



Polyphenols affect the humoral response in cancer, infectious and allergic diseases and autoimmunity by modulating the activity of T_H1 and T_H2 cells

Monica Benvenuto^{1,2,a}, Chiara Focaccetti^{2,3,a}, Sara Ciuffa²,
 Sara Fazi⁴, Arianna Bei⁵, Martino Tony Miele⁶,
 Loredana Albonici², Loredana Cifaldi^{2,7}, Laura Masuelli^{4,b} and
 Roberto Bei^{2,b}

Abstract

Polyphenols are a wide class of natural substances, pleiotropic molecules capable of modulating several processes, involved in the humoral and cellular immune response. The activation, differentiation of B cells, and production of antibodies to protein antigens by plasma cells depend on T helper (T_H) CD4⁺ cells and secreted cytokines. Cancer, infectious, allergic, and autoimmune diseases are characterized by an imbalance of T_H1/T_H2 immunity and abnormal activation of the humoral response. Accordingly, polyphenols modulate the T_H1/T_H2 ratio, the secretion of multiple cytokines, the levels of antibodies, and therefore could contribute to recovering the state of health in these diseases. In this review, we summarize the current knowledge on the effects of polyphenols in modulating the humoral response in cancer, infectious and allergic diseases and in autoimmunity by affecting the activity of T_H1 and T_H2 cells.

Addresses

¹ Saint Camillus International University of Health and Medical Sciences, Via di Sant'Alessandro 8, 00131 Rome, Italy

² Department of Clinical Sciences and Translational Medicine, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy

³ Department of Human Science and Promotion of the Quality of Life, San Raffaele University Rome, Via di Val Cannuta 247, 00166 Rome, Italy

⁴ Department of Experimental Medicine, University of Rome "Sapienza", Viale Regina Elena 324, 00161 Rome, Italy

⁵ Medical School, University of Rome "Tor Vergata", 00133 Rome, Italy

⁶ Department of Experimental Medicine, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy

⁷ Academic Department of Pediatrics (DPUO), Ospedale Pediatrico Bambino Gesù, IRCCS, Piazza Sant'Onofrio 4, 00165 Rome, Italy

Corresponding author: Bei, Roberto (bei@med.uniroma2.it)

^a Authors contributed equally to this work. ^b These last authors contributed equally to this work.

Introduction

Polyphenols are derived from secondary metabolites found in vegetables, fruits, seeds, legumes, herbs, spices, whole-grains, coffee, tea, and wine. They are classified according to their chemical structure in two main classes, flavonoids and non-flavonoids. Flavonoids class comprises flavones, flavonols, flavan-3-ols, anthocyanins, flavanones, and isoflavones, while subclasses of the non-flavonoids are hydroxybenzoic and hydroxycinnamic acids, lignans, stilbenes, curcuminoids, and xanthones [1,2]. The classification of polyphenols is reported in Figure 1. Polyphenols exerted beneficial effects on human health, by counteracting inflammation, tumor development and progression, and cardiovascular diseases. Polyphenols have antioxidant and pro-oxidant activities, modulate several inflammation-associated cell signaling pathways, and multiple targets involved in carcinogenesis [1–5]. The *in vivo* effects of polyphenols are dependent on their bioavailability, which limits the occurrence of an effective dose in the target tissue. In fact, gastrointestinal tract and liver metabolisms, the binding of polyphenols on the blood cell surface, the presence of the oral cavity and gut microbial flora, cells regulatory mechanisms, and dietary factors affect polyphenols bioavailability [2,6].

The production of antibodies to antigens by plasma cells derived from activated and differentiated B cells requires T helper (T_H) CD4⁺ cells [7,8] (Figure 2).

Besides the production of antibodies, B cells act as antigens presenting cells to CD4⁺ and CD8⁺ T cells and can release pro-inflammatory cytokines that regulate T cells behavior [9]. The induction and development of humoral immune responses to antigens, including B cell proliferation, plasma cells differentiation, immunoglobulin (Ig) production, class-switching and affinity maturation, is affected by T cells secreted cytokines, mainly T_H2 cells (IL-4, IL-5, IL-6, IL-13) [9] (Figure 3a).

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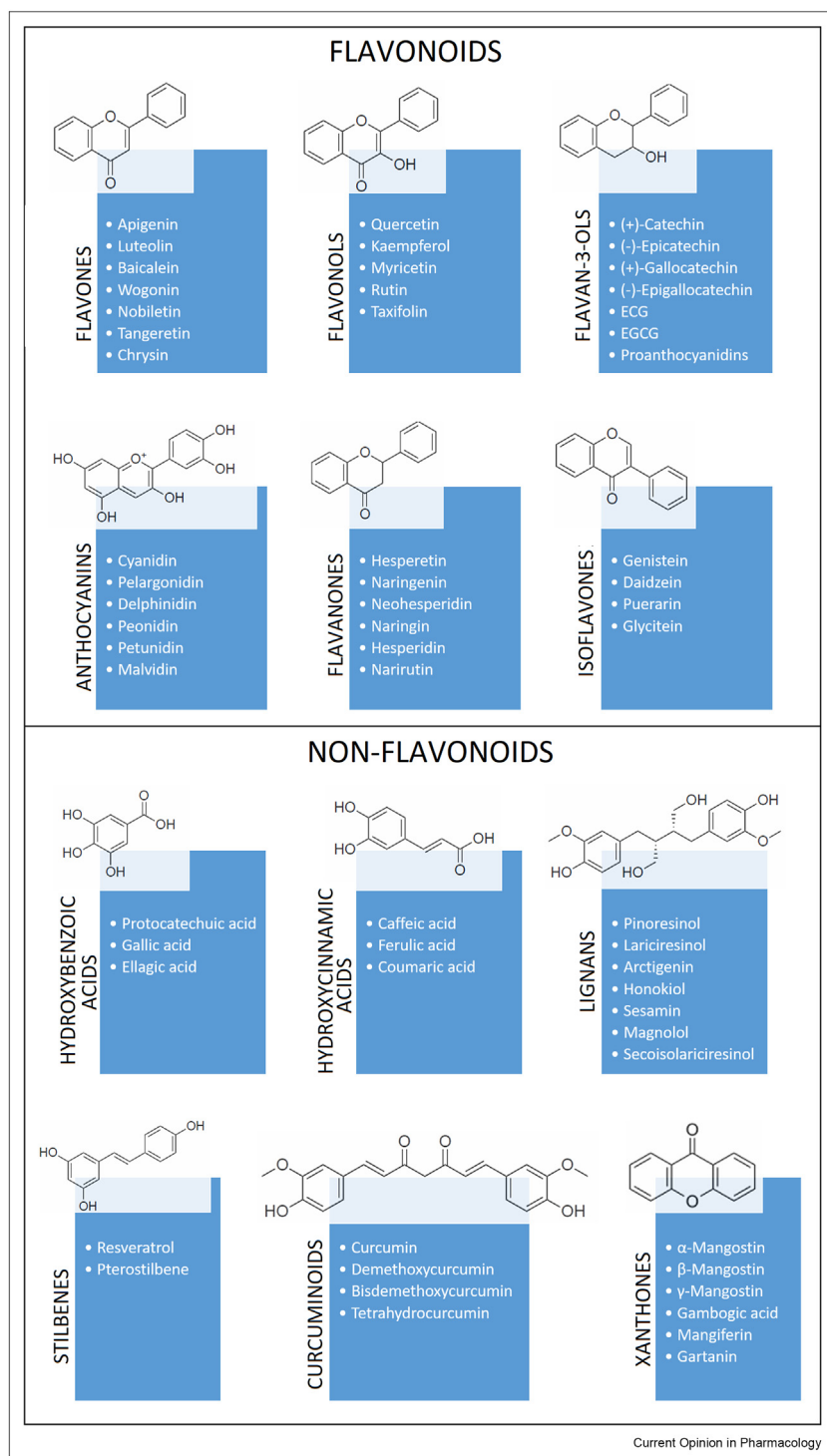
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Figure 1

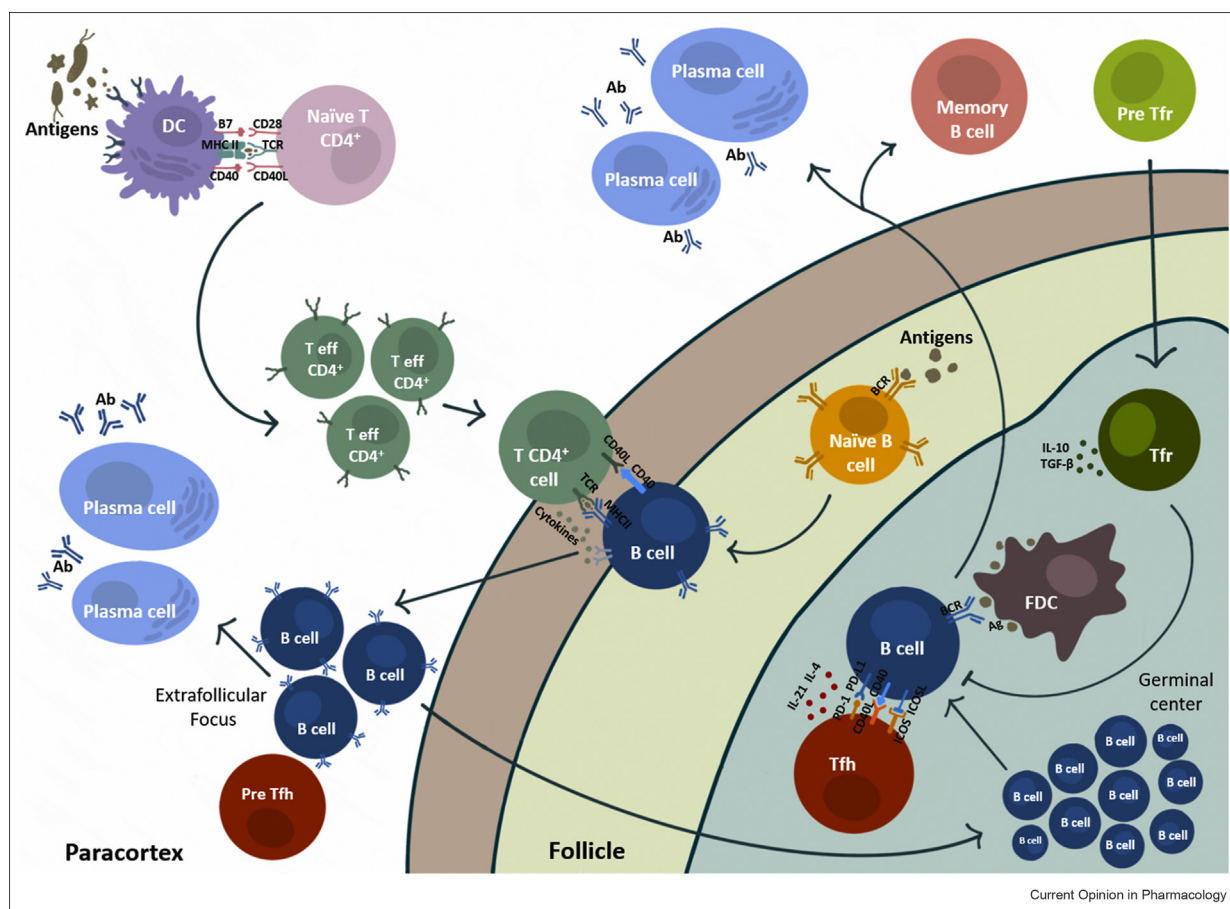


Classification of polyphenols. Polyphenols are classified into flavonoids and non-flavonoids according to their chemical structures. Flavonoids and non-flavonoids classes are also divided into several subclasses reported in the figure [2]. ECG, (-)-Epicatechin-3-O-gallate; EGCG, (-)-Epigallocatechin-3-O-gallate.

The presence of persistent inflammatory signals in several pathophysiological conditions (autoimmune and infectious diseases, cancer and inflammatory disorders) leads to the generation of ectopic lymphoid aggregates,

called tertiary lymphoid structures, which promote the local development of antigen-specific activated T and B cells and correlate with favorable prognosis in patients with cancer [10].

Figure 2



Production of antibodies by B cells. The production of antibodies to antigens by plasma cells derived from activated and differentiated B cells requires T helper (T_H) CD4⁺ cells [7,8]. After priming by an antigen, naïve B cells undergo activation in a T cell–dependent modality at the edge of the follicle, proliferate as an extrafollicular focus, migrate in the lymphoid follicular germinal centers (GCs) and further differentiate into antibody-producing plasma cells and memory B cells [7]. The production of antibodies (Ab) in GCs requires the participation of T follicular helper (Tfh) and T follicular regulatory (Tfr) cells, generated by naïve T cells and thymus-derived Tregs, respectively, after the priming by dendritic cells (DC) and migration into follicles. The correct Tfh/Tfr ratio is mandatory to avoid autoantibodies production typical of autoimmune diseases [7]. The collaboration between B cells, Tfh and follicular dendritic cells (FDC) involves the interaction of different molecules, such as CD40/CD40L, PD-1/PD-L1, ICOS/ICOSL and cytokines including interleukin (IL)-21 and IL-4, that are necessary for the correct activation and differentiation of B cells in the GCs [8]. TCR, T cell receptor; MHC, major histocompatibility complex; T_{eff}, effector T cell.

Several studies have analyzed the effect of polyphenols on B and T_H cells responses in cancer, autoimmune, infectious, and allergic diseases (Figure 3b), both *in vitro* and in mouse models. In this review, we describe recent findings on the effects of polyphenols on T_H and B cells and cytokines affecting the humoral response (Table 1).

Polyphenols and cancer

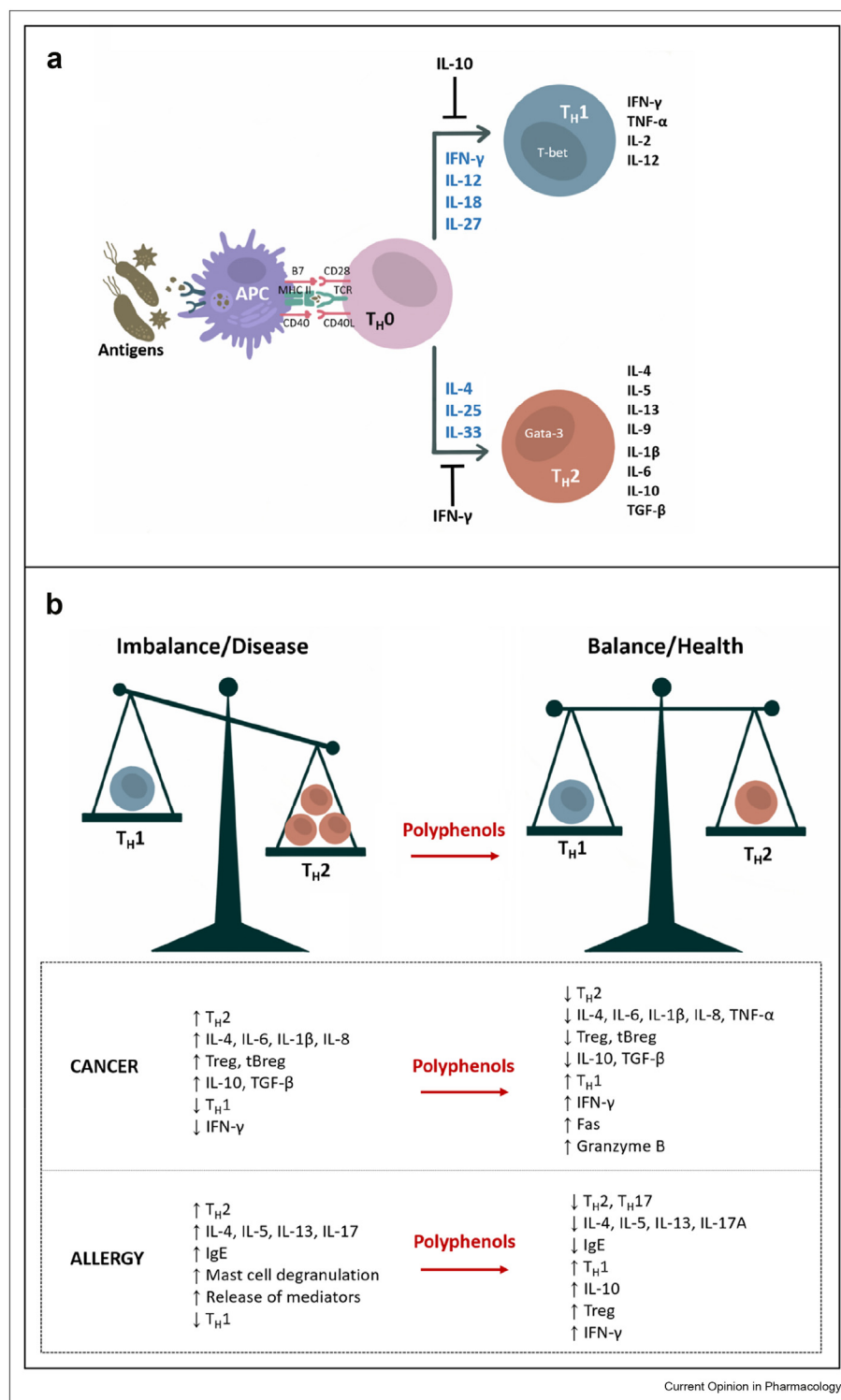
The number of B cells in the tumor microenvironment is usually lower than T cells. The number of B cells in infiltrating colon cancer strongly correlated with the presence of Tfh. B cell density increased at the late stage of disease and was associated with prolonged survival [11]. Similarly, the high densities of CD20⁺ tumor-infiltrating B cells proved to be positive prognostic markers in patients with oropharyngeal carcinoma [12],

patients with lung adenocarcinoma [13], and patients with triple-negative breast cancer [14]. Patients with cancer mount a spontaneous humoral immune response against tumor antigens [15]. However, not only the density of infiltrating B cells is important but also the Ig isotype. The presence of IgG is correlated with increased survival in patients with cancer, while both IgE and IgA have been associated with negative prognosis [16].

Because of their wide immunomodulatory capacities [17], polyphenols modulate the tumor microenvironment [18] and humoral response to tumor antigens.

The tumor microenvironment is infiltrated by regulatory T cells (Tregs) and contains abundant pro-inflammatory T_H2 (IL-4, IL-6, IL-10) and poor T_H1 cytokines (IFN-

Figure 3



Overview of T_H1 and T_H2 cell differentiation and effects of polyphenols in modulating T_H1/T_H2 balance. (a) T_H0 cells are activated by the antigen presenting cells (APC) through the TCR/MHCII and costimulatory molecules (B7/CD28, CD40/CD40L) interactions. The differentiation in T_H1/T_H2 subsets is triggered by different types of cytokines (T_H1: IFN-γ, IL-12, IL-18; T_H2: IL-4, IL-25, IL-33) that induce the activation of different transcription factors (T_H1: T-bet, STAT1, STAT4; T_H2: Gata-3, STAT6). Activated T_H1 and T_H2 cells secrete cytokines that modulate its own development and mediate the effector functions. (b) Both cancer and allergic diseases are characterized by the imbalance between T_H1 and T_H2 cells. Polyphenols contribute to the restoration of the health status by rebalancing the T_H1/T_H2 ratio. IFN, interferon; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; tBreg, tumor-evoked B regulatory cell; TCR, T cell receptor; TGF, transforming growth factor; T_H, T helper; TNF, tumor necrosis factor; Treg, T regulatory cells.

Table 1

Effects of polyphenols on T_H and B cells, and on cytokines affecting the humoral response.

Polyphenol	<i>In vitro/in vivo</i> model	Effects on humoral response and T _H differentiation	Ref.
Cancer			
Curcumin	<i>In vitro</i> : T cells and Treg cells isolated from BALB/c mice spleen, treated with curcumin (5-10-20 μ M)	↓ Tregs T _H 2 → T _H 1 ↓ IL-4, TGF- β ↑ IFN- γ	[20]
	<i>In vivo</i> : BALB/ <i>neuT</i> mice bearing salivary gland carcinoma (SALTO-5), vaccinated with rV- <i>neuT</i> vaccine, and treated orally with curcumin (2 mg/mouse), twice/wk	↑ anti-Neu total Igs ↑ IFN- γ , IL-2 ↑ CD4 ⁺ , CD8 ⁺ T cells	[26]
	<i>In vivo</i> : BALB/c mice bearing colon carcinoma (C26), treated i.v. with curcumin (5 mg/kg bw), on day 7, and with Doxorubicin (2.5 mg/kg bw), i.v., on day 10	↑ T _H 1/T _H 2 ratio ↓ IL-4, IL-6, IL-1 α , IL-1 β	[27]
Gallic acid and other phenolic acids (<i>Ananas comosus</i> vinegar)	<i>In vivo</i> : BALB/c mice bearing breast cancer (4T1), treated with phenolic acids (2 mg/kg bw), for 6 weeks before tumor challenge and 4 weeks after	↓ IL-10, IL-1 β ↑ IFN- γ , IL-2 ↑ CD4 ⁺ , CD8 ⁺	[24]
Laricitrin	<i>In vitro</i> : DCs matured from human monocytes treated with laricitrin (2 μ M) <i>In vivo</i> : C57BL/6 mice bearing lung cancer (LLC) treated with laricitrin (30 mg/kg bw), i.p., daily	↓ STAT3 and IL-10 in human DCs ↓ IL-10, TGF- β ↓ IL-10, ↑ IL-12 in mouse DCs T _H 2 → T _H 1 ↓ IL-4, IL-5 ↑ IFN- γ	[22]
Quercetin	<i>In vivo</i> : BALB/c mice bearing breast cancer (4T1), treated with quercetin added to chow at 100 mg/kg (average 2.0 mg/day/mouse), and doxorubicin (5 mg/kg bw) i.t. on days 1, 8, 15	T _H 2 → T _H 1 ↓ IL-4, IL-10 ↑ IFN- γ , IL-2	[23]
Resveratrol	<i>In vivo</i> : BALB/c mice bearing renal carcinoma cells (Renca), treated with resveratrol (1-2.5–5 mg/kg bw), i.p., daily	T _H 2 → T _H 1 ↓ IL-6, IL-10 ↑ IFN- γ ↑ Fas	[19]
	<i>In vivo</i> : BALB/c mice bearing breast cancer (4T1.2) or C57BL/6 mice bearing melanoma (B16), treated with resveratrol (50 μ g/mouse), i.p., alternate day from day 3	↓ tBregs ↓ STAT3, ↓ TGF- β ↓ Tregs ↑ IFN- γ ⁺ CD8 ⁺	[25]
Infectious diseases			
Baicalin and Resveratrol	<i>In vivo</i> : Rats infected with Respiratory syncytial virus, treated with baicalin (100 mg/kg bw), daily and resveratrol (30 mg/kg bw), daily	↑ TNF- α , IL-2, IFN- γ ↑ secretory IgA ↓ inflammatory infiltrate in the tissues	[31]
Caffeic acid	<i>In vivo</i> : BALB/c mice infected with <i>Leishmania major</i> or immunized with autoclaved <i>Leishmania major</i> , and treated with caffeic acid (25 mg/kg bw) for 5 weeks	T _H 2 → T _H 1 ↑ specific IgG2 ↓ IL-17, MCP-1 ↑ IFN- γ	[34]
Cranberry extract (<i>Vaccinium macrocarpon</i>)	<i>In vivo</i> : pigs infected with <i>E. coli</i> , and fed with a standard diet supplemented with 0.1% or 1% (= 1 or 10 g/kg feed) cranberry extract	↓ total Ig ↓ IgM ↓ IgA ↓ IgG	[33]

(continued on next page)

Table 1. (continued)

Polyphenol	<i>In vitro/in vivo</i> model	Effects on humoral response and T _H differentiation	Ref.
Curcumin	<i>In vivo</i> : CD1 albino mice infected with <i>Schistosoma mansoni cercariae</i> , treated i.p. with curcumin (25 mg/kg bw) twice/week, from week 1 after infection, and for 8 weeks (400 mg/kg bw total)	↓ TNF- α and IL-12 ↑ IgG1/IgG2a	[35]
Quercetin, fisetin, apigenin, rutin and resveratrol	<i>In vitro</i> : Human U937-DC-SIGN macrophages infected with Dengue virus and treated with polyphenols (2.5–100 μ M)	↑ IL-6 and TNF- α ↓ IL-10 ↑ IFN- γ	[29]
Tannic acid	<i>In vivo</i> : C57BL/6 mice, inoculated i.vg. with HSV-2, and treated with tannic acid (5 μ g/ml) for 6, 24, and 48 h after infection	↑ plasma cells number ↑ activated B cells	[30]
Tannins	<i>In vivo</i> : sheep infected with <i>Haemonchus contortus</i> , treated with condensed tannins (1.5% of the diet)	↑ CD8 ⁺ T cells in the vaginal tissues ↑ humoral immune response (IgG) ↑ cellular immune response (DTH)	[36]
Allergy Baicalin	<i>In vivo</i> : BALB/c mice i.p. sensitized with 10 μ g OVA and 2 mg aluminum hydroxide on days 0 and 14, challenged with 1% OVA-PBS for 20 min on days 28, 29, 30, and treated orally with baicalin (10, 20, 40 mg/kg bw) daily, from day 28–30	↓ airway hyperresponsiveness and lung compliance ↓ leukocytosis, eosinophilia and lymphocytosis in BALF ↓ eosinophilia in lung and airway tissues ↓ IL-4, IL-17A and IgE levels in BALF ↑ IFN- γ level in BALF ↓ OVA-specific IgE levels in serum and BALF ↓ IL-17 cells in serum	[43]
Chlorogenic acid	<i>In vivo</i> : BALB/c mice i.p. sensitized with 100 μ g OVA and 1 mg alum on days 1, 5, 8, challenged i.n. with 10 μ g of 10% OVA solution on days 22–28, treated orally with chlorogenic acid (50, 100, 200 mg/kg bw) on days 16–28 <i>In vitro</i> : RBL-2H3 cells sensitized o/n with 100 ng/ml anti-DNP IgE, incubated with chlorogenic acid (2.5–10 μ g/ml for 30 min) and stimulated with 10 μ g/ml DNP-BSA for 2 h <i>In vivo</i> : BALB/c mice i.p. administered with 10.5 mg/kg compound 48/80 and i.p. treated with chlorogenic acid (62.5–500 mg/kg bw) 30 min before injection of compound 48/80 <i>In vivo</i> : Wistar rats i.d. sensitized with 10 ng anti-DNP IgE, challenged i.v. with 10 μ g DNP-BSA and treated i.v. with chlorogenic acid (6–48 mg/kg bw) 30 min before challenge	↓ nasal allergic symptoms ↓ eosinophilia, the thickness of the nasal mucosa, goblet-cell hyperplasia, and mucus secretion ↓ OVA-specific IgE serum levels ↓ ROR- γ T and IL-17A serum levels ↑ IFN- γ serum levels ↓ CD4 ⁺ IL17 ⁺ T _H 17 cells number in peripheral blood ↓ ROR- γ T and IL-17A mRNA and protein levels in nasal mucosa ↓ histamine and TNF- α release from mast cells ↓ antigen-induced intracellular calcium levels ↑ intracellular cAMP levels ↓ of compound 48/80-induced fatal systemic anaphylactic shock in mice ↓ anti- DNP IgE-mediated PCA in rats	[53] [65]
Cocoa	<i>In vivo</i> : Brown Norway rats injected i.p. with 50 μ g OVA, 2.5 mg alum and 50 ng toxin from <i>Bordetella pertussis</i> , orally treated 14 days later with 1 mg/ml OVA daily for 1 week and then challenged orally with 200 mg/ml OVA. Rats fed with diet containing conventional cocoa (0.4% of polyphenols) for the entire treatment protocol	↓ anti-OVA IgG1, IgG2a, IgE antibodies in serum ↓ intestinal anti-OVA IgA antibodies ↓ IL-5, IL-13, IL-1 α , IL-1 β , IFN- γ production in MLN cells ↓ IL-4 production in SPL cells ↓ MCP II in serum ↓ intestinal IgA, MCP II, FC ϵ RI and TGF- β 1 gene expression	[40]

	In vitro: peritoneal macrophages and spleen mononuclear cells obtained from healthy rats incubated with 10 µg/ml of different cocoa extracts for 2 h and then stimulated with 100 ng/ml LPS for 6 or 24 h In vivo: Brown Norway rats i.p. sensitized with 50 µg OVA, 20 mg alum and 50 ng toxin from <i>Bordetella pertussis</i>, i.p. treated one week later with 50 µg OVA in 20 mg alum daily for 1 week and then challenged intranasally with 300 µl of OVA solution (50 mg/ml) at day 28. Rats fed with a diet containing 10% cocoa paste ('Amazonas Peru' cocoa (APC) and 'Criollo de Montaña' cocoa (CMC) for the entire treatment protocol	↓ TNF-α and IgG secretion in SPL cells [58] ↓ ROS production by macrophages ↓ M1/M2 macrophages ratio ↓ rat MCP II serum levels ↓ OVA-specific IgE levels in serum and BALF
Curcumin	In vivo: BALB/c mice i.p. sensitized with 100 µg OVA/alum pellet on day 1, i.n. challenged with 250 µg OVA on days 8 and with 125 µg OVA on days 15, 18 and 21, i.p. or orally treated with curcumin (200 mg/kg bw) daily, on days 1–21	↓ airway hyperresponsiveness [62] ↓ total leukocytes and eosinophils numbers in BALF ↓ infiltration of inflammatory cells and mucus secretion in lung tissues ↓ IgE levels in BALF
EGCG	In vivo: BALB/c mice i.p. sensitized with 20 µg OVA emulsified in 1 mg aluminum hydroxide on days 1, 8, 15, aerosol challenged with 1% OVA for 30 min/day for 7 days, treated i.p. with EGCG (5, 50 mg/kg bw) 1 h before each OVA challenge	↓ airway hyperresponsiveness [51] ↓ OVA-specific IgE serum levels ↓ eosinophils numbers in BALF ↑ IL-10 levels in serum, SPL and BALF ↓ IL-17 levels in serum, SPL and BALF ↑ CD4⁺CD25⁺FoxP3⁺ Treg cells in SPL ↓ ROR-γT mRNA expression levels in lungs
Epicatechin	In vivo: BALB/c mice orally sensitized with 20 mg OVA and 10 µg of cholera toxin daily for 3 days and then at weekly intervals for 7 weeks, orally challenged with 100 mg OVA on day 49, treated with epicatechin (0.3, 1% mixed in powdered mouse chow) for 8 days on days 42–49	↓ allergic symptoms [55] ↓ OVA-specific IgE serum levels ↑ OVA-specific IgG2a serum levels ↓ GATA3, <i>T-bet</i>, <i>IL13</i>, <i>IL12a</i> gene expression levels in ileum
Ferulic acid	In vivo: BALB/c mice sensitized with 200 µl DNCB applied on the dorsal skin, challenged with 0.2% DNCB every 3 days for 2 weeks and treated with 2% ferulic acid	↓ DNCB-induced scratching frequency [41] ↓ DNCB-induced skin hyperplasia ↓ IL-4, IL-13, IL-31, IgE serum levels ↓ IL-4, IL-31, IL-6, TNF-α transcript levels in the local lesion tissue
Gallic acid	In vivo: BALB/c mice i.p. sensitized with 50 µg OVA and 1 mg alum on days 1, 8, 15, challenged i.n. with 20 µl of 10 mg/ml OVA solution in each nasal cavity on days 22–28, treated orally with gallic acid (20, 40, 80 mg/kg) on days 16–28	↓ nasal allergic symptoms [52] ↓ total cells and eosinophils number in NFL ↓ eosinophilia, thickness of nasal mucosa and goblet-cell hyperplasia ↓ IL-4, IL-5, IL-13 and IL-17 levels in NFL ↓ OVA-specific IgE, IgG2a, IgG1 serum levels ↓ IFN-γ and IL-12 levels in NFL
Hesperidin	In vivo: BALB/c mice i.p. immunized with OVA/alum pellet (0.2 ml containing 100 µg OVA and 4 mg aluminum hydroxide) first day of 2, 3, 4 weeks before inhalation exposure, sensitized with i.tr. injection of 250 µg OVA on day 21, challenged with OVA by inhalation for 30 min/day, 3 days/week for 5 weeks, treated orally with hesperidin (5 mg/kg bw) 3 times/week, for 5 weeks starting after sensitization period	↓ airway hyperresponsiveness [47] ↓ leukocytes and eosinophil numbers in BALF ↓ CD3⁺ T cells, Gr-1⁺/CD11b⁺ cells ↓ B220⁺/CD23⁺ B cells in lung ↓ CD3⁺/CCR3⁺ cells, B220⁺/CD23⁺ B cells in BALF ↓ eosinophil infiltration in lung ↓ allergic airway inflammation ↓ IL-5, IL-17 and eotaxin levels in BALF and serum ↓ OVA-specific IgE serum levels
Luteolin	In vivo: BALB/c mice i.p. immunized with alum-precipitated antigen (0.25 ml containing 12.5 µg OVA and 0.26 mg aluminum hydroxide) on days 0, 1, and 2	↓ eosinophil-rich leukocyte infiltration in lung tissues [45] ↓ CD19⁺ B cells, CD4⁺ T cells, CD3⁺CCR3⁺ cells, and

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Table 1. (continued)

Polyphenol	<i>In vitro/in vivo</i> model	Effects on humoral response and T _H differentiation	Ref.
	weeks before inhalation exposure, sensitized with i.tr. injection of 2 mg OVA, challenged with OVA by inhalation for 30 min/day, 3 days/week, for 4 weeks, treated orally with luteolin (20 mg/kg bw) daily, for 6 weeks starting after sensitization period	CD11b ⁺ Gr-1 ⁺ cells in the lung ↓ eosinophil count in BALF ↓ IL-4, IL-5, IL-13 and eotaxin levels in BALF ↓ OVA-specific IgE levels, eotaxin 2 levels and CCR3 expression in BALF	
6-methoxyflavone	<i>In vitro</i> : EL4 mouse lymphoma cells, HEK 293T cells or T cells purified from LNs and SPL of C57BL/6 mice treated with 6-methoxyflavone (20 μM)	↑ IL-10 and TGF-β1 mRNA expression in lung ↓ IL-4, IL-13, IL-10 expression in T _H 2 cells ↓ IFN-γ transcription in T _H 1 cells ↓ IL-10 production from T _H 2 cells ↓ nuclear translocation of NFAT1 in T cells	[42]
Naringenin	<i>In vivo</i> : BALB/c mice i.p. sensitized with 100 μg OVA adsorbed to 100 μl inject alum on days 0, 7, 14, aerosol challenged with 1% OVA for 30 min on days 21, 22, 23, treated i.p. with naringenin (50, 100 mg/kg bw) 1 h before each OVA challenge	↓ inflammatory cells infiltration in lungs ↓ airway hyperresponsiveness ↓ IL-4 and IL-13 levels in BALF ↓ IgE serum levels ↓ <i>CCL5</i> , <i>CCL11</i> and <i>iNOS</i> mRNA expression levels in lung	[48]
<i>Perilla frutescens</i> derived methoxyflavanone (PDMF)	<i>In vitro</i> : RBL-2H3 cells sensitized with 1 ng/ml anti-DNP IgE for 16 h, incubated with PDMF (25–300 μM) for 30 min and stimulated with 12.5 ng DNP-BSA for 30 min <i>In vivo</i> : BALB/c mice i.d. injected with 150 ng/10 μl anti-DNP IgE in one ear, i.v. challenged with 200 μg DNP-HSA and treated orally daily with PDMF 5 mg for 8 days before the i.d. injection <i>In vivo</i> : BALB/c mice i.p. immunized with 100 μg crude Japanese cedar pollen extract absorbed on 1 mg alum, intranasally challenged with 0.5 mg Japanese cedar pollen grains and orally daily treated with PDMF (1.5 mg) for the entire experimental period	↓ NF-κB activation in lung ↓ IgE-mediated histamine release from mast cells ↓ AKT activation and intracellular calcium influx ↓ IgE-dependent PCA ↓ allergic rhinitis-like nasal symptoms	[63]
Polyphenol-enriched areca-nuts extract (PANE)	<i>In vivo</i> : BALB/c mice i.p. sensitized with 50 μg OVA and 1 mg alum, orally challenged with 50 mg OVA, treated with PANE (0.05 and 0.1%) via drinking water throughout the entire treatment protocol	↓ allergic responses, diarrhea, intestinal inflammation ↓ infiltration and degranulation of mast cells in the duodenum ↓ serum levels of OVA-specific IgE ↓ expression of IL-4 ⁺ cells in the duodenum ↑ Gr-1 ⁺ , IL-10 and Gr-1 ⁺ IL10 ⁺ cells in the duodenum	[56]
Procyanidin fraction (APC40)	<i>In vivo</i> : BALB/c mice i.d. injected with 100 ng anti-TNP IgE in one ear, i.v. challenged with 50 ng TNP-BSA and treated orally with procyanidin fraction (250 mg/kg) before challenge	↓ IgE-dependent PCA	[64]
Procyanidin C1 (PC1)	<i>In vitro</i> : BMMCs from BALB/c mice sensitized with 1 μg/ml mouse IgE for 1 h, before or after incubation with PC1 (250–1000 μg/ml) for 1 h and stimulated with 1 μg/ml anti-mouse IgE for different times	↓ β-hexosaminidase and TNF-α, IL-6 and IL-13 release from BMMCs ↓ expression of FcεRI Inhibition of FcεRI-mediated signal transduction	[64]
Quercetin	<i>In vivo</i> : BALB/c mice injected i.v. with 80 mg/kg alloxan to induce type 1 diabetes, i.p. sensitized with 50 μg OVA blended with 2.5 mg alum on days 3 and 8, challenged i.n. with 100 μg OVA on days 13–15, treated orally with quercetin (10–30 mg/kg/bw), daily on days 3–15	↓ nasal hyperresponsiveness ↓ eosinophils in BALF and blood ↓ inflammatory cells infiltration and mucous cell metaplasia in lungs ↓ allergic airway inflammation ↓ IL-4 levels in serum and BALF ↑ IFN-γ levels in serum and BALF ↑ T _H 1/T _H 2 ratio in serum and BALF	[44]

Resveratrol	In vitro: RBL-2H3 cells sensitized o/n with 0.5 µg/ml anti-DNP, incubated with resveratrol (1–25 µM for 2 h) and stimulated with 200 ng/ml DNP-HSA for 8 or 24 h In vivo: BALB/c mice i.d. sensitized with 5 µg DNP- IgE, i.v. challenged with 250 µg DNP-HSA and orally treated with resveratrol (10 mg/kg bw) 1 h before challenge In vitro: RBL-2H3 cells sensitized o/n with 0.1 µg/ml anti-DNP-IgE, incubated with resveratrol (5, 10, 20 µg/ml for 1 h) and stimulated with 0.1 µg/ml DNP-BSA for 15 min In vivo: BALB/c mice sensitized i.p. with 100 µg OVA and 2 mg alum, orally challenged with 50 mg OVA and treated with resveratrol 5, 10, 20 mg/kg bw every day, by gavage starting at the end of sensitization period	↓ histamine and β-hexosaminidase release from mast cells [54] ↓ TNF-α, IL-4, IL-3, and IL-13 from mast cells Inhibition of MAPK signaling Inhibition of FcεRIα-Syk-PLCγ-PKC-signaling cascade ↓ IgE-mediated mast cell degranulation ↓ IgE-mediated PCA in mice ↓ TNF-α and IL-4 plasma levels ↓ Tyk2-STAT1 activation in mice ↓ histamine and β-hexosaminidase release from mast cells [61] ↓ allergic responses, diarrhea ↓ OVA-specific IgE serum levels, histamine and MCP-1 ↓ population of DCs, B cells and mast cells in SPL and MLN ↓ histamine and β-hexosaminidase release in BMDC ↓ mast-cell mediated PCA reactions ↓ IL-4, IL-5, and IL-13 levels in BALF [50] ↓ IgE serum levels ↓ total cells and eosinophils numbers in BALF ↓ eosinophilia, mucus hypersecretion and goblet-cell hyperplasia in lungs ↓ airway hyperresponsiveness ↓ phospho-IkB-α levels and NF-κB nuclear expression ↓ airway hyperresponsiveness and lung compliance [60] ↓ eosinophils, neutrophils, monocytes numbers in BALF ↓ OVA-specific IgE levels in serum and BALF ↓ IL-4, IL-5, IL-17 levels in BALF ↑ IFN-γ levels in BALF ↓ TH17 cells in SPL ↓ infiltration of eosinophils and neutrophils in lung tissues ↓ mucus hypersecretion and goblet-cell hyperplasia in lung tissues ↓ Akt, GSK-3β, phospho-Akt, phospho-GSK-3β protein levels in isolated CD4⁺ T cells ↑ PTEN and p27kip1 protein levels in isolated CD4⁺ T cells ↓ nasal allergic symptoms [57] ↓ IgE and histamine serum levels ↓ total inflammatory cells, eosinophils, goblet-cell hyperplasia in nasal mucosa ↓ migration of eosinophil, neutrophil, and mononuclear cells in BALF [46] ↓ leukocyte infiltration, mucus production and pulmonary edema in lungs ↓ IL-4, IL-5, IL-13 in BALF ↓ total IgE serum levels
Sesamin	In vivo: BALB/c mice sensitized i.p. with 50 µg OVA on days 0, 7 and 14, challenged i.tr. with 100 µg OVA on days 21–23, treated i.p. with sesamin (1, 10, 20 mg/kg/day) on days 24–29	
Tangeretin	In vivo: BALB/c mice i.p. sensitized with 20 µg OVA and 4 mg aluminum hydroxide on days 0 and 14, challenged with 1% OVA aerosol for 30 min on days 22–24, orally treated with tangeretin (25, 50 mg/kg bw) daily, on days 0–14 and 2 h before each OVA challenge	
TAPP-CZ	In vivo: BALB/c mice i.p. sensitized with 500 µl OVA solution on alternate days for 13 days, challenged with 5% OVA on day 21, i.n. treated with TAPP-CZ (10, 30 µg/kg bw, twice daily) on days 14–21	
Vitexin	In vivo: Swiss-Webster mice i.p. sensitized with 200 µl OVA and aluminum hydroxide on days 1 and 10, challenged with 3% OVA by nebulization for 20 min, 2 times daily, from day 19–24, treated orally with vitexin (0.2, 1, 5 mg/kg bw/2 times daily) 1 h before each OVA challenge	

(continued on next page)

Table 1. (continued)

Polyphenol	<i>In vitro/in vivo</i> model	Effects on humoral response and T _H differentiation	Ref.
Autoimmune diseases			
α -Mangostin	<i>In vivo</i> : SLE induced in BALB/c mice, treated with α -mangostin (50 mg/kg bw), twice week, for 2 months	↓ anti-dsDNA antibodies ↓ IL-17 ⁺ and IFN- γ ⁺ cells ↓ IgG deposition in glomeruli ↓ ROR- γ t transcription activity and T _H 17 differentiation ↓ T _H 1 differentiation	[78]
Curcumin	<i>In vitro</i> : ROR- γ t-Jurkat cells treated with 0,08–10 μ M of α -mangostin (0.25, 1, 4 μ M) for 5 days <i>In vivo</i> : lupus-prone female MRL/lpr mice, treated by gavage with curcumin (200 mg/kg bw), daily, from 12 weeks of age for 8 weeks	↓ anti-dsDNA antibody ↓ NLRP3 inflammasome activation ↓ proteinuria and renal inflammation ↓ IL-1 β , IL-6, TNF- α , IFN- γ ↓ T _H 1, CD4 ⁺ T cells, CD8 ⁺ T cells and B cells ↓ antigen-induced T cell proliferation ↑ CD4 ⁺ Foxp3 ⁺ Tregs and IDO expression ↓ type II-collagen-specific IgG2a antibodies in serum ↓ T cell proliferative response ↓ CII-specific IgG2a antibody ↓ IL17 ⁺ cells in the joints ↓ T _H 17 cells in the spleen ↓ TNF- α , IL-6, IL-17, IL-21, and IL-22 ↑ CD4 ⁺ CD25 ⁺ FoxP3 ⁺ ↓ T _H 17 ↓ IL-17, IL-21, IL-22 ↑ CD4 ⁺ CD25 ⁺ FoxP3 ⁺ ↓ IL-17 ↑ IL-10	[80]
EGCG	<i>In vivo</i> : DBA/1 J mice with collagen-induced arthritis, treated by gavage with EGCG (10 mg/kg bw), for 9 times over 3 weeks, beginning a week after boosting immunization;	↓ anti-Bhsp65 specific total Ig, IgG2a and IgM antibodies ↓ autoimmune hepatitis ↓ IL-2, IL-6, TNF- α	[68]
Grape seed proanthocyanidins extract (GSPE)	<i>In vivo</i> : collagen-induced arthritic DBA/1J mice, orally treated with grape seed proanthocyanidins extract (300 mg/kg bw), 3 times a week, for 2 weeks, beginning on day 14 after primary immunization <i>In vitro</i> : DBA/1J mice splenocytes or PBMC from healthy donor cultured in T _H 17 polarizing condition, cultured with grape seed proanthocyanidins extract (10 μ g/ml) for 5 days	↑ CD4 ⁺ Foxp3 ⁺ Tregs and IDO expression ↓ type II-collagen-specific IgG2a antibodies in serum ↓ T cell proliferative response ↓ CII-specific IgG2a antibody ↓ IL17 ⁺ cells in the joints ↓ T _H 17 cells in the spleen ↓ TNF- α , IL-6, IL-17, IL-21, and IL-22 ↑ CD4 ⁺ CD25 ⁺ FoxP3 ⁺ ↓ T _H 17 ↓ IL-17, IL-21, IL-22 ↑ CD4 ⁺ CD25 ⁺ FoxP3 ⁺ ↓ IL-17 ↑ IL-10	[77]
Polyphenolic compounds from green tea	<i>In vivo</i> : <i>Mycobacterium tuberculosis</i> H37Ra-induced autoimmune arthritis in Lewis rat, consuming polyphenolic compounds from green tea (8–12 g/L) in drinking water for 2–3 weeks before arthritis induction	↓ anti-Bhsp65 specific total Ig, IgG2a and IgM antibodies ↓ autoimmune hepatitis ↓ IL-2, IL-6, TNF- α	[76]
Resveratrol	<i>In vivo</i> : Acute autoimmune hepatitis induced in BALB/c mice (ConA 20 mg/kg bw i.v.), treated by gavage with resveratrol (10-20-30 mg/kg bw), daily, for 14 days before injection of ConA <i>In vivo</i> : SLE induced in BALB/c mice, fed with resveratrol (50–75 mg/kg bw) for 7 months <i>In vitro</i> : CD4 ⁺ T cells and CD19 ⁺ B cells from splenic mononuclear cells, treated with resveratrol (10–80 μ M) <i>In vivo</i> : lupus-prone MRL/lpr mice treated i.p. with resveratrol (20 mg/kg bw), 10 injections, daily <i>In vivo</i> : collagen-induced arthritis DBA1 mice i.p. treated with resveratrol (15–20 mg/kg bw), daily, for 10 days <i>In vitro</i> : T _H 17 cells from draining popliteal lymph nodes treated with resveratrol (30 μ M)	↓ total IgG deposition in kidney tissues ↓ IgG1 and IgG2a in serum ↓ ANA ↓ IFN- γ in serum ↓ CD4 ⁺ T cells and CD19 ⁺ B cells proliferation ↓ CD4 ⁺ IFN- γ ⁺ T _H 1 cells ↓ T _H 1/T _H 2 ratio ↓ CD19 ⁺ B cells in the spleen and bone marrow ↓ CD19 ⁺ GL7 ⁺ GC B cells ↓ PCs secreting anti-dsDNA autoantibodies ↑ Fc γ RIIB on B cells and GC B cells ↓ collagen-specific IgG2a and IgG1 in serum ↓ T _H 17 cells ↓ IFN- γ , TNF- α , IL-6, IL-4, IL-1, IL-17 in serum ↓ IL-17, IFN- γ , TNF- α , IL-1 β , GM-CSF, MIP1 α , IL-5, IL-13 in draining lymph node cells	[71] [72] [73] [75]

Resveratrol and Piperine	<i>In vivo</i> : SLE induced in BALB/c mice, treated orally with resveratrol (25–50 mg/kg bw) and/or piperine (1/10th dose of resveratrol), for 6 months	↓ IL-6 and TNF- α	[74]
Abbreviations: ↓, decrease; ↑, increase; →, shift; ↔, stable; ANA, antinuclear antibody; BALF, bronchoalveolar lavage fluid; BhsP65, mycobacterial heat-shock protein 65; BMDC, bone marrow-derived cells; BMMC, bone marrow–derived mast cell; BSA, bovine serum albumin; Bw, body weight; cAMP, cyclic adenosine monophosphate; CII, collagen II; ConA, concanavalin A; DC, dendritic cell; DNCB, 2,4-dinitrochlorobenzene; DNP, 2,4-dinitrophenol; DTH, delayed-type hypersensitivity; EGCG, (–)-epigallocatechin-3-O-gallate; GC, germinal center; GM-CSF, granulocyte-macrophage colony-stimulating factor; i.d., intradermal; i.n., intranasal; i.p., intraperitoneal; i.t., intratracheal; i.v., intravenous; i.vg., intravaginally; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LLC, Lewis lung carcinoma; LPS, lipopolysaccharide; M1 or M2, polarized macrophages; MCP, mast cell protease; MCP-1, monocyte chemoattractant protein-1; MLN, mesenteric lymph node; o/n, overnight; OVA, ovalbumin; PBMC, peripheral blood mononuclear cell; PC, plasma cells; PCA, passive cutaneous anaphylaxis; RBL, rat basophilic leukemia; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SPL, spleen; TAPP-CZ, type-A procyanidins polyphenols (TAPP) based standardized hydroalcoholic extract of <i>Cinnamomum zeylanicum</i> bark; TGF, transforming growth factor; T_H, T helper; TNF, tumor necrosis factor; Treg, T regulatory cells.			

γ). Polyphenols could revert this immunosuppressive condition. Resveratrol reverted the T_H2 cytokines level and increased IFN-γ in the tumor microenvironment, enabling cancer cell-killing mechanisms [19]. The inhibition of Treg-induced T_H2 polarization, the block of TFG-β1 and the shift towards IFN-γ production were also observed after *in vitro* curcumin treatment of Tregs cells collected from BALB/c mice [20]. A nano-curcumin formulation, incubated with activated T cells, reduced inflammatory cytokines and increased IFN-γ [21]. Laricitrin promoted the switch from T_H2 to T_H1 cells and the inhibition of IL-10 production, induced in dendritic cells by lung cancer cells [22]. Quercetin combined with doxorubicin-induced the switch from a T_H2 to a T_H1 microenvironment in breast cancer-bearing mice [23]. B cell-inducing pro-inflammatory and antitumor cytokines were modulated by gallic acid, caffeic acid, and other phenolic acids contained in pineapple vinegar when administered to 4T1-tumor-bearing BALB/c mice [24].

Resveratrol blocked the generation of tumor-evoked regulatory B cells (tBregs) and their TGF-β production and impeded cancer progression by lowering immunosuppressive activity [25].

Among multiple polyphenols, curcumin is particularly effective on humoral immunity when used in combination with vaccines or drugs. We recently demonstrated that curcumin increased the titer of antibodies to ErbB2/Neu and the IFN-γ release by Neu peptides-*in vitro* stimulated T cells induced by the rV-*neu*T vaccine, without perturbing the Igs' isotype distribution. The increased humoral response induced by curcumin to Neu was associated with a stronger antitumor activity induced by the combined treatment [26]. Curcumin, encapsulated with doxorubicin into liposomes and used to treat colon carcinoma-bearing BALB/c mice, increased T_H1/T_H2 cytokine ratios [27].

Overall, polyphenols affect the tumor microenvironment by modulating the type of cytokines produced; therefore, restoring the T_H1 antitumor response and suppressing tBregs, Tregs and T_H2 cells.

Polyphenols and infectious diseases

Microorganisms are recognized by B cells through B cell receptor or pattern recognition receptors [28]. The invading microbe is rapidly hindered by the generation of a polyclonal B cell response composed of short-lived plasma cells and antibodies with low specificity. The protracted B cell activation induces the proliferation and maturation of B cells into long-lived plasma cells producing high-affinity specific antibodies. Cytokines (IL-21, IL-4), T_H cells and dendritic cells coordinate their activity in the germinal centers to obtain B cell maturation to control infections (Figure 2).

The wide immunomodulatory properties of polyphenols make them effective against infections of viral, bacterial, or parasitic origin by affecting innate and adaptive immunity.

Polyphenols showed antiviral activity in Dengue virus-infected macrophages by downregulating viral infective ability and cytokines expression *in vitro* [29]. Genital *Herpes simplex virus-2* infection was affected by tannic acid in infected mice [30]. Other polyphenols (baicalin and resveratrol) have shown immunomodulatory effects in respiratory syncytial virus infection in rats. Treatment with single or combined polyphenols increased TNF- α , IL-2, IFN- γ , and secretory IgA and decreased the inflammatory infiltrate in the tissues [31]. The reduced incidence of influenza infections and the positive correlation between IgA or IgG levels and soluble IL-2R levels were observed in a cohort of Okinawa Island patients that regularly assumed several polyphenols enriched vegetables [32]. Cranberry extract (*Vaccinium macrocarpon*) fed to *Escherichia coli* infected pigs lowered total Ig and IgM levels, while IgA and IgG levels only showed a decreasing trend in serum [33]. An immunization with autoclaved *Leishmania major* combined with caffeic acid accelerated healing of footpad after infection, increased specific IgG2, decreased IL-17 and Monocyte chemoattractant protein-1 (MCP-1) and shifted the immune response toward a T_H1 type [34]. Curcumin intraperitoneal injection in CD1 mice infected with *Schistosoma mansoni* showed schistosomicidal activity and modulation of humoral and cellular response [35]. Tannins-supplemented leaf meals supplied to *Haemonchus contortus* infected sheep induced high serum antigen-specific IgG and cellular immune response [36].

Cumulatively, polyphenols, used in the presence of viral, bacterial, or parasitic diseases, reduced the infective and/or proliferative abilities of pathogens but is not easy to define a common mechanism of action on the humoral compartment because up- or down-modulation of IgG, cytokines, and immune cells is obtained in different settings.

Polyphenols and allergic diseases

Type I hypersensitivity or allergy occurs in atopic individuals who showed an abnormal immune response to allergens. Allergic diseases comprise asthma, rhinitis, dermatitis, food allergy, allergic conjunctivitis, and anaphylactic shock [37]. After the contact with the allergen, the atopic individuals activated allergen-specific T_H2 cells, which secrete cytokines (IL-4, IL-5, IL-13), and production of allergen-specific IgE antibodies. The IgE, by binding to the Fc ϵ R1 receptor, coats mast cells, and the subsequent exposure to the same allergen led to the degranulation of mast cells, with the release of mediators, which induce the associated allergic manifestations [38]. Corticosteroids and

antihistamines are used for treating these diseases, but their long-term use is limited for the side effects. Several studies have demonstrated the beneficial role of dietary polyphenols in allergic diseases by affecting T_H1 and T_H2 cytokines production, inhibiting IgE production or IgE-mediated degranulation of mast cells [39].

Polyphenols reduced allergy by downregulating T_H2 response. A diet containing cocoa downregulated T_H2 response in rats [40]. The suppression of T_H2-mediated immune responses, serum IgE levels, and the reduction of symptoms was also reported after administration of ferulic acid or 6-methoxyflavone in an atopic dermatitis-like murine model [41,42] and other polyphenols in *in vivo* models of allergic asthma [43–48]. Grape seed proanthocyanidin extracts rebalanced T_H1/T_H2 responses in an acute and chronic mouse models of asthma [49]. The decrease of expression levels of IL-4, IL-5 and IL-13, and serum IgE was also reported for sesamin in a murine asthma model [50]. Epigallocatechin gallate (EGCG) decreased airway inflammation in asthmatic mice [51]. In addition, gallic acid showed a similar effect in reducing nasal inflammation in a mouse model of allergic rhinitis [52]. Chlorogenic acid ameliorated allergic rhinitis symptoms in mice by decreasing T_H17 cells and IL-17A, ROR- γ T and by increasing the serum level of IFN- γ [53]. Resveratrol inhibited the release of TNF- α and T_H2 cytokines in cultured rat basophilic leukemic cells and dinitrophenyl-human serum albumin-challenged mice [54]. Epicatechin affected T_H1 and T_H2 cell-related cytokines production in the ileum of allergic mice [55]. A decrease in T_H2 immunity along with increased infiltration of IL-10 producing myeloid-derived suppressor cells was also reported in mice gut with food allergy after oral intake of polyphenols areca-nuts derived extract (PANE) [56].

Other studies demonstrated the activity of polyphenols in reducing IgE synthesis in allergic diseases. Intranasal administration of type-A procyanidins induced an anti-allergic effect in ovalbumin-induced experimental allergic rhinitis, in mice, by decreasing serum IgE [57]. Cocoa diet partially protected rats against anaphylactic response in allergic asthma and food allergy models by decreasing IgE [40,58]. The reduction of specific anti-allergen IgE, and the reduction of allergy signs was also demonstrated in *in vivo* models of different allergic diseases after treatments with several polyphenols, including quercetin [59], luteolin [45], baicalin [43], 6-methoxyflavone [42], tangeretin [60], vitexin [46], gallic acid [52], EGCG [51], epicatechin [55], sesamin [50], hesperidin [47], naringenin [48], resveratrol [61], curcumin [62], chlorogenic acid [53], ferulic acid [41], and PANE [56].

Different studies have highlighted the effect of polyphenols in inhibiting IgE-mediated mast cells activation in allergy. A methoxyflavone inhibited *in vitro* IgE-

mediated mast cell degranulation and its oral administration ameliorated passive cutaneous anaphylaxis and allergic rhinitis-like nasal symptoms in a murine model of Japanese cedar pollinosis [63]. Procyanidin C1, chlorogenic acid and resveratrol *in vitro* inhibited histamine release from mast cells [54,64,65] and *in vivo* suppressed IgE-mediated passive cutaneous anaphylaxis [54,64,65]. Resveratrol and PANE also inhibited IgE-mediated histamine release by mast cells in OVA-induced models of food allergy [56,61].

Overall, these studies demonstrated the abilities of dietary polyphenols in rebalancing T_H1/T_H2 immunity and inhibiting IgE production and IgE-mediated degranulation of mast cells to counteract the immune responses elicited by allergic diseases.

Polyphenols and autoimmune disorders

The dysregulation of the immune system, with the production of autoantibodies against self-antigens, is the basis of the development of autoimmune diseases. More than 100 autoimmune diseases have been identified so far. The mechanism of induction of autoreactive B cells implies collaboration with T_H cells. In addition, the dysregulation of the balance between T_H cells and Tregs is also responsible for such responses. T_H17 cells play a significant role in the pathogenesis of several autoimmune disorders by exerting pro-inflammatory effects and inducing tissue damage [66]. Current treatments for these diseases include non-steroidal anti-inflammatory drugs, glucocorticoids, immunosuppressive and biological agents. The use of dietary polyphenols to treat autoimmune disorders is under evaluation [66]. Several studies reported the beneficial role of different polyphenols in modulating the immune cells and the release of pro-inflammatory cytokines in several autoimmune diseases. Curcumin regulated inflammatory cytokines and IFN- γ in different autoimmune diseases [67]. The oral administration of EGCG could skew T cells from a T_H1/T_H17 phenotype to a T_H2 and Treg phenotype in a mouse model of collagen-induced arthritis (CIA) [68]. A beneficial role of resveratrol was also reported in multiple sclerosis and experimental autoimmune encephalomyelitis (EAE), associated with reduced production of pro-inflammatory cytokines released by B cells [69]. In addition, resveratrol induced apoptosis of activated T cells and downregulated pro-inflammatory molecules in EAE, in imiquimod induced psoriasis-like skin inflammation in mice and mice with ulcerative colitis [70]. Resveratrol also protected against concanavalin A-induced autoimmune hepatitis by reducing cytokines expression in mice [71] and modulated the immune response in systemic lupus erythematosus (SLE) [72]. Resveratrol also regulated immune response in mice with lupus nephritis [73] and when combined with its bioenhancer piperine, it decreased the levels of

antinuclear antibodies and reduced the inflammation by decreasing IL-6 and TNF- α levels, and lupus-associated manifestations in mice with pristane-induced SLE [74].

Different studies reported the effect of polyphenols in modulating IL-17 producing T cells. Prophylactic or therapeutic administration of resveratrol ameliorated clinical parameters and bone erosion in CIA mice with the reduction of T_H17 cell numbers and the levels of pro-inflammatory cytokines and collagen-specific IgG [75]. Green tea decreased the concentration of IL-17 and increased the concentration of IL-10 in the draining lymph nodes of Lewis rats with rheumatoid arthritis [76]. Grape seed proanthocyanidins rebalanced T_H17 and Treg cells ratio *in vitro*, suppressed IL-17 production and increased FoxP3 expression in $CD4^+$ T cells of joints and splenocytes of CIA mice [77]. α -mangostin suppressed T_H17 function *in vitro* and reduced the expression of IL-17 in the splenocytes of mice with pristane-induced lupus nephritis [78].

Other studies reported the effects of polyphenols in reducing the serum levels of autoantibodies in several autoimmune diseases. EGCG reduced the serum levels of type II-collagen-specific IgG2a antibodies in CIA mice [68]. A prospective study reported that the consumption of cranberry juice for 90 days reduced disease activity in women with rheumatoid arthritis by decreasing the levels of anti-cyclic citrullinated peptide antibodies [79]. α -mangostin decreased the levels of anti-dsDNA antibodies in a pristane-induced lupus nephritis mouse model [78]. Moreover, curcumin reduced serum anti-dsDNA antibodies [80] and resveratrol decreased IgG1 and IgG2a serum levels, immunoglobulin deposition in the kidney, proteinuria, and glomerulonephritis in mice with lupus [72].

Overall, polyphenols have shown beneficial effects in autoimmune diseases by modulating the activity of immune cells, the release of pro-inflammatory cytokines and the levels of autoantibodies.

Conclusion

Polyphenols have the ability to modulate the humoral response and T cell-dependent activation of B cells by affecting the T_H1/T_H2 ratio and the secretion of multiple cytokines. This ability makes them particularly attractive as adjuvant treatment for diseases characterized by an imbalance of T_H1/T_H2 immunity. Polyphenols could contribute to recovering the state of health in cancer by restoring the T_H1 antitumor response, in infectious diseases by reducing the infectious capacities of pathogens, in autoimmune diseases by reducing the levels of autoantibodies, and in allergic diseases by inhibiting the production of IgE and IgE-mediated mast cell degranulation.

Conflict of interest statement

Nothing declared.

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