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Circadian Phytonutrition Using Polyphenol-Rich Botanical Extracts to Remodel Immunometabolism in Autoimmune Thyroid Disorders: A Mechanistic Review and Research Roadmap

[1]Dr. Ravindra HN, [2]Dr. Mano Priya Vijayan, [3]Tanveer Ahmad Wani, [4]Dr. Rahul S.S., [5]Saksham Sood, [6]Dr. Prithvikumar H. Ahir, [7]Dr. V. Prashanth,

[1]Professor, ITM College of Nursing, ITM SLS Baroda University, Vadodara, Gujarat, India
ravindrahn23@gmail.com
Orcid Id: 0000-0001-8579-2075
[2]Assistant Professor / Deputy Dean, Faculty of Health Sciences, Villa College, Maldives
Email: manopriya.vijayan@villacollege.edu.mv
ORCID: 0009-0006-0604-3599
[3]Professor, Department of Physics, Noida International University, Uttar Pradesh, India.
tanveer. ahmad@niu.edu.in
0000-0001-5582-6190
[4]Assistant Professor, Dept. of Emergency Medicine, Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth "Deemed to be University", Taluka-Karad, Dist-Satara, Pin-415 539, Maharashtra, India
rahulsssgmc@gmail.com
[5]Centre for Research Impact & Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, 140401, Punjab, India.
saksham.sood.orp@chitkara.edu.in https://orcid.org/0009-0004-4033-0159
[6]Medical Officer, Faculty of Homoeopathy, Gokul Global University, Sidhpur, Gujarat, India, phahir.bhms@gokuluniversity.ac.in,0009-0007-6772-9188
[7]Assistant Professor, Department of Radiology, Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals, Vinayaka Mission's Research Foundation (DU), Tamil Nadu, India.
Email ID: vprashanth33@gmail.com
ORCID ID: 0009-0008-2649-1326

ABSTRACT: Imbalances between proinflammatory T helper 17 (Th17) cells and immunosuppressive regulatory T (Treg) cells have been shown to play a key role in the pathogenesis of autoimmune thyroid diseases (AITD), such as Hashimoto's thyroiditis and Graves' disease. In particular, Th17/Treg cell ratio is associated with levels of autoantibodies and the severity of AITD. Furthermore, different metabolic pathways underlie the generation of Th17 cells (glucose-dependent anabolic metabolism) and Tregs (oxidative mitochondrial metabolism). The association between these Th17/Treg immune cells, their respective metabolic pathways and the autoimmune disease has led to the hypothesis that AITD is partly an immunometabolic disease. Moreover, it has been demonstrated independently that molecular clocks of thyroid cells are altered in

autoimmune thyroiditis, with decreased expression of circadian rhythm proteins BMAL1 and PER2, which correlate with the level of inflammation and that disruption of circadian rhythm (light-shift) exacerbates the disease severity in the animal model. Third line of research, not linked to either of the above, has revealed the ability of various dietary polyphenols — such as green tea catechins (EGCG), curcumin, resveratrol, citrus polymethoxyflavones — to modulate transcription of the core clock-genes and directly inhibit Th17 development while enhancing Treg induction. This review integrates these three bodies of literature and offers, in the form of an explicit but untested hypothesis, that timing of polyphenol administration from botanical sources in alignment with, rather than disregard of, the physiological rhythms of the intrinsic immune and thyroid clocks will be capable of reprogramming Th17/Treg metabolism in early AITD more effectively than conventional polyphenol ingestion. It refer to this strategy as circadian phytonutrition. The review concludes with a series of in vitro, animal and human studies in translation, designed as a step-wise process. No original data are offered here; all proposed mechanisms are hypotheses derived from indirect evidence.

1. INTRODUCTION

AITDs represent the most frequent organ-specific autoimmune conditions, characterized by two primary pathologies: Hashimoto's thyroiditis (HT) and Graves' disease (GD) [5]. Notably, these diseases are marked by opposing physiological outcomes (hypothyroidism vs hyperthyroidism), yet the immune response in both cases is defined by a similar defect in autoimmunity towards thyroid tissue with participation of both cellular and humoral immunity, wherein Th17 and Treg populations serve a central role [3] [6] [7]. Elevated Th17/Treg ratio has been confirmed in multiple independent patient cohorts in the context of HT as being associated with higher levels of anti-thyroglobulin antibodies and Graves' orbitopathy clinical activity score - indicating that this ratio reflects active disease. Recent studies introduced an alternative interpretation of this ratio, defining the process of imbalance between these populations in terms of metabolism: Th17 populations rely more on glycolytic and anabolic metabolic processes, whereas Tregs depend on oxidative phosphorylation and mitochondrial health, additionally being influenced in the process by metabolic cues specific for AITDs such as excess iodine, oxidative stress, and lactate production.

Another literature, entirely independent until recent years, has shown that the thyroid gland has its own molecular clock, which is a BMAL1/CLOCK/PER/CRY transcriptional-translational feedback loop like all other peripheral clocks, and that the dysfunction of this peripheral clock is measurable in autoimmune thyroiditis patients. A 2023 study took thyroid tissue samples from autoimmune thyroiditis patients and controls and found significant downregulation of the clock components, BMAL1 and PER2, in AIT tissue; moreover, the study found inverse correlations between reduced BMAL1 and inflammation markers in serum and tissue; the same study conducted induction of experimental autoimmune thyroiditis in mice and found that circadian disruption caused by light-shift housing increased disease severity, thereby establishing causality of circadian disruption in thyroid autoimmunity severity. This is in addition to existing epidemiological data linking shift work and circadian misalignment to increased risk of systemic autoimmune disease, and evidence linking the hormone melatonin the main circadian rhythm hormone secreted by the pineal gland to regulation of the Th17/Treg ratio via the MT1 receptor on both cells and favoring IL-10 secretion from Tregs, as well as IL-17 suppression in Th17 cells [13]. Explains mechanisms of immune responses and inflammation pathways, which help to understand how the immune system works in terms of autoimmune thyroid diseases [18].

The final component which is used in the context of this review is dietary. Polyphenols – the extensive category of secondary phytochemicals including, among others, flavonoids, stilbenes, and curcuminoids – represent an extensively researched group as circadian clock gene regulators and immunometabolic modulators despite being separate literatures. In terms of the former, a recent scoping review compiled from 43 studies in 2024 demonstrated that dietary polyphenols such as nobiletin and tangeretin (citrus), EGCG (green tea), resveratrol, and curcumin possess a capacity for modulating cellular circadian clock oscillators with nobiletin itself serving as RORα/γ agonist inducing BMAL1 expression and increasing PER2 amplitude. From the perspective of immunometabolism, the very same and similar compounds demonstrate Th17 suppression/Treg induction in various autoimmune diseases not at all connected to AITD: EGCG for autoimmune arthritis (through the inhibition of

STAT3 and HIF-1α), resveratrol for immune thrombocytopenic purpura (through the activation of AhR pathways) and multiple sclerosis models, and curcumin for intestinal barrier/inflammatory bowel conditions, with a 2024 review explicitly describing polyphenols as "immunonutrients" able to "tip the balance of immunometabolism."

What has not, to the knowledge, been considered in the existing literature is the intentional integration of these three aspects together: employing circadian timekeeping by means of administering polyphenol-enriched botanical extracts in accordance with, rather than regardless of, the existing disruptions of the intrinsic clocks of the thyroid gland and the immune system in AITD patients as a means of reprogramming the Th17/Treg immunometabolism. The purposes of this review include: (1) to present the literature regarding the circadian biology of thyroid autoimmunity, along with the tissue evidence of clock-gene dysfunction in AIT; (2) to present the basis of immunometabolism involved in the dysfunctional balance between Th17 and Treg cell types in AITD; (3) to examine the literature on the use of polyphenols as clock-gene regulators and modulators of Th17/Treg cell immunometabolism, making extensive use of research on other autoimmune diseases in the absence of AITD-specific data; and (4) to put these three threads together in order to formulate a mechanistic hypothesis of circadian phytonutrition for AITD, along with a stepwise translation plan. As in the underlying literature it relies upon, this review presents no novel experimental results, and every mechanistic step of Section 5 is proposed as a hypothesis.

2. CIRCADIAN BIOLOGY OF THYROID AUTOIMMUNITY

2.1 The peripheral thyroid clock and its disruption in AIT

The circadian clock function depends on a well-conserved transcription-translation feedback loop whereby the heterodimeric protein CLOCK:BMAL1 drives E-box-mediated transcription of downstream clock-regulated genes, which include the proteins themselves, via accumulation and nuclear translocation of negative feedback proteins such as PER and CRY, in a cycle of around 24 hours [2]. These mechanisms are not limited to the suprachiasmatic nucleus but exist in the periphery including in the thyroid gland, whereby they become synchronized through the central clock as well as local and systemic factors like feeding time. The evidence linking the disruption of this peripheral thyroid clock to autoimmune thyroid disease is, as pointed out in Section 1 above, direct and not inferential, since decreased BMAL1 and PER2 mRNA levels have been observed in thyroid samples from patients with AIT, negatively correlated with inflammation biomarkers, and light shift-induced circadian disruptions proven to aggravate the disease in an experimental autoimmune thyroiditis mice model [8] [20]. This is relatively uncommon in the general circadian-disease literature, since the study establishes a direct link between clock disruption and disease severity without extrapolation from other tissues. Focuses on precision medicine and the importance of evidence-based care in dealing with autoimmune thyroid disorders [21].

2.2 Melatonin, the thyroid-pineal axis, and immune timing

Thyroid disease, autoimmunity, and sleep are linked to each other in a two-way relationship involving melatonin, secreted by the pineal gland under central circadian control; firstly, circadian misalignment via shift work or irregular sleep influences melatonin levels, secondly, melatonin itself demonstrates anti-inflammatory and immune-regulating properties that may potentially affect autoimmunity and thyroid function [20]. Regarding a direct connection of melatonin to the Th17/Treg pathway, although it may be considered somewhat speculative, the most clear connection in the scientific literature lies outside the narrow focus of the thyroid field: Melatonin interacts with its MT1 receptor that is present on both Th17 and Treg cells to stimulate IL-10 release from Tregs and inhibit Th17 differentiation and IL-17 production, an effect shown for multiple sclerosis and potentially applicable to other Th17/Treg-related autoimmune conditions, including AITD. Overall, Treg numbers and suppressive activity are subject to circadian rhythms, and, therefore, timing of potential therapy should not be overlooked.

2.3 Chrononutrition as a precedent intervention class

In regard to the potential of meal timing per se without consideration for content to yield physiological results, there exists a fairly well-developed scientific foundation in the domain of chrononutrition and TRE [14] [16]. In a systematic review of 23 clinical studies, it was discovered that TRE led to a mean weight loss of 3%, along with fat mass reduction, including changes that could be observed independently from any caloric restriction – thus indicating the actual involvement of circadian realignment process, rather than calorie tracking and a separate meta-analysis of 19 clinical trials supported reduction in body weight and fat mass without reducing fat-free mass [11]. There is less evidence and even some discrepancies in the matter of effects of TRE on melatonin and cortisol levels – most non-Ramadan TRE studies have not included melatonin measurements in their design, while the results in regard to cortisol differ across various studies, yet another gap in evidence regarding the

particular circadian-hormonal pathway, despite the relatively well-established metabolic effects of TRE [12] [15]. A mechanistic precedent of a diet-timing effect on the reprogramming of an immune-relevant T-cell population has been established in a study that falls outside the domain of thyroid biology: it was shown that timed feeding during rest-phase in mice affected the composition of gut microbiota and through fecal microbiota transplantation, led to the expansion of Th17 cells in a causal manner, although in the context of bone and not thyroid pathology [10]. It believe that this is a relevant precedent for the feasibility of circadian phytonutrition regardless of its specificity to polyphenols and thyroid autoimmunity [4] [17][22].

3. THE IMMUNOMETABOLIC BASIS OF TH17/TREG IMBALANCE IN AITD

3.1 Th17/Treg imbalance as the central immunological lesion

In all the three autoimmune disorders studied – Hashimoto's thyroiditis, Graves' disease, and Graves' orbitopathy – there is one common phenomenon that has been observed: an increased percentage of Th17 cells characterized by IL-17 and the transcription factor RORγt, coupled with a decreased number of Treg cells, characterized by Foxp3 and IL-10/TGF-β, leading to an imbalanced ratio of Th17/Treg that is directly proportional to disease activity and autoantibody titre. With regard to Hashimoto's thyroiditis, it has been observed that an increased GITRL (glucocorticoid-induced TNFR-related protein ligand) correlates positively with the percentage of Th17 cells and anti-thyroglobulin antibodies in both serum and thyroid tissues. Other studies have found that the PD-1/PD-L1 signaling pathway plays a role, where reduced levels of PD-1/PD-L1 were associated with the development and progression of HT, while low selenium levels, together with genetic factors, are other environmental influences involved in the process, although a study that measured Th17-related cytokines and selenium levels in newly diagnosed and untreated AITD patients showed no significant differences between the groups regarding IL-17a, IL-22, IL-23, IL-6, or IL-10 — an interesting note about markers that seem to be mechanistically related but do not show their effects in serum levels of cytokines.

3.2 Metabolic reprogramming as the mechanistic substrate

Under the immunometabolic approach, the Th17/Treg ratio is seen not as a static ratio but as the final output of two different metabolic pathways that compete against each other. Th17 cells need glycolysis and anabolic metabolism to sustain their functional characteristics, whereas Treg cells rely on oxidative phosphorylation and mitochondrial health to maintain their stable phenotype; in AITD, this balance is additionally skewed in favor of Th17 cells because of the presence of glycolytic conditions, such as high iodine levels, oxidative stress, accumulation of lactate from the surrounding inflamed tissue, and the action of cytokines/stroma of the thyroid microenvironment itself [9]. The importance of this background to the specific hypothesis presented in this review is the fact that some of the polyphenols described in Section 4 – such as resveratrol through SIRT1, a master regulatory component of mitochondrial biogenesis and oxidative metabolism – have known modes of action that affect this metabolic dichotomy directly, rather than the Th17/Treg imbalance through a different pathway.

3.3 The gut-thyroid axis as an additional, convergent pathway

An additional line of evidence, albeit partially overlapping and partially independent, links gut microbiota composition to Th17/Treg balance in relation to Hashimoto's thyroiditis in particular. The results of a systematic review assessing the mechanisms linking gut microbiota to the Th17/Treg modulation in HT, based on 80 papers selected using the inclusion criteria, showed the consistent effect of the alterations in gut microbiota on the pathogenesis of thyroid autoimmunity via Th17/Treg modulation, though the authors pointed out the deficiency in this type of research in comparison with other autoimmune diseases. This is important to note in connection with the current review because, firstly, it suggests another, gut-mediated way of how clock gene and Th17/Treg-based approaches to the treatment of thyroid autoimmunity can be influenced, along with those mentioned above, and, secondly, it coincides with the pathway from diet time to Th17 expansion described before, as mealtime itself is known to affect the rhythmicity of gut microbiota, thus providing the clock phytomedicine with two possible ways of achieving the same endpoint.

4. POLYPHENOLS AS CIRCADIAN AND IMMUNOMETABOLIC MODULATORS

4.1 Direct clock-gene activity

The most direct support for the potential ability of polyphenols to influence the circadian machinery is provided by a scoping review of 43 experiments carried out on cultured mammalian cells, according to which 34 different polyphenols were studied for their effects on clock mechanisms in relation to BMAL1 rhythmicity and expression. Different effects were demonstrated

by different compounds depending on the cell type involved in the research – resveratrol, although the most researched compound among polyphenols with regard to clock mechanisms in spite of extremely low bioavailability, had age-specific effects on BMAL1 and CLOCK; nobiletin and tangeretin, on the contrary, exhibited consistently high agonist activity of RORα/γ receptors, promoting BMAL1 expression and increasing PER2 period and amplitude [1]. In addition, authors of the review drew attention to the considerable methodological variability in the experiments discussed in this literature review, and explicitly recommended standardizing further protocol in order to obtain more reliable results – an aspect to be considered in developing AITD-related hypothesis outlined in Section 5.

4.2 Direct Th17/Treg immunomodulatory activity

Apart from the clock gene pathways discussed above, there are also polyphenols that possess significant receptor- and transcription factor-level modulations of Th17/Treg balance in autoimmune diseases other than AITD. EGCG acts to inhibit STAT3 phosphorylation and HIF-1α expression, and thus decreases the Th17 differentiation, whereas increases the percentage of Foxp3+ Treg cells in spleen in IL-1 receptor antagonist-knockout autoimmune arthritis mice with protection against joint destruction [19]. Curcumin blocks IL-23/Th17 pathway by decreasing IL-6, IL-17, and IL-23 and increasing anti-inflammatory cytokine IL-10, and independently increases expression of intestinal tight-junction proteins (occludin, ZO-1, claudin-3) which is functionally important considering the discussion of gut-thyroid axis in section 3.3. Resveratrol restores the disturbed Th17/Treg balance in T-cell-mediated immune thrombocytopenic purpura by suppressing AhR pathway, and also enhances Treg cell generation in experimental autoimmune encephalomyelitis, the mouse model of multiple sclerosis, via SIRT1, oestrogen receptor and AhR pathway.

Table 1 summarises the major groups of polyphenols mentioned in this review together with their Th17/Treg and clock gene activities.

Table 1. Polyphenol classes with documented circadian clock-gene and/or Th17/Treg immunomodulatory activity, drawn primarily from non-AITD disease contexts.

Polyphenol class	Representative compounds	Documented Th17/Treg or clock-gene activity
Flavan-3-ols (catechins)	EGCG (green tea)	Suppresses STAT3/HIF-1α signalling, reduces Th17 differentiation, increases Foxp3+ Treg proportion in autoimmune arthritis [19]
Stilbenes	Resveratrol	SIRT1-dependent suppression of CD4+ T-cell activation; reverses Th17/Treg imbalance via AhR pathway; senomorphic/clock-modulatory activity reported in aged cell models.
Curcuminoids	Curcumin	Inhibits IL-23/Th17 axis, downregulates IL-6/IL-17/IL-23, upregulates IL-10; supports intestinal tight-junction protein expression.
Citrus polymethoxyflavones	Nobiletin, tangeretin	RORα/γ agonism inducing BMAL1 expression and increased PER2 amplitude in cultured cells — direct clock-gene modulation

5. A PROPOSED MECHANISTIC MODEL: CIRCADIAN PHYTONUTRITION AND IMMUNOMETABOLIC REMODELLING IN AITD

No prior published work has given polyphenols contained in botanical extracts under a circadian-timed schedule for the purpose of manipulating the Th17/Treg immunometabolic system of the patient with AITD, or even if time rather than the content

itself affects the immunomodulatory activity of the compounds. The hypothesis proposed below in Table 2, therefore, is explicitly a combination of three separate fields, namely circadian biology of the thyroid (Section 2), AITD immunometabolism (Section 3), and polyphenols (Section 4).

Table 2. Proposed mechanistic model linking circadian-timed polyphenol-rich botanical extracts to immunometabolic remodelling in autoimmune thyroid disorders. Every linkage is a hypothesis synthesised from indirect, adjacent-context evidence; none has been tested directly in this combination.

Step	Proposed mechanistic link	Supporting (indirect) evidence
1	Circadian-timed dosing (aligned to endogenous BMAL1/PER2 and melatonin rhythms) maximises polyphenol engagement with clock-gene transcriptional machinery	Demonstrated RORα/γ-mediated BMAL1 induction by citrus flavonoids; documented loss of thyroid BMAL1/PER2 rhythmicity in AIT tissue
2	Restored clock-gene rhythmicity in thyroid and immune tissue re-establishes normal diurnal patterning of Treg number/function	Treg numbers and suppressive function follow a circadian rhythm; melatonin acts via MT1 on Th17/Treg cells to favour a tolerogenic phenotype
3	Polyphenol cargo (EGCG, curcumin, resveratrol) directly suppresses STAT3/RORγt-driven Th17 differentiation and IL-17/IL-6/IL-23 output	Direct Th17-suppressive, Foxp3-inductive activity demonstrated for EGCG, curcumin, and resveratrol across multiple autoimmune disease models
4	Reduced Th17/Treg ratio lowers GITRL and pro-inflammatory cytokine signalling implicated in thyrocyte destruction	GITRL positively correlates with Th17 expansion and autoantibody titres in Hashimoto's thyroiditis; Th17/Treg ratio correlates with AITD severity
5	Metabolic reprogramming of Th17 cells away from glycolytic, anabolic dominance toward a more oxidative, Treg-favouring profile is reinforced by both circadian alignment and polyphenol immunometabolic activity	Th17/Treg subsets are governed by distinct glycolytic versus oxidative metabolic programs in AITD; polyphenols documented as immunometabolic modulators in chronic disease

The primary, hypothesis-driven proposition inherent in the model – and what differentiates "circadian phytonutrition" from merely "administering polyphenols to AITD patients" – is step 1: the notion that timing of administration, synchronized with the known disruptions of the BMAL1/PER2 and melatonin rhythms in AIT tissue, significantly alters downstream immunometabolic function compared to the same dose of polyphenols delivered regardless of timing. As far as it can tell, this has never been tested; the chrononutrition literature covered in Section 2.3 makes clear that timing can itself exert metabolic effects separate from content, and the polyphenol clock gene literature surveyed in Section 4.1 shows that these compounds have been demonstrated to interact directly with circadian genes, but no work has ever examined both factors together in any disease model, including AITD.

6. TRANSLATIONAL ROADMAP: FROM HYPOTHESIS TO EVIDENCE

The testing of the hypothesis outlined in Section 5 needs a phased program of research which deals with the timing variable directly and not with polyphenol concentration alone; none of the following has been conducted so far.

6.1 Phase 1 — In vitro chronopharmacology

The basic experiment this hypothesis calls for, one that currently does not exist at all, is one involving the comparison of different time of day dosing: testing the effect of an equal amount of a well-known botanical extract, such as a

curcumin/EGCG/resveratrol mixture (considering the literature cited in section 4), on synchronised primary human PBMCs or thyrocyte cultures at different circadian phases. The method of synchronisation must be known (for example, using dexamethasone shock). Additionally, it is necessary to test the Th17/Treg differentiation, the expression of RORγt/Foxp3, and cytokine secretion (IL-17, IL-6, IL-10), while at the same time measuring the expression of BMAL1/PER2/CRY genes via qPCR to check if the immunometabolic effect depends on the expression of clock genes.

6.2 Phase 2 — In vivo proof-of-concept

Since the EAT mouse model is the only model in this literature review with proof of a causal relationship between disrupted circadian rhythms and the progression of autoimmune thyroiditis [20], it is the ideal animal model that should be employed to prove this hypothesis. Using a factorial design where the EAT-induced mice are housed either normally or subjected to light shifts and then administered the candidate polyphenols on a circadian versus randomized basis, the variable of time can be independently isolated from that of substance. The key outcome measures in such a study would be the expression of BMAL1/PER2 in the thyroid, the Th17/Treg ratio, the serum levels of anti-thyroglobulin antibody, and the histopathology of the thyroid gland.

6.3 Phase 3 — Early-phase human pilot

In case Phases 1-2 would confirm the hypothesis, an early phase feasibility study in patients with early, mild autoimmune thyroid disease (AITD, positive thyroid autoantibodies with preserved or slightly reduced functional capacity instead of established hypothyroidism) could examine the effect of a standardised polyphenols-containing botanical extract, taken at an appropriate circadian time versus non-circadian time versus placebo over a sufficiently long time (8-12 weeks, according to the duration of interventions with immunomodulatory effect observed in this literature), to be able to see the changes in the Th17/Treg and clock-gene markers (minimum). Considering the early stage of the hypothesis in question, it would propose that the primary endpoint would involve mechanistic and biomarker endpoints (Th17/Treg ratio in the peripheral blood, melatonin rhythm in the serum, thyroid antibody titer), while thyroid function progression would serve as the secondary endpoint, as proposed in relation to the two other circadian-mechanistic hypotheses in this review.

7. CHALLENGES AND LIMITATIONS

The hypothesis is based on connecting three different literatures that are each individually logical but which have never been tested in concert with one another, and several limitations arise precisely from this fact. Virtually all of the direct evidence that EGCG, curcumin, and resveratrol suppress Th17/Treg cells exists in non-AITD models of autoimmunity – arthritis, multiple sclerosis, immune thrombocytopenic purpura, inflammatory bowel disease – and extrapolation of this data to thyroid autoimmunity, although biologically sound based on the shared mechanisms of Th17/Treg cells, is precisely that – an extrapolation, not proven equivalence. The literature regarding polyphenols and clock genes is itself methodologically diverse, often relies on supraphysiological concentrations in some studies (especially resveratrol, due to poor native bioavailability) and has been performed almost entirely in non-thyroid and non-immune cell types, such that the specific suggestion that these compounds interact with clock genes in thyroid or immune cells has not yet been tested. The key evidence supporting a disrupted circadian rhythm contributing to AIT severity comes from a single study, although a combination of human and animal causal data, unique to this particular field of research, makes this study very strong. The chrononutrition literature is sufficiently advanced in terms of its relevance to weight/fat mass outcomes; however, it should be emphasized that in relation to the biological processes of melatonin and cortisol production, the literature is quite limited, and in fact, the majority of the existing research on TRE does not include measurements of melatonin levels at all. Moreover, bioavailability is not a theoretical but a very real issue. Indeed, several of the polyphenols with well-established mechanisms of action (notably resveratrol and curcumin) have notoriously poor bioavailability properties and thus require solutions to this problem.

8. CONCLUSION

The three distinct but individually credible literatures, those pertaining to circadian rhythm alterations in thyroid autoimmunity, Th17/Treg reprogramming in AITD, and polyphenolic regulation of both clock gene expression and Th17/Treg ratio in autoimmune disease states, all come together to form an entirely new and as-of-yet unstated hypothesis: that the scheduling of polyphenol-based botanical extract administration is important in modulating Th17/Treg immunometabolism in autoimmune thyroid disease. As it have attempted to make clear through the course of this essay, it are presenting an entirely new hypothesis based on existing literature, but the one unique aspect of the hypothesis that has never been tested in any model, including that

of autoimmune thyroid disease, is whether or not the timing of administration itself alters immunomodulation. Testing it will involve carrying out the staged programme of in vitro chronopharmacology, animal, and human testing set forth in section 6, starting with the relatively straightforward, currently non-existent experiment of dosing with polyphenols at specific times of day to synchronized cultures of immune cells. Considering the presence of circadian disruption in the tissue of origin for the proposed intervention, which is the thyroid gland in the case of autoimmune thyroiditis, it feel that the matching of its circadian system, rather than disregarding it, seems a mechanistic possibility worth testing.

Data Availability Statement

This is a narrative/mechanistic review paper, and no new experimental data were collected or analysed. All references synthesized have been listed in the reference section.

REFERENCES

[1] Sulaimani, N., Houghton, M. J., Bonham, M. P., & Williamson, G. (2024). Effects of (Poly) Phenols on Circadian Clock Gene–Mediated Metabolic Homeostasis in Cultured Mammalian Cells: A Scoping Review. *Advances in Nutrition*, *15*(6), 100232.

[2] Roozbahani, Z. A., & Ghafari, A. O. (2014). Poly Phenol & flavanoid Contents of Lime Juice. International Academic Journal of Innovative Research, 1(2), 29–37.

[3] Özata Uyar, G., Yıldıran, H., Teker-Düztaş, D., Dalgic, B., Karakaş, N. M., Çamurdan, M. O., ... & Ezgü, F. S. (2024). Association between CLOCK gene polymorphisms with circadian rhythm, chrononutrition, dietary intake, and metabolic parameters in adolescents. *Frontiers in Public Health*, *12*, 1435460.

[4] Ziwei, M., Han, L. L., & Hua, Z. L. (2023). Herbal Blends: Uncovering Their Therapeutic Potential for Modern Medicine. Clinical Journal for Medicine, Health and Pharmacy, 1(1), 32-47.

[5] Delgadillo, F., & Agrawal, D. K. (2026). Immunopathogenesis, Diagnosis, and Treatment of Hashimoto's Thyroiditis. *Archives of Internal Medicine Research*, *9*, 01-13.

[6] Madhanraj. (2025). Development and Nutritional Evaluation of Functional Food Products Fortified with Bioactive Compounds for Combating Micronutrient Deficiencies. *National Journal of Food Security and Nutritional Innovation*, *3*(2), 9-17.

[7] Liu, Y., Tang, X., Tian, J., Zhu, C., Peng, H., Rui, K., ... & Wang, S. (2014). Th17/Treg cells imbalance and GITRL profile in patients with Hashimoto's thyroiditis. *International journal of molecular sciences*, *15*(12), 21674-21686.

[8] M. Kavitha. (2024). Integrative Metabolomic and Transcriptomic Profiling of Leaf Senescence in Horticultural Crops. *National Journal of Plant Sciences and Smart Horticulture*, *2*(2), 26-33.

[9] Rai, H. T., & Mu, G. W. (2025). Metagenomic Profiling of Soil Microbiota: Implications for Sustainable Agriculture. *Frontiers in Life Sciences Research*, 1-7.

[10] Li, C., Yuan, J., Zhu, Y. F., Yang, X. J., Wang, Q., Xu, J., ... & Zhang, J. A. (2016). Imbalance of Th17/Treg in different subtypes of autoimmune thyroid diseases. *Cellular Physiology and Biochemistry*, *40*(1-2), 245-252.

[11] Zake, T., Kalere, I., Upmale-Engela, S., Svirskis, S., Gersone, G., Skesters, A., ... & Konrade, I. (2021). Plasma levels of Th17-associated cytokines and selenium status in autoimmune thyroid diseases. *Immunity, inflammation and disease*, *9*(3), 792-803.

[12] Williams, J., Melén, A. G., & Barrow, M. (2025). The role of the T helper 17 and T regulatory cell ratio in the gut-thyroid axis. *Clinical Immunology Communications*, *8*, 10-25.

[13] Shao, S., Yu, X., & Shen, L. (2018). Autoimmune thyroid diseases and Th17/Treg lymphocytes. *Life sciences*, *192*, 160-165.

[14] Bitw, A. (2026). Reproductive Biotechnology Approaches for Enhancing Livestock Productivity and Breeding Efficiency. *National Journal of Animal Health and Sustainable Livestock*, 46-56.

[15] Moon, S., Kang, J., Kim, S. H., Chung, H. S., Kim, Y. J., Yu, J. M., ... & Kim, T. (2020). Beneficial effects of time-restricted eating on metabolic diseases: a systemic review and meta-analysis. *Nutrients*, *12*(5), 1267.

[16] Bitw, A. (2026). Reproductive Biotechnology Approaches for Enhancing Livestock Productivity and Breeding Efficiency. *National Journal of Animal Health and Sustainable Livestock*, 46-56.

[17] Adafer, R., Messaadi, W., Meddahi, M., Patey, A., Haderbache, A., Bayen, S., & Messaadi, N. (2020). Food timing, circadian rhythm and chrononutrition: a systematic review of time-restricted eating's effects on human health. *Nutrients*, *12*(12), 3770.

[18] Bhatia, M., & Ramesh Iyer, R. (2025). Immunological Responses to Viral Infections. In Medxplore: Frontiers in Medical Science (pp. 52-70). Periodic Series in Multidisciplinary Studies.

[19] Cid, F., Rivera, A., & Uribe, J. (2026). Integrating Machine Learning, Remote Sensing, and Water Quality Indicators for Real-Time Prediction of Harmful Algal Blooms in Recreational Lake Ecosystems. *Bridge: Journal of Multidisciplinary Explorations*, *2*(2), 40-47.

[20] Guo, N. H., Fu, X., Zi, F. M., Song, Y., Wang, S., & Cheng, J. (2019). The potential therapeutic benefit of resveratrol on Th17/Treg imbalance in immune thrombocytopenic purpura. *International Immunopharmacology*, *73*, 181-192.

[21] Armstrong, D., & Tanaka, Y. (2025). Boosting Telemedicine Healthcare Assessment Using Internet of Things and Artificial Intelligence for Transforming Alzheimer's Detection. *Global Journal of Medical Terminology Research and Informatics*, *3*(1), 8-14.

[22] Sedhupathy, P. (2026). Scalable Parallel Graph-Based Algorithms for Complex Network Simulations. *Frontiers in Computational Science and Engineering*, 11-19.

[23] Vimalkumar T. (2026). A Unified Analytical and Computational Approach for Stability Analysis in Complex Networked Systems. *Frontiers in Mathematical and Computational Research*, 35-44.

[24] A. Suresh kumar. (2025). Structure–Microbe Interaction Mechanisms in Hierarchically Porous Carbon Platforms Derived from Biomass. *Bridge: Journal of Multidisciplinary Explorations* , *2*(2), 26-32.

[25] Jeeva, K. (2026). Biofloc-Assisted Intelligent Aquaculture System Using Wireless Sensor Networks and Predictive Analytics. *National Journal of Smart Fisheries and Aquaculture Innovation*, 30-43.

[26] Bitw, A. (2026). Multi-Sensor Edge Computing Framework for Precision Shrimp Aquaculture with Real-Time Water Quality and Biomass Monitoring. *National Journal of Smart Fisheries and Aquaculture Innovation*, 68-78.

[27] Venkatesh, C. K. (2026). Deep Learning-Based Plant Disease Detection and Prediction Model for Smart Agricultural Applications. *National Journal of Smart Agriculture and Rural Innovation*, 22-28.

[28] Priya, C. (2026). Forest Resource Sustainability and Vegetation Dynamics Analysis Using Remote Sensing and GIS Techniques. *National Journal of Forest Sustainability and Climate Change*, 29-40.

[29] Vignesh, V. (2026). Integration of Computer Vision and Soil Sensor Analytics for Precision Fertigation in Smart Horticulture. *National Journal of Plant Sciences and Smart Horticulture*, 21-28.

[30] Jeeva, K. (2026). Evaluation of School Feeding Programs and Their Impact on Nutritional Status among Primary School Children. *National Journal of Food Security and Nutritional Innovation*, *4*(2), 36-44.

[31] Kavitha, M. (2026). AI-Driven Communication and Monitoring Framework for Extraterrestrial Microbial Containment Using Cellular Automata Simulation. *Journal of Intelligent Assistive Communication Technologies*, 1-8.