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Natural Antioxidants: Potential Oxidative Stress Inhibitors for the Treatment of Asthma

Shantanu Singh*, Chandan Chauhan, Anshita, Sachin Kumar, Sanjiv Singh

Department of Pharmacology and Toxicology, National Institute of pharmaceutical Education and Research, Hajipur-844102, Bihar, India

Corresponding author: Mr. Shantanu Singh

Email: santanusingh65@gmail.com

ABSTRACT

During the epidemic season, over 90% of respiratory disease is associated with bronchial Asthma. Both Allergens and Inflammatory mediators mediated inflammation have been involved in the pathophysiology of Asthma, but oxidative stress in respiratory cells has been shown to be dominant. The on-going inflammation increases the chemotaxis of oxidative stress to inflamed site providing to their production. The pharmacological production of oxidative stress can be suppressed with Natural Antioxidants. Screening of traditional plants which can be used in treatment of respiratory tracts disorders (e.g. Asthma), we have selected some herbs or plants which can be a potential source of antioxidant compounds for limiting of oxidative stress in Asthma. The books on ethno-medicine, pharmacology and pharmacognosy including Ethnomedicine book by Pamela Erickson, Goodman and Gilman's The Pharmacological Basis of Therapeutics, by Goodman, L. S., Gilman, A., Hardman, J. G., Gilman, A. G., & Limbird, L. E., Trease and Evans Pharmacognosy Textbook by William Charles Evans and etc were explored for Asthma, Antioxidants, *Allium sativum*, *Artemisia annua*, *Anchomanes difformis*, *Saururus chinensis*, *Mentha*, *Petasites japonicas*, *Phytolacca esculenta* and other traditional plants. Additionally, information on the ethno-botany, Phytochemistry, morphology, taxonomy, modern medicinal uses, and pharmacological activities were collected in electronic databases including Google Scholar, Science Direct, Scopus, and PubMed using the keywords "Asthma," "traditional medicine for Asthma," "ethnomedicine," "Natural Antioxidants," "pathogenesis of asthma" and "Oxidative stress in asthma." Then, the available articles from 1975 to 2020 were employed for this study. *Allium sativum*, *Artemisia annua*, *Anchomanes difformis*, *Saururus chinensis*, *Mentha*, *Petasites japonicas*, *Phytolacca esculenta* and some other traditional herbs or plants have shown a potential antioxidant activity for the suppression of oxidative stress. These herbs were used traditionally in formularies or by rural people as Anti-cough, Anti-allergic and etc. In modern medicine, the extract of these natural herbs showed antioxidant activity. Asthma is a chronic airway disease which cannot be cured permanently with anti-asthmatic drugs. Anti-asthmatic drugs have various side effects on the vital organs of the body. Thus, there is necessary to treat the asthma with some natural herbs. The below mentioned Natural herbs having the potential antioxidant activity which exhibits important role in the treatment of the Asthma.

Keywords: Asthma, Natural Antioxidants, Oxidative Stress Inhibitors, Antioxidant treatment of asthma

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways. The chronic inflammation is associated with airway hyper responsiveness (an exaggerated airway-narrowing response to specific triggers such as viruses, allergens and exercise) that leads to recurrent episodes of wheezing, breathlessness, chest tightness and/or coughing that can vary over time and in intensity(1). Asthma is a serious health and socioeconomic issue all over the world, affecting more than 300 million persons all over the world, with approximately 250,000 annual deaths(2). Globally, asthma is ranked 16th among the leading causes of years lived with disability and 28th among the leading causes of burden of disease, as measured by disability-adjusted life years(3). The large multinational studies in children (such as the International Study of Asthma and Allergies in Childhood)(4,5) and in adults (such as the European Community Respiratory Health Survey)(6) are conducted previously. These studies confirmed that asthma is one of the most common chronic diseases across the globe in all age groups and there is substantial variation in asthma prevalence worldwide. Clinical and epidemiological data support the role of sex hormones on asthma incidence and severity. The data confirms that as children, boys have increased prevalence of asthma compared to girls. However, as adults, women have increased prevalence of asthma compared to men(7). During pregnancy, women with more severe phenotypes of asthma are more likely to have worsening condition of asthma(8).Asthma is becoming a major health issue in many developing countries due to the Increasing air pollution, fast modernization, and widespread construction work and the situation is complicated by poor access to medical services, high price of effective drugs, and poor health education among the affected population(9).Asthmatic patients will suffer from the obstruction in the airflow due to Bronchoconstriction, Airway edema, Airway hyper responsiveness and Airway remodeling which was occur due to the over production of the Inflammatory Cells (such as Lymphocytes, Mast cells, Eosinophil's, Neutrophils, Dendritic cells, Macrophages and Epithelial cells) and superabundance of Inflammatory Mediators (such as Chemokine's, Cytokines, Cysteinyl-leukotrienes and Nitric oxide) and also Immunoglobulin E(IgE) antibody is responsible for activation of allergic mediators and development of persistence inflammation(10). But the main reason for the respiratory inflammation had been identified is the generation of oxidative stress by reactive oxygen species (ROS), reactive nitrogen species (RNS) and endogenous nitric oxide (NO) due to the inhalation of different allergens(11).However, there is no permanent treatment of asthma but the

symptoms can be adequately controlled with Anti-Asthmatic drugs(12). Furthermore, the Redox therapy (the antioxidant system) is well developed in the case of allergic asthma which plays a critical role in the inhibition and elimination of damage occurred due to oxidative stress. Mainly, the antioxidants can be categorized into 2 groups, First is enzymatic group [such as glutathione peroxidase and superoxide dismutase (SOD)] and Second is non-enzymatic group (such as vitamin E, vitamin C)(11). Natural Antioxidants plays vital roles in the cell, such as in the detoxification of toxic electrophiles and heavy metals and in the reduction of certain reactive oxygen species (like hydrogen peroxide, superoxide, hydroxyl radical, singlet oxygen, and alpha-oxygen).

PATHOGENESIS OF ASTHMA

Asthma is a heterogenous disease triggered by Allergic and Non-allergic stimuli which influence on the Immune system leads to the release of the inflammatory mediators which causes chronic airway inflammation(1,13). Allergic stimuli's (such as dust mites, pollens grains, Cockroach droppings, Pet dander and Mould spores, etc.) causes the Atopic asthma which involves the exaggerated production of IgE Antibody, Whereas the Non-allergic stimuli's (such as viral infections, air pollution, exposure to tobacco smoke, cold air and exercise, etc.) causes the Non-Atopic asthma where the asthmatic condition appear without any preceding allergic symptom and without any evidence of specific IgE antibody production against the allergens(14). These allergens (Allergic and Non-allergic stimuli) will cause the activation of Antigen-presenting cells (APCs) (such as dendritic cells, macrophage cells and B cells) and mast cells. Dendritic cells and Mast cells are activation by allergens and releases bronchoconstrictor inflammatory mediators (such as histamine, LTD4, and prostaglandin D2) which will able to cause bronchoconstriction, micro vascular leakage, and plasma exudation in airway(1,2). Antigen Presenting cells process the antigenic molecules and present them to the helper T cells and stimulates the T helper type 2 (Th2) cell proliferation, subsequently Th2 cytokines, interleukin (IL)-4, IL-5 and IL-13 production and release. IgE antibody production triggers the release of various inflammatory mediators, such as histamine and cysteinyl leukotriene's, which causes the bronchospasm (airway smooth muscles contraction), airway oedema, and enhanced mucous secretion, which lead to the worsening of asthmatic conditions(1,15). Chronic inflammation in airway results to the airway remodeling including an increase in the number and size of smooth muscle cells, blood vessels, and mucus-secreting cells. There are more than 100 inflammatory mediators' releases during the allergen interaction with the Antigen-Presenting cells (APCs) and

thus causes the worsening condition of asthma(16). See fig.1

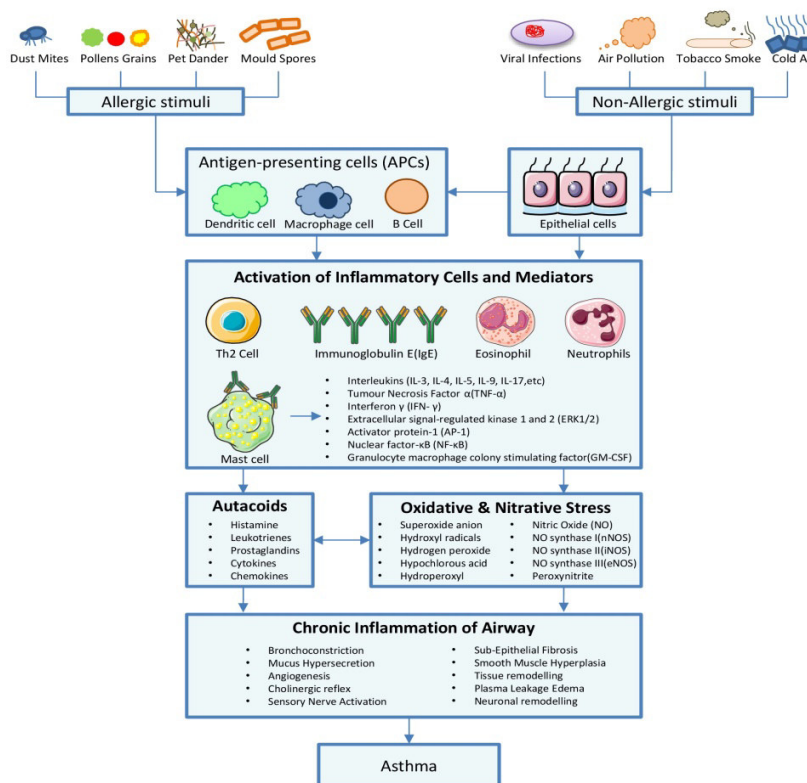


Fig 1. Showing the brief Pathogenesis of Asthma

INVOLVEMENT OF OXIDATIVE STRESS IN ASTHMA PROGRESSION

There are various clinical evidences and data support that airway inflammation and airway hyper responsiveness occur due to the imbalance between the oxidant and antioxidant system in airway(17–19). However, Normal metabolism involves the production of various types of oxidants which plays a crucial role in cell homeostasis. Whereas the main three sources and locations of generation of endogenous ROS and RNS in lungs are: first NADPH oxidase system located in the plasma membrane, second Xanthine oxidase (XO) in the endothelial cells(20) and third is Electron Transport Chain(ETC) located in mitochondria(21). There are various endogenous as well as exogenous toxic oxidants generated by reactive oxygen species(ROS) and reactive nitrogen species(RNS) are continuously exposing on human body, and for the protection from these oxidants the lung contains a well-developed antioxidant system(22,23). ROS and RNS leads to degradation and fragmentation of various proteins and peptide chains which are involved in the normal metabolic processes(24).Reactive oxygen species (ROS) are chemically reactive and toxic

oxygen species which produced during various metabolic reactions in the cell. The generation of ROS was done in within the cell and cell organelles such as peroxisomes, mitochondria and endoplasmic reticulum via various biochemical reactions(25,26). ROS formation was also induced by the various allergens and agents such as heavy metals, tobacco, smoke, drugs, xenobiotics, or radiation(27). Mainly IL-5 is responsible for the generation and activation of eosinophils to mediate ROS and RNS generation(11).ROS have been shown to increase smooth muscle contraction, enhance airway hyper-responsiveness and stimulate mucus secretion(28). Reactive oxygen species (ROS) such as superoxide anion, hydroxyl radicals, hydrogen peroxide, hypochlorous acid, ozone, and peroxynitrite are responsible for the transfer of stimulating signals which acts as critical intracellular second messenger, resulting in the modulation of inflammatory immune response. There are various chemokines and chemokine receptors which promote invasion and metastasis of chronic inflammation and tumours such as of COX-2, inflammatory cytokines (TNF α , interleukin 1 (IL-1), IL-6), chemokines (IL-8, CXCR4) and pro-inflammatory transcription factors (NF- κ B) all these are induced and promoted by the ROS(29).

Superoxide anion (O₂⁻) was also involved in the inflammation of asthmatic airways due to the upregulation of xanthine oxidase (XO) in

microvascular endothelial cells and NADPH oxidase in the infiltrated eosinophils(30,31). See fig.2

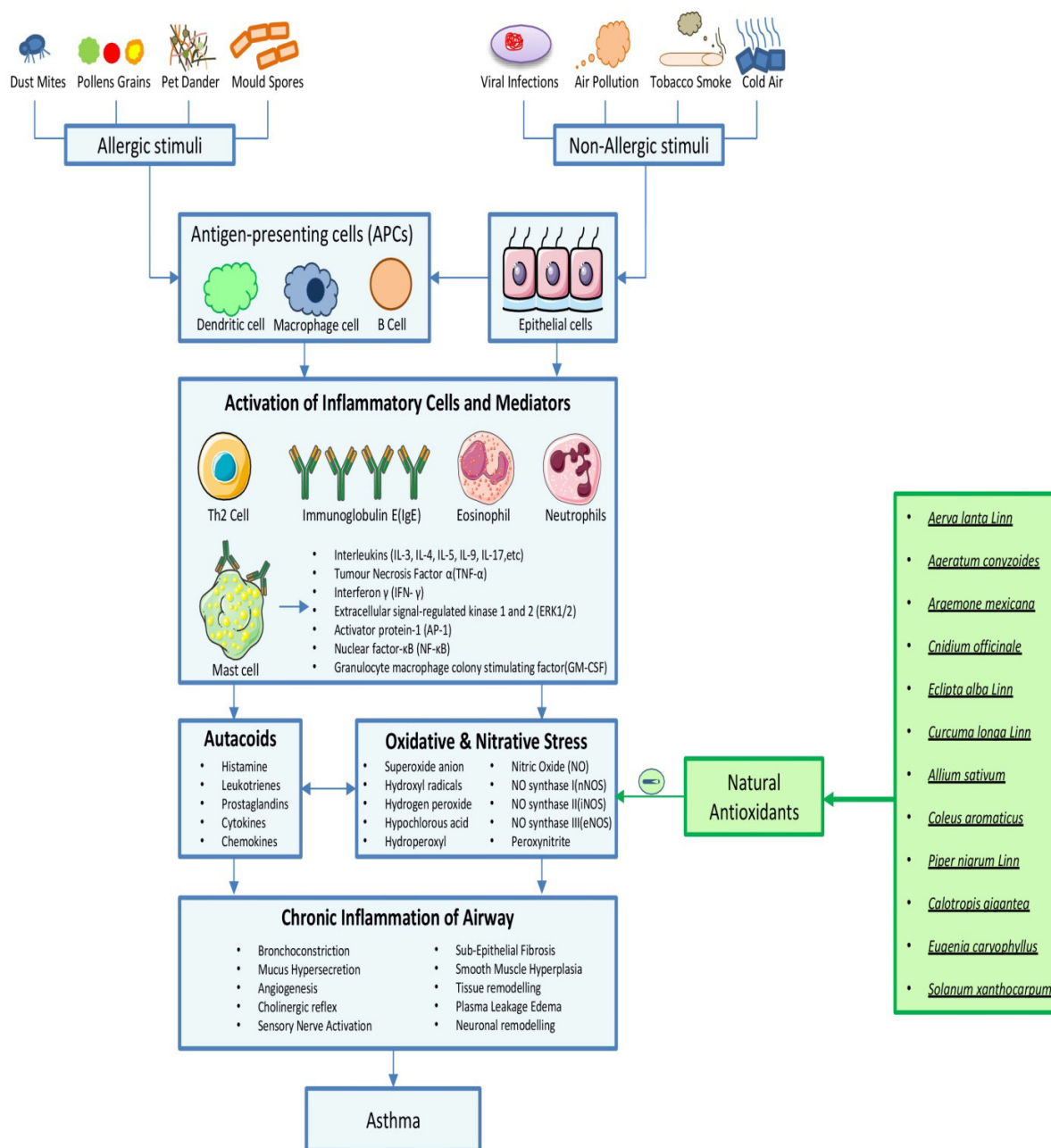


Fig 2. Showing the target of Natural Antioxidant in the Oxidative stress Inhibition

NATURAL ANTIOXIDANTS AS POTENTIAL OXIDATIVE STRESS INHIBITOR

Natural herbs were an excellent source of medicine since ancient times. Current asthma therapy lacks adequate results due to its side effects, so the asthmatic patients are seeking for asthmatic treatment with alternative medicine [See fig.2 & fig.3]. Brief introductions of some traditional herbs with their potential antioxidant activity are described below.

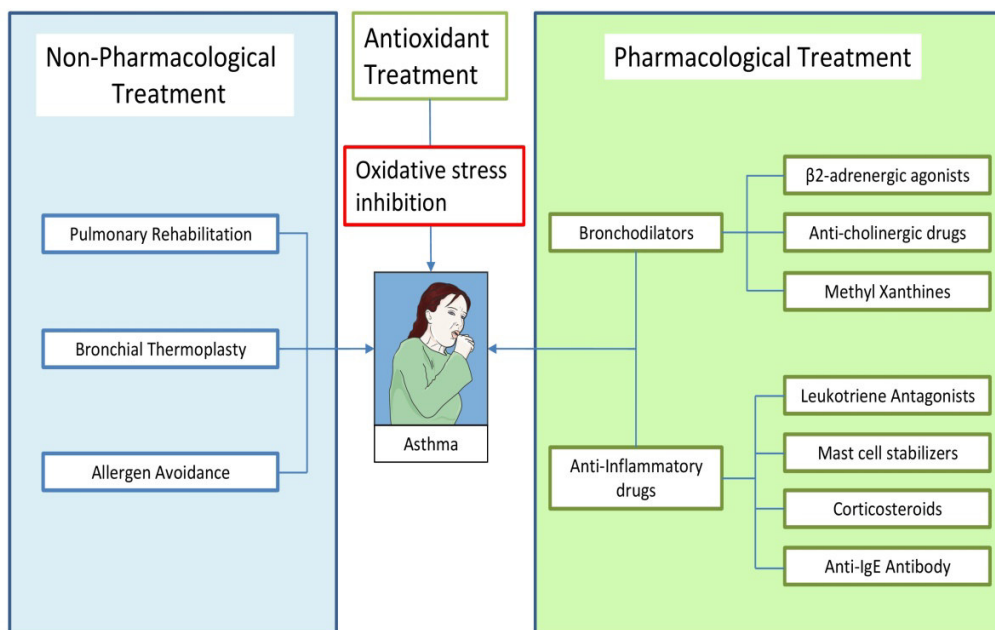
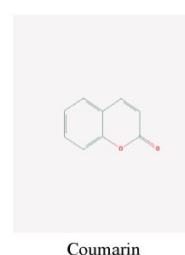
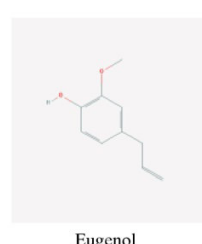
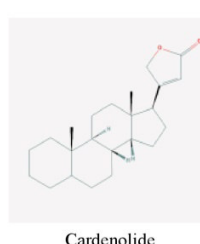
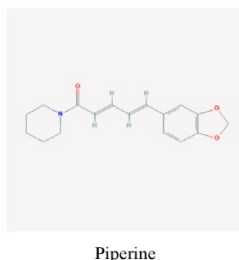
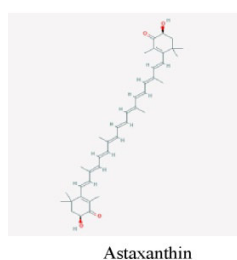
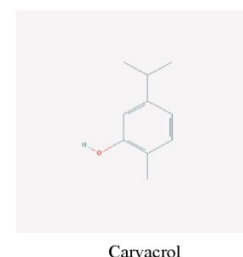
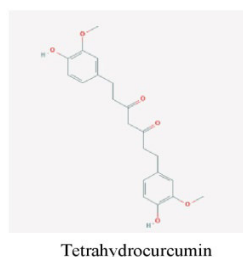
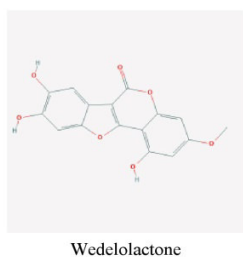
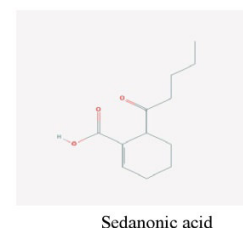
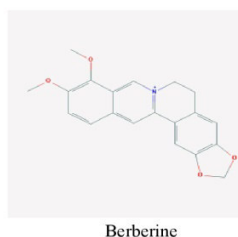
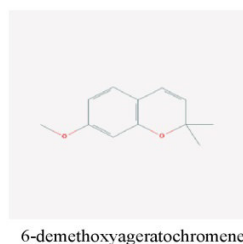
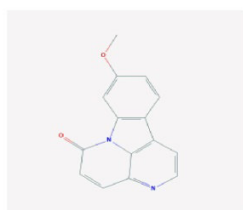


Fig 3. Showing the Treatment strategies of Asthma



AERVALANTA LINN

Aervalanta is a prostrate typical herbaceous weed which is identified by tiny woolly flowers in its white axillary bunches. It belongs from Amaranthaceae

Family. It contains phenolic compounds, saponins, flavonoids, tannins and phytosterols as major phytochemical groups. The extract 2, 2-diphenyl-1-picrylhydrazyl possess high amount of radical scavenging activity which can be beneficial for asthma treatment. *A. lanata* stem possesses high antioxidant

activity and can be used for the development of natural and safe antioxidant compounds(32).

Scientific Name of herb	Common name	Part of herb	Extract used	Asthmatic Model involved	Route of administration	Dose concentration	Mechanism of action	Property	Reference
<i>Allium sativum</i>	Garlic	Oil	Diallyl sulphide (DADS)	Ovalbumin induced asthmatic model	Oral	30 mg/kg/day for 3 days	levels of Reactive oxygen species (ROS) in Broncho-alveolar lavage fluid (BALF) is decreased	Antioxidant	(Shin et al., 2013)
<i>Allium sativum</i>	Garlic	Oil	Diallyl sulphide (DADS)	Murine RAW264.7 macrophage cell	In-vitro	62.5 to 500 ng/mL for 1 hour	Upregulation of HO-1 expression and also activates Nrf-2	Antioxidant	(Shin et al., 2013)
<i>Artemisia annua</i>	sweet wormwood	----	Artesunate	Ovalbumin induced asthmatic model	Intra-peritoneal injection	30 mg/kg/day	Suppression of prooxidants and restoration of antioxidant expression by activation of Nrf-2	Antioxidant	(Ho et al., 2012)
<i>Anchomanes difformis</i>	Blume	Leaf	Aqueous extract	Ovalbumin sensitized guinea pigs group	Oral	100 to 400 mg/kg	Radical scavenging activity	Antioxidant	(Oghale and Idu, 2016)
<i>Saururus chinensis</i>	Asian lizard tail	aerial part	Subfraction 4 (SCF4) of the ethanol extract's n-hexane layer	BALB/c mice-derived RAW264.7 cells	In-vitro	5 to 50 µg/mL for 2 hours	Upregulated the HO-1 expression	Antioxidant	(Meng et al., 2016)
<i>Saururus chinensis</i>	Asian lizard tail	root	Saucerneol D	Ovalbumin induced BALB/c mice asthmatic model	Oral	20 to 40 mg/kg/day for 3 days	Upregulated the HO-1 expression	Antioxidant	(Meng et al., 2016)
<i>Saururus chinensis</i>	Asian lizard tail	aerial part	Sauchinone	BALB/c mice-derived RAW264.7 cells	In-vitro	2.5 , 5 to 10µg /mL for 2 hours	Upregulated the HO-1 expression	Antioxidant	(Min et al., 2009)
<i>Mentha</i>	peppermint	aerial part	ethanol extract (70%)	Ovalbumin induced BALB/c mice asthmatic model	Oral	100 mg/kg/day for 6 days	Inhibit the increase of IgE, IL-4, and IL-5 in BALF and lung tissue and Reduces the levels of oxidative stress in BALF	Antioxidant	(M. Y. Lee et al., 2011)
<i>Petasites japonicus</i>	Japanese sweet coltsfoot	Leaf	ethanol extract (80%)	Ovalbumin induced BALB/c mice asthmatic model	Oral	500 mg/kg/day for 4 weeks	Reduces the levels of oxidative stress in BALF	Antioxidant	(J. S. Lee et al., 2011)
<i>Phytolacca esculenta</i>	Indian pokeweed	----	Esculentoside A (EsA)	Ovalbumin induced BALB/c mice asthmatic model	Intra-peritoneal injection	15 mg/kg/day for 4 days	Reduces the levels of oxidative stress in BALF	Antioxidant	(Ci et al., 2015)
<i>Phytolacca esculenta</i>	Indian pokeweed	----	Esculentoside A (EsA)	A549 alveolar epithelial human cells	In-vitro	10 to 20 mg/L for 6 hours	Upregulation of HO-1 expression and also activates Nrf-2	Antioxidant	(Ci et al., 2015)
<i>Soshiho-tang (SST)</i>	Sho-saikoto	-----	Aqueous extract	Ovalbumin induced BALB/c mice asthmatic model	Oral	100 to 200 mg/kg/day for 6 days	Upregulated the HO-1 expression	Antioxidant	(Jeon et al., 2015)

Table 1.Evidences, Clinical trials and Researches on the natural herbs for their antioxidant activity on various asthmatic models which showed the potential antioxidant activity and can be beneficial for the treatment of asthma.

AGERATUM CONYZOIDES

Ageratum conyzoides is an annual branching herb belongs to the family Asteraceae (Compositae).The different extracts N-hexane, ethyl acetate, and ethanolic extracts of from its stems and flowers exhibit antioxidant activity. The stem and flowers of *Ageratum conyzoides* species could be a potential choice for the

development of an alternative therapy to inhibit free radicals-induced oxidative stress in asthma and oxidative stress associated diseases(33).

ARGEMONE MEXICANA

Argemonemexicana is an extremely hardy pioneer herb belongs to the family Papaveraceae. It is resistant

of drought and poor soil and has bright yellow latex. The stem contains methanolic extract which has been reported to possess strong antioxidant activity. The antioxidant activity may be due to the total phenolic and flavonoid content in the methanol extract that shows the presence of alkaloids, flavonoids, terpenoids, saponins, tannins which could be responsible for the antioxidant activities(34).

CNIDIUMOFFICINALE

Cnidiumofficinale is a perennial herb which belongs to the family Umbelliferae. The dried rhizomes of *Cnidiumofficinale* contains methanolic extracts of butylphthalide, sedanonic acid, cnidilide, ligustilide, neocnidilide, and several other compounds which possess the free radical scavenging antioxidant properties(35).

ECLIPTAALBA LINN

Ecliptaalba is a prostrate annual herbaceous plant which belongs to the family Asteraceae. It contains Wedelolactone, Demethylwedelolactone and Oroboside which possess potential anti-asthmatic activity where it's alcoholic extract exhibits antioxidant activity(36,37).

CURCUMA LONGA LINN

Curcumin is extracted from dried rhizome of *curcuma longa* Linn belonging to the family Zingiberacea. Curcumin and tetrahydrocurcumin exhibits anti-inflammatory and antioxidant property. As it has some beneficial effect in asthma treatment, it could be effective in the development of natural antioxidants(38).

ALLIUM SATIVUM

Allium sativum is perennial herb having bulbs with several clove enclosed in a white or pink membranous envelope. It is obtain from ripe bulb of *Allium sativum* belonging to the family Liliaceae. It contains allin, volatile oil, essential oil, fatty oils and mucilage. Essential oil contains diallyldisulfide, diallyltrisulfide, allicin act as scavenging property of free radicals and antioxidant. *Allium sativum* could be a potential choice for the development of an alternative to inhibit free radicals-induced oxidative stress in asthma(39).

COLEUS AROMATICUS

The herbs *coleus aromaticus* is a semi-succulent perennial plant belonging to the family Lamiaceae.

Coleus aromaticus contains essential oil rich in carvacrol and thymol responsible for flavour. It also contains chlorogenic acid, rosamarinic acid and caffeic acid as phenolic compounds which is responsible for free radicals scavenging antioxidant properties(40).

PIPER NIGRUM LINN

Piper nigrum is also known as sack piper consisting of dried unripe fruits from family Piperaceae. *Piper nigrum* Linn contains essential oils, steroids, alkaloids, flavonoids and phenolics as main chemical constituents. Phenolics and flavonoids extract shows antioxidant property. Ethanolic extract of *piper nigrum* was evaluated by 1,1-diphenyl-2-picrylhydrazyl assay. Free radicals scavenging and reducing power assay showed better results for Ethanolic extracts, while nitric oxide scavenging activity showed better for water extracts(41).

CALOTROPISGIGANTEA

Calotropisgigantea is the large shrub has cluster of waxy flower that are either white or lavender in colour from family Apocynaceae. *Calotropisgigantea* contains active chemical includes cardenolides, steroids, tannins, glycosides, phenols, flavoids, terpenoids, saponins and alkaloids. The chloroform extracts of *calotropisgigantea* of leaf and flower showed free radicals scavenging and antioxidant activities. *Swarnabhasma* an Ayurvedic preparation contain *calotropis gigantea* R.Br is used to treat bronchial asthma(42).

EUGENIA CARYOPHYLLUS

Eugenia caryophyllus is aromatic flower bud belonging to the family Myrtaceae. The essential oil extracted from the dried flower bud of *Eugenia caryophyllus* has main chemical constituents such as carvacrol, thymol, eugenol and cinnamaldehydes. Essential oil is responsible for its many medicinal properties like anti-inflammatory, antioxidant and antifungal etc. The antioxidant activity of methanol, acetone and chloroform extracts was evaluated by 1,1-diphenyl-2-picrylhydrazyl(DPPH) assay and the methanolic extract showed better radicals scavenging activity, hence it could be helpful in asthma treatment(43,44).

SOLANUMXANTHOCARPUM

Solanumxanthocarpum is perennial herbs. The whole plant parts of *solanumxanthocarpum* are used for medicinal purposes. It contains different extracts of tannins, flavonoids, terpenoids, alkaloids, saponins and steroids. The Ethanolic extract of *solanumxanthocarpum*

showed anti-inflammatory and radicals scavenging properties(45).

CONCLUSION

Asthma is a chronic airway disease which cannot be cured permanently with anti-asthmatic drugs. Anti-asthmatic drugs have various side effects on the vital organs of the body. Thus, there is necessary to treat the asthma with some natural herbs. The above mentioned Natural herbs having the potential antioxidant activity which exhibits potential role in the treatment of the Asthma.

HIGHLIGHTS

- Therapeutic treatment of asthma by suppressing the ROS production.
- Natural antioxidants are the oldest class of herbal drugs.

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- Natural antioxidants or oxidative stress inhibitors are emerging as a new therapeutic approach to manage asthma.
- Current available treatments for asthma such as Bronchodilators, Anti-inflammatory drugs have more side effects or adverse effects on vital organs.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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