

**Deciphering inflammatory skin diseases dynamics:
Elucidating the role of TRPA1 in allergic contact
dermatitis and psoriasis**

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Pécs, 2026

1. INTRODUCTION

The skin is an active, multifunctional immune organ that serves as the primary interface between the host and the external environment. Beyond functioning as a physical barrier, it actively senses and responds to chemical, microbial, and mechanical stimuli through integrated structural and immunological defence mechanisms¹⁻³. Keratinocytes, which constitute the majority of epidermal cells, are now recognised as key non-professional immune cells. They express pattern recognition receptors and produce cytokines, chemokines, and antimicrobial peptides in response to danger signals, thereby playing a central role in cutaneous immune surveillance and inflammation^{4,5}.

Disruption of epidermal barrier integrity represents a critical initiating event in inflammatory skin diseases. Environmental irritants, allergens, and mechanical injury facilitate the penetration of exogenous substances into the epidermis, triggering innate immune activation. Keratinocytes therefore function as early sensors of tissue stress and release pro-inflammatory mediators that shape subsequent immune responses^{6,7}.

Two major inflammatory skin diseases illustrate distinct modes of cutaneous immune dysregulation: allergic contact dermatitis (ACD) and psoriasis. ACD is a prototypical type IV delayed-type hypersensitivity reaction induced by low-molecular-weight electrophilic chemicals that form hapten-protein complexes after penetrating the skin^{8,9}. The disease evolves through a sensitisation phase, during which antigen-specific T cells are primed, and an elicitation phase, in which re-exposure leads to rapid activation of memory T cells and the development of clinical inflammation. Importantly, early epithelial danger signalling plays a pivotal role in determining whether sensitisation occurs, highlighting the importance of keratinocyte-derived signals in disease initiation^{9,10}.

In contrast, psoriasis is a chronic immune-mediated inflammatory skin disease characterised by persistent immune activation and keratinocyte hyperproliferation. Its pathogenesis is driven by a self-amplifying inflammatory loop between keratinocytes and immune cells, dominated by IL-23/IL-17 signalling¹¹⁻¹³. Cytokines such as IL-17 and IL-22 act directly on keratinocytes, inducing proliferation, altered

differentiation, and the production of chemokines that recruit additional immune cells, thereby sustaining chronic inflammation.

A critical distinction between acute and chronic inflammation lies in the mediators that initiate and sustain the inflammatory response. Acute tissue injury rapidly induces the release of pre-formed alarmins, among which interleukin-1 α (IL-1 α) is a central epithelial danger signal. Keratinocytes constitutively express IL-1 α , which can be rapidly released following cellular damage to initiate local inflammation^{14,15}. In contrast, chronic inflammatory diseases such as psoriasis are maintained by inducible cytokine networks, particularly TNF- α and IL-23/IL-17 signalling, which perpetuate immune activation through positive feedback loops.

Among the molecular sensors involved in cutaneous inflammation, the transient receptor potential ankyrin 1 (TRPA1) ion channel has emerged as an important mediator of inflammatory signalling. TRPA1 is best known for its expression in nociceptive sensory neurons, where it detects electrophilic chemicals, reactive oxygen species (ROS), and environmental irritants, contributing to pain, itch, and neurogenic inflammation^{16,17}. However, increasing evidence demonstrates that TRPA1 is also expressed in several non-neuronal skin cells, including keratinocytes, where it participates in regulating inflammatory responses^{18,19}.

Recent studies indicate that TRPA1 exerts context-dependent functions in inflammatory skin diseases. In allergic contact dermatitis, activation of TRPA1 promotes inflammatory responses through the detection of reactive electrophilic allergens and oxidative stress. In contrast, its role in psoriasis appears more complex and context-dependent, with evidence suggesting that TRPA1 may also regulate homeostatic and anti-inflammatory pathways under chronic inflammatory conditions^{18,20}.

Based on these observations, the present dissertation investigates the role of TRPA1 as a context-dependent regulator of keratinocyte-mediated inflammatory responses in both acute and chronic inflammatory skin diseases, with particular emphasis on chemically induced allergic contact dermatitis and human psoriatic skin.

2. HYPOTHESIS AND AIMS

2.1 Central hypothesis

Allergic contact dermatitis (ACD) and psoriasis are traditionally viewed as distinct inflammatory skin diseases: ACD as an acute, antigen-specific, T cell-mediated hypersensitivity reaction, and psoriasis as a chronic immune-mediated inflammatory disease driven by IL-23/IL-17 signalling. Despite these differences, both diseases share several fundamental features, including keratinocyte stress, barrier disruption, early danger signalling, and amplification of inflammation through interactions between epithelial cells, immune cells, and sensory neurons ^{1,8,9,11,12}.

TRPA1 is a polymodal cation channel activated by electrophilic compounds, oxidative stress products, and inflammatory mediators, and is expressed in both sensory neurons and skin-resident cells, including keratinocytes ^{19,21,22}. This positions TRPA1 as a potential integrator of chemical injury, reactive oxygen species, and immune activation within the epidermis.

The central hypothesis of this dissertation is that TRPA1 expressed in keratinocytes functions as a context-dependent danger sensor that integrates electrophilic activation with oxidative stress, thereby promoting cytotoxicity and IL-1 α -dominated alarmin signalling in allergic contact dermatitis while regulating broader transcriptional programmes involved in inflammatory and homeostatic pathways in psoriatic skin.

2.2 Specific aims

To test this hypothesis, the work presented in this dissertation was organised into two complementary experimental arms.

2.2.1 Allergic contact dermatitis

The aims of the ACD study were:

- To determine the role of TRPA1 in oxazolone-induced allergic contact dermatitis using genetic deletion and pharmacological inhibition.

- To characterise TRPA1-dependent keratinocyte cytotoxicity induced by strong contact sensitisers.
- To investigate TRPA1-dependent release of inflammatory mediators from keratinocytes following allergen exposure.
- To analyse the interaction between contact sensitisers and the TRPA1 binding pocket using *in silico* molecular modelling.

2.2.2 Psoriatic human skin

The aims of the psoriasis study were:

- To characterise baseline transcriptomic differences between healthy, non-lesional, and lesional psoriatic skin.
- To investigate the effects of pharmacological TRPA1 activation and inhibition on global gene expression in *ex vivo* human skin using RNA sequencing.
- To identify TRPA1-regulated pathways involved in inflammation, epidermal differentiation, circadian rhythm, and cellular stress.
- To evaluate how TRPA1-dependent transcriptional changes relate to psoriasis-associated signalling pathways.

3. MATERIALS AND METHODS

3.1 Experimental approaches in allergic contact dermatitis (ACD)

3.1.1 *In vivo* model

Allergic contact dermatitis was induced in wild-type (WT) and *Trpa1* knockout (KO) mice using an oxazolone-induced contact hypersensitivity (CHS) model. The role of TRPA1 was investigated using both genetic deletion and pharmacological inhibition with the selective TRPA1 antagonist HC-030031. Experimental groups consisted of WT, WT treated with HC-030031, and *Trpa1* KO mice (n = 6 per group; total n = 18).

The severity of cutaneous inflammation was evaluated by measuring ear thickness, tissue perfusion using laser speckle contrast analysis (LASCA), and histological assessment of haematoxylin and eosin-stained ear sections.

3.1.2 *In vitro* keratinocyte experiments

Keratinocyte responses to contact sensitisers were investigated using primary murine keratinocytes and TRPA1-expressing cell systems. Cells were stimulated with electrophilic contact sensitisers, including DNFB, DNCB, oxazolone, and formaldehyde.

TRPA1 activation was assessed by intracellular calcium measurements using Fura-2 microfluorimetry, while ATP-based luminescent assays were used to evaluate cytotoxicity. Cytokine release was analysed using a multiplex Luminex assay to characterise TRPA1-dependent inflammatory responses.

3.1.3 Molecular and imaging analyses

TRPA1 expression in human and mouse skin was examined using RNAscope *in situ* hybridisation combined with cytokeratin-14 immunofluorescence. Fluorescent signals were visualised by confocal microscopy to determine the localisation of TRPA1 within the epidermis.

3.1.4 *In silico* modelling

Molecular docking studies were performed using human and modelled mouse TRPA1 structures to investigate the interaction of electrophilic contact sensitisers with the TRPA1 binding pocket, with particular emphasis on electrophile-sensitive cysteine residues and predicted binding modes.

3.2 Experimental approaches in psoriatic human skin

3.2.1 Human skin samples and *ex vivo* treatment

Full-thickness 6-mm skin biopsies were obtained from four healthy volunteers and four patients with psoriasis. For each patient, both lesional and non-lesional skin samples were collected. Biopsies were cultured *ex vivo* and treated with vehicle, mustard oil (TRPA1 agonist), or HC-030031 (TRPA1 antagonist) before RNA isolation.

3.2.2 RNA sequencing and bioinformatic analysis

Global gene expression was analysed using RNA sequencing. Sequencing libraries were prepared using the QuantSeq 3' mRNA-Seq protocol and sequenced on an Illumina platform. Differential gene expression, principal component analysis, and pathway enrichment analyses were performed to identify TRPA1-dependent biological processes associated with inflammation, epidermal differentiation, circadian regulation, cellular stress responses, and psoriasis-related signalling pathways.

3.3 Statistical analysis

Results are presented as mean $\pm$ SEM. Statistical analyses were performed using GraphPad Prism version 10.5.

Calcium influx and ATP-based cell viability assays were analysed using one-way ANOVA followed by Šídák's multiple comparisons test when appropriate. Ear thickness and laser speckle contrast imaging data were analysed using two-way ANOVA with Šídák's multiple comparisons test. Owing to the limited number of biological replicates and the exploratory nature of the multiplex cytokine analysis, Luminex cytokine data are presented descriptively without formal statistical testing. Statistical significance was defined as $P < 0.05$.

4. RESULTS

4.1 Allergic contact dermatitis (ACD)

In the first part of the study, the role of TRPA1 in allergic contact dermatitis was investigated, with particular emphasis on keratinocyte activation, cytotoxicity, and inflammatory signalling induced by contact sensitisers.

4.1.1 TRPA1 is required for oxazolone-induced cutaneous inflammation

In the oxazolone-induced model of allergic contact dermatitis, wild-type mice developed marked ear oedema and increased tissue perfusion after challenge, whereas both genetic deletion of *Trpa1* and pharmacological inhibition with HC-030031

significantly attenuated these responses. Histological analysis confirmed reduced epidermal and dermal thickening, inflammatory cell infiltration, and Munro's microabscess formation in *Trpa1* knockout and antagonist-treated animals. In contrast, no significant structural differences were detected between genotypes under baseline vehicle-treated conditions, indicating that TRPA1 does not affect normal skin morphology in the absence of inflammatory challenge.

4.1.2 Strong contact sensitisers directly activate TRPA1

Calcium imaging experiments in TRPA1-expressing CHO cells showed that DNCB, DNFB, formaldehyde, and oxazolone induced concentration-dependent intracellular calcium influx. These responses were absent in naïve CHO cells and were abolished by TRPA1 antagonism, confirming that these contact sensitisers directly activate TRPA1.

4.1.3 TRPA1 activation is associated with cytotoxicity

In TRPA1-expressing CHO cells, all tested contact sensitisers caused concentration-dependent loss of viability, whereas naïve cells remained largely unaffected. Pharmacological inhibition of TRPA1 reduced this cytotoxicity, indicating that allergen-induced cell death is largely TRPA1-dependent.

4.1.4 Keratinocytes express TRPA1 in mouse and human skin

RNAscope *in situ* hybridisation demonstrated TRPA1 mRNA expression in both mouse and human epidermis. In both species, the signal was predominantly localised to basal keratinocytes, supporting the presence of TRPA1 in epidermal keratinocytes under physiological conditions.

4.1.5 Keratinocyte TRPA1 mediates allergen-induced cytotoxicity

To test whether these effects were relevant in a more physiological setting, primary keratinocytes isolated from wild-type and *Trpa1* knockout mice were exposed to contact sensitisers. Wild-type keratinocytes exhibited marked concentration-dependent cytotoxicity, whereas *Trpa1*-deficient keratinocytes were protected. Similarly, pharmacological blockade of TRPA1 significantly reduced cytotoxicity in

wild-type cells. These findings identify keratinocyte TRPA1 as a key mediator of allergen-induced cell damage.

4.1.6 TRPA1-dependent IL-1 α release from keratinocytes

Multiplex cytokine analysis revealed that among the tested mediators, IL-1 α showed the clearest TRPA1-dependent response pattern after allergen exposure. Wild-type keratinocytes released higher levels of IL-1 α than *Trpa1*-deficient cells, and this response was reduced by HC-030031. In contrast, the other measured cytokines remained low or showed no consistent TRPA1-dependent pattern. MCP-1 levels were comparable across groups, suggesting TRPA1-independent regulation. Because these measurements were performed with limited biological replication, they were interpreted descriptively as exploratory evidence supporting a selective link between TRPA1 activation and IL-1 α -dominated alarmin signalling.

4.1.7 Binding mode partly explains sensitiser potency

In silico docking studies provided structural support for the observed functional differences among contact sensitisers. DNFB showed covalent interaction with C621 and stabilising contacts within the agonist-binding region, consistent with its strong biological activity. DNCB also bound covalently but with fewer stabilising interactions, whereas formaldehyde showed only limited interaction, in line with its weaker activity. Oxazolone bound non-covalently but formed multiple stabilising contacts, consistent with intermediate potency. Comparable docking scores and binding modes were observed in human and mouse TRPA1 models, supporting translational relevance.

4.2 Psoriatic human skin RNA sequencing

In the second part of the study, the role of TRPA1 in chronic inflammatory skin disease was explored by analysing gene expression changes in healthy and psoriatic human skin.

4.2.1 Baseline transcriptomic differences between healthy and psoriatic skin

Principal component analysis showed a clear separation between lesional psoriatic skin and both healthy and non-lesional psoriatic skin, whereas non-lesional samples clustered closer to healthy controls. This confirmed the expected transcriptomic distinction between inflamed and non-inflamed skin. Baseline differential expression analysis also identified well-established psoriasis-associated genes, and comparison with previously published large-cohort datasets showed substantial overlap, supporting the robustness of the present dataset.

4.2.2 Effects of TRPA1 activation differ by inflammatory context

To assess the effects of TRPA1 activation, mustard oil-treated samples were compared with vehicle-treated controls. In healthy and non-lesional skin, mustard oil induced a mixed transcriptional response, with downregulation of interferon-related, antimicrobial, and inflammatory genes, alongside upregulation of transcription factors and structural skin components associated with differentiation and barrier function.

In lesional psoriatic skin, mustard oil treatment produced a more pronounced transcriptional shift, with dominant downregulation of inflammation-associated genes. Several key psoriasis-related mediators, including IL36G, NFKBIA, and HIF1A, were reduced after treatment, suggesting partial normalisation of the lesional inflammatory transcriptome. These findings indicate that the effects of TRPA1 activation are context-dependent and differ substantially between homeostatic and inflamed skin.

4.2.3 Pathway enrichment highlights anti-inflammatory and homeostatic effects

Pathway enrichment analysis further supported these context-dependent effects. In healthy skin, downregulated pathways included interferon signalling, IL-10-related pathways, neutrophil degranulation, and keratinisation. In non-lesional skin, treatment was associated with reduced matrix remodelling pathways and increased pathways related to collagen metabolism and lipid homeostasis.

In lesional psoriatic skin, downregulated pathways included TGF β and MET signalling, circadian clock regulation, and cytokine-related signalling. Analysis of the

most strongly downregulated genes also highlighted attenuation of senescence-associated secretory phenotype (SASP)-related programmes. In parallel, genes associated with lipid and cholesterol biosynthesis were upregulated, suggesting a shift toward a more homeostatic transcriptional state.

5. DISCUSSION

5.1 TRPA1 as a context-dependent epithelial danger sensor

TRPA1 has traditionally been recognised as a neuronal irritant receptor involved in nociception, itch, and neurogenic inflammation. However, increasing evidence demonstrates that TRPA1 is also expressed in keratinocytes and other skin-resident cells, where it integrates electrophilic and oxidative stress signals and contributes to cutaneous immune regulation^{19,20,23}. The findings presented in this dissertation extend this concept by demonstrating that TRPA1 functions as a context-dependent epithelial danger sensor whose biological effects are determined by the inflammatory environment. Rather than exerting a uniformly pro-inflammatory role, TRPA1 promotes epithelial danger signalling during acute chemical injury while modulating broader transcriptional programmes in chronic inflammatory skin disease.

5.2 TRPA1 in allergic contact dermatitis

The allergic contact dermatitis arm of this dissertation demonstrates that both genetic deletion and pharmacological inhibition of TRPA1 markedly attenuate oxazolone-induced skin inflammation, supporting an important role for TRPA1 in the initiation and amplification of contact hypersensitivity. These findings complement the current understanding of allergic contact dermatitis, in which keratinocyte activation precedes and shapes the subsequent adaptive immune response⁷⁻⁹.

The *in vitro* studies further demonstrated that strong contact sensitisers directly activate TRPA1 and induce calcium influx and cytotoxicity in a TRPA1-dependent manner. The observation that primary keratinocytes exhibited similar responses confirms that keratinocyte TRPA1 represents an important non-neuronal mediator of epithelial injury following allergen exposure. Among the inflammatory mediators examined, IL-1 α displayed the clearest TRPA1-dependent release pattern, supporting

the concept that TRPA1 contributes to an epithelial alarmin response that promotes early inflammatory amplification^{10,24,25}.

5.3 TRPA1 in psoriasis

The transcriptomic analyses revealed that pharmacological activation of TRPA1 produces markedly different effects in healthy, non-lesional, and lesional psoriatic skin, demonstrating that TRPA1 signalling is highly dependent on the inflammatory context. While relatively modest transcriptional changes were observed in healthy skin, substantially broader alterations occurred in lesional psoriasis.

TRPA1 activation was associated with reduced expression of several psoriasis-associated inflammatory mediators and attenuation of pathways involved in inflammatory signalling, matrix remodelling, circadian regulation, and the senescence-associated secretory phenotype. Concurrent enrichment of pathways related to lipid metabolism and epidermal homeostasis suggests that TRPA1 activation may contribute to partial restoration of tissue homeostasis rather than simply suppressing inflammatory responses. These findings are consistent with the emerging concept that TRPA1 may exert both pro-inflammatory and homeostatic functions depending on the inflammatory milieu^{13,18,20,26}.

5.4 Overall conclusions and perspectives

This dissertation establishes TRPA1 as a pivotal epithelial regulator of inflammatory tone in human skin. By combining *in vivo*, *in vitro*, *in silico*, and transcriptomic approaches, the work demonstrates that TRPA1 is not confined to neuronal irritant sensing but functions as a keratinocyte-intrinsic stress integrator with disease context-dependent outcomes.

Across two distinct inflammatory contexts, this work demonstrates that TRPA1 functions as a keratinocyte-intrinsic regulator of inflammatory tone whose biological output depends on disease state and activation dynamics. In allergic contact dermatitis, TRPA1 contributes to early epithelial danger signalling and immune initiation, whereas in psoriasis it is associated with transcriptional recalibration rather than inflammatory escalation. Together, these findings reconcile previously divergent

views of TRPA1 function and support a broader framework in which TRPA1 acts as a redox- and electrophile-responsive epithelial stress integrator with context-dependent downstream consequences^{19,20,23,26}.

Importantly, this context-dependent functionality carries translational implications. In allergic contact dermatitis, TRPA1 activation drives keratinocyte cytotoxicity, calcium overload, and IL-1 α -mediated alarmin release, placing the channel upstream of immune activation. Pharmacological inhibition of TRPA1, as demonstrated with the selective antagonist HC-030031, attenuates these early pathogenic events and reduces inflammation, highlighting its therapeutic potential in acute chemically induced dermatitis. Collectively, these findings position TRPA1 as a dual-function therapeutic target: inhibition may be beneficial in acute allergen-driven injury, whereas controlled modulation may be required in chronic immune-mediated disease. Therapeutic strategies targeting TRPA1 must therefore consider inflammatory baseline, activation dynamics, and disease stage.

Beyond its disease-specific implications, this work advances the conceptual understanding of keratinocytes as active immunological regulators and highlights the importance of integrating structural, cellular, and transcriptomic approaches in dissecting epithelial signalling pathways.

Future studies should define the downstream signalling intermediates linking TRPA1 activation to large-scale transcriptional reprogramming and clarify how redox-sensitive channel modulation interacts with cytokine and metabolic networks *in vivo*. Such work will be essential for translating TRPA1-targeted strategies into clinically meaningful interventions.

6. SUMMARY OF NEW FINDINGS

1. Keratinocyte TRPA1 was identified as a key mediator of allergic contact dermatitis. Using both genetic deletion and pharmacological inhibition, this work demonstrates that TRPA1 significantly contributes to oxazolone-induced cutaneous inflammation *in vivo*.
2. Strong contact sensitisers directly activate keratinocyte TRPA1 and induce TRPA1-dependent cytotoxicity. Electrophilic contact sensitisers elicited intracellular

calcium influx and reduced cell viability in a TRPA1-dependent manner, establishing keratinocyte TRPA1 as a direct sensor of chemically induced epithelial stress.

3. TRPA1 activation promotes IL-1 α release from keratinocytes. The findings indicate that TRPA1-dependent cytotoxicity is associated with the release of the epithelial alarmin IL-1 α , supporting a role for keratinocyte TRPA1 in the initiation of early inflammatory signalling during allergic contact dermatitis.

4. The structural interactions between contact sensitisers and TRPA1 correlate with their biological activity. Molecular docking analyses demonstrated that stronger contact sensitisers exhibit more favourable interactions with the electrophile-sensitive TRPA1 binding pocket, providing a structural explanation for differences in sensitising potency.

5. TRPA1 regulates transcriptional responses in human psoriatic skin in a context-dependent manner. RNA sequencing revealed that pharmacological activation of TRPA1 induces distinct gene expression profiles in healthy, non-lesional, and lesional psoriatic skin, demonstrating that the biological effects of TRPA1 depend on the inflammatory status of the tissue.

6. TRPA1 activation in lesional psoriatic skin is associated with attenuation of inflammatory pathways and enrichment of homeostatic pathways. Transcriptomic analyses showed reduced expression of several psoriasis-associated inflammatory mediators together with enrichment of pathways involved in epidermal differentiation, lipid metabolism, and tissue homeostasis.

7. The findings support a unified model of TRPA1 function in inflammatory skin diseases. While TRPA1 amplifies epithelial injury and alarmin signalling during acute allergen-induced inflammation, it modulates transcriptional programmes associated with inflammatory regulation and tissue homeostasis in chronic psoriasis, demonstrating that TRPA1 functions as a context-dependent regulator of cutaneous inflammation.

List of Publications

The thesis is based on the following publications:

1- **Jaber A**, Horváth S, Zsidó BZ, Kormos V, Konkoly J, Hetényi C, Pintér E, Kemény Á, Gyulai R. Contact sensitizers activate keratinocytes and induce cytotoxicity via TRPA1 in allergic contact dermatitis. **British Journal of Pharmacology**. 2025. doi:10.1111/bph.70479. **IF:7.7; Q1; D1 (Published online)**.

2- Kemény Á, Horváth S, Szabéni J, Oláh P, Németh V, Urbán P, Kun J, Gyenesi A, **Jaber A**, Pintér E, Gyulai R. TRPA1 ion channel activation context-dependently regulates gene expression in normal and psoriatic human skin. **British Journal of Pharmacology**. 2025 Aug 6. doi:10.1111/bph.70153. **IF:7.7; Q1; D1 (Published online)**.

Cumulative IF: 15.4

MTMT ID: 10090632

Acknowledgements

First and foremost, I would like to express my deepest gratitude to my supervisor, Dr. Ágnes Kemény, whose guidance, expertise, and continuous support have been indispensable throughout my PhD studies. Her insightful feedback, critical perspective, and dedication to scientific excellence have profoundly shaped both this dissertation and my development as a clinician-scientist. I am truly grateful for the opportunity to work under her mentorship.

I am also sincerely grateful to my supervisors, Prof. Rolland Gyulai and Prof. Erika Pintér, whose support and trust made this work possible. They provided me with the opportunity to pursue this PhD and played a decisive role in initiating and shaping the direction of this project. Their guidance was fundamental in developing the core ideas, defining the research strategy, and advancing the work. I am particularly thankful to Prof. Rolland Gyulai for his clinical perspective and leadership, which have had a strong influence on my professional development, and to Prof. Erika Pintér for her scientific expertise and essential role in conceptualizing the project and supporting its realization, including guidance in securing resources and funding.

I would like to sincerely thank all members of the Department of Pharmacology and Pharmaceutical Sciences, as well as the Department of Dermatology at the University of Pécs, for providing a welcoming and supportive working environment. I am especially grateful for the collaboration, shared knowledge, and everyday encouragement throughout this journey.

I am thankful to my colleagues, collaborators, and co-authors for their valuable contributions, discussions, and assistance, which were essential for the completion of this work.

I would also like to thank the members of my doctoral committee and the reviewers for their time and constructive evaluation.

Finally, I am deeply grateful to my family and friends for their unwavering support, patience, and encouragement. Their belief in me has been a constant source of strength and motivation, and this work stands as much as theirs as it does mine.

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