLES AND TREATMENT GOALS

Management of Sjogren's syndrome is guided by disease severity, extent of organ involvement and patient-reported symptoms.

The goals of treatment are:

1. Managing symptoms of dryness and preventing local complications.
2. Controlling systemic inflammation and immune-mediated organ damage.
3. Improving quality of life and functional capacity
4. Minimizing long term complications such as lymphoma.

Evaluating the disease activity with clinical scores as ESSDAI and ESSPRI, and guiding therapeutic decisions accordingly are current practices. A stepwise and individualized approach is crucial.

## MANAGEMENT OF GLANDULAR MANIFESTATIONS

**Eyes** (Ocular Involvement): Sjogren's syndrome can be characterized by the most early and distressing sign of dry eye.

### Lubricants

Preservative free artificial lubricant, gel or cream is used as the initial treatment for mild ocular symptoms to reduce symptoms that occur due to lack of adequate tear production. Although these treatments may provide some relief from symptoms, they do not treat the inflammation that occurs in the ocular surface.

### Topical Immunosuppressants

The use of topical cyclosporine A has provided a significant reduction in inflammation of the ocular surface, an increase in tear production and improvement in symptoms of patients whose symptoms were not adequately improved with other treatments.

### Supportive Interventions

In addition to treatments for ocular and salivary gland manifestations, supportive interventions such as occlusion of the nasolacrimal ducts, modification of the environment and protective eyewear are common and can assist in controlling symptoms.

**Mouth** (Oral Involvement)

Severe xerostomia produces considerable disability including dental caries, oral infections, loss of ability to taste and difficulty in swallowing.

### Saliva Replacement Products

Saliva replacement products contain artificial saliva that provides short term moisture, however they have no effect on stimulating the glands to produce saliva.

### Muscarinic Receptor Agonists

Pilocarpine and cevimeline act on muscarinic receptors to stimulate saliva and lacrimal secretions in patients with residual glandular function. Cevimeline is generally better tolerated than pilocarpine due to its relative specificity for M3 receptors. Common side effects of these medications include excessive sweating, gastrointestinal complaints and flushing.

### Prevention

Long term management requires comprehensive oral hygiene, fluoride therapy and regular dental care.

## SYSTEMIC PHARMACOLOGICAL THERAPIES

### Antimalarial agents

Hydroxychloroquine is frequently prescribed for fatigue, arthralgia and cutaneous manifestations. Although its impact on sicca symptoms is limited, it remains valuable for mild systemic disease due to its immunomodulatory effects and favorable safety profile.

### Corticosteroids

Systemic glucocorticoids are effective in controlling acute inflammatory flares and severe organ involvement. their use is generally restricted to short-term ir induction therapy due to the risk of metabolic, cardiovascular and skeletal adverse effect.

### Conventional immunosuppressive drugs

Immunosuppressant has selected according to the affected organ system:

- Methotrexate for inflammatory arthritis
- Azathioprine for systemic and renal involvement
- Mycophenolate mofetil for pulmonary manifestation
- Cyclophosphamide for severe, life-threatening disease

The evidence base for these agents in Sjogren's syndrome is limited, and treatment decision are often other autoimmune conditions.

## BIOLOGIC THERAPIES

B-cell depletion and modulation.

### Rituximab

Rituximab targets CD20-positive B cells and has been investigated extensively in Sjogren's syndrome. While randomized trails have produced mixed results, clinical experience suggested benefits in selected patients with systemic disease, vasculitis or neuropathy. Effects on glandular functions are variable.

### BAFF inhibition

Belimumab reduces B cell survival by inhibiting BAFF signaling. Early studies indicate immunological improvement are reduced disease activity, particularly when used sequentially with B-cell depletionstrategies.

### Co-stimulatory pathway inhibition

Targeting the CD40-CD154 pathway disrupts T-cell and B-cell interactions critical for autoimmune activation. Agents such as iscalimab and dazodalibep have shown encouraging efficacy in reducing systemic disease activity with acceptable safety profiles, representing a promising therapeutic avenue.

## SMALL-MOLECULE TARGETED THERAPIES

### Janus kinase inhibitors

JAK inhibitors interfere with intracellular cytokine signaling involved in immune activation, preliminary studies suggest potential benefits in both glandular and systemic manifestations. However, safety concern related to cardiovascular risk, infection and malignancy necessitate cautions evaluation before routine clinical use.

## CONCLUSION

The management of Sjogren's syndrome has evolved from purely symptomatic treatment toward targeted immunomodulation informed by advances in disease pathogenesis. While conventional therapies remain

essential for symptom control, emerging biologic and small-molecule agents offer promising opportunities for improve outcomes, particularly in patients with systemic disease. Continued research, robust clinical trials and personalized treatment approaches are critical to advancing care and improving quality of life for individuals with Sjogren's syndrome.

**REFERNCE**


1. Ngo, D. Y. J.; Thomson, W. M.; Nolan, A.; Ferguson, S. The Lived Experience of Sjögren's Syndrome. *BMC Oral Health*, 2016; *16*(1). https://doi.org/10.1186/s12903-016-0165-4.
2. Juarez, M.; Toms, T. E.; de Pablo, P.; Mitchell, S.; Bowman, S.; Nightingale, P.; Price, E. J.; Griffiths, B.; Hunter, J.; Gupta, M.; Bombardieri, M.; Sutcliffe, N.; Pitzalis, C.; Pease, C.; Andrews, J.; Emery, P.; Regan, M.; Giles, I.; Isenberg, D.; Moots, R. Cardiovascular Risk Factors in Women with Primary Sjögren's Syndrome: United Kingdom Primary Sjögren's Syndrome Registry Results. *Arthritis Care & Research*, 2014; *66*(5): 757–764. https://doi.org/10.1002/acr.22227.
3. Greenan, E.; Pilson, Q.; J. Ní Gabhann-Dromgoole; Murphy, C. C. Quality of Life Questionnaires Validate a Remote Approach to Ophthalmic Management of Primary Sjögren's Syndrome. *Scientific Reports*, 2022; *12*(1): 18761–18761. https://doi.org/10.1038/s41598-022-23676-x.
4. Lu, M.-C.; Fa, W.-H.; Tsai, T.-Y.; Koo, M.; Lai, N.-S. Increased Utilisation of Eye Disorder-Related Ambulatory Medical Services prior to the Diagnosis of Sjögren's Syndrome in Female Patients: A Longitudinal Population-Based Study in Taiwan. *BMJ Open*, 2014; *4*(5): e003862–e003862. https://doi.org/10.1136/bmjopen-2013-003862.
5. Kaba Condé; Carlos Othon Guelngar; Mamadou Ciré Barry; Hugues Ghislain Atakla; Mohamed, A.; Fodé Abass Cissé. Sjögren's Syndrome in Children: About 15 Cases in Guinea Conakry. *European journal of medical research*, 2021; *26*(1). https://doi.org/10.1186/s40001-021-00534-6.
6. Schmidt, N. S.; Voss, A.; Nilsson, A. C.; Terslev, L.; Just, S. A.; Lindegaard, H. M. Salivary Gland Ultrasound Is Associated with the Presence of Autoantibodies in Patients with Sjögren's Syndrome: A Danish Single-Centre Study. *PLOS ONE*, 2022; *17*(12): e0265057. https://doi.org/10.1371/journal.pone.0265057.
7. Wu, X.-F.; Huang, J.-Y.; Chiou, J.-Y.; Chen, H.-H.; Wei, J. C.-C.; Dong, L.-L. Increased Risk of Coronary Heart Disease among Patients with Primary Sjögren's Syndrome: A Nationwide Population-Based Cohort Study. *Scientific Reports*, 2018; *8*(1). https://doi.org/10.1038/s41598-018-19580-y.
8. Flament, T.; Bigot, A.; Chaigne, B.; Henique, H.; Diot, E.; Marchand-Adam, S. Pulmonary Manifestations of Sjögren's Syndrome. *European Respiratory Review*, 2016; *25*(140): 110–123. https://doi.org/10.1183/16000617.0011-2016.
9. Gau, S.-Y.; Leong, P.-Y.; Lin, C.-L.; Tsou, H.-K.; Wei, J. C.-C. Higher Risk for Sjögren's Syndrome in Patients with Fibromyalgia: A Nationwide Population-Based Cohort Study. *Frontiers in Immunology*, 2021; *12*: https://doi.org/10.3389/fimmu.2021.640618.
10. Hackett, K. L.; Deary, V.; Deane, K. H.; Newton, J. L.; Ng, W.-F.; Rapley, T. Experience of Sleep Disruption in Primary Sjögren's Syndrome: A Focus Group Study. *British Journal of Occupational Therapy*, 2018; *81*(4): 218–226. https://doi.org/10.1177/0308022617745006.
11. Šijan Gobeljić, M.; Milić, V.; Pejnović, N.; Damjanov, N. Chemosensory Dysfunction, Oral Disorders and Oral Health-Related Quality of Life in Patients with Primary Sjögren's Syndrome: Comparative Cross-Sectional Study. *BMC Oral Health*, 2020; *20*(1). https://doi.org/10.1186/s12903-020-01169-5.
12. Wu, M.-C.; Xu, X.; Chen, S.-M.; Tyan, Y.-S.; Chiou, J.-Y.; Wang, Y.-H.; Lin, L.-C.; Chen, C.-M.; Wei, J. C.-C. Impact of Sjogren's Syndrome on Parkinson's Disease: A Nationwide Case-Control Study. *PLOS ONE*, 2017; *12*(7): e0175836. https://doi.org/10.1371/journal.pone.0175836.
13. Sivakumar, G. K.; Patel, J.; Malvankar-Mehta, M. S.; Mather, R. Work Productivity among Sjögren's Syndrome and Non-Sjögren's Dry Eye Patients: A Systematic Review and Meta-Analysis. *Eye*, 2021. https://doi.org/10.1038/s41433-020-01282-3.
14. \Armen Sanosyan; Daien, C.; Nutz, A.; Bollore, K.; Anne-Sophie Bedin; Morel, J.; Zimmermann, V.; Gaetane Nocturne; Peries, M.; Guigue, N.; Jacques-Eric Gottenberg; Van; Mariette, X.; Edouard Tuaillon. Discrepancy of Serological and Molecular Patterns of Circulating Epstein-Barr Virus Reactivation in Primary Sjögren's Syndrome. *Frontiers in immunology*, 2019; *10*. https://doi.org/10.3389/fimmu.2019.01153.
15. Melo, J.; Carolina Gomes Coelho; Fernanda; Heller, D.; Daniela Corrêa Grisi; Maria; NailêDamé-Teixeira. A Scoping Review on Hyposalivation Associated with Systemic Conditions: The Role of Physical Stimulation in the Treatment Approaches. *BMC Oral Health*, 2023; *23*(1). https://doi.org/10.1186/s12903-023-03192-8.
16. Liquidato, B. M.; de Cássia Soler, R.; Filho, I. B. Evaluation of the Concordance of Sialometry and Salivary Glands Scintigraphy in Dry Mouth Patients. *Brazilian Journal of Otorhinolaryngology*, 2006; *72*(1): 116–119. https://doi.org/10.1016/s1808-8694(15)30043-4.
17. L Ingolotti; Bejarano, M.; N Tamborenea; A Mercé; C Arguissain; Martin, L.; J Morbiducci; Azcona, V.; L Teplizky; Casals, E.; Hernandez, A.; M Marseillan; Secco, A. Oral Health-Related Quality of Life in Primary Sjögren's Syndrome. *Medicina*

*oral, patología oral y cirugíabucal*, 2020; https://doi.org/10.4317/medoral.26934.
18. Harrold, L. R.; Shan, Y.; Rebello, S.; Kramer, N.; Connolly, S. E.; Evo Alemao; Kelly, S.; Kremer, J. M.; Rosenstein, E. D. Disease Activity and Patient-Reported Outcomes in Patients with Rheumatoid Arthritis and Sjögren's Syndrome Enrolled in a Large Observational US Registry. *Rheumatology International*, 2020; *40*(8): 1239–1248. https://doi.org/10.1007/s00296-020-04602-8.
19. He, Y.; Feng, J.; Shi, W.; Ren, Y.; Liu, Y.; Kang, H.; Tian, J.; Jie, Y. Correlation among Ocular Surface Changes and Systemic Hematologic Indexes and Disease Activity in Primary Sjögren's Syndrome: A Cross-Sectional Study. *BMC Ophthalmology*, 2025; *25*(1). https://doi.org/10.1186/s12886-025-04050-7.
20. Cui, Y.; Xia, L.; Li, L.; Zhao, Q.; Chen, S.; Gu, Z. Anxiety and Depression in Primary Sjögren's Syndrome: A Cross-Sectional Study. *BMC psychiatry*, 2018; *18*(1): 131. https://doi.org/10.1186/s12888-018-1715-x.
21. Stankeviciene, I.; Stangvaltaite-Mouhat, L.; Aleksejuniene, J.; Mieliauskaite, D.; Talijuniene, I.; Butrimiene, I.; Bendinskaite, R.; Puriene, A. Oral Health Status, Related Behaviours and Perceived Stress in Xerostomia, Sicca and Sjögren's Syndromes Patients - a Cross-Sectional Study. *BMC Oral Health*, 2024; *24*(1). https://doi.org/10.1186/s12903-024-04224-7.
22. Liu, X.; Wang, H.; Wang, X.; Jiang, X.; Jin, Y.; Han, Y.; Zhang, Z. Identification and Verification of Inflammatory Biomarkers for Primary Sjögren's Syndrome. *Clinical Rheumatology*, 2024; *43*(4): 1335–1352. https://doi.org/10.1007/s10067-024-06901-y.
23. Song, Y.; Sun, L.; Cui, G.; Feng, D.; Sun, Q.; Wang, Y. Childhood-Onset Primary Sjögren's Syndrome Presenting as Nephrotic Syndrome: A Case Report and Literature Review. *BMC Pediatrics*, 2025; *25*(1): 721–721. https://doi.org/10.1186/s12887-025-06029-1.
24. Hackett, K. L.; Davies, K.; Tarn, J.; Bragg, R.; Hargreaves, B.; Miyamoto, S.; McMeekin, P.; Mitchell, S.; Bowman, S.; Price, E. J.; Pease, C.; Emery, P.; Andrews, J.; Lanyon, P.; Hunter, J.; Gupta, M.; Bombardieri, M.; Sutcliffe, N.; Pitzalis, C.; McLaren, J. Pain and Depression Are Associated with Both Physical and Mental Fatigue Independently of Comorbidities and Medications in Primary Sjögren's Syndrome. *RMD Open*, 2019; *5*(1): e000885. https://doi.org/10.1136/rmdopen-2018-000885.
25. Wu, J.; Feng, R.; Wang, R.; He, J. Impact of Disease Duration on Systemic Clinical Profile in Sjogren's Syndrome. *Arthritis research & therapy*, 2025; *27*(1): 39. https://doi.org/10.1186/s13075-025-03490-2.
26. ALSHAMMAR, S. M. A. A. H. Unmasking a Rare Entity: Steroid-Induced Diabetic Ketoacidosis in a Patient with Sjogren Syndrome and Uncontrolled Diabetes: A Case Report. *Medical Reports*, 2026; 100417. https://doi.org/10.1016/j.hmedic.2026.100417.
27. Li, J.; Li, S.; Liu, W. Data-Driven Classification of Primary Sjögren's Syndrome: From Cluster Analysis to Clinical Immune Phenotypes and Predictive Biomarkers. *Journal of Translational Autoimmunity*, 2026; *12:* 100338. https://doi.org/10.1016/j.jtauto.2025.100338.
28. Li, J.; Li, S.; Liu, W. Corrigendum to "Data-Driven Classification of Primary Sjögren's Syndrome: From Cluster Analysis to Clinical Immune Phenotypes and Predictive Biomarkers" [J. Transl. Autoimmun. 12 (2026) 100338]. *Journal of Translational Autoimmunity*, 2025; 100343. https://doi.org/10.1016/j.jtauto.2025.100343.
29. Cui, T.; Geng, Z.; Wang, N.; Luo, J.; Li, Z. Sphinganine as a Potentially Relevant Metabolite in Pulmonary Involvement of Primary Sjögren's Syndrome. *Journal of Lipid Research*, 2026; *67*(1): 100961. https://doi.org/10.1016/j.jlr.2025.100961.
30. Chopra, P.; Fatima, A.; Mohapatra, S.; Kavipriya Murugaiyan; Vemuganti, G. K.; Aravind Kumar Rengan; Watson, S. L.; Singh, V.; Basu, S.; Singh, S. Extracellular Vesicles in Dry Eye Disease and Sjögren's Syndrome: A Systematic Review on Their Diagnostic and Therapeutic Role. *Survey of Ophthalmology*, 2025; *70*(3): 499–515. https://doi.org/10.1016/j.survophthal.2025.01.003.
31. Decup, F.; Rihab, B.; Nocturne, G.; Gosset, M. The Role of Dental Professionals in Identifying Patients with a Suspected Primary Sjögren's Syndrome and Suggestions for Prevention and Treatment of Oral Complications: A Narrative Review. *Heliyon*, 2025; *11*(13): e43564. https://doi.org/10.1016/j.heliyon.2025.e43564.