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Homeopathic Treatment Protocol for Asthma

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ABSTRACT

The protocol involves following criteria:
1. Remodeling the respiratory passage by inhibiting transforming growth factor *β*1/Smad signal pathway.
2. Relaxing the respiratory smooth muscles.
3. Reducing the oxidative stress marker reactive oxygen species.
4. Activating Nuclear Factor E2-Related Factor 2.
5. Managing the steps of Arachidonic Acid Metabolism Pathway.
6. Managing the Imbalance of T-helper-1 & T-helper-2 cytokines.
7. Decreasing the ratio of GATA binding protein-3 / transcription factor T-box expressed in T-cells expression levels.
8. Inhibition of Signal transducer and activator of transcription 6 expression.
9. Regulating & inhibiting the activation of Mitogen-activated protein kinase and Nuclear factor-κappa-B signaling pathways.
10. Increasing the regulatory-T cells and enhancing Transcription Factor Fork-Head Box P3 mRNA expression.
11. Inhibiting the mast cell de-granulation.
12. Inhibiting the functional differentiation of pulmonary immature DC to mature DC.
13. Reducing the dependence on Corticosteroids.
14. Improvement in symptom syndrome of Asthma.
15. Reducing the levels of Interleukin-4, and that of Interferon-*γ and* PEFR.

Keywords: *Asthma, Homeopathy, Natural, Plants, Tincture, Protocol, Inflammation, Airway Remodeling*

1. INTRODUCTION

Asthma is a chronic inflammatory disease condition characterized by a reversible obstruction of the airway, the airway hyper responsiveness, infiltration of the inflammatory cells, hyper secretion of mucus, and remodeling of the airway. It affects millions of people worldwide. The pathogenesis of Asthma is contributed by: several kinds of "immune cells, structure cells in the lung, chemokines, cytokines, adhesion molecules, and it's signaling pathways". The prevailing protocol is "to use inhaled corticosteroid in a combination with **long acting *β*2 agonist"** to control the symptoms of asthma. Other than this complementary and alternative medicine including Homeopathy is also commonly used all over the world. An American survey showed that 40% adult population suffering from asthma frequently used Homeopathy including complementary and alternative medicine for reducing the symptoms of asthma.

Since Homeopathy and alternative medicine is so widely used to control asthma, a number of clinical researches were performed to investigate their clinical applications and molecular mechanisms in controlling asthma. As we know that the pathogenesis of asthma is very complex, hence the part played by the active ingredients of Homeopathic medicines in controlling asthma is also very complicated.

Here in this manuscript we will shed a light on the major clinical researches done on different active ingredients extracted from Homeopathic tinctures and their efficacy and achievements in controlling asthma.

2. QUOTING RESEARCHES IN SUPPORT OF THE PROTOCOL

2.1 Remodeling the respiratory passage by inhibiting transforming growth factor *β*1/Smad signal pathway.

a. "It was reported that Skullcapflavone II extract from *Scutellaria baicalensis*, and Astragaloside IV extract from *Astragalus* respectively, inhibited Transforming Growth Factor-β1 and hence attenuated the allergen-induced airway remodeling in mice [15], [41]".
b. " Skullcapflavone II's function on Smad/ Transforming Growth Factor-β1 signaling pathways was shown in experiments by Jang et al.'s [41]. The following was observed in his experiments: It suppressed Smad2/3, elevated Smad7 expression, and a decreased level of Transforming Growth Factor-β1 in BALF. The Transforming Growth Factor-β1 is a multifunctional and pleiotropic growth factor, which also exerts immunosuppressive effects on the progression of asthma. Although the respiratory passage remodeling potential of Transforming Growth Factor-β1 has been elaborately discussed but still the therapies targeting Transforming Growth Factor-β1 are continued to be controversial [62]".
c. "Several formulas using *Astragalus* as a key component acting on the Transforming Growth Factor-β1/Smad signal pathway has been researched and studied. In one such study *Cordyceps and Astragali* mixture recovered Smad7 protein expression and decreased the Transforming Growth Factor-β1 expression [50]. In another such study *Astragali radix Antiasthmatic Decoction* (AAD) [56] was also found to inhibit the Th2 cytokines and Transforming Growth Factor-β1 and hence improved the symptoms of allergic airway remodeling".
d. "In another study of Suhuang antitussive capsule, composed of 9 traditional medicines including Eriobotryae Folium (Pipaye), and Perillae Fructus (Zisuzi), Pheretima (Dilong), Cicadae Periostracum (Chantui), Ephedrae Herba (Mahuang), Perillae Folium (Zisuye), Arctii Fructus (Niubangzi), Schisandrae Chinensis Fructus (Wuweizi), Peucedani Radix (Qianhu), inhibited the Transforming Growth Factor-β1 and Interleukin-13 and hence significantly attenuated the allergen-induced AHR, inflammation, and remodeling in mice [57]".
e. "*Scutellaria roots extract containing* Skullcap-flavone II [41], acting on *Ovalbumin* -induced Balb/c mice, via oral route, in effective dose of 10, 30 mg/kg/day for 7 days, acting on Transforming Growth Factor-β1/Smad. Result: Reduced the Transforming Growth Factor-β1 in BLAF, elevated Smad7, and suppressed Smad2/3 expressions".
f. "*Astragalus roots extract containing* Astragaloside IV [15], [45], [27], [47], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 50 mg/kg/day for 8 weeks, acting on Transforming Growth Factor-β1/Smad. Result: Reduced Transforming Growth Factor-β1 expression".
g. "*Astragalus + Cordyceps combination* suspensions [50] acting on *Ovalbumin* -induced C57BL/6 mice via Oral route, in effective dose of 6.5 g/kg/day for 4 weeks, acting on Transforming Growth Factor-β1/Smad. Result: Reduced Transforming Growth Factor-β1 and elevated Smad7 expression in lung tissue".

2.2 Relaxing the respiratory smooth muscles.

a. "Mokhtari-Zaer et al. in a review [51] The effect of *Crocus sativus*'s (saffron) on relaxing the Respiratory smooth muscle. According to this article and four other published studies the aqueous-ethanolic extract of *Crocus sativus* and safranal showed multiple effects like stimulating the β2-adrenoreceptors, antihistamine, anticholinergic, properties".
b. "Yang et al. [52] The inhibition of acetylcholine induced Respiratory Smooth Muscle contraction independent of the β2-adrenoceptors by trifolirhizin, a flavonoid compound isolated from *Sophora flavescens*".
c. "Ghayur et al. [53] The effect on acetylcholine induced airway contraction by an aqueous methanolic extract from *Zingiber officinale* (ginger). Who described that the effect was associated with Ca2+ signaling and also indicated that its effects were possibly via blocking the Ca2+ channels on the plasma membrane".
d. "*Crocus sativus* Flower extract containing Safranal [51] (A review), acting on Relaxing Respiratory Smooth Muscle. Result: Antihistamine and anticholinergic and β2-adrenoreceptors stimulation and Ca2+ signaling blocking".
e. "*Sophora flavescens* extract containing Trifolirhizin [52], acting on Tracheal rings of *Ovalbumin*-induced Balb/c mice, acting *In vitro*, in effective dose of 6 μg /mL, acting on Relaxing Respiratory Smooth Muscle. Result: Inhibiting acetylcholine mediated Respiratory Smooth Muscle contraction".
f. "*Zingiber officinale* Root extract containing 70% methanol extract [53], acting on Lung slices of Balb/c mice acting *In vitro*, in effective dose of 0.3, 1 mg/mL, acting on Relaxing Respiratory Smooth Muscle. Result: Inhibiting acetylcholine mediated Respiratory Smooth Muscle contraction via blocking Ca2+ channels".
g. "*Moringa oleifera* Lam. Seed extract containing β-Sitosterol [65], acting on *Ovalbumin* -induced guinea pigs, via Oral.route, in effective dose of 2.5 mg/kg/day for 12 days, acting as Antihistamine. Result: Antihistamine".

2.3 Reducing the oxidative stress marker Reactive Oxygen Species.

a. "Research shows an increased expression of HO-1 can suppress Interleukin-13-induced goblet cell hyperplasia and MUC5AC production [40], [41], [42] and thereby mitigate the symptoms of asthma. Result: Targeting the HO-1 or its transcription factor - Nuclear Factor E2-Related Factor-2 is a considerable strategy in controlling asthma [43]".
b. "Research shows HO-1 activation from the extracts of *Saururus chinensis* [44], [45], *Phytolacca esculenta* [46], *Allium sativa* [18], and *Soshiho-tang* [47]".
c. "A reduced level of oxidative stress marker Reactive Oxygen Species were observed in other studies from certain extracts like the ethanol extracts of *Petasites japonicus* [49] and *Mentha* [50]". Their mechanisms of reducing Reactive Oxygen Species levels need further study".
d. "*Saururus chinensis roots* extract containing Saucerneol D [44], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 20, 40 mg/kg/day for 3 days, acting on Antioxidant. Result: Upregulated the expression of HO-1".
e. "*Saururus chinensis* Aerial parts extract containing A subfraction of ethanol extract [45], acting on RAW264.7 cells derived from BALB/c mice acting i*n vitro*, in effective dose of 5, 50 μg /mL for 2 hours, acting on Antioxidant. Result: Upregulated the expression of HO-1"
f. "*Saururus chinensis* Aerial parts extract containing Sauchinone [45], [56], acting on RAW264.8 cells derived from BALB/c mice acting i*n vitro*, in effective dose of 2.5, 5, and 10 μg /mL for 2 hours, acting on Antioxidant. Result: Upregulated the expression of HO-1".

a. .g. "*Mentha* Aerial parts Ethanol extract [50], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 100 mg/kg/day for 6 days, acting on Antioxidant. Result: Reduced the levels of Reactive Oxygen Species in BALF".
g. "*Artemisia annua* extract containing Artesunate [48], acting on *Ovalbumin* -induced Balb/c mice via intraperitoneal injection.route, in effective dose of 30 mg/kg/day, acting as Antioxidant. Result: Suppressed prooxidants and restoring expression of antioxidants via activation of Nuclear Factor E2-Related Factor-2".
h. "*Petasites japonicus* tincture containing 80% ethanol extract [49], acting on *Ovalbumin* -induced Balb/c mice via Oral.route, in effective dose of 500 mg/kg/day for 4 weeks, acting as an Antioxidant. Result: Reduced the levels of Reactive Oxygen Species in BALF".
i. "*Phytolacca esculenta* tincture extract containing Esculentoside A (EsA) [46], acting on *Ovalbumin* -induced Balb/c mice via intraperitoneal injection.route, in effective dose of 15 mg/kg/day for 4 days, acting as an Antioxidant. Result: Reduced the levels of Reactive Oxygen Species in BALF".
j. "*Phytolacca esculenta* tincture extract containing Esculentoside A (EsA) [46], acting on A549 human alveolar epithelial cells acting *In vitro*, in effective dose of 10, 20 mg/L for 6 hours, acting as an Antioxidant. Result: Nuclear Factor E2-Related Factor-2 activator. Upregulated the expression of HO-1".
k. "*Allium Sativa* Oil extract containing Diallyl-disulfide (DADS) [18], acting on *Ovalbumin*-induced Balb/c mice via Oral.route, in effective dose of 30 mg/kg/day for 3 days, acting as an Antioxidant. Result: Reduced the levels of Reactive Oxygen Species in BALF".
l. "*Allium Sativa* Oil extract containing Diallyl-disulfide (DADS) [18], acting on RAW264.7 murine macrophage cell, acting *In vitro*, in effective dose of 62.5–500 ng/mL for 1 hour, acting as an Antioxidant. Result: Nuclear Factor E2-Related Factor-2 activator. Upregulated the expression of HO-1".
m. "*Soshiho-tang* containing Aqueous extract [47], acting on *Ovalbumin* -induced Balb/c mice, via Oral.route, in effective dose of 100, 200 mg/kg/day for 6 days, acting on Antioxidant. Result: Upregulated the expression of HO-1".

2.4 Activating Nuclear Factor E2-Related Factor 2.

a. "The active ingredient, artesunate obtained from *Artemisia annua* was shown to be suppressing the pro-oxidants and activating the Nuclear Factor E2-Related Factor-2 [48] thereby restoring the expression of the antioxidants. Also diallyl-disulfide (isolated from *Allium sativa*) [18] and esculentoside A (isolated from *Phytolacca esculenta*) [46] have been proven as Nuclear Factor E2-Related Factor-2 activators".

2.5 Managing the steps of Arachidonic Acid Metabolism Pathway.

a. "Research shows that strategies targeting the arachidonic acid metabolism are very effective in many of the inflammatory diseases including asthma. The leukotrienes in asthma especially LeukotrineB4, LeukotrineC4, LeukotrineD4, etc. are considered to be important mediators of the airway inflammation and the airway obstruction. LeukotrineB4 acts as a **neutrophil chemo-attractant** [53], [58], [59]".
b. "The following medicines are shown in research to target different steps of the Arachidonic Acid Metabolism Pathway *Scutellaria baicalensis* [42], *Panax ginseng* [53], *Saururus chinensis* [57], *Sceptridium ternatum* [58], *Aralia cordata* [60], and Eucalyptus eucalyptol (1.8-cineole) [61]".
c. "*Scutellaria roots extract containing* Baicalein [42], acting on *Ovalbumin* -induced Balb/c mice via intraperitoneal injection. route, in effective dose of 10 mg/kg/ day for 6 days, acting on AAMP. Result: Reduced 12/15-LOX activity".
d. "*Ginseng roots* extract containing Ginsan [53], acting on *Ovalbumin* -induced Balb/c mice via intraperitoneal injection. route, in effective dose of 100 mg/kg/2 day for 4 weeks, acting on AAMP pathway. Result: Upregulated COX-1 and COX-2 expression, leading to the increase of PGE2 in BALF".
e. "*Saururus chinensis* Aerial parts extract containing 70% ethanol extract [57], acting on Bone marrow-derived mast cells from Balb/c mice, acting *In vitro*, in effective dose of 0.8–50 μg /mL for 30 min, acting on AAMP. Result: It inhibited LTC4 and PGD2 level".
f. "*Aralia cordata* Root extract containing 7-Oxo-sandaracopimaric acid [60], acting on *Ovalbumin*-induced guinea pigs via Oral.route, in effective dose of 25–100 mg/kg for 3 times in 24 hours, acting on AAMP. Result: Inhibiting phospholipase A2 (PLA2) eosinophil peroxidase (EPO) activity in BALF".
g. "Eucalyptus Q containing Eucalyptol (1.8-cineole) [61], acting on *Ovalbumin* Monocytes from patients with asthma, acting *In vitro*, in effective dose of 200 mg/day for 3 days, acting on AAMP. Result: Inhibits LTB4 and PGE2".

2.6 Managing the Imbalance of T-helper-1 & T-helper-2 cytokines.

a. "Studies by *Sam So Eum* and *Qu Feng Xuan Bi.*, revealed the efficacy of *Taraxacum officinale*, *Duchesnea chrysantha*, *Echinacea purpurea*, *Sophora flavescens*, *Zingiber officinale*, *Actinidia polygama* on T-helper-1 or T-helper-2 cytokines".
b. "*Astragalus* aqueous extract [49], acting on *Ovalbumin* -induced C57BL/6 mice via intraperitoneal injection. route, in effective dose of 10 g/kg/day for 4 weeks. Result: Increased T-helper-1 or T-helper-2 cytokines' ratio".
c. "*Sceptridium ternatum* 70% ethanol extract [58], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 2, 10, and 20 g/kg/day for 10 days. Result: Elevated the ratio of T-helper-1 or T-helper-2".

2.7 Decreasing the ratio of GATA binding protein-3 / transcription factor T-box expressed in T-cells expression levels.

a. "Jin et al. investigated the effects of ***Psoralea*** and psoralen, (an active ingredient of Psoralea), on Th2 clone (D 10. G. 4. 1) cells *in vitro* and *in vivo*, and interpreted their effect as suppressor of the GATA binding protein-3 protein expression".
b. "Chen et al. found that a single compound, Bavachinin, isolated from *Psoralea* decreased the GATA binding protein-3 function by reducing the stability of GATA binding protein-3 mRNA and further suggested that Bavachinin may suppress it's binding or

co-activating function but not the expression of p-*Signal Transducer and Activator of Transcription-6*. They also found [1], two more derivatives of Bavachinin, having a better water solubility and which were further investigated, and one of these two derivatives not only increased transcription factor T-box expressed in T-cells mRNA production but also inhibited GATA binding protein-3 mRNA production".

c. "The extracts (ginsan, CVT-E002, and RG-II) from the tincture of *Panax Ginseng* were studied. The different pathways of its action includes GATA binding protein-3/ transcription factor T-box expressed in T-cells, Mitogen-activated protein kinase, and regulatory-T cells and arachidonic acid metabolism pathway in animal models or *in vitro*. But it's application on human's is undetermined. It is a well known fact that CVT-E002 is very well proven to reduce the respiratory infections in the patients suffering from chronic lymphocytic leukemia and is also effective in preventing acute respiratory illness in the older adults [63], [64]. It is also very popular for its immunoregulator function on the humans. Further research on its efficacy on the patients suffering from asthma is required".

d. "*Astragalus* aqueous extract [44], acting on *Ovalbumin* -induced C57BL/6 mice, via Oral route, in effective dose of 3 μg/kg/2 day for 9 days, acting on GATA binding protein-3/ transcription factor T-box expressed in T-cells. Result: Decreased the ratio of the GATA binding protein-3/ transcription factor T-box expressed in T-cells mRNA levels".

e. "*Astragalus roots extract containing* Astragaloside IV [15], [45], [27], [47], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 50, 150 mg/kg/day for 4 weeks, acting on GATA binding protein-3/ transcription factor T-box expressed in T-cells. Result: Decreased the ratio of the GATA binding protein-3/ transcription factor T-box expressed in T-cells expression level".

f. "*Ginseng* leaves Purified aqueous extract (RG-II) [51], acting on *Ovalbumin* -induced Balb/c mice via intraperitoneal injection. route, in effective dose of 20, 100 mg/kg/day for 3 days, acting on GATA binding protein-3/ transcription factor T-box expressed in T-cells pathway. Result: Decreased the ratio of the GATA binding protein-3/ transcription factor T-box expressed in T-cells expression level".

g. "*Saururus chinensis* Aerial parts extract containing Sauchinone [45], [56], acting on *Ovalbumin* -induced Balb/c mice via intraperitoneal injection.route, in effective dose of 10, 100 mg/kg/2 day for 5 days, acting on GATA binding protein-3/ transcription factor T-box expressed in T-cells. Result: Suppressed GATA binding protein-3 activity".

h. "*Psoralea* Fructus extract containing Psoralen [10], acting on ConA stimulated D10.G4.1 cells acting *In vitro*, in effective dose of 0.08 mM for 2 hours, acting on GATA binding protein-3/ transcription factor T-box expressed in T-cells. Result: Suppressed the upregulation of Interleukin-4, Interleukin-5, Interleukin-13, and GATA binding protein-3 protein expression".

i. "*Psoralea* Fructus Aqueous extract [10], acting on ConA, Interleukin-2, Interleukin-4 stimulated 4GET mice spleen cells acting *In vitro*, in effective dose of 0.01 mM, acting on GATA binding protein-3/ transcription factor T-box expressed in T-cells. Result: Suppressed GATA binding protein-3 mRNA levels".

j. "*Ligustrazine* extract containing Ligustrazine [9], acting on *Ovalbumin* -induced C57BL/6 mice via intraperitoneal injection.route, in effective dose of 80 mg/kg/day for 3 days, acting on GATA binding protein-3/ transcription factor T-box expressed in T-cells. Result: Decreased the ratio of the GATA binding protein-3/ transcription factor T-box expressed in T-cells expression level".

2.8 Inhibition of Signal transducer and activator of transcription 6 expression.

a. "Chiu et al. had explored the effects of Osthol (an extract *of Cnidii monnieri*) on the human bronchial epithelial cells (BEAS-2B) *in vitro*. It was demonstrated in their research that Interleukin-4-induced eotaxin was suppressed by Osthol (which is a key mediator in allergic diseases with eosinophilic infiltration) in the epithelial cells by the inhibition of Signal transducer and activator of transcription 6 expression".

b. "*Scutellaria roots extract containing* Wogonin [14], acting on *Ovalbumin* -induced Balb/c mice via oral route, in effective dose of 10, 30 mg/kg/day for 3 days, acting on *Signal Transducer and Activator of Transcription-6*. Result: Suppressed *Ovalbumin* -induced *Signal transducer and activator of transcription 6* activation".

c. "*Scutellaria roots extract* acting on Interleukin-4 induced BEAS-2B cells, acting i*n vitro*, in effective dose of 10, 30, and 50 μM for 4 hours, acting on *Signal Transducer and Activator of Transcription-6*. Result: Suppressed Interleukin-4-induced eotaxin-3 expression via suppressing JAK1 and *Signal Transducer and Activator of Transcription-6* activation".

d. "*Cnidii monnieri* Fructus tincture containing Osthol [15], acting on Interleukin-4/ tumor necrosis factor-α induced BEAS-2B cells acting *In vitro*, in effective dose of 1–10 μM for 2 hour, acting on *Signal Transducer and Activator of Transcription-6*. Result: Suppressed Interleukin-4-induced eotaxin expression via suppressing *Signal Transducer and Activator of Transcription-6* activation".

2.9 Regulating & inhibiting the activation of Mitogen-activated protein kinase and Nuclear factor-κappa-B signaling pathways.

a. "The multiple effects of extracts of *Boswellia serrata* was shown in a review by Ammon [69] on the modulation of immune system, as well as inhibiting the activation of the nuclear factor kappa light chain enhancer of activated B cells, stabilisation of mast cell, and the antioxidant and inhibitory action on the 5-lipoxygenase".

b. "Nuclear factor kappa B (NF-κB) is an important transcription factor involved in the expression of various pro-inflammatory genes. Increased activation of Nuclear factor-κB has been observed in the lungs after allergen challenge & in the airway epithelial cells & macrophages from the asthmatic patients [3]. Studies show improvement in allergic asthma by regulating the activation of Mitogen-activated protein kinase and Nuclear factor-κB signaling pathways [4], [5]".

c. "Studies show *Scutellaria* [6], [7], *Ginseng* [8], *Saururus chinensis* [9], *Artemisia annua* [10], *Magnoliae flos* [11], [12], and *Crocus sativus* [13] targets Mitogen-Activated Protein Kinases".

d. "Studies show *Scutellaria* [14], *Astragalus* [15], [16], *Saururus chinensis* [9], *Astilbe chinensis* [17], *Artemisia annua* [10], and *Allium Sativa* [18] acts as inhibitor of Nuclear Factor-*kappa*-B".

e. "Some extracts like di-hydro-artemisinin [10] (isolated from *Artemisia*) and meso-Di-hydro-guaiaretic acid [9] (isolated from *Saururus chinensis*) acts as inhibitors of Mitogen-activated protein kinases and Nuclear factor-κB meanwhile, whereas some active ingredients isolated from the same Homeopathic tincture might inhibit either Nuclear factor-κB or Mitogen-activated protein kinases, respectively, for example, Oroxylin A [14] and Baicalin [6], [7] (both of which are isolated from *Scutellaria*)".
f. "All three extracts of *Saururus chinensis:* a subfraction of its ethanol extract, saucerneol D [44] and sauchinone [45] have shown antioxidant effects through the up-regulation of the expression of HO-1. While sauchinone also have a suppressor activity on GATA binding protein-3 [56]. A novel extract of *Saururus chinensis* was also expounded by Song and his colleagues and was named meso-Di-hydro-guaiaretic acid [9]. Which has a protective effect on the allergic airway inflammation by inhibiting the Th2 inflammation, which is attributed to its inhibition of the Mitogen-activated protein kinase and NF-*κ*B. Also, the ethanol extract's is shown to have an action on the arachidonic acid metabolism pathway [57]. The above extracts of *Saururus chinensis* is drawing worldwide attention in the last few years for its anti-asthmatic effects".
g. "*Scutellaria extract containing* Oroxylin A [36, 43], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 15, 30, and 60 mg/kg/day for 3 days, acting on NF-*κ*B. Result: Suppressed Nuclear factor-κB activation".
h. "*Scutellaria roots extract containing* Baicalin [6], [7], acting on *Ovalbumin* -induced Balb/c mice, via Oral. route, in effective dose of 25, 50, and 100 mg/kg/day for 4 weeks, acting on Mitogen-activated protein kinase. Result: Inhibited RASM cell proliferation and migration by suppressing Mitogen-activated protein kinase signal pathway".
i. "*Scutellaria roots extract containing* Baicalin [6], [7], acting on the airway smooth muscle cells from SD rats (RASM), i*n vitro*, in effective dose of 10, 25, and 100 nM for 1 hour, acting on Mitogen-activated protein kinase.. Result: Inhibited RASM cell proliferation and migration by suppressing Mitogen-activated protein kinase signal pathway".
j. "*Astragalus roots extract containing* Astragaloside IV [15], [45], [27], [47], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 50 mg/kg/day for 8 weeks, acting on NF-*κ*B. Result: Inhibited TSLP expression".
k. "*Astragalus containing* formononetin & calycosin [16], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 0.5 g/kg/2 day for 4 weeks, acting on NF-*κ*B. Result: Suppressed Nuclear factor-κB activation".
l. "*Ginseng roots* aqueous extract [8], acting on *Ovalbumin* -induced C57BL/6 mice via intraperitoneal injection. route, in effective dose of 20 mg/kg/day for 3 days, acting on Mitogen-activated protein kinase pathway. Result: Inhibited CD40/CD40L ligation and Mitogen-activated protein kinase signal pathway".
m. "*Saururus chinensis roots* extract containing Meso-Dihydroguaiaretic acid [9], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 10, 30 mg/kg for 2 weeks, acting on Nuclear factor-κB & Mitogen-activated protein kinase. Result: Inhibited Th2 inflammation via inhibiting Nuclear factor-κB and Mitogen-activated protein kinase".
n. "*Astilbe chinensis extract containing* Astilbic acid [5], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 30 mg/kg/d ∗ 3 d, acting on NF-*κ*B. Result: Suppressed the Nuclear factor-κB activation".
o. "*Crocus sativus* Flower extract containing Crocin [13], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 100 mg/kg/day for 5 days, acting on Mitogen-activated protein kinase. Result: Inhibited the expression of lung eotaxin, p-ERK, p-JNK, and p-p38 level".
p. "*Artemisia annua* extract containing Dihydroartemisinin [10], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 30 mg/kg/day for 3 days, acting on Nuclear factor-κB & Mitogen-activated protein kinase. Result: Inhibited Th2 inflammation via inhibiting Nuclear factor-κB and Mitogen-activated protein kinase".
q. "*Magnoliae flos* Leaves extract tincture containing Fargesin and epimagnolin [12], acting on A549 human alveolar epithelial cells, acting *In vitro*, in effective dose of 3.1–100 μg /mL, acting on Mitogen-activated protein kinase. Result: Modulated NO synthesis via inhibiting ERK in human respiratory epithelial cells".
r. "*Allium Sativa* Oil extract containing Diallyl-disulfide (DADS) [18], acting on *Ovalbumin*-induced Balb/c mice via Oral.route, in effective dose of 30 mg/kg/day for 3 days, acting on NF-*κ*B. Result: Suppressed Nuclear factor-κB activation".

2.10 Increasing the regulatory-T cells, T-helper-17 cells, and enhancing Transcription Factor Fork-Head Box P3 mRNA expression.

a. "T-regulatory cells are a heterogeneous group of cells that play a central role in maintaining the homeostasis of pulmonary immunity by establishing immune tolerance to non-harmful antigens or suppressing the effector T-cell immunity. The Transcription Factor Fork-Head Box P3 [5], [19], [20], [21], [22] is driven by the specification of regulatory-T cells subset".
b. "Studies show interleukin-17 also directly affects the airway smooth muscles by inducing allergen-induced airway hyper-responsiveness [23], [24], [25], [26]. The transcription factor related to T-helper-17 is found to be Retinoic acid-related orphan receptor gamma-t, which is essentially required to activate Interleukin-17 production in the T-helper-17 cells [5]. Increased expressions of Interleukin-17A and Interleukin-17F have been shown in the lung tissue of asthma patients [6]".
c. "Extracts of *Astragalus* [27], [28], *Panax ginseng* [29], *Crocus sativus* [30], *Ligustrazine* [9], *and Anoectochilus formosanus* [31] were observed to increase the regulatory-T cells and enhancing Transcription Factor Fork-Head Box P3 mRNA expression".
d. "*Chuan Qiong* reported that ligustrazine, isolated from *Ligustrazine* was modulating the expression of not only the Transcription Factor Fork-Head Box P3 / Retinoic acid-related orphan receptor gamma-t but also transcription factor T-box expressed in T-cells / GATA binding protein-3 [9]".
e. "Ji et al. [9] found that eosinophils and neutrophils in the BALF of asthmatic mouse models were reduced by ligustrazine. Hence it is implying that it could have a potential for use in the alleviation of neutrophilic and eosinophilic asthma".
f. "Extracts from *Andrographis paniculata, Scutellaria baicalensis, Tripterygium wilfordii, and Wedelia chinensis* [11], [32], [33], [34] were studied for treatments in other T-helper-17-related inflammatory diseases, but whether these will work similarly in asthma needs further investigations".
g. "*Astragalus roots extract containing* Astragaloside IV [15], [45], [27], [47], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 20, 40 mg/kg/day for 4 weeks, acting on Transcription Factor Fork-Head Box P3 / Retinoic acid-related

orphan receptor gamma-t. Result: Increased CD4+CD25+ Transcription Factor Fork-Head Box P3 + regulatory-T cells and enhanced Transcription Factor Fork-Head Box P3 mRNA expression".

h. "*Astragalus* aqueous extract [28], acting on *Ovalbumin* -induced SD rats via Oral route, in effective dose of 5, 10 g/kg/day for 4 weeks, acting on Transcription Factor Fork-Head Box P3 / Retinoic acid-related orphan receptor gamma-t. Result: Increased CD4+CD25+ Transcription Factor Fork-Head Box P3 + regulatory-T cells and enhanced Transcription Factor Fork-Head Box P3 + mRNA expression".

i. "*Ginseng roots* aqueous extract (CVT-E002) [29], acting on *Ovalbumin* -induced Balb/c mice via oral route, in effective dose of 200 mg/kg/day for 7 days, acting on Transcription Factor Fork-Head Box P3 / Retinoic acid-related orphan receptor gamma-t pathway. Result: Increased regulatory-T cells function and Interleukin-10 level in BALF".

j. "*Crocus sativus* Flower extract containing Crocetin [30], acting on *Ovalbumin* -induced C57BL/6 mice via Intranasal route, in effective dose of 3 μg /day for 1 week, acting on Transcription Factor Fork-Head Box P3 / Retinoic acid-related orphan receptor gamma-t. Result: Increased Transcription Factor Fork-Head Box P3 through TIPE2 to activate regulatory-T cells".

k. "*Ligustrazine* extract containing Ligustrazine [9], acting on *Ovalbumin* -induced C57BL/6 mice via intraperitoneal injection.route, in effective dose of 80 mg/kg/day for 3 days, acting on Transcription Factor Fork-Head Box P3 / Retinoic acid-related orphan receptor gamma-t. Result: Increased the ratio of Transcription Factor Fork-Head Box P3 / Retinoic acid-related orphan receptor gamma-t".

l. "*Anoectochilus formosanus* Whole plant Aqueous extract [31], acting on *Ovalbumin Ovalbumin* -induced Balb/c mice, in effective dose of 0.5, 1 g/kg/day for 7 days, acting on Transcription Factor Fork-Head Box P3 / Retinoic acid-related orphan receptor gamma-t. Result: Inhibited the decrease of regulatory-T cells in BALF".

2.11 Inhibiting the Mast Cell Degranulation.

a. "Studies show the following three extracts are associated with inhibiting the mast cell degranulation which might be helpful for treating asthma. They are Bakkenolide B [37], Petatewalide B [38], and Oroxylin A [39]. Oroxylin A is isolated from *Scutellaria baicalensis*, whereas Bakkenolide B, and Petatewalide B are isolated from *Petasites japonicus*. It is very important to mention that both Bakkenolide B and Petatewalide B do not inhibit the antigen induced Ca2+ increases in the mast cells, which explains that Petatewalide B or Bakkenolide B induced inhibition of the de-granulation might not be mediated by the Ca2+ increase in the mast cells or the inhibition of the Ca2+ channel. No detailed mechanisms are known for the Oroxylin A to explain the phenomenon of inhibition of mast cell degranulation. Hence more studies and investigations are necessary on these extracts".

b. "*Scutellaria* acting on Specific Immunoglobulin-E induced rat RBL-2H3 mast cells, i*n vitro*, in effective dose of 10 mg/kg/day for 6 days, acting on Mast cells. Result: inhibited the degranulation of mast cells".

c. "*Petasites japonicus* tincture Leaves extract containing Bakkenolide B [37], acting on Rat RBL-2H3 mast cells & C57BL/6 mouse peritoneal macrophages acting *In vitro*, in effective dose of 1–10 μg /mL for 1 hour, acting on Mast cells. Result: Inhibited degranulation in mast cells and suppressed iNOS in macrophages".

d. "*Petasites japonicus* tincture Leaves extract containing Petatewalide B [38], acting on Rat RBL-2H3 mast cells & C57BL/6 mouse peritoneal macrophages acting *In vitro*, in effective dose of 10, 30 μg /mL for 1 hour, acting on Mast cells. Result: Inhibited degranulation in mast cells and suppressed iNOS in macrophages".

2.12 Inhibiting the functional differentiation of pulmonary Immature Dendritic Cells to Mature Dendritic Cells.

a. "The effect of *Artemisia* polysaccharide-1 on Dendritic Cells functions was described by Lee et al. [35]. They observed significantly reduced levels of MHC II in Dendritic Cells of the *Artemisia* polysaccharide-1 in the treated group. Hence suggesting that *Artemisia* polysaccharide-1 could reduce the expression of MHC II molecules on pulmonary Dendritic Cells. It was also observed that *Artemisia* polysaccharide-1 could diminish the allergenic T cell stimulating ability of the Dendritic Cells derived from the bone marrow in an another study. Hence these data suggests that *Artemisia* polysaccharide-1 can inhibit the functional differentiation of pulmonary Dendritic Cells *in vivo"*.

b. "*Artemisia iwayomogi* Leaves extract containing Purified aqueous extract (AIP1) [35], acting on *Ovalbumin* -induced Balb/c mice via intraperitoneal injection.route, in effective dose of 5 mg/kg for 6 times in 14 days, acting on Dendritic cell. Result: Reduced levels of MHC II in dendritic cells".

2.13 Reducing the dependence on Corticosteroids.

a. "Arnold et al. [66] evaluated effects of natural medicines on lung function, reduction in use of corticosteroids, symptom scores, physical sign scores, use of reliever medications, health related quality of life, and adverse effects comparing with placebo, involving 21 different tinctures or tincture combinations. Although a few of them had some effects on relief of symptoms, only boswellic acids (isolated from ***Boswellia serrata***) were reported to exert a relatively comprehensive effect on lung function, while the effects of other tinctures were limited or inexact".

b. "Clark et al. [67], Mai-Men-Dong-Tang, Pycnogenol, Jia-Wei-Si-Jun-Zi-Tang, and ***Tylophora indica*** also showed potential to improve the lung function. Moreover, 1.8-cineol (eucalyptol) from **Eucalyptus** tincture was observed to reduce the use of corticosteroids and corticosteroid reduction tolerance (< 7.5 mg) in both of their studies [66], [67]".

c. "Arnold et al [66] had analyzed the significant effect of ***Magnolia*** on the function of lungs and mentioned it in his studies. Related clinical research with LABAs + ICS in recent times shows the reduced need for inhalation therapy" [70]. More research on this is required".

2.14 Improvement in symptom syndrome of Asthma.

a. "An extract of ***Magnolia*** was used in a non-comparative, multicenter trial [68], with 148 patients having mild asthma under ICS who received NDC-052 for eight weeks. There were improvements in the symptoms of asthma and Δ PEFR by using NDC-052 extract of Magnolia as a supplement along with ICS therapy as was shown in the results".

b. "A randomized, placebo controlled and single-blind trial (of sample size = 60) on children aged 2 to 5 years with intermittent asthma, was performed by Geng et al. [71]. The combination includes Concha Ost, Endoconcha Sepiella, Ligustrum luci, Psoralia, Schisandra chinensis, Astragalus molli, Pseudo-stellaria, Polygonam odo. Results showed: reduced airway resistance, decreased syndrome scores, and reduction in the number of attacks of intermittent asthma".
c. "In uniformity with the above, an another combination, composed of seven tinctures of: Schizonepeta, Glycyrrhiza, Platycodon grandiflorus, Stemona tuberosa, Tangerine, Aster tataricus, Cynanchum staun. The results of their study is also observed to decrease the cough score and the syndrome score of the cough variant of asthma, but it didn't have any effect on the responsiveness of the airway [72]".
d. "Tang and colleagues [73] performed a randomized controlled research trial on 143 patients with moderate to severe asthma. The combination of tinctures containing extracts from 21 herbs and excipients was applied as an add-on therapy of standard medication. The results of which showed improvement of the related syndrome scores, like, the Asthma Control Test Score and a decrease of the frequency of exacerbations".

2.15 Reducing the levels of Interleukin-4, and that of Interferon-*γ and* PEFR.

a. "The effect of *Astragalus* plus hormone treatment in 90 children with asthma were studied by Lin et al. [74]. The effective rate of the *Astragalus* plus hormone group was shown to be significantly higher as compared to using *Astragalus* or the hormone only. The levels of Interleukin-4 decreased, and that of Interferon-*γ and* PEFR significantly increased in their effective cases. Similar effects were also reported in a combination containing Astragalus, Atractylodes, Macrocephala and Saposhnikovia divaricata [76]".
b. "*Astragalus roots extract containing* Astragaloside IV [15], [45], [27], [47], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 50, 150 mg/kg/day for 4 weeks. Result: Increased Interferon-*γ* level".
c. "*Mentha* Aerial parts Ethanol extract [50], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 100 mg/kg/day for 6 days. Result: Inhibit increases in Immunoglobulin-E, Interleukin-4, and Interleukin-5 in BALF and lung tissue".
d. "*Psoralea* Fructus Aqueous extract [10], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 10 g/kg/day for 4 weeks. Result: Inhibited the upregulation of Interleukin-4 and Interleukin-13 levels in BALF".
e. "*Psoralea* Fructus extract containing Bavachinin [11]], acting on *Ovalbumin* -induced Balb/c mice via Oral route, in effective dose of 50 mg/kg/day for 7 days. Result: Suppressed Interleukin-4, Interleukin-5, and Interleukin-13 in lung tissue and serum levels of Interleukin-4, Immunoglobulin-E".
f. "*Petasites japonicus* tincture containing 80% ethanol extract [49], acting on *Ovalbumin* -induced Balb/c mice via Oral.route, in effective dose of 500 mg/kg/day for 4 weeks. Result: Inhibit increases in *Ovalbumin* -specific Immunoglobulin-E and Interleukin-5 in BALF".
g. "*Moringa oleifera* Lam. Seed extract containing *β*-Sitosterol [65], acting on *Ovalbumin* -induced guinea pigs, via Oral.route, in effective dose of 2.5 mg/kg/day for 12 days,. Result: Decreased the levels of **tumor necrosis factor-*α*,** Interleukin-4, and Interleukin-5 in BALF and serum".

3. CONCLUSION AND REMARKS

As we have seen above that the study of Homeopathy and alternative medicines in the cases of asthma and as an adjuvant therapy in clinical researches seems to be becoming a trend. The effectiveness of Homeopathy, complementary medicine and alternative medicine in controlling the symptoms and reducing the doses of standard medicines in asthma has been proven by a number of researches [66], [78], [67], [68], [69], [70], [73]. Even then more research in the clinical use of Homeopathy is required for treating patients of asthma as there is very little evidence based papers in this field. As we know that asthma is a complex disease involving several mechanisms hence targeting a few factors won't help. Hence it would be a good research idea to study different formulations (combination of Homeopathic tinctures) covering all the above factors and mechanisms simultaneously. Simultaneously it would also be a good research idea to study different Homeopathic tinctures with different active ingredients individually and as a combination. Hence in this way significant benefits of treating asthma can be explored further when this combination of tinctures will act synergistically and more precisely then when they are used individually.

In the past few years we have seen remarkable achievements in the treatment of asthma by the active ingredients in natural tinctures. Hence it is a promising field of study and we should address the following while researching further in the future:

1) Standard procedures and quality control should be used to prepare the extract, formulations and decoctions. Only the good quality extracts should be used for researching in asthma.
2) Translational research is the need of the time. More large scale, well performed and well designed clinical trials is required to establish the effectiveness of Homeopathic tincture combinations in the treatment of asthma. Such studies are well accepted by world class journals hence it should be encouraged while researching for the treatment of asthma also [79].
3) We should re-study the proven animal models clinically, as those proven on animals might not work on humans. Hence clinical studies are required to establish the effectiveness of Homeopathic tinctures in treating different aspects of asthma individually. The preparation of medicines from the active ingredients is also required to increase the effectiveness of the treatment.
4) The clinical research can be aimed with three different targets. The first is to study the effectiveness of the formulation to reduce the usage of inhaled corticosteroids. Second is to study the effectiveness of the formulation as an add-on therapy. Third is to study the effectiveness of the formulation as a sole strategy to control asthma.
5) Both clinical and basic Homeopathic research should be encouraged for the following two phenotypes of asthma. The first is the neutrophilic asthma which is usually the most severe form and quite hard to control by the present approaches. We have discussed a few studies above and very few studies were focused on this. The second is the most studied eosinophilic type.

The Homeopatic treatment protocol for asthma holds a bright prospect and further research will eventually prove to help reduce the mortality and morbidity of asthma and might prove to be helpful in reducing the symptom severity.

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