

Environmental Factors and Protective Effects of Epigallocatechin-3-Gallate to Systemic Lupus Erythematosus: A Review Study

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Abstract

SLE (Systemic Lupus Erythematosus) is one of autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. Etiology and pathogenesis are not clearly mention until now by the scientist, but environmental factor is contribute to development of Lupus and Flare disease. The objective of this study to explain the relationship between environmental factors and pathogenesis development of SLE, and how the Epigallocatechin-3-Gallate (EGCG) can protect or prevent of organs damage and environmental effects.

Method: The research design of this study was used literature review. The data sources collected from Electronic database in Pubmed, Sage, Google Scholar and website of science including reports, journals and mostly published in the last 10 years.

Results: The pathomechanism of SLE was influenced by environmental factors and this was caused an increasing of oxidative stress, chronic inflammation, dysregulation of immune system and decreased the clean of immune complex and apoptosis of cells. The production of autoantibodies and immune complex are related with target tissue with is it was caused chronic inflammation and the end it caused irreversible damage in glomerulus of the kidneys, arteries, lungs and other tissues. EGCG plays a protecting role in environmental factors as a trigger because it works as an antioxidant, anti-inflammatory and immunomodulator. So EGCG can as a potential agent to protect SLE.

Conclusion: Environmental factors plays an important role as a trigger of SLE and flare. Moreover, EGCG as a potential agent to protect the presence of oxidative stress, inflammation and immune dysregulation.

Keywords: *Environmental Factors; Epigallocatechin-3-Gallate; Systemic lupus erythematosus*

Introduction

SLE (Systemic lupus erythematosus) is one of

lupus type. SLE is an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels. It is also one of leading killer among young women. In 2000 - 2015, SLE was ranked 10th occurred among people who aged 15-24 years, and it was ranged 5th occurred among women who has black skin and Hispanic and aged 15-24 years, and 6th of rank

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was occurred among people who aged 25-34 years⁽¹⁾.

At least more than 100 thousand new SLE cases suffered in the world. In 2012, the prevalence of SLE reached 1 in 1000 population in UK and 2-7.6 per 100,000 population occurred of SLE or 19-159 cases per 100,000 population in USA. In Asia Pacific an estimated 4.3-45.3 per 100,000 population or 0.9-3.1 cases per 100,000 population per year. The average of SLE in America was 7.9 and in Taiwan was 8.1. Now, this disease not one of rare disease occurred in every level of people. In some countries the prevalence of SLE was up to 80-120 per 100,000 occurred among adults people^(2,3,4,5).

Mortality rates increased in 20th century with 60% of 10-year of life expectancy in 1950 and reached 90% in 1980s and 1990s. This was due to an increasing of the severity of disease activity although the development of diagnosis and treatment were progressed^(4,6). Now, the life expectancy of SLE was increased 80-90% among the patients and they can normal live⁽⁷⁾ Previous research explained that people who diagnosed SLE will life up to 40 years. However, the deaths cases due to SLE still high in recent years. Mortality HRs estimated 2.15 in early (1999-2006) and 2.12 in late (2007-2014) cohorts⁽⁷⁾. In 2008-2016, In high-income countries mentioned that the survival rates was 0.95 among 5 years old, 0.89 among 10 years old, and 0.82 among 15 years old people of SLE. In low / middle income countries mentioned that the SLE were 0.92, 0.85, and 0.79,^(8,9) At the past the death was caused by the own disease but now days it was caused the effect of the drug side effects (for the example, serious infections for patients who received potential immunosuppressive drugs) or cardiovascular problems⁽⁹⁾.

The health problems impact of this disease was very large including bio-social psychology and economics, because most of the patients are young women and in childbearing age. SLE also affected the life of their partner such as financial problems, emotional, relationship and sexual condition. In addition, the disease and the treatment can inhibit the possibility of pregnant. Moreover, this disease also give an impact of quality of life such as marital relations, emotional problems (sad, depression, fear, anxiety, fear, anger, guilt), sleep disorders, pain, fatigue, rash, pregnancy,

work and economy, daily activities, comorbid condition (hypertension, arterial diabetes, osteoporosis etc), as a result of treatment⁽¹⁰⁻¹³⁾.

The causative factors of SLE are not yet clearly until now, there was relationship between environmental and genetic factors. Genetic factor was contributed 50% of the SLE pathogenesis and the various environmental factors⁽⁷⁾. The results of previous research described that the environmental factors was contributed to this disease. This review study will describe how the relationship between environmental factors and the disease activities. Meanwhile various kinds of treatments have been approved by the FDA as a drug for SLE treatment. Natural or herbal medicines also have potential effect to prevent environmental factors that aggravate the condition of SLE disease. How EGCG which found in green tea can protect SLE will also described in this review study.

Environmental Factors in SLE pathogenesis

Systemic pathophysiology of lupus erythematosus (SLE) begins with the presence of autoantibodies and immune complexes that bind together with tissues and give multisystem inflammation. One of the causes of SLE is environmental factors. Biologic mechanisms of environmental exposures, high oxidative stress, development of systemic inflammation and upregulation of inflammatory cytokine, and hormonal, and epigenetic modifications were influenced the development of SLE.

In immune systems of SLE patients both innate or adaptive were provided an inappropriate immune response to the body cell particles. The abnormal immune responses are: 1) activation of innate immune systems (dendritic cells, monocytes / macrophages) in DNA, RNA from self-antigen proteins; 2) activation of adaptive immune cells (T lymphocytes and 3) lymphocytes; 3) ineffective regulation of CD4 + and CD8 + T cells, B cells and suppressor cells; 4) decreased the cleansing of immune complexes and cells who apoptosis process^(14, 15).

Furthermore, autoantibodies recognize self-antigens that exist on the surface of apoptotic cells and make immune complexes. Because the process of cell debris cleaning was disrupted so autoantigens, autoantibodies and immune complexes were available for a long time,

lead to inflammatory process and causing symptoms. Immune cell activation was also increased the secretion of type 1 and 2 interferons (IFN), tumor necrosis factors α (TNF- α), interleukin (IL) 17, stimulator of B cell maturation, and IL-10 which all support for inflammatory reactions. In this stage also has decreasing cytokines production such as natural killer cells which failed to produce IL-2 and transforming growth factor beta (TGF- β) which regulate CD4 + and CD8 + T cells, consequently the production of autoantibodies and immune complexes were uncontrolled and continues to autoantibody and complex, then binds to the target tissues, causes the activation of the complement system and released the cytokines, chemokines and vasoactive peptides, oxidants and proteolytic enzymes. This condition caused the activation of endothelial cells, tissue macrophages, mesangial cells, podocytes in tissue and causes B cells, T cells, dendritic cells and macrophages to reach the target tissue and also caused an inflammatory process. This chronic inflammation caused irreversible damage of tissue in glomerulus of kidneys, arteries, lungs and other tissues (4, 9, 14, 16).

Lifestyle and Behavioral Factors

Lifestyle and behavior as triggers for SLE, it include eating patterns, activities, smoking, lack of sleep, stress and emotional factors. Obesity is one of the result of unhealthy behavior and lifestyle, and it also correlates with the incidence of SLE. The NHS studies said that more than 5,600,000 people / year were indicated that obesity was associated with an increasing of SLE incidence with hazard ratio (HR) was 1.85. A meta-analysis study said that there was no relationship between lifestyle and SLE therefore further confirmation was needed (7). A study showed that the risk factors for lupus occurred among people who had sleep patterns problems. Data obtained that less than 7 hours of sleep at night have a risk of lupus and the lack of sleep can occur due to stress, sunlight, smoking and others (17).

Triggers for fatigue in SLE are influenced by behavioral and lifestyle factors such as smoking, exercise, sedentary behavior, sleep and rest patterns. In group patients who have regularly exercise and low smoking habits were negatively correlated with fatigue. One of the reason was explained because smoking induces the pain (18). Tobacco smoke has an effect on the immune system

functioning. Macrophages were activated in alveoli, increasing myeloperoxidase activity and high production of free radical. In long-term smoking consumption can damage the secretion of proinflammatory cytokines and reduced the activity of natural killer cells (19). There is a mechanical evidence which mentioned that there was an involving of smoking in the pathogenesis of SLE. Toxic components of cigarette (eg Tar, nicotine, carbon monoxide, polycyclic aromatic hydrocarbons and free radicals) were induced oxidative stress and corrupt the proteins and DNA endogen and lead to genetic mutations and gene activation. In a retrospective case-control study in SLE patients, mentioned that smokers were significantly more likely to have anti-double stranded DNA than who had never smoked (OR 4.0, 95% CI 1.6-10.4 (20).

Radiation, Nutritional and Diet Factors

Autoimmune diseases associated with daily of food consumption such as consuming foods exposed with chemicals like toxic oil syndrome and eosinophilic myalgia syndrome (19). Food intake was a potential risk factor for SLE pathogenesis because it was gave an effects on lipid and glucose metabolism, oxidative stress, and intestinal microbiomas (21). The low level of SLE disease activity in patients was associated with lower intake of omega-3 of fatty acids and higher carbohydrates (22) and high alcohol consume (20, 23).

Nutritional risk index (NRI) associated with the increasing of organ damage and disease development of SLE. The excessive nutrition consumption was increasing the inflammation and it lead the risk for autoimmune diseases. Nutritional problems in SLE patients were associated with chronic weakness, depression and the presence of comorbidities so this changed in appetite and commonly marked by low serum albumin levels during inflammation and malnutrition (23, 24).

Various dietary factors play a role in the pathogenesis of SLE by using epigenetic changes (DNA methylation) and / or intestinal microbiota. Black tea Consumption and coffee showed that there was a relationship with SLE (25). In addition, there was a mechanism of increasing salt intake and lupus autoimmunity by promoting the expansion and function of follicular helper T cells (7).

Meanwhile, there was relationship between serum trace and SLE development. Serum trace elements affected oxidative stress and involved the pathogenesis of SLE trace elements such as Zinc (Zn), Copper (Cu) and Selenium (Se). Zn has function to modulate the cellular interactions including DNA and protein synthesis, cell proliferation, electron transport and defense against free-radical damage. Zn has anti-inflammatory and antioxidant effects. Cu is a major component of antioxidant enzyme superoxide dismutase. Se is an essential constituent of anti-oxidative enzymes including selenoprotein P, glutathione peroxidases and thioredoxin reductases (26,27).

Various studies reported that low levels of vitamin D associated with increasing of B cell proliferation, polymorphism receptor of vitamin D (VDR) among SLE patients. Lack of sun exposure was a major cause of vitamin D deficiency among Caucasian race, because about 80% of vitamin D in the body comes from previtamin D which produced by the skin and induced by ultra violet light B. Many factors influenced the absorption in the skin, increasing of melanin pigmentation on the skin, topical sunscreen will absorb ultraviolet B and it was significant with producing vitamin D in the skin. Moreover, geographical location, time/ hour, cloudy on atmosphere, haze were influenced the exposure of UV radiation and vitamin D synthesis. Various studies suggested approximately 5 - 30 minutes sunbathe when the sun come in the morning, and 3 times a week, especially some part of body such as hand, face, legs and back without used sunscreen. And for patient who experienced limited sun exposure were advised to supplement their vitamin D which contain on food and supplements. Vitamin D contains in some foods such as salmon, tuna, and mackerel and fish liver oil. Small amounts of vitamin D also found in beef, liver, cheese, egg yolks and mushrooms also contain ergocalciferol (28-30).

Ultraviolet (UV) rays is main environmental factors for SLE. UV rays effects DNA, apoptosis, autoantigen, cytokine, inflammatory cells process, and systemic flare induction. Kind of UV light are based on wavelength: UVA = 400-320 nm; UVB = 320-280 nm; UVC = 280-1100 nm, and some studies also said that there was relationship between shorter level of wavelength and high level of energy (31,32).

UV exposure also affects the production of ROS, DNA damage, and apoptosis. The decreasing of apoptotic cells clean in the skin contributed to induce inflammatory process in lupus and it increased automatic antigens exposure. Besides that, it also occurred dysfunctional and reduce phagocytosis, and in the end occurred the reduction in apoptotic cell clearance. HMGB₁ skewed polarization macrophage and diminished M₁-like phenotype in apoptotic cells. Another mechanism was regulated apoptotic clearance of complement opsonization (25).

Occupational factors was associated with the pathogenesis of SLE include exposure to Silica and Silicates, Solvents and Pesticides, Heavy Metals. Silica is stimulant immune. Silica increased proinflammatory cytokines, TNF and IL-1. Some studies said that there were relationship between silica and SLE with the risks was 3.0 - 10.0 (19,33). However, solvent or chemical liquid related with SLE pathogenesis. Chemical liquid are alcohols, glycols, aromatic hydrocarbons (e.g. benzene, toluene, xylene), and chlorine (carbon tetrachloride and trichloroethylene). Previous experimental study found that metals (cadmium and mercury) were associated with accelerating diseases of lupus (19). Air pollution also associated with SLE pathogenesis. Kind of the pollution are Particulate Matter (PM₁₀), Sulfur Dioxide, Nitrogen Dioxide (NO₂), Ozone, and Carbon Monoxide (34).

Infection

Infection process also on of factors influence of SLE but the involvement was indirect relationships. The majority of previous studies said that there was a correlation between seroprevalence of Epstein-Barr virus (anti-virus capsid IgG antigen) with SLE (OR 2.08), while the other agents of infection were less evidences (7).

Protective Effects of Epigallocatechin-3-Gallate in Systemic Lupus Erythematosus.

An estimated more than 50% of systemic lupus erythematosus (SLE) patients used complementary and alternative medicine (CAM) to reduce the symptoms and gain their health (35). Chemosynthetic medicines such as non-steroidal anti-inflammatory drugs and corticosteroids are limited to find and in other this medicines also kind of medicines with extreme toxicity.

Heterogeneity of SLE disease is very difficult to managed by one component of the drug. Therefore, it is very important to use products of herbal medicines as additional treatment to SLE. Herbal medicines also has some functions such as to reduce of the symptoms, prophylactic drugs in cerebrovascular cases, liver, nephropatological, haematological, cardiopulmonary, mucocutaneous and musculoskeletal manifestations of SLE⁽³⁶⁾.

In this section will review how the natural products such as EGCG have potential to be used as complementary medicine. Epigallocatechin gallate (EGCG) is a type of vegetable compound and it called catechin. Catechins are categorized into a larger group of plant and known as polyphenols. EGCG and catechins are powerful antioxidants and can protect to cell damage which caused by free radicals. EGCG becomes a stronger lipid antioxidant than vitamins C and E^(37,38).

Epigallocatechin-3-Gallate as an antioksidant

EGCG and catechins are work as potential antioxidants and they can protect cell damage caused by free radicals. EGCG is very hydrophilic and as an antioxidant in an aqueous compartment. The invitro antioxidant activity of EGCG reported in the plasma lipid compartment. Compared to vitamins, EGCG is a stronger antioxidant. The EGCG antioxidant is stronger than vitamins C and E to delay the LDL oxidation in cell free trials^(37,38). EGCG neutralized the Reactive Oxygen Species (ROS) level such as the level of Superoxide Anions, Hydroxyl Radicals, Singlet Oxygen, Reactive Nitrogen Species, Nitric Oxide, Nitrogen Dioxide, and Peroxynitrite⁽³⁴⁾.

The chemical structure of EGCG is an antioxidant. The phenol ring in EGCG as an catcher of electron and free radical scavengers. EGCG is effectively inhibit the oxidation of tyrosine protein in blood platelets and improving mitochondrial function⁽³⁹⁾. In autoimmune diseases such as Sjogren's syndrome (SS) and diabetes type-1 there are a decreasing of anti-oxidant and defense of enzyme levels in the affected tissue. PRDX6 is a general anti-oxidant enzyme which influenced by autoimmune because of high level of H₂O₂, ROS, and EGCG at physiological concentrations able to restore PRDX6 and anti-oxidant levels by using signal transduction of MAPK and it provide the protection to

organs from oxidative damage.⁽⁴⁰⁾ In arthritis studies, EGCG improved the mice sample who has arthritis by using DC which this is a producing of indoleamine enzyme 2,3 dioxygenase (IDO), increasing the frequency of T regs and inducing the activation of the antioxidant pathway of NRF-2⁽⁴¹⁾.

Cells that express IDO can mediate strong local effects on nature immunology and adaptive toward the response of inflammatory disorders. The IDO activity was promoted local metabolic changes that affect cellular and systemic responses to inflammation and immunological signals. IDO helps to produce Treg cells and the NRF-2 activated in everywhere by the cell so this can fast protect against oxidative stress, inflammatory, and metabolic. Moreover, EGCG is known able to induce both IDO and NRF-2^(41,42).

Epigallocatechin-3- Gallate as an antiinflammation

The intervention of EGCG 120 mg/kg body weight per day to mice with lupus and 34 weeks old gain some effect such as (1) preventing of proteinuria, renal problems; (2) the increasing of E2 2 (Nrf2) in renal nuclear and glutathione peroxidase activity; (3) reduce renal oxidative stress, activation of NF-κB, and expression of mRNA/ NLRP3 protein and protein levels of mature caspase-1, IL-1β, and IL-18; and (4) increase Lien cell regulation (Treg). This data showed that EGCG has prophylaxis effect on nephritis lupus among mice and this really related with the effect of the increasing of antioksidan NRF2 signals level^(43, 44).

The description of inflammatory was characterized by aggregation of immune cells in inflammation process, proinflammatory cytokines production and reactive oxygen / nitrogen (ROS/ RNS). ROS/ RNS associated with NF-κB activation and activator of protein (AP-) 1. After the activation, NF-jB. and AP-1 will send to nucleus by cytoplasm and manage the inflammatory gene variation. EGCG also decreased the proinflammatory regulation by using P2X4 receptors than blocked the JAK1 / 2 tyrosine kinase signal in vascular endothelial cells⁽³⁹⁾.

Epigallocatechin-3-Gallate as an imunoregulator

EGCG as an immunoregulatory drug candidate, it can reducing the immune cells function or controlling the

inflammatory cytokines production, thereby maintaining immune homeostasis (45). The main mechanism of natural immunosuppressants action is depends on the antagonistic action of oxidative stressors, and in the end it leads to the formation of free radicals which targeted cytokines and autoantibodies. EGCG can also act as a modulator of cytokine production and B-T cell costimulation, therefore it eliminating the possibility of autoantibody formation and hyperactivation of the immune response in SLE cases (36).

The green tea effects / EGCG in innate immunity are 1) Neutrophils. The effect of EGCG on neutrophils are protects in limiting information and tissue damage caused by the inflammation, it has the effect to reducing migration and recruitment also decreasing proteolytic enzymes (46,47). 2) Macrophages. EGCG affects the various aspects of macrophages including migration, cytokines and chemokines which they produced by suppressing method and including the suppressing of pro-inflammatory genes such as IL-6, IL-12p40, MCP-1, ICAM-1, and VCAM-1. Suppression of NF- κ B, the main transcription factor regulates the expression of inflammatory molecular genes. EGCG inhibits inflammation process by induce lipopolysaccharides and turned off Notch signaling in primary macrophages of human (48, 49). 3) Dendritic cells. EGCG inhibits and reduces the DC function. The main function of DC is catch and process Ag, as APC. So the effect is to reduce MHC class I and 2, CD80, CD86, CD11, IL-12, TNF- α , IL-6, IL-1b, IL-10 and NF- κ B (50, 51). 4) NK cells. EGCG has the effect of reducing the level and frequency of NK cells. 5) Mast cells and basophils. EGCG inhibits the degranulation by use histamine reducing and blocke the 67LR, inhibiting the expression of high-affinity IgE Fc3RI receptors and reduce the ability of mast cells to cytokines out (TNF- α , IL-6, and IL-8) by using NF- κ B suppress activation (52).

The efek of green tea/EGCG in adaptive immunity are 1) as T cells (CD4+). T cells as an immunomodulator, it regulates T cell expansion, differentiation, and effector functions and manage the function of other cells like macrophage cells and B. The effect shows from the following parameters: proliferation and the decreasing of cell cycle, IL- 2, IL-10, IFN-g also decrease or increase, decreasing of IL-2R, IL-15R, IL-7 and pSTAT5. 2) EGCG inhibits the stages of T cell by activate Zap70,

Cg1 of Phospholipase, extracellular signaling-regulated kinase, MAPK level and activates AP-1.3). CD4 + T cell differentiation. Specifically, EGCG can suppress Th1 responses but not affects Th2 responses. EGCG can inhibit the differentiation of T cell CD4 + naive to be Th1, Th9 and Th17 and small amounts prevents IL-6 induction of Treg suppression, EGCG suppresses T-bet, PU.1, and ROR γ t, specific transcription factors of Th1, Th9, differentiation and Th17. EGCG suppresses main transducer signals such as p-STAT1 for Th1 and p-STAT3 for Th17. The effect of EGCG on B cells may occur due to their effect on T cells (53).

Innate and adaptive immune systems express TLRs, NK cells express TLRs 1, 3 and 6, DC express TLRs 2,4,7,9, T cells of human peripheral blood express TLRs 1-5, 7 and 9. B cells express TLRs 3, 4 and 9. TLR signals plays important roles in progenitors of myeloid and lymphoid. TLR activates the ligand to signaling cascade and produces chemokines and cytokines. After pathogenic recognition, TLR's signal transduction started through the Tol / Interleukin 1 receptor domain (TIR). Most TLR use MyD88 and TIRcontaining adapter to activate the signaling pathways of NF- κ B to inflammatory cytokines process. While, TLRs are dysregulated, there is high risk of serious inflammation and immunology diseases including autoimmune disease (54).

Phytochemicals was found in green tea because it have anti-inflammatory effects. This mechanism was explained that the targets affected are TLRs and downstream molecular signaling. It was also explained that the EGCG green tea flavonoid showed that modulator activity in specify pathways. EGCG flavonoids inhibit IKK β downstream signaling from the MyD88 way and inhibit NF κ B and it caused by TLR4 and TLR2 agonists. The TLR family and intracellular downstream have an important role in immunity of innate and adaptive. Activation of this signaling way shows in expression of various pro and anti-inflammatory molecules, which they are regulate homeostasis and metabolism. The changes or disability in this system will cause the infection, inflammatory diseases including autoimmune (54-58).

Conclusion

Environmental factors as trigger and flare for SLE, EGCG also a potential agent to protect the presence of

oxidative stress, inflammation and immune dysregulation and also EGCG can be as an immunomodulation and inflammation respond by involving innate or adaptive immune functions. EGCG can be an antioxidant, anti-inflammatory and suppression of T cells. So, this can be as an alternative strategy to prevent and reduce autoimmune inflammation by T cells media. EGCG affects the human immune system and has therapeutic potential for autoimmune and inflammation process.

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