Asian Journal of Applied Sciences (ISSN: 2321 – 0893)
Volume 01– Issue 04, October 2013

Oxidants and Antioxidants Status in Bronchial Asthma

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ABSTRACT—*Asthma is a respiratory disease that is common in Saudi Arabia and characterized by sporadic occurrence of bridge, chronic inflammation of the airways involving recurrent airflow obstruction and increased responsiveness to a variety of stimuli. Recent research suggests that airway inflammation is the most cause of the episodes of airflow limitation in asthma which lead to increase oxidative stress. This imbalance between oxidant and antioxidant has been increasingly recognized as a big factor contributing to the chronic inflammation. Therefore, the aim of this review is to describe the role and origin of the oxidant-antioxidant disturbances that participate in the pathophysiology of airway inflammatory diseases. We have updated existing information about effects (effects of oxidants in the lung) of reactive oxygen and nitrogen species in the lung including the mechanisms of their damaging effect. The first section focuses entirely on the symptoms, the types and stages of bronchial asthma. The second section investigates the role of oxidant-antioxidant imbalance in disease progression of asthma. The last section outlines the therapeutic value of available antioxidant herbals and vitamins that could improve oxidant-antioxidant balance in bronchial asthma disease.*

Keywords— Bronchial asthma, antioxidants, vitamins, inflammation.

1. INTRODUCTION

Asthma continues to cause considerable disability in children and adults throughout the world. Saudi Arabia is a country that has developed rapidly over the last three decades as a consequence of the importance of oil to the world's economy. The prevalence of asthma and asthma related symptoms is high among 16- to 18-year-old adolescents in Saudi Arabia, and the symptoms are more common in boys than in girls. Asthma and asthma related symptoms are also associated with a high rate of rhinitis symptoms and hay fever. The high prevalence of asthma in Saudi Arabia is within the reported prevalence ranges from many other parts of the world [1].

Most people in the population live in large modern cities, in a style far removed from that of their forefathers. Nevertheless, in country districts and villages a much more traditional lifestyle is maintained. Previous studies have suggested that doctor-diagnosed asthma occurs in 4–17% of urban Saudi [2].

1.1 Bronchial Asthma

Bronchial Asthma is a chronic disease, which is the result of the inflammatory condition in the bronchi. The body needs oxygen from the air in order for cells to do their work. When the breathing in air containing oxygen enters through the mouth or nose, and descends through the windpipe to tubes called the bronchi. The bronchi branch out into each lung where oxygen is picked up by passing blood. The blood then carries the oxygen throughout the body [3]. For a variety of reasons, inflammation occurs in the airways. In which inflammation of the airways are tubes that carry air in and out of the lungs cause air flow into and out of the lungs to be restricted. The muscles of the bronchial tree become tight and the lining of the air passages swells, reducing air flow and producing the characteristic wheezing sound. This is known as an asthma attack (Figure 1). During an asthma attack smooth muscles located in the bronchioles of the lung constrict and decrease the flow of air in the airways [4].

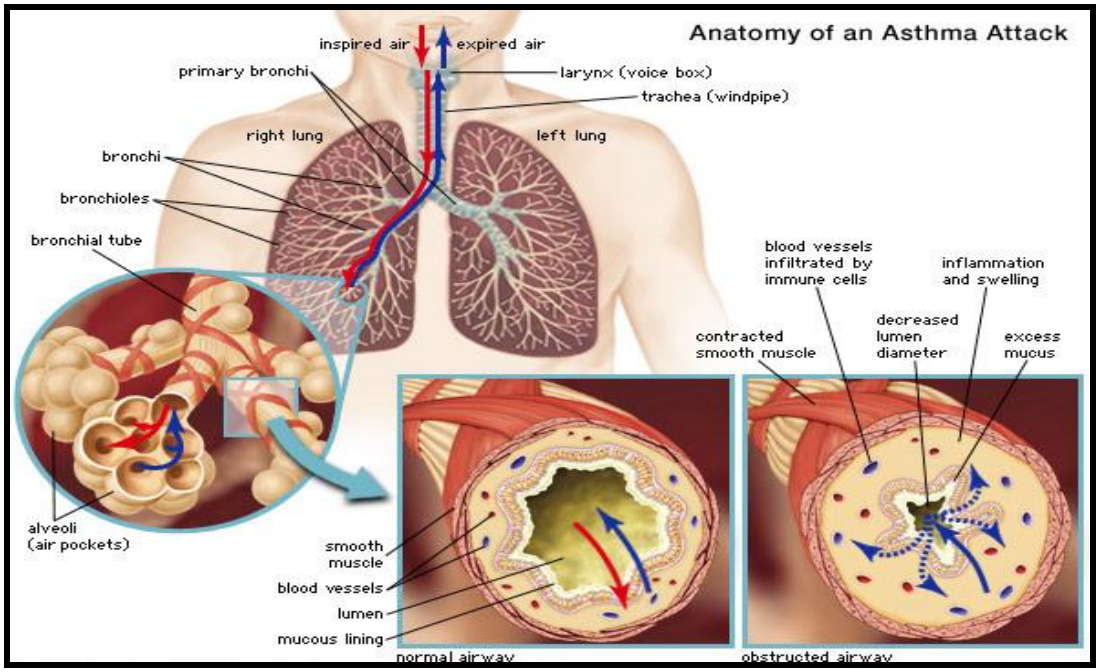

Figure 1: A comparison of normal bronchioles and those of an asthma sufferer [5].

The amount of air flow can be decreased by inflammation or excess mucus further secretion. But some asthmatics can produce an overabundance of mucus, and the bronchi can become chronically inflamed, resulting in blocked airways and asthmatic symptoms **[6]**.

1.2 Asthma symptoms:

The following are the four major recognized asthma symptoms:

1-Shortness of breath, especially with exertion or at night

2-Wheezing is a whistling or hissing sound when breathing out

3-Coughing may be chronic, is usually worse at night and early morning, and may occur after exercise or when exposed to cold, dry air.

4-Chest tightness may occur with or without the above symptoms.

Not every person with asthma has the same symptoms in the same way. You might not have all of these symptoms, or you might have different symptoms at different times. The symptoms might also vary from one asthma episode to the next, being mild during one asthma episode and severe during another **[7].**

1.3 Severity of disease:

1.3.1 Stage 1:

The first stage of asthma is called "intermittent" because symptoms such as wheezing come. This stage is defined by symptoms occurring no more than two times per week and nighttime awakening occurring no more than twice per month. There is no interference with normal activity and normal lung function. Inhaler use is less than three days per week. Suggested initial treatment is with a short-acting inhaler such as albuterol as needed. Albuterol is a "beta agonist," a class of drugs that dilates the airways when inhaled **[8].**

1.3.2 Stage 2:

Stage 2 asthma is called "mild persistent." It is characterized by symptoms that occur greater than two days per week but not daily, and three to four nighttime awakenings each month. Inhaler use may be greater than two days per week, although not on a daily basis, and not more than one time per day. There may be minor limitation in normal activity. Treatment includes a short-acting beta agonist rescue inhaler as in the first stage and also adds a long-acting medication, usually inhaled steroids to suppress the overactive immune response in the lungs **[9].**

1.3.3. Stage 3:

Stage 3 asthma is called "moderate persistent." In this stage, the asthmatic will have daily symptoms of asthma, nighttime awakenings more than once per week, daily need of short-acting rescue medication, some limitation in normal activity and decreased lung function. Treatment at this stage is either a low-dose inhaled steroid or a long-acting beta

agonist. Alternatively medium-dose inhaled steroids may be used in addition to a short-acting beta agonist such as albuternol **[10].**

1.3.4 Stage 4:

Stage 4 asthma is known as "severe persistent asthma." Symptoms occur throughout the day, and nighttime awakening may occur every night. The asthma attacks severely limit normal activity. A short-acting rescue drug may be required several times per day. Lung function is noticeably reduced. Treatment is high-dose inhaled steroids and a long-acting beta agonist. If that does not control the symptoms, oral steroids are added. Alternative drugs are available at all stages, as are allergy shots if the asthma is a result of general allergies **[10].**

1.4. Types of disease:

Asthma is a growing worldwide problem. Asthma is classified in various ways. Traditionally, doctors have categorized asthma into two general groups, Extrinsic (allergic) asthma and Intrinsic (non-allergic) asthma, depending upon the types of stimuli that flare up these attacks **[11]**.

1.4.1 Extrinsic (allergic) asthma:

More prevalent in the younger age group, extrinsic asthma is caused by the immune system's response to inhaled allergens such as pollen, animal dander or dust mite particles. People with allergic asthma frequently have other allergy-related problems such as hay fever, rhinitis, skin rashes, and eczema. Extrinsic asthma responds quite well to the use of inhaled steroids as these suppress the immune system **[12].**

1.4.2. Intrinsic (non-allergic) asthma:

Intrinsic asthma is caused by anything except an allergy. It may be caused by an infection, stress, laughter, exercise, cold air, food preservatives or a host of other factors. Treatment of intrinsic asthma is not easy as it may not be known what triggers the asthma in the first place and therefore avoiding triggers can be impossible **[12].**

1.4.3 Mixed asthma:

Mixed asthma is a mixture of intrinsic and extrinsic asthma. Not only do people react to some allergies but their asthma is also triggered by other factors. It is common for someone with an extrinsic form of asthma to experience attacks when he has a chest infection an intrinsic trigger **[13].**

1.5.Triggers of disease:

Figure 2: Some Triggers of Asthma Attack **[14].**

The lung is susceptible to oxidative injury by virtue of myriads of reactive forms of oxygen species and free radicals. The generation of reactive oxygen species in the lungs is enhanced after exposure to numerous exogenous chemical and physical agents, which include mineral dusts, ozone, nitrogen oxides, ultraviolet and ionizing radiation and tobacco smoke. Oxidant stress can lead to peroxidation of membrane lipids, depletion of nicotinamide nucleotides, rises in intracellular calcium ions, cytoskeleton disruption and DNA damage **[4].**

1.5.1 Oxidative stress in asthma:

Increased generation of oxidants has been reported in asthma [15] which aggravated airway inflammation by inducing diverse pro-inflammatory mediators including macrophages, Neutrophiles and Eosinophiles. Several studies have suggested that oxidative stress is caused by overproduction of different free radicals or by an insufficient antioxidant defense system in asthma which is induced by inflammatory cells. The oxidant–antioxidant status was

investigated in blood because it is an available source and also considered as an important pool of antioxidant defenses in the body [15].

Rahman *et al*. reported that the plasma MDA level was increased in asthmatic patients as well as in patients with asthma exacerbation as compared to stable asthma [16]. Similarly, another study entails that MDA level in bronchoalveolar ravage (BAL) fluid was higher in mild to moderate asthmatic patients. Moreover, protein carbonyl content was also significantly higher in asthmatic patients because most of the amino acids can be oxidized by ROS [17]. Peroxynitrite anion is a strong oxidant that mediates not only the oxidation of both non-protein and protein sulfhydryls but also induces lipid peroxidation**.**

The alterations in antioxidant defenses may involve either an increase or a decrease depending on the changes occurring due to a defense response. Glutathione peroxidase (GPx) plays a significant role in peroxyl scavenging mechanism and maintaining functional integration of the cell membrane. Lower GPx level in asthmatic patients can be related to the clinical presentation of the disease and it indicates the presence of H_2O_2 in breath condensate of exhaled air which is elevated in asthmatics patients. Selenium is an essential component of GPx and it indirectly helps in protecting cells against damage caused by free radicals. This might arise as a result of deficiency of selenium or inactivation caused by $OH\cdot$ and $O_2\cdot$. A number of studies have been done to measure the selenium deficiency in asthma through the antioxidant effects of GPx and it has been found that plasma levels of selenium was significantly lower in asthmatic patients [18]**.** Glutathione peroxidase (GPx) is essential for removing toxic lipid oxidation products and H_2O_2, which are continuously generated as a result of sequestration and infiltration of inflammatory leukocytes in the lung. Low SOD activity together with low GPx activity in asthmatic patients proved the contribution of oxidative stress in the etiology of asthma. It was reported that the glutathione system is altered in lung inflammatory conditions such as asthma and many reports have shown that alterations in glutathione level have been found in asthmatic airways.

Mak *et al*. have also reported that the total glutathione level increased in erythrocytes of asthmatic individuals [19]. There have been several reports on the decreased antioxidant capacity in asthmatic patients with intense oxidative load.

Al-Abdulla *et al*. also reported that the mean serum level of MDA was significantly raised with increasing severity of asthmatic attack among patients grouped according to degree of severity [20]**.** Previously, Kanazawa *et al*. have also found differences related to severity in patients with acute exacerbations. The association between asthma severity and anthropometric measurement demonstrates that age and gender was unrelated to disease severity similar to our findings**.** Some workers also demonstrated that the superoxide anion release was greater in patients with exacerbation of their disease and it was also inversely correlated with FEV1 [21].

1.6. Therapy of asthma:

1.6.1. Vitamin therapy

The relationship between lung function and the reported frequency of consumption of winter fresh fruit and fruit juice was studied, among 1502 life-long non-smokers and 1357 current smokers aged 18-69 years. The mean (FEV_1) among those who never drank fruit juice and ate fresh fruit less than once a week in winter, was lower than for other subjects after adjusting for age, sex, height, smoking, region of residence and socio-economic group by about 80 ml. More specifically to asthma, demonstration that in adults the lowest intakes of vitamin C were associated with a more than five-fold increased risk of bronchial reactivity, has provided evidence that antioxidants may have a modulatory effect in asthma, This would be consistent with the hypothesis**,** that the observed reduction in antioxidant intake in the (U.K). Diet over the last 25 years has been a factor in the increase in the prevalence of asthma over the same period. This concept was taken a step further by the MORGEN study, which investigated the relationships between the antioxidant vitamins C, E and b-carotene and the presence of respiratory symptoms and level of lung function. In this large study (6555 adults) a high intake of vitamin C or b-carotene was associated with higher lung function but did not appear to protect against respiratory symptoms **[15].**

In experimental models oxidants induce many features of asthma by inducing release of proinflammatory mediators, including cytokines, chemokines, and eicosanoid metabolites **)**

Oxidant stress also activates gene expression of 2 pivotal inflammatory regulators, nuclear factor (kB) and activator protein 1 **[23].**

There is an obvious disparity between the consistent beneficial associations reported from epidemiologic studies of antioxidants and the generally disappointing results of supplementation studies in established asthma. One postulated reason for the ineffectiveness of intervention is that antioxidant supplementation is only effective when there is an antioxidant deficiency, but subgroup analyses of supplementation studies make this unlikely **[18].**

The criticism that supplementation studies have been of short duration has been partly addressed by several recent well designed studies **[18].**

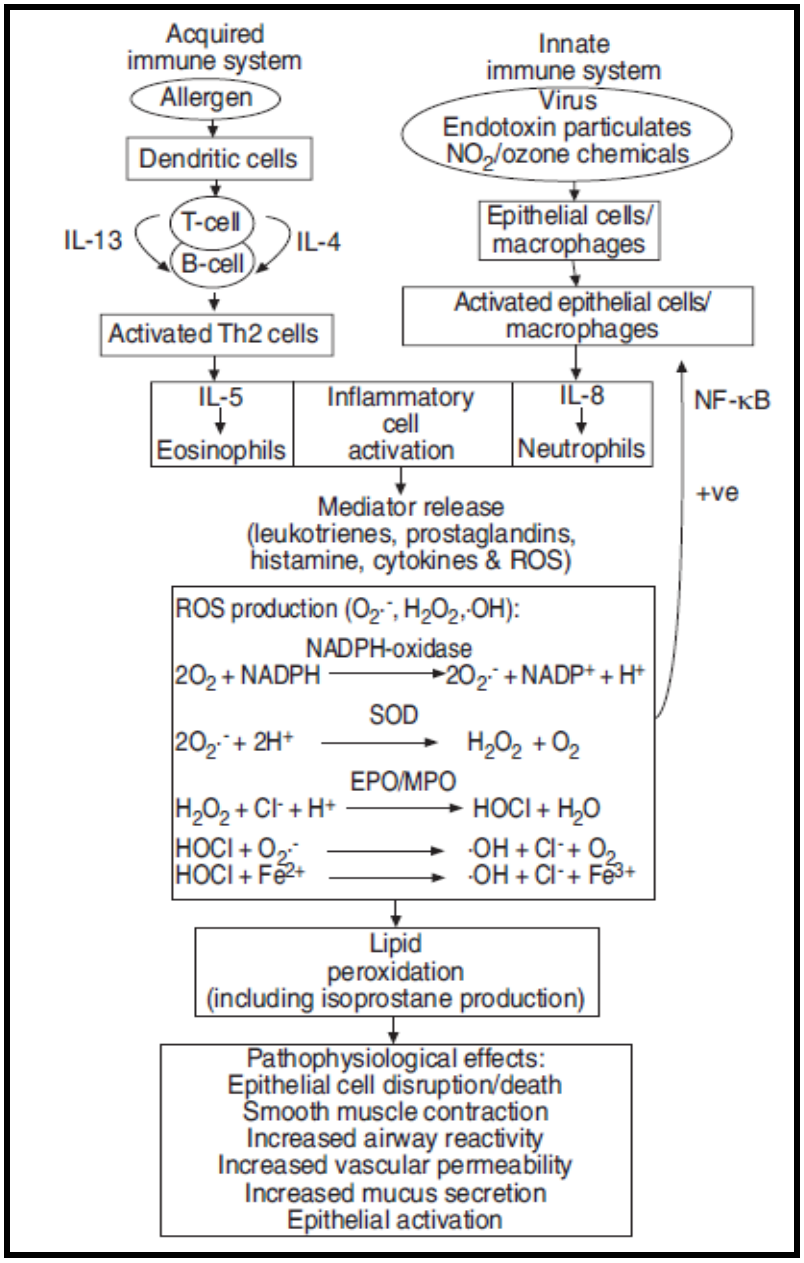

Figure 3: Mechanisms in asthma **[22].**

Thus the epidemiologic associations with adult antioxidant status might be an indirect association with childhood diet. Furthermore, if antioxidants exert their beneficial influences early in life, intervention during adulthood would be highly unlikely to be effective; there is thus a need for intervention studies during early childhood. As suggested in our original hypothesis, maternal dietary antioxidant intake during pregnancy might also be particularly important. In fetal rat models in vivo and in vitro antioxidant supplementation corrects hypoplastic lung growth**.**

It therefore seems plausible that reduced maternal dietary antioxidant intake during pregnancy might be associated with the impaired lung development that is associated with wheeze, asthma, and reduced lung function later in life. This model predicts that increased fetal oxidant stress should be associated with reduced lung function and asthma. Such associations have been demonstrated with maternal cigarette smoking (an oxidant stress) during pregnancy **[24].**

The antioxidant properties of vitamin E, selenium, and fruit fail to explain associations with (IgE) and atopic sensitization. Of particular relevance to these associations is the recognition that some antioxidants have nonantioxidant properties, and it has even been suggested that vitamin E acts principally as a nonantioxidant **[25].**

The nonantioxidant properties of vitamin E, selenium, and flavonoids pertinent to asthma and atopic disease are those exerted on table header (TH) cells that play pivotal roles in the initiation and perpetuation of the chronic inflammatory process associated with asthma and atopic disease. In animal models and human subjects, vitamin E, selenium, and quercetin (a flavonoid) have been reported to promote TH1 differentiation by increasing TH1 cytokine secretion, inhibiting TH2 cytokine secretion, or both **[26].**

Human TH cells supplemented with physiologic quantities of vitamin E demonstrate reduced IL-4 secretion in a dose dependent manner**.** Vitamin E appears to act by downregulating IL-4 mRNA expression in human TH cells by inhibiting binding of the transcription factors nuclear factor kB and activator protein 1 to the IL-4 promoter region**.** Immunologic considerations of TH cell differentiation suggest that antioxidants should probably exert their most potent influences on TH cell polarization during the earliest exposures of the immune system to allergens (i.e., fetal and early life [0-5 years]). It is possible that reduced antioxidant status during fetal and early life increases the likelihood that the initial critical encounters between TH cells and allergens result in TH2-biased responses. Reduced dietary intake of vitamin E, selenium, flavonoids, and fruit by mothers during pregnancy and by young children has the potential to predispose toward asthma not only by affecting airway development but also by promoting TH2 differentiation and atopic sensitization. This model is consistent with the general ineffectiveness of intervention studies in adults and, because of the concordance between infant and adult diet, is also consistent with the results of epidemiologic studies of children and adults. At the present time, there are few studies investigating the effects of maternal diet during pregnancy and early (0-5 years) childhood diet. Umbilical cord selenium concentrations have been reported to be negatively associated with persistent wheeze in children up to 3½ years.48 We have found maternal dietary vitamin E intake during pregnancy to be negatively associated with cord blood mononuclear cell responses and, in the second year of life, with ‘‘wheeze in the absence of a cold ‘and with eczema in children born to atopic mothers **[27].**

1.6.2. Fruit Therapy:

Potential advantages of investigating dietary fruit are that intake tends to be easily remembered, portion size is obvious, and fruits contain many potentially important antioxidants that cannot be currently quantified. Furthermore, by demonstrating associations with fruit, the nature of potential intervention studies and public health measures are obvious and more acceptable. Beneficial associations have been reported between fruit intake and asthma [28]**.**
Change in ventilatory function between the 2 surveys was related to changes in dietary fruit intake rather than the mean fruit intake over the 7-year interval. The authors suggested that the cross-sectional effects of fruit consumption on ventilatory function appeared to be reversible and not progressive, with consistently low levels of fruit intake appearing not to increase the rate of ventilator decrease. The Caerphilly heart disease study demonstrated a positive association between apple consumption and (FEV_1) in adults **[29]**.

It was suggested that the beneficial effects of apples could be a consequence of certain types of flavonoids (e.g., anthocyanins and phloridzin) because of beneficial associations with red wine consumption and lack of associations with carotene and vitamins C and E intakes [30].

1.6.3 Pharmacotherapy:

The pharmacological management of asthma depends upon frequency and severity of patient’s symptoms. Infrequent attacks can be managed by treating each attack when it occurs, but with more frequent attacks preventive therapy needs to be used. The following categories of drugs are used in asthma:

I- ***Bronchodilators:***

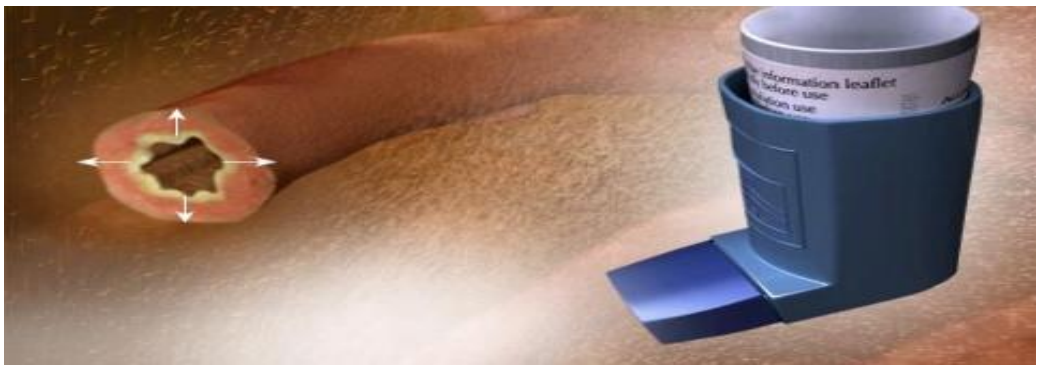

Figure 4: Bronchodilators [31].

Bronchodilators promptly reverse airway obstruction in asthmatics. This action believed to be mediated by a direct effect on airway smooth muscle. However, additional pharmacologic effects on the other airway cells (such as capillary endothelium to reduce microvascular leakage and mast cells to reduce release of bronchoconstrictor mediators)

may contribute to the overall reduction in airway narrowing. Only three types of bronchodilators are in current clinical use: β-adrenergic agonists, methylxanthines, and anticholinergics **[32].**

The inhaled route of administration is preferable to the oral route because adverse effects caused by systemic action of the drug are less and also because this route may be more effective. The inhaled drug reaches surface cells (e.g., mast cells or epithelial cells), which are less accessible to the orally administered drug. e.g., (Metaproterenol, terbutaline, albuternol, formopterol, bitolterol, salmeterol, and pirbuterol are the classic examples of selective β2-adrenergic agonists **[32]**.

1. ***B*-adrenergic agonists**

B- Agonists improve respiratory symptoms and exercise tolerance despite the small improvement in spirometric measurements. The long acting β agonists decrease infection exacerbations as an additional potential benefit. Salmeterol has been shown to reduce adherence of bacteria such as H. influenza to airway epithelial cells **[32].**

β2 selective agents cause tachycardia and palpitation by reflex cardiac stimulation secondary to peripheral vasodilatation. Muscle tremor is caused by stimulation of β2 adrenergic receptors in skeletal muscle and is the primary adverse effect of albuterol and bitolterol. Transient hypokalemia may be induced by high dose of these agents **[32]**.

2- Anticholinergics:

Datura plants contain the muscarinic antagonist and were smoked for relief of asthma centuries ago. Now a days, atropine and ipratropium bromide are the most commonly available anticholinergics **[32]**.

Antimuscarinic agents specifically antagonize muscarinic receptors. They inhibit reflex cholinergic bronchoconstrictor and do not significantly block the direct effects of inflammatory mediators such as histamine and leukotrienes on bronchial smooth muscle and vessels. When given by inhalation, anticholinergics produce bronchodilator by competitively inhibiting cholinergic receptors in bronchial 78 R.G. Mali, A.S. Dhakesmooth muscle. This activity blocks acetylcholine with the net effect being a reduction in cyclic guanosine monophosphate (cGMP) that normally acts to constrict bronchial smooth muscle. Anticholinergic drugs usually are less effective as bronchodilators in asthmatic subjects than β adrenergic agonists. Nevertheless, they may have an additive effect with β adrenergic agonists. Ipratropium has a slower onset of action and a more prolonged bronchodilator effect compared use on an as needed basis for immediate relief of bronchospasm **[32]**.

The lack of systemic absorption of ipratropium greatly diminishes the anticholinergic side effects such as blurred vision, urinary retention, nausea, and tachycardia associated with atropine. A significant unwanted effect of inhaled ipratropium bromide is dryness of mouth and throat, bitter taste, cough and nausea. Nebulized ipratropium bromide may precipitate glaucoma in elderly patients because of its direct mydriatic effect on the eye. During sleep, ipratropium also has been shown to improve arterial oxygen saturation and sleep quality. Tiotropium bromide is a long acting quaternary anticholinergic agent. Tiotropium in human lungs shows approximately 10 fold more potency than ipratropium and protects against cholinergic bronchoconstriction for greater than 24 h **[32]**.

3- Methylxanthines:

Methylxanthines such as theophylline are related to caffeine and have been used to treat asthma since 1930. Theophylline inhibits some functions of T lymphocytes, which may be relevant to control of chronic inflammation of the airway.

For nocturnal asthma, a single dose of slow release theophylline at bedtime often is effective. This has been demonstrated to reduce overnight declines in (FEV1) and morning respiratory symptoms. Taken alone it increases exercise tolerance without improving spirometric Tests **[32].**

II-Anti-inflammatory drugs:

Anti inflammatory drugs suppress the inflammatory response by inhibiting infiltration and activation of inflammatory cells as well as their synthesis or release of mediators or effects of inflammatory mediators themselves **[32]**.

1- *Corticosteroids*:

Since asthma is viewed as a chronic inflammatory disease and inhaled corticosteroids are known to have low toxicity, they may be considered as first line therapy. Prednisolone and dexamethasone were effective when they were given systematically to treat asthma but they had no anti-asthmatic activity when they were given by inhalation. Other corticosteroids e.g. beclomethasone dipropionate (BDP), betamethasone and budesonide, were effective in treating asthma when given by inhalation. The antiasthmatic potency of an inhaled steroid is approximately proportional to its potency as an anti-inflammatory agent **[32]**.

Corticosteroids inhibit the release of arachidonic acid metabolites and platelet activating factor (PAF) from lungs and macrophages by enhancing the production of proteins called lipocortin. Thereby they inhibit the formation of prostaglandins and leukotrienes. These effects occur because of ability of steroid—receptor complex to be transported to the nucleus, where it initiates Deoxyribonucleic acid. (DNA) transcription of specific Messenger Ribonucleic acid (mRNAs). Corticosteroids potentially inhibit the accumulation of Neutrophiles, inhibit secretion of human pulmonary macrophages of leukotrienes and prostaglandin dins, inhibit formation of interleukins (ILs) such as IL-1, IL-2, IL-3 and IL-5, inhibit degranulation and adherence of Eosinophiles, reduce number of circulating T lymphocytes and formation of an Immunoglobulin E.(IgE) binding suppressive factor **[32]**.

Methylprednisolone is given intravenously to patients with severe acute asthma. Inhaled steroids have no proven value in the management of acute asthma. Patients with chronic bronchitis occasionally respond to steroids, possibly because some have an element of undiagnosed asthma **[32]**.

Corticosteroids inhibit release of (ACTH) and secretion of cortisol by a negative feedback effect on the pituitary gland. Adverse effects of corticosteroids include fluid retention, increased cell mass, increased appetite, weight gain, osteoporosis, capillary fragility, hypertension, peptic ulceration, diabetes, cataract, and psychosis.

2- Anti-leukotrienes:

Leukotrienes possess potent pro-inflammatory actions resulting in increased vascular permeability, mucus secretion and bronchial hyperresponsiveness. They are derived from the 5-lipoxygenase pathways in mast cells, Eosinophiles and macrophages. Anti-leukotrienes improve lung function and diminish symptoms, exacerbation rate and the need for rescue bronchodilator. These are drugs of choice in case of aspirin induced asthma, in which patients have high leukotrienes predominantly (LTE4) levels in urine and nasal secretions and even higher after taking aspirin**,** Leukotrienes modifiers are drugs that modify the response of these mediators of inflammation by one of the four ways **[33].**

a) Cysteinyl LT receptor inhibitors

(C-LTs) promote Eosinophil influx, bronchospasm and mucus hypersecretion, all are considered hallmarks of asthma. (C-LT) receptor inhibitors antagonize or inhibit leukotrienes predominantly (LTD_4). These agents inhibit phospholipases, prostaglandins, leukotrienes, and (IL)-1 synthesis. Probilukast and Iralukast belong to this class **[34].**

b) 5-lipoxygenase inhibitors

They prevent the formation of leukotrienes by blocking a 5-lipoxygenase pathway in their synthesis. Zileuton, ZD-2138, ABt-761 belongs to this class.

c) 5-lipoxygenase activating protein (FLAP) inhibitors MK-0591 and MK-886 attenuated the early and late asthmatic response following antigen challenge but not the attendant increase in airway responsiveness to spasmogens **[35].**

d) Leukotrienes receptor antagonists

Zafirlukast has been demonstrated to attenuate the acute airway obstructive response to allergen and exercise challenge and to improve chronic asthma control both objectively (FEV1), nocturnal awakenings, β-agonist use and subjectively **[32]**.

Montelukast has been shown to block the early and late response to allergen challenge following single dosing, to improve (FEV1) in both children (6–14 years) and adults and to protect against the development of exercise induced bronchoconstrictor in both children and adults. Tolerance to the bronchoprotective effects of montelukast in attenuating exercise-induced bronchospasm does not develop following at least 12 weeks of therapy.
Iralukast increases (FEV1) within 1 h of dosing, improves patient summary symptom and nighttime asthma scores and reduces the use of rescue bronchodilators. In patients with moderate persistent asthma, it prevents exacerbations of asthma during reduction of high dose inhaled corticosteroids therapy **[36]**.

III- Mediator release inhibitors:

Cromolyn Sodium (Sodium cromoglycate) is a derivative of khellin, an Egyptian herbal remedy. Cromolyn inhibited the release of mediators by allergen in passively sensitized animal and human lung preparations; Cromolyn was classified as mast cell stabilizer. Cromolyn has variable inhibitory actions on other inflammatory cells including macrophages and Eosinophiles that may participate in allergic inflammation. In vivo Cromolyn can block both the early response that may be mediated by mast cells to allergens and the late response and bronchial hyper responsiveness; Cromolyn Sodium is used for prophylactic treatment and consequently needs to be taken regularly. It is the first choice anti- inflammatory drug for children because it has few adverse effects. Cromolyn sodium is classified as an antiallergic drug because it appears to have a specific effect on allergy based inflammation. Several other drugs also may be included in this category [32].

Nedocromil sodium is a new drug used for prophylaxis. It has a similar pharmacologic profile of activity to Cromolyn, is more potent in various tests, and may have a longer duration of action. Ketotifen also is described as a drug to be used for prophylaxis against asthma **[32]**.

1.6.4. Herbal therapy:-

Some herbal alternatives employed in asthma are proven to provide symptomatic relief and assist in the inhibition of disease development as well. These herbs therefore have multifaceted roles to play in the management of asthma suggesting different sites of action within the body. Herbs that have shown some promise in treating asthma symptoms include:
Butterbur
Dried ivy
Ginkgo extract
Tylophora indica
French maritime pine bark extract (pycnogenol)
Indian frankincense (Boswellia serrata)
Choline
Blends of different types of herbs are commonly used in traditional Chinese, Indian and Japanese medicine. Certain combinations of herbs may be more effective than taking one herbal remedy on its own. More studies are needed before researchers can make a clear judgment about which complementary and alternative asthma therapies are likely to help. If you do decide to try any alternative treatment for asthma, talk to your doctor about it first — and don't stop prescribed medications. Some complementary and alternative treatments may be beneficial when used in combination with traditional medical treatment, but they aren't a substitute for prescribed medications and advice from your doctor [37].

2. CONCLUSIONS

Asthma is respiratory disease characterized by ongoing inflammation and accompanied by increased oxidative stress and subsequent lung injury. Prevalence of asthma has increased considerably throughout the world especially in developed countries. Excessive reactive oxygen species production in asthma leads to alteration in enzymatic and non nonenzymatic antioxidants leading to oxidant—antioxidant imbalance in airways. Oxidant—antioxidant imbalance leads to pathophysiological effects associated with asthma. Plant antioxidants have been demonstrated their anti-inflammatory effects through regulation of various inflammatory cells and mediators, and controlling roles in a wide range of signaling pathways. Natural biological compounds could be used in association with other available anti-inflammatory drugs,

allowing a reduction in costs and side effects. Future studies must search for more effective, powerful natural biological compounds should be continued.

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