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BETA-2-AGONISTS IN THE MANAGEMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Acc. to history, β-agonists, the cognate ligand of the 2 adrenoreceptor, have been used as bronchodilators for around 5,000 years, and they are still the first-line treatment for asthma and chronic obstructive pulmonary disease (COPD) today. The human 2-adrenergic receptor (2AR) is a member of the G protein-coupled receptor (GPCR) family and is a popular therapeutic target due to its major involvement in bronchodilation. The human β2-adrenoceptor is a 7-transmembrane receptor that is encoded by a gene on chromosome 5 and is found throughout the respiratory system. Intracellular signalling is significantly influenced by cyclic adenosine monophosphate and protein kinase after β2-adrenoceptor activation. Beta-2 adrenergic receptors are cell-surface receptors clinically taken advantage of in the management of bronchospasm as in patients with bronchial asthma and chronic obstructive pulmonary disease. Agonist or antagonistic medications are used to target these receptors. While there are no selective beta-2 antagonists, agonists used to stimulate receptors are either selective to the beta-2 subtype or nonselective, stimulating all beta subtypes, including beta-2. Long-acting β2- agonists (LABAs) should be used only when asthma symptoms persist in individuals who are already taking frequent inhaled corticosteroids, according to major asthma management guidelines (ICSs). b2-Adrenoceptor agonists cause fast bronchodilation and are used to treat asthma symptoms all over the world. Chronic obstructive pulmonary disease (COPD) is characterised by debilitating symptoms and gradual airflow limitation. Long-acting bronchodilators are the backbone of therapy for individuals with moderate-to-severe COPD; if symptoms worsen, recommendations advocate mixing bronchodilators from several classes to optimise efficacy.

Keywords: Bronchodilation, Corticosteroids, Inflammation, Muscle contraction, Neurotransmitter, Narrowing of airway, Chronic Obstructive Pulmonary Disease.

INTRODUCTION

The beta-2 adrenergic receptor (β2 adrenoreceptor), also known as ADRB2, is a cell membrane spanning beta-adrenergic receptor that binds epinephrine (adrenaline) [1-2], a hormone and neurotransmitter whose

signalling, via adenylate cyclase stimulation through trimeric Gs proteins, increased cAMP, and downstream L-type calcium channel interaction, mediates physiologic responses such as smooth muscle relaxation and bronchodilation [3-5]. Robert J. Lefkowitz [6] and Brian Kobilka [7] ,studied beta 2 adrenergic receptor as a model system which rewarded them the 2012 Nobel Prize in Chemistry[8] "for ground breaking discoveries that reveal the inner workings of an important family of such receptors: G-protein-coupled receptors"[9].

Beta adrenoceptors are activated by the catecholamines norepinephrine and epinephrine, and are members of the adrenoceptor family of the 7-transmembrane superfamily of receptors. There are three beta adrenoceptor subtypes: β1, β2, and β3. The prototypical beta agonist and antagonist are isoproterenol and propranolol, respectively [10]. Beta adrenoceptors are implicated in diverse physiological functions in the body, especially in the cardiovascular and pulmonary systems. Activation of adenylate cyclase through Gs is the classic, but not the only, mechanism of beta adrenoceptor action. Adrenergic receptors are central to the overall regulation of cardiac function. From the first proposed receptor transmitter concept to the latest clinical -blocker trials, AR have been shown to play an important role in cardiac disease and heart failure in particular. Adrenergic receptors and their associated guanine nucleotide regulatory protein (G protein)/adenylyl cyclase (AC) signal transduction pathways are central to the overall regulation of cardiac function. In particular, AR stimulation is a primary control point for modulation of heart rate and myocardial contractility [11].

I. β2-AGONIST THERAPY IN LUNG DISEASE:

β2-Agonists are effective bronchodilators due primarily to their ability to relax airway smooth muscle (ASM). They exert their effects via their binding to the active site of β2-adrenoceptors on ASM, which triggers a signalling cascade that results in a number of events, all of which contribute to relaxation of ASM.

Mechanism of action:

β2-Agonists are effective bronchodilators due primarily to their ability to relax airway smooth muscle (ASM). They exert their effects via their binding to the active site of β2-ARs, which are densely located on ASM [12]. The presumed cellular mechanism of action involves the canonical signalling pathway via activation of adenylyl cyclase (AC) and generation of intracellular cAMP, which in turn can activate the effector molecules cAMP dependent protein kinase A (PKA) and Epac, a Rap1 guanine nucleotide exchange factor. (Figure 1), PKA phosphorylates key regulatory proteins involved in the control of ASM tone, Epac induces ASM relaxation in a largely PKA-independent manner through down-regulation of Rho, and cAMP results in sequestration of intracellular Ca21, leading to relaxation of the ASM. However, it has become increasingly clear that signalling through adenylyl cyclase–coupled pathways is considerably more complex and sophisticated than was previously considered, although there is still little known regarding these pathways in airway cells [13].

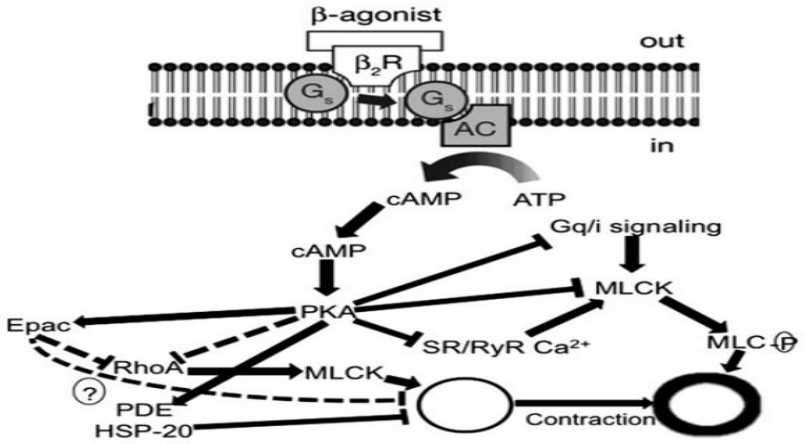

Figure 1. Mechanism of action of β2-agonists (based on information from Reference 3). AC ¼ adenylyl cyclase; b2R ¼ b2 receptor; cAMP ¼ cyclic adenosine monophosphate; Epac ¼ exchange protein directly activated by cAMP; Gs ¼ stimulatory G-protein; HSP-20 ¼ heat shock– related protein 20; MLCK ¼ myosin light chain kinase; MLC-P ¼ myosin light chain phosphatase; PDE ¼ phosphodiesterase; PKA ¼ protein kinase A; SR/RyR Ca21 ¼ sarcoplasmic reticular ryanodine Ca21 channel.

II. Role of β2-AR on diseased condition of lungs:

1. Asthma:

The term "asthma" comes from the Greek meaning, "to breathe hard." Asthma is disease of the human respiratory system in which the airways constrict and become narrow, often in response to a "trigger" such as exposure to an allergen, cold air, exercise or emotional stress. Bronchial Asthma according to the GINA guidelines final update November 2006 is clearly defined as: A chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.

Pathophysiology of Asthma:

Bronchial asthma is characterized pathologically by an infiltration of eosinophils into the airway submucosa. Eosinophil activation results in the secretion of an array of highly charged cytotoxic cationic proteins such as major basic protein, and is believed to play a central role in the etiology of this disease by inducing damage to the airway epithelium. The pathophysiology of asthma involves the development of acute and chronic inflammation in airway narrowing by producing increased vascular permeability, edema, and airway smooth muscle contraction. The gross pathology of asthmatic airways displays lung hyperinflation, smooth muscle hypertrophy, lamina reticularis thickening, mucosal edema, epithelial cell sloughing, cilia cell disruption, and mucus gland hypersecretion It is observed that those patients who have died due to asthma are due to considerable increase in the thickness of the airway wall throughout the bronchial tree, partly as a result of smooth muscle hypertrophy.

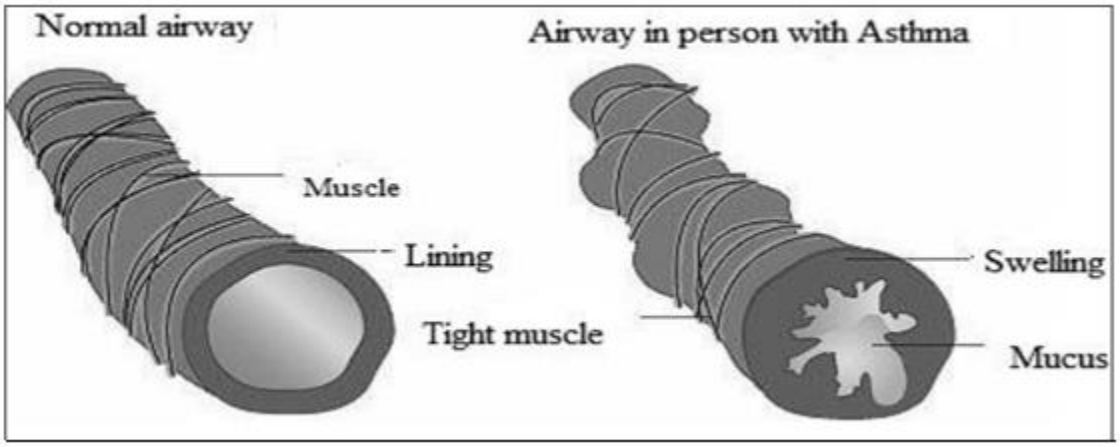

Fig2. Pathophysiology of asthma

The role of the beta 2-adrenergic receptor in both the pathogenesis and treatment of asthma has been a subject of intense speculation and investigation for 25 years. The physiological effects of endogenous circulating catecholamines and exogenous adrenergic agonists in the lung are mediated by the beta 2-adrenergic receptor, which is present on a variety of cell types. Documented effects of beta 2-adrenergic receptor activation in the human lung include smooth muscle relaxation, inhibition of acetylcholine release from cholinergic nerve terminals, stimulation of serous and mucous cell secretion, increases in ciliary beat frequency, promotion of water movement into the airway lumen by stimulation of ion secretion across the apical membrane of epithelial cells, increase in bronchial blood flow, reduction in venular permeability, and inhibition of mediator release from some, but not all, inflammatory cells. Beta 2-Adrenergic receptors are present in normal or increased numbers on asthmatic airway smooth muscle but are uncoupled in severe asthma, leading to functional hyperresponsiveness, probably due to the effects of inflammatory mediators. There is also evidence for dysfunction of beta 2-adrenergic receptors on circulating inflammatory cells following mediator release. However, dysfunction of the receptors on airway smooth muscle and inflammatory cells is unlikely to be of primary importance in the pathogenesis of asthma. There is increasing concern that regular beta 2-adrenergic receptor agonist use in the therapy of asthma is deleterious. Although a number of theories have been advanced to explain such an effect, none is well established and further research is urgently required. β-Adrenoceptors regulate many aspects of airway function, including airway smooth muscle tone, mast cell mediator release, and plasma exudation. The possibility that β-receptors are abnormal in asthma has been extensively investigated. The suggestion that there is a primary defect in β-receptor function in asthma has not been substantiated and any defect in β-receptors is likely to be secondary to the disease, perhaps as a result of inflammation or as a consequence of adrenergic therapy. Some studies have demonstrated that airways from asthmatic patients fail to relax normally to isoproterenol, suggesting a possible defect in β-receptor function in airway smooth muscle. Whether this is due to a reduction in β-receptors, a defect in receptor coupling, or some abnormality in the biochemical pathways leading to relaxation, is not yet known, although the density of β-receptors in airway smooth muscle appears to be normal and there is no reduction in the density of β_1- or β_2-receptors in asthmatic lung, either at the receptor or at the mRNA level.

Treatment: The following category of drugs can be used alone or in combination for the treatment of asthma

1. Bronchodilators
   - Beta 2 Adrenergic agonists
   - Muscarinic antagonists
   - Methyl xanthine's
2. Anti-inflammatory agents
   - Glucocorticoids
   - Mast cell degranulation blockers (Mast cell stabilizers)
3. Newer drugs
   - Leukotriene antagonists
   - Anti Ig E antibodies
   - Allergy vaccination

Herbal Drugs used for Asthma:

Though the large numbers of drugs are available for the treatment of asthma, the relief offered by them is mainly symptomatic and short lived. Moreover, this side effects of these drugs are also quite disturbing. Recently there has been a shift in universal trend from synthetic to herbal medicine, which we can say 'Return to Nature'. A large number of medicinal plants have been used traditionally for the treatment of asthma and have been scientifically proven to have anti-asthmatic properties.

Important medicinal plants having anti-asthmatic potential are:

Achyranthes aspera [14] Allium cepa [14-15], Adhatoda vasica [16-17], Albizzia lebbeck [18-19], Achillea mellifolium [20], Asystasia gangetica [21] ,Acorus calamus, Ammi visnaga, Boswellia serrata [22], Balanites roxburghii [23], Cedrus deodara [24], Curculigo orchioides [25], Clerodendron phlomidis[26], Curcuma longa[27] ,Cassia sophera [28], Centipeda minima[29], Ephedra gerardiana [30], Eucalyptus globules[31], Aegle marmelos [32] ,Hedychium spicatum[33-34], Glycyrrhiza glabra[35-36], Moringa oleifera [37], Myrica sapida [38], Nigella sativa, Ocimum sanctum, Picorrhiza kurroa [39],Lipidum sativum [40] , Passiflora incarnata [41], Solanum xanhocarpum [42-43] ,Terminalia belerica [44], Tinospora cordifolia [45], Tamarandus indica [46].

Table 1: Important medicinal plants having anti-asthmatic potential

Plants	Family	Part used	Chemical constituents	Mechanism of action
Achyranthes aspera	Amaranthaceae	Fruit	Saponin C, Saponin D	Mast cell stabilizer
Allium cepa	Liliaceae	Bulb	Quercetin	1.Mast cell stabilizer 2.Lipooxygenase inhibitor 3. PAF inhibitor 4.COX inhibitor
Adhatoda vasica	Acanthaceae	Leaves, Root	Alkaloids	1.Bronchodilator

				2. Anti-anaphylactic
Albizzia lebbeck	Leguminosae	Bark	Alkaloids, tannins, flavonoids	1.Bronchodilator 2.Mast cell stabilizer
Achillaea melifollium	Asteraceae(composite)	Flower	Alkaloids	Inhibits action of histamine, acetylcholine ,5-HT
Asystasia gangetica	Acanthaceae	Leaves	Triterpenoids, saponins, steroidal aglycon	1.Bronchodilator 2.Antiinflammatory
Acorus calamus	Araceae	Rhizome	Asarone	Inhibits action of histamine, acetylcholine ,5HT
Ammi visnaga	Umbelliferae	Seeds	Khellin	Bronchodilator
Boswellia serrata	Burseraceae	Root	Boswellin Bowellic acid	Inhibits leukotriene biosynthesis
Balanites roxburghii	Simarubeceae	Stem bark	Alkaloids	1.Mast cell stabilizer 2.Bronchodilator
Cedrus deodara	Pinaceae	Wood	Himacholol	Mast cell stabilizer
Curculigo orchioides	amarylliaceae	Rhizomes	Triterpenoids, sapogennins and saponin glycosides	1.Antihistaminic 2.Anti-inflammatory
Clerodendron phlomidis	Verbenaceae	Leaves	Flavonoids, terpenoids, steroids	1.Anti-histaminic 2.Mast cell stabilizer
Curcuma longa	Zingiberaceae	Rhizomes	Cuecuminoids	Inhibits histamine release
Cassia sophera	Caesalpiniaceae	Leaves	Flavonoids, glycosides	1.Bronchodilator 2.Anti-histaminic 3.Antiallergic 4.Anti-inflammatory
Centipedia minima	Compositae	Whole plant	Pseudoguainolide, sesquiterpene, lactone, flavonoids	Antiallergic
Ephedera gerardiana	Ephedraceae	Stem	Ephedrine	Bronchodilator
Eucalyptus globules	Myrtaceae	Leaves	Volatile oil	Anti-inflammatory
Aegle marmelos	Rutaceae	Leaves	Alkaloid-aegeline	Antihistaminic

Hedychium spicatum	Zingiberaceae	Rhizome	Sitosterol, Volatile oil	Anti-inflammatory
Glycyrrhiza glabra	Leguminosae	Root	Glycyrrhizinic acid	1.Antihistaminic 2.Antiallergic
Inula racemosa	Asteraceae	Roots	Inulin, sesquiterpene lactonealantolactone	Antihistaminic
Moringa oleifera	Morangaceae	Seed	Tannins, steroids, triterpenoids, flavonoids, alkaloids, saponins	Antihistaminic
Myrica sapida	Myricaceae	Bark	Glycosides	Mast cell stabilizer
Nigella sativa	Ranunculaceae	Seed	Volatile oil, fatty acid	Bronchodilator
Ocimum sanctum	Labiateae	Leaves	Ursolic acid	Mast cell stabilizer
Picorrhiza kurroa	Scrophulareaceae	Roots	Picorrhizin	Antihistaminic
Lipidum sativum	Cruciferae	Seeds	Alkaloids, Flavonoids	Bronchodilator
Passiflora incarnata	Passifloraceae	Leaves	Benzoflavone	Bronchodilator
Solanum xanhocarpum	Solanaceae	Flowers	Phyto-sterol, alkaloids, flavonoooids, Steroids	1.Antihistaminic 2. Mast cell stabilizer
Terminalia belerica	Combrataceae	fruits	Beta sitosterol, Gallic acid, ellagic acid, glycoside	Mast cell stabilizer
Tinospora cordifoli	Mensipermaceae	Stem	Alkaloids	1. Antihistaminic 2. Mast cell stabilizer
Tamarindus indica	Caesalpiniaceae	leaves	Flavone, Glycosides	1.Brochodialator 2.Antihistaminic 3. Anti-inflammatory

Looking in to the future: ultra-long β2-agonists

Recently, new ultra-long β2-agonists with higher potency and selectivity to β2-receptors, like vilanterol, olodaterol, indacaterol and abediterol [46-47] with 24-h treatment duration and rapid onset of bronchodilation have been studied. Of these, only vilanterol, in association with inhaled corticosteroids, has been approved for treatment of asthma [48]. The once-a-day posology might increase adherence in long-term treatment of asthma. However, superiority to twice-a-day LABA still cannot be concluded with the currently available evidence. In addition, no serious adverse effects have been observed, although the follow-up periods of the trials are short. Due to the high selectivity to β2-receptors of these drugs, it is not expected for them to have greater adverse cardiovascular effects than LABA. Conversely, this

selectivity may potentially be correlated with a greater loss of adrenoreceptors but this has not been associated with functional desensitisation [49]. Moreover, with an increasing human life expectancy, these new drugs should be shown to be safe and efficacious in an older population that may have a higher rate of cardiovascular comorbidities and use of multiple medications. The use of ultra-long β2-agonists is increasing, prescribed in monotherapy for chronic obstructive pulmonary disease (COPD), and frequently asthma– COPD overlap syndrome. New data are emerging every day and will continue this story in the future.

III. CONCLUSION:

Many synthetic drugs are used to treat asthma, but they are not completely safe for long term use. Nature has bestowed our country with an enormous wealth of medicinal plants; therefore, India has often been referred to as the Medicinal Garden of the world. Scientifically explored exhaustive reports published in Indian and international journals suggest the importance of herbal medicine in the treatment of asthma is indisputable.

2. COPD:

Chronic obstructive pulmonary disease (COPD) is a life-threatening condition that affects your lungs and your ability to breathe. For people with COPD, this starts with damage to the airways and tiny air sacs in the lungs. Symptoms progress from a cough with mucus to difficulty breathing. Chronic obstructive pulmonary disease (COPD) is one of the world's leading causes of morbidity and is now the third leading cause of mortality, amounting to 3 million deaths in 2010 [50-51]. To understand COPD's pathophysiology, it's important to understand the structure of the lungs.

When you inhale, air moves down your trachea and then through two tubes called bronchi. The bronchi branch out into smaller tubes called bronchioles. At the ends of the bronchioles are little air sacs called alveoli. At the end of the alveoli are capillaries, which are tiny blood vessels.

Oxygen moves from the lungs to the bloodstream through these capillaries. In exchange, carbon dioxide moves from the blood into the capillaries and then into the lungs before it's exhaled.

Emphysema is a disease of the alveoli. The fibers that make up the walls of the alveoli become damaged. The damage makes them less elastic and unable to recoil when you exhale, making it hard to exhale carbon dioxide out of the lungs.

If the lung airways become inflamed, this results in bronchitis with subsequent mucus production. If the bronchitis persists, you can develop chronic bronchitis. You also can have temporary bouts of acute bronchitis, but these episodes aren't considered to be the same as COPD. Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms, poorly reversible airflow obstruction, and acute exacerbations, marked by worsening of lung function and increased symptoms. Current pharmacologic therapies for COPD consist primarily of long-acting inhaled bronchodilators, which reduce symptoms and the frequency of exacerbations but do not prevent or reverse progressive loss of lung function [52]. COPD is associated with chronic inflammation, airway fibrosis, and lung parenchymal destruction with loss of elasticity, leading to air trapping and airflow obstruction. Airway inflammation in COPD is characterized by increased numbers of neutrophils, macrophages, and T and B lymphocytes, as well as increased oxidative stress and production of proinflammatory mediators [53]. Interestingly, airway inflammation persists, and progressive lung destruction continues, despite removal of the offending agent (e.g., smoking cessation). One of the prevailing theories of COPD pathogenesis is

that there is an imbalance between proteases and antiproteases in the lung [54-56]. This imbalance leads to enhanced protease- mediated destruction of the lung parenchyma.

Other signs of COPD progression: As COPD progresses, many other health complications can follow. Besides coughing, you may notice yourself wheezing when you breathe. The build-up of mucus and the narrowing of the bronchioles and alveoli may also cause chest tightness. These aren't normal symptoms of aging. If you experience them, see your doctor. Less oxygen circulating throughout your body can leave you feeling light-headed or fatigued. Lack of energy can be a symptom of many conditions, and it's an important detail to share with your doctor. It may help determine the seriousness of your condition. In people with serious COPD, weight loss also can occur as your body requires more and more energy to breathe.

COPD and the heart:

The main accepted clinical indications for the use of beta-blockers in COPD are for patient's post-myocardial infarction and for patients with heart failure. However, the presence of untreated or unrecognised (i.e. silent) cardiovascular disease may contribute to mortality in COPD and may also be an underlying causative factor in exacerbations, which can be difficult to separate from respiratory aetiologies (box 1) [57-58]. It is also possible, if not likely, that the burden of cardiovascular disease may be underrated by pulmonologists when treating COPD patients because symptoms are presumed to be primarily driven by airflow obstruction, especially during exacerbations. The prevalence of left ventricular systolic dysfunction ranges between 10% and 46% in patients with COPD, and although the occurrence of heart failure with preserved left ventricular ejection fraction is less clear, estimates in patients with severe COPD are as high as 90% . The benefits of beta-blockers in patients with heart failure due to left ventricular systolic dysfunction are well established from pivotal trials as well as meta-analysis[59-62]. The challenge in COPD may be more with respect to diagnosis of heart failure with echocardiography, where image acquisition is difficult due to lung hyperinflation [63]. Beta-blockers only have proven benefits in patient's post-myocardial infarction but not in stable coronary arterial disease[64-65]. Nevertheless, the presence of coronary calcium on chest computed tomography scans is associated with mortality in COPD [66] and known coronary arterial disease is also associated with longer exacerbations, more dyspnoea, and lower health status and exercise capacity in stable patients with COPD [67].There is also an acute increase in arterial stiffness, particularly during infective exacerbations of COPD, along with increases in cardiac enzymes especially in patients with coronary arterial disease[68]. one particular study found that one in 12 patients admitted to hospital with an exacerbation of COPD met the criteria for a myocardial infarction [69]. The presence of coronary heart disease in COPD, along with the adverse effects of hypoxaemia [70] may be compounded by the positive chronotropic effects of concomitant inhaled beta-agonist therapy [71-72], further compromising cardiac reserve. It has been shown that even a low dose of a beta-1 selective antagonist such as atenolol might protect against chronotropic, inotropic and electrocardiographic effects of inhaled beta-agonists, which are mediated by cardiac beta-2 receptor stimulation [73]. In addition to these COPD-related risks, patients with the disease commonly have other comorbidities such as coronary artery disease, hypertension and diabetes, which can all adversely affect diastolic function. This was addressed in a recent prospective longitudinal study of healthy young adults followed over 25 years, where a fall in the ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) was associated with reduced left atrial size and cardiac output [74].

Left ventricular end diastolic and end systolic wall stress measured by magnetic resonance imaging is associated with increasing severity of airflow obstruction in patients with COPD and coexistent heart failure [75] . Impaired left ventricular filling is clinically important because it can eventually produce left atrial enlargement, which is a key risk factor for atrial fibrillation and associated mortality during exacerbations of COPD [76].

Furthermore, the presence of impaired diastolic filling in patients with COPD is also related to impaired walking distance [77]. Thus, the absence of benefits of beta-blockers in diastolic dysfunction may not apply in COPD and deserves re-evaluation in this patient group.

- **Potential cardiac targets for beta-blockers in chronic obstructive pulmonary disease (COPD)**
- **Potential cardiac targets for beta-blockers in COPD**
  - Improved left ventricular systolic and diastolic function
  - Reduced left ventricular dilatation
  - Protection against myocardial ischaemia
  - Reduced left ventricular mass
  - Reduced heart rate
  - Anti-arrhythmic effects
  - Inhibition of myocyte apoptosis
  - Protection against hypoxic sympathetic drive
  - Protection against adverse effects of beta-agonists
- **Potential noncardiac targets for beta-blockers in COPD**
  - Inhibition of endothelin-1 release
  - Reduction in circulating pro-inflammatory cytokines
  - Inhibition of neutrophil chemotaxis and respiratory burst
  - Reduction in goblet cell number and mucus release
- **Prescribing of beta-blockers in chronic obstructive pulmonary disease for cardiovascular disease**
  - Beta-1 selective antagonists including metoprolol, bisoprolol and nebivolol exhibit dose related beta-2 receptor blockade
  - Carvedilol is a nonselective beta-antagonist that is more likely to cause bronchoconstriction than beta-1 selective antagonists
  - Slowly titrate the dose of beta-blockers at 1–2 weekly intervals up to the usual maintenance dose
  - Monitor supine and erect blood pressure, heart rate and spirometry during dose titration
  - Concomitant long-acting muscarinic antagonists may obviate potential bronchoconstriction
  - Symptomatic bradycardia may occur if beta-blockers are used with other rate-limiting drugs such as calcium blockers (e.g. verapamil and diltiazem), ivabradine or anti-arrhythmic agents (e.g. digoxin, amiodarone and flecainide)
  - Symptomatic hypotension may occur when beta-blockers are used with other vasodilatory drugs (e.g. angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and alpha receptor blockers)

Causes of COPD:

The main cause of COPD is tobacco smoking. Breathing in smoke and its chemicals can injure the airways and air sacs. This leaves you vulnerable to COPD.

Exposure to second-hand smoke, environmental chemicals, and even fumes from gas burned for cooking in poorly ventilated buildings can also lead to COPD.

β2-agonists:

The principal action of β2-agonists is to relax airway smooth muscle by stimulating β2-adrenergic receptors. This increases the intracellular messenger cyclic AMP that is responsible for the control of smooth muscle tone [78]. Thus, activation of the β2-adrenergic receptor results directly in bronchodilation. Muscarinic antagonists also facilitate bronchodilation but work by competing with acetylcholine for muscarinic receptors. By inhibiting the action of acetylcholine at receptor sites in the lung, they indirectly inhibit contraction of airway smooth muscle [79,80] Figure 3. Illustrates the pathways by which each class of bronchodilator produces smooth muscle relaxation. β2-adrenergic receptor agonists may also attenuate cholinergic neurotransmission due to stimulation of β2-adrenergic receptors on parasympathetic ganglia[81,82].

β2-agonists are widely used in the management of COPD, either alone or in combination with other bronchodilators, corticosteroids, or both. Short-acting β2-agonists (SABAs) were the first agents of the class to become available for the treatment of COPD. LABAs with a 12-hour duration of action were subsequently introduced in the late 1990s, following positive experience in asthma [83]. providing improvements in bronchodilator efficacy and patient outcomes compared with SABAs which have a duration of action of only 4-6 hours [84,85,86]. The currently available SABAs and LABAs are summarized in Table 2[79].

Table 2: Currently available SABAs and LABAs

Drug	Dose delivered by inhaler(µg)	Other formulations	Recommended dose	Duration of action (hours)	Onset of action
Short-acting salbutamol (albuterol)	100,200(MDI&DPI)	Solution for nebulizer; oral (syrup, tablets), vials for injection	200µg up to 4 times daily	4-6	5 mins
Terbutaline	400-500 (DPI)		500µg up to 4 times daily	4-6	30 mins
Long acting Formoterol	4.5-12 (MDI& DPI)	Solution for nebulizer (20µg /2ml)	12µg twice daily (Aerolite/Easy haler 9µg^ twice daily (Subhauler) 20µg twice daily (Nebulizer)	12+	$< 5min$*
AR formoterol		Solution for Nebulizer (15µg/2ml)	15µg twice daily	12+	6.7min*
Salmeterol	25-50 (MDI & DPI)		50µg twice daily	12+	2 hours**

DPI-dry powder inhaler; MDI-metered dose inhaler, * mean FEV increase of 15%; ** mean FEV increase of 12% or more and at least 200ml; ^ delivered dose (equivalent to 12 µg metered dose)

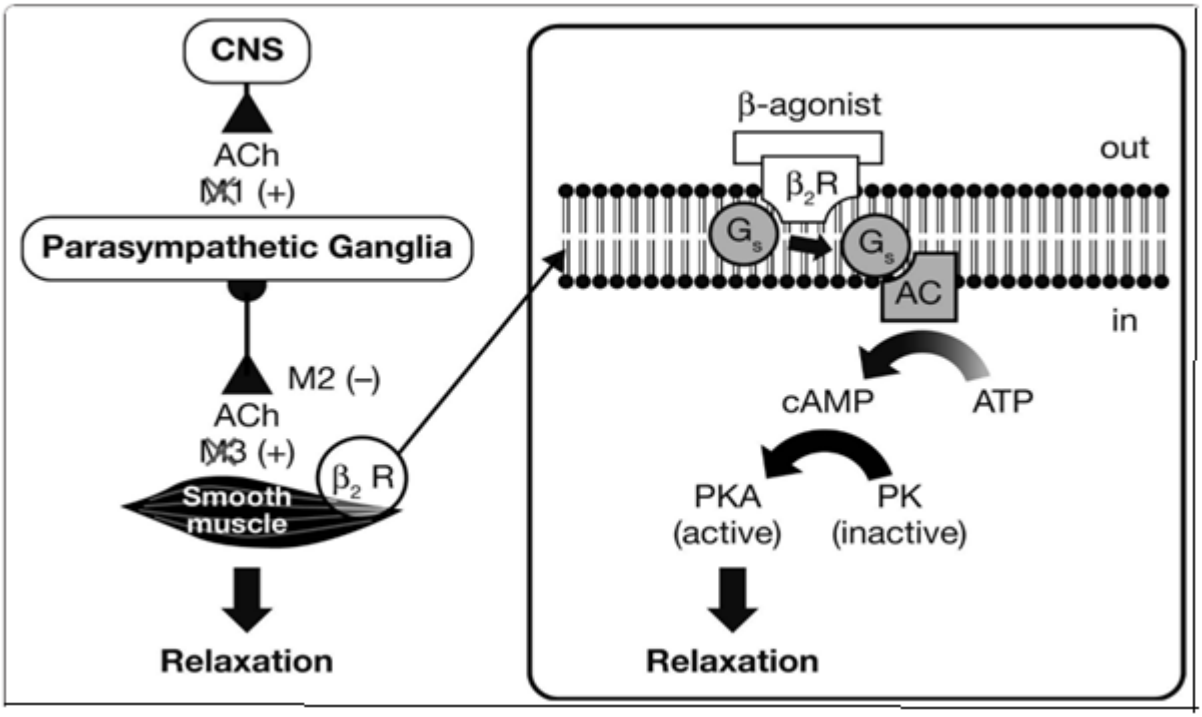

Figure 3. Pathways by which each class of bronchodilator produces smooth muscle relaxation

The role of anticholinergics in COPD: Achievement of maximal airway function through regular use at the maximum tolerated levels of bronchodilators. improves symptoms and exercise tolerance [80-81]. The short-acting bronchodilators, ipratropium and positronium, are slower in onset for bronchodilatation than the beta-2-agonists, but have a sustained mode of action and may be considered at least as effective and possibly more so in COPD (Table 3). Guidelines advocate that, for severe COPD, combination therapies with regular β2 -agonist and anticholinergic therapy should be given.

Table 3: THE BETA-2 AGONISTS AND ANTICHOLINERGICS:

Medication	**Mode of action**	**Reported side effects**
Salbutamol	Rapid onset of action Duration of action 3-5 hours	Fine tremor Headache
Terbutaline	Rapid onset of action Duration of action 3-5 hours	Nervous tension Muscle cramps
Salmeterol	Maximum effect after 40 minutes Duration of action 12 hours	Tachycardia Arrythmias
Formoterol	Rapid onset of action Duration of action 12 hours	Paradoxical bronchospasm Hypokalaemia Urticaria Angioedema Sleep and behaviour disturbance in children Fall in oxygen saturations
Ipratropium	Maximum effect after 15-90 minutes Duration of action 3-6 hours	Dry mouth Nausea Headache

Oxitropium	Maximum effect after 30-60 minutes Duration of action 6 hours* (little evidence of longer duration than 6 hours)	Urinary retention Blurred vision Glaucoma risk Paradoxical bronchospasm
Tiotropium	Onset of action Duration of action 35 hours	Tachycardia and atrial fibrillation have been reported

Adverse Effects:

Despite being used extensively for the treatment of asthma for over half a century, β2 agonists have an almost equally long history of adverse effects. Although the reasons for such adverse effects are multiple, with some still unknown, the majority of adverse effects can be attributed to either: 1) a lack of selectivity for the β2AR, resulting in "off-target" effects mediated by either alpha or β1 adrenoceptors; or 2) ill-defined β2AR-mediated effects that appear to involve either β2AR desensitization or exacerbation of airway inflammation and its consequences [82]. Although a thorough discussion of adverse effects associated with β-agonist use is beyond the scope of this review, we will summarize below the current consensus belief [83-86].

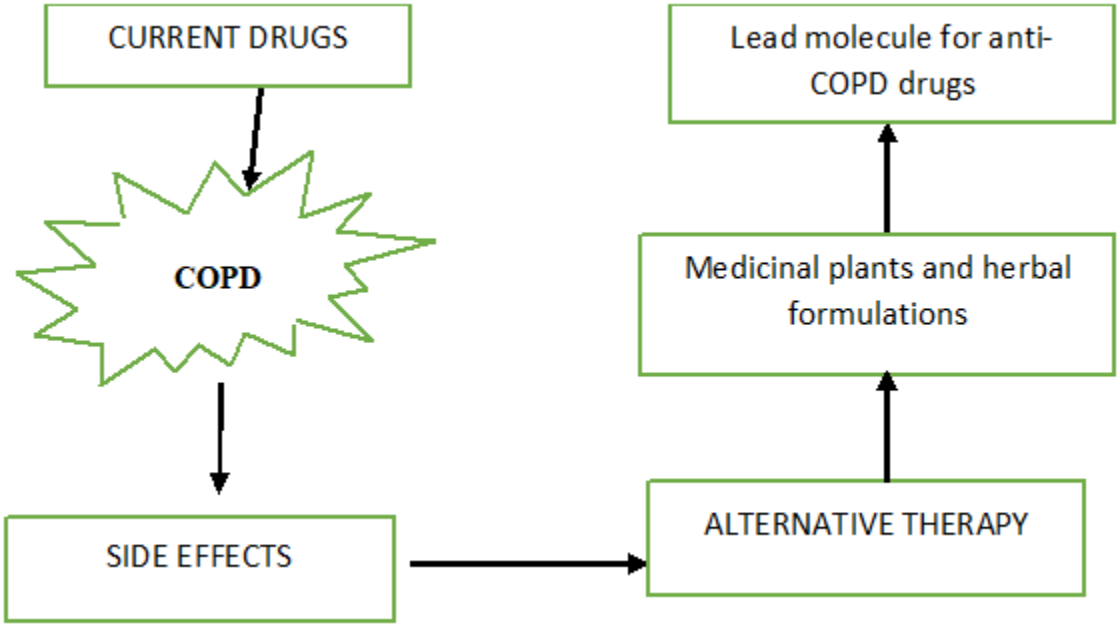

Fig 4: Medicinal plant and herbal formulations could be used for developing safer and effective drugs in chronic obstructive pulmonary

CONCLUSIONS AND PLACE IN THERAPY

In the past, the care, management, and treatment of COPD has not been optimal. Treatment has often followed asthma treatment, although the causes, disease process, management and treatments differ. COPD is increasingly seen as a separate disease so studies into specific treatments increase and our knowledge improves. From available evidence anticholinergic therapy is better than placebo and appears in some studies to be superior to the beta-2-agonists. While Oxitropium and specifically ipratropium has shown benefits, tiotropium has an edge over its precursors in terms of its selectivity and clinical effects,

specifically in terms of patients' symptoms. Although guidelines support long-acting bronchodilators if patients remain symptomatic after short-acting bronchodilators. it may be that earlier use of these agents and specifically tiotropium may lead to objective and subjective improvements. Whilst there is evidence that anticholinergics may be the preferential treatment of choice over agonists increasingly the long acting bronchodilators are being tested together and there is some evidence of synergism. Clearly anticholinergics have been used in obstructive disease for many years and they still have a relevant and useful place in therapy. Benefits now require further evaluation in clinical practice and the place of the therapies substantiated over the long term. Additionally, patients enrolled in clinical trials, the level of severity of their disease, and exacerbation rates requires examination to ascertain if they are truly representative of the patient groups we see in clinical practice.

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