Introduction

Background

Historically, the majority of new drugs have been generated (secondary metabolites) from compounds derived from natural products \[^1\]. The R&D thrust in the pharmaceutical sector is focused on development of new drugs, innovative/indigenous processes for known drugs and development of plant-based drugs through investigation of leads from the traditional systems of medicine. In addition, many nutraceuticals are being consumed in unregulated markets for perceived benefits in health care and improvement of quality of life \[^2\]. Indian medicinal system has a long history, and one of the oldest organized systems of medicine. It is mainly influenced by Ayurveda, Siddha, Unani and Homeopathy. These systems used natural products such as plant, terrestrial and marine animals, micro-organisms derived preparations to cure the dreadful diseases \[^3\].

1.1 Ayurveda – the ancient science of life

Ayurveda remains one of the most ancient and yet living traditions practised widely in India, Sri Lanka and other countries and has a sound philosophical and experiential basis \[^4, 5\]. Indian healthcare consists of medical pluralism and ayurveda still remains dominant compared to modern medicine, particularly for treatment of a variety of chronic disease conditions. India has about 45,000 plant species; medicinal properties have been assigned to several thousands; about 2000 are found in the literature; indigenous systems commonly employ about 500–700. Government of India has formal structures to regulate quality, safety, efficacy and practice of herbal medicine \[^6\]. With unique holistic approach, ayurvedic medicines are usually customized to an individual constitution. Exhaustive information is available in ayurvedic literature that can be converted into a large database giving information of various foods, herbs, medicines and other materials with their taste, actions and utility in different disorders \[^7\]. Current estimate indicates that about 80% of people in developing countries still rely on traditional medicine based largely on various species of plants and animals for their primary healthcare \[^8\].
1.2 Evolving role of natural product drug discovery

Natural product remains a prolific source for the discovery of new drugs. Natural product compounds are the source of numerous therapeutic agents [9]. Recent progress to discover drugs from natural product sources has resulted in compounds that are being developed to treat cancer, immune suppressive disorders and to resist bacteria and viruses. The need for new chemical entities for health care is explored and served through plant sources. In the last few decades, there has been an exponential growth in the field of herbal medicine. In olden times Vaidyas used to treat patients on individual basis and prepare drugs according to the requirement of the patient. Side effects of conventional allopathic medicine, efficiency of plant derived drugs and growing interest in natural products has increased the scientific interest in medicinal plants which are being cultivated on large scale [10]. Clinical, pharmacological, and chemical studies of these traditional medicines, which were derived predominantly from plants, were the basis of most early medicines such as aspirin, digitoxin, morphine, quinine, and pilocarpine [11-14]. The output from the early years of penicillin antibiotic research was prolific and included examples such as streptomycin, chloramphenicol, chlortetracycline, cephalosporin C, erythromycin, and vancomycin [15, 16]. All of these compounds, or derivatives thereof, are still in use as drugs today. Despite this success, pharmaceutical research into natural products has experienced a slow decline during the past two decades. It has long been recognized that natural-product structures have the characteristics of high chemical diversity, biochemical specificity and other molecular properties that make them favorable as lead structures for drug discovery, and which serve to differentiate them from libraries of synthetic and combinatorial compounds [17]. Various investigators have worked to measure by means of computational chemistry, the desirable chemical features that distinguish natural products from other sources of drug leads. Other investigators have differentiated natural products, trade drugs or other synthetic molecular libraries on the basis of scaffold architecture and pharmacophoric properties [18], or other molecular descriptors [19]. Recent advances in genomics and structural biology during the past 5–10 years are painting a clear picture of the diversity of proteins targeted by natural-product molecules. It has been shown that the
number of unique protein architectures (or folds) in nature is much smaller than the number of protein families predicted by sequence similarity \[^{20,21}\].

Natural products isolated from plants, animals and microorganisms have made an important impact on curing the dreadful human diseases. The examples of few natural product compounds are taxol, vinca alkaloids (vincristine and vinblastine), podophyllotoxin derivatives (etoposide, teniposide), camptothecin derivatives (topotecan and irinotecan) for cancer treatment, quinine and artemisinin for malaria treatment, captopril for hypertension treatment, premarin for induction of ovulation and pencillins, streptomycins, tetracyclines for the treatment of bacterial infections \[^{22}\].
1.3 Challenges of drug discovery from natural Sources

Drug discovery is a complex, interdisciplinary pursuit of chemistry, pharmacology, and clinical sciences, which has benefited humankind immensely over the last 100 years [23, 24]. Natural products continue to play a dominant role in the discovery of leads for the development of drugs to treat human diseases. Such chemical agents have traditionally played a major role in drug discovery and still constitute a prolific source of novel chemotypes or pharmacophores for medicinal chemistry. Natural product-based scaffolds find key importance in drug discovery as well as in optimizing chemical diversity for human use. The major bottleneck that continues to affect natural product drug discovery is the isolation and purification of the active principles from an exceptionally complex matrix. Often the target compounds represent much less than 1% by weight of the crude extract, and the approach remains highly experimental. Although advances in separation technology such as high performance liquid chromatography (HPLC), supercritical fluid chromatography (SFC) and capillary electrophoresis (CE) have had a major impact on resolving power, often the purification step in the process is rate-limiting. The challenge is two fold: first, one must correlate the biological signal of interest with the effector compounds, and second one must then device preparative separation methods to yield sufficient quantities of the pure material [25]. Another major worry is that the complex nature of some natural product chemical structures, which are critical for the biological activity of the compound, may impede the lead optimization process. However, over the past few years there has been significant effort devoted to the semi-synthesis and synthesis of complex natural products [26].

![Figure 3. Number of drugs approved in the United States from 1981 to 2007](image-url)
Despite of advantages and the past successes, many large pharmaceutical companies have decreased the use of natural products in drug discovery screening. This has been because of the perceived disadvantages and difficulties of natural products in access and supply, complexities of natural product chemistry and inherent slowness of working with natural products, and concerns about intellectual property rights [27, 28, 29].

**Road ahead for natural product drug discovery**

The natural product drug discovery process generally involves the testing of extracts of source organisms of plant, marine or microbial origin in appropriate *in vitro* assays (cell or enzyme/target based), followed by bioassay-guided fractionation of the active extracts and isolation and purification of active constituents. Those constituents showing significant *in vivo* activity in appropriate animal models are considered as lead molecules which may be selected as candidates for preclinical development. Initially, such leads may be structurally modified through use of medicinal or combinatorial chemistry techniques to provide agents having superior activity or decreased toxicity (optimization of the therapeutic index) and acceptable pharmacological properties. The development of natural product-derived drugs poses significant challenges in several areas. Of prime concern is the supply of the drug in sufficient quantities to permit preclinical, and hopefully clinical, development, and ultimately, if given, a successful, clinical outcome, the commercial production. Following picture depicts in brief the process of natural product drug discovery [30].

![Figure 4 Drug discovery process in brief](image-url)
Asthma

Asthma is one of the commonest diseases in industrialized countries and there is convincing evidence to suggest that its prevalence and morbidity are increasing, despite better recognition and increased prescriptions for anti-asthma therapy [31]. Asthma is characterized by allergic inflammatory responses with airway hyper responsiveness, and its prevalence is increasing in many countries as one of the important socio-medical problems [32]. Both clinical and experimental studies suggest that eosinophils and Th2 type lymphocytes play a key role in the induction of airway inflammation and mucosal injury, which closely links to non-specific hyper responsiveness in asthma [33]. Many inflammatory cells participate in the inflammatory process in asthma and mediate a complex mixture of mediators. Cytokines are of particular importance as mediators of chronic inflammation and the means by which cytokines amplify and perpetuate the inflammatory process is now emerging. The inflammatory process in asthma results not only in bronchoconstriction, but also plasma exudation, the activation of neural mechanisms and mucus secretion. The chronic inflammation may lead to structural changes, including an increase in airway smooth muscle and fibrosis that are essentially irreversible [34].

Figure 5. Inflammation in the airway of asthmatic patients leads to airway hyperresponsive and symptoms.
During an asthma episode, inflamed airways react to environmental triggers such as smoke, dust, or pollen as shown in figure 6. The airways narrow and produce excess mucus, making it difficult to breathe. In essence, asthma is the result of an immune response in the bronchial airways.[35]

***Figure 6. Major triggers for asthma***

**Pathophysiology of Asthma**

The concepts underlying asthma pathogenesis have evolved dramatically in the past 25 years and are still undergoing evaluation as various phenotypes of this disease are defined and greater insight links clinical features of asthma with genetic patterns. Asthma is the presence of underlying airway inflammation, which is variable and has distinct but overlapping patterns that reflect different aspects of the disease.[36] It had been recognised for many years that patients who die of asthma attacks have grossly inflamed airways. Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway which includes bronchoconstriction, airway edema, airway remodeling, and airway hyperresponsiveness. This airway inflammation leads to occlusion of lumen by a tenacious protein mucus plug composed of plasma proteins exuded from airway vessels and mucus glycoproteins secreted from surface epithelial cells. The airway wall is oedematous and infiltrated with inflammatory cells, which are predominantly eosinophils.
and lymphocytes. The airway epithelium is invariably shed in a patchy manner and clumps of epithelial cells are found in the airway lumen [37].

**Figure 7. Pathophysiological stages in asthma**

**Treatment of Asthma**

While there is no cure for asthma, symptoms can typically be improved, a specific, customized plan for proactively monitoring and managing symptoms should be created. This plan should include the reduction of exposure to allergens, testing to assess the severity of symptoms, and the usage of medications. The treatment plan should be written down and advise adjustments to treatment according to changes in symptoms [38]. The most effective treatment for asthma is identifying the triggers, such as cigarette smoke, pets, or aspirin, and eliminating exposure to them. If trigger avoidance is insufficient, the use of medication is recommended. Pharmaceutical drugs are selected based on, among other things, the severity of illness and the frequency of symptoms. Specific medications
for asthma are broadly classified into fast-acting and long-acting categories. The goal of asthma treatment is to achieve and maintain clinical control. Clinical studies have shown that asthma can be effectively controlled by intervening to suppress and reverse the inflammation as well as treating the bronchoconstriction and related symptoms. Medications to treat asthma can be classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. They include inhaled and systemic glucocorticoids, leukotriene receptor antagonists, long-acting inhaled β2-agonists in combination with inhaled glucocorticoids, sustained-release theophylline, cromones, anti-IgE, and other systemic steroidsparing therapies. Inhaled glucocorticoids are the most effective controller medications currently available. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms. They include rapid-acting inhaled β2-agonists, inhaled anticholinergics, short-acting theophylline, and short-acting oral β2-agonists. Thus these medications that control and relieve asthma can be used for prophylaxis and treatment of acute episodes. Following figure describes the classification of commonly prescribed drugs in asthma.

Despite increased understanding of the pathogenesis of asthma and allergic diseases, control of severe asthma is still difficult. Many of the medications prescribed for
asthma have serious side effects; some herbal remedies allow the medications to be taken at lower dosages, helping to lower the incidence of side effects. World Health Organisation has recognized the potential of traditional and folk medicine in the management of health care system and currently it is encouraging and promoting the traditional systems in National Health Care programmes of various countries. Unlike synthetic substances the natural drugs do not give symptomatic relief, rather provide complete cure of many diseases. Herbal formulation used in the management of asthma, judiciously combine herbs for breathing with antioxidant herbs to support the digestive, cardiac, and nerve functions and expectorant as well as soothing herbs for successful prevention and treatment of respiratory tract conditions [44]. Some of the herbal plants used in the treatment of bronchial asthma are listed in table given below [45].

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Parts used</th>
<th>Name of the plant</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bark</td>
<td><em>Acacia catechu</em></td>
<td>Mimosaceae</td>
</tr>
<tr>
<td>2</td>
<td>Leaf</td>
<td><em>Adhatoda zeylanica</em></td>
<td>Acanthaceae</td>
</tr>
<tr>
<td>3</td>
<td>Bulb</td>
<td><em>Allium sativum</em></td>
<td>Alliaceae</td>
</tr>
<tr>
<td>4</td>
<td>Leaf</td>
<td><em>Datura stramonium</em></td>
<td>Solanaceae</td>
</tr>
<tr>
<td>5</td>
<td>Whole plant</td>
<td><em>Eclipta prostrata</em></td>
<td>Asteraceae</td>
</tr>
<tr>
<td>6</td>
<td>Roots, bark</td>
<td><em>Fiscus hetrophylla</em></td>
<td>Moraceae</td>
</tr>
<tr>
<td>7</td>
<td>leaves</td>
<td><em>Hedyotis puberula</em></td>
<td>Rubiaceae</td>
</tr>
<tr>
<td>8</td>
<td>Leaf</td>
<td><em>Hibiscus mutablis</em></td>
<td>Malvaceae</td>
</tr>
<tr>
<td>9</td>
<td>Seed</td>
<td><em>Iberis amara</em></td>
<td>Brassiaceae</td>
</tr>
<tr>
<td>10</td>
<td>Flower</td>
<td><em>Jasminum arborescences</em></td>
<td>Oleaceae</td>
</tr>
</tbody>
</table>
Of the several drugs currently available, the patients are not completely satisfied with their effects. There is no doubt that there is an urgent need of new and effective herbal drugs, which are able to treat or even possibly cure the allergic inflammation. With the thrust to search effective antiasthmatic plant drug, this study is undertaken to validate medicinal plants used by the tribes of India for their antiasthmatic potential.

In order to evaluate the ethnobotanical claim and to identify a potential lead for the treatment of asthma, the present work entitled “Pharmacognostical, phytochemical and biological evaluation of *Ventilago maderspatana* and *Ziziphus xylopyrus* for their antiasthmatic activity” has been carried out.