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# Drug Interactions in Autoimmune Systemic Lupus Erythematosus (SLE)

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ABSTRACT

One of the factors that influence the success of therapy in autoimmune diseases such as SLE is the interaction of drugs with other active compounds. Several studies have stated that there are drug interactions with drugs or with other active compounds such as herbs which can support therapy or inhibit the effects of drug therapy. This review aims to investigate drug interactions in autoimmune diseases with a focus on systemic lupus erythematosus (SLE). The method used is a systematic review with literature sources in the form of international journals or research articles, and 31 articles met the inclusion criteria. There is evidence of interactions between drugs for the treatment of SLE, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressants. In addition, results were obtained regarding the interaction of SLE therapy with herbal plants such as Cecendet or Physalis angulata L, horsetail, and fertilizing plants such as Manjakani, Kacip Fatimah, Chlorophyll, and Spirulina as well as interactions between drugs in both SLE therapies with other types of SLE drugs and with herbal medicine, these interactions can support or hinder the therapeutic effect of the drug

## INTRODUCTION

Autoimmune disease is a disease that attacks the human immune system, autoimmune is a disorder of the immune system due to the failure of the defense to stabilize the body's condition so that the immune system attacks a healthy body and is considered a foreign object that must be destroyed. This autoimmune disease causes harm to human organs because it can damage healthy cells in a person's body. Autoimmune diseases are conditions that result from the complex interaction between genetic background and environmental triggers, such as infections, dysbiosis, and drugs. Autoimmune is also an immune response to one's tissue antigens which is caused by a failure of normal mechanisms that play a role in maintaining self-tolerance of B cells, T cells, or both. The autoimmune potential is found in all individuals because lymphocytes can express specific receptors for many self-antigens. Autoimmune occurs because self-antigens can cause activation, proliferation, and differentiation of autoreactive T cells into effector cells which cause tissue and various organ damage. Both antibodies and T cells can play a role in the pathogenesis of autoimmune diseases, such as Rheumatoid arthritis (RA) and Systemic Lupus Erythematosus (SLE) (Watad et al., 2019).

One autoimmune disease is lupus. Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease that has a very varied prognosis. This disease mainly attacks women of reproductive age with a fairly high mortality rate. Genetic, immunological, and hormonal factors as well as the environment are thought to play a major role in this disease process. In SLE, the body forms various types of antibodies, including antibodies against nuclear antigens (ANAs), causing damage to various organs. Lupus epidemiology throughout the world more often attacks women of childbearing age whose average age is 15-44 years. The ratio of women to men with SLE incidence is 13:1 and the ratio of SLE incidence in children to the elderly is 2:1. The pathogenesis of SLE is characterized by the occurrence of abnormal immune system abnormalities such as B cells continuously forming antibodies and forming autoreactive T cells. Apart from that, immune system disorders cause it to occur the build-up of damaged immune cells that are not apoptotic which causes the buildup of autoantigens. This causes inflammation and failure of organs including the kidneys, heart, skin, and nervous system. Risk factors for SLE include the use of drugs such as procainamide, hydralazine, chlorpromazine, isoniazid, phenytoin, and penicillamine. Dietary factors such as excessive consumption of foods high in saturated fat can increase the occurrence of autoimmune diseases. Hormonal and estrogen factors from the environment such as oral contraceptive pills can cause an increase in autoimmunity. Apart from that, there are various types of SLE, namely SLE which attacks the skin. This case of SLE can be caused by the use of certain drugs. SLE which attacks the kidneys is the type of SLE most often experienced by SLE sufferers. Lupus nephritis is an autoimmune condition that triggers the body to produce proteins, namely antibodies. These antibodies will later attack kidney tissue and organs (Fava & Petri, 2019).

SLE is an autoimmune disease with the characteristic of having a level of disease activity whose periods are not constant. The aim of providing SLE therapy is to control inflammatory disease activity and prevent the severity of symptoms or complications due to lupus. Mortality and morbidity associated with SLE have increased significantly from year to year. The therapies commonly used in SLE patients are non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, immunosuppressants, and antimalarial agents (AMs). Medication therapy is also used to help manage disease activity. NSAID drugs are also used in SLE therapy, especially to treat the symptoms that appear, such as pain, swelling, and fever (Nimesh et al., 2021). Corticosteroid drugs are useful for controlling immune system activity in autoimmune diseases (Balushi et al., 2018). Corticosteroid drugs such as prednisolone can treat inflammation in SLE, the use of other corticosteroids such as methylprednisolone usually also used to control complications due to lupus such as the kidneys or

brain (Nimesh et al., 2021). Meanwhile, AMs drugs such as hydroxychloroquin are useful for controlling the level of disease and preventing tissue damage, such as preventing thrombosis, preventing bone mass loss, increasing lipid profile levels, and maintaining the uterus during pregnancy (Balushi et al., 2018).

Immunosuppressant drugs are used to suppress high immune activity in SLE sufferers. The immunosuppressant drugs that are often used are azathioprine and methotrexate. Medicines to control biological function or biological agents that are often used in SLE sufferers are rituximab and belimumab to balance antibody function. Rituximab also plays a role in targeting B-cells and treating complications in the kidneys or brain. Meanwhile, belimumab is used to stimulate and activate B lymphocyte cells. Other drugs that are often used in SLE patients are tumor necrosis factor inhibitors and tocilizumab (Nimmesh et al., 2021).

Drugs are active compounds that can interact with other active substrates, drug interactions with other active compounds can have positive or negative effects on the function of the therapy provided. Drug interactions can occur with nutrients, herbal medicines, or other medicines. For example, giving warfarin to SLE patients when combined with herbs or other drugs can have the risk of causing fatal bleeding or thrombosis (Duran et al., 2021). Medicines can also interact with nutrients in food, nutrients in food can cause a decrease in the absorption of the drug so that it can inhibit or even reduce the therapeutic effect of the drug. Drug interactions with herbal medicines can also occur, the use of herbal medicines has the potential to block enzymes that function in carrying out the drug metabolism process. The administration of drug therapy must be carried out according to the correct prescription and there is a need for monitoring during therapy to avoid drug interactions with other active compounds which can cause a decrease in the therapeutic effect of the drug or even trigger side effects that can worsen the level of SLE pain (Honoré, 2014).

## METHODS

The method used in this article review is a systematic review with literature sources in the form of journals or international research articles and secondary data that is appropriate to the topic of discussion. The keywords used are autoimmune, SLE, lupus, immunosuppressants, SLE pharmacotherapy, lupus pharmacotherapy, and drug interactions. The words "or" and "and" are used to combine keywords so that the search results obtained can be more specific.

The inclusion criteria for compiled this review article are (a) articles written in English with publication years 2000 – 2021 (b) experimental studies, Case study, and Review article (c) literature discussing the influence and interactions of drugs on SLE therapy. The exclusion criteria are (a) literature containing only abstracts, (b) literature in the form of letters to editors, theses, books, and papers. The literature obtained will be summarized and reviewed to determine whether it meets the inclusion criteria.

31 pieces of literature were obtained that met the inclusion criteria. The literature obtained was in the form of experimental studies with prospective and retrospective designs.

## RESULTS AND DISCUSSION

Table 1. Summary of Study Characteristics

| Title, Author, Year | Abstract Resume | Research Procedure | Journal Resume |
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| 1.Immunosuppressant Drugs and Covid-19: Associated Risks, Drug-Drug Interaction and Contraindication. (Talukdar, D, et al. 2021). | Etanercept, mycophenolate, mofetil, sirolimus, cyclosporine, and rituximab are types of immunosuppressant drugs that can weaken the immune system in autoimmune patients exposed to COVID-19, making them vulnerable to complications and increasing mortality and morbidity. | Analysis directly at the hospital with experimental study to the autoimmune patients with COVID-19. | Patients with autoimmune diseases who are exposed to COVID-19 consume immunosuppressant drugs such as Etanercept, mycophenolate, mofetil, sirolimus, cyclosporine, and rituximab which will be associated with a decrease in the immune system, so the dose of immunosuppressant drugs in autoimmune patients exposed to COVID-19 can be reduced. or stop treatment for some time when exposed to COVID-19. |
| 2. Interaction of Prednisolone, and Other Immunosuppressants Used in Dual Treatment of Systemic Lupus Erythematosus in Lymphocyte Proliferation Assays, (Kamal, MA. et al, 2004). | Therapy for autoimmune people with lupus erythematosus has less than optimal effects caused by the side effects of immunosuppressants, namely corticosteroids. The corticosteroid drugs that have side effects in people with autoimmune disease are prednisolone, tamoxifen, mycophenolic acid, azathioprine, and chloroquine, where the drug is associated with the process of stimulating proliferation in T lymphocytes which is stimulated by lectins. | The method used in this research was female subjects aged 30-47 years provided they did not take birth control pills, were drug-free, and were in good health. The sample taken from the subject is a blood specimen. Pick-up takes place at 09.00. | There are several drugs that can be synergistic with prednisolone and there are several drugs that cannot be synergistic with prednisolone |
| 3. Interactions of Prednisolone and Other Immunosuppressants Used in Dual Treatment of Systemic Lupus Erythematosus in Lymphocyte Proliferation Assays. (Wiliam. 2014). | This study examines the interactions between prednisolone and other corticosteroid drugs such as tamoxifen, mycophenolic acid, 2-chloro-2'-deoxyadenosine, azathioprine, and chloroquine. This experiment was carried out on 10 women whose blood samples were taken and the research process was carried out. | The method in this research was to use instruments from 10 women who were healthy, drug-free, did not consume birth control pills, aged 30-47 years, and were willing to have their blood drawn on the day of the trial at 9 am. The medicinal ingredients were purchased in St. Louis and stored at -20 degrees. | It was concluded that administering Prednisolone with other corticosteroid drugs such as tamoxifen, prasterone, and mycophenolic had different effects on Prednisolone. The drug that works synergistically with Prednisolone in treating SLE is mycophenolic |

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| 4. Drug Reaction With Herbal Supplement: A Possible Case Drug-Induced Lupus Erythematosus (Leelavathi, M.,et al. 2010). | Drug-induced lupus Erythematosus (DILE) is a disease that can be caused by consuming herbal medicines which begin with symptoms of a non-pruritic rash, ankle pain, and swelling. In this study, it was found that a female patient with symptoms 4 days ago had a non-pruritic rash and had consumed herbal supplements for five days before the onset of symptoms. The examination results showed that there were erythematous maculo-papular lesions in areas exposed to sunlight and the patient was diagnosed with DILE | Case Study in female DILE patient who consume herbal supplement for infertility. | The conclusion of this case report research is that there is an increase in the consumption of herbal supplements which can result in reactions between herbal medicines and chemical drugs which can be detrimental. The use of the herbal must be stopped if an adverse reaction occurs, besides that the safety of the herbal product must be ensured in order to prevent undesirable things from happening. |
| 5. A prospective multicentre study of mycophenolate mofetil combined with prednisolone as induction therapy in 213 patients with active lupus nephritis (Lu F, et al., 2008). | The interaction between Mycophenolate and prednisolone is an interaction that can be used as a treatment for lupus nephritis patients. In this study, we investigated the efficacy and impact of the interaction of mycophenolate with prednisolone given to 213 patients with cases of active lupus nephritis for 24 weeks. | Cohort Experimental Study in 213 patients from China with SLE diagnosed. Patients had renal biopsy evidence of class III, IV or V active lupus nephritis and urinary protein excretion exceeding 1 g per 24 hours. Patients had not received CTX or other immunosuppressive agents 6 months before the study. The average course of disease was 2 years, ranging from 3 months to 10 years. Patients received oral MMF and prednisolone after renal biopsy. Patients were followed up monthly for 24 weeks, with pathological profiles made and target blood pressure and urinary excretion below the target. | Patients with class V lupus nephritis still do not have a significant therapeutic effect with prednisolone with mycophenolate compared to patients with class III or IV lupus nephritis who have significant effects after being given treatment with prednisolone with mycophenolate |

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| 6. Combination Effect of Cecendet (*Physalisangulata L.* ) Extract and Methylprednisolone in Reducing Inflammation and Improving Renal Functions in Pristane-induced Lupus Rat Models (Sheba, S., et al. 2019). | Cecendet, an Indonesian herbal plant, has been found to have immunosuppressive properties in lupus treatment. A study involving four female mice showed that cecendet extract combined with methylprednisolone can overcome inflammation, reduce proteinuria, and serum creatinine levels, a significant improvement compared to a control group. This finding could potentially improve lupus treatment. | The experimental study uses female wistar rats aged 3 months as an animal model. The mice are induced with pristane. The mice are divided into four groups, each with 5 rats. After pristane induction, the mice are given treatment with cecendet extract and methylprednisolone. The anti-inflammatory effect is observed through edema measurements and serum creatinine levels. | Cecendet extract has potential effects for SLE medication therapy and is more optimal if given in combination with methylprednisolone |
| 7. Drug Use in Systemic Lupus Erythematous (SLE) Outpatients (Setiawati, M., et al. 2021). | The study evaluates drug therapy for SLE patients, focusing on 220 patients, 98,2% of whom are women of productive age. The most common drug therapy is a combination of methylprednisolone and mycophenolate mofetil, with 55,41% receiving calcium and vitamin D supplements to reduce side effects. | The study design used was non-experimental research conducted from April-August 2017. The subjects used were patients diagnosed with SLE for more than 3 months. Data will be analyzed descriptively using SPSS 19. | The drug therapy most widely used in SLE patients is corticosteroids and a combination of calcium, vitamin D, anti-nausea and vomiting to reduce side effects. |
| 8. Combination immunosuppressant therapy and lupus nephritis outcome: a hospital-based study (Chen, Y.M., et al. 2019). | Lupus nephritis (LN) is the main cause of death in lupus patients. This study aims to examine the results of therapy and risk factors for renal histology in LN patients. This study used a retrospective observation model of 149 LN patients with a history of biopsy. The therapeutic response of the patients was evaluated by measuring protein in urine and urinalysis for 2 years after induction of therapy. This study also analyzes comparisons and | Cohort study from 2006-2017, a retrospective cohort study was conducted on SLE patients with a history of kidney biopsy due to LN at Taichung Veterans Hospital, Taiwan. Therapeutic induction treatment LN patients were separated into 4 groups based on the induction therapy given. Patients received systemic glucocorticoid and | Lupus activity is a good prognostic sign that therapy is effective. The effectiveness of the MPA-azathioprine or MBA-cyclosporine combination can support the therapy of LN patients. |

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| | Effectiveness of the combination of mycophenolate and azathioprine or with cyclosporine in LN patients. | immunosuppressant with cyclosporine (50-100 mg/day) or azathioprine (25-50 mg/day) in combination with MPA in the so-called MPA-combination group. In addition, some are given IV cyclophosphamide (500-750 mg/m2 of TBSA per month for 6x) or azathioprine (50-100 mg/day) | |
| 9. Spinal and cerebral hematoma in systemic lupus erythematosus and antiphospholipid syndrome: is drug interaction the culprit? (Duran, E., et al. 2021). | This study presents cases of patients with SLE and APS who developed complications of spinal and cerebral hematoma due to warfarin interaction with other active compounds. The patient, who used herbal medicinal products and phenyramidol, developed hematomas in the cerebral and spinal cord, which were treated with plasma and vitamin K. | Case Study in a patient SLE and APS who consume herbal supplements (shepherd's purse and horsetail) and phenyramidol which treated with vitamin K. | Warfarin can cause drug interactions, leading to hemorrhage or thrombosis, especially in patients with SLE or APS who are prescribed warfarin and should avoid other medications or herbal medicines. |
| 10.Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus (Bailin liang, et al 2006). | Systemic lupus erythematosus (SLE) is an autoimmune disease caused by immune system dysregulation. IL-6, a cytokine stimulates b-cell differentiation and T cell function, suppressing anti-dsDNA autoantibodies and preventing severe renal disease. | Random mice were used for the experiments, and from the age of 12 to 34 weeks, they received weekly intraperitoneal injections of saline, isotype control antibody, or anti mIL-6. | Anti-IL-6 mAb treatment inhibits autoreactive T-cell and B-cell responses to the self-antigens while maintaining normal immune responses to exogenous antigens, according to the study. Corresponding to the proposed paradigm of autoreactive T-cell and B-cell interaction in SLE autoimmunity regulation, this treatment is beneficial for murine SLE with minimal immune suppression risk. |
| 11. Lupus: An Overview of the Disease and Management Options (William Maidhof et al, 2012). | Lupus is an autoimmune disease affecting various organ systems, categorized into four types: neonatal, discoid, drug-induced, and systemic lupus erythematosus. Its etiology is unknown but linked to genetic, hormonal, environmental, immunological, and age-related factors. | Literature review with some of articles which provide information about Lupus and its management. | Lupus erythematosus (SLE) is a chronic inflammatory disease characterized by autoantibodies and immune complexes, leading to organ damage. It is influenced by genetic, hormonal, immunological, and environmental factors. SLE is more common in women and affects various systems, including the cardiovascular, |

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| | | | gastrointestinal, renal, hematological, and central nervous system. Diagnosis involves symptoms, laboratory tests, and individualized tests. Lupus treatment involves sun protection, diet, exercise, smoking cessation, immunizations, and managing comorbid conditions. NSAIDs, corticosteroids, monoclonal antibodies, and stem-cell transplantation are used for mild-to-moderate lupus. |
| 12. Medication adherence in patients in treatment for rheumatoid arthritis and systemic lupus erythematosus in a university hospital in Brazil (Prudente, et al, 2016). | Medication adherence is important for controlling symptoms and progression of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) The aim of this study was to investigate medication adherence in outpatients. RA and SLE groups for rheumatic diseases and more than six chronic comorbidities. | A quantitative, cross-sectional, analytical study conducted by the Golas Federal University Clinical Hospital in Brazil, between June 2013 and February 2014. | Only discusses a general description of RA and SLE and touches a little on medication but not specifically on medication compliance in RA and SLE patients. |
| 13. Treatment of Systemic Lupus Erythematosus: new advances in targeted therapy (Mindy S Lo et al 2012). | Treatment for Systemic Lupus Erythematosus (SLE) is limited to broad-based immunosuppression, with glucocorticoids at the center of treatment. SLE has been treated with broad-spectrum immunosuppressive agents, with varying degrees of success. | Cumulative research over the past several decades has yielded many insights into specific disorders of the immune system of lupus patients. because of the need for SLE research. | Belimumab is a treatment for SLE, and each individual's disease will be different and have different immune abnormalities, the development of biomarkers to monitor treatment and allow individual treatment regimens to be tailored to each patient's immune system, thus immunosuppression-related toxicities. |
| 14. Advances in Lupus Nephritis Pathogenesis: From Bench to Bedside (Obriȿcă, B., et al 2021). | Systemic lupus erythematosus (SLE) is a prototypical autoimmune disorder caused by loss of tolerance to endogenous nuclear antigens triggering aberrant autoimmune responses targeting various tissues. Lupus nephritis (LN), a major cause of morbidity and mortality in SLE patients, affects up to 60% of patients. | Literature Review with several articles providing information on SLE pathogenesis and future SLE drug design | The type I interferon system is an important component of innate and adaptive immunity that, for decades, was considered the main line of defense against viral infections. However, the type I IFN system has an important additional role in the pathogenesis of autoimmune disorders, especially in SLE and LN. |

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| | | | Patients with SLE had increased expression of type I IFN-stimulated genes in peripheral blood leukocytes, while patients with LN showed higher IFN scores, especially during active renal disease.<br>These anti-LL-37 and anti-HNP autoantibodies appear to have a dual role in SLE, first, by facilitating FcγRII-mediated endocytosis of self-DNA antimicrobial peptides by pDCs and subsequent stimulation of TLR9-mediated type I IFN release, and second, by enhancing release of NETs from IFN-primed neutrophils, The complement system has a dual role in the pathogenesis of SLE, especially LN. First, the complement has a protective role against the development of autoimmune disease. |
| 15. Leflunomide Versus Cyclophosphamide in the Induction treatment of proliferative lupus nephritis in Chinese patients: a randomized trial (Zhang, Minfang, et al.2019). | A prospective, multicenter, randomized controlled study was conducted to illuminate the efficacy and safety of leflunomide Low dose for 24 weeks combined with prednisone in the induced treatment of proliferative lupus nephritis in Chinese patients. | Patients (n = 100) with biopsy-proven proliferative lupus nephritis were enrolled in the study. They were randomized into two groups and received leflunomide or cyclophosphamide along with prednisone for 24 weeks. Leflunomide is given orally with a loading dose of 40 mg/day for 3 days followed by 20 mg/day. Intravenous cyclophosphamide is administered monthly at a dose of 0.8-1.0 g. The primary efficacy outcome was the frequency of complete remissions and partial remissions at week 24. Secondary outcomes included changes in urinary protein excretion, serum | In summary, low-dose leflunomide combined with glucocorticoid is effective in the induction treatment of proliferative lupus nephritis in Chinese patients, and its efficacy and safety are similar to those of cyclophosphamide.<br>Leflunomide is generally well tolerated; However, a precaution is necessary during leflunomide treatment to monitor for infection especially when larger doses of steroids are used concomitantly Long-term randomized studies are needed to elucidate the efficacy and safety of leflunomide in treating lupus nephritis. |

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| | | albumin, complement 3, anti-dsDNA antibody levels, and systemic lupus erythematosus disease activity index (SLEDAI). after 24 weeks of therapy. | |
| 16. Eurolupus cyclophosphamide plus repeated pulses of methyl-prednisolone for the induction therapy of class III, I and V lupus nephritis, Ruiz-Irastorza (Guillermo, et al., 2021). | To study whether repeated addition of 125 mg methyl-prednisolone pulses (MP) to biweekly intravenous Eurolupus cyclophosphamide (CYC) improves remission of lupus nephritis (LN) compared with the recommended schedule Approximately 40% of patients with systemic lupus erythematosus (SLE) will eventually develop lupus nephritis (LN), most of them during the early phase of the disease In a recent systematic review with Bayesian meta-analysis by Tektonidou et al., the estimated risk of patients with LN progressing to end-stage renal disease (ESRD) at 15 years was more from 20% in developed countries, without significant improvement since then. In the last 1990s, patients with LN experienced damage at a higher rate than lupus patients without kidney involvement due to multiple corticoid therapy. | Observational comparative study of patients with biopsy-confirmed grade III, IV, or V LN: 30 in the mycophenolate (MMF) group, 25 in the CYC group, and 38 in the CYC-MP group. The primary efficacy outcome was complete response at 12 months. | Regular and repeated administration of MP in the CYC-MP group of this study allowed rapid reduction of oral prednisone dose while increasing, at the same time, the level of renal response. The rationale for GC pulse therapy relies on the different biological effects of GC administered at different dose ranges. Doses of more than 100 mg/day of prednisone equivalent activate non-genomic pathways, which, either by blocking the activation of phospholipase A2 by the GC/GC-cytoplasmic receptor complex or through direct interaction with the cell membrane with inhibition of ATP production or the p38 MAP kinase pathway, result in faster and stronger anti-inflammatory effect. Moreover, this pathway is free from intrinsic side effects by genomic means. |
| 17. Immunosuppressive medication use and risk of herpes zoster (HZ) in patients with systemic lupus erythematosus (Hu, et al., 2016). | Seeing the relationship between the use of corticosteroids and the incidence of HZ (herpes zoster) in SLE patients | Population-based case study using a health insurance research database | In essence, the use of this drug can increase the risk of developing HZ disease due to the high dose of treatment given. The effect of the medicine is that it lowers the immune system. |

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| 18.Immunosuppressive Therapies on Survival of Systemic Lupus Erythematosus: a Propensity Score Analysis of a Longitudinal Cohort (Mok, et al., 2017). | After testing the use of immunosuppressant drugs in SLE patients, it was found that there was an increase in the survival of patients who were given the drugs hydroxychloroquine and azathioprine, whereas there was no significant increase in the use of high-dose prednisolone, mycophenolate mofetil, or high-dose cyclophosphamide. | The study monitored individuals diagnosed with SLE, investigating their clinical features, utilization of immunosuppressive agents, and mortality rates. The research study employed Cox regression analysis to examine the association between treatment and survival. | An analysis of 803 individuals with SLE revealed that the utilization of immunosuppressive medicines, including high-dose prednisolone, azathioprine, cyclosphamide, mycophenolate mofetil, calcineurin inhibitors, and hydroxychloroquine< WAS linked to a decrease in death. Nevertheless, these medicines did not exhibit a substantial correlation with enhanced survival. The study also observed comparable advantages in individuals with lupus nephritis. |
| 19. Use of Belimumab Throughout Pregnancy to Treat Active Systemic Lupus Erythematosus- a Case Report (Danve, 2014). | SLE occurs more often in women of childbearing age compared to men. The condition of a pregnant woman will be a challenge in itself in treating the SLE she is experiencing because this can affect the pregnant woman and the fetus she is carrying. | Case Study on pregnant woman active SLE who use Belimumab | 1. A lady of Caucasian ethnicity with SLE received guidance on the management and treatment of her pregnancy. She was prescribed belimumab, an effective medication that managed her SLE and enabled her to discontinue mychophenolate. Belimumab was consistently administered over the entire duration of pregnancy, resulting in effectively managed SLE and a smooth progression of the pregnancy, with the infant exhibiting mild case of Ebstein's abnormality. |
| 20. The Treatment of Lupus Pernio* Results of 116 Treatment Courses in 54 Patients (Stagaki et al., 2009). | Explains lupus pernio patients who are given various types of treatment such as corticosteroids, non-corticosteroids, and infliximab and it can be concluded that the use of infliximab has a superior impact than corticosteroid treatment. | Collection of demographic data and clinical data. | Infliximab is good for treating SLE in patients because it is an immunosuppressant drug that can inhibit cytokines. |

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| 21. Intermittent Intravenous Cyclophosphamide Arrests Progression of the Renal Chronicity Index in Childhood Systemic Lupus Erythematosus (Thomas, 2000). | The research was used to see the efficacy and progress of SLE pediatric patients with cyclophosphamide therapy | This method used 16 children aged before 18 years who had diffuse proliferative glomerulonephritis and were given corticosteroid treatment at 40 mg/day or 1 mg/kg/day and previous attempts had failed. Cyclophosphamide was given as an intravenous bolus for 3 months for a total of 36 months. The initial dose is 500 - 750 mg/m2. Intravenous pulse methylprednisolone therapy of 30 mg/kg/dose is given every day for up to 3 days. and children are evaluated with SLEDAI. all children continued to use corticosteroids but reduced the dose gradually with controlled trials using adults treated with corticosteroids alone or corticosteroids + cyclophosphamide rather than without cyclophosphamide. | During therapy, namely At 36 months, there was a decrease in kidney biopsy activity with good disease control. In addition, there was also a reduction in corticosteroid doses from the average. |
| 22. The effect of lupus disease on the Pregnant women and embryos: a retrospective study from 2010 to 2014 (Elham Rajaei, 2014). | Pregnant women who experience SLE are a challenge in current research, where to prevent recurrence in pregnant women, mothers must take medication both before pregnancy and after, but on the other hand, this treatment takes into account the health and development of the fetus. | Descriptive and retrospective epidemiologic. | Antiphospholipid syndrome which occurs in women with SLE who later plan to become pregnant will interfere with fetal development, besides that consuming methotrexate and cyclosporine will cause permanent fetal growth disorders. |
| 23. Cyclosporine for the treatment of lupus nephritis in patients with systemic lupus erythematosus (Tzu-Han, et al., 2012). | The study aims to retrospectively assess the therapeutic efficacy and safety of CsA in LN patients. Results: between 60 patients there were 11.7%, 20%, 25% achieved CR and 65.0%, 51.7%, 40% achieved their respective PRs respectively at 1, 6, and 12 months. SCr and eGFR were found to remain stable during follow-up. CsA caused a decrease in median uPCR (3.79 to 5.7 IU/mL, an increase in median C3 (75.9 to 88.5 mg/dL) and C4 (15.9 to | Retrospective study from 2005-2012 with lupus nephritis patients still on cyclosporine treatment who met the requirements and enrolled in the study. | Cyclosporine is a safe drug for the treatment of lupus nephritis. |

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| | 19.5 mg/dL as well as a decrease in glucocorticoid dose in a period of 1 year. | | |
| 24. High-dose cyclophosphamide for severe systemic lupus erythematosus (DE Gladstone, et al. 2002). | Intravenous cyclophosphamide has been considered the standard drug in the treatment of proliferative lupus nephritis, although its use is limited due to its potential for severe toxic effects. Cyclosporin A has been suggested as more efficient and safe as an alternative treatment. | 4 patients were seen in 1982 by the association. | High-dose cyclophosphamide is able to reduce disease severity in SLE patients with poor prognosis. |
| 26. Artificial Intelligence in Healthcare: Review and Prediction Case Studies. Guoguang, Rong., *et al.,* 2020. | This research discusses the latest developments in AI in biomedicine, especially in patients on medication. | Case Study | In biomedicine, AI is used for various functions, some of which include diagnosing and predicting diseases and providing health care. |
| 25. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study (J Zavada, et al., 2018). | Intravenous cyclophosphamide has been considered a standard drug in the treatment of proliferative lupus nephritis, although its use is limited due to its potential for severe toxic effects. Cyclosporin A has been suggested as more efficient and safe as an alternative treatment. | A multicenter, randomized, open-label, controlled trial from January 2002 through December 2006. | Cyclosporine has similar efficacy to cyclophosphamide-based on sequential trials of induction and treatment in patients with proliferative lupus nephritis and renal function. |
| 26. Artificial Intelligence in Healthcare: Review and Prediction Case Studies. Guoguang, Rong., *et al.,* 2020. | This research discusses the latest developments in AI in biomedicine, especially in patients on medication. | Case Study | In biomedicine, AI is used for various functions, some of which include diagnosing and predicting diseases and providing health care. |
| 27.Immunosuppression in Chronic Autoimmune Neurological Disorders During The COVID-19 Pandemic. Sukanthi, K., *et al.,* 2021. | This research was conducted to determine the risk of COVID-19 and the outcomes of patients with chronic ANDM (autoimmune neuromuscular disorders and multiple sclerosis who were given immunosuppressive therapy (IST). | Collaborative research to collect medical record data of patients with ANDM and MS who experienced COVID-19 per year 2019 (one year before January 20, 2020) and statistical analysis. | The majority of patients with chronic autoimmune diseases generally experience mild to moderate exposure to Covid-19. The influence of specific immunosuppressive therapy, initial autoimmune neurologic disease status/severity, and other |

| Title, Author, Year | Abstract Resume | Research Procedure | Journal Resume |
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| | | | comorbidities on relative risk and outcome remain unanswered in this study. |
| 28. Studies of Drug Interactions with Alpha1-acid Glycoprotein by Using On-line Immunoextraction and High-Performance Affinity Chromatography,. Cong, Bi, *et al.,* 2017. | This research was conducted to determine the binding of drugs to AGP (Alpha 1-Acid Glycoprotein). The combination of disopyramide and imipramine for the GP form provides good suitability for combining saturable and non-saturable interactions with AGP. | Experimental | This report investigates the combined use of disopyramide and imipramine and online immunoextraction with an antibody microcolumn to study the binding of disopyramide and imipramine to normal vs. imipramine. SLE-derived AGP samples. It is known that the changes that occurred in Non-saturable interactions may occur due to links with structural changes in the AGP group of carbohydrates. |
| 29. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. Loana, R.,A., *et al.*, 2014. | This research was conducted with the aim of analyzing the relationship between glucocorticoids and damage accrual in SLE. The research was conducted on patients treated with prednisone at different doses. | This observational cohort study included 230 enrolled patients diagnosed with SLE. Damage is calculated using the SLICC damage index. The dose of prednisone given, namely without prednisone, low dose (<7.5 mg/day), medium-high dose (>7.5 mg/day). | Providing medication therapy using high doses of prednisone makes a good contribution in inhibiting the activity of lupus disease but provides a higher risk for patients experiencing severe organ damage. So giving prednisone to SLE patients should always be supervised by health workers. |
| 30. Comparison of high versus low–medium prednisone doses for the treatment of systemic lupus erythematosus patients with high activity at diagnosis. Arruza, *et al.*, 2015 | The study was conducted to compare the efficacy and safety of administering prednisone doses from low to high in providing treatment to highly active lupus patients, where 30 patients were used in each group with different prednisone doses administered for each group. | Measurement using cohort analysis in SLE with SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index), using descriptive data with percentages, means, and standard deviations. | Consumption of glucocorticoids in high doses of lupus patients reduces lupus activity which can be seen from the SLEDAI score but increases the risk of accrual damage in patients where the damage is irreversible. |

| Title, Author, Year | Abstract Resume | Research Procedure | Journal Resume |
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| 31. Manifestations of Systemic Lupus Erythematosus (Manole Cojocaru.et al 2011). | Systemic lupus erythematosus (SLE) is a chronic, multifaceted autoimmune inflammatory disease that can attack all parts of the body. The etiology and manifestations of this SLE are not yet known. Improved diagnostic methods have resulted in a significant increase in the number of cases recognized. It turns out that this disease is not a rare disease, the symptoms that each person causes are different/varied, can come and go depending on which part of the body is attacked, can be moderate, mild or severe, and the diagnosis is difficult because it resembles other diseases. | Literature review from some articles which discussed about the manifestations of SLE | This text elucidates the signs or symptoms of lupus, which can present in multiple bodily systems. It provides a detailed account of the impact on the skin, kidneys, hematological, and musculoskeletal systems. The general symptoms of SLE are not defined and can vary widely. SLE is characterized by a diverse range of symptoms and typically involves periods of worsening symptoms followed by periods of improvement. The disease's severity will result in organ damage and coagulation abnormalities. |

SLE is a type of lupus disease that usually attacks fertile women (Maidhof et al., 2012). SLE is known as a disease that affects people of various ages, ethnic groups, and genders, of which 90% are experienced by women of childbearing age (Cojocaru et al., 2011). SLE can also attack pregnant women and pregnant women cause pregnancy complications and affect fetal development (Rajaei et al., 2019). SLE attacks the respiratory tract, urinary tract, and skin. The symptoms caused by SLE are quite varied, including being characterized by multisystem microvascular inflammation with the formation of many autoantibodies, especially antinuclear antibodies (ANA). SLE patients will often experience opportunistic infections, salmonella infections, herpes zoster, and candida which are caused by changes in immune status (Cojocaru et al., 2011).

According to the Indonesian Lupus Foundation (YLI), the total number of SLE patients has increased in this decade, and the use of drug therapy in SLE patients is necessary to improve maximum health outcomes for patients (Setiawati et al., 2021). Treatment plays an important role in regulating immune responses and inflammatory activity (Bailin Liang et all, 2006). Apart from that, treatment is also important in fighting viral infections and treating complications (Obirisca et al., 2021). Treatment for SLE is also useful for slowing the progression of the disease. Compliance with drug therapy is also very important for the success of therapy (Prudente et all, 2016).

SLE therapy can generally be applied through various types and methods of administration. In this review, 8 articles were found that discussed drug therapy in SLE. As explained by (Stagaki, 2009), for SLE disease with the Lupus Pernio type, treatment using infliximab is very useful in inhibiting cytokines because infliximab is a type of immunosuppressant drug. However, treatment using infliximab takes quite a long time, so a combination with other drugs is needed. However, the weakness of this study is that the researchers did not include the side effects of administering the drug. In a research study conducted by Mok (2017) it was stated that treatment of SLE by administering glucocorticoids, cyclophosphamide, MMF, or CNI did not increase the survival of patients with SLE. However, treatment using hydroxychloroquine and azathioprine can improve the quality of life of

patients with SLE because these drugs are anti-inflammatory drugs that have immune-modulating properties by reducing pro-inflammatory cytokines such as TNF-a and IL 6, inhibiting TLR signaling, and secreting inflammatory mediators and producing autoantibodies. (Mok, 2017).

SLE patients are also given immunosuppressants to suppress the immune system. However, a study conducted by Danve (2014) stated that the use of immunosuppressant drugs such as methotrexate, mycophenolate, and cyclophosphamide is not recommended for pregnant women because they can harm the fetus. This drug can enter through the mother's placenta and the child born is at risk of congenital heart defects. Apart from being harmful to the fetus, this drug can also increase the mother's risk of experiencing preeclampsia, thrombosis, hematological and high infectious complications. Therefore, there is an alternative treatment using belimumab to treat SLE in pregnant women which is proven to have a low risk to the fetus and mother. However, this article does not explain further research on whether belimumab can cause congenital heart defects in children born.

Another type of treatment that can be given to SLE patients is giving cyclophosphamide to children. This is proven by the results of research by Thomas (2000) that the use of drugs with cyclophosphamide is more effective than the use of methylprednisolone. Supported by the explanation that the use of drugs other than cyclophosphamide in children can cause long-term damage to cognitive and psychological function and is a contributor to the morbidity and mortality of patients with SLE. Patients on treatment using cyclophosphamide, over several decades of follow-up, did not experience relapse. This idea is supported by an article by Zavada (2010) where it is explained that the use of cyclophosphamide can also be used by adult SLE patients. Apart from treatment using cyclophosphamide, SLE treatment can be carried out using the drug cyclophorine A which has the same effectiveness as cyclophosphamide. Based on the results of trials conducted by Zavada (2010) in lupus nephritis patients. However, this idea contradicts the idea put forward by (Yang, 2018) where it is explained that treatment of lupus nephritis using cyclophosphamide can cause toxicity, decreased spinal activity (myelosuppression), and increased risk of cancer.

Of all the treatments that have been carried out, all types of treatment have good effectiveness and effectiveness according to the patient's needs. However, these drugs can reduce the function of the body's organs, thereby reducing the immune system, and making patients susceptible to infections and other diseases (Kovvuru, 2021).

In this review, 13 research literature were found that discussed drug-drug interactions in SLE therapy. In general, the literature states that there are interactions between drugs given simultaneously to SLE sufferers, these interactions can cause an increase in the therapeutic effect of the drug or failure of therapy, there are even drug interactions that can cause side effects, making the condition of SLE sufferers worse. The therapies commonly used in SLE patients are non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, immunosuppressants, and antimalarial agents (AMs) (Nimesh et al., 2021). The use of glucocorticoids is one of the most common treatments given to SLE patients. One of the glucocorticoids used in SLE therapy is prednisolone. A study conducted by Loana et al (2014) with a total of 230 patients in the study, of which 42-87 patients experienced organ damage caused by the use of prednisolone drugs, especially prednisolone-4. The study examined the administration of prednisolone in different doses. Organ damage that occurs includes cataracts, osteoporosis, necrosis, and irreversible diabetes mellitus. Although administration of prednisolone can inhibit the activity of lupus disease, organ damage due to use of prednisolone in high doses cannot be avoided. To minimize the side effects of prednisolone, pulse therapy can be performed, reducing the dose of prednisolone, or stopping the use of prednisolone if the side effects are severe. Therefore, administration of prednisolone to SLE patients must always be under medical supervision (Loana et al., 2014). Similar results occurred in research conducted by Arruza et al (2015), this study also examined the administration of glucocorticoids

in high doses which caused side effects of organ damage. This study has the advantage of describing organ damage that occurs by looking at the systemic lupus erythematosus disease activity index (SLEDAI) score (Loana et al., 2014). However, this study does not explain the mechanism of organ damage that occurs due to the use of high doses of glucocorticoids.

In the study by Trisnia et al (2020), research was conducted on children diagnosed with severe lupus aged 0-18 years. Therapy was carried out immediately after the patient was diagnosed with SLE, including IV methylprednisolone 30 mg/kg/day (maximum 1000 mg) for 3 days, followed by cyclophosphamide 500 mg every 2 weeks. Several clinical manifestations observed in patients were renal manifestations (85.7%), alopecia (76.1%), serositis (71.4%), and acute cutaneous lupus (61.9%), as well as neurological manifestations ( 23%). SLE therapy can use methylprednisolone and cyclophosphamide. Cyclophosphamide is an immunosuppressant drug that is often used in severe SLE conditions, including lupus nephritis and neuropsychiatric disorders. There are two intravenous regimens recommended for lupus nephritis induction therapy. First, namely a low dose of cyclophosphamide, as much as 500 mg IV once every 2 weeks with a total of 6 doses, followed by oral azathioprine or mycophenolate mofetil therapy. The second is a high dose of cyclophosphamide, 500-1000mg/m2 IV once every month with a total of 6x doses, followed by mycophenolate mofetil or azathioprine. In this study, SLEDAI scores were monitored after diagnosis, after administration of methylprednisolone and cyclophosphamide. The median SLEDAI score after diagnosis was 23, after administration of methylprednisolone it decreased to 13, and after administration of cyclophosphamide, it decreased to 2. Patients with clinical manifestations in the kidneys and CNS showed improvement after 6 months of therapy with the SLEDAI score decreasing from 18.2 to 1.9. However, researchers do not routinely carry out examinations related to SLEDAI such as DNA binding and complement levels due to medical assessments and costs (Trisnia et al., 2020). Research on methylprednisolone and cyclophosphamide was also carried out by Zhang et al (2021) who found that regular and repeated administration of methylprednisolone enabled a reduction in oral prednisone doses and increased renal response rates.

In SLE sufferers, administering immunosuppressant drugs such as prednisolone has become a common medical therapy. In a study conducted by Kamat et al (2004), it was found that female subjects diagnosed with SLE were aged 30-47 years with the inclusion criteria of not taking birth control pills and being drug-free. This study used blood samples taken from subjects every 09.00 in the morning. The therapy given to this subject was prednisolone, tamoxifen, prasterone, chloroquine, bromocriptine, mycophenolic acid, and azathioprine. The results of this study indicate that there is an interaction of prednisolone with other immunosuppressant drugs given to the subject. The drug prednisolone given with tamoxifen can produce the effect of increasing the body's immunity and reducing the side effects of corticosteroids, the interaction of prednisolone with prasterone will cause a decrease in the effectiveness of prednisolone in the body, the interaction of prednisolone with choloroquine does not reduce the effectiveness of prednisolone in the body, the interaction of prednisolone with bromocriptine will have a positive impact and helps suppress the immune system by increasing the formation of autoantibodies, the interaction of prednisolone with mycophenolic acid can reduce the immune system if the dose given is 75 mg, and the interaction of prednisolone with azathioprine will have a positive impact in the treatment of SLE. This study has a weakness, namely that it does not explain in detail the dosage of medication that can cause positive or negative interactions when given with prednisolone (Kamat et al., 2004). However, these researchers carried out updated experiments in 2014 with mouse subjects. The types of drugs given are prednisolone, tamoxifen, prasterone, mycophenolic, and bromocriptine with specific dosages given for each drug. Prednisolone 8 mg given with tamoxifen 10 mg provides an immunodynamic effect like prednisolone 10 mg. Giving prednisolone 7.3 mg

with prasterone 200 mg every day for 9 months can reduce the prednisolone dose to <7.5 mg/day. Prednisolone combined with 75 mg of mycophenolic produces an immunosuppressive effect and is antagonistic to prednisolone (Kamal et al., 2014).

Another study from Lu et al (2008) also explained that administering mycophenolic therapy with prednisolone to stage V lupus nephritis patients had a slightly more effective effect than stages IV and III as evidenced by a significant reduction in proteinuria over six months and a slow decline in kidney function (Lu et al., 2008). Meanwhile, the drug bromociptine 25 mg which has the effect of reducing SLE activity when combined with prednisolone will have an antagonistic effect. However, this study was only carried out on mice, studies on humans have not been carried out so it is not yet known whether the same drug interaction effects occur in humans (Kamal et al., 2014).

Apart from glucocorticoids, there are types of immunosuppressant drugs that are used in SLE sufferers. The types of immunosuppressant drugs are etanercept, mycophenolate mofetil, sirolimus, and cyclosporine. In a study conducted by Talukdar et al (2021), the study subjects were found to be patients with autoimmune SLE who were exposed to COVID-19 and were taking immunosuppressant drugs. In these patients, there is a decrease in the immune system due to the administration of immunosuppressants. Immunosuppressant administration in this situation can be given in low doses or stopped first while still exposed to COVID-19. The etanercept or enbrel type of drug is an immunosuppressant given to autoimmune sufferers. This drug has an antagonistic interaction with immunosuppressant drugs such as methotrexate and corticosteroids which if taken together can cause death. It is not recommended to administer etanercept simultaneously with the drugs cyclophosphamide and sulfasalazine. This study also examined the interaction of the drug mycophenolate mofetil with antacids. The results of the study stated that the interaction of the two drugs would cause a decrease in the effectiveness of the drug mycophenolate mofetil. Apart from that, there is also the drug sirolimus which, if given with the drugs cimetidine, diltiazem, and fluconazole, will inhibit the CYP3A4 enzyme and increase the concentration of sirolimus in the blood. On the other hand, if sirolimus is given together with the drugs phenytoin, rifapentine, and carbamazepine, it can reduce the concentration of sirolimus in the blood. This study also examined the interaction of the drug cyclosporine with NSAID drugs such as naproxen and sulindac which can cause a decrease in kidney function in people with autoimmune SLE, especially those exposed to COVID-19. The advantage of this study is that researchers conducted interaction experiments between different drugs in SLE sufferers with the specific specifications of exposure to COVID-19. However, this study does not discuss whether these drug interactions will also have the same effect on SLE sufferers without exposure to COVID-19 (Talukdar et al., 2021).

In a study on immunosuppressant drug interactions also conducted by Zhang et al (2019), an interaction between prednisone and leflunomide was found. Studies conducted on 100 SLE patients were divided into two groups, one group received prednisolone-leflunomide and the other group received prednisone-cyclophosphamide. Of the 100 patients, 48 received leflunomide combined with prednisone, and the other 52 received cyclophosphamide with concomitant prednisone. No significant differences were seen in changes in clinical parameters and side effects after therapy between the two groups. This can be seen from the SLEDAI score, serum albumin, complement 3, anti-dsDNA antibody levels, and urinary protein excretion increased significantly in both groups. However, it was found that low-dose prednisone-leflunomide showed effectiveness and safety in lupus nephritis therapy compared to prednisone-cyclophosphamide (Zhang et al., 2019).

In research by Chen et al (2019), research was conducted on 149 patients who were separated into 4 groups based on the induction therapy given. Patients received systemic glucocorticoids and immunosuppressants with cyclosporine (50-100 mg/day) or azathioprine (25-50 mg/day) in combination with MPA in the so-called MPA-combination group. Additionally, there is a given IV

cyclophosphamide (500-750 mg/m2 of TBSA per month for 6x) or azathioprine (50-100 mg/day). This study also analyzed the effectiveness of the combination of mycophenolate and azathioprine or cyclosporine in lupus patients. The results of this study explain that the combination of mycophenolic therapy combined with tacrolimus is effective in treating lupus nephritis. Apart from that, mychophenolic can also be combined with cyclosporine which has also been proven to be effective and safer to use in SLE therapy. In severe lupus conditions, the combination of drugs can be increased or given for a longer duration. However, in this study, hematuria and urine analysis were not measured so this study could not measure the clinical manifestations of the SLEDAI score. In addition, the samples obtained were only small and the SLEDAI score used to measure the success of therapy was the median SLEDAI score, not the SLEDAI score for each patient (Chen et al., 2019).

In SLE patients, one of the other drugs given is warfarin. Warfarin is a drug that is often used to support anticoagulant therapy in VKA conditions. In addition, warfarin is the drug that has the highest incidence of death and is ranked first in interactions with food, herbs, and other drugs. The result of this interaction can be failure or overdose of anticoagulants which can cause fetal bleeding and thrombosis. In a study conducted by Duran et al (2021), it was found that SLE patients had antiphospholipid syndrome (APS) with spinal and cerebral hematomas due to the use of a combination of warfarin and phenyramidol. Phenyramidol is a non-narcotic analgesic drug that functions in muscle relaxation activities. This drug is conjugated by glucuronic acid in the liver and excreted in the urine as phenyramidol glucuronide. Meanwhile, warfarin is metabolized by the CYP29 enzyme in the liver, assisted by other enzymes, such as CYP2C19 and CYP3A4. The interaction of phenyramidol and warfarin is related to the inhibition of the CYC2C9 enzyme due to phenyramidol itself. Previous research also stated that the addition of phenyramidol to patients receiving anticoagulant therapy could cause hypoprothrombinemia and hemorrhage. However, the incident reported by researchers was only in one patient, who was also post-natal, so the interaction effect of warfarin on different individual conditions is not yet known.

In a review of drug interactions for SLE therapy with herbs, 3 pieces of literature were obtained that analyzed the interactions. In a research study by Sheba (2019), it is explained that there are plants that can be used as herbal medicine that can help the Lupus treatment process, one of which is cecendet or Physalis angulata L. It is explained in this article that this cecendet plant contains Withangulatin A (WA) which has the ability as a good immunosuppressant so it can be used to control autoimmune diseases. In addition, WA has been proven to reduce the expression of BAFF, BAFF-R, and lymph-related genes so that it has the potential to be used to treat SLE more effectively if combined with methylprednisolone. However, this article does not explain the interaction between the administration of cecendet plants and methylprednisolone with detailed. However, in Leelavathi's (2010) research, excessive consumption of herbal medicines was found to induce the occurrence of DILE-type SLE in individuals. This is proven in case reports of consumption of herbal medicines used to increase fertility such as Manjakani, Kacip fatimah, chlorophyll, and spirulina which can cause individuals to have symptoms and signs similar to SLE but without renal manifestations. The symptoms experienced by the patient were a rash on the skin and bilateral edema. After going through the examination, the patient was indicated to have DILE (Drug Inducing Lupus Erythematosus) but had a low risk of developing SLE. The drawback of this article is that it does not explain in detail what herbal medicine reactions and interactions cause DILE in patients.

Drug and herbal interactions were also found in a study conducted by Duran et al (2021), it was found that an SLE patient had antiphospholipid syndrome (APS) with spinal and cerebral hematomas due to the use of herbal supplements combined with warfarin after he received rituximab (RTX) therapy. Warfarin has potential interactions with other drugs, herbs and foods which can increase the incidence of side effects. Interactions with herbs can inhibit or

induce the P45 enzyme. The anticoagulant effect of warfarin can be increased when given together with herbs containing coumarin or antiplatelets. This patient also consumed shepherd's purse and horsetail herbs, which caused an increase in platelet aggregation which is used to control bleeding. The content of hydroalcoholic extract in shepherd's purse has been proven to control bleeding as in. However, this is influenced by several factors, such as patient comorbidities, herbal medicine structure, and acceptable dose regimen tolerance.

## CONCLUSION

There are interactions between drugs in SLE therapy, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, immunosuppressants, and antimalarial agents (AMs). Apart from that, there are interactions between SLE therapy drugs and herbal medicines, such as Cecendet or Physalis angulata L, horsetail, and fertility herbs such as Manjakani, Kacip Fatimah, Chlorophyll, and Spirulina. These interactions can support or inhibit the therapeutic effects of drugs, and even cause drug side effects that can worsen the condition of SLE patients. Therefore, it is necessary to monitor and make appropriate prescriptions to avoid negative impacts due to drug-drug interactions or drug-herb interactions.

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