Review Article

Hacettepe University Journal of the Faculty of Pharmacy
Volume 40 / Number 2 / July 2020 / pp. 83-92

Phytochemicals Used in Autoimmune Disorders

Otoimmün Hastalıklarda Kullanılan Fitokimyasallar

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Received date : 08.04.2020
Accepted date : 17.09.2020

ABSTRACT

The use of phytochemicals and herbs is as ancient as human due to their therapeutic effects, and then the effective, safety and inexpensive properties are the main reasons of their usage. Phytochemicals have beneficial effects against different diseases including autoimmune disorders. Immune system provides the protection of human body from pathogens like bacteria, virus, and fungi. Therefore, a breakdown in immune system often causes infections, diseases and autoimmune disorders. When immune system recognizes healthy cells as foreign cells and attacks them, an immune disorder can develop. Autoimmune disorders are identified as a specific adaptive immune response mounted against a self-antigen. They are chronic, life-threatening diseases of which the therapy is often impossible. Multiple sclerosis, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, thyroiditis, uveitis, systemic lupus erythematosus, and myasthenia gravis are some of the known autoimmune disorders. This review aims to provide information about the use of phytochemicals against different autoimmune diseases by affecting the immune system.

Keywords: autoimmune disorder, phytochemical, plant

ÖZET

Fitokimyasal maddeler ve bitkilerin terapi amaçlı kullanımları insanlık kadar eskidir. Aynı zamanda, bu bileşiklerin ve bitkilerin halk arasında kullanım şekli ve dozları ile güvenli kullanımları, tedariklerinin kolay ve ucuz olması sıklıkla kullanımlarının ana nedenlerindedir. Fitokimyasal maddeler otoimmün hastalıkları da kapsayan farklı hastalıklara karşı yararlı etkilere sahiptir. İmmun sistem insan vücuduna bakteri, virus ve mantar gibi patojenlere karşı koruma sağlar. Bununla birlikte, bağışıklık sistemindeki bir bozulma genellikle enfeksiyonlara, hastalıklara ve otoimmün bozukluklara neden olur. İmmun sistem sağlıklı hücreleri yabancı hücre olarak algılayıp bu hücrelere saldırdığında immün bozukluk oluşabilir. Otoimmün bozukluklar, kendi antijenine karşı spesifik bir adaptif immün yanıt olarak tanımlanır. Kronik, hayatı tehdit eden ve tedavisi genellikle imkansız olan hastalıklardır. Multipl skleroz, romatoid artrit, tip 1 diyabet, enflamatuvar bağırsak hastalığı, tiroidit, üveit, sistemik lupus eritramatoz ve miyastenia gravis

bazı bilinen otoimmün hastalıklardandır. Bu derleme immün sisteme etki ederek farklı otoimmün hastalıklara karşı fitokimyasal maddelerin kullanımı hakkında bilgi sunmayı amaçlamaktadır.

Anahtar Kelimeler: otoimmün hastalık, fitokimyasal, bitki

1. Introduction

Phytochemicals are naturally occurring compounds with various bioactive potential. The thousands of phytochemicals, that have been discovered, are grouped based on their functions and sometimes sources and phytochemicals with potential immunostimulant activity can be classified as high- and low-molecular compounds. Terpenoids, phenolic compounds, and alkaloids are among low-molecular immunomodulatory compounds, whereas polysaccharides are among the high-molecular weight compounds [1].

Phenolic compounds are derived from the secondary metabolism of plants and have at least one aromatic ring to which one or more hydroxyl groups are bonded. They can be grouped into flavonoids and non-flavonoids: (1) Flavonoids which usually occur in nature as glycosides are composed of two aromatic rings linked through an oxygen heterocycle. Depending on the degree of hydrogenation and the replacement of the heterocycle, they can be sub-classified as flavonols, flavones, isoflavones, anthocyanins, etc.; (2) Non-flavonoids, of which benzoic and cinnamic acid are the most representative compounds, which are commonly known as phenolic acids. Stilbenes, tannins, and lignins are the other well-known phenolic acids. Stilbenes, tannins and lignins are some of the other known phenolic acids [2].

Immune system, which works in harmony with cells, cell products, tissues, and organs to protect the body against foreign organisms such as infectious agents (viruses, bacteria, fungi, parasites) and neoplastic cells, is a complex and dynamic system. Unlike other systems, immune system consists of different cell groups with various functions and multiple lymphoid organs. Immune system removes the non-self by recognizing foreigner with cellular and humoral mechanisms. For the identification, processing and response of foreign matter, the system has highly complex functions such as the activation, differentiation and proliferation of effective cells, the production and regulation of cytokines [3, 4].

The immune system cells have two functional responses against the non-self, non-specific (innate immunity) and specific (acquired or adaptive) immune reactions. Innate immunity is a non-specific first-line defence of the body response to foreign organisms, cells, and substances with non-immunologic memory. Acquired immunity produces a character-specific response with immunologic memory. Prior exposure to foreign organisms/substances is required for the acquired immunological response. Due to the memory following the initial exposure, there is a faster and more rapid response at the next exposure. Some defects in the innate immune system are related a predisposition to infections or to autoimmune diseases. In the defence of the organization, antibody and cell-mediated immunity interact in harmony with specific and non-specific mechanisms. In general, a suitable immunological response includes that B lymphocytes form antibodies for neutralizing foreign antigens, macrophages phagocytose the antigens and present to T lymphocytes, natural killer (NK) cells and T lymphocytes are regulated to remove foreign cells, and the required cytokines are released [3, 4].

Phytochemicals have beneficial effects against different diseases including autoimmune disorders. This review aims to provide the readers knowledge on the usage of phytochemicals against different autoimmune disorders.

2. Autoimmune Disorders

Autoimmune disorders are identified as a specific adaptive immune response mounted against a self-antigen. They are chronic, life-threatening diseases of which the therapy is often impossible. Although they occur generally relatively rare, their effects on mortality and morbidity are quite high [5, 6]. In autoimmune disorders, the components and the activities of immune system are damaged. Humoral and cellular immune mechanisms can be involved in autoimmune conditions. The main reason of occurrence of autoimmune disorders has not been yet known, but it has been found that several factors may cause autoimmune disorders. The possible causes of autoimmune disorders are age, gender, poor health hab-

its, alcohol abuse, tobacco, stress and heredity. All of these factors make immune system weaker and cause autoimmune disorders [7].

Younger and middle-aged groups are the most sensitive groups to autoimmune disorders (e.g. myasthenia gravis, multiple sclerosis). However juvenile idiopathic (e.g. arthritis) specifically start in childhood. Rheumatoid arthritis and primary systemic vasculitis are mostly occurred in older adults [6]. Type 1 diabetes also primarily occurs in childhood and adolescence [6, 7].

Autoimmune diseases are suggested to be relatively higher in the developed countries compared to the developing countries. The incidence of rheumatoid arthritis is suggested to be about 1% in the United States compared to about 0.2–0.3% in China and South Africa [6, 7]. In 2013, the International Diabetes Federation (IDF) reported that 79000 children under 15 years develop autoimmune diabetes annually in the worldwide, that the prevalence is rising [8].

Symptoms of autoimmune disorders are not always obvious, and the diagnosis of these diseases is difficult. However, fever, cough, weight gain and muscle weakness are the common symptoms of these disorders. The signs and symptoms are associated with several organs and tissue damages. Several body systems including blood and blood vessels, lymphocytes, thyroid, connective tissue, intestine, kidney, heart, lung, liver, muscles, nerves and brain, skin may be affected in autoimmune diseases [9, 10].

It is known that there are at least 80 known autoimmune disorders. The organ-specific autoimmune diseases include autoimmune hepatitis (liver), type 1 diabetes (pancreas), Celiac disease, Crohn's disease and ulcerative colitis (gastrointestinal tract), multiple sclerosis (brain/spinal cord), myasthenia gravis (acetylcholine nicotinic postsynaptic receptors in neuromuscular cells), and haemolytic anaemia (erythrocytes). The non-organ-specific autoimmune diseases are systemic lupus erythematosus (SLE) (joints, skin, brain, kidneys, heart, etc.), rheumatoid arthritis (joints, lungs, heart, eyes), scleroderma (skin, intestine, lungs, joints), juvenile idiopathic arthritis (joints, skin, lungs) and dermatomyositis (skin, muscles) [9, 10].

Although the immunopathogenesis of the autoimmune disease is not well understood, the activation of B and T lymphocytes reacting against antigens of the body's self-tissues is suggested to play the major role. Generally, multiple mechanisms are involved in the immunopathogenesis of the autoimmune disorders. Antibody-dependent cell-mediated cytotoxicity, complement-dependent antibody-mediated lysis, or direct/indirect effects of cytotoxic T lymphocytes can contribute to the pathogenesis of the diseases [9, 10].

Meanwhile, tumour necrosis factor-alpha (TNF-α) and possibly other related cytokines are well known to be important in the progression of the inflammatory cascades in autoimmune disorders.

The activity and expression of TNF-α is regulated by a transcription factor, nuclear factor-kappa B (NF-kB), however TNF-α induce NF-kB activity. Since mediators of inflammation are also regulated by NF-kB, the regulation and down-regulation of NF-kB by gene products have been intended in the treatment of inflammatory diseases [11-15].

It has also been reported that oxidative stress might affect immune system leading to autoimmune disorders. Hence, antioxidants have been suggested to be used in certain diseases through their role as immune modulators. Some phytochemicals such as 2-hydroxy-4-methoxy benzoic acid, epigallocatechin-3-O-gallate, caffeine, carotenoids, chlorogenic acid, chlorophyllin, curcumin, ellagic acid, emblicanin, genistein, gingerol, glabridin, glycyrrhizin, lycopene, quercetin, pedunculagin, punigluconin, and vanillin are known to have potent antioxidant activity [1].

Effective safe therapeutic agents and treatment regimens have anti-inflammatory and/or immune system blocking properties like selective immunosuppression agents in the management of autoimmune diseases. But these drugs are not completely efficient in the treatment of some disorders. At the beginning of therapy, drugs show quick beneficial effect, however their prolonged consumption can cause severe adverse effects and a high cost. Clinical immunosuppressants have produced many side effects such as risk of infections, nephrotoxicity, neurotoxicity, headaches, nausea, and intestinal discomfort, reduction in platelet count, anaemia, and delay of wound healing. Patients with immunosuppression regimes have also a significantly higher risk in cancer developing than the general population, particularly lymphomas and skin cancer [16-19]. Due to this reason, these drugs may not be useful in the long-term therapy of autoimmune diseases. Replacement therapy is another way to cure the diseases. Immu-

ISSN: 2458 - 8806

nomodulation with medicinal plants can provide an alternative to conventional chemotherapy. Phytochemicals has been gained significant interest not because to reduce the conventional treatment toxicity and improve compliance but also reduce the high drug cost associated with clinical immunosuppression [5]. Plants contain numerous and diverse nutrients including polyphenols, antioxidants, vitamins and potent chemoprotectants, which have significant contributions to their protection effects on health. Many investigations have proved the beneficial effects of phytochemicals including the prevention and the delay of chronic degenerative diseases. The phytochemicals seem to have promising potential for the development of novel pharmaceuticals.

3. Phytochemicals Used in Autoimmune Disorders

Phytochemicals from different plants have different health beneficial effects including anti-inflammatory and antioxidant. They are often used for the treatment of autoimmune disorders.

3.1. Tetrandrine (Tet)

Tetrandrine (Tet), a bis-benzyl isoquinoline alkaloid which has been used in autoimmune disorders in China for decades, is isolated from the root of the plant *Stephania tetrandra*. The *in vivo* and *in vitro* studies revealed that its immunosuppressive effects, apart from its antioxidant and anticancer activities, are different from known antirheumatic drugs such as sulfalazine, methotrexate, cyclosporine. Tet has been suggested to be used effectively in rheumatoid arthritis since it is found that Tet inhibited the proliferation of CD28-costimulated T cell and the production of cytokine in T cells lymphocytes. Both T helper 1 (Th1) and Th2 cytokines are found to be susceptible to Tet suppression. Tet effectively inhibited CD28-costimulated NF-kB activities. Tet may reduce the activation of T cell receptor by blocking protein kinase C and NF-κB signaling pathways. Tet in combination with cyclosporin and also in combination with FK506 (an immunosuppressive agent more potent than cyclosporin) were shown to have a synergist effect. Tet may also play a role in the regulation of autoimmune disorders through its apoptotic mechanisms [20].

Besides its autoimmune regulation effects, some data from the animal studies indicated the potential accumulation and injury to human livers from chronic administration of tetrandrine. Tetrandrine was reported to cause liver injury in rats treated with tetrandrine (57 mg/kg by orally) for 8 day [Xin-ming, 2013]. It is relatively non-toxic to humans, even at the administration of 180 mg, intramuscularly three times daily [Dai, 2007].

3.2. Green Tea Polyphenols

Green tea is the most commonly consumed beverage in the world. Tea and its polyphenols, a product of the dried leaves of *Camellia sinensis*, have been suggested to have many pharmacological properties. The major green tea polyphenols (GTPs) are (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-epigallocatechin-3-gallate (EGCG). Studies also demonstrated that certain fractions of green tea such as epigallocatechin-3-gallate (EGCG) promote apoptosis and cell cycle arrest of transformed cells. EGCG was shown to suppress autoimmune encephalomyelitis (EAE) in *in vivo* experimental animal model. EAE is the experimental animal model of multiple sclerosis which is a multiphasic autoimmune disease of central nervous system where myelin-specific CD4+ Th1 cells are suggested to orchestrate the effector processes resulting in the injury of myelin sheath [21]. EGCG reduced the severity of symptoms when given at initiation or after the onset of EAE by limiting brain inflammation and reducing neuronal damage. Zipp et al. (2006) showed that orally treatment of EGCG suppressed the inflammation via inhibiting the proliferation and TNF-α synthesis of T cells and effectively prevented the recurrence of autoimmune disease in central nervous system *in vivo*. The anti-inflammatory potential of EGCG are mediated by down-regulation of NF-κB in T cells. It prevented the catalytic activity of proteasome in activated-T cells, which results in the intracellular accumulation of ubiquitinated proteins including NF-κB -suppressor I-kB [22].

EGCG might be useful in delaying or managing Sjogren's syndrome (SS)-like autoimmune disorders that can affect multiple tissues or organs. Primary SS is related to the lymphocytic infiltrations from salivary and lacrimal glands and finally atrophies, which leads to a loss of fluid production. The prevalence of SS seems to be higher in the US population compared to Japanese and Chinese population [23-28]. Apoptosis, cytotoxicity, and autoantigen expression,

which are involved in SS pathogenesis, are the main cellular mechanisms [29]. Hsu et al. (2005) reported that EGCG inhibited autoantigen expression in normal human keratinocytes and immortalized normal human salivary acinar cells [30]. Gillepsie et al. (2008) also investigated whether EGCG ameliorated the autoimmune-induced pathological changes in the salivary glands of the experimental non-obese diabetes induced SS mouse and found that EGCG significantly retarded the onset of diabetic autoimmune disease and effectively protected the salivary gland cells from autoimmune-induced damage at multiple levels. EGCG supplementation has been suggested to lead the regulation of serum total autoantibody levels and to reduce the development of insulin-dependent diabetes in animals. It was demonstrated that oral administration of green tea extract reduced the serum total autoantibody levels and the autoimmune lymphocytic infiltration in the submandibular glands of the non-obese diabetic mice [31]. EGCG protected normal human salivary acinar cells from NF-induced cytotoxicity. It has been suggested that GTPs may prevent glandular damage by the activation of protective systems early in disease onset via both gene regulation by p38 MAPK pathway and antioxidant activities [32].

Varilek et al. (2001) showed that GTPs reduced the inflammation in IL-2 mice, they suggested that GTPs had an important role in the treatment of chronic autoimmune inflammatory diseases such as inflammatory bowel disease [33]. Green tea was shown to increase the changes of arthritis-related immune responses and the further systematic exploration of dietary supplementation with green tea extract as an adjunct nutritional strategy for the management of rheumatoid arthritis has been proposed [34].

In general, use of standardized green extracts substances has been well tolerated in human clinical trials (Kapetanovic, 2009). Chronic 9-month and the follow-up 13-week subchronic dog studies showed that the No-Observed-Adverse-Effect-Level (NOAEL) was higher than 600 mg/kg body weight (highest dose tested) in fed dogs treated with the standardized green tea extract (85-95% total catechins and the main component is EGCG) (Johnson et al. 1999). Food supplements containing green tea catechins provide a daily dose of EGCG in the range of 5–1000 mg/day, for adult population. The EFSA concluded that catechins from green tea infusion, prepared in a traditional way, and reconstituted drinks with an equivalent composition to traditional green tea infusions, are in general considered to be safe according to the presumption of safety approach provided the intake corresponds to reported intakes. However, rare cases of liver injury have been reported after consumption of green tea infusions, most probably due to an idiosyncratic reaction. Based on the available data on the potential adverse effects of green tea catechins on the liver, it was concluded that there is evidence from interventional clinical trials that intake of doses equal or above 800 mg EGCG/day taken as a food supplement has been shown to induce a statistically significant increase of serum transaminases in treated subjects compared to control (EFSA, 2018).

3.3. Curcumin

Curcumin (diferuloylmethane), a phenolic compound isolated from the rhizome of turmeric (*Curcuma longa*), has been conventionally used for pain and wound-healing. Curcumin, the main active compound of turmeric, is responsible for its various activities. It is accepted as a healthy phytochemical with antioxidant, anti-inflammatory, and anti-carcinogenic activities. Recent studies have shown that curcumin improved rheumatoid arthritis, psoriasis, multiple sclerosis, and inflammatory bowel disease in human or in vivo experimental models. It has been shown to regulate various factors, enzymes, protein kinases, adhesion molecules, redox status, and gene expression of cytokines that are associated with inflammation [35-37]. Curcumin prevents the activation of NF-κB through the inhibition of IkB alfa kinase and AKT against the induction of inflammatory stimuli. Curcumin was suggested to decrease proliferation, invasion and angiogenesis due to blocking NF-κB-dependent gene products that suppress apoptosis [38]. It was also found to suppress NF-κB activation in most tumour cells, which leads to suppression of anti-apoptotic proteins [39].

A strong suppression of human T-lymphocyte proliferation by curcumin was reported [40-42]. Curcumin significantly inhibited IL-2 production *in vitro* [41].

In various chronic illnesses, where inflammation is well known to possess a remarkable role in many inflammatory diseases such as neurodegenerative diseases, diabetes, allergy, asthma, and autoimmune diseases, curcumin has been shown to exhibit therapeutic potential. Curcumin has been suggested to have

ISSN: 2458 - 8806

a potential in the treatment of rheumatoid arthritis (RA). Jackson et al. (2006) reported that curcumin can inhibit inflammatory processes associated with arthritis. Curcumin administration reduced the glycoprotein (Gp) A72 (an acidic protein with antitypic activity) levels by 73% with concomitant lowering of paw inflammation in arthritic rats [43]. Funk et al (2006) investigated the *in vivo* efficacy of curcumin in an animal model of RA using streptococcal cell wall-induced arthritis to determine its protective effect on the arthritis. Curcumin was found to prevent joint inflammation when treatment was started before [44]. Park et al (2007) showed that curcumin induced apoptosis and inhibited the production of prostaglandin (PGE)2 in synovial fibroblasts of patients with RA. Curcumin reduced the anti-apoptotic Bcl-2 expression and the X-linked inhibitor of the apoptosis protein as well as increased the pro-apoptotic Bax expression [45].

Although Food and Drug Administration (FDA) has declared curcumin as generally regarded as safe (GRAS), there are no long-term studies with curcumin to show its toxic or adverse effects. Therefore, the chronic toxicity studies are required in both rodents as well as in humans to determine the safety of curcumin.

Most of the evidence that supports the therapeutic potential of curcumin is mainly based on in vitro studies in which curcumin was tested at concentrations in the micromolar range. Several reports have demonstrated, however, that the plasma concentrations of curcumin in people taking relatively high oral doses of this compound are very low, typically in the nanomolar range. This means that the oral administration of curcumin does not lead to cytotoxic concentrations outside the gastrointestinal tract because of its poor bioavailability. A relatively high number of reports suggests that curcumin may cause toxicity under specific conditions (Burgos-Moró, 2010).

Experimental studies have demonstrated that, although low concentrations of curcumin induce antioxidant effects, higher concentrations of this compound increase the cellular levels of ROS (McNally, 2007). Several other lines of evidence raise concern about curcumin safety. Curcumin was recently found to be an active iron chelator in vivo and to induce a state of overt iron deficiency anaemia in mice fed with diets poor in iron. This suggests that curcumin has the potential to affect systemic iron metabolism, particularly in people with suboptimal iron status (Jiao, 2009). Curcumin has also been shown to inhibit the activity of the drug-metabolizing enzymes cytochrome P450, glutathione-S-transferase, and UDP-glucuronosyltransferase. The inhibition of these enzymes in people taking curcumin may lead to an undesired increase in the plasma concentrations of some drugs and cause toxicity (Oetari, 1996).

3.4. Resveratrol

Many polyphenolic compounds including stilben, resveratrol, and the flavonoids quercetin, catechin, and anthocyanins that have anti-inflammatory and antioxidant activity are found in grapes. Resveratrol, quercetin, and catechin can inhibit the activity of NF-κB and enzyme cyclooxygenase-2 which are an important mediators of inflammatory responses. Type I juvenile diabetes mellitus is a T-cell-mediated inflammatory autoimmune disease. In developed countries, 0.5% of the population has been currently affected by this situation. It is characterized by the infiltration of activated T lymphocytes and monocytes into the islets of Langerhans of the pancreas, resulting in inflammation and progressive destruction of the insulin-producing B cells. The production of TNF-α after LPS stimulation was found to be decreased in splenocytes of mice treated with orally grape powder when compared to control mice. In histological investigation, the degree of insulitis in pancreatic tissue was significantly higher in mice treated with grape powder than in the control. They suggested that diets with high content of polyphenols have preventive potential against autoimmune inflammatory attack of islet beta cells and decrease the onset and pathogenesis of autoimmune diabetes [46].

Plant-derived flavonoids have affected various intracellular processes, notably to inhibit the phosphorylation pathways and potentially to prevent cellular autoimmunity. The inhibiting effects of some plant-derived flavonoids on antigen-specific proliferation and interferon-gamma (IFN-γ) production were investigated in human and murine autoreactive T cells. T-cell responses were evaluated for the human autoantigen α-B crystallin, a candidate autoantigen in multiple sclerosis, and for the murine encephalitogen proteolipid protein peptide. The flavones apigenin and luteolin inhibited both murine and human T-cell responses, however there were not any effects

for fisitin, quercetin, morin and hesperitin, members of the subclasses of flavonoles and flavanones. The production of antigen-specific IFN-γ was found to be reduced more effectively by flavones than T-cell proliferation, suggesting that the intracellular pathway for IFN-γ production in T cells is particularly sensitive to flavone inhibition. These results show that flavones are effective inhibitors of the potentially pathogenic function of autoreactive T cells, whereas flavanols or flavanones do not. For further studies investigating the effects of flavonoids on autoimmune diseases, observing the same effects for flavones in human and murine autoreactive T cells has highlighted the use of autoimmune animal models [47].

In rats, experimental autoimmune myocarditis (EAM) is a model for human giant cell myocarditis and post-myocarditis dilated cardiomyopathy, of which the pathogenesis has not been clarified. However, there is increasing evidence that cytokines secreted from monocytes/macrophages and T cells play a crucial role in the initiation and progression of disease. Flavonoids including quercetin which are abundantly present in the human diet, scavenge oxygen radicals and have anti-inflammatory activities. Quercetin was found to ameliorate EAM, by interfering production of pro-inflammatory (TNF-α and IL-17) and/or anti-inflammatory (IL-10) cytokines [48].

Quercetin in BALB/c mice, it modestly suppressed splenocyte proliferation. It also *in vitro* significantly inhibited IL-2 production and T-cell proliferation [41].

Resveratrol does not appear to have side effects at short-term doses (1.0 g). Otherwise, at doses of 2.5 g or more per day, side effects may occurs, like nausea, vomiting, diarrhea and liver dysfunction in patients with non-alcoholic fatty liver disease [Brown, 2010]. Interestingly, no major side effects were stated in long-term clinical trials [Tomé-Carneiro, 2013]. In fact, resveratrol has been found to be safe and well-tolerated at up to 5 g/day, either as a single dose or as fraction of multiple-day dosing schedule [Patel, 2011].

3.5. Other chemicals of plant origin

Amla *(Emblica officinalis*), also known as Indian gooseberry and shankpushpi (*Evolvulus alsinoides*), have been used in ajurvedic medicines for many years because of their immunomodulatory activities. Ganju et al. (2003) evaluated the protective effects of amla and shankpushpi in adjuvant induced arthritic (AIA) rat model. AIA involves both the humoral and cell- mediated immune response, which is quite similar to human rheumatoid arthritis. Since both herbal extracts gave rise to immunosuppression in AIA rats, they were suggested to provide an alternative approach to the arthritis therapy. Both extracts significantly reduced the inflammation and oedema. The nitric oxide production was markedly decreased in the treated animals compared to controls. They were as potent as dexamethasone which is a traditionally used as immunosuppressant for arthritis [49].

Beta-sitosterol (BSS) and its glycoside (BSSG), sterol molecules that are synthesized by plants. In animals, BSS and BSSG was reported to have immunomodulatory activity and BSS:BSSG mixture seemed to target specific T-helper lymphocytes, Th1 and Th2 cells, improving the functions of T lymphocytes and natural killer cell activity. BSS:BSSG complex was suggested to be a promising agent in the therapy of autoimmune diseases [50].

Sulforaphane, a component of broccoli and other Cruciferous vegetables, suggested to induce phase II enzyme and hence show cytoprotective and anticarcinogenic activity. It is also found to inhibit the proliferation of T-cell and the production of IL-2 *in vitro* [41, 51, 52].

Rose hip (*Rosa canina*) has been traditionally used in infections and inflammatory diseases. In *in vitro* studies, extracts of rose hips were shown to have potent anti-inflammatory activities and to inhibit cyclooxygenase-1 and -2 [53]. In a double-blind placebo-controlled trial, the rose-hip powder 5 g daily for 6 months was found to be beneficial in the treatment of rheumatoid arthritis [54].

Andrographis paniculata has long been used as the traditional herbal medicine. The main component of *Andrographis paniculata* is effective in the treatment of inflammation. In a randomized, prospective, double-blind, placebo-controlled study of the effect of *Andrographis paniculata*, the extract including 30% total andrographolides were orally given to the patients with rheumatoid arthritis three times a day for 14 weeks. The extract was found to relieve the symptoms of rheumatoid arthritis symptoms. It is suggested that *Andrographis paniculata* may be a beneficial in the treatment of rheumatoid arthritis [55]. Andrographolide has been shown to provide anti-inflammatory benefits in a variety of inflamma-

ISSN: 2458 - 8806

tory disease models. Among the signaling pathways, inhibition of NF-κB activity is the main anti-inflammatory mechanism of andrographolide [56]. It was suggested to have protective effects on autoimmune arthritis through inhibiting MAPK pathways [57].

4. Conclusion

In conclusion, phytochemicals may be useful in autoimmune disorders, via affecting inflammatory pathways and also antioxidant activities. The suppressive effects and the proper dosage regime of phytochemicals should be determined with their chronic consumption in detail. Beneficial effects through the traditional dietary intake of phytochemicals at low levels for long time has been achieved but the advantages of the consumption of the purified active compounds such as curcumin, resveratrol at higher doses for the therapy need extreme concern. The studies are promising, but additional research is required before the use of phytochemical supplements in patients with autoimmune disorders and organ transplantation.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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ISSN: 2458 - 8806

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