

Anti-Asthmatic Effects of *Portulaca Oleracea* and its Constituents, a Review

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Key Words

Portulaca oleracea, Quercetin, smooth muscle, anti-inflammatory effects, antioxidant effects, relaxant effects

Abstract

Objectives: The medicinal plants are believed to enhance the natural resistance of the body to infections. Some of the main constituents of the plant and derived materials such as, proteins, lectins and polysaccharides have anti-inflammatory effects. *Portulaca oleracea* (*P. oleracea*) were used traditionally for dietary, food additive, spice and various medicinal purposes. This review article is focus on the anti-asthmatic effects of *P. oleracea* and its constituents.

Methods: Various databases, such as the PubMed, Scopus, and Google Scholar, were searched the keywords including "*Portulaca oleracea*", "Quercetin", "Anti-inflammatory", "Antioxidant", "Cytokines", "Smooth muscle", and "Relaxant effects" until the end of Jul 2018.

Results: *P. oleracea* extracts and its constituents increased IFN- γ , IL-2, IFN γ /IL-4 and IL-10/IL-4 ratio, but decreased secretion of TNF- α , IL-4 and chemokines in both in vitro and in vivo studies. *P. oleracea* extracts and quercetin also significantly decreased production of NO,

stimulated β -adrenoceptor and/or blocking muscarinic receptors in tracheal smooth muscles. Conclusion: *P. oleracea* extracts and quercetin showed relatively potent anti-asthmatic effects due to decreased production of NO, inflammatory cytokines and chemokines, reduced oxidant while enhanced antioxidant markers, and also showed potent relaxant effects on tracheal smooth muscles via stimulatory on β -adrenoceptor or/and blocking muscarinic receptors.

1. Introduction

Asthma is a complex inflammatory disorder which characterized by airway inflammation and hyper-responsiveness, hyper-secretion of mucus by goblet cells and eosinophilic inflammation [1]. Asthma is triggered by a very complex interaction between high serum levels of immunoglobulin E (IgE) and production of inflammatory mediators such as; interleukin (IL)-4, IL-5, and IL-13 by T-helper 2 (Th2) cells [2]. Asthma disease could be as a result of airway inflammation [3] and smooth muscle dysfunction [4]. Corticosteroids inhibiting eosinophil function and bronchodilator drugs contribute to the treatment of asthma [5, 6]. It has been reported that combination therapy with corticosteroids and β_2 -agonists reduced tracheal hyper-responsiveness and lung inflammation in ovalbumin sensitized animal model [7, 8].

Medicinal plants used in traditional medicine have been revealed to treatment of various inflammatory disorders such as asthma. The medicinal plants used for asthma should have anti-inflammatory, antihista-

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minic, immunomodulatory and smooth-muscle relaxants activity[9]. *Portulaca oleracea* (*P. oleracea*) or Purslane belongs to the Portulacaceae family (Fig. 1). This plant is an annual and grassy plant with small-yellow flowers, which grows in different areas of the world including; Southern Europe, Indies, China, Japan, north and north-west of Iran [10].



Figure 1 Leaf and flowers of *Portulaca oleracea*

P. oleracea has several pharmacological effects including; neuroprotective [11], hepatoprotective [12], antioxidant [13], anti-inflammatory [14] and immunomodulatory effects [15]. In this review, we reviewed the anti-asthmatic properties of *P. oleracea* with several mechanisms such as anti-inflammatory, smooth muscle relaxant and antioxidant effects.

2. Methods

The databases such as, PubMed, Scopus and Google Scholar were considered for searching until the end of Jul 2018. The search terms "*Portulaca oleracea*", "Quercetin", "Anti-inflammatory", "Cytokines", "Smooth muscle", "Relaxant effects" and "antioxidant" were used. All studies such as, in vitro studies, animal studies, review articles and clinical studies were included. Letter to Editor and unpublished data were the exclusion criteria.

3. Constituents of *P. oleracea*

P. oleracea or Purslane contains omega-3 fatty acids and alpha-linolenic acid more than other leafy vegetable plant [16]. It also has 0.01 mg/g of eicosapentaenoic acid (EPA). EPA is an Omega-3 fatty acid found mostly in fish and some algae. Purslane contains vitamins as well as nutritive minerals such as iron, magnesium, potassium, and calcium. Purslane also contains potent antioxidants and anti-mutagenic agents including betalain alkaloid pigments and the yellow betaxanthins [17] as well as flavonoids (kaempferol, apigenin, myricetin, portulacacyanones A, B, C and D), alkaloids (opleraceins A, B, C, D and E), fatty acids, terpenoids (portulacalactone A and B), polysaccharides, and vitamins [18].

4. Anti-inflammatory and antioxidant effects

4.1. *P. oleracea*

The hydro-ethanolic extracts (10, 40 and 160 µg/ml) of *P. oleracea* significantly increased IFN- γ , IFN- γ /IL-4 ratio and IL-10/IL-4 ratios in non-stimulated and stimulated human lymphocytes cells. In stimulated lymphocytes, the extract of *P. oleracea* significantly decreased inflammatory cytokines such as, IL-4, IL-10 and free radicals such as nitric oxide (NO). In addition administration of *P. oleracea* extract significantly increased IFN- γ /IL-4 and IL-10/IL-4 [19]. The aqueous extracts of *P. oleracea* (10, 25, 50 and 100 µg/ml) in a dose-dependent manner significantly inhibited TNF- α -induced intracellular reactive oxygen species (ROS) production. *P. oleracea* also suppressed the TNF- α -induced degradation of I κ B- α and reduced the TNF- α -induced NF- κ B binding protein in the vascular endothelial cells. The plant extracts in a dose-dependent manner also effectively reduced mRNA expression of Monocyte chemoattractant protein-1 (MCP-1) and IL-8 caused by TNF- α [20]. The ethanol extract of *P. oleracea* (50, 100 and 200 µg/ml) inhibited production of inflammatory mediators such as NO and pro-inflammatory cytokines including; TNF- α , IL-1 β and IL-6 in LPS-induced inflammation in RAW 264.7 cells (derived from BALB/c mice). In addition, *P. oleracea* extract inhibited the phosphorylation of (ERK1/2), c-Jun NH2-terminal kinase (JNK) and NF- κ B activation in cells [21]. POL-P3b as a polysaccharide fraction purified from *P. oleracea* (250 µg/ml) up-regulated the expression of CD80, CD86, CD83, and stimulated production of more IL-12, TNF- α , and less IL-10 on the maturation and function of murine bone-marrow-derived dendritic cells (DCs). Moreover, POL-P3b significantly increased the expression of Toll-like receptor 4 (TLR-4) on DCs treated. These results suggested that POL-P3b may induce DCs maturation through TLR-4 [22]. The orally administration of *P. oleracea* polysaccharides (100, 200, 300, 400, 500 and 600 µg/ml) significantly increased stimulation indices (SI) of T lymphocytes and B lymphocytes dose-dependently in Wistar rats [23]. The polysaccharide (POP) from *P. oleracea* showed preventive effect on reduction of the spleen weight and the number of murine spleen T cells after 30 days of inducing age in the mice with D-galactose [24].

Besides anti-inflammatory effect, *P. oleracea* has been shown to have antioxidant effects [25]. It has been reported that *P. oleracea* improves oxidative stress in vitamin A deficient rats [26]. Researchers also documented that hydro-ethanolic extract of *P. oleracea* decreased the serum level of oxidant agents such as NO₂, NO₃ and malondialdehyde (MDA) and enhanced the serum level of antioxidant parameters such as superoxide dismutase (SOD) and catalase (CAT) in sensitized rats. It has been indicated that this effect of *P. oleracea* is comparable with effect of dexamethasone [27]. In addition, it has been documented that pretreatment with extract of *P. oleracea* ameliorated oxidative stress in streptozotocin-induced diabetic rats via reducing MDA concentration and enhancing the level of glutathione (GSH). In another study, ethanol extract of *P. oleracea* has been shown to protect the lungs of mice exposed to hypoxia due to its antioxidant effects [28]. The ethanol extract of *P. oleracea* reduced ROS and MDA level in the lung tissue and enhanced the level of GSH and SOD

when it was orally (100, 200 and 400 mg/kg) injected [29]. In addition, *P. oleracea* has been reported to a significant increase in level of glutathione peroxidase (GPx), glutathione-S-transferase (GST) and glutathione reductase (GR) in hepatic and renal tissues of rats [30].

4.2. Quercetin

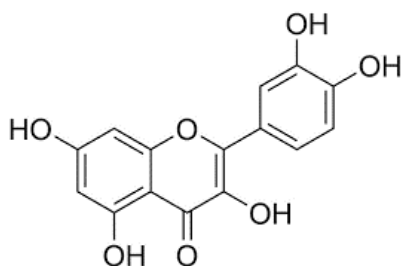


Figure 2 Quercetin

Quercetin (a natural flavonoid found in many vegetables and fruits including *P. oleracea*), dose dependently inhibited TNF- α production and attenuated the cytokines and chemokines production by LPS-stimulated DCs. The quercetin (6.25, 12.5, 50 and 100 μ g/ml) treatment significantly decreased the generation of inflammatory cytokines such as IL-1 α , IL-1 β , IL-6, and IL-12 and chemokines such as MCP-1, MIP-1a, MIP-1b in LPS-stimulated DCs. Quercetin administration also significantly reduced the levels of CD40, CD80, and CD86 in DCs stimulated by LPS. Quercetin also down regulated the cytokines and chemokines secreted by activated DCs [31]. Quercetin (40 μ M) suppressed gene transcription of IL-2 and IFN- γ cytokines while it could not attenuate IL-4 transcript. Quercetin has been shown to inhibit the increased expression of IL-2Ra in response to exogenous recombinant human IL-2 and TCR stimulation [32].

Quercetin (1, 10, 50 μ M) inhibited the iNOS, TNF- and IL-1 β expression and I κ B- α phosphorylation induced by LPS in bone marrow-derived macrophages (BMDM). In addition quercetin treatment (1 mg/kg/day, p.o.) in vivo, inhibited TNF- α , IL-1 β and iNOS, expression induced by dextran sulfate sodium (DSS) in rats [33].

The level of eosinophils were significantly reduced 68.79% and 73.35% by quercetin (8 and 16 mg/kg/day, i.p, respectively) in Bronchoalveolar lavage fluid (BALF) of mice airway challenge with ovalbumin (OVA). Quercetin also reduced the concentration of IL-4, IL-5, and mRNA expression of matrix metalloproteinase-9 (MMP-9) and increased the concentration of IFN- γ in the BALF as compared to OVA-sensitized mice [34]. Anti-inflammatory effects of *P. oleracea* and quercetin were showed in the Table 1.

4.3. Alpha Linolenic Acid

Alpha linolenic acid (ALA) is considered as one of the main constituent of *P. oleracea* [35]. This omega-3 fatty acid has been reported to modulate the immune system function through affecting T lymphocytes [36]. It has been

documented that ALA can enhance the level of eicosapentaenoic acid in the cell membrane as well as reduction of pro-inflammatory cytokines including IL-1 and TNF- α . These changes were associated with a reduction response to allergens in asthma [37]. Scientific evidence have also been indicated that treatment of sensitized rats with two concentration of ALA (0.2 and 0.4 mg/kg) resulted in a decrease in NO₂, NO₃ and MDA concentration and an increase in the serum level of thiol, SOD and CAT [27]. These reports confirm the anti-inflammatory and antioxidant of ALA.

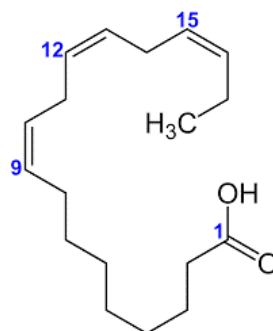


Figure 3 Alpha Linolenic Acid

4.4. Other constituents

Besides Flavonoids such as quercetin and fatty acids including ALA, *P. oleracea* possesses other several constituents such as alkaloids, terpenoids, vitamins, sterols, proteins and minerals [18]. Alkaloids presence such as dopa, dopamine and noradrenalin in leaves of *P. oleracea* has been confirmed [38]. Monoterpenes including portulic acid and B, as well as diterpens have been reported in extract of *P. oleracea* [39]. In addition, *P. oleracea* is a rich source of vitamins such as vitamin A, ascorbic acid and B-complex vitamins. Vitamin A and ascorbic acid are natural antioxidant found in *P. oleracea* [18, 40]. *P. oleracea* also contains several minerals including manganese, calcium and phosphorus as well as amino acids like proline, leucine, isoleucine, lysine, cysteine and tyrosine [41].

Table 1 Anti-inflammatory and antioxidant effects of *P. oleracea* and its constituents

Plants	Extract	Effective doses	Model of study	Effects	Ref.
<i>P. oleracea</i>	Hydro-ethanolic	160 µg/ml	Lymphocyte	Increased IL-4, IL-10, IFN-γ, IFN-γ/IL-4 and IL-10/IL-4 ratios	[19]
	Aqueous extract	100 µg/ml	Vascular endothelial cells	Decreased mRNA expressions of MCP-1 and IL-8	[20]
	Ethanol	200 µg/ml	RAW 264.7 cells	Decreased TNF-α, IL-1β and IL-6	[21]
	POL-P3b	(250 µg/ml)	DCs	Increased IL-12, and IL-10	[22]
	polysaccharide	600 µg/ml, p.o.	Rat	Increased T lymphocytes and B lymphocytes	[23]
	Hydro-ethanolic	1, 2 and 4 mg/mL, p.o.	Rats	Decreased the serum level of NO ₂ , NO ₃ and (MDA) and enhanced the serum level of SOD and CAT	[27]
	Ethanol	100 and 250 mg/kg	Mice	Shown antioxidant effects on the lungs	[28]
	Ethanol	100, 200, and 400 mg/kg	Mice	Reduced ROS and MDA level in the lung tissue and enhanced the level of GSH and SOD	[29]
Component of <i>P. oleracea</i>	Quercetin	100 µg/ml	DCs	Decreased IL-1α, IL-1 β, IL-6, IL-10, IL-12 p70) and MCP-1, MIP-1 a, MIP-1 b	[31]
		40 µM	Th cells	Decreased IL-2, IFN-γ and IL-2Ra expression	[32]
		50 µM	PBMC	Decreased IL-4 Increased IFN-γ	[42]
		50 µM+IFN-β	PBMC	Decreased IL-1β, TNF-α, MMP-9, and TIMP-1	[43]
		50 µM	BMDM	Decreased expression of iNOS, TNF-α, IL-1β and IκB-α phosphorylation	[33]
		1 mg/kg/day, p.o.	Rat	Decreased TNF-α, IL-1β expression and iNOS	[33]
		1500 mg/day, p.o.	Human	Decreased IL-6, ICAM-1 Increased IL-10	[44]
Alpha Linolenic Acid	0.2 and 0.4 mg/ml	Rats	Significantly decreased BALF levels of TP, PLA ₂ , IgE and IL-4	[37]	
	0.2 and 0.4 mg/kg	Rats	Decreased NO ₂ , NO ₃ and MDA concentration and an increase in the serum level of thiol, SOD and CAT	[27]	

IL: interleukin, IFN-γ: Interferon Gama, POL-P3b: polysaccharide fraction, MCP-1: Monocyte chemoattractant protein-1, TNF-α: Tumor necrosis factor-α, NO: Nitrogen oxide, MDA: malondialdehyde, SOD: superoxide dismutase, CAT: catalase, MIP: Macrophage Inflammatory Proteins, MMP-9: Matrix Metalloproteinase-9, TIMP-1: Tissue inhibitors of metalloproteinases-1, iNOS: Inducible nitric oxide synthase, ICAM-1: Intercellular Adhesion Molecule 1. BALF: bronchoalveolar lavage fluid, TP: total protein, PLA₂: phospholipase A₂, IgE: immunoglobulin E.

5. Smooth muscle relaxant effects

5.1. *P. oleracea*

The relaxant effect of *P. oleracea* on skeletal muscle [45] and smooth muscle [46] has been shown. In asthmatic patients, bronchodilatory effect of boiled extract of *P. oleracea* was evaluated. The results showed that boiled extract of *P. oleracea* significantly enhanced all measured pulmonary function tests (PFTs). It has been reported that this bronchodilatory effect is similar to theophylline syrup [46]. Aqueous extract of *P. oleracea* reduced pristicaltic index by antagonistic effects on calcium channel in the isolated guinea pig ileum strip [47].

The Aqueous extract of the plant also showed relaxant effect on smooth muscle and reduced blood pressure in guinea pig fundus, rabbit jejunum and rabbit aorta [48]. The hydro-ethanolic extract of *P. oleracea* (0.06, 0.12 and 0.25 mg/ml) in dose depend manner showed a stimulatory effect on β -adrenoceptor in tracheal smooth muscles of guinea pigs [49]. The relaxant effect of *P. oleracea* on tracheal smooth muscles via blocking of muscarinic receptor was also investigated [50]. The researchers suggested that bronchodilatory effects of *P. oleracea* can attribute to stimulation of β_2 adronceptors [51], stimulation of inhibitory non- adrenergic and non-cholinergic nervous system [46], opening potassium channels [52], inhibition of phosphodiesterase [53] and calcium antagonism [54]. Ethyl acetate (EA) of *P. oleracea* extract has been indicated to decrease intestinal motility in ICR mice receiving this fraction compared to those of treated with acetylcholine [55]. Based on the results of scientific studies, the aqueous extract of *P. oleracea* has been shown to ameliorate impairment of acetylcholine (Ach)- and sodium nitroprusside (SNP) induced vascular relaxant of aortic rings in diabetic db/db mice, which this improving effect is as-

sociated with a significant decrease in the level of vasoconstrictor endothelin (ET) -1. It has also been suggested that the aqueous extract of *P. oleracea* suppresses overexpression of vascular cell adhesion molecule (VCAM) -1, intracellular cell adhesion molecular (ICAM) - 1, E- selectin and matrix metalloproteinase (MMP) -2 in aortic tissue in db/db mice [56].

Extracted quercetin from *P. oleracea* has been proposed to have relaxant effect on smooth muscle of vascular endothelium which this effect is attributed to more release of prostaglandins than of nitric oxide (NO) from endothelium [57]. The mechanism of pharmacological action of *P. oleracea* on respiratory system were shown (Fig. 4).

5.2. Quercetin

It has been reported that quercetin inhibits the contraction caused by phenylephrine in aorta of rat [58] as well as the contraction induced by anaphylaxis in guinea pig ileum [59]. Quercetin inhibited smooth muscle cells proliferation, G1 cell-cycle arrest, decreased in the kinase activities, inhibit TNF- α induced induction of MMP-9 enzyme activity, decreasing the nuclear factor kappa B (NF- κ B) binding activity in Human aortic smooth muscle cells [60]. Scientific evidence demonstrated that quercetin suppressed the high KCl - induced contractions and noradrenaline in rat isolated aorta [61]. The results of studies determined that quercetin inhibited smooth muscle cells proliferation and suppressed migration them from the media into intima [62]. In addition, quercetin (10-80 μ g/mL) inhibited the effect of TNF- on DNA synthesis and ERK1/2 activation as well as inhibition of cyclin D1/CDK4 and cycline E/CDK2 activities in human aortic smooth muscle cells [60]. Quercetin has also been indicated to inhibit angiotensin II (Ang II) - induced C-Jun N- terminal kinase (JNK) activation in cultured rat aorta smooth muscle which this inhibitory effect may be attributed to its antioxidant effects [63]. The relaxant effects of quercetin includes by inhibition of Ca²⁺ influx and release of Ca²⁺ from intracellular stores [57]. Quercetin enhanced relaxation of rat aortic ring segments [64]. This results indicated that quercetin-mediated stimulation of eNOS phosphorylation increases NO bioavailability in endothelial cells. Oral administration of quercetin significantly reduced hyperreactivity of airways smooth muscle in Guinea pig [65]. Smooth muscle relaxant effects of *P. oleracea* and quercetin were showed in the Table 2.

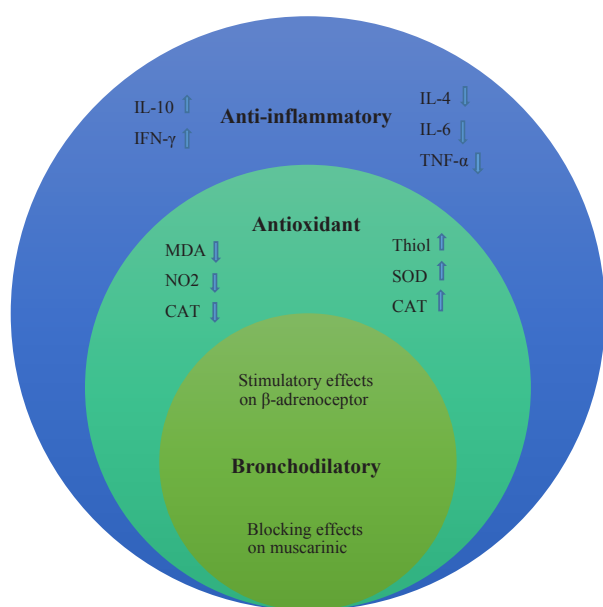


Figure 4 The mechanism of pharmacological action of *P. oleracea*.

Table 2 Smooth muscle relaxant effects of *P. oleracea* and quercetin

Plants	Extract	Effective doses	Model of study	Effects	Ref.
<i>P. Oleracea</i>	Aqueous extract	0.25 mg/kg	Asthmatic patients	Increased measured PFTs	[46]
	Boiled and aqueous extracts	Boiled (1.25ml) aqueous (6.25ml)	Tracheal chains of guinea pig	Relaxant effect on tracheal chains	[66]
	Ethanollic extract	(250 µg/ml)	Mice	Reduced intestinal motility	[55]
	Aqueous extract	600 µg/ml p.o.	Isolated guinea pig ileum strip	Reduced pristaltic index	[47]
	Aqueous extract	7×10^{-4} g/ml	Guinea pig fundus, rabbit jejunum and rabbit aorta	Relaxant effect on smooth muscle and reduced blood pressure	[48]
	Hydro-ethanollic		Guinea pigs tracheal smooth muscles	Stimulatory effect on β -adrenoceptor and blocking of muscarinic receptor	[50, 67]
Component of <i>P. Oleracea</i>	Quercetin	10^{-4} mol	Isolated rat aorta	Vasodilator effect on Isolated rat aorta	[61]
		10^{-5} mol	Rat vascular smooth muscle	Inhibitory effect on phasic contractions	[68]
		10–80 µg/ml	Human aortic smooth muscle cells	Inhibit smooth muscle cells proliferation, inhibited TNF- α induced induction of MMP-9 enzyme activity, decreased the NF-kB binding activity	[60]
		0.3 mm	Rat aorta	Vasorelaxant response	[57]
		5 and 10 µm	Rat thoracic aortas	Reduced vasoconstrictor sensitivity in rat aortic ring	[64]
		20 mg/kg oral	Guinea pig	Relaxed tracheal smooth muscle	[65]

PFT: pulmonary function tests, NF-kB: nuclear factor kappa B, TNF- α : Tumor necrosis factor- α , MMP- 9: Matrix Metalloproteinase-9.

6. Clinical evidences

Therapeutic effects of *P. oleracea* in the airway of asthmatic patients showed that the oral admomition of 5% boiled extract (0.25 ml/kg) increased pulmonary function tests similar to theophylline [46]. Quercetin (0.5, 1, 10, 25, 50 μ M) significantly induced the gene expression of IFN- γ and down regulated IL-4 in normal human peripheral blood mononuclear cell (PBMC). Additionally, treatment with quercetin increased the phenotypic expression of IFN- γ cells and decreased IL-4 in positive cells [42].

Quercetin (5, 10, 25, 50, 100, 200 μ M) by itself and in combination with human IFN- β (50 μ M+ IFN- β), in PBMC isolated from multiple sclerosis (MS) patients and from normal healthy subjects has been demonstrated to reduce the proliferation of PBMC and to modulate the level of IL-1 β and TNF- α . The combination of quercetin with IFN- β , showed additive effects in modulating TNF- α and MMP-9. Furthermore, quercetin reduced the MMP-9/ tissue inhibitor of metalloproteinases-1 (TIMP-1) ratio via lowering MMP-9 production in a dose-dependent manner. These effects of quercetin were similar between MS patients and healthy control subjects [43].

Oral administration of quercetin (1500 mg/day) in rheumatoid arthritis patients significantly reduced IL-6, C3 and C4 levels and elevated IL-10 level in treated group with quercetin plus 100 mg azathioprine, compared to treated group with azathioprine + placebo eight weeks after treatment [44].

7. Conclusion

Asthma disease is characterized by airway inflammation and smooth muscle dysfunction. *P. oleracea* and quercetin reduced the production of NO, inflammatory cytokines and chemokines such as; IL-4, IL-1 β , TNF- α , MMP-9 and TIMP-1. They also increased anti-inflammatory cytokines such as, IFN- γ and IL-10 in in vivo and in vitro studies. This plant and its component has also been shown to have relaxant effects on tracheal smooth muscle by stimulatory effects on β -adrenoceptor as well as inhibitory effects on muscarinic receptors in tracheal smooth muscles. The results of this review articles indicated *P. oleracea* and its constituents particularly quercetin have anti-inflammatory and smooth muscle relaxant effects and potential therapeutic effects on allergic asthma.

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