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THERAPEUTIC EFFECTS & NEW PERSPECTIVE OF AN OLD DRUG THEOPHYLLINE

Suman Ghosh[1], Sumit Nandi[2*], Soumik Bhattacharjee[2]

[1]*Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata, West Bengal, 700114.*

[2]*Gupta College of Technological Sciences, Asansol, West Bengal, 713301.*

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ABSTRACT

Theophylline, also known as dimethyl xanthine, has been utilized for over 80 years to treat airway diseases. Initially used as a bronchodilator, its usage declined due to side effects associated with relatively high doses. Recent studies have demonstrated theophylline's effects that reduce inflammation in conditions such as asthmas well as long term obstructive lung disease at low level of concentration. The mechanism include: Inhibition of PDE3 for bronchodilator and suppression of PDE4, along with enhances histone deacetylase -2 (HDAC 2), as a result the suppression of genes involved in inflammation that are activated. Theophylline can reverse resistance to corticosteroids, particularly in chronic asthma as well as COPD, where activity of histone deacetylase -2 (HDAC 2) has decreased. Theophylline has provided by systemic administration, either taken orally as a long-term remedy or administered intravenously for severe asthma. Blood concentrations and effectiveness are related, primarily influenced by metabolism in the liver that can be altered by various diseases and concomitant drug therapies. Typically used as additional form of therapy for patients with chronic lung disease not adequately regulated when using long-acting β2-agonists in conjunction using corticosteroids that are inhaled. Also used in patients with long-term obstructive lung disease along with a severe disease that cannot be controlled with bronchodilator medication. The adverse consequences are concentration-dependent and consist of headache, nausea, as well as vomiting at lower concentrations because of a blockage of phosphodiesterase. In greater concentration, side effects may include irregularities of heartbeat and seizures because of adenosine A_1receptor antagonism. At low doses of theophylline can hold promise in the future for lowering the resistance to corticosteroids in long-term obstructive lung disease and asthma. This summary highlights the dual role of theophylline serving to be anti-inflammatory as well as bronchodilator, with potential implications for the management of severe respiratory conditions. This study clarifies the mechanism of action of theophylline and investigates its synthesis. Theophylline, a common bronchodilator, is produced in large part thanks to the effective synthesis technique that is being presented. Our comprehension of the drug's pharmacological properties is improved by the clarification of its mechanism of action, which provides future developments in its therapeutic uses.

Corresponding author

Sumit Nandi

Gupta College of Technological Sciences,
Ashram more, GT Road, Asansol, 713301
sumitrx27@gmail.com
7001494972/7797869351

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INTRODUCTION

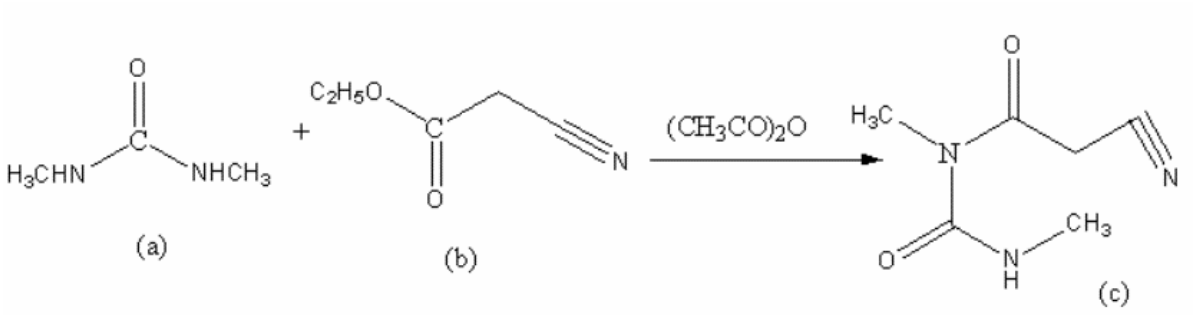
Theophylline is among the medications that are frequently administered to treat chronic bronchitis or bronchial allergies in the globe due to its affordability and accessibility. Trace levels of theophylline, are found in cocoa beans and tea. It was chemically synthesized and applied as a diuretic in 1895. The xanthine family, to which theophylline belongs, is closely connected to plant alkaloids and has unique pharmacological and biological properties. Theophylline has been used medicinally since 1902 and derived from tea leaves. It was first used as a clinical asthma treatment in 1922 after its bronchodilator characteristic was discovered[1]. Xanthine like theophylline is used to treat lung diseases like COPD, asthma, and others that are brought on by reversible airflow restriction. The medication theophylline, referred to as 1, 3-dimethylxanthine, blocks adenosine receptors and phosphodiesterase enzyme. It's pharmacology comparable to that of other methylxanthine medications, such as caffeine and theobromine. Natural sources of theophylline include withered mate, cocoa cotyledon, green coffee, and to a lesser degree in black tea, and guarana. Theophylline (additionally known as dimethylxanthine) has been successfully used to treat bronchial disorders over the eight decades. First of all, intended as a bronchodilator, decreased as inhaled β2-agonists gained traction due to the comparatively high doses needed and their often-adverse effects. At smaller doses, it has been demonstrated more recently to be beneficial for reducing inflammation in breathing difficulties and chronic obstructive lung disease [2]. Nowadays, patients with asthma who are not adequately managed utilizing long-acting β2-agonists in conjunction with corticosteroids that are inhaled and those with severe long-term obstructive lung disease who are not managed with bronchodilator medication typically receive the drug theophylline as an adjunctive treatment. As a result of PDE inhibition, side effects linked among the plasma concentrations are headaches, feeling sick, and vomiting. At greater doses, adenosine A1-receptor antagonism can cause cardiac arrhythmias and seizures. Low-dose theophylline may prove helpful in the future for treating severe asthma and COPD by reversing corticosteroid resistance [3].The term 'theophylline' originates from the combination of 'Thea' [previous genus of tea] + the Greek φύλλον [phúllon, means 'leaf'] + [ine].The primary purpose of this review is to provide an overview of the bronchodilator effect of theophylline. It facilitates the relaxation of the smooth muscles in the bronchi, which opens up the airways. Breathing becomes easier for those who suffer from conditions like COPD or asthma as a result.

Steps of Theophylline synthesis: -

There is a trace amount of theophylline (1, 3-dimethylxanthine) present in tea leaves. It is produced synthetically using the Traube method, which is a standard technique recommended for the synthesis of purine bases. Here's a step-by-step process of the Theophylline synthesis is given below:-

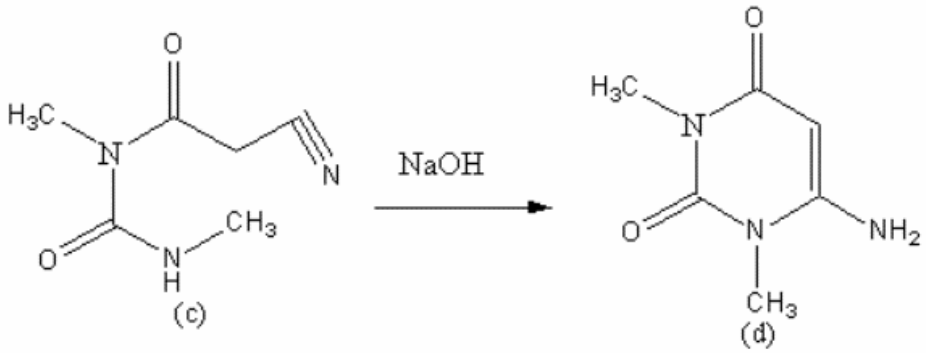
Formation of Cyanoacetylmethylurea: -

Cyanoacetic ether (b) and N, N-dimethyl urea (a) reacts in presence of acetic anhydride, to form (c) cyanoacetylmethylurea.



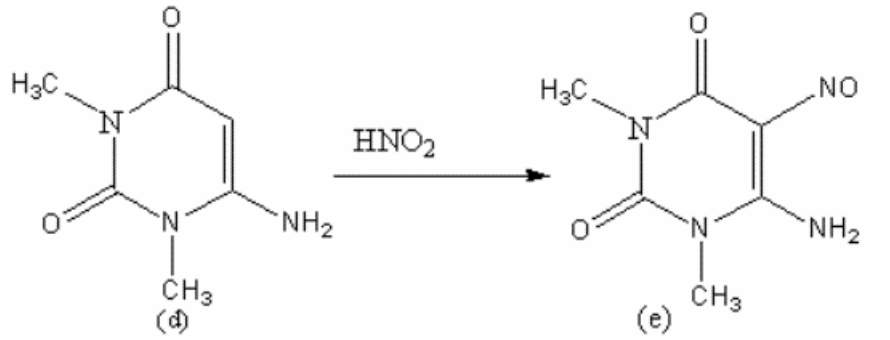
2.2. Formation of 6-Amino-1, 3-dimethyluracil: -

Cyanoacetylmethylurea(c), it cyclized into 6-amino-1, 3-dimethyluracil (d) in the presence of sodium hydroxide (NaOH).



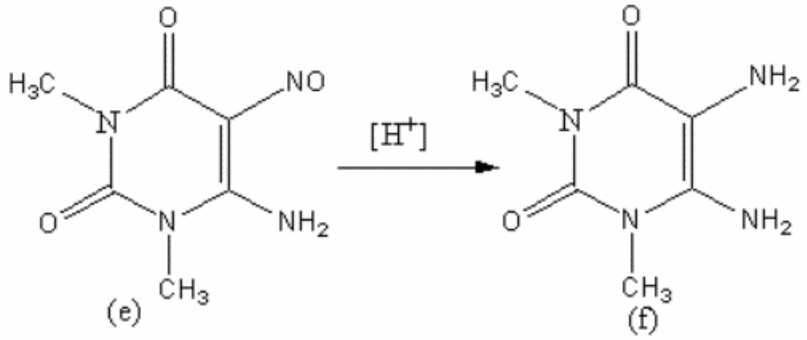
2.3. Formation of 5-Nitroso-6-amino-1, 3-dimethyluracil: -

That resulting compound (6-Amino-1, 3-dimethyluracil) reacts with nitrous acid and will form 5-Nitroso-6-amino-1, 3-dimethyluracil (e).



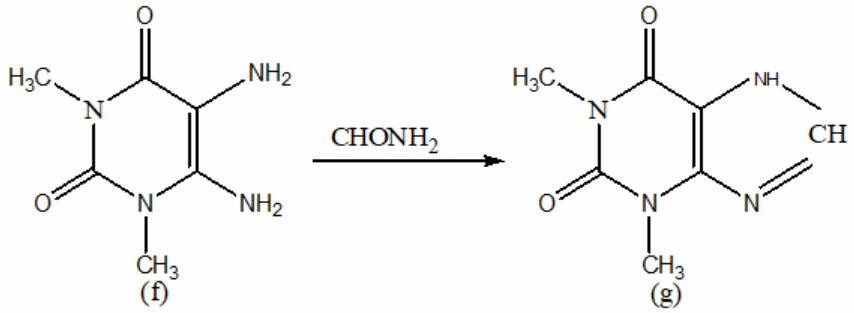
2.4. Formation of 5, 6-Diamino-1, 3-dimethyluracil: -

Now 5-Nitroso-6-amino-1,3dimethyluracil (e) reacts with acid [H^+] present in the solution and will form 5, 6-Diamino-1, 3-dimethyluracil (f) by the reduction of nitroso group.



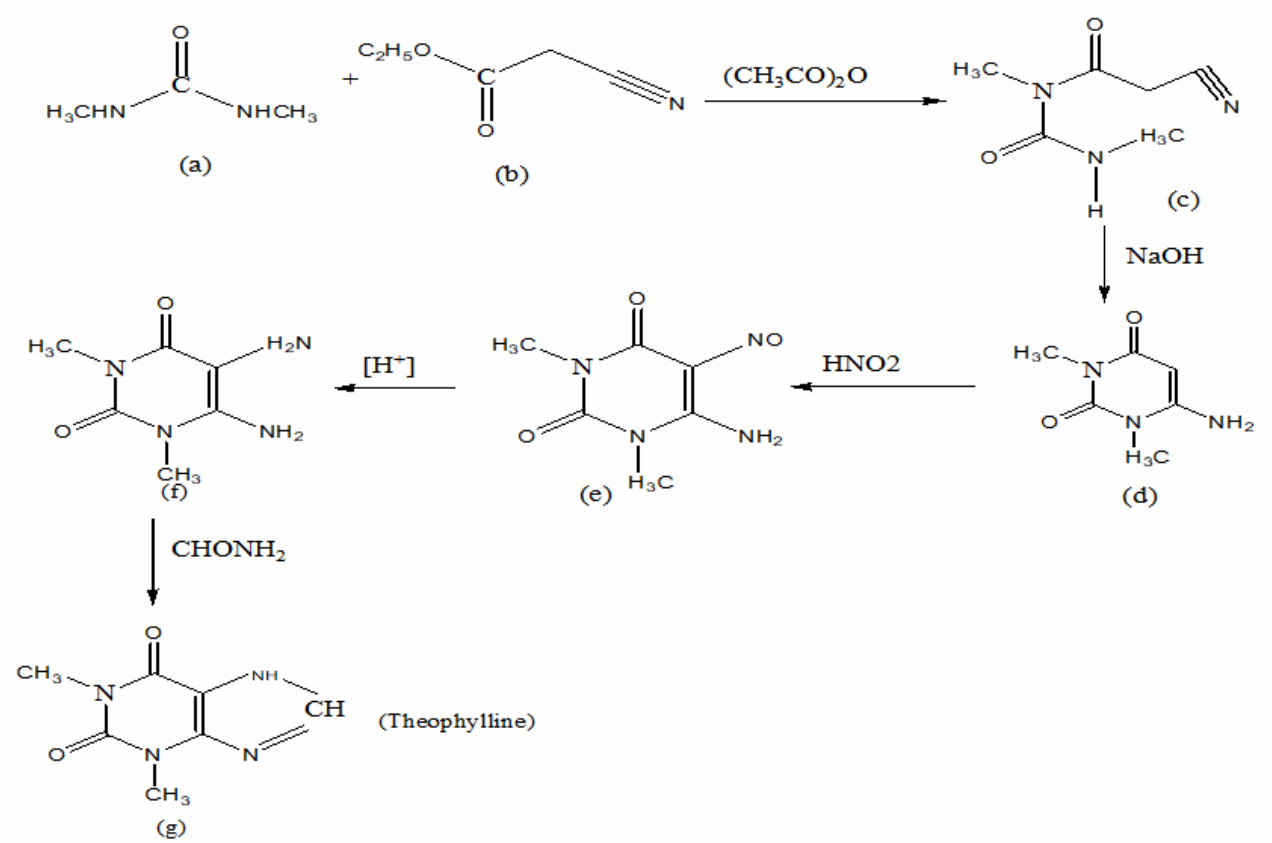
2.5. Formation of theophylline: -

Now, 5, 6-diamino-1, 3-dimethyluracil (f) reacts with formamide and will gives the desired product theophylline.



3. Synthetic diagram of theophylline synthesis: -

Theophylline (g) drug can be synthesized by the following steps: -



4. Mechanism of action: -

Theophylline has a number of molecular modes of action, most of which only work at doses greater than 10−5 M, which is below the threshold for clinical efficacy.

Suggested theophylline action mechanisms:

4.1. Blocking Phosphodiesterase:

Cyclic nucleotide's breakdownin the cell by phosphodiesterase (PDE) isoenzymes, which results in elevated intracellular levels of cAMP as well as cyclic 3′, 5′ guanosine monophosphate, is inhibited by theophylline, a weak nonselective inhibitor (Figure 1). At therapeutic dosages, the degree of inhibition is minimal, though. By primarily inhibiting PDE3 activity, theophylline relaxes airway smooth muscle; however, relatively high doses are required for maximum relaxation [4], its PDE4 activity suppression mediates its restraining action on the release of mediators by respiratory macrophages [5]. Although there should be a synergistic interaction between PDE inhibition and β-agonists, this remains to be definitively shown in vivo or in the clinical investigation. Theophylline side effect is mostly common in result from inhibition of PDEs.

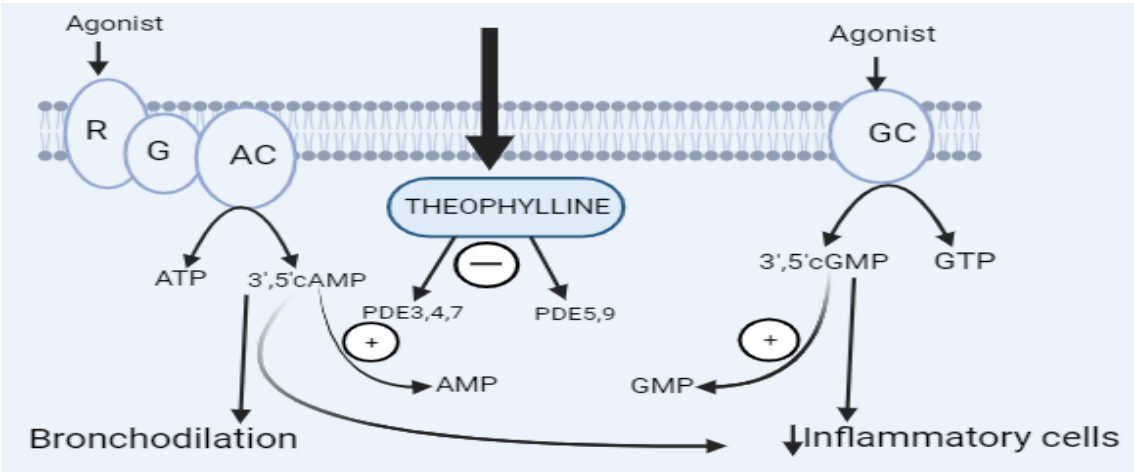


Figure 1

Fig1: Impact of inhibitors of phosphodiesterase (PDE) on cyclic nucleotide degradation in inflammatory cells and smooth muscle of the airways. G is for stimulatory G-protein; AC stands for adenylyl cyclase; GC stands for guanylyl cyclase, GTP stands for guanosine triphosphate, R for receptor, and cGMP = is cyclic guanosine monophosphate.

4.2. Adenosine Receptor Antagonism:

Therapeutic dosages of theophylline inhibit adenosine receptors A1, A2, but are less successful in inhibiting Receptors A3, which may be the reason for theophylline's bronchodilator effects. Adenosine constricts asthma patients' airways by releasing histamine and leukotriene, while having no impact on the in vitro normal smooth muscle in the human airways. This suggests, mediators are released by adenosine from patients' mast cells via A2B receptors [6]. Therapeutic doses of theophylline inhibit bronchoconstriction caused by inhaled adenosine in asthmatic patients by blocking the histamine released by mast cells of airway, albeit does not imply that theophylline's antiasthma properties are dependent on it. However, the major adverse effects of theophylline, like seizures and cardiac arrhythmias, are probably caused by adenosine antagonism, which blocks A1 receptors.

4.3. Increased IL-10:

With its wide range of anti-inflammatory properties, IL-10 is secreted less frequently in people with COPD and asthma. Relatively high theophylline concentrations enhance IL-10 release through PDE inhibition [7], however, at the modest dosages that are beneficial for asthma, this has not been observed [8].

4.4. Effects on Transcription:

By inhibiting the breakdown of I-kBα, an inhibitor, theophylline limits the nuclear factor-kappa B, a proinflammatory transcription factor, translocating into nucleus and possibly decreasing the level of expression of inflammatory genes in Long-term obstructive lung disease (COPD) and Breathing difficulties (asthma) [9].

4.5. Effects on Cell Survival:

Theophylline decreases the protein (B cell lymphoma-2) that prevents apoptosis, which causes the death in neutrophils in vitro [10]. Additionally, theophylline causes Apoptotic death of T cells, which lowers their perseverance rate. That action seems to be facilitated by inhibition of PDE [11]. Theophylline further prevents the oxidative stress-induced enzyme Poly ADP ribose polymerase1 (PARP 1), that lowers NAD levels and causes an energy crisis that kills cells [12].

4.6. Histone Deacetylase Activation:

Histone deacetylases are activated by theophylline at low therapeutic concentrations (about 5 mg/L), particularly when oxidative stress has decreased the enzymes' activity [13]. Theophylline (10−6 M) reverses the corticosteroid resistance in COPD cells by restoring HDAC2 activity to normal. Trichostatin A, an inhibitor of HDAC activity, prevents this action. COPD cells have dramatically lower HDAC2 activity and expression (Figure 2) [14]. Theophylline's action is caused by the specific suppression regarding phosphoinositide 3-kinase delta or PI3K-delta, which is made active by the effects of oxidized damage as well as takes part in phosphorylation-mediated suppression as HDAC2 function. This action is independent of adenosine receptor antagonistic activity and PDE inhibition [15]. Increased nitric oxide as well asspecies of reactive oxygen from increased the nitric oxide synthase that is induced expression lead to the generation of peroxynitrite, which make HDAC2's tyrosine residues nitrate and cause it’s breakdown as well as inactivation [16]. Peroxynitrite production is reduced by theophylline, which offers an additional method of enhancing HDAC2 performance in COPD and asthma [17].

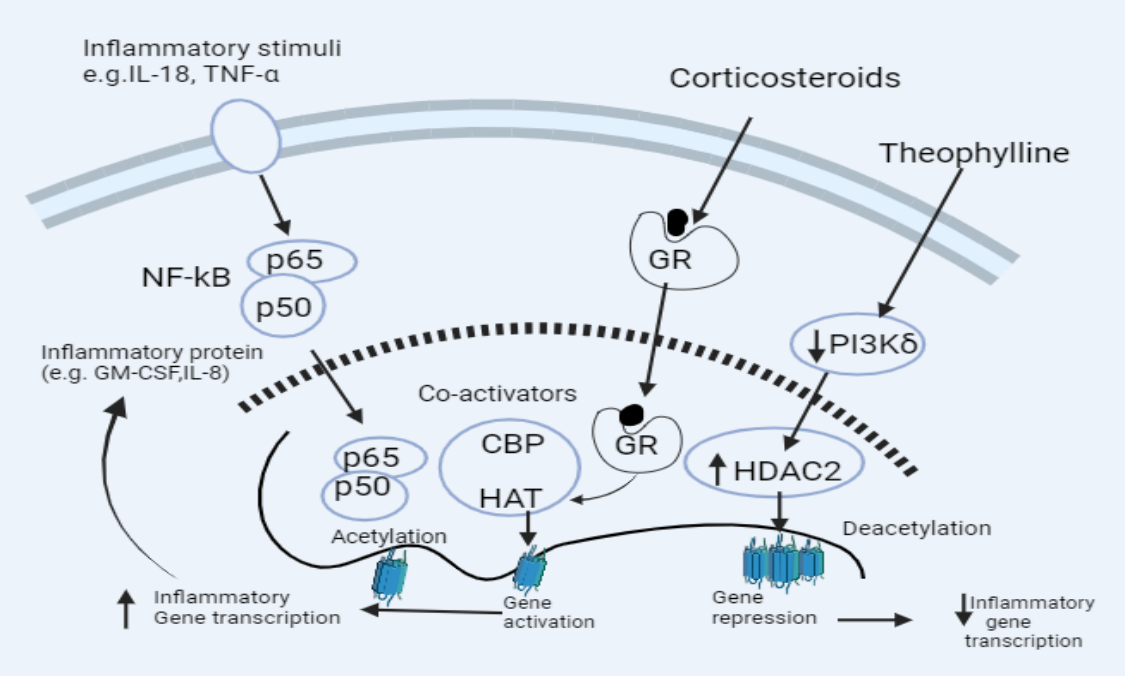


Figure 2

Fig2: By inhibiting phosphoinositide 3-kinase delta or PI3K-delta, that induced through oxidized damage as well as phosphorylates and reduces HDAC2, theophylline enhances histone deacetylase-2 (HDAC2). When coactivators like CREB-binding protein (CBP) activate histone acetyltransferase (HAT), they acetylate core histones. These histones are deacetylated by HDAC2. Resulting in, proinflammatory transcription factors like nuclear factor-kappa B (NF-kappa B) decreases expression of the inflammatory genes as well as proteins like granulocyte macrophage colony that stimulates the factors like GM-CSF and CXCL8. Though by a different method, corticosteroids can activate HDAC2, bringing the active complex of transcription through the receptor's activation for glucocorticoid (GR), which operate as molecular magnets. This clarifies how decreased HDAC2 activity caused by theophylline could reverse corticosteroid resistance.

Medicinal uses: -

The medical uses of theophylline: -

a. Relaxing smooth muscle in the bronchi.
b. Enhancing the effectiveness and contractility of the cardiac muscle (positive inotrope).
c. Elevating the pulse rate (positive chronotropism).
d. Blood pressure rising.
e. Raising the flow of blood to the kidneys.
f. Effect of anti-inflammatory.

Theophylline is mostly used therapeutically to treat: -

a. Long-term obstructive lung disease.
b. Breathing difficulties.
c. Inhibits adenosine effects, inhibition-promoting neurotransmitter that relaxes heart muscle, contracts the smooth muscles, and causes sleep.
d. Therapy of headache following a spinal puncture. [18]

CONCLUSION

There are various ways to synthesize the derivative of methylxanthine, theophylline. The synthesis of theophylline from xanthine is one of the frequently used synthetic pathways. The methylation of xanthine, usually by N-methylation, to provide theophylline, is a crucial step in achieving this. Theophylline is synthesized and is important because it is a bronchodilator in medicine, mainly used in the treatment of lung conditions (bronchial allergies) including long-term obstructive lung disease and breathing disorders. Furthermore, theophylline is a methylxanthine molecule with stimulant and central nervous system effects. To produce a pure form of the desired substance, theophylline synthesis entails a number of chemical processes and purifying stages. Depending on the procedure and environment used in the lab, the synthesis's precise details may change. It's crucial to remember that the synthesis of pharmaceutical substances, such as theophylline, is a difficult procedure that calls for knowledge of organic chemistry, exact control over reaction conditions, and rigorous purification procedures to guarantee the quality and effectiveness of the finished product for its intended medical uses. In conclusion, the synthesis of theophylline and its mode of action clarify its function as a bronchodilator, highlighting its significance in the treatment of respiratory disorders.

Future research is still being conducted to determine how to maximize its benefits and reduce its drawbacks, guaranteeing its continued applicability as a treatment for respiratory conditions.

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ABBREVIATION:

PDE - Phosphodiesterase
HDAC - Histone deacetylase
COPD - Cronic Obstructive Pulmonary Disease
Camp - Cyclic adenosine monophosphate
IL-10 - Interleukin 10
NAD - Nicotinamide adenine dinucleotide
CREB - Cyclic AMP response element binding
GM CSF - Granulocyte macrophage colony stimulating factor
CXCL8 - C-X-C Motif Chemokine Ligand 8.

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