



The role of flavonoids in autoimmune diseases: Therapeutic updates

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ABSTRACT

Flavonoids are natural polyphenolic compounds which are included in a panoply of drugs and used to treat and/or manage human ailments such as metabolic, cardiovascular, neurological disorders and cancer. Thus, the purpose of this review is to emphasize the importance of flavonoids for the treatment of autoimmune diseases and put into the limelight of the scientific community several health-promoting effects of flavonoids which could be beneficial for the development of novel drugs from natural products. Despite available reviews on flavonoids targeting various disease conditions, a comprehensive review of flavonoids for autoimmune diseases is still lacking. To the best of our knowledge, this is the first attempt to review the potential of flavonoids for autoimmune diseases. The structure–activity relationship of flavonoids in this review revealed that the rearrangement and introduction of other functional groups into the basic skeleton of flavonoids might lead to the development of new drugs which will be helpful in relieving the painful symptoms of various autoimmune diseases.

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Abbreviations: AD, autoimmune diseases; BNF, British National Formulary; CD, Crohn's disease; DMA, disease-modifying agents; DMARDs, disease modifying anti-rheumatic drugs; EAE, experimental autoimmune encephalomyelitis; EGCG, epigallocatechin-3-gallate; HO-1, heme oxygenase-1; IFN β , interferons beta; iNOS, inducible NO synthase; IBD, inflammatory bowel disease; MAPK, mitogen-activated protein kinase; MS, multiple sclerosis; NO, nitrous oxide; NF- κ B, nuclear factor- κ B; PK, pharmacokinetics; PTPN22, protein tyrosine phosphate non-receptor type 22; RA, rheumatoid arthritis; SAR, structure activity relationship; SLE, systemic lupus erythematosus; TNF- α , Tumor necrosis factor-alpha; T1DM, type 1 diabetes mellitus; UD, ulcerative disease.

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1. Introduction

Given the prominence of the autoimmune response in a human system, there exists a general notion that immune system could be a 'double-edged sword' which can either heal or even harm our physiological mechanisms. The integrity of the immune system is being maintained by mediators, which accomplish the balanced regulation of various cells and tissues. The definitive attribute of a healthy immune system is its ability to differentiate between the self and non-self-cells, and subsequently eliminate non-self-cells. Thus, the immune system plays an indispensable role in the destruction of undesirable non-self-cells and eventually protects the host against the entry of foreign bodies. Any interruption in this process, possibly due to the destruction of body's cells would ultimately lead to autoimmunity. Therefore, autoimmunity is defined as the disturbance in the process of antigenic recognition and elimination by immune cells (Rosenblum, Remedios, & Abbas, 2015).

The imbalance between activation and regulation of immune cells due to the failure of the self-tolerance mechanism by lymphocytes is believed to be the chief drive for the progression of autoimmune diseases (AD) in humans (Rosenblum et al., 2015). ADs were considered to be rare, but epidemiological data depicts that nearly 3–5% of the population are affected with type 1 diabetes mellitus (T1DM) and autoimmune thyroid diseases (Mariani, 2004). Altogether, a plethora of distinct autoimmune ailments have been identified and characterised. In fact, the most common AD includes; type I diabetes mellitus (T1DM), primary biliary cirrhosis, autoimmune hepatitis, Graves'; Crohn's (CD); ulcerative (UD); coeliac and Addison's disease, Sjogren's syndrome, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

Pathological studies of ADs deciphered several immunological dysfunctions involving multiple organs (SLE for instance) (Davidson & Diamond, 2014). Entirely a few strategical concepts are recommended to decipher the immune tolerance including, central tolerance, T regulatory cells (Tregs), homeostasis of proinflammatory cytokines, chemokines alongside its cognate receptors. Central tolerance, particularly in bone marrow and thymus has critical roles in determining the homeostasis of the immune system. Given the strict supervision of central tolerance, few self-reacting lymphocytes leak out into the periphery and produce autoantibodies (Arbuckle et al., 2003; Davidson & Diamond, 2014; Marshak-Rothstein, 2006; Nielsen et al., 2004; von Mühlen & Tan, 1995).

Many cell types such as CD4+ T cells participate in the immune response in autoimmunity and the IL-17 producing CD4+ T cells (Th17 cells) are central to disease pathogenesis. Depending on the local cytokine milieu, naive CD4+ T cells can be induced to differentiate into at least four functionally distinct kinds of effector T-helper cells, namely, type 1 and type 2 helper (Th1 & Th2), Th17 and regulatory (Treg) T cells each of them secreting their own group of cytokines (Astry, Venkatesha, & Moudgil, 2015). T-cell receptor engagement and co-stimulation initiates differentiation of native CD4+T cells into these different subsets in the presence of specific cytokines secreted by the innate immune system cells when come across particular pathogens and other antigens. Th1 cells produce IFN- γ dependent upon IL-12, while Th2 produce IL-4 (in the absence of IL-12), and Tregs usually identified by the CD4+CD25+Foxp3+ phenotype produce the anti-inflammatory/regulatory cytokines TGF- β , IL-10 and IL-35 (Astry et al., 2015).

The Th17 cells differentiate from T cells stimulated by TGF- β and the inflammatory cytokines IL-1 β and 6, but IL-23 is needed for Th17 proliferation. In addition to IL-17 A and 17F, human Th17 cells produce other pro-inflammatory cytokines, namely IL-6, 21, 22, and TNF- α , critical players in acute inflammation (neutrophils recruitment) and in chronic autoimmunity. Nevertheless, it should be also mentioned the plasticity of these cells that can additionally participate in regulatory responses, as IL-17 expressing cells can simultaneously secrete the regulatory cytokine IL-10 or the inflammatory IFN- γ (Boirivant & Cossu, 2012).

Activation of Th17 cells is believed necessary for destruction of bacteria and fungi, notably when not shielded by Th1 or Th2. Although these responses make part of normal immunity, a dysregulated response becomes harmful, as in autoimmune diseases. Treg cells induce peripheral tolerance and protect against autoimmunity, suppressing effector cells through different mechanisms that prevent dendritic cells from activating and expanding the effector T cell population, and by producing inhibitory anti-inflammatory cytokines (Astry et al., 2015). Up-regulation of Th1 and 17 activity and inhibition of Treg cells seem essential components of EAE and other autoimmune pathologies. During the last decades, several non-HLA loci have been linked with T1DM, ulcerative colitis, SLE and RA (Davidson & Diamond, 2014; James, Harley, & Scofield, 2006). These menaces depend on the gene product involved in both innate and adaptive immune response and lead to the occurrence of multiple AD in an individual, which simultaneously increase the genetic risks (Blank, Barzilai, & Shoenfeld, 2007; Davidson & Diamond, 2014). This phenomenon is seen on the protein tyrosine phosphatase non-receptor type 22 (PTPN22) coding gene (Bonsor, Grishkovskaya, Dodson, & Kleanthous, 2007; Powell & Black, 2001) regulated by hematopoietic cells. PTPN22 plays a critical role in regulating the signals from immune cells. In the adaptive immune response, PTPN22 suppressed the activation of T-cell by hampering the downstream signalling of the T-cell receptor. On the other hand, in the innate immune response, the PTPN22 selectively promotes the release of myeloid cell type I interferon by augmenting the downstream signalling of pattern recognition receptors. Interestingly, PTPN22 is a classical autoimmune gene found in individuals with many autoimmune disorders viz. T1DM, SLE, RA and CD (Davidson & Diamond, 2014; Pasare & Medzhitov, 2003; Turley, 2002).

Likewise, the somatic mutations in the genes encoded for pre-B-cell antigen receptor (pre-BCR), B-cell development (Christensen et al., 2006), and regulator and effector of T cells (Millar et al., 2003) affect the innate and adaptive immune response of the host. The transcription regulatory protein BACH2 plays a vivid role in controlling the balanced tolerance and immunity and its associated loss of tolerance in CD (Fruman & Walsh, 2007) T1DM (Serrano, Millan, & Páez, 2006) and multiple sclerosis (MS) (Michou et al., 2007). The other HLA molecules that are shared by ADs include; signal transducer and activator of transcription 4 (STAT4), cytotoxic T lymphocyte-associated protein 4 (CTLA4), CD80, IL-12B, IL-12RB2, intracellular adhesion molecule 3 (ICAM3), mitogen-activated protein kinase 1 (MAPK1), RNA-binding motif protein (RBM17) and tyrosine kinase 2 (TYK2). The prevalence of these loci suggests the hypothesis that 'single target to treat many diseases' could be possible (Chu et al., 1996).

Strikingly, the American Autoimmune Related Diseases Association (AARDA), autoimmune disease prevalence is higher (75%) among women compared to men. Incidence and prevalence of autoimmune diseases have increased significantly worldwide, which account for 19.1 and 12.5 % respectively. The percentage increase per year for various autoimmune diseases was 3.7, 6.2, 6.3 and 7.1 % respectively for neurological, gastrointestinal, endocrinological and rheumatic autoimmune diseases (Lerner, Jeremias, & Matthias, 2015). The exact aetiology is still unknown; but it may be triggered by multiplicity of genetic factors, abnormal immune regulation, hormonal and external environmental factors (Becker et al., 1998; Theofilopoulos & Kono, 1999).

In 1930, a Hungarian physiologist Szent-Gyorgyi succeeded in the isolation of a new chemical substance from orange, and it was named as 'Vitamin P'. However, it was later proved that this new substance was a flavonoid (Coppock & Dziwenka, 2016; Harborne & Williams, 2000). Flavonoids became more popular among the researchers after the discovery of the 'French Paradox', where it was noticed that the occurrence of cardiovascular diseases in people living in the Mediterranean region was less as compared to other parts of the world due to their consumption of red wine, which is a rich source of flavonoids (Bandawane, Beautikumari, Gate, & Patel, 2014; Tapas, Sakarkar, & Kakde, 2008). Flavonoids are widely distributed secondary metabolites synthesized through the phenylpropanoid pathway in plants.

Chemically, flavonoid is a polyphenolic compound comprising two aromatic rings A and B and a heterocyclic ring identified as ring C (Fig. 1). In some flavonoids instead of ring C, there may be an open chain of three carbon atoms (Guan & Liu, 2016; Iwashina, 2000).

Flavonoids are classified based on the oxidation and degree of unsaturation of ring C (Fig. 2). Some classes of flavonoids are flavonols and flavones, flavanols, (or catechins), flavanones, anthocyanins and isoflavones (Edewor, 2016; Jiménez-Aguilar & Grusak, 2017; Y. Kang, Kim, Kim, Lee, & Yoon, 2017). These are considered to be the most representative compounds with protective actions in autoimmune pathologies displayed in Fig. 2.

2. Current status of treatment against autoimmune diseases

Current treatment and/or management strategies of autoimmune diseases are quite challenging due to their multifactorial nature and have attracted the interest of the scientific community and clinicians. Nonetheless, looking for the right drug for the right patients remains a serious challenge (Tavakolpour, 2017). Furthermore, the criteria employed clinically for autoimmune diseases are based on their manifestations complemented with laboratory test results including; the level of complement proteins and serum. However, given the varied symptoms in any particular disease, combined with the similarities among distinct diseases creates a grey zone for diagnosis, particularly among young clinicians (Wu et al., 2018).

During recent years, much effort has been devoted to introducing a new generation of treatments, which are targeted to be more efficient, more specific, and safe. For instance, the recently developed biological drugs, including janus kinase (JAK) inhibitors and different types of monoclonal antibodies, are proposed as promising therapeutic options for some autoimmune and inflammatory diseases, with fewer or no life-threatening adverse effects (Tavakolpour, 2017).

Additionally, much interest has been laid upon personalized medicine as a novel approach for autoimmune diseases. There is growing evidence that many individuals who do not presently possess any signs of autoimmunity are nonetheless tested positive for different auto-antibodies. However, not all patients respond well to these specific treatments and it requires to be well-established for autoimmune diseases. Hence, identifying and recognizing the drugs based on the genetics and molecular profile of patients requires a comprehensive protocol (Giles & Salama, 2018; Tavakolpour, 2017).

Advances in genetics and biomarkers may allow the progress of personalized medicine. Currently, biomarkers are emerging as disease modifying agents (DMAs) in the management of relapsing–remitting MS (RRMS). Biomarkers play a crucial role in the personalized treatment in therapeutic decision-making in MS. The altered level of fetuin-A, a serum protein in cerebrospinal fluid (CSF), was connected with early conversion to RRMS (Lehmensiek et al., 2007; Tumani et al., 2009). The increase of CSF fetuin-A levels is significantly associated with inflammatory disease activity in patients with MS- specific brain pathology (Harris et al., 2013).

Novel therapeutic approaches are focused on B-cell targets including anti-CD20 monoclonal antibody (Rituximab) and anti-B lymphocyte stimulator (BLYS) (Ding, Foote, & Jones, 2008; Murdaca, Colombo, &

Puppo, 2011). Infusion reactions, neutropenia, and human anti-chimeric antibodies production are the adverse effects associated with the treatment of Rituximab (Roccatello et al., 2011). T-cell directed therapies include drugs like Abatacept, Tacrolimus, Leflunomide, Edratide, Rigerimod, Laquinimod and N-acetylcysteine (Jayne et al., 2013; Lai et al., 2012; Liu et al., 2015; Tam, Li, Wong, Lam, & Szeto, 2004; Urowitz, Isenberg, & Wallace, 2015; Wofsy et al., 2013; Zimmer, Scherbarth, Rillo, Gomez-Reino, & Muller, 2012), cytokine inhibition drugs anti-TNF- α (adalimumab, certolizumab pegol, golimumab and infliximab) (Aringer et al., 2009; Tracey, Klareskog, Sasso, Salfeld, & Tak, 2008) and anti-IFN- α / γ (Rontalizumab and Sifalimumab) (Kennedy, 2011; Wallace, 2007). A plethora of other conventional drug classes are employed in the prophylaxis, management, and treatment of auto-inflammatory disorders as listed in Table 1. Nonetheless, given their inefficacy in certain cases coupled with low success rates as well as numerous adverse or side effects experienced opens new avenues for the role of natural products particularly flavonoids as novel therapeutic agents in auto-inflammatory disorders.

3. Pre-clinical effects of flavonoids as therapeutic agents for autoimmune disease

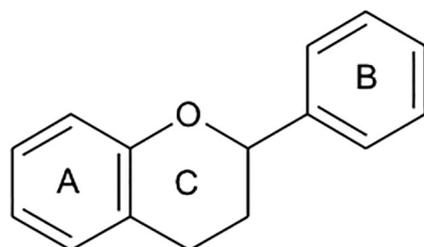
Epidemiological and experimental data widely support the anti-inflammatory and neuroprotective activities of flavonoids (Cardenas et al., 2016; Gutierrez-Merino et al., 2011; Park, Sapkota, Kim, Kim, & Kim, 2011; Warford et al., 2014). Therefore, it is not surprising that their pharmacological potential are being regarded with great interest for autoimmune diseases still requiring effective therapeutic alternatives. In addition to the classical antioxidant-related anti-inflammatory capacities and neuronal cytoprotective actions, current research is revealing the essential immunomodulatory potential of flavonoids in these diseases.

Particular attention has been focused on the potential of flavonoids to modulate the balance between different immune cells playing an imminent role in the inception and progress of autoimmune diseases.

The imbalance between Th1 and Th2 cells has been traditionally suggested to play the principal roles, but the more recently described Th17 and Treg subsets have conquered the central stage in autoimmune response. To reduce T-cell proliferation and activity are the traditional therapeutic approaches for these pathologies, but T-cell-mediated autoimmune dysfunction is no longer discussed only within the context of the Th1 versus Th2 frame, and modulation of Th17 and suppressive Treg cells are presently the primary focus of research for new drugs.

3.1. Effects of flavonoids in models of multiple sclerosis

The available MS drugs are more effective in reducing relapses but have limited ability to retard irreversible damage, for example neuronal and axonal injury, which occurs during both the initial and further phases of the disease. Neurological disability during relapsing–remitting MS occurs in reversible episodes driven by focal inflammatory damage to white matter, the death of oligodendrocytes (myelin-forming cells), and loss of myelin. Cumulative axonal and neuronal injury is thought to be a significant contributor to disease progression



Biological activity
Antioxidant actions
Anti-inflammatory actions
Hepatoprotective actions
Neuroprotective actions
Immunomodulatory actions

Fig. 1. The chemical structure of flavonoids backbone and general biological actions implicated in their therapeutic capacity against autoimmune diseases.

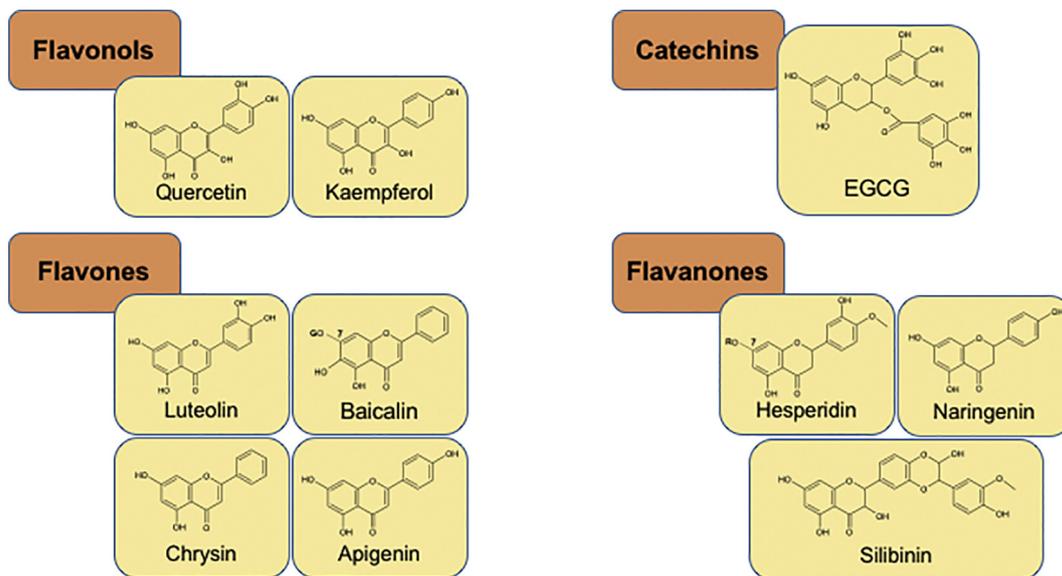


Fig. 2. The molecular structures of key flavonoids with documented therapeutic potential in autoimmune diseases. Compounds are grouped by the corresponding classes of flavonoids. G in baicalin structure (C7): glucuronic acid; R in hesperidin structure (C7): disaccharide rutinose; EGCG: epigallocatechin-3-gallate.

that eventually affects the majority of MS patients. Although remyelination can help restore axonal conduction and contributes to clinical recovery or remission, the remyelination capacity decays during the progressive phase of the disease. Therefore, pharmacological stimulation of endogenous remyelination would potentially have a significant impact (Kremer, Küry, & Dutta, 2015).

Animal models of experimental autoimmune encephalomyelitis (EAE) are well-established models for human MS pathophysiology. Indeed, they are crucial to investigate the aspects of autoimmunity, neurodegeneration, and potential therapies for MS (Lovett-Racke, 2017). Fig. 3 displays the flavonoids showing pharmacological potential for MS supported by the use of these models and referred in this section. Isoflavones are not discussed in this review due to their possibly confounding estrogenic activity, but some data on genistein and daidzein can be found in Schmitz et al. (2015).

Quercetin and epigallocatechin-3-gallate (EGCG) have been studied by different authors that described beneficial effects by reducing symptoms and pathological features (infiltration of immune cells into the CNS and demyelination), as well as decreasing the production of inflammatory mediators such as IL-17, 6, 1 β , and TNF- α in EAE animals (references in Fig. 3). A flavonoid fraction extracted from apple peel and rich in quercetin showed protective effects in an EAE mouse model and promoted the expression of genes required for remyelination as stearyl-CoA desaturase-1 (Warford et al., 2014). Quercetin is a promising agent to stimulate myelin repair by interfering with Notch pathway and Wnt signalling implicated in the (re) myelination process (Kremer et al., 2015).

Wang et al. (2012) found EGCG decreased the expansion of autoreactive T cells and modulated their differentiation into different populations, namely, reducing Th1 and Th17 cells while stimulating the Treg subset. These data tend to advocate the beneficial effects of EGCG on EAE is not merely resulting from suppression of antigen-induced T cell proliferation, but instead, the flavonoid affects CD4⁺ T cell groups differentially, being able to inhibit pro-inflammatory subsets and favour pro-tolerant/anti-inflammatory subsets of CD4⁺ T cells, leading balance towards relieving pathology. These authors compared the efficacy of different EGCG dietary supplementation protocols, and the results suggested flavonoid's effect is mostly therapeutic, rather than preventive. *Ginkgo biloba*, quercetin, resveratrol, and EGCG are commonly included in supplements, and functional foods for MS treatments (Plemel et al., 2015), and a recent study with MS patients at the United Kingdom (UK) detected signs of suboptimal nutrition (Coe et al., 2018).

Experimental shreds of evidence are also accumulating supportive of the potential of flavones for MS (Fig. 3). In a chronic encephalomyelitis model, i.p. administration of luteolin significantly reduced clinical symptoms, leukocytes infiltration and amyloid precursor protein level, while oral luteolin delayed disease onset and reduced clinical severity in a first phase, but not at a later phase of the disease (Hendriks et al., 2004). Comparison of the effect of quercetin and luteolin in an acute model indicated luteolin was much more effective in suppressing the incidence and maximum clinical symptoms (Hendriks et al., 2004).

Baicalin and chrysin also ameliorated EAE symptoms, CNS infiltration and demyelination, as well as Th1 and Th17 cell differentiation (Zhang et al., 2015a; Zhang et al., 2015b), possibly by the inhibition of the NF- κ B pathway implicated in the anti-inflammatory action of flavonoids in different settings (Gutierrez-Merino et al., 2011). The oriental medicine Samhwangsasim-tang contains baicalin, sennoside A and berberine, among other compounds, limited the progression of EAE by inhibiting the infiltration and activation of microglia and macrophages, the expression of inflammatory mediators, and maintenance of BBB function (Lee, Choi, Lee, & Cho, 2017). The extract inhibited demyelination and neural injury, by inhibiting Th1 cell response and activating Treg cell response.

The study by Verbeek, van Tol, and van Noort (2005) demonstrated that oral flavonoids could reduce autoimmune antigen-specific T cell reactivity *in vivo*, although may also affect recovery following acute inflammatory damage. Luteolin and apigenin reduced antigen-specific T cell proliferation but unexpectedly stimulated IFN- γ production. Quercetin equally increased, while hesperidin-glycoside decreased, the production of IFN- γ by T cells. In different EAE models, flavonoids were reported to aggravate clinical scores or delay recovery, in spite that none affected the onset of the pathology (Verbeek et al., 2005). In a work by Sato et al. (2013), resveratrol also aggravated the clinical progression in EAE and viral models of MS, increasing inflammatory demyelinating lesions in the treated mice. These studies illustrate variable results might be obtained *in vivo* and further research is required to understand the factors determining the outcomes of flavonoid treatments.

Ginwala et al. (2016) tested apigenin in progressive and relapse-remitting mouse models and observed decreased EAE disease severity and relapse, associated to reduced immune cell migration into the spinal cord, a shift from a pro-inflammatory to a more tolerogenic phenotype of dendritic cells, and reduction of Th17 cells and Treg's increase. In a different model, the immunomodulatory action of apigenin and reduced leukocyte infiltration in lungs was related to counteracting

Table 1
Current treatments for autoimmune disorders.

Disease	Current treatment	Reported side effects	Reference	
Primary biliary cirrhosis	Bile acids Ursodeoxycholic acid	Diarrhea	BNF, 2018	
	Colestyramine	Intestinal obstruction (Rare)		
Crohn's disease	Aminosalicylates Sulfasalazine	Blood disorders, cough, dizziness, fever, Heinz body anaemia, insomnia, megaloblastic anaemia, proteinuria, pruritus, stomatitis, taste disturbances, tinnitus		
	Monoclonal antibodies (anti-lymphocyte) Vedolizumab	Acne, arthralgia, back pain, constipation, cough, dyspepsia, eczema, erythema, flatulence, gastroenteritis, headache, hypertension, infections, malaise, muscle spasms, muscular weakness, nasal congestion, nausea, night sweats, oropharyngeal pain, paraesthesia, pharyngitis, pruritus, pyrexia, rash, upper respiratory tract infection	BNF, 2018	
	Antibacterial Ciprofloxacin	Flatulence		
	Antimetabolites Azathioprine	Hepatic veno-occlusive disease, lymphoma, pancreatitis, pneumonitis, red cell aplasia	Seela, Sheela, & Boyer, 2005	
	Mercaptopurine	Rare Pancreatitis, transient oligospermia		
	Tumor necrosis factor alpha inhibitors Adalimumab	Anxiety, benign tumours, chest pain, cough, dehydration, dermatitis, dizziness, dyspepsia, dyspnea, electrolyte disturbances, eye Disorders, flushing, gastrointestinal haemorrhage, haematuria, hyperlipidaemia, hypertension, hyperuricaemia, impaired healing, mood changes, musculoskeletal pain, oedema, onycholysis, paraesthesia, rash, renal impairment, skin cancer, sleep disturbances, tachycardia, vomiting.	BNF, 2018	
	Infliximab	Alopecia, arthralgia, constipation, diarrhea, dizziness, dry skin, dyspepsia, ecchymosis, epistaxis, flushing, gastro-intestinal haemorrhage, gastro-oesophageal reflux, hyperhidrosis, hypertension, hypoesthesia, hypotension, myalgia, new onset or worsening psoriasis, palpitation, paraesthesia, rash, sleep disturbances, tachycardia		
	Ulcerative colitis	Aminosalicylates Balsalazide sodium	Cholelithiasis	BNF, 2018
		Mesalazine	Dizziness (Rare)	BNF, 2018
		Olsalazine	Watery diarrhoea	
Sulfasalazine		Blood disorders, cough, dizziness, fever, Heinz body anaemia, insomnia, megaloblastic anaemia, proteinuria, pruritus, stomatitis, taste disturbances, tinnitus	BNF, 2018	
Corticosteroids Beclometasone dipropionate		Constipation, drowsiness	BNF, 2018	
Antimetabolites Azathioprine		Hepatic veno-occlusive disease, lymphoma, pancreatitis, pneumonitis, red cell aplasia	Seela et al., 2005; Czaja & Carpenter, 2006; Heneghan, Allan, Bornstein, Muir, & Tendler, 2006;	
Mercaptopurine		Rare Pancreatitis, transient oligospermia	BNF, 2018	
Monoclonal antibodies (anti-lymphocyte) Vedolizumab		Acne, arthralgia, back pain, constipation, cough, dyspepsia, eczema, erythema, flatulence, gastroenteritis, headache, hypertension, infections, malaise, muscle spasms, muscular weakness, nasal congestion, nausea, night sweats, oropharyngeal pain, paraesthesia, pharyngitis, pruritus, pyrexia, rash, upper respiratory tract infection	BNF, 2018	
Monoclonal antibodies Belimumab		Infusion-related side-effects are reported commonly, including severe or life-threatening hypersensitivity and infusion reactions.	BNF, 2018	
Rheumatoid arthritis		Sulfasalazine	Blood disorders, cough, dizziness, fever, Heinz body anaemia, insomnia, megaloblastic anaemia, proteinuria, pruritus, stomatitis taste disturbances, tinnitus	BNF, 2018
	NSAIDs Corticosteroids Glucocorticoids		Ghosh, Alajbegovic, & Gomes, 2015; Kamal & Baldi, 2015	
	Surgical treatment		Joseph, Hunter, Ray, & Dixon, 2016; Banse et al., 2015; Brady, Tkacz, Lofland, Meyer, & Bolge, 2015; Zengin et al., 2017; Tavakolpour, 2017;	
	Antimetabolites		Krause & Matteson, 2014	

(continued on next page)

Table 1 (continued)

Disease	Current treatment	Reported side effects	Reference
Psoriasis	Azathioprine	Hepatic veno-occlusive disease, lymphoma, pancreatitis, pneumonitis, red cell aplasia	Seela et al., 2005; Czaja & Carpenter, 2006; Heneghan et al., 2006
	Mercaptopurine	Rare Pancreatitis, transient oligospermia	
	DMARDs		
	Hydrochloroquine sulfate	Gastro-intestinal disturbances, headache, pruritus, rashes, skin reactions	Donahue et al., 2008; Kapoor, Singh, Gulati, Gupta, & Vaidya, 2014; Luo et al., 2013; Pincus, Yazici, Sokka, Aletaha, & Smolen, 2003; Harris et al., 2013; Lucchinetti, Brück, Rodriguez, & Lassmann, 1996; Askanase, Yazdany, & Molta, 2014; Borchers, Keen, Shoenfeld, & Gershwin, 2004; Guiducci et al., 2010; Shum & Askanase, 2012
	Penicillamine	Anorexia. fever. nausea. proteinuria. rash. thrombocytopenia	BNF, 2018
	Sodium aurothiomalate	Alopecia, blood disorders (sometimes sudden and fatal), colitis, gold deposits in eye, hepatotoxicity with cholestatic jaundice, irreversible pigmentation in sun-exposed areas (on prolonged parenteral treatment), mouth ulcers, nephrotic syndrome, peripheral neuropathy, proteinuria, pulmonary fibrosis, severe anaphylactic reactions, skin reactions, stomatitis, taste disturbances	BNF, 2018
	Tocilizumab	Abdominal pain, antibody formation, dizziness, gastritis, headache, hypercholesterolaemia, hypersensitivity, hypertension, infection, leucopenia, mouth ulceration, neutropenia, peripheral oedema, pruritus, raised hepatic transaminases, rash, upper respiratory-tract infection	BNF, 2018
	T-cell activation inhibitors		
	Abatacept	Abdominal pain, conjunctivitis, cough, diarrhea, dizziness, dyspepsia, fatigue, flushing, headache, hypertension, infection, leucopenia, nausea, pain in extremities, paraesthesia, stomatitis, vomiting	BNF, 2018
	Tumor necrosis factor alpha inhibitors		
	Adalimumab	Anxiety, benign tumours, chest pain, cough, dehydration, dermatitis, dizziness, dyspepsia, dyspnea, electrolyte disturbances, eye disorders, flushing, gastrointestinal haemorrhage, haematuria, hyperlipidaemia, hypertension, hyperuricaemia, impaired healing, mood changes, musculoskeletal pain, oedema, onycholysis, paraesthesia, rash, renal impairment, skin cancer, sleep disturbances, tachycardia, vomiting	BNF, 2018
	Certolizumab pegol	Hypertension, rash, sensory abnormalities	BNF, 2018
	Etanercept	Interstitial lung disease, new onset or worsening psoriasis, rash, skin cancer, uveitis	BNF, 2018
	Infliximab + methotrexate	Alopecia, arthralgia, constipation, diarrhea, dizziness, dry skin, dyspepsia, ecchymosis, epistaxis, flushing, gastro-intestinal haemorrhage, gastro-oesophageal reflux, hyperhidrosis, hypertension, hypoaesthesia, hypotension, myalgia, new onset or worsening psoriasis, palpitation, paraesthesia, rash, sleep disturbances, tachycardia	Luo et al., 2013; Pincus et al., 2003; Haleagrahara et al., 2017; Giles & Salama, 2018
Interleukin Inhibitors			
Ustekinumab	Arthralgia, diarrhea, dizziness, headache, infections (sometimes severe), injection-site reactions, malaise, myalgia, nausea, oropharyngeal pain, pruritus	BNF, 2018	
Tumor necrosis factor alpha inhibitors			
Adalimumab	Anxiety, benign tumours, chest pain, cough, dehydration, dermatitis, dizziness, dyspepsia, dyspnoea, electrolyte disturbances, eye disorders, flushing, gastrointestinal haemorrhage, haematuria, hyperlipidaemia, hypertension, hyperuricaemia, impaired healing, mood changes, musculoskeletal pain, oedema, onycholysis, paraesthesia, rash, renal impairment, skin cancer, sleep disturbances, tachycardia, vomiting	Dass, Vital, & Emery, 2007; Sharma et al., 2016; Tavakolpour, 2017	
Etanercept	Uncommon Interstitial lung disease. new onset or worsening psoriasis, rash, skin cancer, uveitis	BNF, 2018	
Calcineurin inhibitors and related drugs			
Pimecrolimus	Burning sensation, erythema Folliculitis, pruritus, skin infections	BNF, 2018	
Tacrolimus	Application-site infections, application-site reactions. herpes simplex infection, irritation (at application-site), Kaposi's varicelliform Eruption, pain at application-site, rash	BNF, 2018	
Retinoid and related drugs			
Acitretin	Abdominal pain, abnormal hair texture, alopecia (reversible on withdrawal), arthralgia, brittle nails, dermatitis. Diarrhoea, dryness and inflammation of mucous membranes, dryness of conjunctiva (causing conjunctivitis and decreased tolerance to contact lenses), epidermal fragility	BNF, 2018	

Table 1 (continued)

Disease	Current treatment	Reported side effects	Reference
Irritable bowel disorder	Tazarotene	Dry or painful skin, stinging and inflamed skin (Rare)	BNF, 2018
	Vitamin D analogues		
	Calcipotriol	Burning, dermatitis, erythema, itching, local skin reactions, paraesthesia	BNF, 2018
Irritable bowel disorder	Tacalcitol	Burning, dermatitis, erythema, itching, local skin reactions, paraesthesia	
	Corticosteroids	Dose-dependent side effects such as moon face, infections, diabetic disease, and osteoporosis	Matsumoto et al., 2008
relapsing–remitting MS (RRMS)	Cytapheresis (leukocyte removal therapy)	suppressed the immune response	Matsumoto et al., 2008
Systemic lupus erythematosus	Natalizumab	reduced serum levels hypersensitivity and reduced therapeutic efficacy	Calabresi et al., 2007; Rudick, Lee, Simon, Ransohoff, & Fisher, 2004; Mahomoodally & Suroowan, 2018
Neuromyelitis optica (NMO)	glucocorticoids, antimalarial drugs, and NSAIDs		
	Belimumab		Mahomoodally & Suroowan, 2018
	Intravenous corticosteroid therapy with methylprednisolone and plasma exchange		Wingerchuk, Lennon, Lucchinetti, Pittock, & Weinschenker, 2007; Weinschenker & Wingerchuk, 2017; Collongues & de Seze, 2011;
	Aquaporin-4 antibody (AQP4-Ab)		Papadopoulos & Verkman, 2012; Tradtrantip et al., 2012; Papadopoulos & Verkman, 2012; Saadoun et al., 2012
	Ecilizumab		Papadopoulos & Verkman, 2012; Pittock et al., 2013
	Tocilizumab	Meningococcal meningitis	Araki et al., 2014; Papadopoulos & Verkman, 2012; Pittock et al., 2013

inflammation-induced NF- κ B activity and mitochondrial dysfunction (Cardenas et al., 2016). Mitochondrial dysfunction is emerging as possible target in the search for alternative MS therapies (Fetisova, Chernyak, Korshunova, Muntyan, & Skulachev, 2017), and it should be remembered that mitochondrial dysfunction can contribute to the oxidative damage seen in the pathogenesis of demyelination and neuronal injury in MS even if occurring only after NADPH oxidases activation (Fischer et al., 2012; Lagoa, Gañán, López-Sánchez, García-Martínez, & Gutierrez-Merino, 2014).

Hesperidin and naringin are natural citrus flavanones and more recently studied for MS therapy, providing protective effects by inhibiting EAE development and symptoms (Fig. 3). Hesperidin reduced leukocyte infiltration and production of IL-17 and IL-6, while analysis of peripheral immune cell subpopulations indicated an increase in Treg and decrease of Th17 cells (Haghmorad et al., 2017). Hesperidin administered subcutaneously also afforded protective effects (Ciftci et al., 2015). A detailed study in an EAE mouse model showed naringenin administration reduced populations of Th1, Th17, Th9, and IFN- γ +IL-17+CD4+ T cells, while not affecting Th2 and Treg subsets in peripheral lymphoid tissue, and similarly in the brain and spinal cord (Wang et al., 2018a).

It is worth mentioning that we have not found studies dedicated to the anthocyanidins class of flavonoids. Nevertheless, dietary blueberry reduced disease incidence in a chronic EAE model and improved disease symptoms in a relapsing–remitting model, reducing demyelination and TNF- α levels (Xin, Feinstein, Hejna, Lorens, & McGuire, 2012).

3.2. Effects of flavonoids in models of rheumatoid arthritis

Assessment of flavonoid's therapeutic potential for RA is progressing rapidly as supported by rodent models of collagen-induced arthritis (Table 2). Epigallocatechin gallate is the primary bioactive catechin present in green tea and was described to reduce arthritis activity in mouse, modulating B and T cells populations, and enhancing nuclear factor erythroid 2-related factor 2 (Nrf-2) activity through a mechanism dependent on indoleamine-2,3-dioxygenase expression in dendritic cells (Min et al., 2015).

A shift of the balance between different T cell subsets was also reported in arthritic mice after treatment with a grape seed proanthocyanidin extract (Ahmad et al., 2013). The composition of

this extract was not defined, but the typical polyphenol profile includes gallic acid and catechin derivatives, and treatment effectively induced an immunosuppressive protective effect against arthritis by inhibiting the infiltration of inflammatory cells into the affected tissues.

As indicated in Table 2, naringenin also showed protective effects in collagen-induced arthritic mice, being able to inhibit the production of anti-collagen IgG (autoantibodies) and limiting the proliferation of Th1 and Th17 cells in the spleen (Li et al., 2015).

The levels of IL-15, IL-17 and IL-23 are elevated in the serum and synovial fluid of patients with RA, in positive correlation with the disease severity, and stimulate synoviocytes to release diverse inflammatory mediators (Astry et al., 2015; Ziolkowska et al., 2000). Fibroblast-like synoviocytes of the synovial lining are major players in pannus formation and eroding activity, by producing local inflammatory cytokines and proteolytic enzymes, such as matrix metalloproteinases (MMP), which degrade the extracellular matrix. As discussed above, Treg cells have an essential role against autoimmunity, their cytokines are involved in regulation or antagonism of Th17 cell functions, and anti-IL-17A treatment alleviated experimental arthritis (Chao et al., 2011). Elevated levels of IL-17 have also been reported in IBD, both in CD and in UC (Boirivant & Cossu, 2012).

Haleagrahara et al. (2017) compared the effect of quercetin with the standard DMARD methotrexate in a mouse model of RA (Table 2). The authors found that the flavonoid treatment dwindled the levels of circulating cytokines (such as IL-17) and produced anti-inflammatory protective effects on the joint tissue similar to methotrexate. A group of mice was also treated with the two compounds in combination, but weight loss and death were observed in this experimental group.

A robust modulatory action by quercetin was recently described in the collagen-induced arthritis model (Yang et al., 2018). Administration of the flavonoid produced almost complete inhibition of arthritis-induced biosynthesis of the pro-inflammatory cytokine IL-17A and alleviated the histopathological score (infiltration of inflammatory cells, congestion and hyperplasia of synovium, damage of cartilage and bone erosion) in the ankle of treated rats (Table 2). Production of IL-21 and IL-23 were also inhibited, as well as inflammatory mediators, while IL-10 and TGF- β were increased, associated to modulation of the balance between Th17 and Treg cells populations (Table 2). Moreover, assays *in vitro* indicated heme oxygenase-1 (HO-1) participates in the anti-inflammatory action of quercetin (Yang et al., 2018).

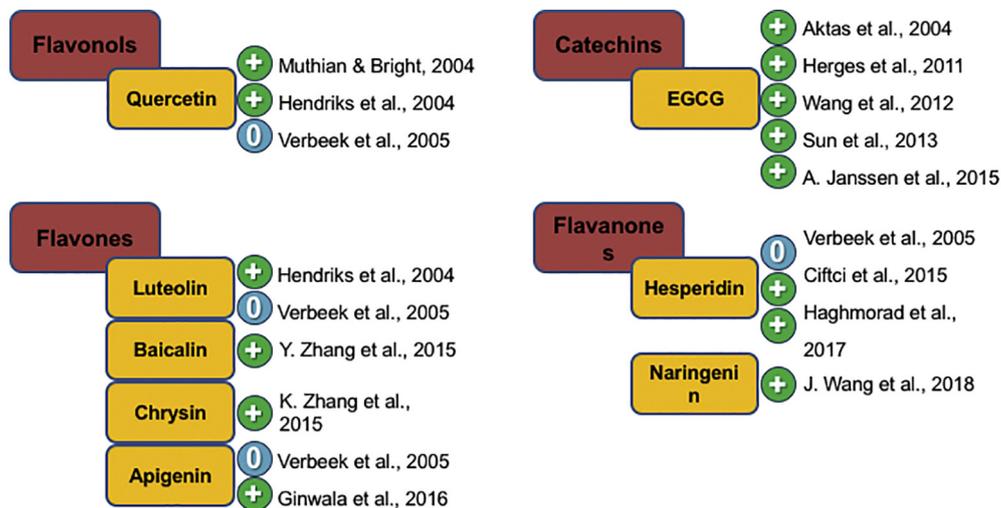


Fig. 3. Flavonoids studied in experimental autoimmune encephalomyelitis as an animal model of multiple sclerosis. Flavonoids are organized in classes, and only studies with purified compounds were considered. (+) means beneficial action was described; (0) means conflicting or no significant effects were observed. EGCG: epigallocatechin-3-gallate. (Aktas et al., 2004; Ciftci et al., 2015; Ginwala et al., 2016; Haghmorad et al., 2017; Hendriks et al., 2004; Herges et al., 2011; Janssen et al., 2015; Muthian & Bright, 2004; Sun et al., 2013; Verbeek et al., 2005; Wang et al., 2012; Wang, Men, et al., 2018b; Zhang, Ge, Xue, et al., 2015a; Zhang, Li, Tang, & Wang, 2015c).

It is also worth noting that an aqueous-alcoholic extract of *Camellia sinensis* containing different flavonoids (quercetin and catechins), in addition to gallic acid and caffeine, also afforded protection against joint tissue injury in the collagen-induced arthritis model (Tanwar et al., 2017).

Very recently, the anti-arthritis potential of silibinin (molecular structure in Fig. 2) was examined at different levels by Tong et al. (2018). Silibinin is presented as the prime constituent in silymarin extracted from milk thistle (*Silybum marianum*) and, in a dose-dependent manner, alleviated arthritis scores and diminished the preponderance of pro-inflammatory cytokines in a rat model (Table 2). Studies *in vitro* showed that silibinin inhibited TNF- α -induced activation of NF- κ B pathway and production of IL-6 and IL-1 β in human RA fibroblast-like synoviocytes. The flavonoid also downregulated the expression of SIRT1, inducing apoptosis and inhibiting autophagy of those cells (Tong et al., 2018). Still, in the same work, silibinin was found to induce M2 polarization in RAW264.7 macrophages and inhibit Th17 cell differentiation from naive CD4⁺ T cells.

Apoptosis resistance, mitochondrial dysfunction and autophagy of fibroblast-like synoviocytes in the pannus may be important targets of flavonoids for RA therapy. IL-17 and/or Th17 cells can accelerate or augment mitochondrial malfunction and induce autophagy that seems connected to synoviocytes anti-apoptosis survival and proliferation behind pannus formation in the joints (Kim et al., 2017). In this context, it should be remembered that flavonoids such as EGCG, quercetin or kaempferol have shown potential to modulate mitochondrial signalling and autophagy (Lagoa, Samhan-Arias, & Gutierrez-Merino, 2017; Wu et al., 2017).

Kaempferol inhibited the proliferation and migration of fibroblast-like synoviocytes from RA patients and, in an animal model (Table 2), reduced the incidence and severity of clinical and histologic arthritic scores (Lee et al., 2018). Inhibition of Th17 differentiation and osteoclastogenesis were also described as protective mechanisms of kaempferol as supported by combined *in vitro* and *in vivo* assays (Lee et al., 2018). Importantly, the cell modulating actions were significant even with low micromolar concentrations of the flavonoid.

Overall, the current data point to quercetin, EGCG, naringenin, hesperidin and apigenin as the best candidates for the design of experimental therapies for major diseases MS and RA. Different studies demonstrated these compounds attenuate clinical symptoms, inflammatory markers and T cell imbalances in *in vitro* and murine models mimicking AD pathological features. Regulation of the NF- κ B and Nrf-

2/HO-1 pathways were implicated in the beneficial effects, but the mode of action of the flavonoids is probably mediated by different targets as discussed in next section.

4. Intracellular signalling pathways targeted by flavonoids

Autoimmune diseases comprise diverse structural and pathological conditions. Thus, selection of various specific targets and more sensible methods are essential for their treatment. Flavonoids exert the renowned beneficial effect in human by targeting multiple cell systems. The effect of flavonoids in the inflammatory response incorporates suppression of several inflammatory mediators for instance nitric oxide (NO) and reactive oxygen species (ROS) and; control of inflammatory enzymes activity, like inducible nitric oxide synthase (iNOS) and cyclooxygenases (COXs); the decline in formation and expression levels of cytokines and the modulation of transcription factors like the activator protein-1 (AP-1) and nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) (Leyva-López et al., 2016; Tunon, Garcia-Mediavilla, Sanchez-Campos, & Gonzalez-Gallego, 2009; Ribeiro, Freitas, Lima, & Fernandes, 2015; González-Gallego, García-Mediavilla, Sánchez-Campos, & Tuñón, 2010). Here, we discuss in more detail about the potential of targeting different cell signalling pathways and molecular immunomodulatory mechanism of the members of flavonoids in mitigating a few major autoimmune diseases.

4.1. Flavonoids in multiple sclerosis and neurodegeneration

A mounting body of evidence that documented the inhibitory efficacy of flavonoids towards demyelination, neuroinflammation, neuronal cell death and immune dysfunction. Notably, luteolin (Hendriks et al., 2004) and EGCG (Herges et al., 2011) exhibited a remarkable neuroprotective propensity through alleviating neuroinflammation and axonal damage in MS. Furthermore, the protective action of flavonoids such as quercetin and fisetin could occur through inhibiting the myelin being phagocytosed by macrophages as observed *in vitro* (Hendriks et al., 2003). Interestingly, the results by Herges et al. (2011) in EAE model suggest the combined use of EGCG with the classical DMA glatiramer acetate for MS therapy, with synergistic effects, because EGCG is pointed to act mainly by reducing oxidative stress and NF- κ B activity.

In some familial case of amyotrophic lateral sclerosis (ALS) result from mutations in the gene of superoxide dismutase 1 (SOD1), cytosolic

Table 2

Studies of flavonoid therapeutic potential in collagen-induced arthritis models of rheumatoid arthritis. Only studies with purified flavonoids were included. Cellular and molecular mechanisms investigated *in vivo* are also referred.

Flavonoid, dose, animal	Effects of flavonoid treatment against arthritis pathology	Reference
Epigallocatechin-3-gallate 10 mg/kg, three times a week, oral, Mouse	Ameliorated swelling, redness and erythema of the hind paws and the forepaws Reduced paw thickness and inflammatory cells infiltration Decreased autoantibodies, IL-6, TNF- α , and IFN- γ , and increased IL-10 Reduced the prevalence of CD4 T, CD8 T cells as well as of B cell subsets including marginal zone B cells, T1 and T2 transitional B cells Attenuated antigen-induced T cell proliferation Increased CD4+CD25+Foxp3+ T-regulatory (Treg) cells in draining lymph nodes Increased levels of Nrf-2 and HO-1 in joints	Min et al., 2015
Naringenin 100 or 200 mg/kg, daily, oral, Mouse	Reduced arthritis severity, bone erosion in ankle joints, cartilage destruction, infiltrating inflammatory cells, synovial hyperplasia Decreased collagen-specific antibodies Reduced frequency of CD4+IFN- γ + Th1 and CD4+IL-17A+ Th17 cells in splenocytes Reduced RNA expression of Th11-related transcription factor T-bet and Th17-related transcription factor ROR γ t in the spleen	Li et al., 2015
Quercetin 30 mg/kg, daily, oral, Mouse	Decreased TNF- α , IL-1 β , IL-17, and MCP-1 Ameliorated paw edema, but not ankle edema Reduced synovitis with moderate pannus formation and inflammatory cell infiltration in knee Dwindled destruction of cartilage and bone	Haleagrahara et al., 2017
Quercetin 150 mg/kg, daily, oral, Rat	Reduced paw edema, arthritis index and histopathological score of ankle tissues Decreased autoantibodies Decreased serum levels of IL-17A and IL-21, and induced IL-10 and TGF- β Reduced mRNA levels of IL-17A, IL-21, IL-23 and ROR γ t, while increased IL-10, TGF- β and Foxp3 in draining lymph nodes Decreased proportion of CD4+ IL-17A+ T cells and increased Treg cells in draining lymph nodes Reduced protein levels of NLRP3, caspase-1 and IL-1 β , and increased HO-1 in synovium Decreased serum levels of the inflammatory mediators TNF- α , IL-1 β , IL-6 and PGE2	Yang et al., 2018
Silibinin 50 to 150 mg/kg, daily, oral, Rat	Reduced joint inflammation, pannus formation, inflammatory cell infiltration and bone erosion Decreased serum levels of TNF- α , IL-6, and IL-1 β	Tong et al., 2018
Kaempferol 2 mg/kg, three times a week, i.p., Mouse	Decreased arthritis incidence and severity of inflammation, cartilage damage, and bone erosion Reduced osteoclastogenic activity in the joints and inhibited <i>ex vivo</i> osteoclast formation Decreased expression of IL-17, Ahr, CCL20 and ROR γ t in draining lymph node cells Decreased number of CD4+/IL-17+ /pSTAT3+ and Src+ splenic T-cells	Lee et al., 2018

enzyme in first line of defence against superoxide-triggered oxidative stress (Rosen et al., 1993). EGCG was reported to protect motor neurons from oxidative stress-induced cytotoxicity in wild/G93A SOD1 mutant ALS mouse model (Koh et al., 2006). Further, the EGCG has been reported for the substantial increase in the number of motor neurons by inhibiting the NF- κ B pathway, microglial activation and inducible NO synthase (iNOS) (Xu et al., 2006). Genistein, another member of flavonoid was also reported to act as an anti-ALS prophylactic agent (Trieu & Uckun, 1999).

Neuronal cell death is central in MS and ALS, and signalling pathways like, JNK and p38 MAPK are associated strongly with the transcription-dependent apoptotic cell death of neuron through regulating c-Jun (Behrens, Sibilia, & Wagner, 1999) and AP-1 such as JunB and JunD. Flavonoids such as epicatechin, 3'-O-methyl-epicatechin (Schroeter, Spencer, Rice-Evans, & Williams, 2001), kaempferol, quercetin (Ishikawa & Kitamura, 2000), hesperetin and its structural counterparts namely, isorhamnetin and isosakuranetin have reduced the neuronal apoptosis through inhibiting JNK pathway and activation of caspase-3 (Schroeter et al., 2001). Activation of JNK and nitric oxide synthase (NOS) in oxidative stress-related neuronal death are linked to cell calcium homeostasis and modulation of superoxide/calcium/NO signalling was implicated in kaempferol neuroprotective action (Marques-da-Silva & Gutierrez-Merino, 2014; Samhan-Samhan-Arias, & Martín-Romero, & Gutiérrez-Merino, 2004; Schroeter et al., 2001). Similar to other flavonoids such as genistein (Vallés et al., 2008), epicatechin (Vallés et al., 2008) protect the oxidative stress-induced neurodegeneration in diseased cases by activating the p38 MAPK pathway. In addition to the capacity to directly scavenge reactive oxidant species, antioxidant flavonoids such as catechins and kaempferol can inhibit enzymatic systems implicated in MS oxidative injury, namely, mitochondria and membrane NAD(P)H oxidases systems in neuronal and glial cells (Fischer et al., 2012; Gutierrez-Merino et al., 2011).

Neuroinflammation is believed to have a critical role in the development of several neurodegenerative disorders. Various flavonoids viz. luteolin (Zhu et al., 2011), kaempferol (Park et al., 2011), wogonin, baicalein (Lee et al., 2003), EGCG (Li, Huang, Fang, & Le, 2004) and quercetin (Chen et al., 2005; Kao et al., 2010) were reported to suppresses the biosynthesis of proinflammatory molecules such as NO, TNF- α , IL-1 β , iNOS, cyclooxygenase-2 and NADPH oxidase. The activation of these proinflammatory molecules by flavonoids are mediated through the inactivation of signalling pathways namely, p38 MAPK and ERK that control both iNOS as well as TNF- α . The molecular mechanisms of flavonoids in combating the autoimmune neuronal disorders are shown in Fig. 4.

4.2. Flavonoids in psoriasis

The flavonoid quercetin was reported to possess anti-psoriatic activity by inhibiting orthokeratosis, epidermal thickness and inflammatory response like the migration of leukocyte in psoriasis mice model (Vijayalakshmi, Ravichandiran, Velraj, Nirmala, & Jayakumari, 2012). Later in 2014, Vijayalakshmi and Geetha (2014) described the anti-psoriasis activity of luteolin, quercetin, formononetin, rutin, kaempferol and luteolin by attenuating the skin lesion and hyperproliferation of epidermal and keratinocytes layer by inhibiting the movement of neutrophils in psoriasis rat model. Furthermore, the flavonoids EGCG, chrysin and quercetin as well as curcumin (a curcuminoid polyphenol), reduced the complications of psoriasis by reducing the inflammatory cells by suppressing the activity of macrophages and reducing the ROS production (Skurić et al., 2011). Another polyphenol, resveratrol (stilbene type) that displays anti-psoriasis activity in keratinocyte cell line by stimulating the SIRT1 that independently triggered the activation of protein kinase B (Akt), aryl hydrocarbon receptor nuclear translocator (ARNT) and impaired the regulation of critical regulators of cell survival

and proliferation such as aquaporin 3 (AQP3) and extracellular signal-regulated kinase (ERK) (Lee, Kim, Park, & Lee, 2016). Additionally, resveratrol has also been ameliorated psoriasis in a mouse model by decreasing the IL-17 and IL-19 which were the critical cytokine marker for the progression of disease (Kjær, Thorsen, Jessen, Stenderup, & Pedersen, 2015). They also demonstrated the protective effect against psoriasis by upregulating the proteins encoding for atrophy and cellular hypertrophy such as phosphoenolpyruvate carboxykinase 1 (PKC1) and tripartite motif containing 63 (TRIM63). The molecular mechanism of flavonoids and other polyphenols in combating psoriasis is shown in Fig. 5.

4.3. Flavonoids in type 1 diabetes mellitus (T1DM)

The immunological aspects of the T1DM majorly depend on the anti- and pro-inflammatory response of the cells such as TNF- α and IFN- γ which stimulates NO to inhibit the apoptosis of β -cells and recruited antigen presenting cells (APCs) (Cnop et al., 2005). Thus, recruited APCs along with CD4⁺- or CD8⁺-T cells and macrophage to release pro-inflammatory substances and enhances the cytotoxicity of islet cells (Wällberg & Cooke, 2013). Resveratrol restrained the biosynthesis of inflammatory cytokines through suppressing the NF- κ B, MAPK, src family tyrosine kinase, plasma creatine kinase and phosphoinositide-3-kinase (PI3K) (Lee et al., 2011) and ameliorated the severity of T1DM. Additionally, treatment with resveratrol in monocytes of T1DM victims and acute monocytic leukaemia cell lines (THP-1) (You & Chatenoud, 2016) controlled the innate and adaptive immune regulators such as forkhead transcription factors assigned to the O3a class (FoxO3a) and nicotinamide adenine dinucleotide (NAD) deacetylase-mediated SIRT1. The deacetylation of FoxO3a by SIRT1 prevented the oxidative stress-mediated apoptosis in T1DM cells (Jagani, Singh, & Khosravi-Far, 2008; van der Horst & Burgering, 2007). Likewise, resveratrol in animal models of T1DM restored the hallmark markers of pathogenesis such as elevated insulinitis (Lee et al., 2011) and damages of islets of Langerhans, and B-cells in pancreases (Kaur, Abmwani, & Mehta, 2014). The elevated insulinitis in T1DM mice has been controlled by blocking the migration of cells from peripheral lymphoid organ from pancreas through reducing the expression of chemokine receptor 6 (CCR6) and CD11b⁺ in T helper (Th17) cells and macrophages, respectively (Lee et al., 2011). Protective effect of surface layer proteins isolated from four Lactobacillus strains on hydrogen-peroxide-induced HT-29 cells oxidative stress. The anti-diabetic property of flavonoids and their specific mode of action are given in Table 3. The overall molecular mechanism of flavonoids in combating T1DM is shown in Fig. 6.

4.4. Flavonoids in systemic lupus erythematosus

Systemic lupus erythematosus (SLE), or lupus, is an autoimmune disease biologically characterized by the production of autoantibodies against self-components and its mediated tissue damage (Rahman & Isenberg, 2008; Sestak, Nath, Sawalha, & Harley, 2007). The hallmark pathogenesis of SLE through autoantibodies to stimulate immune responses by activating T-cell and B-cell shifts and elevate the levels of IL-10, (Houssiau et al., 1995; Klinman, Shirai, Ishigatsubo, Conover, & Steinberg, 1991). Administration of the flavonoid astilbin has been reported to inhibit the overproduction of antibodies and lupus nephritis by reducing the activation of T- and B-cells which in turn reduced the elevated marker cytokines such as IL-17, IL-1b, IL-6 and TNF- α in lupus mice model (Guo et al., 2015). (Liao et al., 2016). Also reported that icaritin, a biologically active flavonoid used in Chinese traditional medicine decreased the hyperactivation of CD4⁺ t cells and rectified renal damage in mice during SLE. Apigenin suppressed the production of autoantibodies, IFN- γ , IL-6, IL-17, and increased the expression of COX-2 in CD4⁺ T cell, B cell and macrophages and ameliorate the SLE in a mouse model. The production of Th1 cells by IFN- γ and Th 17 cells by IL-6 is critical for the overproduction of autoantibody and lupus nephritis in

SLE condition (Haas, Ryffel, & Le Hir, 1998; Hsu et al., 2008). Catechin and EGCG prevented the complications of SLE progression and increased the survival rate by decreasing the serum levels of anti-DNA antibodies and renal damage (Peairs et al., 2010; Sayama, Oguni, Tsubura, Tanaka, & Matsuzawa, 2003; Tsai et al., 2011). Furthermore, the oral administration of EGCG to lupus-prone mice exhibited prophylactic activity by activating Nrf-2 antioxidant signalling pathway, suppressing the activation of NLR family pyrin domain-containing 3 (NLRP3) inflammasome in kidney and encourage Treg activity (Tsai et al., 2011). EGCG has also reported to activate AMPK and block several pro-inflammatory cytokines and ameliorated the iNOS and NO-mediated destruction in kidney mesangial cells of SLE mice. Peairs et al. (2010) has reported that the EGCG suppressed the inflammatory response via phosphoinositide- s-kinase/Akt/mammalian target of rapamycin (PI3K-Akt-mTOR) pathway. It should be referred that immune response to flavonoids therapy may depend not only on the compound and dose, but also on pathophysiological factors still to be unveiled, as suggested by the results in (Kim et al., 2014) indicating that quercetin inhibited the expansion of Treg cells in mice under heat stress (Fig. 7).

Resveratrol, a well-known activator of SIRT1 was reported to alleviate the pathogenesis of lupus in BALB/c mouse model through decreasing the deposition of IgG and IgM, and diminishing proteinuria as well as lesions in the kidney (Satoh & Reeves, 1994). Catechin and quercetin induced the expression of antioxidant defence mechanism through the activation of SOD and Paraoxonase 1 and reduced the oxidative stress-mediated renal damage in lupus conditions (Amengual-Cladera et al., 2011). Similarly, rutin inhibits the activation of TGF- β 1 smad signalling pathway and prevent the release of pro-inflammatory cytokines and protect the renal damages (Han, Lu, Xu, Zhang, & Hong, 2015). The mode of actions of different flavonoids against SLE is described in Table 4.

4.5. Flavonoids in inflammatory bowel disease

The Crohn's disease (CD) and ulcerative colitis (UC) are the most predominant forms of inflammatory bowel disease (IBD) occurs due to genetic variation, imbalanced immune response and bacterial infection contribute the onset of IBD. The genes encoding for intelectin 1 (galactofuranose binding) (ITLN1), signal transducer and activator of transcription 3 (STAT 3), (Fakhoury, Negruj, Mooranian, & Al-Salami, 2014) non-receptor type PTPN2, protein tyrosine phosphatase and interleukin 23 receptor play a vital part in host immune defence and epithelial barrier function. Individuals with genetic mutations of any of these genes would eventually become vulnerable to IBD (Hisamatsu et al., 2013; McGovern et al., 2010).

Quite a few anthocyanins such as, cyanidin-3-glucoside (Schreiber et al., 2002), kaempferol and EGCC (Hämäläinen, Nieminen, Vuorela, Heinonen, & Moilanen, 2007; Lee, Lin, Lee, Hsieh, & Yang, 2013b; Liu et al., 2013) are reported to impede the activated STAT and JAK/STAT pathway in IBD patients. Mutation in the chromosome 16q12 (encodes for nucleotide-binding oligomerization domain-containing protein-2 (NOD2)) has increased the vulnerability for the onset of diseases. This gene is essential for the regulation of intracellular defence protein activated by NF- κ B in response to infection in the intestinal region (D. H. Kim & Cheon, 2017). In case, the acute infection is not eliminated by the anti-inflammatory process the immune homeostasis is disturbed leading to the chronic intestinal inflammation in response to the foreign antigens (Hisamatsu et al., 2013). During the pathogenesis of IBD, the dysregulated activation of T-cell effector molecules -Th1 and -Th17 ensue in the CD, and the other T-cell effector molecules -Th2 and -Th217 in UC, collectively trigger the uncontrolled inflammatory process. The activation of Th1 lymphocyte intricate the release of IL-12, IL-4, IL-5, IL-6 IL-10, IL-23, TNF- α , and IFN- γ in both CD and UC (Singh, Singh, & Pandey, 2012). The dissemination of inflammation in UC and CD activate the anti-apoptotic T lymphocyte pathways in lamina

propria of the mucosa with augmented IL-17 level (Boirivant & Cossu, 2012). For instance, the gavage of flavonoids such as EGCG, chrysin, cardamonin, quercetin, glabridin, naringenin or rutin have been reported to attenuate the increased level of proinflammatory cytokines in inflamed colon (Azuma, Shigeshiro, Kodama, Tanabe, & Suzuki, 2013; Boirivant & Cossu, 2012; Brückner, Westphal, Domschke, Kucharzik, & Lügering, 2012; Camuesco et al., 2004; Kwon, Oh, & Kim, 2008; K. H. Kwon, Murakami, Tanaka, & Ohgashi, 2005; Oz, Chen, & de Villiers, 2013; Ren et al., 2015; Shin, Kwon, Kim, Shin, & Kim, 2009). Furthermore, the administration of baicalin mitigates the expression of FOXP3, RORC and T-bet genes associated with Treg, Th17, and Th1 cells respectively in IBD patients (Yu et al., 2014). Macrophage has been considered as a primary source of several proinflammatory mediators in IBD, which dynamically contribute to the pathology of inflammatory intestinal condition (Grip, Janciauskiene, & Lindgren, 2003; Grisham et al., 2002). Besides, many studies have evident the efficacy of flavonoids in alleviating the NO and proinflammatory cytokine mediators during intestinal inflammation/IBD (Alzoghbi, 2013; Camuesco et al., 2004; Comalada et al., 2006; Kim, Son, Chang, & Kang, 2004). In experimental colitis model, flavonoids showed a significant reduction of colonic myeloperoxidase (Al-Rejaie et al., 2013; Brückner et al., 2012; Camuesco et al., 2004; Dou et al., 2013; Kwon et al., 2008; Mascaraque et al., 2014; Oz et al., 2013; Ren et al., 2015; Seibel, Molzberger, Hertrampf, Laudénbach-Leschowski, & Diel, 2009) and ameliorate the intestinal inflammation. The members of flavonoids viz. cardamonin, resveratrol, rutin and quercetin exert anti-inflammatory potential by impeding the NF- κ B and I κ B α (Camuesco et al., 2004; Dou et al., 2014; Mascaraque et al., 2014; Samsami-kor, Daryani, Asl, & Hekmatdoost, 2015). The polyphenols reduced the prophylactic cytokine TGF- β 1 as well as inflammatory cytokines (IL-1 β , IL-6 and TNF- α) in CD models (Rahal et al., 2011). The molecular mechanism of flavonoids in combating IBD is shown in Fig. 8.

4.6. Flavonoids in Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease which is predominant in women than men. The pathogenesis of the disease chiefly depends on the hormonal and genetical background. Genetically, individuals with the mutation in genes like HLA (*HLA-DRB1*), peptidyl arginine deiminase type 4 (*PAD14*), cytotoxic T-lymphocyte associated

protein 4 (*CTLA-4*) and protein tyrosine phosphatase non-receptor 22 (*PTPN22*) are vulnerable to RA (Smolen, Aletaha, & McInnes, 2016). Several cytokines like IFN- γ , IL-12, IL-21 and IL-23 contributed to the severity of RA, but the IL-6 and IL-7 are has been the primary cytokines which promoting synovial inflammation, bone and cartilage destruction (Chao et al., 2011). The dysregulation of TNF- α and IL-1 releases the matrix metalloproteinase (MPPs) and degrades the bone as well as cartilage by increasing the expression of both COX2 and NO synthase (Brzustewicz & Bryl, 2015; Krause & Makol, 2016; Tanaka, Hishitani, & Ogata, 2014). The resveratrol not only inhibits the pro-inflammatory cytokines (TNF- α and IL-1 β), but also suppresses the genes like COX1 and COX2 through the activation of NF- κ B (Lee et al., 2014; Ma, Wang, Dong, Li, & Cai, 2015; Xuzhu et al., 2011). Besides, it attenuates the severity of RA by inhibiting the MPP, SIRT1 (Ahmed et al., 2015). The role of flavonoids in modulating the immune system and its specific mode of action in reducing the pathogenesis of RA is in presented in Table 5 and Fig. 9.

Growing evidences highlights that the molecular mechanisms of flavonoids are not only limited to ROS regulations but also by direct association with some specific proteins as well. An important study done by Arango et al. to identify human cellular targets for apigenin, a well-known flavone depicted that 160 human cellular targets for apigenin were identified by phage display coupled with second generation sequencing technique. The results of their study revealed that most of the candidate targets were felled within one out of the GTPase activation, membrane transport, and mRNA metabolism/alternative splicing categories that showed the involvement of specific type of proteins in producing specific actions by the flavonoids (Arango et al., 2013).

5. Structure-activity relationship (SAR) of flavonoids

Flavonoid's bioactivity is closely associated with their structure. Flavonoids are not uniformly therapeutic, and it is presumed that it is due to various substitutions on different atoms of carbon in the fundamental flavonoid structure and variations in lipid solubility (Amic et al., 2007). Understanding the structure-activity relationships of flavonoids may assist in the development of more potent and effective derivatives for specific targets.

The structures, ring labelling and carbon numbering of flavonoid molecules is illustrated in Figs. 1 and 2. Several findings revealed that three Bors' criteria i.e. (i) presence of the structure of o-dihydroxy

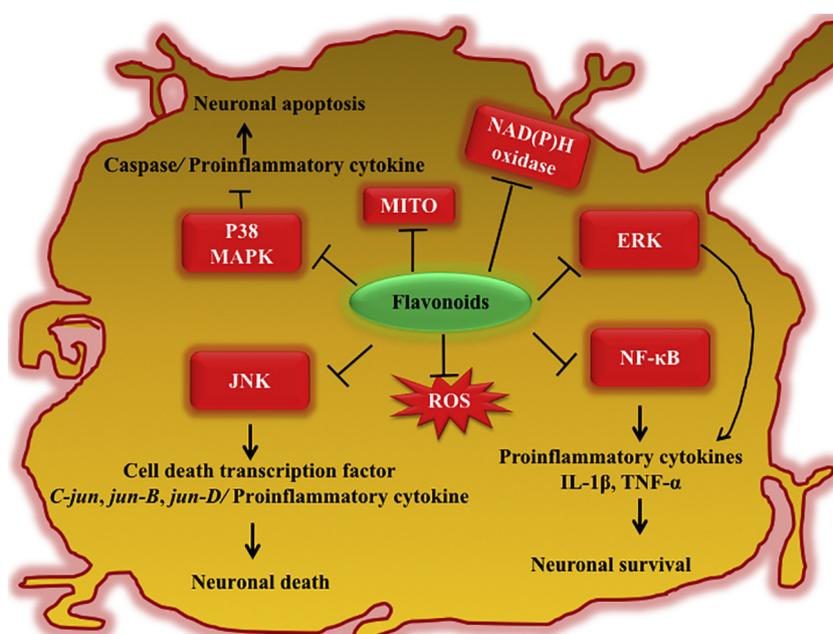


Fig. 4. The cell signalling pathways triggered by flavonoids in preventing neurodegenerative autoimmune disease. MITO-Mitochondria; ROS-reactive oxygen species.

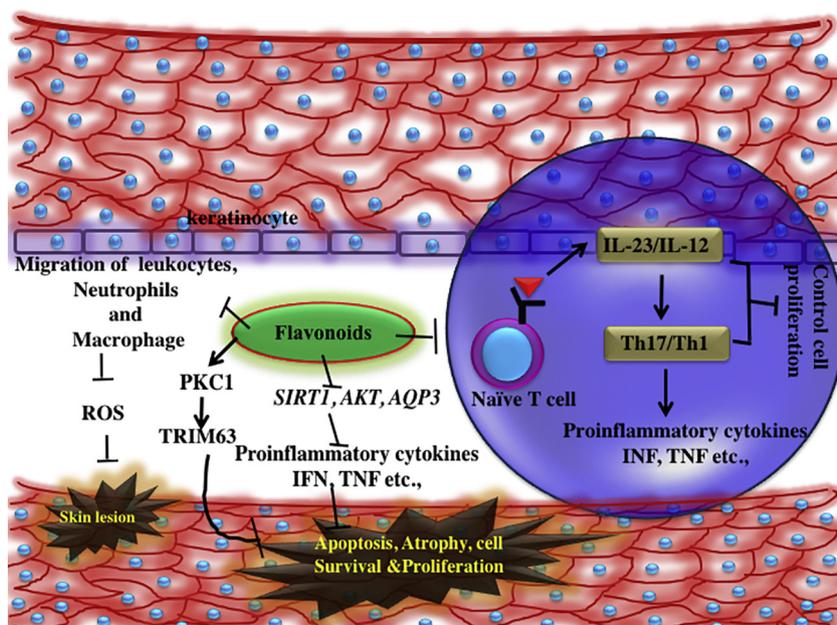


Fig. 5. The molecular protective mechanism of flavonoids in combating psoriasis.

(3',4'-diOH, i.e., catechol) structure in the B ring, (ii) existence of both 3-OH and 5-OH groups, and (iii) C2-C3 double bond are some standard

Table 3

The anti-diabetic property of other member of flavonoids and their specific mode of action.

Members of the flavonoid	Specific mode of action	References
Quercetin	Inhibit the production of NO in streptozotocin (STZ)- induced T1DM rat	Coskun, Kanter, Korkmaz, & Oter, 2005
Epicatechin	Inhibit insulin release from islets	Kim et al., 2003
Silymarin	Inhibited the production of inflammatory cytokine such as IL-1 β , IFN- γ , and TNF- α in macrophages and T-cells and protect from tissue destruction	Matsuda et al., 2005
EGCG	Reduce ROS production in host cells Increase the insulin levels, anti-inflammatory cytokine IL-10 and inhibiting caspase-3 in T1DM mice model	Fu, Zhen, Yuskavage, & Liu, 2011
Anthocyanin	Increase insulin resistance, level of serum insulin and improved glucose utilization in tissue	Nizamutdinova et al., 2009
Genistein	Stimulate the activation of tyrosine kinase activity and protect β -cells against apoptosis through up-regulating Bcl-2 and downregulating Bax and caspase-3 Enhance the glucose stimulated insulin secretion and mass of β -cells in clonal insulin-secreting cell lines (INS-6 and MIN6), human islets, fresh mouse and mouse models	Fu et al., 2012; Fu & Liu, 2009; Liu et al., 2006
Hesperidin	Improve wound angiogenesis by suppressing SOD and FoxO1/iNOS pathway in STZ-induced T1DM rat Stimulate anti-inflammatory cytokine in STZ-induced T1DM rat	Tie et al., 2013 Shi et al., 2012
Wogonin	Inhibit blood glucose level through glucose regulating enzymes STZ-induced T1DM rat Inhibit p38 MAPK pathway and stimulates peroxisome proliferator-activated receptor alpha (PPAR α) activity in STZ-induced T1DM rat	Akiyama et al., 2009 Zhang, et al., 2015
Rutin	Decrease MDA level and increase the level of antioxidants SOD and CAT in STZ-induced T1DM rat	Akondi, Kumar, Annapura, & Pujari, 2011

requirements for the antioxidant or radical scavenging potential of flavonoids (Amic et al., 2007; Benavente-García, Castillo, Marin, Ortuño, & Del Río, 1997; Pietta, 2000; Soobrattee, Neergheen, Luximon-Ramma, Aruoma, & Bahorun, 2005). Criteria (i) is responsible for stability elevation of flavonoid phenoxyl radicals through expansion of electron delocalization and hydrogen bonding; criteria (ii) establish the coplanarity of the hetero ring and partake in stabilization of radicals through electron delocalization over the three rings and criteria (iii) provide utmost radical scavenging ability and highly potential radical absorption (Amic et al., 2007).

According to the SAR study, the inhibitory property of flavonoids in the development of immunological memory in immune cells (T & B cells) depends on the structure of flavonoids. The inhibitory activity of flavonoid taxifolin was decreased by abolishing double bond amid C2 and C3. A ketone functional group at position C4 increases the activity of flavones in cellular and humoral immunosuppression. Flavonoids have a benzene ring at C2, and C3 shows comparable activity in inhibiting an immune response. By the opening of the C-ring of the flavonoids, the activity of hesperidin and neohesperidin is not lost (Kim & Cho, 1991). The anti-inflammatory action of a flavonoid is dependent on the position and presence of the number of hydroxyl groups (-OH) at ring A and B, especially at C5 and C7 position in ring A and at carbon 3 and carbon 4 in ring B. Removal of hydroxyl groups from B ring diminishes its activity. Flavonoids like quercetin and luteolin exhibited stronger inhibition on the release of TNF- α because of hydroxyl groups at 3' and 4' (catechol type B-ring, Fig. 2) compared to other flavonoids having unsaturation at C2-C3 (Leyva-López, Gutierrez-Grijalva, Ambriz-Perez, & Heredia, 2016). A catechol or pyrogallol group in ring B was also found important for the ability of flavonoids to reduce cytochrome c, while the hydroxyl groups at ring A (e.g. chrysin) are enough to inhibit the cardiolipin-induced peroxidase activity associated to cell apoptosis (Lagoa et al., 2017).

Glycosylation of rutin with rutinose at position C3 decreases its activity from quercetin which is its parent aglycone. The inhibitory action of hesperidin was found lower than its aglycone (hesperidin) in cellular immune reaction, but the humoral immune response was not affected. The hydroxyl group at C3 does not affect the activity of flavonoids; this is apparent from the comparable activity of flavones and flavonols. By increasing the number of hydroxyl groups in ring B from 1 (kaempferol) to 2 and three (quercetin and myricetin) increasing the

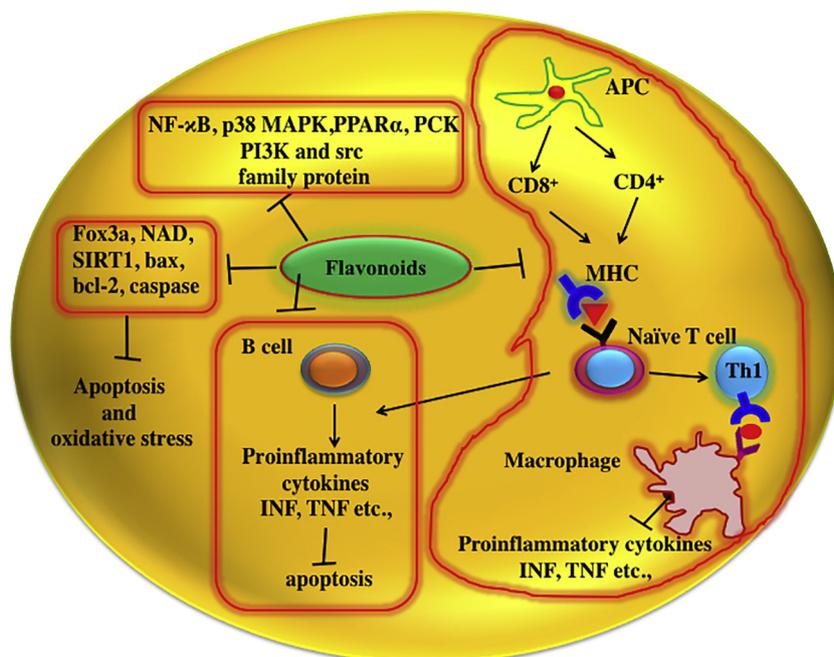


Fig. 6. The overall molecular mechanism of flavonoids in combating Type 1 diabetes mellitus.

inhibitory action of flavonoids against cellular immune response. In flavonols the quercetin resulting from ortho-hydroxylation at ring B is more potent than meta hydroxylated morin in humoral immune response, but there was no effect on the cellular immune response (Kim & Cho, 1991).

It was revealed from a SAR study on five methoxylated flavonoids which were obtained from Chromolaena species that for antioxidant activity two free hydroxyl groups at ring A are essential. Moreover, the antioxidant activity significantly reduced by substitution of a hydroxy group by a methoxy group at C3 position (Taleb-Contini et al., 2006). Another study revealed the modulatory effector function in rheumatoid arthritis in patients and healthy individuals' immune complex-stimulated the neutrophils by kaempferol, myricetin, quercetin, and galangin. The biological impact was not altered after the elimination of

one hydroxyl group from ring B, but the addition of one hydroxyl or removal of two hydroxyl group diminished the H₂O₂ scavenging efficiency (Santos et al., 2014). These results highlight how biological activity of flavonoids cannot be predicted with full confidence from their free radical scavenging efficiency and advocate the use of flavonols such as quercetin and kaempferol in the treatment of rheumatoid arthritis (Table 2).

A recent SAR study was performed using docking studies of 100 plant flavonoids along with the NS2B-NS3 protein, a protein as an active site for dengue. The results of this study showed that after little or no modifications in the chemical structures, the plant flavonoids could be used as potent anti-dengue drugs (Sarwar et al., 2018). Another recent study by Li et al. was conducted to evaluate the inhibition activities of 44 flavonoids structures toward human CYPs. The study by utilizing

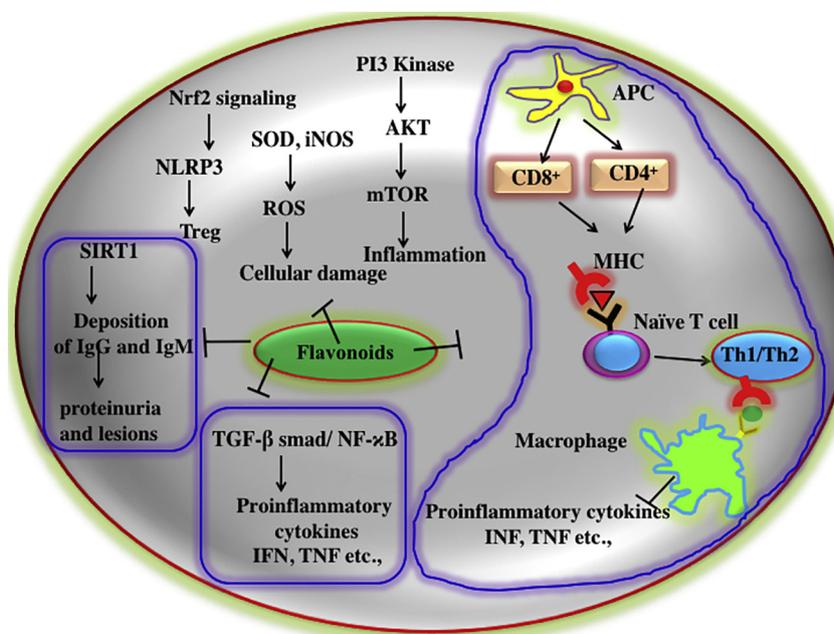


Fig. 7. The molecular mechanism of flavonoids in combating systemic lupus erythematosus.

Table 4
The mode of action of different flavonoids and other antioxidants against SLE.

Members of the flavonoid	Specific mode of action	References
Apigenin	Suppressed IFN- γ and having anti-dsDNA, anti-ssDNA activity Decreased IL-6, IL-17 in T and B cells Reduced cox-2 and lupus nephritis in SNF1 mice	Kang, Ecklund, Liu, & Datta, 2009
Daidzen	Decreased anti-dsDNA and IFN- γ in mitogen-activated T cells from spleen in MRL/1pr mice	Hong, Wang, Huang, Cheng, & Lin, 2008
Coumestrol	Delayed onset of proteinuria and improved renal function by inhibited the TNF- α and IL-1 β in MRL/1pr mice Reduced the serum level of TNF- α , IL-6, IL-1 β in BALB/c mice Suppressed I-6 and TNF- α production in macrophage and subsequently reduced splenoegaly and proteinuria	Hong, Huang, Wang, & Lin, 2009b Hong, Chao, Chen, & Lin, 2009a Schoenroth, Hart, Pollard, & Fritzler, 2004
Curcumin	Modulated the balance between Th17/Treg in CD4 ⁺ and reduced the Th17 response and IL-17A release. Activated the TGF- β in patients of SLE Delayed proteinuria, a, salivary gland infiltration, lymphadenopathy in MRL/1pr mice Decreased proteinuria, IgG1, IgG2a and anti-dsDNA. Suppressed TNF- α and MCP-1 in kidney and FoxP3 in spleen of NZB/W F ₁ mice	Handono, Pratama, Endharti, & Kalim, 2015 Kurien et al., 2015; Lee, Kim, Lee, Chung, & Bae, 2013a Lee, Kim, et al., 2013a
Resveratrol	Decreased proteinuria, IgM and IgG deposition in kidney, glomerulonephritis and serum IgG1 and 2 in pristane BALB/c mice	Wang et al., 2014
Indole-3-carbinol	Increased life span by decreasing the proteinuria, glomerulonephritis, renal abnormalities, intestinal nephritis and activation of B cell and T cells in NZB/W F ₁ mice.	Yan et al., 2009

computational methods established the quantitative structure-activity relationship of flavonoids beneficial to observe the herb-drug interaction. This study revealed that some of the flavonoids like irilone and licoflavone selectively inhibited CYP3 A4 somewhat inhibition of other human CYPs (Li et al., 2018). Another study on over 50 flavonoids showed that the vital presence of C3 and C6 hydroxyl groups for the inhibition of human carboxylesterases enzymes and the study further explored that C-glycosylation or O-glycosylation leads to the forfeiture of inhibition of human carboxylesterases enzymes (Weng et al., 2018). To evaluate the effect of flavonoids structure on mast cell degranulation inhibition, a SAR study was conducted which revealed that the number of B ring's hydroxyl group was necessary for the activity and introduction of a sugar moiety in flavanone's A ring lead to the vanishing of the degranulation activity, additionally, it was also observed that introduction of double bond in the C ring has shown a substantial increase in the degranulation inhibitory effect and such chemical modifications might be beneficial for the drug development for type I allergy (Noshita et al., 2018).

After a comprehensive literature search, it was found that the area of structure-activity relationship, more specifically targeting autoimmune diseases through flavonoids has tremendous potential, and insufficient studies are available in this regard. It was also observed in different studies that little modifications in functional groups could be beneficial for enhancing the efficiency of flavonoids against different disease conditions. Therefore, substantial research in the field of drug development after the concurred evidence from SAR studies are required. Additionally, the modification of the hydroxyl group present in the B-ring might be of tremendous importance to unravel the potential of

structure-activity relationship of flavonoids against a range of autoimmune disorders.

6. Regulatory effect of flavonoids on genes involved in autoimmune diseases

Previous studies have determined the various effects of flavonoids on gene expression involved in the attenuation of inflammatory autoimmune diseases. One of the important anti-inflammatory pathway is the inhibition of transcriptional factor nuclear factor-kappa B (NF- κ B) transcriptional factor signalling pathway. Sen and Baltimore recognized the NF- κ B in 1986 which regulates the expression of kappa light-chain gene in B-lymphocytes (Kasi Pandima, Perumal Vijayaraman, & Karutha Pandian, 2009). In a study, the effect of flavonoids on NF- κ B signalling pathway-dependent gene expression was observed using the dual-luciferase reporter gene assay. It was noticed that there was a two-fold amplification in luciferase activity when macrophage cells RAW 264.7 were stimulated with interferon- α as compared to control unstimulated cells (Y. C. Park, Rimbach, Saliou, Valacchi, & Packer, 2000). Flavonoids can restrain the gene expression related to pro-inflammatory mediators, in addition to inhibition of cyclooxygenase enzymes. Thus, it is assumed that flavonoids can regulate the transcriptional factors in inflammatory signalling pathways, and there are many studies carried out to prove this property including the inhibition of NF- κ B inflammatory pathway (Leyva-López et al., 2016). A study was conducted in which flavonoids quercetin, kaempferol, fisetin and chrysin were tested to find its effect on gene the involved in provoking inflammatory signalling pathway. This study pointed out the inhibitory action of those compounds on IL-8 promoter induced by TNF- α activation and expression of gene in human embryonic kidney cells 293 (Lee et al., 2009). Epicatechin a flavonoid found mostly in grapes effectively blocks NF- κ B inflammatory signalling pathway by p65 nuclear translocation (Mackenzie & Oteiza, 2006). In activated lymphocytes flavonoids of the *Theobroma cocoa* extract modulate the secretion of IL-2 and expression of IL-2 Ra (CD25) gene and down-regulate the pro-activation of lymphocyte. This might be helpful in some conditions of abnormal immune response like autoimmune diseases and hypersensitivity (Ramiro et al., 2005).

Hesperidin regulated the gene expression Nrf2/ERK. Nrf2 is a leucine zipper protein, and ERKs are protein kinase signalling molecules, whose activation protect cells against oxidative harm by inflammation and injury. Activation of Nrf2/ERK also upstream regulate the expression of genes associated with Heme-oxygenase 1 (HO-1) whose expression increases the level of antioxidants in cells and protects them from inflammation and apoptosis (Chen, Ye, Ji, & Liu, 2010). The flavonoid afforded significant anti-arthritis effects when administered orally (Kawaguchi, Maruyama, Kometani, & Kumazawa, 2006) probably by modulating oxidative stress and neutrophil activation and infiltration (Ahmed, Messiha, & Abo-Saif, 2015; Li, Li, Cai, Hu, & Zhang, 2008; Umar et al., 2013). In allergic encephalomyelitis that induced multiple sclerosis in experimental mice, hesperidin treatment caused downstream regulation of oxidative species, IL-1 β and TNF- α , while upstream regulation of IL-17, induced caspase-3-like immune-reactivity, and pro-inflammatory cytokines show apoptosis (Ali et al., 2011; Ciftci et al., 2015; Haghmorad et al., 2011; Haghmorad et al., 2017).

Flavonols extracted from *Clitoria ternatea* showed a robust repression of COX-2 activity and also exhibited inhibition of ROS partially, at the same time its anthocyanins ternatin slow down the NF- κ B translocation, NO production and iNOS protein expression (Nair, Bang, Schreckinger, Andarwulan, & Cisneros-Zevallos, 2015). The important transcription factor is associated with the activation of various immune cells (Uluçkan, Guinea-Viniegra, Jimenez, & Wagner, 2015). Polyphenols like resveratrol, curcumin and several other phytoconstituents exhibit potential regulatory effects on AP-1. For instance, resveratrol has the potential to regulate AP-1, along with modulatory effects on NF- κ B signalling pathway negatively (Diaz-Gerevini et al., 2016; Tewari et al., 2017).

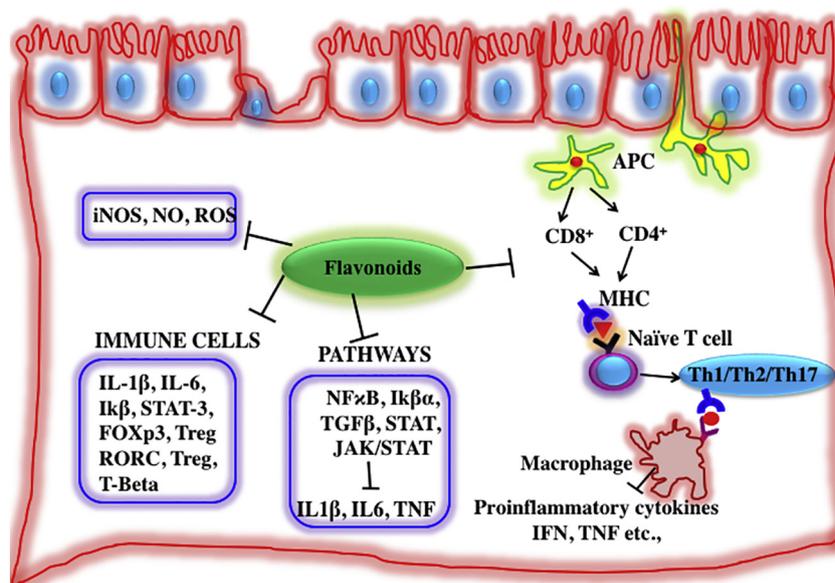


Fig. 8. The molecular mechanism of flavonoids in combating inflammatory bowel disease.

Flavonoids possess a mechanism of action similar to non-steroidal anti-inflammatory drugs NSAIDs. Additionally, flavonoids have capability to inhibit pro-inflammatory mediator gene expression other than cyclooxygenase, and they can either up or down regulate different transcriptional factors like Nrf-2 and NF- κ B in inflammatory and antioxidant pathways (Maroon, Bost, & Maroon, 2010). A hypothetical scheme related to the mechanism of flavonoids in inflammation are presented in Fig. 10.

A study with total flavonoid content of *Bidens bipinnata* L. on rheumatoid arthritis demonstrated that the flavonoids could inhibit IL-6, TNF- α and IL-1 β production from serum and also enhanced the caspase 3 activation in synovium as well (Shen, Li, Hu, & Chen, 2015).

Fisetin inhibited phosphorylation of c-Jun N-terminal kinase (JNK), extracellular-regulated kinase (ERK), and p38 mitogen-activated protein kinase (MAPK) and suppressed NF- κ B activation which is induced by phorbol-12-myristate 13-acetate plus calcium ionophore A23187 (PMACI). Moreover, fisetin is believed to be a possible remedial agent against inflammatory and inflammation-related diseases by its distinct mechanism including down-regulation effect of mast cell activation (Park et al., 2007). Another study on bioactive flavonoid Baicalin obtained from the roots of commonly used herb *Scutellaria baicalensis* aimed to evaluate the mechanism of this flavonoid against experimental autoimmune encephalomyelitis. The study revealed that Baicalin trim down permeation of immune cells into the CNS, restrains the expression of chemokines and proinflammatory molecules, and disallowed cell differentiation of Th1 and Th17 cell differentiation through STAT/NF- κ B signalling pathways. The effect of Baicalin was also associated with the SOCS3 induction, and the effect was mostly diminished on knocking down of SOCS3 signalling. These results suggested that baicalin has the ability for being the novel anti-inflammatory candidate for various autoimmune diseases in general and MS in particular (Zeng et al., 2007; Zhang, Li, Tang, & Wang, 2015c).

7. Pharmacokinetic and clinical studies of flavonoids

A plethora of studies have investigated into the pharmacokinetic (PK) profile of flavonoids. For example, artichoke, a plant rich in flavonoids has traditionally been employed against indigestion and hepatic disorders. To generate more information on surrounding the absorption, distribution, metabolism and elimination (ADME) of artichoke *in vivo*, 14 healthy volunteers were administered with two different extracts of artichoke in a crossover study. Each subject involved in the

study were administered with both artichoke extracts. Extract A constituted of caffeoylquinic acids corresponding to 107.0 mg caffeic acid (CA) and luteolin (LUT) glycosides equivalent to 14.4 mg luteolin. Extract B composition was caffeoylquinic acids corresponding to 153.8 mg caffeic acid and luteolin glycosides equivalent to 35.2 mg luteolin. Urine and plasma were collected and analysed by HPLC employing 12-channel coulometric array detection. The flavonoid luteolin administered as glucoside was retrieved from plasma and urine in the sulfate or glucuronide form. The results showed that extract B had higher Cmax than extract A which showed the maximum plasma concentration. The PK details are listed in Table 6 (Wittemer et al., 2005).

Scutellarin is a widely active flavonoid for disease conditions. A study included 20 healthy subjects who were administered 60 mg of the flavonoid as a single dose to determine the PK properties of scutellarin. Altogether, four metabolites were detected in the urine employing liquid chromatography combined with electrospray multi-stage mass spectrometry. Nonetheless, only the metabolite scutellarein 6-O- β -d-glucuronide was identified in the plasma employing mass spectrometry, nuclear magnetic resonance and ultraviolet absorbance spectra. Following administration, a shallow plasma concentration of scutellarin was recorded, and the plasma time-concentration curve was atypical. On the other hand, the plasma concentration of scutellarein 6-O- β -d-glucuronide was relatively high resulting in a peak plasma concentration of 7.0 ± 29.1 ng/ml, and Tmax of 7.85 ± 1.62 h as well as double peaks were recorded indicated that scutellarin could be reabsorbed into the intestine succeeding its hydrolysis to aglycones by bacterial enzymes. Reconjugation ensued in intestinal or liver cells with glucuronic acid enhanced by phase II enzymes (X. Chen, Cui, Duan, Ma, & Zhong, 2006).

Licorice (*Glycyrrhiza glabra* L.) exhibited their potential role in autoimmune diseases like RA (Huang et al., 2016). Licorice flavonoid oil (LFO) contains licorice flavonoids dissolved in medium chain triglycerides. The most active flavonoid from *G. glabra* L. consists of glabridin as one of the most active flavonoids. A study regrouping healthy human volunteers involved in the administration of a single dose and two multiple doses of LFO administered daily at a concentration of 300, 600 and 1200 mg in a placebo-controlled single-blind design. The PK profile in 5 healthy males demonstrated that glabridin was absorbed and reached the maximum concentration (Cmax) at the steady-state and Cmax was 1.42 to 4.4 ng/mL after approximately 4 h (Tmax), and then eliminated relatively slowly in a single phase with a T1/2 of approximately 10 h at all doses. As the dose increased, the AUC0–24 h

Table 5
The role of other flavonoids in modulating the immune system and its specific mode of action in reducing the pathogenesis of rheumatoid arthritis

Members of the flavonoid	Specific mode of action	References
Quercetin	Decreased the activation of B lymphocyte and neutrophils and inhibited the expression of proinflammatory cytokines IL-1 β , MCP-1 and IL-6 Downregulate the NF- κ B and COX2	Choi, Bae, Yu, Youn, & Sung, 2009; Drummond et al., 2013; Kauss et al., 2008
Catechin	Inhibit IL-1 α	Ansari, Neha, & Khan, 2014; Min et al., 2007 Adcocks, Collin, & Buttle, 2002; Natarajan, Madhan, & Tiku, 2015
Epicatechin	Inhibit IL-1 α	Adcocks et al., 2002; Natarajan et al., 2015
EGCG	Inhibit TNF- α , IL-1 α , IL-6 Inhibit the MMP-1, MMP-2 and MMP-9 Inhibit the activation of NF- κ B and IL-1 β Inhibit the activation of B-cells apoptosis by inhibiting IGF-1 and reduced the macrophages	Adcocks et al., 2002; Ahmed et al., 2008; Natarajan et al., 2015; Yun et al., 2008 Morinobu et al., 2008; Oka et al., 2012 Rasheed et al., 2009 Lin et al., 2008
Hesperidin	Inhibit the expression of IL-1 β , IL-6, IL-10 and TNF- α by peritoneal macrophages Inhibit C-reactive protein and NO Inhibit the expression IL-1 β , TNF- α and IL-1 β	Ahmed et al., 2015; Li et al., 2008 Kometani et al., 2008 Choi & Lee, 2010
Apigenin	Inhibit the expression of IFN- γ , IL-1 β , CXCL-9 and CXCL-10 Inhibit the expression of chemokine receptor 4 (CXCR 4) and mitigate the immune response Reduced the number of DCs and Langerhans cells in draining lymph Inhibit the activation of NF- κ B and IL-1 β	Bandyopadhyay et al., 2006 Li et al., 2015 Liu, Zhang, et al., 2015 Chang et al., 2015; Chen et al., 2013; Wang et al., 2014
Kaempferol	Inhibit the expression of IL-1 β Suppress the Trge, FOXp3	Lee, Quach, et al., 2014 Lin et al., 2015
Luteolin	Inhibit the expression of TGF- β , IL-6, IL-8 and IL-15	Hou, Wu, Huang, & Guo, 2009
Naringin	Increased the Th2 response and inhibit the Th1 response and decrease the CD4 ⁺ and CD25 ⁺ T cells Inhibit the production of IL-17 CD4 ⁺ , IFN- γ CD4 ⁺ T cells	Ahmad et al., 2014 Li et al., 2015

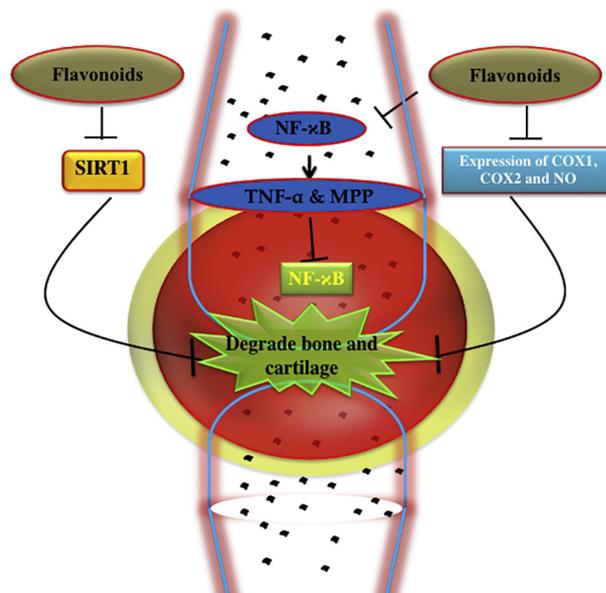


Fig. 9. The molecular mechanism of flavonoids in combating rheumatoid arthritis.

Following administration of β -glucuronidase, the concentration of the flavonoids increased significantly (Matsumoto et al., 2018). The treatment with β -glucuronidase demonstrated the C_{max} of different compounds in the range of 2.52–1320 ng/ml and the t_{max} in the range of 6h–24 h for various flavonoids evaluated.

The concentration of glycyrrhizic acid another flavonoid in KGT reached a maximum concentration (C_{max}) of 2.88 ng/ml following the first hour after KGT administration while the main metabolite was recorded at C_{max} : 121 ng/ml after 6 h. The concentration of berberine remain constant at 0.181 ng/ml at all points in time irrespective of β -glucuronidase treatment (Matsumoto et al., 2018)

Another study investigated the PK profile of flavonoids from the Chinese preparation xiexin. Rats were administered a dose of 12 g/kg, and the presence of flavonoid components was determined by HPLC profiling of their plasma and urine. The DAS software package was employed to input the plasma concentration-time and urinary excretion-time data to generate the PK properties of the flavonoids. Interestingly, ensuring administration of xiexin decoction in rats, the flavonoids, baicalin and wogonoside demonstrated double peak phenomena concerning their plasma concentrations. The first peaks were recorded at 10 ± 8 and $1.5 \pm 0.5 \text{ mg} \times L(-1)$ at T_{max1} of 0.27 ± 0.09 and 0.17 ± 0.00 h, while the second peaks reached C_{max2} of 3.9, 0.5 and $0.74 \pm 0.11 \text{ mg} \times L(-1)$ at T_{max2} of 7.6 ± 2.6 and 16.0 ± 0.0 h, respectively. The $T(1/2)$ of baicalin and wogonoside were 7 ± 3 and 6.4 ± 2.1 h, $AUC_{0-\infty}$ were 57 ± 12 and $15 \pm 3 \text{ mg} \times h \times L(-1)$, respectively. The urine samples revealed the presence of baicalin, wogonoside and of wogonin as well. Excretion profiles of baicalin, wogonoside, baicalein and wogonin were during the first 72 h was 1.4 ± 0.3 , 3.4 ± 1.3 , 2.2 ± 0.97 , $10 \pm 4\%$ of dose given in rats, respectively while the excretion profile $T(1/2)$ of the corresponding flavonoids were 6.9 ± 2.1 , 9 ± 4 , 8.2 ± 2.0 and 7.2 ± 1.8 h (J. Yan, Liu, Wang, Shi, & Ma, 2007).

The pharmacokinetic profile of three chiral flavonoids namely hesperetin, naringenin and eriodictyol were undertaken for the first time in an investigation executed by Yáñez et al. In fact, a dose of 20 mg/kg was intravenously administered to 18 Sprague-Dawley rats. The concentration of different flavonoids from plasma and urine was determined via HPLC and verified by LC/MS. Short half-lives of flavonoids ranging from 3–7 h were noticed in the serum while a better estimation of half-life and other pharmacokinetic profile (12–48 hr) was possible employing the urine samples. The flavonoids are excreted via non-renal routes undergoing fast and profound phase II metabolism. The results revealed that the three flavanones evaluated, each

increased almost linearly. Conversely, in the multiple-dose investigation among healthy male and female carried along 1 week and 4 weeks displayed that plasma glabridin reaches a steady state concentration within 2 weeks provided that a single daily administration of 300 to 1200 mg/day LFO is maintained (Aoki et al., 2007).

Recently, it has been demonstrated that flavonoid glucuronides can be deconjugated to their aglycone form following the action of β -glucuronidase-expressing macrophages. One such traditional Japanese medicine rich in flavonoids, keigaiirengyoto (KGT) was assayed for the PK properties of its flavonoids as well as to identify the flavonoids contributing to its complementary pharmacological activity. Rats were orally administered 2g/kg KGT, and their plasma was examined for the presence of flavonoids. Since KGT contains a plethora of flavonoids, the PK profile of only 8 flavonoids were duly investigated. Indeed, the pharmacokinetic properties of apigenin, baicalein, genistein, hesperetin, liquiritigenin, luteolin, naringenin, and wogonin were assayed prior and after the administration of β -glucuronidase. Prior to the introduction of β -glucuronidase, the concentration of the 8 flavonoids was very low.

underwent glucuronidation upon its administration intravenously, as recorded through serum and urine concentrations and which was later on confirmed by β -glucuronidase treatment of plasma and urine samples (Yáñez et al., 2008).

In the year 2004, it was reported that more than 100 studies had been carried out investigating the pharmacokinetic profile of individual flavonoids in healthy volunteers. In general, it has been established that the small intestine absorbs only between 0 to 60% of all flavonoids consumed while the elimination half-life ($t_{1/2}$) ranges from 2 to 28 h. Succeeding absorption, flavonoids undergo extensive first-pass phase II metabolism in small intestinal epithelial cells and the liver. The most common metabolites in plasma are conjugated with glucuronate, methyl and sulfyl groups (Manach & Donovan, 2004). A recent study by Zhao et al. evaluated the PK studies of chrysin, tectochrysin in rats by ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) coupled with a one-step liquid-liquid extraction method and it was demonstrated in their study that the AUC and Cmax of both the flavonoids were remarkably increased in dementia rats than normal rats (Zhao, Su, Liu, & Jia, 2018). Another study has shown that biliary excretion of fisetin was mediated by P-glycoprotein (Huang, Hsueh, Cheng, Lin, & Tsai, 2018).

Autoimmune disorders involve a diversified range of chronic disorders with severe inflammation being the cause of these disease category. It is initially driven based on several factors including infection, injury or genetic changes (Pan, Lai, Dushenkov, & Ho, 2009).

Fortunately, nature is an armamentarium of protective molecules against the damaging effects of oxidants which ultimately lead to the occurrence of an inflammatory environment that undeniably leads to autoimmune disorders. Many foods occurring naturally are rich sources of flavonoids, for example, apple, berries, broccoli, cocoa, curcuma, grapes, and green tea (Hanneken, Lin, & Maher, 2005). Indeed, flavonoids are known to possess diverse pharmacological properties the most important ones being anti-inflammatory, oxidant, viral, bacterial, thrombogenic, atherogenic. It is recommended that up to 650 mg of flavonoids should form part of our diet on a daily basis.

A plethora of cellular mechanisms are associated with the *in vivo* anti-inflammatory action of flavonoids. In addition to their antioxidant activities, flavonoids are capable of inhibiting eicosanoid generating enzymes as well as modulate the expression of pro-inflammatory molecules by inhibiting the activation of transcription factors involved in the process. They exert their anti-inflammatory actions through a wide range of mechanisms. The mechanism of action of each flavonoid

is dependent upon its structure and act on different sites on the cellular machinery (Kim et al., 2004)

Matricaria recutita L. commonly known as chamomile, belongs to the family Asteraceae. A panoply of traditional uses is associated with this plant such as its use against gastrointestinal discomfort, as the mouthwash as well as to combat the oral mucosa inflammation. Topical preparations consisting of chamomile are being used against dermatitis and related skin irritation conditions as well (Brown & Dattner, 1998). Interestingly, the flowers of the plant are rich in flavonoids namely; apigenin which is the primary constituent while luteolin and quercetin are present in smaller amounts (Middleton & Drzewiecki, 1982). The mechanism of action through which these flavonoids act has been elucidated with apigenin and quercetin bearing the potential to impair histamine production from human basophilic polymorphonuclear leukocytes stimulated by antigen. A clinical trial regrouping healthy volunteers ($n = 9$) showed that topical permeation of flavonoids was significant (Merfort, Heilmann, Hagedorn-Leweke, & Lippold, 1994).

An extensive epidemiological study regrouping 9959 men and women were followed for 24 years demonstrated an inverse relationship between the administration of the flavonoid quercetin and lung cancer (Knekt et al., 1997). This may be attributed to the fact that the flavonoid is non-toxic to healthy body cells but destroys cancer cells even being mutagenic *in vitro* (Lakhanpal & Rai, 2007). A scientific report on the safety of quercetin in animal toxicity studies has highlighted that quercetin is unable to result in adverse events even if the mention of specific doses administered is lacking (T. Okamoto, 2005).

Another plant rich in flavonoids is *Cardiospermum halicacabum* L. also known as the balloon vine in many parts of the world has been employed traditionally mainly for its anti-inflammatory and antipruritic effects (Reuter, Wölfle, Weckesser, & Schempp, 2010). A double-blind investigation concluded that an ointment based from the plant was slightly more useful than placebo among patients suffering from mild eczema. Nonetheless, further investigations need to be undertaken to understand how the formulation brings about such an effect (Merklinger, Messemer, & Niederle, 1995).

Around 13 flavonoids are known to occur in licorice. Interestingly, in a clinical study, a flavonoid, licochalcone A (LCA) affected similarly to 1% hydrocortisone in moderate childhood atopic dermatitis. In furtherance, transdermal water loss occurred at a lower extent in comparison to the baseline. Besides, the use of LCA improved the clinical condition when applied consecutively for at least 4 weeks (Wananukul, Chatproedprai, & Charutragulchai, 2012).

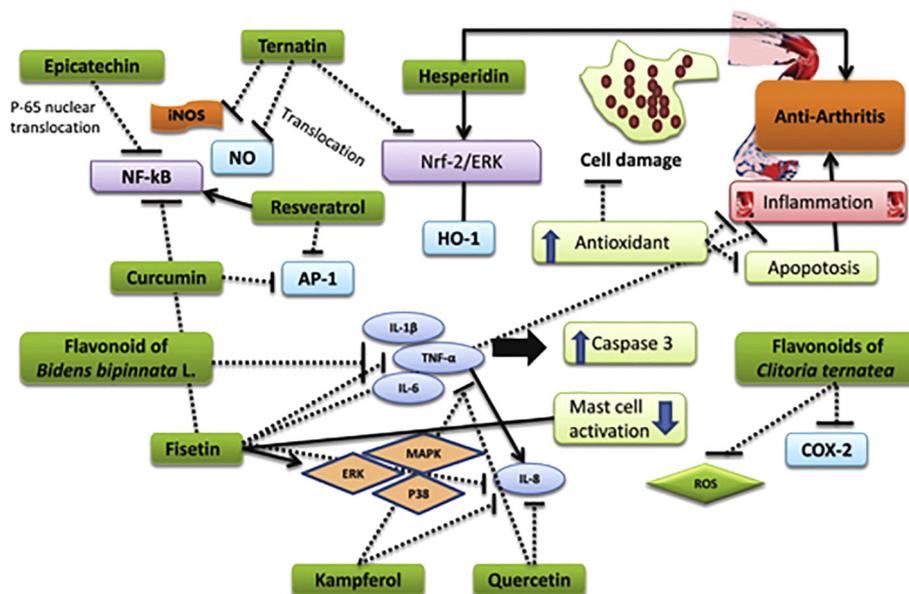


Fig. 10. Possible mechanisms of the flavonoids in autoimmune diseases.

Table 6
Pharmacokinetic profile of the two extracts administered^a

Pharmacokinetic details	Extract A (107.0 mg CA; 14.4 mg LUT)	Extract B (153.8 mg CA; 35.3 mg LUT)
Cmax (ng ml ⁻¹)	59.077±32.82	156.5±92.29
tmax (h)	0.367±0.18	0.46±0.18
AUC _{0–last} (ng ml ⁻¹ ·h)	159.0±73.87	464.8±183.1
AUC _{tot} (ng ml ⁻¹ ·h)	168.6±76.85	499.6±194.0
kel (h ⁻¹)	0.32±0.13	0.37±0.24
t _{1/2} (h)	2.50±0.85	2.45±1.14

Cmax: peak plasma concentration; tmax: time to reach Cmax; AUC_{0–last}: area under the curve from 0 to the last sampling time, AUC_{tot}: area under the curve from 0 to infinity; kel: elimination constant; t_{1/2}, elimination half-life. Data are expressed as mean ± SD (n = 14).

^a This table was adapted from Wittemer et al., 2005.

The plant species *Silybum marianum* belonging to the Asteraceae family is a rich source of flavonoids. In fact, a standardized extract from this plant commonly referred to as the National Centre has evaluated silymarin for Complementary and Alternative Medicine for its therapeutic properties. The extract consists of active flavonoid constituents silybinin, silydianin and silychristin which are antioxidants which prevent lipid peroxidation. They also cushion cells from genomic injury alongside increasing the manufacture of proteins in hepatocytes, neutralize the activity of tumor promoters as well as stabilize mast cells and favor iron chelation (Saklani & Kutty, 2008).

As a final note, it can be declared that flavonoids are potent antioxidants which can be useful candidates in auto-immune disorders prophylaxis and management. They occur widely in many different plant species and are essential components of the diet. A few clinical studies mentioned in this article point to the fact that such studies are scarce and their purported health claims cannot be fully validated based on limited data on their safety and efficacy.

8. Marketed flavonoid drugs for inflammatory responses

Flavonoids rutin and venorutin are available in the form of capsule and tablets by the marketed name of Rutoside®. It is used in combination with enzymes to treat painful signs of painful autoimmune diseases like arthritis (Kaur et al., 2014). Hesperidin and diosmin are available by the name of Detralex®, and its anti-inflammatory actions are confirmed by (Crespo, Galvez, Cruz, Ocete, & Zarzuelo, 1999) in animal studies. Troxerutin a flavonoid mostly found in green tea, coffee and fruits are effective in the protection of cell damage against oxidative stress and inflammation (Panat, Maurya, Ghaskadbi, & Sandur, 2016). Its capsule and gel dosage form are available internationally by the name of Troxevasin®. Liquoritin a flavonoid available by the proprietary name preparation of licorice roots flavonoids® is used for the treatment of spasms, inflammation and ulcer. (Pavlova, Albegova, Vorob'eva, Laptsev, & Kozlov, 2016). Quercetin and dihydroquercetin flavonoids obtained from fruits and vegetables are helpful in treating painful symptoms of rheumatoid arthritis. This activity is proved by *in vitro* and *in vivo* studies (Li, Yao, et al., 2016). Quercetin® is available in the form of tablets and is also used as angioprotective (Pavlova et al., 2016).

9. Toxicity of flavonoids

Given their diverse therapeutic properties ranging from anti; carcinogenic, inflammatory and oxidant properties, flavonoids are sometimes thought of being non-toxic. Notably, flavonoids act as antioxidants in their reduced forms but are pro-oxidants in their oxidised forms. In fact, flavonoids can be toxic while investigations on the toxicity of flavonoids remain scarce as they are not marketed as drugs and hence do not require FDA approval. In the presence of redox-active metals, phenolics such as flavonoids exerts pro-oxidant properties. For example, in the presence of oxygen, reactive oxygen species (ROS) and phenoxyl radicals are generated by the redox cycling of

phenolics catalysed by metals such as copper and iron consequently leading to deoxyribonucleic acid (DNA), lipids as well as other biological molecules damage (Decker, 1997; Li & Trush, 1994; Yamanaka, Oda, & Nagao, 1997).

The LD₅₀ of flavonoid aglycones in rats was established in 1986 by Casley-Smith & Casley-Smith, 1986 following their injection into the blood of rats. It was found to be ~2g/kg of body weight. When injected directly into the bloodstream, soluble flavonoids such as hydroxyethylrutinosides reach maximal level 0.3 to 0.5 percent of the maximum LD₅₀ for rats. Hence, the safety margin for the use of flavonoids in humans is large. On the other hand, there are other forms of toxic flavonoids especially in eastern parts of the world particularly in Africa. A particular example is a type of flavonoid which colours the propolis dark and is highly toxic and must be avoided unless assayed. Moreover, impure plant extracts should not be injected directly into the blood due to the high risks of anaphylactic reactions arising (Havsteen, 2002).

Quercetin is a unique flavonoid that has been studied for over 30 years. It is a powerful antioxidant which can neutralize the damaging effects of reactive oxygen species (ROS) and has been found useful in diverse autoimmune disorders such as arthritis. A plethora of adverse effects has been reported following oral intake of quercetin including nausea, headache as well as tingling of the extremities. *In vitro* studies conducted on quercetin have unveiled numerous toxic side effects of the compound. The conference of the Federation of American societies for experimental biology in 1984 highlighted carcinogenicity in one among seventeen feeding studies involving laboratory animals (Lakhanpal & Rai, 2007).

Interestingly, flavonols constituting of pyrogallol or catechol B rings tend to autoxidize when coexisting with transition metals undeniably leading to the production of ROS which accentuates low-density lipoprotein oxidation in the propagation phase. Fortunately, *in vivo*, a negligible amount of transition metals is released by tissues most of which are unable to catalyse such ROS generating processes. Nonetheless, the green tea component EGCG at the high concentration of 200 μM was demonstrated to trigger hydrogen peroxide generation and induce oxidative damage to DNA in the presence of transition metals *in vitro* (Furukawa, Oikawa, Murata, Hiraku, & Kawanishi, 2003; Hirose et al., 2001).

Of particular concern is the formation of phenoxyl radicals from flavonoids consisting of phenol rings catalysed by peroxidases. Upon oxidation by peroxidases, flavonoids consisting of phenol rings form phenoxyl radicals which are cytotoxic; co-oxidise unsaturated lipids; ascorbate, glutathione, NADH and nucleic acids eventually producing ROS and causing mitochondrial toxicity. In general, peroxidases consist of heme which catalyses a one-electron oxidation of a plethora of xenobiotics by hydrogen peroxide. Different forms of this enzyme such as myeloperoxidase, eosinophil peroxidase and lactoperoxidase are present in various locations of the body and can be commonly found in granules of white blood cells such as neutrophils, eosinophils as well as secretory cells of the exocrine gland. Myeloperoxidase and eosinophil peroxidase are found in plasma and the phagocytic vacuole while lactoperoxidase is secreted in milk, plasma and tears (Galati & O'brien, 2004).

Activated leukocytes can co-oxidise xenobiotics and their corresponding metabolites accumulating in plasma or bone marrow. A particular form of cancer namely secondary acute myelogenous leukaemia results following cancer therapy with etoposide or leukaemia being a consequence of chronic exposure to the phenol metabolite benzene. These forms of cancers are also the outcome of DNA damage by pro-oxidant phenoxyl radicals formed by myeloperoxidase or hydrogen peroxide (Kagan et al., 1999).

Results from many investigations depict that phenoxyl radicals are involved in the initiation of a plethora of disease conditions most striking of which is atherosclerosis. This occurs from the oxidation of tyrosine, a plasma phenol to tyrosyl radical which then co-oxidises low-density

lipoproteins during the initiation step. Activated neutrophils also bear the potential of oxidising tyrosine (Heinecke, Li, Francis, & Goldstein, 1993)

Catalytic concentrations of flavonoids possessing a phenol B ring, for example, apigenin and naringenin upon oxidation by peroxidase/H₂O₂ led to the formation of phenoxyl radicals leading to the oxidation of glutathione and NADH co-oxidation thereby generating ROS. Hence, the consumption of large amounts of flavonoids is not considered a safe practice until their potential of inducing oxidative stress is thoroughly evaluated. Investigation of the flavonoid EGCG in mice has led to hepatotoxicity and increased risk of intracerebral haemorrhage in rats. Supplements rich in flavonoids should be avoided as evidence suggests that these can induce or inhibit drug-metabolizing enzymes (Galati & O'Brien, 2004). Interference with the intestinal absorption of metal ions, such as iron, was also reported after oral intake of flavonoids in quite high doses, and other possible adverse effects have been pointed, but studies with common flavonoids in animal model and clinical trials indicate a good drug tolerability (de la Torre et al., 2016; Gutierrez-Merino et al., 2011).

Recently, green tea showed deleterious effects in instances of chronic renal failure (CRF). In fact, green tea contains high proportions of putative substrates of anion transporters such as OAT1 and OAT3. On the other hand, CRF is associated with the occurrence of indoxyl sulfate, p-cresyl sulfate and nephron cardiovascular toxins in substantial amounts. The administration of green tea in adenine induced chronic renal failure in rats was found to escalate the systemic levels of; blood urea nitrogen, endogenous indoxyl sulfate, p-cresyl sulfate as well as serum creatinine. Hence, the phytochemicals in green tea were found to disrupt normal renal function by dwindling the elimination of nephrocardiovascular toxins through the inhibition of the transporting functions of OAT1 and OAT3 (Peng et al., 2015; Vargas et al., 2018).

10. Conclusion and future perspectives

Given their supported scientific validation, flavonoids are striking candidates for the development of novel anti-inflammatory drugs. Indeed, flavonoids exerts beneficial effects among a wide range of auto-inflammatory disorders discussed in this review article ranging from MS and ALS, psoriasis, T1DM, SLE and IBD. Flavonoids exert their anti-inflammatory and immune-regulatory actions through the modulation of diverse mechanistic processes. Notably, flavonoids can suppress the central regulator of inflammation NF- κ B hence inhibiting the production of pro-inflammatory cytokines as well as subsiding the deleterious effects of NO and ROS. Diverse other valuable properties of flavonoids have been confirmed by numerous studies conducted worldwide including prompting the repair of myelin and being neuroprotective. In comparison to conventional drugs, therapy with flavonoids appear subtle particularly regarding adverse and side effects of most synthetic drugs. Nonetheless, despite the fact that numerous studies have been conducted on a panoply of flavonoids, it is irrefutable to carry further investigations. There is no denying that employing human models in *in vitro* studies, performing more *in vivo* investigations and the conductance of more randomised clinical trials will polish the quality of data available regarding flavonoids. The possibility of diverse and distinct flavonoids to induce herb-drug interactions should also be screened thoroughly as well as the possibility of synergistic activities of flavonoids in combination with conventional drugs must also be exploited all of which aim at improving the quality of life of autoimmune disorders sufferers. Consequently, it can be concluded that with the advancement of research in the field of natural flavonoids, a new era of medicinal supplements will be explored, which may be helpful for the researchers and pharmaceutical industries in the production and development of safe health-promoting agents from natural sources.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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