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An Attempt to Reverse Bio-Engineer Asthma by Homeopathic Tinctures: A Review

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ABSTRACT

Asthma is a chronic inflammatory disease condition characterized by a reversible obstruction of the airway, the airway hyper responsiveness (AHR), infiltration of the inflammatory cells, hyper secretion of mucus, and remodeling of the airway. It affects almost 300 million individuals worldwide, with the prevalence ranging from 1% to 18% of the population in different countries. A variety of the immune cells, structure cells in the lung, chemokines, cytokines, adhesion molecules, and the signaling pathways, all of which contributes to the asthmatic pathogenesis. Although standardized therapeutics such as inhaled corticosteroid (ICS) in combination with long acting β2 agonist (LABA) have been used to control asthma symptoms, complementary and alternative medicine (CAM) including Homeopathy is still common all over the world. A survey involving 7685 individuals, aged 55 or older with asthma was recently performed in USA, and it showed that adult asthmatic population was frequently using Homeopathy including CAM with as much as 40% using some or other type of CAM.

Based on these facts that CAM including Homeopathy is widely used in asthma control, increasing basic or clinical studies have been conducted to investigate the molecular mechanisms or clinical applications of Homeopathic medicines for asthma therapy. Given the fact that asthma pathogenesis is very complex, the roles and effective targets of these Homeopathic medicines in asthma therapy are also very complicated.

In general, basic researches are all trying to separate effective monomers from the Homeopathic tinctures for asthma study, while most clinical researches still only focus on their efficacy for the patients using an intact traditional formula. We will shed a light on the major achievements of them, respectively, in this manuscript.

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 (AHR), infiltration of the inflammatory cells, hyper secretion of mucus, and remodeling of the airway. It affects almost 300 million individuals worldwide, with the prevalence ranging from 1% to 18% of the population in different countries. A variety of the immune cells, structure cells in the lung, chemokines, cytokines, adhesion molecules, and the signaling pathways, all of which contributes to the asthmatic pathogenesis. Although standardized therapeutics such as inhaled corticosteroid (ICS) in combination with long acting β2 agonist (LABA) have been used to control asthma symptoms, complementary and alternative medicine (CAM) including Homeopathy is still common all over the world. A survey involving 7685 individuals, aged 55 or older with asthma was recently performed in USA, and it showed that adult asthmatic population was frequently using Homeopathy including CAM with as much as 40% using some or other type of CAM.

Based on these facts that CAM including Homeopathy is widely used in asthma control, increasing basic or clinical studies have been conducted to investigate the molecular mechanisms or clinical

applications of Homeopathic medicines for asthma therapy. Given the fact that asthma pathogenesis is very complex, the roles and effective targets of these Homeopathic medicines in asthma therapy are also very complicated.

In general, basic researches are all trying to separate effective monomers from the Homeopathic tinctures for asthma study, while most clinical researches still only focus on their efficacy for the patients using an intact traditional formula. We will shed a light on the major achievements of them, respectively, in this manuscript.

2. Basic Researches

The basic researches on the Homeopathic asthma therapy can be summarized according to their mechanism into nine aspects as summarized below. Those researches that only reported some T helper 1 (Th1) cell or T helper 2 (Th2) cell cytokines, e.g, Interleukin-4 (IL-4), IL-5, IL-13, and interferon-*γ* (IFN-*γ*), altered after Homeopathic treatment but without any further detailed studies will not be discussed in detail in our paper, as they can be modified by many other factors.

2.1. The Homeopathic tinctures targeting the Th1/Th2 Imbalance

As it is generally accepted that Th1/Th2 imbalance is responsible for the development of allergic asthma. Th1 cells secrete tumor necrosis factor-*β* (TNF-*β*), IFN-*γ*, and IL-12, whereas Th2 cells secrete IL-4, IL-5, and IL-13. IL-4 together with IL-13 which causes the isotype class-switching of B-cells for the Immunoglobulin-E (IgE) synthesis, which can bind to the high-affinity receptors on the mast cells and the basophils, and which subsequently leads to the activation of these cells.

IL-5 activates the **eosinophils** and *attracts them to the lungs*, where they secrete several inflammatory cytokines and chemokines.

IL-13 also directly affects the epithelium of the airways, which also includes increase in the differentiation of goblet cells, activation of the fibroblasts, and the bronchial hyper-responsiveness. These cytokines also affects the Th1/Th2 balance.

It is also known that two transcription factors, i.e., T-bet and GATA-3, are responsible for Th1/Th2 balance. Also, GATA-3 and T-bet can be influenced by IFN-*γ*, IL-12, or IL-4 via the signal transducers and activators of transcription (STAT), i.e., STAT1, STAT4, and STAT6, respectively.

The following Homeopathic tinctures reported decreasing the ratio of GATA3/T-bet expression levels:
Astragalus mollissimus Q,
Ginseng Q,
Saururus chinensis Q,
Psoralea Q, and
Ligustrazine Q

Psoralea:

Jin et al. investigated the effects of ***Psoralea*** and psoralen, (an active ingredient of Psoralea), on Th2 clone (D10.G.4.1) cells *in vitro* and *in vivo*, and interpreted their effect as suppressor of the GATA-3 protein expression.

Chen et al. found that a single compound, Bavachinin, isolated from *Psoralea* decreased the GATA-3 function by reducing the stability of GATA-3 mRNA and further suggested that Bavachinin may suppress it's binding or co-activating function but not the expression of pSTAT6.

They also found [12], two more derivatives of Bavachinin, having a better water solubility and which were further investigated, and one of these two derivatives not only increased T-bet mRNA production but also inhibited GATA-3 mRNA production.

However, clinical research for *Psoralea* in treating asthma is lacking. Only a few case reports involving *Psoralea* related treatments in medicine can be found, but they provided limited evidence.

Efficacy on STAT6 was reported from:-

***Scutellaria* and *Cnidii monnieri*.**

Chiu et al. had explored the effects of Osthol (an extract *of Cnidii monnieri fructus*) on the human bronchial epithelial cells (BEAS-2B) *in vitro*. It was demonstrated in their research that ***IL-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 STAT6 expression*.**

Studies by *Sam So Eum* and *Qu Feng Xuan Bi*., without further mechanism revealed that the efficacy on **Th1/Th2 cytokines** were also observed in the following Homeopathic tinctures:
*Taraxacum officinale, (*taraxasterol)
Duchesnea chrysantha,
Echinacea purpurea,
Sophora flavescens, (matrine)
Zingiber officinale,
Actinidia polygama fructus

2.2. Effect of Homeopathic medicines on MAPK and NF-*κ*B Signaling Pathways

Mitogen-activated protein kinases (MAPKs), which comprises three major subgroups, that is, (a) extracellular signal-related kinase 1/2 (ERK1/2), (b) p38, and (c) c-Jun N-terminal kinase 1/2 (JNK1/2), which plays critical roles in the activation of the inflammatory cells [24].

Nuclear factor kappa B (NF-*κ*B) is an important transcription factor involved in the expression of various pro-inflammatory genes. Increased activation of NF-*κ*B has been observed in the lungs after allergen challenge & in the airway epithelial cells & macrophages from the asthmatic patients [25].

Many studies have reported that allergic asthma could be improved by regulating the activation of MAPK and NF-*κ*B signaling pathways [26], [27].
The Homeopathic tinctures targeting MAPKs are:
Scutellaria [28], [29],
Ginseng [30],
Saururus chinensis [31],
Artemisia annua [32],
Magnoliae flos [33], [34], and
Crocus sativus [35].

The Homeopathic NF-***κ***B inhibitor tinctures are:
Scutellaria [36],
Astragalus [37], [38],
Saururus chinensis [31],
Astilbe chinensis [39],
Artemisia annua [32], and
Allium Sativa [40].

Even though they performed similar actions, but some minor differences could still be noticed.

The Homeopathic tincture which inhibits of both MAPKs and NF-*κ*B are:
Artemisia
Scutellaria
Saururus chinensis

Some extracts like di-hydro-artemisinin [32] (isolated from ***Artemisia***) and meso-Di-hydro-guaiaretic acid [31] (isolated from ***Saururus chinensis***) acts as inhibitors of MAPKs and NF-*κ*B meanwhile, whereas some active ingredients isolated from the same Homeopathic tincture might inhibit either NF-*κ*B or MAPKs, respectively, for example, Oroxylin A [36] and Baicalin [28], [29] (both of which are isolated from ***Scutellaria***).

2.3. Effect of Homeopathic medicines targeting the Treg/Th17 Cells

T-regulatory cells (Tregs) 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 (Foxp3) [5], [75], [76], [77], [78] is driven by the specification of Treg subset.

Th17 cells plays a special and important role in asthma and the chronic inflammation of the lungs.

Neutrophil-mediated asthma and steroid-resistant asthma and have been repeatedly shown and proven to be related to Th17 cells.

IL-17 also directly affects the airway smooth muscles by inducing allergen-

induced airway hyper-responsiveness [79], [80], [81], [82]. The transcription factor related to Th17 is found to be RORγt, which is essentially required to activate IL-17 production in the Th17 cells [5]. Increased expressions of IL-17A and IL-17F have been shown in the lung tissue of asthma patients [6]. Thus, Homeopathic treatments targeting Foxp3 and RORγt have been revealed gradually.

Extracts from the following Homeopathic tinctures were observed to be increasing the Tregs and enhancing Foxp3 mRNA expression:
Astragalus [46], [48],
Panax ginseng [52],
Crocus sativus [60],
Ligustrazine [9], *and*
Anoectochilus formosanus [64]

Chuan Qiong reported that ligustrazine, isolated from *Ligustrazine* was modulating the expression of not only the Foxp3/RORγt but also T-bet/Gata-3 [9].

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.

Also, more Homeopathic tinctures were studied for treatments in other Th17-related inflammatory diseases, such as
Andrographis paniculata,
Scutellaria baicalensis,
Tripterygium wilfordii, and
Wedelia chinensis [33], [83], [84], [85].

However, whether these Homeopathic tinctures work similarly in asthma needs further investigations.

2.4. Effect of Homeopathic medicines on Lung Dendritic Cells (DCs)

Dendritic Cells (DCs) participated not only in the differentiation of T helper cells but also in IL-12 production and CD8+ T cell stimulation via antigen uptake. Two subsets of blood DCs, that is, myeloid DCs and plasmacytoid DCs, were identified based on the expression of CD11c [5]. Most CD11c+ myeloid DCs in the lung are immature, which express relatively low levels of major histo-compatibility complex (MHC) class II, and have a high capacity of antigen uptake but poor T cell stimulating activity [5]. Hence the strategy to restrict the activation of T cells can be achieved by inhibiting the functional differentiation of pulmonary immature DC to mature DC.

The effect of *Artemisia iwayomogi* polysaccharide-1 (AIP1) on DC functions was described by Lee et al. [63]. They observed significantly reduced levels of MHC II in DCs of the AIP1 in the treated group. Hence suggesting that AIP1 could reduce the expression of MHC II molecules on pulmonary DC. It was also observed that AIP1 could diminish the allergenic T cell stimulating ability of the DCs derived from the bone marrow in an another study. Hence these data suggests that AIP1 can inhibit the functional differentiation of pulmonary DCs *in vivo*.

Homeopathic Tincture:
Artemisia

2.5. Effect of Homeopathic medicines on Mast Cell Degranulation

Mast cell degranulation, which can be triggered by an antigen-mediated cross-linking of IgE bound to the FcεR1 surface receptors or by the changes in the surrounding local tissue environment, plays an important role in the asthmatic response. Thereby, several mediators which were stored or newly synthesized by the mast cells are subsequently released attracting the leukocytes (neutrophils, basophils, eosinophils and Th2 lymphocytes) to the site of inflammation and hence to amplify the inflammatory response [86]. Hence, inhibiting the mast cell degranulation might be quiet helpful for treating asthma.

The following three extracts from Homeopathic tinctures are associated with this process: Bakkenolide B [66], Petatewalide B [67], and Oroxylin A [43]. 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 Bakkenolide B or Petatewalide B induced inhibition of the degranulation seems not to be mediated by the inhibition of the Ca2+ channel or Ca2+ increase in the mast cells. 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.

Homeopathic tinctures:
Scutellaria baicalensis
Petasites japonicus

2.6. Effect of Homeopathic medicines on Oxidative Stress

The oxidative stress is an important factor in the pathogenesis of most of the airway diseases, especially where inflammation is found to be prominent. In recent studies, heme oxygenase-1 (HO-1) was described to be induced in the airways of the patients suffering from asthma. The body tries to protect itself using HO-1 as a natural antioxidant defense mechanism which exerts cyto-protective reactions against oxidative injury to the cells. Hence an increased expression of HO-1 can suppress IL-13-induced goblet cell hyperplasia and MUC5AC production [87], [88], [89] and thereby mitigate the symptoms of asthma. Hence a considerable strategy for controlling asthma should be to target the HO-1 or its transcription factor - nuclear factor E2-related factor 2 (Nrf-2) [90].

As of now, a variety of HO-1 activator can be extracted from the following Homeopathic tinctures:
Saururus chinensis [54], [55],
Phytolacca esculenta [68],
Allium sativa [40], and
Soshiho-tang [73].

Among the above, diallyl-disulfide (isolated from *Allium sativa*) [40] and esculentoside A (isolated from *Phytolacca esculenta*) [68] have been further proved also as Nrf-2 activators. The active ingredient, artesunate obtained from *Artemisia annua* was shown to be suppressing the pro-oxidants and activating the Nrf-2 [62] thereby restoring the expression of the antioxidants.

Hence among Homeopathic tinctures the nuclear factor E2-related factor 2 (Nrf-2) activators are:
Allium Sativa
Phytolacca esculenta
Artemisia annua

A reduced level of oxidative stress marker reactive oxygen species (ROS) were observed in other studies from certain extracts like the ethanol extracts of *Petasites japonicus* [65] and *Mentha* [59]. Their mechanisms of reducing ROS levels need further study.

Hence the Homeopathic tinctures to reduce the levels of oxidative stress marker reactive oxygen species (ROS) are:
Petasites japonicus
Mentha

2.7. Effect of Homeopathic medicines on Relaxing Airway Smooth Muscle

The contraction of the airway is an important feature of asthma, and the more recent strategies to tackle the contraction and to relax the airway smooth muscle includes the stimulation of β2-adrenoreceptors, blocking Ca2+ signaling, anti-histaminic and anti-cholinergic [61].

The effect of *Crocus sativus*'s (saffron's) on relaxing the airway smooth muscle was summarized by Mokhtari-Zaer et al. in a review [61]. 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.

The inhibition of acetylcholine induced airway smooth muscle (ASM) contraction independent of the β2-adrenoceptors by trifolirhizin, a flavonoid compound isolated from *Sophora flavescens* were identified by Yang et al. [69].

The effect on acetylcholine induced airway contraction by an aqueous

methanolic extract from *Zingiber officinale* (ginger) was reported by Ghayur et al. [70]. 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.

Homeopathic tinctures for relaxing airway smooth muscle:

Crocus sativus
Sophora flavescens
Zingiber officinale

2.8. Effect of Homeopathic medicines on Airway Remodeling

The most important roles in airway remodeling is believed to be played by the airway smooth muscle (ASM) cell proliferation and migration. Both transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) are reported to be related to airway remodeling [91]. Recently, the important mechanisms for signal conduction in asthma airway remodeling was found to be one of TGF-β1/Smad signal pathway [92].

It was reported that Skullcapflavone II extract from *Scutellaria baicalensis*, and Astragaloside IV extract from *Astragalus* respectively, inhibited TGF-β1 and hence attenuated the allergen-induced airway remodeling in mice [37], [41].

Skullcapflavone II suppressed Smad2/3 expression and elevated the Smad7, which was responsible for inhibition of TGF-β1, which was further indicated in the research performed by Jang et al. [41].

Several formulas using *Astragalus* as a key component acting on the TGF-β1/Smad signal pathway has been researched and studied. In one such study *Cordyceps and Astragali* mixture recovered Smad7 protein expression and decreased the TGF-β1 expression [50]. In another such study *Astragali radix Antiasthmatic Decoction* (AAD) [93] was also found to inhibit the Th2 cytokines and TGF-β1 and hence improved the symptoms of allergic airway remodeling.

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 TGF-β1 and IL-13 and hence significantly attenuated the allergen-induced AHR, inflammation, and remodeling in mice [94].

Homeopathic tinctures are:

Astragalus
Scutellaria baicalensis
Cordyceps

2.9. Effect of Homeopathic medicines on the Arachidonic Acid Metabolism Pathways (AAMP)

Arachidonic acid (AA) obtained from the diet or from synthesis is stored in the phospholipids of the membranes and under appropriate stimulatory conditions by the enzyme phospholipase A2 (PLA2) it is liberated. It is then metabolized by the three main classes of enzymes (p450 epoxygenases, lipoxygenases (LOX), and cyclooxygenases (COX)) and all the products of these three pathways like leukotrienes (LTs), prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), and so forth are related to the anaphylactic and inflammatory reaction. Specifically, PGE2 is considered as a potent pro-inflammatory mediator and its functions in the lung tissues is very beneficial, such as decreasing the Th2 differentiation, reduction of leukotrienes and PGD2, the inhibition of the inflammatory cell recruitment, and hence modulating the tissue repair and the inflammation. The leukotrienes in asthma especially LeukotrineB4, LeukotrineC4, LeukotrineD4, etc. are also considered to be important mediators of the airway inflammation and the airway obstruction. LeukotrineB4 acts as a neutrophil chemoattractant [53], [95], [96]. Hence, strategies targeting the arachidonic acid

metabolism are very effective in many of the inflammatory diseases.

Homeopathic tinctures targeting different steps of the arachidonic acid metabolism pathway (AAMP) are:
Scutellaria baicalensis [42],
Panax ginseng [53],
Saururus chinensis [57],
Sceptridium ternatum [58],
Aralia cordata [71], and
Eucalyptus eucalyptol (1.8-cineole) [74]
Details are given in "mechanism of action".

Particularly, there are 4 Homeopathic tinctures we would like to review individually as follows for their multiple function of anti-asthma properties and popularity in the basic researches.

Scutellaria baicalensis: It is a multifunctional traditional medicine. Its extracts contains the following active ingredients: Skullcap flavone II, Baicalin, Baicalein, wogonin, and Oroxylin A, which has shown varied and some cooperative functions in the treatment of asthma. All the above active ingredients have been proven well in the animal experiments or *in vitro* but not yet published any proven records in the humans as we have mentioned before. And in their published papers we have seen some simple functions on some cytokines or genes related to the asthma. Hence more human research is required to become clear whether they can benefit the humans during asthma. For example, Skullcapflavone II's function on Smad/TGF-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 TGF-β1 in BALF. The TGF-β1 is a multifunctional and pleiotropic growth factor, which also exerts immunosuppressive effects on the progression of asthma. Although the airway remodeling potential of TGF-β1 has been elaborately discussed but still the therapies targeting TGF-β1 are continued to be controversial [97].

***Astragalus membranaceus*:** It is an another multifunctional Homeopathic tincture with relatively sufficient studies. We have shown above and in several studies that within the last few years its extract has been reported to be acting on Tregs, NF-κB signal pathway, TGF-β1/Smad, and GATA3/T-bet. Among all it's active ingredients the Astragaloside IV should be considered most important, as it has performed all the effects of this medicine in the studies for treating asthma. Even though several studies have been recorded on Astragaloside IV, but still no clinical research on humans is available to date.

Ginseng: The extracts (ginsan, CVT-E002, and RG-II) from the tincture of *Panax Ginseng* were studied. The different pathways of its action includes GATA3/T-bet, MAPK, and Tregs 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 [98], [99]. 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.

***Saururus chinensis* (SC):** It is an effective Homeopathic antioxidant tincture. All 3 of its extracts (a subfraction of its ethanol extract, saucerneol D [54] and sauchinone [55]) have shown similar antioxidant effects through the up-regulation of the expression of HO-1. While sauchinone also have a suppressor activity on GATA-3 [56]. Very recently, a novel extract of *Saururus chinensis* was expounded by Song and his colleagues and was named meso-Di-hydro-guaiaretic acid [31]. Which has a protective effect on the allergic airway inflammation

by inhibiting the Th2 inflammation, which is attributed to its inhibition of the MAPK and NF-κB. 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.

3. The Mechanism of Action of the Active Ingredients in Homeopathic Tinctures:

3.1 Scutellaria:

Scutellaria roots extract containing Skullcap-flavone II [41], acting on OVA-induced Balb/c mice, via oral route, in effective dose of 10, 30 mg/kg/day for 7 days, acting on TGF-β1/Smad. Result: Reduced the TGF-β1 in BLAF, elevated Smad7, and suppressed Smad2/3 expressions.

Scutellaria roots extract containing Baicalein [42], acting on OVA-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.

Scutellaria extract containing Oroxylin A [36, 43], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 15, 30, and 60 mg/kg/day for 3 days, acting on NF-κB. Result: Suppressed NF-κB activation.

Scutellaria acting on Specific IgE 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.

Scutellaria roots extract containing Wogonin [14], acting on OVA-induced Balb/c mice via oral route, in effective dose of 10, 30 mg/kg/day for 3 days, acting on STAT6. Result: Suppressed OVA-induced STAT6 activation.

Scutellaria roots extract acting on IL-4 induced BEAS-2B cells, acting i*n vitro*, in effective dose of 10, 30, and 50 μM for 4 hours, acting on STAT6. Result: Suppressed IL-4-induced eotaxin-3 expression via suppressing JAK1 and STAT6 activation.

Scutellaria roots extract containing Baicalin [28], [29], acting on OVA-induced Balb/c mice, via Oral. route, in effective dose of 25, 50, and 100 mg/kg/day for 4 weeks, acting on MAPK. Result: Inhibited RASM cell proliferation and migration by suppressing MAPK signal pathway.

Scutellaria roots extract containing Baicalin [28], [29], 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 MAPK.. Result: Inhibited RASM cell proliferation and migration by suppressing MAPK signal pathway.

3.2 Astragallus:

Astragalus aqueous extract [44], acting on OVA-induced C57BL/6 mice, via Oral route, in effective dose of 3 μg/kg/2 day for 9 days, acting on GATA3/T-bet. Result: Decreased the ratio of the GATA3/T-bet mRNA levels.

Astragalus roots extract containing Astragaloside IV [37], [45], [46], [47], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 50, 150 mg/kg/day for 4 weeks, acting on GATA3/T-bet. Result: Decreased the ratio of the GATA3/T-bet expression level.

Astragalus roots extract containing Astragaloside IV [37], [45], [46], [47], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 50, 150 mg/kg/day for 4 weeks. Result: Increased IFN-γ level.

Astragalus roots extract containing Astragaloside IV [37], [45], [46], [47], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 20, 40 mg/kg/day for 4 weeks, acting on Foxp3/RORγt. Result: Increased CD4+CD25+Foxp3+ Tregs and enhanced Foxp3 mRNA expression.

Astragalus roots extract containing Astragaloside IV [37], [45], [46], [47], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 50 mg/kg/day for 8 weeks,

acting on TGF-β1/Smad. Result: Reduced TGF-β1 expression.

Astragalus roots extract containing Astragaloside IV [37], [45], [46], [47], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 50 mg/kg/day for 8 weeks, acting on NF-κB. Result: Inhibited TSLP expression.

Astragalus aqueous extract [48], acting on OVA-induced SD rats via Oral route, in effective dose of 5, 10 g/kg/day for 4 weeks, acting on Foxp3/RORγt. Result: Increased CD4+CD25+Foxp3+ Tregs and enhanced Foxp3+ mRNA expression.

Astragalus aqueous extract [49], acting on OVA-induced C57BL/6 mice via intraperitoneal injection. route, in effective dose of 10 g/kg/day for 4 weeks. Result: Increased Th1/Th2 cytokines' ratio.

Astragalus containing formononetin & calycosin [38], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 0.5 g/kg/2 day for 4 weeks, acting on NF-κB. Result: Suppressed NF-κB activation.

3.3 Combination of Astragalus & Cordyceps:

Astragalus + Cordyceps combination suspensions [50] acting on OVA-induced C57BL/6 mice via Oral route, in effective dose of 6.5 g/kg/day for 4 weeks, acting on TGF-β1/Smad. Result: Reduced TGF-β1 and elevated Smad7 expression in lung tissue.

3.4 Ginseng:

Ginseng roots aqueous extract [30], acting on OVA-induced C57BL/6 mice via intraperitoneal injection. route, in effective dose of 20 mg/kg/day for 3 days, acting on MAPK pathway. Result: Inhibited CD40/CD40L ligation and MAPK signal pathway.

Ginseng leaves Purified aqueous extract (RG-II) [51], acting on OVA-induced Balb/c mice via intraperitoneal injection. route, in effective dose of 20, 100 mg/kg/day for 3 days, acting on GATA3/T-bet pathway. Result: Decreased the ratio of the GATA3/T-bet expression level.

Ginseng roots aqueous extract (CVT-E002) [52], acting on OVA-induced Balb/c mice via oral route, in effective dose of 200 mg/kg/day for 7 days, acting on Foxp3/RORγt pathway. Result: Increased Tregs function and IL-10 level in BALF.

Ginseng roots extract containing Ginsan [53], acting on OVA-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.

3.5 Saururus chinensis:

Saururus chinensis roots extract containing Saucerneol D [54], acting on OVA-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.

Saururus chinensis Aerial parts extract containing A subfraction of ethanol extract [55], acting on RAW264.7 cells derived from BALB/c mice acting in *vitro*, in effective dose of 5, 50 μg /mL for 2 hours, acting on Antioxidant. Result: Upregulated the expression of HO-1.

Saururus chinensis Aerial parts extract containing Sauchinone [55], [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.

Saururus chinensis Aerial parts extract containing Sauchinone [55], [56], acting on OVA-induced Balb/c mice via intraperitoneal injection.route, in effective dose of 10, 100 mg/kg/2 day for 5 days, acting on GATA3/T-bet. Result: Suppressed GATA-3 activity.

Saururus chinensis roots extract containing Meso-Dihydroguaiaretic acid [31], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 10, 30 mg/kg for 2 weeks, acting on NF-κB &

MAPK. Result: Inhibited Th2 inflammation via inhibiting NF-κB and MAPK.

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.

3.6 Sceptridium ternatum:

Sceptridium ternatum 70% ethanol extract [58], acting on OVA-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 Th1/Th2.

Sceptridium ternatum 70% ethanol extract [58], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 2, 10, and 20 g/kg/day for 10 days, acting on AAMP. Result: Decreased the cysLT1 mRNA levels.

3.7 Mentha:

Mentha Aerial parts Ethanol extract [59], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 100 mg/kg/day for 6 days. Result: Inhibit increases in IgE, IL-4, and IL-5 in BALF and lung tissue.

Mentha Aerial parts Ethanol extract [59], acting on OVA-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 ROS in BALF.

3.8 Psoralea:

Psoralea Fructus Aqueous extract [10], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 10 g/kg/day for 4 weeks. Result: Inhibited the upregulation of IL-4 and IL-13 levels in BALF.

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 GATA3/T-bet. Result: Suppressed the upregulation of IL-4, IL-5, IL-13, and GATA-3 protein expression.

Psoralea Fructus extract containing Bavachinin [11], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 50 mg/kg/day for 7 days. Result: Suppressed IL-4, IL-5, and IL-13 in lung tissue and serum levels of IL-4, IgE.

Psoralea Fructus Aqueous extract [10], acting on ConA, IL-2, IL-4 stimulated 4GET mice spleen cells acting *In vitro*, in effective dose of 0.01 mM, acting on GATA3/T-bet. Result: Suppressed GATA-3 mRNA levels.

3.9 Astilbe chinensis:

Astilbe chinensis extract containing Astilbic acid [27], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 30 mg/kg/d $*$ 3 d, acting on NF-κB. Result: Suppressed the NF-κB activation.

3.10 Crocus sativus:

Crocus sativus Flower extract containing Crocetin [60], acting on OVA-induced C57BL/6 mice via Intranasal route, in effective dose of 3 μg /day for 1 week, acting on Foxp3/RORγt. Result: Increased Foxp3 through TIPE2 to activate Tregs.

Crocus sativus Flower extract containing Crocin [35], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 100 mg/kg/day for 5 days, acting on MAPK. Result: Inhibited the expression of lung eotaxin, p-ERK, p-JNK, and p-p38 level.

Crocus sativus Flower extract containing Safranal [61] (A review), acting on Relaxing ASM. Result: Antihistamine and anticholinergic and β2-adrenoreceptors stimulation and Ca2+ signaling blocking.

3.11 Artemisia annua:

Artemisia annua extract containing Dihydroartemisinin [32], acting on OVA-induced Balb/c mice via Oral route, in effective dose of 30 mg/kg/day for 3 days, acting on NF-κB & MAPK. Result: Inhibited Th2 inflammation via inhibiting NF-κB and MAPK.

Artemisia annua extract containing Artesunate [62], acting on OVA-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 Nrf-2.

3.12 Artemisia iwayomogi:

Artemisia iwayomogi Leaves extract containing Purified aqueous extract (AIP1) [63], acting on OVA-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.

3.13 Ligustrazine:

Ligustrazine extract containing Ligustrazine [9], acting on OVA-induced C57BL/6 mice via intraperitoneal injection.route, in effective dose of 80 mg/kg/day for 3 days, acting on GATA3/T-bet. Result: Decreased the ratio of the GATA3/T-bet expression level.

Ligustrazine extract containing Ligustrazine [9], acting on OVA-induced C57BL/6 mice via intraperitoneal injection.route, in effective dose of 80 mg/kg/day for 3 days, acting on Foxp3/RORγt. Result: Increased the ratio of Foxp3/RORγt.

3.14 Anoectochilus formosanus:

Anoectochilus formosanus Whole plant Aqueous extract [64], acting on OVA OVA-induced Balb/c mice, in effective dose of 0.5, 1 g/kg/day for 7 days, acting on Foxp3/RORγt. Result: Inhibited the decrease of Tregs in BALF.

3.15 Petasites japonicus:

Petasites japonicus tincture containing 80% ethanol extract [65], acting on OVA-induced Balb/c mice via Oral.route, in effective dose of 500 mg/kg/day for 4 weeks. Result: Inhibit increases in OVA-specific IgE and IL-5 in BALF.

Petasites japonicus tincture containing 80% ethanol extract [65], acting on OVA-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 ROS in BALF.

Petasites japonicus tincture Leaves extract containing Bakkenolide B [66], 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.

Petasites japonicus tincture Leaves extract containing Petatewalide B [67], 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.

3.16 Cnidii monnieri:

Cnidii monnieri Fructus tincture containing Osthol [15], acting on IL-4/TNF-α induced BEAS-2B cells acting *In vitro,* in effective dose of 1–10 μM for 2 hour, acting on STAT6. Result: Suppressed IL-4-induced eotaxin expression via suppressing STAT6 activation.

3.17 Magnolia:

Magnoliae flos Leaves extract tincture containing Fargesin and epimagnolin [34], acting on A549 human alveolar epithelial cells, acting *In vitro,* in effective dose of 3.1–100 μg /mL, acting on MAPK. Result: Modulated NO synthesis via inhibiting ERK in human respiratory epithelial cells.

3.18 Phytolacca:

Phytolacca esculenta tincture extract containing Esculentoside A (EsA) [68], acting on OVA-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 ROS in BALF.

Phytolacca esculenta tincture extract containing Esculentoside A (EsA) [68], 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: Nrf-2 activator. Upregulated the expression of HO-1.

3.19 Allium Sativa:

Allium Sativa Oil extract containing Diallyl-disulfide (DADS) [40], acting on OVA-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 ROS in BALF.

Allium Sativa Oil extract containing Diallyl-disulfide (DADS) [40], acting on OVA-induced Balb/c mice via Oral.route, in effective dose of 30 mg/kg/day for 3 days, acting on NF-κB. Result: Suppressed NF-κB activation.

Allium Sativa Oil extract containing Diallyl-disulfide (DADS) [40], 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: Nrf-2 activator. Upregulated the expression of HO-1.

3.20 Sophora flavescens:

Sophora flavescens extract containing Trifolirhizin [69], acting on Tracheal rings of OVA-induced Balb/c mice, acting *In vitro*, in effective dose of 6 μg /mL, acting on Relaxing ASM. Result: Inhibiting acetylcholine mediated ASM contraction.

3.21 Zingiber officinale:

Zingiber officinale Root extract containing 70% methanol extract [70], acting on Lung slices of Balb/c mice acting *In vitro*, in effective dose of 0.3, 1 mg/mL, acting on Relaxing ASM. Result: Inhibiting acetylcholine mediated ASM contraction via blocking Ca2+ channels.

3.22 Aralia cordata:

Aralia cordata Root extract containing 7-Oxo-sandaracopimaric acid [71], acting on OVA-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.

3.23 Moringa oleifera:

Moringa oleifera Lam. Seed extract containing β-Sitosterol [72], acting on OVA-induced guinea pigs, via Oral.route, in effective dose of 2.5 mg/kg/day for 12 days, Result: Decreased the levels of TNF-α, IL-4, and IL-5 in BALF and serum.

Moringa oleifera Lam. Seed extract containing β-Sitosterol [72], acting on OVA-induced guinea pigs, via Oral.route, in effective dose of 2.5 mg/kg/day for 12 days, acting as Antihistamine. Result: Antihistamine.

3.24 Soshiho:

Soshiho-tang containing Aqueous extract [73], acting on OVA-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.

3.25 Eucalyptus:

Eucalyptus Q containing Eucalyptol (1.8-cineole) [74], acting on OVA 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.

4. Clinical Studies

The clinical research of Homeopathic tincture therapy application in asthma is limited. Several meta-analysis were done but still it lacks sufficient evidence and more published research is required.

Arnold et al. [100] evaluated effects of Homeopathic tincture/herbal 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 Homeopathic 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.

In Clark et al.'s study [102], 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 [100], [102].

In the last five years, some new clinical trials on Homeopathic tincture/herbal treatment emerged but most of them still focus on the efficacy for patients using an intact traditional or modified formula. The application of monomer extracts in clinic usually acts as adjuvant of standard asthma therapy according to the recent studies. In a noncomparative, multicenter trial [103], 148 patients with mild asthma taking ICS received NDC-052 (an extract from ***Magnoliae flos***) for eight weeks. Their results showed that add-on NDC-052 besides ICS therapy had benefits in both ΔPEFR and asthma symptoms. Last year, a review by Ammon [104] showed multiple effects of *Boswellia serrata* extracts on immune system modulation in basic research, including inhibiting activation of NFκB, mast cell stabilisation, and antioxidant and inhibitory action on 5-LOX. However, related clinical research in the past five years can only be found for reducing the need for inhalation therapy with ICS + LABAs [105]. Although its significant effect on lung function had been analyzed by Arnold et al. as mentioned before [100], further research is still lacking.

The following three types of research interests are reported recently regarding the intact traditional or modified formula for asthma, in the past five years.

1) A combination of tinctures to be used to relieve the symptoms of asthma. These studies paid special attention to the frequency of acute attack of asthma and the syndrome scores. Even though these combinations of tinctures might have limited efficacy on the improvement of lung function and in the process of asthma. 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. [106].

The following are the contents of the combination:

Concha Ostreae - 10 g,
Endoconcha Sepiellae - 10 g.
Fructus Jujubae - 10 g,
Fructus Ligustri Lucidi - 10 g,
Fructus Psoraleae - 10 g,
Fructus Schisandrae Chinensis - 3 g,
Radix Astragali Mongolici - 10 g,
Radix Pseudostellariae - 3 g,
Rhizoma Polygonati Odorati - 10 g,

The results of their study showed that the above combination reduced the airway resistance, decreased the syndrome scores, and it reduced the number of attacks of intermittent asthma in the study group of children.

In uniformity with the above, an another combination, composed of seven tinctures of:

Schizonepeta - Fine Leaf,
Liquorice - root.
Platycodon grandiflorum,
Sessile Stemona root/Japanese Stemona root/Tuber Stemona root,
Tangerine - peel,
Tatarian Aster - root,
Willowleaf Swallowwort - Rhizome,

The results of their study are 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 [107].

2) The most popular method is the use of Homeopathic tincture combinations as an add-on therapy of standard medication, in order to relieve the symptoms of asthma, and to reduce the rate of recurrence or to strengthen the effect of the standard medications.

Tang and colleagues [108] 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 (ACT) score and a decrease of the frequency of exacerbations.

The effects of Astragalus plus hormone treatment in 90 children with asthma were studied by Lin et al. [109]. 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 IL-4 decreased, and that of IFN-*γ and* PEFR significantly increased in their effective cases. Whereas, in another study, the benefit of "chaipo granule" combined with routine treatment on the refractory asthma was also discovered. According to their results the "Chaipo granule" can act as a synergist of routine treatment [110]. Similar effect of strengthening was also reported in the "Yupingfeng powder" combination containing Radix Astragali, Rhizoma Atractylodis Macrocephalae and Radix Saposhnikoviae [111].

3) Finally is the method of using percutaneous absorption and inhalation of Homeopathic medicinal combinations. In age old method of Moxibustion/Jiu the medicinal herbs were burnt at the related acupoints of the patients. The method in now modified to apply medicines using percutaneous absorption and inhalation. The inhalation of salmeterol fluticasone and percutaneous absorption of medicinal herbal patch for asthma of paracmasis was studied by Chen et al. [112]. Significant improvement in clinical symptom scores was shown in their results.

5. 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 [100], [101], [102], [103], [104], [105, [108]. 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 [113].
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 Homeopathic 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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