Volume 3, No. 3 March 2024 (634-647)
p-ISSN 2980-4868 | e-ISSN 2980-4841
https://ajesh.ph/index.php/gp

Preliminary Study on Total Glucoside of Peony (TGP) Administration in Organ-Specific Autoimmune Diseases at Prof. dr. R. D. Kandou Hospital, Indonesia

Nancy Cecilia Mongdong[1*], Eulis Alwi Datau[2], Eko Edi Surachmanto[3], Juwita Soekarno[4], Dennis Thezar[5]
[1,2,3,4,5]Rumah Sakit Umum Pusat Prof. dr. R.D. Kandou, Manado, Sulawesi Utara, Indonesia.
Email: eulisdatau@gmail.com, subscribe.dthez@gmail.com

ABSTRACT
Autoimmune diseases are a diverse group of conditions characterized by immune disturbances that cause aberrant B cell and T cell reactivity to normal constituents of the host. These diseases can involve essentially any organ system and affect individuals of any age, with a much greater prevalence among women. Although certain mechanisms unite these conditions into a single category, the clinical manifestations of autoimmune disease are highly varied. This research is an original and interventional study. It is a preliminary with analytic observational. The design is "the one group pre-test – post-test design". This study was conducted at RSUP Prof. dr. R. D. Kandou over a six-month period from July 2016 to December 2016. The study included patients diagnosed with Graves' disease, Hashimoto's disease, and aplastic anemia, who were diagnosed based on their medical history, physical examination, and diagnostic workups. This study also aimed to evaluate the improvement in clinical symptoms within the Aplastic Anemia group, tracking the number of complaints reported each week. Four patients were included in the study, each receiving individualized basic therapy.
Keywords: Autoimmune Diseases, Total Glucoside of Peony, Clinical, Laboratory Observations.

INTRODUCTION

Autoimmune diseases are a diverse group of conditions characterized by immune disturbances that cause aberrant B cell and T cell reactivity to normal constituents of the host (Bieber et al., 2023; Zhang et al., 2022). These diseases can involve essentially any organ system and affect individuals of any age, with a much greater prevalence among women. Although certain mechanisms unite these conditions into a single category, the clinical manifestations of autoimmune disease are highly varied (Pisetsky, 2023).

Genetic and environmental factors are thought to be the major factors contributing to the development of autoimmunity (Antonelli et al., 2020; Miller, 2023). There are several

environmental factors such as pathogens (viral, bacterial, etc.), toxic chemicals, and dietary influences. When autoimmunity is induced by an inciting event, the autoreactivity is generally self-limited (Couser & Johnson, 2014; Stern et al., 2024). When such autoimmunity does persist, however, pathology may or may not result. However, persistent autoimmunity can lead to pathological consequences, although determining the cause of tissue damage due to the autoreactivity presents diagnostic challenges (Basu et al., 2020). Autoimmune diseases affect approximately one in ten individuals, and their burden continues to increase over time at varying rates across individual diseases (Cooper & Stroehla, 2003; Hayter & Cook, 2012).

Autoimmune disorders often present with a diverse array of autoantibodies, some of which may exert pathogenic effects while others serve diagnostic purposes without clear pathogenicity (Addison et al., 2023; Scherlinger et al., 2020). There are some examples of autoantibodies that have a clear pathogenic role in autoimmune disorders like Grave's disease, in which patients have thyrotropin receptor autoantibodies that induce the overproduction of the thyroid hormone leading to hyperthyroidism. Another example is myasthenia gravis, in which autoantibodies bind to the acetylcholine receptor on the muscle fiber membrane and block the neurotransmitter acetylcholine from the nerves to the muscle inducing muscle weakness and fatigue.

Central tolerance eliminates high-affinity autoantigen-reactive cells in primary lymphoid organs (Gao et al., 2021; Yu, 2019). Peripheral tolerance, in secondary lymphoid organs and tissues, controls escaped autoantigen-reactive cells through various means. Genetic and environmental factors can disrupt immune tolerance mechanisms, such as the function of regulatory T cells (Tregs), which may lead to autoimmunity. Tregs typically regulate immune responses by producing IL.

Autoimmune diseases can be roughly divided into organ-specific and systemic diseases, based both on the extent of their involvement and the type of autoantibodies present in the patients (Harsini & Rezaei, 2023; Karsdal et al., 2021; Lenti et al., 2022). In organ-specific autoimmune diseases, only specific cell types within an organ system are affected, such as thyroid gland cells in Graves' disease and Hashimoto's disease. Aplastic anemia, a rare example of autoimmune cytopenia which is a subset of organ-specific autoimmune diseases, is a T-cell mediated autoimmune disorder targeting hematopoietic progenitors, resulting in bone marrow failure.

Autoimmune diseases are generally treated with drugs with broadly acting, non-disease specific, and, consequently, associated with side effects such as infection and malignant disease (Montaño et al., 2021). Total glycosides of peony (TGP) from Paeonia lactiflora Pallas, recognized as a Chinese herb, have shown promise in treating autoimmune disorders. TGP/paeoniflorin demonstrates anti-inflammatory properties, reducing prostaglandins, leukotrienes, and proinflammatory cytokines (Mehta et al., 2023). Unlike conventional drugs, TGP rebalances the immune system without serious side effects. The aim of this study is to

explore TGP's efficacy and side effects as a complement therapy to low-dose basic therapy for organic autoimmune diseases (Montaño et al., 2021).

RESEARCH METHODS

This research is an original and interventional study. It is a preliminary with analytic observational (Del Borrello et al., 2021). The design is "the one group pre-test – post-test design". This study was conducted at RSUP Prof. dr. R. D. Kandou over a six-month period from July 2016 to December 2016. The study included patients diagnosed with Graves' disease, Hashimoto's disease, and aplastic anemia, who were diagnosed based on their medical history, physical examination, and diagnostic workups. There were 4 patients with aplastic anemia, 3 with Graves' disease, and 2 with Hashimoto's disease, all of whom were observed for 8 weeks after receiving TGP.

For clinical observations, Wayne's score is employed to evaluate the improvement of Graves' disease patients, while Zulewski's score is utilized for patients with Hashimoto's disease. In assessing laboratory improvements, pre-test and post-test evaluations of anti-TPO, TSHS, and FT4 levels are conducted for patients with Hashimoto's and Graves' diseases. Additionally, pre-test and post-test examinations of Hb, WBC, platelets, AST, ALT, CRP, and ESR are performed to evaluate laboratory improvements in patients with Hashimoto's disease, Graves' disease, and aplastic anemia.

Data analysis was performed using IBM SPSS statistics version. Univariable analysis was employed to examine frequencies, means, and standard deviations. Bivariate analysis, involving two variables, was conducted to assess the pre- and post-administration effects of TGP and baseline therapy. Paired t-tests were employed for normally distributed data, while Wilcoxon rank-sum tests were utilized for non-normally distributed data concerning TGP and low-dose baseline therapy. Statistical significance was considered when a p-value was < 0.05.

RESULTS AND DISCUSSION

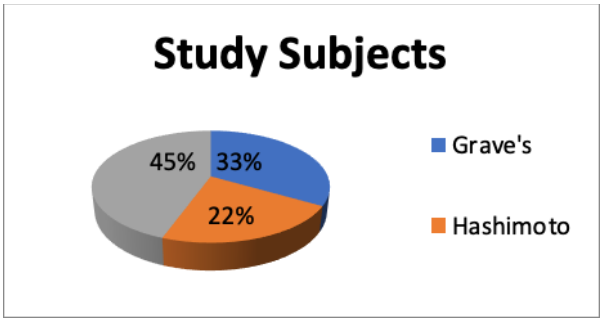

Figure 1. Percentage distribution of study subjects

In Figure 1, the disease distribution among 9 subjects consists of 4 cases (45%) of aplastic anemia, 3 cases (33%) of Graves' disease, and 2 cases (22%) of Hashimoto's disease.

Table 1. Base characteristics of Study Subjects (Graves, Hashimoto, and Aplastic Anemia)

Variable	N	Mean	Median	SD	Min	Max
Age	9	48,11	45	14,26	30	65
CRP	9	45,33	24	40,15	0	96
ESR	9	45,44	40	30,03	20	120
Creatinine	9	0,76	0,80	0,19	0,40	1,10
eGFR	9	96,54	101,8	19,7	54,9	117,2
AST	9	33,22	25	16,51	19	68
ALT	9	30,89	30	9,14	19	46

The subjects' ages ranged from 30 to 65 years, with an average of 48.11 years and a median of 45 years. CRP levels ranged from 0 mg/dl to 96 mg/dl, with an average of 45.33 mg/dl and a median of 24 mg/dl among the 9 subjects. ESR values varied from 20 mm/hr to 120 mm/hr, with an average of 45.44 mm/hr and a median of 40 mm/hr. Creatinine levels ranged from 0.40 mmol/l to 1.10 mmol/l, with an average of 0.76 mmol/l and a median of 0.80 mmol/l. The eGFR values ranged from 54.9 ml/min/1.73m² to 117.2 ml/min/1.73m², with an average of 96.54 ml/min/1.73m² and a median of 101.8 ml/min/1.73m². AST levels varied from 19 IU/L to 68 IU/L, with an average of 33.22 IU/L and a median of 25.0 IU/L among the 9 subjects. ALT levels ranged from 19 IU/L to 46 IU/L, with an average of 30.89 IU/L and a median of 30.0 IU/L.

Table 2. Changes in the mean Wayne's score on Graves' patients.

Variable	N	Mean	SD	p- value
Wk0	3	28.33	6.50	
Wk2	3	18.66	3.21	
Wk4	3	15.33	2.51	
Wk6	3	11.00	2.00	
Wk8	3	7.66	0.57	
Wk0-Wk2	3	9.66	3.78	0.024
Wk0-Wk4	3	13.00	6.08	0.033
Wk0-Wk6	3	17.33	5.85	0.018
Wk0-Wk8	3	20.66	6.50	0.015

Wk0: week before treatment, Wk2: second week of treatment, Wk4: fourth week of treatment, Wk6: sixth week of treatment, Wk8: eighth week of treatment

Based on the analysis of three cases of Graves' disease (Table 2), Wayne's score at week 0 averaged 28.33 with a standard deviation (SD) of 6.50. By the second week, the mean decreased to 18.66 (SD: 3.21), further dropping to 15.33 (SD: 2.51) by the fourth week, and to 11.00 (SD: 2.00) by the sixth week. At week 8, the mean reached 7.66 with an SD of 0.57. Between weeks 0 and 2, a significant decrease of 9.66 points in the mean was observed (SD: 0.72, p-value: 0.024), followed by a similar reduction (9.66 points) between weeks 0 and 2 with a different SD (3.78, p-value: 0.024). Further significant reductions in the mean were observed between weeks 0-4 (13.00 points, SD: 6.08, p-value: 0.033), weeks 0-6 (17.33 points, SD: 5.85, p-value: 0.018), and weeks 0-8 (20.66 points, SD: 6.50, p-value: 0.015).

Table 3. Change in the mean Zulewski's score on Hashimoto's patients.

Variable	N	Mean	SD	p- value
W0	2	9.500	0.70	
W2	2	8.500	0.70	
W4	2	6.00	1.41	
W6	2	3.500	0.70	
W8	2	2.00	0.00	
W0-W4	2	3.500	0.70	0.045
W0-W8	2	7.500	0.70	0.021

Wk0: week before treatment, Wk2: second week of treatment, Wk4: fourth week of treatment, Wk6: sixth week of treatment, Wk8: eighth week of treatment

Zulewski's score (Table 3) for two Hashimoto's patients was analyzed. At week 0, the average score was 9.5 with a standard deviation (SD) of 0.70. By the second week, the mean decreased to 8.5 (SD: 0.70), further dropping to 6 (SD: 1.41) by the fourth week, and to 3.5 (SD: 0.70) by the sixth week. At week 8, the mean reached 2.00 with an SD of 0.00. A significant decrease of 3.5 points in the mean was observed between weeks 0 and 5 (SD: 0.70, p-value: 0.045). Further significant reductions in the mean were observed between weeks 0-8 (7.5 points, SD: 0.70, p-value: 0.021).

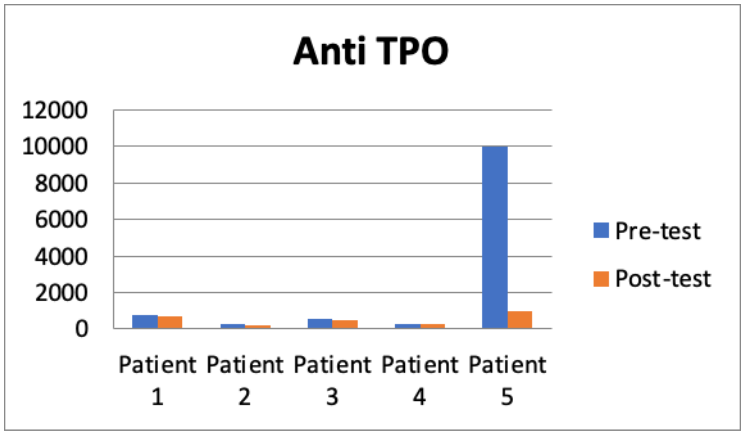

Figure 2. Comparison of mean Anti TPO on patient with autoimmune thyroiditis pre-post-test

To ascertain the variance in mean anti-TPO levels between Graves' and Hashimoto's disease groups before and after treatment, paired t-tests were employed. In Figure 2, a decrease in anti-TPO levels is observed in 4 out of 5 autoimmune thyroiditis patients, notably in patient 5, who exhibited a substantial reduction from pre-treatment to post-treatment. However, statistically, the mean difference was not significant (p=0.36)

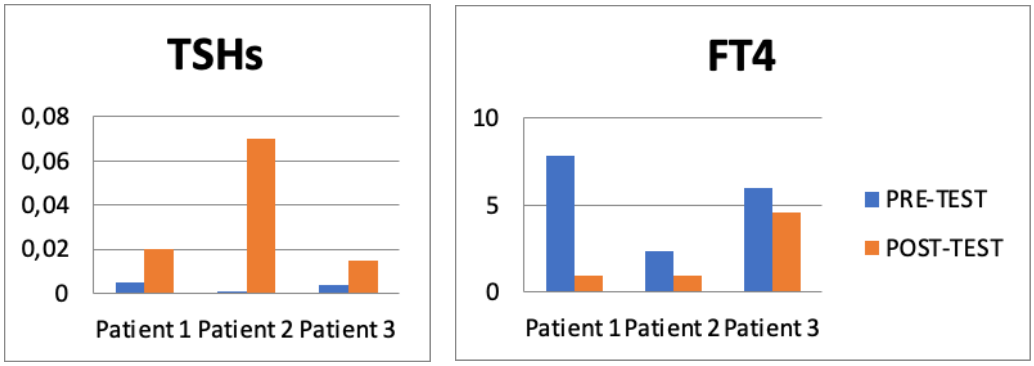

Figure 3. Comparison of TSHS and FT4 between pre-test and post-test in Graves' patients

Paired t-tests were utilized to evaluate the changes in mean TSHS and FT4 levels within the Graves' disease group before and after treatment. As illustrated in Figure 3, a noticeable decrease in TSHS and an increase in FT4 levels are observed post-treatment, although statistically insignificant (TSHS: p=0.23; FT4: p=0.21) across all Graves' patients.

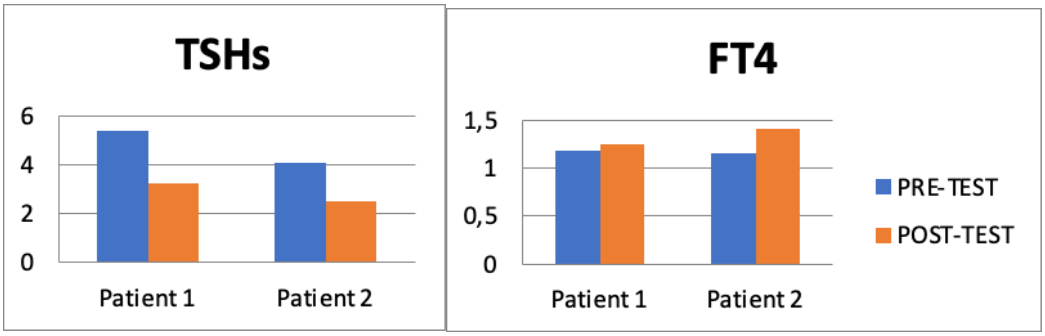

Figure 3. Comparison of TSHS and FT4 between pre-test and post-test in Graves' patients

Paired t-tests were utilized to evaluate the changes in mean TSHS and FT4 levels within the Graves' disease group before and after treatment. As illustrated in Figure 3, a noticeable decrease in TSHS and an increase in FT4 levels are observed post-treatment, although statistically insignificant (TSHS: p=0.23; FT4: p=0.21) across all Graves' patients.

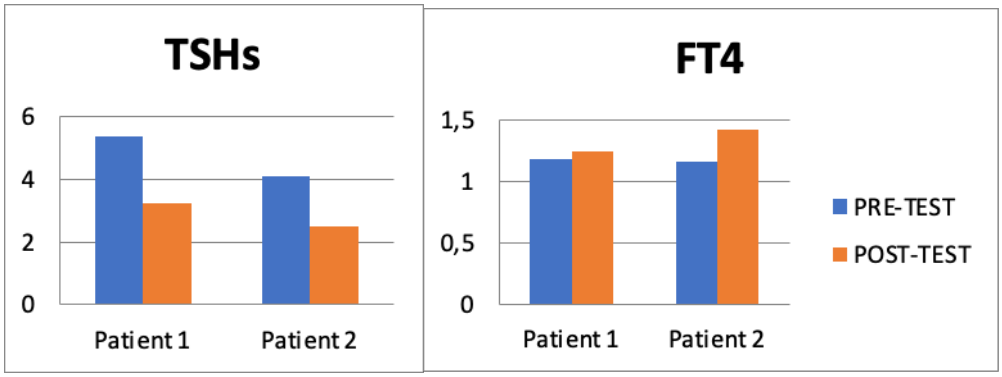

Figure 4. Comparison of TSHS and FT4 between pre-test and post-test in Hashimoto patients

The same results were also observed in Hashimoto's disease, as seen in Figure 4. A decrease in TSHS levels and an increase in FT4 levels occurred, although statistically insignificant (TSHS: p=0.94; FT4: p=0.33).

Table 4. Aplastic anemia patients with clinical symptoms

No	Sign and symptoms	W0	W1	W2	W3	W4	W5	W6	W7	W8
1	Bleeding	2	1	1	0	0	0	1	1	0
2	Dizziness	4	2	2	2	1	2	2	2	2
3	Palpitation	4	2	0	0	0	0	0	0	0
4	Fever	2	2	2	1	0	2	1	2	1
5	Weakness	4	4	3	3	2	1	1	2	2
6	Low appetite	4	4	2	2	1	1	1	2	1
7	Paleness	4	4	4	4	3	3	4	4	3
8	Shortness of breath	4	3	2	2	1	1	0	0	0
9	Blurred vision	0	0	0	0	0	0	0	0	0
10	Tinnitus	0	0	0	0	0	0	0	0	0
Total		28	22	16	14	8	10	10	13	9

Wk0: week before treatment, Wk1: first week of treatment, Wk2: second week of treatment, Wk3: third week of treatment, Wk4: fourth week of treatment, Wk5: fifth week of treatment, Wk6: sixth week of treatment, Wk7: seventh week of treatment, Wk8: eighth week of treatment

The group of aplastic anemia comprised of 4 individuals. Clinical symptoms were assessed based on the number of complaints reported by all patients each week from pre-treatment (pre-test) to post-treatment, which was in the 8th week. From the table 4, it can be observed that there was clinical improvement in this aplastic anemia group, where the number of complaints decreased from 28 before treatment to 9 by the 8th week, despite a slight increase from week 6 to week 7 (the number of complaints increased from 10 to 13). In the week before treatment, there were 28 complaints including bleeding, dizziness, palpitations, fever, weakness, decreased appetite, paleness, and shortness of breath. Almost all patients experienced these complaints in the pre-treatment week. In the last week (post-test), the number of complaints decreased significantly to 9, including dizziness, fever, weakness, decreased appetite, and paleness.

Table 5. Comparison of mean Hb, WBC, and platelet pre-post test in patients with Aplastic Anemia

Variable	Test	N	Mean	SD	p-value
Hb	Pre-test	4	6.3750	2.13	0.362
	Post-test	4	7.4250	4.00	

	Pre-post-test	4	-1.05000	5.42	
WBC	Pre-test	4	2299.00	638.96	0.015
	Post-test	4	4210.00	1299.89	
	Pre-post-test	4	-1911.00	975.62	
Platelet	Pre-test	4	15500.00	8226.4	0.033
	Post-test	4	50000.00	51762	
	Pre-post-test	4	-34500.00	49990	

To evaluate the difference in mean levels of HB and leukocytes in the aplastic anemia group before and after treatment, paired t-tests were employed, while the Wilcoxon test was utilized for mean platelet levels. The statistical analysis revealed a statistically insignificant increase in HB levels (p=0.36). However, significant increases were observed in WBC and platelet levels among aplastic anemia patients, with p-values of 0.015 for leukocytes and 0.033 for platelets. Table 5 displays the alterations in HB, WBC, and platelet levels in aplastic anemia patients.

Tabel 6. Comparison of mean CRP and ESR pre-post-test in patients with Graves, Hashimoto, and Aplastic Anemia

Variable	Test	N	Mean	Median	SD	p-value
CRP	Pre-test	9	45,33	24	40,15	0,011
	Post-test	9	12,00	0	16,97	
ESR	Pre-test	9	45,44	40	30,03	0.007
	Post-test	9	24,22	20	13,85	

The Wilcoxon test was utilized to assess the disparity in mean levels of CRP and ESR among all autoimmune patients before and after treatment. This statistical examination revealed a notably significant decrease in CRP (p=0.011) and ESR (p=0.007) levels.

Table 7. Comparison of mean WBC, Hb, platelet, AST, ALT pre-post test in patients with Graves, Hashimoto, and Aplastic Anemia

Variable	Test	N	Mean	SD	p-value
WBC	Pre-test	9	5932.8	3608.9	0.261
	Post-test	9	6691.1	2647.2	
	Pre-post-test	9	1758.2	836.8	
Hb	Pre-test	9	10.18	4.14	0.842
	Post-test	9	10.43	3.88	

	Pre-post-test	9	2.6	2.22	
Platelet	Pre-test	9	161444	143535	0.028
	Post-test	9	228000	177499	
	Pre-post-test	9	71888	68341	
AST	Pre-test	9	33.22	16.51	0.500
	Post-test	9	29.56	22.67	
	Pre-post-test	9	10.11	11.92	
ALT	Pre-test	9	30.89	9.14	0.603
	Post-test	9	27.67	15.36	
	Pre-post-test	9	12.78	12.09	

To investigate the potential adverse effects on blood components (HB, WBC, and platelets) and liver function (AST and ALT), paired t-tests were employed for pre-posttest means of WBC, platelet, and ALT levels, while the Wilcoxon test was utilized for pre-posttest means of HB and AST levels. Table 7 indicates that WBC levels exhibited an insignificant decrease after treatment (p=0.261), whereas platelet levels showed a significant increase (p=0.028). Notably, the significant change in platelet levels may be attributed solely to the aplastic anemia group. Furthermore, there was a non-significant decrease in AST levels (p=0.500), ALT levels (p=0.603), and HB levels before and after treatment (p=0.842).

Adverse effects of TGP

During the initial week, three cases reported nausea, which diminished in the second week and completely subsided by the third week. Notably, no side effects, including vomiting, abdominal pain, diarrhea, respiratory tract infections, urinary tract infections, or skin infections, were observed from Week 0 to Week 8.

Total glucoside of peony (TGP) is recognized for its multi-component, multi-target, and multi-pathway effects. in which important targets such as IL-6 and eGFR have been proven to be closely related to autoimmune thyroiditis (AIT). TGP may mainly play a role in the treatment of AIT through the MAPK signaling pathway, PI3K-Akt signaling pathway, and is related to the IL-6 and EGFR, which have been shown to be related to AIT. There is a study by Su J., et. al in 2023 which used a network pharmacology approach to investigate the possible mechanism of action of TGP in the treatment of AIT, which may offer a theoretical reference for further research.

In the investigation of Graves' Disease, our research elucidated a discernible amelioration of clinical symptoms. Employing the Wayne score for symptom quantification, a statistically significant improvement was documented from the second week of treatment (p=0.024) until

the eighth week (p=-0.015). The conventional therapeutic intervention involved PTU 100 mg thrice daily and propranolol 10 mg twice daily. Previous literature has emphasized the enduring challenge associated with achieving remission from Graves' disease, commonly reported at rates ranging from 30% to 40%. Within our study, a notable alleviation of clinical symptoms manifested within the initial two weeks of treatment, concomitant with the administration of TGP.

A study conducted by Wu LP et al. (2023) on mice, aimed at investigating the protective effect and immunoregulatory mechanism of TGP against Graves' Disease, reveals a significant protective effect. The mechanism appears to be associated with alterations in regulatory T cell function and the restoration of Th1/Th2 cytokine balance.

Clinical improvement in Hashimoto's disease was observed from the fourth week of treatment until the end of the study (p=0.045). The conventional therapeutic intervention involved levothyroxine 50 mg once daily. Hashimoto's thyroiditis exhibits diverse clinical presentations, with patients presenting either as hypothyroid or euthyroid. Approximately 20% of patients initially present with mild hypothyroid symptoms, with the severity escalating in correlation with the degree of thyroid gland damage.

Research on traditional Chinese medicine has explored a concoction containing Paeonia Alba Radix, primarily composed of TGP, commonly used to treat the hypothyroidism stage of autoimmune thyroiditis. This concoction has been found to decrease the expression levels of thyroid peroxidase antibody (TPOAb), thyroid microsomal autoantibody (TMAb), and thyroglobulin antibody (TGAb), thereby improving thyroid cell damage. Regrettably, there is currently no published research focusing on the use of TGP alone in patients with Hashimoto's disease.

This study revealed non-statistically significant changes in anti-TPO levels, TSHs, and FT4 in both Graves' and Hashimoto's groups (p=0.36). Graphically, a general decrease in anti-TPO levels was observed across all samples, though not substantial. Patient 5 demonstrated a significant decrease in anti-TPO from 10,000 to 999.52. TSHs showed a non-significant increase in Graves' (p=0.23) and a non-significant decrease in Hashimoto's (p=0.94). FT4 levels improved in both groups but were not statistically significant (p=0.21 for Graves' and p=0.33 for Hashimoto's).

The increase in anti-TPO and TSHs is characteristic of Hashimoto's, while anti-TPO is present in more than 80% of both Graves' and Hashimoto's cases. The study's discovery of reduced anti-TPO across autoimmune thyroid patients is promising. This is notable because, despite clear clinical remission and a decrease in thyroid size in conventional therapy for Graves' and Hashimoto's cases, anti-TPO levels still increase. Although, according to one reference, anti-TPO levels can decrease after approximately 50 months of treatment.

This study also aimed to evaluate the improvement in clinical symptoms within the Aplastic Anemia group, tracking the number of complaints reported each week. Four patients

were included in the study, each receiving individualized basic therapy. Patient 1 underwent transfusions of packed red cells (PRC) totaling 10 units, thrombocyte concentrate (TC) totaling 29 units, and oral methylprednisolone 16 mg three times a day for the final 2 weeks of the 2-month treatment. Patient 2 received PRC transfusions totaling 7 units, Patient 3 received transfusions of 10 units of PRC along with oral methylprednisolone 16 mg three times a day, and Patient 4 received PRC transfusions totaling 6 units and 1 unit of whole blood (WB).

The administration of conventional therapy showed some variability, reflecting individualized approaches based on symptoms and laboratory results. The fluctuating nature of complaints and conditions in this Aplastic Anemia group was observed week by week. However, an overall improvement in clinical symptoms became evident, with a significant reduction in complaints noted in the final week of treatment compared to the initial stages.

In this cohort, two patients received additional methylprednisolone therapy at a dose of 16 mg three times a day, while the other two did not. Notably, the available complaint data did not reveal any significant differences between those who received methylprednisolone and those who did not. At the study's conclusion, patients reported complaints irrespective of the use of methylprednisolone. As of now, there have been no other published research studies or case reports on the use of TGP in patients with autoimmune aplastic anemia.

CONCLUSION

Significant clinical improvement was observed across various subgroups during the 2-month TGP treatment. In the Graves' Disease subgroup, a notable 100% improvement in symptom presentation was evident in three cases, spanning from the 2nd week ($p=0.024$) to the 8th week ($p=0.015$). Similarly, the Hashimoto’s Disease subgroup exhibited noteworthy improvement, with a 100% presentation improvement in 2 cases as early as the 4th week ($p=0.045$) and continuing through the 8th week ($p=0.021$). Although clinical symptoms fluctuated in the aplastic anemia subgroup, by the 8th week, a significant improvement was evident, with the number of complaints decreasing from 28 to 9. Additionally, while there were non-statistically significant changes in anti-TPO levels and thyroid hormone levels in both Graves' and Hashimoto's subgroups, there was a significant reduction in CRP and ESR levels across all subgroups of Organic Autoimmune diseases. Moreover, there was a significant increase in WBC and platelet levels in the aplastic anemia subgroup. Importantly, no prominent or severe side effects necessitating discontinuation of TGP were found in any case, suggesting its overall safety profile.

BIBLIOGRAPHY

Addison, M. L., Ranasinghe, P., & Webb, D. J. (2023). Novel pharmacological approaches in the treatment of hypertension: a focus on RNA-based therapeutics. *Hypertension*, *80*(11), 2243–2254.

Antonelli, A., Ferrari, S. M., Ragusa, F., Elia, G., Paparo, S. R., Ruffilli, I., Patrizio, A., Giusti, C., Gonnella, D., & Cristaudo, A. (2020). Graves' disease: Epidemiology, genetic and environmental risk factors and viruses. *Best Practice & Research Clinical Endocrinology & Metabolism*, *34*(1), 101387.

Basu, S., Elkington, P., & Rao, N. A. (2020). Pathogenesis of ocular tuberculosis: new observations and future directions. *Tuberculosis*, *124*, 101961.

Bieber, K., Hundt, J. E., Yu, X., Ehlers, M., Petersen, F., Karsten, C. M., Köhl, J., Kridin, K., Kalies, K., & Kasprick, A. (2023). Autoimmune pre-disease. *Autoimmunity Reviews*, *22*(2), 103236.

Cooper, G. S., & Stroehla, B. C. (2003). The epidemiology of autoimmune diseases. *Autoimmunity Reviews*, *2*(3), 119–125.

Couser, W. G., & Johnson, R. J. (2014). The etiology of glomerulonephritis: roles of infection and autoimmunity. *Kidney International*, *86*(5), 905–914.

Del Borrello, G., Giraudo, I., Bondone, C., Denina, M., Garazzino, S., Linari, C., Mignone, F., Pruccoli, G., Scolfaro, C., & Spadea, M. (2021). SARS-COV-2–associated coagulopathy and thromboembolism prophylaxis in children: A single-center observational study. *Journal of Thrombosis and Haemostasis*, *19*(2), 522–530.

Gao, S., Liang, X., Wang, H., Bao, B., Zhang, K., Zhu, Y., & Shao, Q. (2021). Stem cell-like memory T cells: a perspective from the dark side. *Cellular Immunology*, *361*, 104273.

Harsini, S., & Rezaei, N. (2023). Autoimmune diseases. In *Clinical Immunology* (pp. 123–244). Elsevier.

Hayter, S. M., & Cook, M. C. (2012). Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. *Autoimmunity Reviews*, *11*(10), 754–765.

Karsdal, M. A., Kraus, V. B., Shevell, D., Bay-Jensen, A. C., Schattenberg, J., Surabattula, R. R., & Schuppan, D. (2021). Profiling and targeting connective tissue remodeling in autoimmunity-a novel paradigm for diagnosing and treating chronic diseases. *Autoimmunity Reviews*, *20*(1), 102706.

Lenti, M. V., Rossi, C. M., Melazzini, F., Gastaldi, M., Bugatti, S., Rotondi, M., Bianchi, P. I., Gentile, A., Chiovato, L., & Montecucco, C. (2022). Seronegative autoimmune diseases: A challenging diagnosis. *Autoimmunity Reviews*, *21*(9), 103143.

Mehta, J. M., Hiremath, S. C., Chilimba, C., Ghasemi, A., & Weaver, J. D. (2023). Translation of cell therapies to treat autoimmune disorders. *Advanced Drug Delivery Reviews*, 115161.

Miller, F. W. (2023). The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention. *Current Opinion in Immunology*, *80*, 102266.

Montaño, J., Garnica, J., & Santamaria, P. (2021). Immunomodulatory and immunoregulatory nanomedicines for autoimmunity. *Seminars in Immunology*, *56*, 101535.

Pisetsky, D. S. (2023). Pathogenesis of autoimmune disease. *Nature Reviews Nephrology*, *19*(8), 509–524.

Scherlinger, M., Mertz, P., Sagez, F., Meyer, A., Felten, R., Chatelus, E., Javier, R.-M., Sordet, C., Martin, T., & Korganow, A.-S. (2020). Worldwide trends in all-cause mortality of auto-immune systemic diseases between 2001 and 2014. *Autoimmunity Reviews*, *19*(6), 102531.

Stern, M. E., Theofilopoulos, A. N., Steven, P., Niederkorn, J. Y., Fox, R., Calonge, M., Scheid, C., & Pflugfelder, S. C. (2024). Immunologic basis for development of keratoconjunctivitis sicca in systemic autoimmune diseases: Role of innate immune sensors. *The Ocular Surface*.

Yu, F.-L. T. (2019). Neo-mercantilist policy and China's rise as a global power. *Contemporary Issues in International Political Economy*, 175–196.

Zhang, Y., Tian, J., Xiao, F., Zheng, L., Zhu, X., Wu, L., Zhao, C., Wang, S., Rui, K., & Zou, H. (2022). B cell-activating factor and its targeted therapy in autoimmune diseases. *Cytokine & Growth Factor Reviews*, *64*, 57–70.