



# Epigallocatechin gallate, the primary bioactive component from *Camellia sinensis*: A review on immunomodulatory effects in autoimmune diseases by balancing the differentiation of Th and Treg cells

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## ABSTRACT

Autoimmune disease is a chronic condition that requires treatment with prolonged use of drugs. Consequently, there is a significant occurrence of adverse effects and toxicity associated with the medicine. On the other hand, epigallocatechin gallate (EGCG), the primary bioactive catechin in green tea (*Camellia sinensis*), has been demonstrated to possess anti-inflammatory properties and exhibit therapeutic effects in autoimmune disorders. Therefore, EGCG can be considered a complementary and alternative medicine to address the limitations of current treatment. Turning to the disease pathology, the balance between helper T-cell (Th) and regulatory T-cell (Treg) differentiation is the crucial aspect that needs to be regulated in order to attain immunological tolerance and suppress the incidence and severity of autoimmune disease. Here, we aim to comprehensively review the immunomodulatory effect of EGCG on the balance of Th/Treg cell differentiation in diverse autoimmune disorders. Scientific databases, including Scopus, PubMed, Science Direct, and Google Scholar, were searched using the keywords autoimmune AND (epigallocatechin-3-gallate OR epigallocatechin gallate OR EGCG) AND (Thelper OR Th OR Treg OR CD4). Our review revealed that EGCG has ability to repair the imbalance of Th/Treg cell differentiation in rheumatoid arthritis (RA), multiple sclerosis (MS), ulcerative colitis (UC), and autoimmune uveitis (AU) by inhibiting the differentiation of Th1 and Th17 cells while promoting the differentiation of Th2 and Treg cells, as well as improving the clinical conditions of the tested animals. Hence, it might be inferred that EGCG exhibits considerable promise as a viable complementary and alternative therapeutic option for autoimmune disease.

### Implication for health policy/practice/research/medical education:

This review emphasises the pharmacological effect of epigallocatechin gallate (EGCG) from *Camellia sinensis* in ameliorating the imbalance of Th/Treg cell differentiation observed in autoimmune disorders. The efficacy of EGCG in attaining immunological tolerance through this mechanism makes it a promising candidate for the invention of a safe and potent novel medicine. This review not only discusses the benefits of EGCG in autoimmune treatments but also considers the necessity for prospective studies to address the stability issue of EGCG.

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## Introduction

Autoimmune disease refers to a condition in which the immune response attacks healthy cells due to a failure in immunological tolerance (1). The imbalance of differentiation among CD4+ T-cell subsets, specifically

helper T-cell (Th) and regulatory T-cell (Treg), has been reported to be involved in the pathogenesis of autoimmune disorders (2,3). In this context, while Th cell is responsible for inducing inflammatory and autoimmune responses, Treg cell plays a contrasting role by exerting negative

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regulatory functions to maintain immunological tolerance and suppress autoimmunity (2,4,5).

Currently, the management of autoimmune diseases requires prolonged use of drugs, which has been associated with significant adverse effects and considerable toxicity. Furthermore, the currently available medicine is limitedly effective for a particular group of patients (6,7). Therefore, the development of a complementary and alternative medicine that demonstrates both efficacy and safety in the treatment of autoimmune diseases is indispensable.

Epigallocatechin gallate (EGCG), the primary bioactive compound present in green tea (*Camellia sinensis*), has been reported to possess potent anti-inflammatory and immunosuppressive properties in animal models of autoimmune disease (4,8-10). EGCG is the most dominant catechin contained in green tea, constituting a range of 3.31% to 5.94% of the total composition of dry green tea leaves. Meanwhile, the proportions of other catechins present in green tea are as follows: epigallocatechin (EGC) ranges from 1.31% to 5.35%, epicatechin gallate (ECG) ranges from 1.51% to 3.54%, and epicatechin (EC) ranges from 0.54% to 0.87% (11). In addition to its higher proportion in green tea, EGCG has been demonstrated to possess the greatest biological activity as an anti-inflammatory, antioxidant, and anticancer agent when compared to EGC, ECG, and EC (2,12). This article highlights the considerable potential of EGCG to be utilised as a complementary and alternative therapy for autoimmune disease by comprehensively reviewing the immunomodulatory effect of EGCG on the balance of Th and Treg cell differentiation in diverse autoimmune disorders.

## Methods

This review was conducted by searching scientific search engines, including Scopus, PubMed, Science Direct, and Google Scholar, using the keywords autoimmune AND (epigallocatechin-3-gallate OR epigallocatechin gallate OR EGCG) AND (Thelper OR Th OR Treg OR CD4). We only included original research articles that were published between the years 2000 and 2023 and have been indexed with a minimum Scopus Q3 ranking. In order to obtain reliable data that aligns with the objectives of this study, we excluded articles that examined the effects of EGCG in combination with other substances and those that lacked a negative or normal control group for comparison with the treatment group.

## Results

### Autoimmune diseases that are mediated by CD4+ T-cells

The pathogenesis of several autoimmune diseases is reportedly mediated by the effector subsets of CD4+ T-cells. These diseases, also known as T-cell mediated autoimmune disorders, include rheumatoid arthritis (RA), multiple sclerosis (MS), ulcerative colitis (UC), Crohn's disease, autoimmune uveitis (AU), autoimmune

premature ovarian failure, autoimmune myocarditis, and autoimmune thyroid diseases (13-20). In this review, our primary focus was directed towards RA, MS, UC, and AU. RA is characterised by systemic autoimmunity with chronic inflammation of the synovial joints. This condition can eventually lead to cartilage and bone degeneration (9,21). MS is a persistent inflammatory condition characterised by the immune system's attack on the central nervous system (CNS) resulting in the formation of lesions and the development of significant neurological and cognitive impairments (22). UC, a type of inflammatory bowel disease, is a chronic inflammation affecting the rectum and colon due to an immune reaction targeting self-tissues (23,24). AU refers to intraocular inflammation caused by an autoimmunity response that affects the middle layer of the eye or the uveal tract, including the iris, cylindrical body, and choroid (25).

### An imbalance in the differentiation of CD4+ T-cell in various autoimmune diseases

The incidence and severity of T-cell mediated autoimmune disorders in mouse models have been linked to the increased differentiation of Th1 cells and Th17 cells, as well as the decreased differentiation of Th2 cells (13,17,19,26-28). Moreover, it has been observed that another subset of CD4+ T-cells, known as Treg cells, may also play a function similar to that of Th2 cells. Othy et al (29) observed a correlation between diminished differentiation of Treg cells and the worsening of nerve inflammation in a mouse model of MS. Meanwhile, increased Treg cell differentiation has been shown to ameliorate the clinical scores and autoimmune symptoms in mouse models of RA, MS, UC, and AU diseases (30-34). The phenomenon explained in this section provides evidence that T-cell mediated autoimmune disorders are characterised by an imbalance in the differentiation of Th1 and Th17 cells versus Th2 and Treg cells. This condition has been found to be more strongly associated with the development of autoimmune diseases, as it has been reported in patients with RA, MS, UC, and AU (20,35-38). An indication of this imbalance can be observed through fluctuations in cell populations and the expression of associated cytokines, as elaborated in the next section.

### The mechanism of naive CD4+ T-cell differentiation becomes a subset of effectors

The naive CD4+ T-cell differentiates into a minimum of four distinct subsets of effectors, namely Th1, Th2, Th17, and Treg cells (39-42). Prior to this phase of differentiation, an innate immune system is activated by antigenic stimulation, leading to the production of specific promoter cytokines that stimulate the activation of the T-cell receptor (TCR). Following this, TCR engages with a major histocompatibility complex class II and binds to an antigen-presenting cell. Subsequently, naive CD4+ T-cells are encouraged to enter the cell cycle

and subsequent differentiation into distinct subsets, as dictated by specific promoter cytokines that activate the TCR during the preceding step (2,43,44). Furthermore, a formed subset thereafter produces the effector cytokines, which possess the ability to induce inflammatory responses and autoimmunity (proinflammatory cytokines) or suppress them (anti-inflammatory cytokines). To sum up, the promoter cytokines, transcription factors, and effector cytokines for each subset have been recapped in Table 1.

Referring to Table 1, it can be observed that TGF- $\beta$  acts as a promoter cytokine in both Th17 and Treg cell differentiation. This ambivalent role of TGF- $\beta$  tends to be confusing due to the contrasting effects of Treg and Th17 cell on the pathogenesis of autoimmune disease. Nonetheless, numerous scientific evidence indicates that the upregulation of TGF- $\beta$  in test specimens, such as the spleen and plasma, are more closely associated to the increased differentiation of Treg cell rather than that of Th17 cell. Previous investigations have emphasised IL-6 and IL-1  $\beta$  as the prominent promoter cytokines involved in the differentiation of Th17 cells (9,24,32,52).

#### The role of Th1, Th2, Th17, and Treg cells in inflammatory response and autoimmunity

In previous studies, Wang et al (51), Wong et al (5), and Wu et al (2) reported that Th cells are responsible for inducing inflammatory responses and autoimmunity. However, as it turns out, the role of Th1 and Th17 cells in the pathogenesis of autoimmune diseases differs from that of Th2 cells. To clarify, the Th1 and Th17 cells induced inflammatory responses and autoimmunity via the secretion of proinflammatory effector cytokines, as outlined in Table 1 (73,74). On the other hand, Maspi et al (67) stated that the Th2 cell inhibits the differentiation of Th1 and Th17 cells, as well as inflammatory responses and autoimmunity. More specific to the inhibition of Th1 cell differentiation, the effector cytokines of the Th2 cell, namely IL-4 and IL-13, have the ability to inhibit the production of IL-12 (67). Similar to the Th2 cell, the Treg cell also possesses the ability to suppress the differentiation of Th1 and Th17 cells as well (29,32,67,72,75,76). According to Guo et al (32), it has been reported that Treg cell acts as the negative regulator of the adaptive immune

system. This role makes Treg cell crucial in suppressing the excessive immunological response and maintaining immune homeostasis that occur in autoimmune diseases (32).

#### The immunomodulatory effect of EGCG on the differentiation of Th1, Th2, Th17, and Treg cells in various autoimmune diseases

As mentioned in previous section, an imbalance in the differentiation of Th1 and Th17 cells versus Th2 and Treg cells is observed in the pathogenesis of RA, MS, UC, and AU. Prior studies have demonstrated that EGCG, a bioactive compound in green tea (*C. sinensis*), has the ability to modulate this imbalance in the mentioned diseases. The data has been summarised respectively for each disease in Tables 2-5.

#### Discussion and prospective views

The data summarised in Tables 2, 3, 4, and 5 indicate that EGCG could improve the clinical condition of the tested animal with autoimmune disorders such as RA, MS, UC, and AU through its ability to modulate the balance of CD4+ T-cell subsets differentiation. In this particular instance, EGCG could reduce the differentiation of Th1 and Th17 cells by inhibiting the activation of transcription factors and decreasing the availability of promoter cytokines. Subsequently, it resulted in an elevation in the rate of Th1 and Th17 cells differentiation and the production of effector cytokines by these cells. Meanwhile, an opposite pattern was noticed in the transcription factors, promoter cytokines, differentiation, and effector cytokines of Th2 and Treg cells (4,8,9,21,24,50,77-80). The mechanism by which EGCG modulates the differentiation of Th1, Th2, Th17, and Treg cells is illustrated in Figure 1.

Furthermore, prior studies reported that the ability of EGCG to modulate the function of Th1 cells is not only resulting in an incline in IL-2 expression (78), but EGCG could also lower the expression of the IL-2 receptor (IL-2R), which is essential for the biological effects of IL-2 (44,81,82). Moreover, Wang et al (81) confirmed that EGCG has the ability to diminish STAT5 phosphorylation, an indicator of IL-2/IL-2R signaling. Based on these data, it can be signified that EGCG has the ability to exert a

**Table 1.** Profile of promoter cytokines, transcription factors, and effector cytokines of Th1, Th2, Th17, and Treg cells

CD4+ T-cell subsets	Promoter cytokines	Transcription factors	Effector cytokines		References
			Proinflammatory	Anti-inflammatory	
Th1	IL-12	T-bet, STAT1, STAT4	IFN- $\gamma$ , TNF $\alpha$ , IL-2	-	(15,16,45-50)
Th2	IL-4	GATA3, STAT6	-	IL-4, IL-5, IL-13	(51-58)
Th17	TGF- $\beta$ /IL-6 or IL-6/IL-1 $\beta$	ROR $\gamma$ t, STAT3	IL-17A/F, IL-21, IL-22, IL-23, IL-26	-	(50,59-65)
Treg	TGF- $\beta$	FOXP3, SMAD2, SMAD3	-	TGF- $\beta$ , IL-10	(32,43,66-72)

FOXP3: fork-head box P3; IL: interleukin; ROR $\gamma$ t: retinoic acid-related orphan receptor gamma t; STAT: signal transducer and activator of transcription; TGF: transforming growth factor; TNF: tumor necrosis factor; Th: helper T-cell; Treg: regulatory T-cell; T-bet: T-box transcription factor TBX21; IFN: interferon.

**Table 2.** Immunomodulatory effect of epigallocatechin gallate (EGCG) on Th and Treg cells differentiation in rheumatoid arthritis (RA)

No.	Method	Dosage of EGCG	T-cells	Immunomodulatory effect of EGCG			Clinical improvement	References
				Effects on T-cell populations	Effects on transcription factors	Effects on cytokines		
1	In vivo	40 mg/kg i.p. 3x/week for 2.5 weeks on CIA mouse	Th1	-	-	TNF- $\alpha$ expression in joint $\downarrow$	Incidence and arthritis score $\downarrow$ ** Level of inflammation and cartilage damage in joints $\downarrow$	(9)
			Th17	Th17 cell population in the spleen $\downarrow$	p-STAT3 expression in the spleen $\downarrow$	IL-1 $\beta$ , IL-6, and IL-17 expression in joint $\downarrow$		
			Treg	Treg cell population in the spleen $\uparrow$	-	IL-10 and TGF- $\beta$ mRNA expression in splenocytes $\uparrow$		
	In vitro	1–50 $\mu$ M on splenocytes	Th17	-	p-STAT3 expression $\downarrow$	IL-17 mRNA expression $\downarrow$	-	
			Treg	-	FOXP3 mRNA expression $\uparrow$	IL-10 mRNA expression $\uparrow$		
2	In vivo	50 mg/kg i.p. 3x/week for 6 weeks on CIA mouse	Th1	-	-	TNF- $\alpha$ expression in joint $\downarrow$ *	Arthritis score $\downarrow$ ** Level of inflammation and cartilage damage in joints $\downarrow$	(21)
			Th17	Th17 cell population in the spleen $\downarrow$	p-STAT3 expression in the spleen and joint $\downarrow$ ***	IL-1 $\beta$ , IL-6, and IL-17 expression in joint $\downarrow$ *		
			Treg	Treg cell population in the spleen $\uparrow$	-	-		
				Th17	-	p-STAT3 expression $\downarrow$	IL-17 and IL-21 mRNA expression $\downarrow$	-
			Treg	-	FOXP3 mRNA expression $\uparrow$	-		
3	In vivo	10 mg/kg p.o. 3x/week for 3 weeks on CIA mouse	Th1	-	-	TNF- $\alpha$ $\downarrow$ ** and IFN- $\gamma$ expression in plasma $\downarrow$ * TNF- $\alpha$ $\downarrow$ ** and IFN- $\gamma$ expression in joint $\downarrow$ **	Arthritis score and joint thickness $\downarrow$ ** Swelling and erythema in the front and back paws $\downarrow$	(76)
			Th17	-	-	IL-6 expression in plasma $\downarrow$ ** IL-1 $\beta$ $\downarrow$ * and IL-6 expression in joint $\downarrow$ ****		
			Treg	Treg cell population in dLNs $\uparrow$	-	IL-10 expression in joint $\uparrow$ *		
4	In vivo	20 mg/kg i.p. 3x/week on CIA mouse	Th17	Th17 cell population in the spleen $\downarrow$	ROR $\gamma$ t mRNA expression in splenocytes $\downarrow$	IL-17 and IL-21 mRNA expression in splenocytes $\downarrow$	Weight loss and arthritis score $\downarrow$ ** Level of inflammation and cartilage damage in joints $\downarrow$ ****	(8)
			Treg	Treg cell population in the spleen $\uparrow$	FOXP3 mRNA expression in splenocytes $\uparrow$	-		

-: not analyzed;  $\downarrow$ : decreased;  $\uparrow$ : increased; \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.005$ ; \*\*\*\*  $P < 0.001$ ; p.o.: per oral; i.p.: intraperitoneal; CIA: collagen-induced arthritis; FOXP3: fork-head box P3; mRNA: messenger ribonucleic acid; IL: interleukin; ROR $\gamma$ t: retinoic acid-related orphan receptor gamma t; STAT: signal transducer and activator of transcription; TGF: transforming growth factor; TNF: tumor necrosis factor; Th: helper T-cell; Treg: regulatory T-cell; IFN: interferon.

**Table 3.** Immunomodulatory effect of epigallocatechin gallate (EGCG) on Th and Treg cells differentiation in multiple sclerosis (MS)

No.	Method	Dosage of EGCG	T-cells	Immunomodulatory effect of EGCG			Clinical improvement	References
				Effects on T-cell populations	Effects on transcription factors	Effects on cytokines		
1	In vivo	15 mg/kg p.o. 2x/day for 10 days on mouse before the EAE mouse model was established	Th1	-	-	TNF-α expression in dLNs↓*	Disease index↓* Inflammation in the CNS↓*	(77)
			Th1	Th1 cell population in CNS↓**	T-bet mRNA expression in CNS↓*	IL-4 expression in dLNs↔ IL-12 mRNA expression in plasma ↓* and splenocytes↓* IFN-γ expression in spleen ↓*** and LN↓** TNF-α expression in spleen and LN↓**		
2	In vivo	EGCG supplementation at 0.6%(w/w) together with feed for 30 days before the EAE mouse model was established	Th17	Th17 cell population in CNS↓**	RORγt mRNA expression in CNS↓*	IL-6 expression in spleen and LN↓** IL-1β expression in plasma↓* IL-17 expression in spleen↓*** and LN↓*** IL-23 mRNA expression in plasma↓* and splenocytes↓*	Disease index↓ Inflammation and demyelination in the CNS↓*	(4)
			Treg	Treg cell population in spleen and LN↑*** Treg cell population in CNS↑***	-	-		
			Th1	Th1 cell population↓***	T-bet expression, STAT1 phosphorylation, and STAT4 phosphorylation↓**	-		
3	In vitro	10 μM on splenocytes	Th17	Th17 cell population↓**	RORγt expression ↓*** and STAT3 phosphorylation↓**	IL-23R expression↓*	-	50
			Treg	Treg cell population↑	SMAD2 and SMAD3 expression↔	-		
			Th1	-	-	IL-6 and IL-6R expression in plasma↓*		
	In vivo	EGCG supplementation at 0.6%(w/w) together with feed for 42 days before the EAE mouse model was established	Th17	-	-	IL-6 and IL-6R expression in plasma↓*	-	

-: not analyzed; ↓: decreased; ↑: increased; ↔: not affected; \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.005$ ; CNS: central nervous system; dLNS: draining lymph nodes; LN: lymph nodes; EAE: experimental autoimmune encephalomyelitis; mRNA: messenger ribonucleic acid; IL: interleukin; RORγt: retinoic acid-related orphan receptor gamma t; STAT: signal transducer and activator of transcription; TNF: tumor necrosis factor; Th: helper T-cell; Treg:regulatory T-cell; T-bet: T-box transcription factor TBX21; IFN: interferon.

**Table 4.** Immunomodulatory effect of epigallocatechin gallate (EGCG) on Th and Treg cell differentiation in ulcerative colitis (UC)

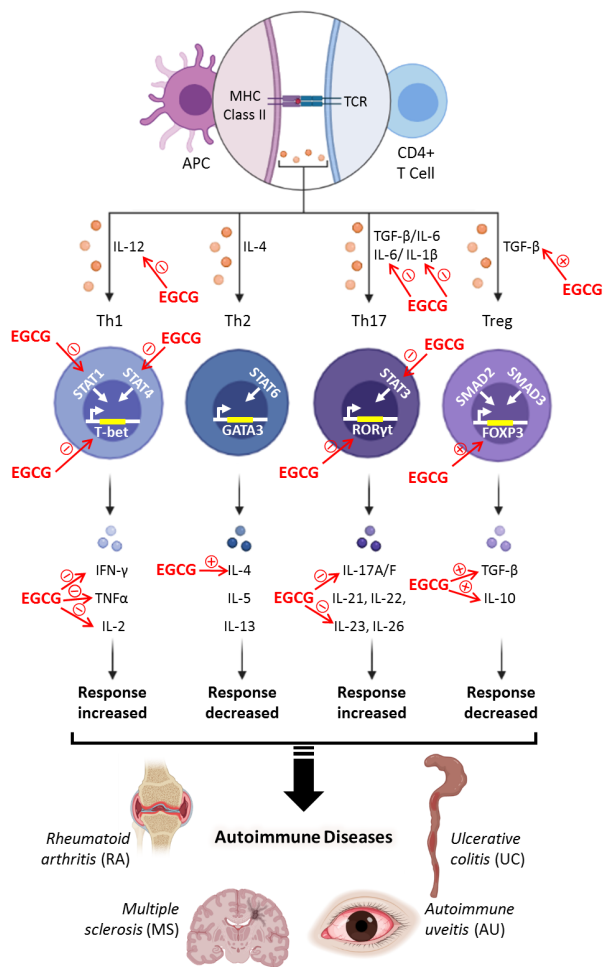
No.	Method	Dosage of EGCG	T-cells involved	Immunomodulatory effect of EGCG			Clinical improvement	References
				Effects on T-cell populations	Effects on transcription factors	Effects on cytokines		
1	In vivo	50 mg/kg/d i.p. for 10 days on DIC mouse	Th1	-	-	IL-2 and IFN- $\gamma$ expression in plasma $\downarrow$ *	DAI score and colon mucosal injury score $\downarrow$ *	(78)
			Th2	-	-	IL-4 expression in plasma $\uparrow$ *		
			Treg	-	-	IL-10 expression in plasma $\uparrow$ *		
2	In vivo	50 and 100 mg/kg/d p.o. for 7 days on DIC mouse	Th17	Th17 cell population in spleen $\downarrow$ *** (dose-dependent)	STAT3 expression in colon $\downarrow$ *** (dose-dependent)	IL-6 and IL-17 expression in plasma and colon $\downarrow$ * (dose-dependent)	DAI score $\downarrow$ * (dose-dependent)	(24)
			Treg	Treg cell population in spleen $\uparrow$ ** (dose-dependent)	-	TGF- $\beta$ and IL-10 expression in plasma and colon $\uparrow$ * (dose-dependent)		
3	In vivo	50 mg/kg/d p.o. for 3 days on DIC mouse	Th1	-	-	TNF- $\alpha$ expression in plasma $\downarrow$ **** and colon $\downarrow$	DAI score, body weight loss, and colon shortening $\downarrow$ ****	(79)
			Th17	-	-	IL-1 $\beta$ expression in plasma $\downarrow$ **** IL-6 expression in plasma $\downarrow$ **** and colon $\downarrow$ *		
		50 mg/kg/d p.o. for 4 weeks before the DIC mouse model was established	Th1	-	-	TNF- $\alpha$ expression in plasma $\downarrow$ and colon $\downarrow$ ****		
			Th17	-	-	IL-1 $\beta$ expression in plasma $\downarrow$ IL-6 expression in plasma and colon $\downarrow$ ****		

-: not analyzed;  $\downarrow$ : decreased;  $\uparrow$ : increased; \* $P$  < 0.05; \*\* $P$  < 0.01; \*\*\* $P$  < 0.005; p.o.: per oral; i.p.: intraperitoneal; DIC: dextran sulfate sodium-induced colitis; DAI: disease activity index; IL: interleukin; STAT: signal transducer and activator of transcription; TNF: tumor necrosis factor; TGF: transforming growth factor; Th: helper T-cell; Treg: regulatory T-cell.

**Table 5.** Immunomodulatory effect of epigallocatechin gallate (EGCG) on Th cell differentiation in autoimmune uveitis (AU)

No	Method	Dosage of EGCG	T-cells	Immunomodulatory effect of EGCG			Clinical improvement	References
				Effects on T-cell populations	Effects on transcription factors	Effects on cytokines		
1	In Vivo	192,5 mg/kg/2 days p.o. for 26 days on mouse before the EAU mouse model was established	Th1	-	-	TNF- $\alpha$ mRNA expression in retina $\downarrow$ *	Diameter enlargement of major retinal vessels $\downarrow$ Attenuation of visual functions $\downarrow$ * Clinical score $\leftrightarrow$	(80)
			Th17	-	-	IL-1 $\beta$ , IL-6, IL-17A mRNA expression in retina $\downarrow$ *		

-: not analyzed;  $\downarrow$ : decreased;  $\leftrightarrow$ : not affected; \* $P$  < 0.05; p.o.: per oral; EAU: experimental autoimmune uveoretinitis; mRNA:messenger ribonucleic acid; IL: interleukin; TNF: tumor necrosis factor; Th: helper T-cell; Treg:regulatory T-cell.



**Figure 1.** Illustration of epigallocatechin gallate (EGCG) in modulating the balance of Th1, Th2, Th17, and Treg cells differentiation. The red arrow with a negative sign indicates that EGCG decreased the expression of the designated molecule, while a red arrow with a positive sign indicates that EGCG increased the expression of the designated molecule. APC: antigen-presenting cell; FOXP3: fork-head box P3; IL: interleukin; MHC: major histocompatibility complex; RORγt: retinoic acid-related orphan receptor gamma t; STAT: signal transducer and activator of transcription; TGF: transforming growth factor; TNF: tumor necrosis factor; Th: helper T-cell; Treg: regulatory T-cell; T-bet: T-box transcription factor TBX21; TCR: T-cell receptor; IFN: interferon.

suppressive effect on the biological effects of IL-2 through the inhibition of the IL-2/IL-2R signalling pathway (81).

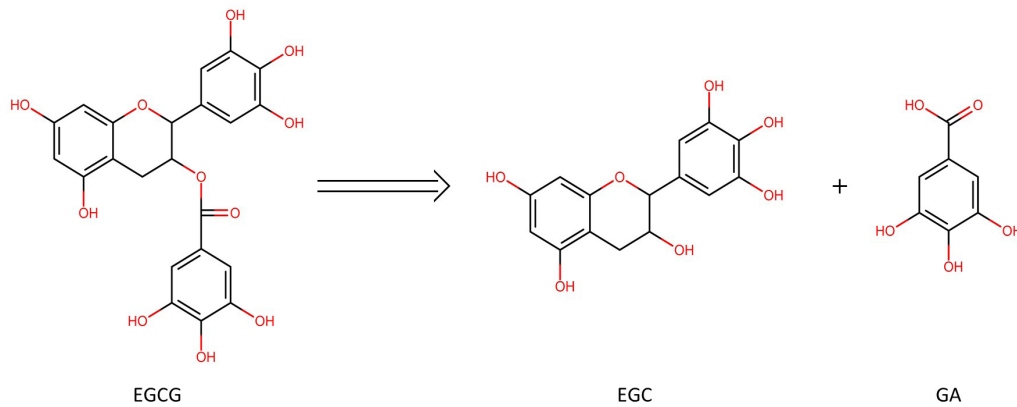
Upon closer examination of Table 3 and Table 4, it becomes apparent that there is a difference in the effect of EGCG on modulating Th2 cell differentiation. In a previous study conducted by Aktas et al (77), it was demonstrated that the expression of IL-4 was unaffected by the administration of EGCG (15 mg/kg per oral) to animal models with MS (Table 3). However, Bing et al (78) then reported that EGCG (50 mg/kg intraperitoneal) could significantly raise IL-4 expression in animal models with UC (Table 4). This difference may be attributed to several factors, including the difference in the dosage and administration of EGCG as well as the type of disease being studied. Moving further, previous investigations have highlighted that the balance of Treg/

Th17 cells differentiation plays a crucial role in attaining immunological tolerance and curing autoimmunity conditions. In light of this observation, it is noteworthy that TGF-β plays a dual role as a promoter cytokine for both Treg and Th17 cells. Consequently, the absence of IL-6 and the inactivation of IL-6/IL-6 receptors (IL-6R) signalling are considered to be the limiting factors that promote TGF-β-induced Treg cell differentiation by reversing the IL-6-induced inhibition of Treg cell differentiation (2,50,83). Wang et al (50) clarified that this reversing effect is an essential mechanism of EGCG regulating the balance of Treg/Th17 cells differentiation rather than directly affecting FOXP3 activation, as the expression of SMAD2 and SMAD3 that regulate FOXP3 activation was unaffected by EGCG administration (Table 3) (50,70).

The explanation above gives a promising outlook and potential for EGCG to be considered as a complementary and alternative medicine for autoimmune disorders such as RA, MS, UC, and AU. The current treatment for these diseases is still associated with a significant occurrence of adverse effects and toxicity. The beneficial effect of EGCG in autoimmune disorders is attributed to its ability to modulate the balance of Th1 and Th17 versus T2 and Treg cell differentiation, which has been linked to the incidence and severity of the disease. Moreover, EGCG has demonstrated the ability to improve the clinical parameters of the animal being tested. Referring to the prior studies, EGCG can be proposed as a future medicine to treat (8,9,21,24,76,79) or prevent (4,50,77,79,80) the autoimmune disease. However, due to the limitations of previous research, we suggest undertaking continued exploration of EGCG on AU. This is because the current data shows an incomplete understanding of the clinical effect of EGCG on animal models with AU. According to the available report, EGCG could reduce the enlargement of major retinal vessel diameters and diminish the attenuated visual function of the EAU mouse, but it has not demonstrated the ability to improve the clinical score of EAU mouse (80).

Moving further, it has been discovered that several clinical trials of EGCG have been conducted on patients with MS. In their study, Mähler et al (84) reported that EGCG could ameliorate muscle weakness and fatigue, which are prevalent symptoms of MS. This effect was observed through a significant reduction in postprandial energy expenditure, carbohydrate oxidation rates, adipose tissue perfusion, and glucose supply. However, the current trials are still unable to demonstrate the efficacy of EGCG in curing brain atrophy or hyperintense lesions in the brain, as well as radiologic and clinical parameters (85,86). This limited efficacy of EGCG in MS patients may be attributed to the inadequate stability of EGCG within the gastrointestinal system due to the intestinal pH and microflora (87-89).

The degradation of EGCG in the human ileal fluid,



**Figure 2.** Degradation of epigallocatechin gallate (EGCG) into gallic acid (GA) and epigallocatechin (EGC).

which refers to the condition of the small intestine, results in the formation of gallic acid (GA) and EGC (Figure 2) (88,90). In other terms, this degradation causes the elimination of the GA moiety in the EGCG structure, whereas the GA component plays a vital role in the antioxidative function of EGCG, which is thought to contribute to its ability to modulate the balance of CD<sup>+</sup>T-cell subsets differentiation (9,21,91). In addition, there have been reports indicating that the GA moiety of EGCG enhances its antioxidant activity, thereby potentially augmenting its therapeutic effects in the management of MS. This is achieved through the prevention of N-methyl-D-aspartate-induced injury to brain neurons and the direct inhibition of the formation of neurotoxic reactive oxygen species within these neurons (77). Furthermore, the GA moiety in the EGCG structure has been found to inhibit the conjugation of EGCG with other substances, hence preventing its degradation (91).

The stability of EGCG can be improved through structural modification or using nano-drug delivery systems. According to Dai et al (87), the modification of certain phenolic groups in EGCG through methylation, acylation, or glycosylation could significantly improve the stability and increase the absorption by up to ninefold. Moreover, this effort could also increase the molecular weight and the hydrophobicity of EGCG, thereby escalating the permeability to the blood-brain barrier, which will significantly enhance the benefit of EGCG in MS treatment (22,87,92). Furthermore, the foregoing research indicated that EGCG encapsulated in nanoparticles, nanoemulsion, nanoliposome, and nanophytosome as a drug delivery platform can increase stability and bioavailability, hence improving the efficacy of EGCG (87,93). These approaches can be applied to prospective research to improve the therapeutic effect of EGCG, especially in clinical trial scenarios.

## Conclusion

To sum up, prior investigations have demonstrated that EGCG, the most biologically active component from

*Camellia sinensis*, exhibits considerable promise as a complementary and alternative medicine for diverse autoimmune diseases through its ability to modulate the balance of Th and Treg cell differentiation. Given the inherent stability limitations of EGCG, it is expected that prospective investigations will focus on structural modifications and the development of a drug delivery platform utilising nanotechnology to mitigate its degradation.

## Authors' contributions

**Conceptualization:** Vigha Ilmanafi Arifka, Retno Murwanti.

**Data curation:** Vigha Ilmanafi Arifka.

**Formal analysis:** Vigha Ilmanafi Arifka.

**Investigation:** Vigha Ilmanafi Arifka.

**Methodology:** Vigha Ilmanafi Arifka.

**Project administration:** Vigha Ilmanafi Arifka, Retno Murwanti, Andayana Puspitasari Gani.

**Resources:** Vigha Ilmanafi Arifka.

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## Ethical considerations

Ethical aspects have been thoroughly evaluated by the authors, including plagiarism, misconduct, data fabrication, manipulation, falsification, double submission, and redundancy.

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