Effects of Resveratrol on Inflammatory Bowel Disease: A Review

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Abstract

Inflammatory bowel disease (IBD) is an autoimmune disease characterized by chronic inflammation in the colon and small intestine. IBD produces many symptoms that can cause discomfort and a modified lifestyle. IBD has no cure, only drugs used to suppress its inflammation, which have exhibited harmful side effects. Resveratrol, 3,5,40 -trihydroxy-trans-stilbene, is a natural phenol with anti-inflammatory attributes. Studies have found consistent results showing that resveratrol supplementation in experimental rodent models of IBD can reduce inflammatory biomarkers. This review presents experimental animal models of IBD showing that resveratrol supplementation can down-regulate inflammatory pathways of MAPK and NF- κ B, lessen COX-2, modify cytokines, diminish leukocytes, alter intestinal microflora, and decrease clinical symptoms *in vivo*, all of which contribute to an improved state of the disease. These outcomes, however, have not yet been studied in naturally occurring IBD in humans. Future research should attempt and refine to determine if resveratrol could be an effective therapy for IBD in humans.

Keywords: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Inflammation; Resveratrol

Abbreviations

BI: Bowel Injected; CD: Crohn's Disease; CI: Colon Injected; COX: Cyclooxygenase; DSS: Dextran Sodium Sulfate; FOXP3: Forkhead Box P3; GSH: Glutathione; IBD: Inflammatory Bowel Disease; ICAM-1: Intracellular Adhesion Molecule 1; IFN- γ : Interferon Gamma; IL: Interleukin; INOS: Inducible Nitric Oxide; LPO: Lipid Peroxide; MAPK: Mitogen Activated Protein Kinase; MDA: Malondialdehyde; MIG: Monokine Induced by Interferon Gamma; MPO: Myeloperoxidase; NF- κ B: Nuclear Factor Kappa B; NO: Nitric Oxide; O.I: Orally Injected; OXA: Oxazolone; PGE: Prostaglandin E; PGES: Prostaglandin E Synthase; PG-PS: Peptidoglycan Polysaccharide; RANTES: Regulated on Activation Normal T cell Expressed and Secreted; RI: Rectum Injected; ROS: Reactive Oxygen Species; SAA: Serum Amyloid A; SIRT: Silent Mating Type Information Regulation; SOD: Superoxide Dismutase; SPHK1: Sphingosine Kinase 1; STAT: Signal Transducer and Activator of Transcription; TGF: Transforming Growth Factor; TNBS: 2,4,6-Trinitrobenzenesulfonic acid; TNF:

Tumor Necrosis Factor; UC: Ulcerative Colitis; VCAM- 1: Vascular Cell Adhesion Molecule.

Introduction

The Center for Disease Control and Prevention (CDC) estimates 1.4 million diagnosed cases of inflammatory bowel disease (IBD) in the United States costing the health care industry between \$1.7 and \$5.2 billion each year [1,2]. IBD accounts for more than 700,000 physician visits, 100,000 hospitalizations, and disability in 119,000 patients annually in the United States [1]. IBD, which includes Ulcerative Colitis (UC) and Crohn's disease (CD), is an autoimmune disease and poses painful digestion and malnutrition risk due to a compromised gastrointestinal tract. The etiology of this disease remains unknown, but is thought to be a combination of immune responses, environmental factors and genetic dynamics [3]. Although IBD alone is not fatal, those with UC and CD have a six times increased risk of developing colon cancer [4]. Current drugs and surgeries used to treat the symptoms of IBD can cause negative side effects [1,5]. For these reasons, it is important to find a treatment that is able to reduce the development of IBD with little side effects.

Resveratrol, 3,5,40 -trihydroxy-trans-stilbene, is a natural phenol and phytoalexin that can be found in red wine, grapes, peanuts, and Japanese knotweed. It has been widely researched for its antioxidant properties, most specifically in cancer and cardiovascular diseases [6-9]. In some human studies, resveratrol can decrease signs of inflammation with virtually no side effects [8,10]. No human studies, however, exist to show anti-inflammatory effects of resveratrol in IBD. The objective of this review is to discuss the effects of resveratrol on inflammatory signaling pathways, inflammatory biomarkers, intestinal microflora and clinical symptoms in animal models of experimental IBD. To our knowledge, this is the first review assessing the effect of resveratrol on IBD.

Resveratrol's Effect on Experimental-IBD

Inhibited signaling pathways

Resveratrol reduces inflammation through mitogen activated protein kinase (MAPK) and nuclear factor kappa B (NF- κ B)

pathways. P38 MAPK, one of four, general MAPK signaling systems in mammals, has been recognized as a critical part in the pathogenesis of CD [11,12]. Activation of p38 MAPK, by the pro-inflammatory cytokine tumor necrosis factor (TNF)- α , is down regulated with resveratrol administration [11,13].

Reactive oxygen species (ROS), bacteria, and inflammatory cytokines activate NF- κ B, [14] the pathway specifically linked to the pathogenesis of UC [12,15,16]. With resveratrol supplementation, NF- κ B p65 subunit activity is inhibited through attenuating nuclear factor of kappa B inhibitor, alpha (I κ B α) phosphorylation, I κ B kinase beta (IKK β) activation, extracellular signal-regulated kinases (ERK) phosphorylation, signal transducer and activator of transcription 3 (STAT3) activation and NF- κ B DNA binding in animal models [16-18]. Resveratrol also amplifies silent mating type information regulation 1 (SIRT1) gene expression, [18,19] which indirectly inhibits NF- κ B.

Reduced oxidative stress

Oxidative stress increases inflammation by stimulating MAPK and NF- κ B pathways. Resveratrol supplementation, however, decreases several biomarkers of ROS including malondialdehyde (MDA), p22^{phox} and gp91^{phox}, and myeloperoxidase (MPO) [15,20,21-25]. In one study using experimental colitis, specifically induced by 2,4,6-trinitrobenzenesulfonic acid (TNBS), glutathione (GSH) was reduced by 44% [21]. Even a moderately low dose of resveratrol (10 mg/kg/day) increased GSH [20,21] and superoxide dismutase (SOD) [20].

Reduced proinflammatory mediators

Excess nitric oxide (NO) has been associated with the etiology and progression of IBD [26,27]. Inducible nitric oxide synthase (iNOS), which initiates NO production, is up regulated in a state of chronic intestinal inflammation [27]. Resveratrol generally diminishes iNOS protein expression [13,16,28] and NO production [29,30]. One study dissimilarly found resveratrol to raise NO levels above baseline values [21]. Since constitutive NO is also involved in gut homeostasis, [27] restoring NO after resveratrol supplementation may be beneficial for gastrointestinal maintenance of equilibrium, however, prolonged large quantity of NO would be harmful.

Cyclooxygenase (COX) is an enzyme present in sites of inflammation [31,32]. With dextran sodium sulfate (DSS) treatment, COX-2 potentially increases 2.3-fold [30] which can be attenuated by Resveratrol [13,17,18,24,25,28] both directly and through suppressed ROS levels [31]. The effects of resveratrol supplementation on COX-1 have been equivocal; one study showed no significant changes in COX-1 [25] while others showed COX-1 was decreased [18,24].

Diminished leukocytes

Neutrophils increase in experimental IBD [28]. Resveratrol administration significantly reduces markers for neutrophil infiltration including MPO activity, intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1

(VCAM-1) [15,20,21-25,28,33]. In one study, the resveratrol-treated group had 20% less neutrophils in the lamina propria compared to the placebo group [28].

IBD comprises excess CD3⁺ and CD3⁴⁺ T-cells; [34] however, as a result of resveratrol they are decreased to normal levels [18,23,28]. Forkhead box P3 cells are typically reduced in IBD, [35] but increase with Resveratrol [23] signifying decreased natural T regulatory cells and reduced severity of IBD [36]. CD11b⁺ and Gr-1⁺ were increased during resveratrol supplementation leading to decreased effector T-cell function and a decline in clinical symptoms [33].

Modulated cytokines

TNF- α , the central, most effective cytokine in IBD, becomes less pronounced with resveratrol in experimental animal models of IBD [13,15,18,20,28,33,37,38]. Reduced TNF- α can also directly decline VCAM-1 and ICAM-1, [39] which further improves IBD symptoms by inhibiting neutrophil function. Other inflammatory cytokines similarly decrease with resveratrol administration including interleukin (IL)-1 β , [13,15,18,24,33,38] IL-6, [13,15,18,23,33,38] IL-8 [20] and IL-12 [33]. IFN- γ , which is elevated in DSS-included colitis [28,40] also reduces with resveratrol supplementation [18,20,23]. Anti-inflammatory cytokine IL-10 increases with Resveratrol [13,23] which further prevents activation of the NF- κ B pathway. Additionally, chemokines including monokine induced by interferon gamma (MIG) (CXCL9), macrophage inflammatory protein-1 gamma (MIP-1 γ) (CCL9), monocyte chemotactic protein-1 (MCP-1) (CCL2), CXCL10⁺, CXCR3⁺ and RANTES (regulated on activation, normal T cell expressed, secreted, CCL5) decreased in animal models of IBD supplementing Resveratrol [23,33,41].

Modification of intestinal microflora

Rise in colonic permeability in IBD allows interaction between microbiota and immune responses [30,42]. Resveratrol administration reduces *Escherichia coli*; *Enterococci*, and total bacteria load in the intestine 1.0 - 3.0 orders of magnitude [23,30,37]. Resveratrol simultaneously increases *Lactobacilli* and *Bifidobacteria* 1.0 order of magnitude, peaking after 20 days of administration [23,30]. Resveratrol is not only able to reduce bacteria overgrowth, but also limit bacteria translocation into sub-epithelial tissues, [23] which can be a crucial factor in disease progression.

Reduced clinical symptoms

Clinical symptoms of IBD include weight loss, abdominal pain, fever and bloody diarrhea [5]. In a majority of studies, weight loss was less in animals given Resveratrol [13,15,16,20,21,23, 24,28,33,39]. While few studies showed no difference between groups [37,38]. Complete recovery in body weight was only seen at a resveratrol dose of 100mg/kg/day [18]. Colon weight, [13,21,24,25], histological scores, [13,15,18,20,21-25,30,33] fibrosis, [38] rectal bleeding and diarrhea, [13,15,20,22] also diminished after resveratrol supplementation, signifying reduced inflammation. Studies were inconclusive regarding colon length and its relation to inflammation [13,16,18,23-25,28,30].

Table 1: Studies Examining the Effect of Resveratrol on Experimental IBD.

Author, Year	Animal Models of IBD	Route & Timing of Model	Dose	Duration of Resveratrol	Physical/Clinical Outcomes	Other Measured Outcomes
Abdallah et al., 2011[22]	OXA in Wister albino rats	r.i., Day 1	10	7 days	↓ Ulcerative area ↓ Wt. loss ↓ Colon wt. ↓ Histological score	↓ MPO activity ^a ↓ MDA activity ^a ↓ ICAM-1 ^a ↓ VCAM-1 ^a ↓ LPO ↓ NO ^a ↓ GSH ^a
Abdin et al., 2013[22]	100 T. gondii cysts in C57BL/10 mice	c.i., Day 1	10	14 days	↓ Rectal bleeding ↓ Diarrhea ↓ Histological score	↓ MPO activity ^c ↓ SphK1 activity ^c ↓ Capase-3 activity
Bereswill et al., 2010[23]	DSS in male and female C57BL/6 mice	o.i., Day 3	10	10 days	↓ Wt. loss ↓ Bacteria translocation ↓ Total Bacteria Load ^a ↓ Enterococci ^c ↓ E. Coli ^c ↓ Lactobacilli/ Bifidobacteria ^a ↓ Lt. of small intestines	↓ IL-6 ^a ↓ MPO-7 ^{++a} ↓ MCP-1 ^a ↓ IFN- γ ^a ↑ FOXP3 ^{++a} ↓ CD3 ^{++a} ↑ Ki-67 ^{++b} ↑ IL-10 ^a
Cui et al., 2010[28]	DSS in male and female C57BL/6 mice	o.i., First 7 days	42	70 days	↓ Wt. loss ↑ Colon lt.	↓ CD3 ^{++a} ↓ Neutrophils ^b ↓ COX-2 ^b ↓ TNF- α ^b ↓ iNOS ^b ↓ p53 ^b
Larrosa et al., 2010[41]	DSS in male Fischer F344rats	o.i., Last 8 days	2.1	29 days	↓ E. Coli ^a ↓ Enterobacteria ^a ↓ Enterococci ↓ Lactobacilli ↓ Bifidobacteria ↓ Clostridia ↓ Wt. loss ↓ Colon wt. & lt.	↓ IL-6 ^a ↓ Haptoglobin ^a ↓ Fibrinogen ^a ↓ TNF- α ^a ↓ MIG ^a ↓ MPIP-1 γ ^a ↓ MPO ↑ IL-10 ^a
Larrosa et al., 2009[30]	TNBS in male Wistar rats	o.i., Last 5 days	1	25 days	↓ Enterobacteria ^a ↓ E. Coli ^a ↓ Wt. loss ^a ↓ Histological score ^b ↓ Clostridia ↑ Food intake ^b ↑ Colon lt. ^b ↑ Lactobacilli ^c ↑ Bifidobacteria ^c	↓ PGE ₂ ^b ↓ COX-2 ^b ↓ NO ^b ↓ PTGES ^b ↓ Haptoglobin ↓ Albumin
Martin et al., 2006[25]	TNBS in male Wistar rats	c.i., Day1	10	14 days	↓ Macroscopic damage score ↓ Colon lt. & wt.	↓ MPO activity ^b ↓ TNF- α ^a ↓ NF- κ B p65 ^b ↓ COX-2 ^b ↓ COX-1 ↓ PGD ₂ ↑ PGE ₂ ^c
Martin et al., 2004[24]	PG-PS in female Lewis rats	c.i., Day 3	10	4 days	↓ Macroscopic damage score ^a ↓ Wt. loss ↓ Colon lt. & wt. ↓ COX-2 in mucosa	↓ IL-1 β ^c ↓ PGD ₂ ^a ↓ MPO ^a ↓ PGE ₂
Rahal et al., 2012[38]	DSS in female C57BL/6 mice	b.i., Day 1	100	27 days	↓ Histologic fibrosis score ^a ↓ Wt. loss	↓ IL-1 β ^b ↓ IL-6 ^a ↓ TNF- α ^b ↓ TGF- β 1 ^b

Sanchez-Fidalgo et al., 2010[13]	DSS in female C57BL/6 mice	o.i., Day 30	~3	30 days	↓ Histological damage ↓ Rectal bleeding ^c ↓ Wt. loss ^a ↓ Diarrhea ^c ↓ Colon wt./lt. ^b	↓ TNF- α ^a ↓ IL-1 β ^a ↓ PGES-1 ^b ↓ COX-2 ^a ↓ iNOS ^a ↓ p38 MAPK ^a ↑ IL-10 ^a
Singh et al., 2010[18]	IL-10 deficient female mice	o.i., for first 7 days	100*	14 days	↓ Histological score ↑ Wt. loss ^b ↑ Colon lt.	↓ SAA ^b ↓ TNF- α ^b ↓ IL-6 ^b ↓ IL-1 β ^b ↓ IFN- γ ^b ↓ COX-2 ^b ↓ SIRT1 ^b ↓ CD4 ^{+b} ↓ CD11b+ cells ^b
Singh et al., 2012[33]	DSS in male BALB/c mice	Naturally developed chronic colitis by day 126	100*	196 days	↓ Wt. loss ↓ Histological score	↓ SAA ^a ↓ IgA ^b ↓ IgG ^b ↓ IFN- γ ^a ↓ TNF- α ^a ↓ IL-6 ^a ↓ RANTES ^a ↓ IL-12 ^a ↓ IL-1 β ^a ↓ CD4 ^{+a} ↑ CD11b+ Gr-1 ^{+a}
Yao et al., 2010[20]	DSS in male BALB/c mice	o.i., First 7 days	60	14 days	↓ Histological score ^a ↓ Disease activity index ^a	↓ MDA activity ^a ↓ MPO activity ^a ↓ TNF- α ^a ↓ IL-8 ^a ↓ IFN- γ ^a ↓ p22 ^{phox a} ↓ gp91 ^{phox a} ↓ SOD activity ^a ↑ GSH-Px ^a
Yao et al., 2011[15]	DSS in male BALB/c mice	o.i., First 7 days	35	14 days	↓ Disease activity index ^a ↓ Histological score ^a	↓ MPO activity ^a ↓ NF- κ B ^a ↓ TNF- α ^a ↓ IL-6 ^a ↓ IL-1 β ^a
Youn et al., 2009[16]	DSS in male ICR mice	c.i., 7 days	10	7 days	↓ Wt. loss ^a ↓ Histological changes ↔ Fluid intake ↑ Colon lt. ^b	↓ iNOS ^b ↓ NF- κ B ↓ STAT3 ^b

Notes. This table summarizes the results of studies examining the effects of resveratrol in experimental models of IBD, in comparison to groups not supplementing resveratrol.

^a, $p < 0.05$; ^b, $p < 0.01$; ^c, $p < 0.001$; ~, average ad lib dosage; ↔ no significant difference;

*, mg/kg/every other day. (Doses in mg/kg/day).

Discussion

Based on current research, 1 to 100 mg/kg/day of resveratrol appears to improve clinical symptoms of experimentally-induced IBD in animals by beneficially modulating inflammatory signaling pathways, oxidative stress, COX-2, acute phase proteins, leukocytes, cytokines, and intestinal microflora. Positive results such as these indicate a potential role for resveratrol in actual cases of IBD.

Anti-inflammatory drugs currently used in the treatment of IBD can induce headache, nausea, pain, diarrhea, sleep

disturbance, glucose intolerance, hepatotoxicity, pneumonitis, and tremor [5]. These drugs are used to moderate cytokines, COX-2, and ROS, [5] which, based on current literature, can also be accomplished with resveratrol. In one animal study, 10 mg/kg/day of resveratrol was equally effective to 300 mg/kg of sulphasalazine in reducing signs of IBD [21]. Although few studies have directly compared the effects of resveratrol to current medical treatments, resveratrol appears to have characteristics that match such treatments. Studies in both animals with IBD and humans without IBD, have determined no adverse effects of Resveratrol [10,43,44]. Its supplementation and effects have not yet been determined for patients with IBD.

Although experimental induced IBD is a well-established animal model, the reviewed studies are limited by the controlled living conditions and diet, which do not mimic the varying stress factors of free-living conditions that can affect intestinal inflammation [45-47]. Additionally, although many studies contained significance values of findings, they did not report exact values, which hindered quantitative synthesis of data. All studies, however, measured both physical and biological markers of IBD, confirming the results and the true progression of the disease. The strength and significance seen in these studies encourages the continuation of research on resveratrol supplementation on IBD.

Resveratrol appears to improve many attributes of IBD in experimental animal models, suggesting resveratrol as a promising complimentary therapy for IBD. Further research is needed to confirm if such attributes remain effective in humans while refining optimal dosage, discovering pro-drug administration and standardizing measures including instillation of resveratrol, supplementation duration and histological scores.

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