2.1. Asthma

Asthma is a "**Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration between attacks**" (Hoareau and DaSilva, 1999). National institute of health (NIH) defines asthma as a distinctive chronic inflammatory disorder of the airways in which many cells and cellular elements play a vital role, in particular, mast cells, eosinophils, T-lymphocytes, neutrophils and epithelial cells (Gilfillan and Beaven, 2011). However, the father of modern medicine Sir William described asthma in the terms including:

1. Spasm and swelling of the bronchial muscles
2. Special inflammation of the smaller bronchioles
3. Resemblances to hay fever
4. The affection running in families.
5. Often beginning in childhood and sometimes lasting into old age.
6. Bizarre and extraordinary variety of circumstances which at times induce a paroxysm; Climate and atmosphere (e.g. hay, dust, cat), fright or violent emotion, diet (overloading of stomach) or certain foods, and cold infection.
7. Sputum is distinctive (Walker *et al.*, 2013).

The prevalence of asthma is estimated up to 38% in children and from 2-12 % in adults (Cavkaytar and Sekerel, 2014). Initially, this disease is characterized by recurrent attacks of breathlessness and wheezing, which might vary in severity and frequency from person to person. In an individual, these occurrences may switch from hour to hour and day to day. This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. In an attack, the lining of the passages swell causing the airways to narrow and reducing the flow of air in and out of the lungs (Jain *et al.*, 2006). Biologically, there are two general categories; extrinsic and intrinsic depending upon the types of stimuli that trigger attacks. The first is caused by a type of immune system response to inhaled allergens such as pollen, animal dander or dust mite particles. Later one is caused by inhalation of chemicals such as cigarette smoke or cleaning agents, taking aspirin, a chest infection,
stress, laughter, exercise, cold air, food preservatives or a myriad of other factors (Romanet-Manent et al., 2002).

Globally, between 100 and 150 million people suffer from asthma and this number is rising every year. Worldwide mortality from this condition has reached over 180,000 annually. Over the years, achievement and maintenance of control via assessment of clinical manifestations and future risk has become the aim of treatment over the years (Moorman et al., 2012). Few stats have been presented below.

- Around 8% of the Swiss population suffers from asthma as against only 2% some 25-30 years ago.
- In Germany, there are an estimated 4 million asthmatics.
- In Western Europe as a whole, asthma has doubled in ten years, according to the UCB Institute of Allergy in Belgium.
- In the United States, the number of asthmatics has leapt by over 60% since the early 1980s and deaths have doubled to 5,000 a year.
- There are about 3 million asthmatics in Japan of whom 7% have severe and 30% have moderate asthma.
- In Australia, one child in six under the age of 16 is affected.

About 15 million disability adjusted life years (DALYs) are lost annually due to asthma which represents 1% of the total global disease burden. The estimated annual death rate due to asthma is ~ 250,000 and the majority of deaths occur in low and middle income countries (To et al., 2012). The socio-economic status (SES) is an important determinant of health and nutritional status as well as of mortality and morbidity. SES also influences the accessibility, affordability, acceptability and actual utilization of various available health facilities. There have been several studies conducted to establish the relationship between the healths related problems and SES.

COPD in India has been studied in several small surveys which have enormously varied in their methodology, results and scope of interpretation. The prevalence rates of from 2 -
22% in men and from 1.2 - 19% in women were generally based on invalidated questionnaire interviews which could not be relied for any national assessment (Jindal et al., 2001). The Indian Council of Medical Research (ICMR) took the initiative to study the epidemiology of chronic respiratory diseases and sponsored the Indian study on epidemiology of asthma, respiratory symptoms and chronic bronchitis (INSEARCH) which included 4 centers in the Phase I and 12 other centers in the Phase II study. The results of the Phase I study from Chandigarh, Delhi, Kanpur and Bangalore reported the overall prevalence rates of ~ 5.0% respectively in men and women of, and over 35 years of age.

Asthma is not just a public health problem for developed countries. In developing countries, however, the incidence of the disease varies greatly.

- India has an estimated 15-20 million asthmatics.
- In the Western Pacific Region of WHO, the incidence varies from over 50% among children in the Caroline Islands to virtually zero in Papua New Guinea.
- In Brazil, Costa Rica, Panama, Peru and Uruguay, prevalence of asthma symptoms in children varies from 20% to 30%. In Kenya, it approaches 20%.
- In India, rough estimates indicate a prevalence of between 10% and 15% in 5-11 year old children.

Importantly, it can be seen from the results of the in-search (Phase I) report and the median prevalence-rates assessed from the earlier studies, that the overall rates are generally similar in both men and women. The contemporary prevalence from several other Asian countries is also comparable. The mean rates in India have not really changed when compared for different time periods. But the total burden of COPD has more than doubled to about 14.84 million in 2011 from about 6.45 million in 1971. This is generally attributable to the overall increase in the population of India (Jindal, 2012; Agarwal, 2008).
2.2 Airway associated factors and mechanism in pathophysiology of asthma

2.2.1 Bronchoconstriction

The dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle (Adams et al., 1997). Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin are also reported to cause acute airflow obstruction in some patients. In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway inflammation. However, stress might also precipitate asthma exacerbations. Yet, no scientific mechanism has been established (Stevenson and Szezeklik, 2006). The pathophysiology has been presented in Fig. 2.1.

![Fig. 2.1: Pictorial representation of: A) The location of the lungs and airways in the body, B) A cross-section of a normal airway, and C) A cross-section of an airway during asthma symptoms.](image-url)
2.2.2. Airway edema

Asthma becomes more persistent and inflammations more progressive, whilst other factors further limits the airflow. These may include edema, inflammation, mucus hypersecretion and the formation of mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle (Brown et al., 1995).

2.2.3. Airway hyper-responsiveness

The degree to which airway hyper-responsiveness can be defined by contractile responses to challenges with methacholine correlates with the clinical severity of asthma. The mechanisms influencing airway hyper-responsiveness are multiple and include inflammation, dysfunctional neuro-regulation and structural changes. Inflammation appears to be a major factor in determining the degree of airway hyper-responsiveness. Treatment directed toward reducing inflammation can reduce airway hyper-responsiveness and improve asthma control (Kudo et al., 2012).

2.2.4. Airway remodeling

Some persons who have asthma, airflow limitation may be only partially reversible. Permanent structural changes can occur in the airway that is associated with a progressive loss of lung function and is not prevented by or fully reversible by current therapy (Holgate and Polosa, 2006). These structural changes can include thickening of the sub-basement membrane, sub-epithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion. Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response (Sagalani et al., 2005). The exact cause of asthma is not yet known. It is believed that a person gets asthma for different reasons, including the genes they get from their parents (genetics), changes in the way some of their genes work (epigenetics) and things in their life that are not healthy (unhealthy or negative environmental factors) as shown in Fig. 2.2.
Inflammation holds a central role in the pathophysiology of asthma. The mechanistic pathophysiology has been presented in Fig. 2.3. Asthma occurrence is due to airway inflammation because of interaction of many cell types and multiple mediators with the airways. These eventually results in the characteristic pathophysiological features of bronchial inflammation and airflow limitation leading to recurrent episodes of cough, wheeze, and shortness of breath (Evas et al., 2009).

**Fig. 2.2:** Various causes of asthma.
The processes by which these interactive events occur and lead to clinical asthma are still under investigation. Although, distinct phenotypes of asthma exist (e.g. intermittent, persistent, exercise-associated, aspirin-sensitive, or severe asthma), airway inflammation remains a consistent pattern. The pattern of airway inflammation in asthma, however, does not necessarily vary depending upon disease severity, persistence, and duration of disease. The cellular profile and the response of the structural cells in asthma are quite consistent (Holgate, 2008).

Often, having one medical problem makes it more likely a person will also have one or more other medical or psychiatric problems. These other disorders are the "comorbid problems" or "comorbidities" (Hickey, 2013). There are various comorbid medical and psychiatric conditions associated with asthma as presented in Fig. 2.4.
2.3. Pharmacologic therapy

Asthma is classified according to its severity, mild intermittent, mild persistent and moderate persistent or severe persistent. Whilst, the treatment of asthma is always based on the frequency and severity of exacerbations in addition to the degree of impairment of lung function (Louis et al., 2000). The national asthma education and prevention program (NAEPP) guidelines recommend a stepwise approach in treatment starting with the most aggressive therapy necessary to achieve control, followed by a “step down” to the minimal therapy, as maintenance treatment. The aims of anti-asthmatic therapy are to reduce day-time/night-time symptoms, asthma episodes in addition to maintain normal activities without producing adverse effects (Braman and Vigg, 2008).

2.3.1. Quick-relief medications

These drugs (oral β2 agonists; inhaled) are short acting, short-course oral corticosteroids likely, ipratropium (Atrovent). These are used as in need for immediate relief and also to avoid induced bronchospasm. Short acting β2 agonists quickly relax bronchial smooth muscle and relieve acute symptoms in order to prevent exercise induced bronchospasm.

Fig. 2.4: Comorbid problems or comorbidities associated with asthma.
These agents have a good safety and efficacy record (Chapman et al., 2008). Overuse of these agents reduces their efficacy and has been associated with adverse side effects such as bronchial hyper-reactivity, CNS overstimulation, worsening asthma and leading to death. Most MDIs hold 120 two-spray doses and should last one month if used four times daily. On the other hand, oral corticosteroids have broad anti-inflammatory effects and may be used in a limited, short course (3 - 10 days) to gain initial control of the asthma (Alhegagi, 2009). Ipratropium (anticholinergic drug) has been prescribed for children and may be helpful in those rare children who do not tolerate β2 agonists (Jara et al., 2012).

2.3.2. Long-term control medications

A medication for long-term control is prescribed to take daily in order to maintain control of asthma and prevent exacerbations. Inhaled corticosteroids are the most potent and effective long-term anti-inflammatory medications. They act via reducing inflammation in airways, improving pulmonary function, and reducing bronchial hyper-responsiveness thus transforming disease development. Some corticosteroids are effective in once or twice-daily dose regimen in all patient groups (Bennett et al., 1994). The FDA recently approved budesonide inhalation suspension (Pulmicort Respules), the only nebulizable corticosteroid for children 1-8 years. It is available in unit doses of 0.25 mg and 0.50 mg for once or twice daily dose. Long-term use at high doses may inhibit growth velocity, therefore, children's growth should be monitored regularly (Hickey, 2013). Adverse effects (e.g., oropharyngeal candidiasis or inhibited growth) resulting from the use of inhaled corticosteroids also discourage the compliance (Lai et al., 2003).

Long-acting β2 agonists are not as effective as inhaled corticosteroids in reducing airway hyper-responsiveness or controlling the inflammation of asthma. However, long-acting β2 agonists are effective that can be used as add-on therapy. The FDA has approved salmeterol (Serevent), a long-acting β2 agonist for treatment of asthma in children of age 12 years or more. It can provide 24 hour bronchodilation with twice-daily dose (Bateman et al., 2008). As reported, long-acting β2 agonists when used in combination with inhaled corticosteroids produce an additive effect. However, in August 2000, the FDA approved a combination of almeterol and fluticasone (Advairdiskus) with a dosage of single inhale twice daily (Greenstone et al., 2005). Methylxanthines likely, theophylline is related to caffeine and has been used in treatment of asthma. Theophylline inhibits release of
mediators from mast cells, increases mucociliary clearance, and prevents the
development of micro vascular leakiness, as would an “anti-inflammatory” drug.
Theophylline also inhibits few functions of T lymphocytes in order to control of chronic
inflammation of the airway (Moon et al., 2006). Theophylline produces mild-to-moderate
bronchodilation and can be used as add-on therapy with anti-inflammatory medications.
Theophylline is reserved for the treatment of patients with severe asthma (Holgate and
Polosa, 2006; Bousquet et al., 2005). Cromolyn sodium (Intal) and nedocromil (Tilade)
are first-line place in therapy daily that inhibit early and late-phase bronchoconstriction,
with minimal side effects and does not produce any drug interactions. These are available
in MDI and nebulizer formulations. In addition, the bitter taste of Nedocromil
discourages compliance in case of some reported children (Cote et al., 2005).

From the class of anti-inflammatory drugs, antileukotriene agents were developed to
inhibit the effects of leukotrienes. As, leukotrienes possess potent pro-inflammatory
actions resulting in elevated permeability (vascular), mucus secretion and bronchial
hyper-responsiveness. Anti-leukotrienes act via improving lung function and diminish
symptoms, exacerbation rate and the need for rescue bronchodilator. This class of drugs
represents a strategic therapy in asthma in 25 years (Baumgartner et al., 2003). The
leukotriene antagonist smontelukast (Singulair), zafirlukast (Accolate) and the 5-
lipoxyge-nase inhibitor zileuton (Zyflo) are distinctive of their mechanism of action with
respect to asthmatic inflammation. Montelukast block the early and late response to
allergen following single dosing, to improve FEV1 in both children (6–14 years) and
adults in order to protect against the development of exercise induced bronchoconstriction in both children and adults. A 10 mg tablet is approved for use in
children with age more than 15 years (Spector and Tan, 2004; Chan and Kuhun, 2009),
and a 4 or 5 mg chewable tablet for children 2-5 years. Zafirlukast (10 mg twice daily) is
also FDA labelled for the treatment of children older than 7 years. Inaddition, zileuton is
also FDA-labelled for paediatric treatment (Silverman et al., 2004).

Although the role of these drugs continue to demonstrate the role of antileukotrienes
likely, efficacy against bronchoconstriction, and an additive benefit treatment for
moderate asthma that rely on corticosteroids. The safety data of montelukast and

School of Pharmaceutical Sciences, Shoolini University, Solan
zafirlukast are excellent. Rarely, Churg-Strauss syndrome has been associated with corticosteroid withdrawal (Pearlman et al., 1999).

### 2.4. Management of acute severe asthma

The guidelines provided are based on the British Thoracic Society. Life-threatening asthma includes silent chest, exhaustion, cyanosis, peak flow 33% of predicted or best, saturation 92%, that requires immediate treatment with following management provided in Table 1 (Moneret –Vautrin, 2005; Sydow et al., 1993).

In case of chronic asthma, the primary objectives that management includes are to control associated symptoms, thereafter to prevent exacerbations with minimal side effects. The British Thoracic Society/Scottish Intercolligate Guideline Network (BTS/SIGN) proposed a five-step management plan, as presented in Fig. 2.4, that describes the treatment in an adult (Smith et al 2005; Agarwal et al 2015).

#### Table 2.1: Strategies for management of asthma

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High flow oxygen (FiO₂ 40-60% oxygen)</td>
</tr>
<tr>
<td>2</td>
<td>Glucocorticosteroids</td>
</tr>
<tr>
<td>3</td>
<td>Nebulized β2 agonist (e.g. salbutamol) plus ipratropium employing nebulizer</td>
</tr>
<tr>
<td>4</td>
<td>In case the above bronchodilator treatment does not produces effective response, consider i.v. infusion β2 agonist (e.g. salbutamol), or slow i.v. injection of aminophylline/theophylline</td>
</tr>
<tr>
<td>5</td>
<td>In refractory cases; slow i.v. injection should be considered of magnesium sulphate</td>
</tr>
<tr>
<td>6</td>
<td>If bacterial infection is suspected use of an antibiotic (e.g. co-amoxiclav or clarithromycin) is recomended</td>
</tr>
<tr>
<td>7</td>
<td>If the patient fails to respond and develops increasing tachycardia, with increasing respiratory rate and a fall in PaO₂ to 8 kPa or a rise in PaCO₂ to 6 kPa, assisted ventilation will probably be needed.</td>
</tr>
<tr>
<td>8</td>
<td>Contraindication: sedation</td>
</tr>
</tbody>
</table>
General care with monitor fluid/electrolyte status (especially hypokalaemia)

Fig. 2.5: Approach to asthma therapy in a non-acute situation.

2.5. Natural therapy for asthma

Natural therapy, regarded as an “alternative medicine”, is one of the complementary approaches using extracts from natural origin as medicines or health promoting agents. In recent years, natural products have received great attention for disease prevention due to their various health benefits and noticeable lack of toxicity and side effects. Many dietary plant products such as grains, nuts, cereals, soy, spices, flaxseed oil, fruits, vegetables, medicinal plants, and herbs contain various phytochemical constituents, such as phenolics, carotenoids, alkaloids, nitrogen and organosulfur compounds, and vitamins. Despite gaps in our knowledge of how phytochemicals interfere with cellular functions,
several natural plant products are utilized to prevent or treat various diseases and disorders. Identification of a plant agent with therapeutic potential requires multiple steps involving *in vitro* studies, efficacy and toxicity studies in animal models, and then human clinical trials.

### 2.5.1. Genus *Onosma* (*Boraginaceae*)

The genus *Onosma* *(Boraginaceae)* includes about 150 species distributed worldwide in which only about 75 plants have been described for its morphology and less than 10 plants for their chemical constituents and clinical potential. The phytochemical reports of this genus reveal that it comprises mainly aliphatic ketones, lipids, napthazarins, alkaloids, phenolic compounds, napthoquinones, flavones while most important are shikonins and onosmins. The plants are also equally used in eye, blood diseases, bronchitis, abdominal pain, stangury, thirst, itch, lecderma, fever, wounds, burns, piles and urinary calculi. The flowers of various plants are prescribed as stimulants, cardiotonic, in body swelling while leaves are used as purgative and in cutaneous eruptions. The roots are used for coloring food stuffs, oils and dyeing wool and in medicinal preparations.

The genus *Onosma* *(Boraginaceae)* represents about 150 known species in Asia (El-shazly A *et al.*, 2003) including 29 species in China, (Shu, 1995) 95 species in Turkey (Reidl, 1978) and 8 in Pakistan, (Nasir, 1989) but recent studies and revisions have increased the number of species in this genus to over 230 species.(Binzet and Orcan, 2010). The name *onosma* for this genus was introduced into modern botanical nomenclature by Linnaeus, which is derived from a Latin word “osma” originated from a Greek word, “osma” means smell (Stearn, 1993). All species grow in dry or moist and sunny habitats usually in rock crevices and popularly known as rock garden plants (Reidl, 1978). *Onosma* L. is a species-rich genus with complicated patterns of morphological, karyological variation and taxonomic treatments within the groups of this genus are highly controversial. Many similar species were described based on minor morphological
differences and consequently they have often been confused. In addition, in the European area, their distribution is rather fragmented and classifications have often been done on the basis of geographically limited studies, (Kolarcik et al., 2010) which appears to be partly artificial and there is a need for re-investigation that new data may provide useful reference in a future classification (Reidl, 1978). According to “The Plant List” of Royal Botanic Garden, Kew and Missouri Botanical Garden, includes 387 scientific plants names of species rank for this genus in which only 37 are accepted species names and further 19 scientific plant names are of infra-specific rank. This list also shows that only 9.6% names are accepted and 6.2% names are synonyms while 84.2% names are still not assessed.

2.5.2. *Onosma bracteatum*

*Onosoma. bracteatum* belongs to family *Boraginaceae*. It is generally known as Gaozaban, Gojihva and Sedge. The plant is found in western Himalayas, from Kashmir to Kumaon between 3600-4500m elevations. In Himachal Pradesh, it is reported from districts of Kangra (chhota and barabhangal), Pangi-Bharmour, Kinnaur, Lahaul, and spiti in driers areas.

2.5.2.1. **Description**

It is large, herbaceous perennial with black, woody root stock, Knotty head from which arise several stems, erect or ascending. Root is purplish red from inside and the stem is simple and rarely branched, thickly studded with calcareous tubercles and armed with bristles. The leaves are entire, thick, petiolate and ovate-acuminate. It is an average sized perennial herb and the stems are as many, simple, hairy, arising from an importunate cluster of radical leaves, which are lanceolate and with conspicuous hairy pallid bases. The picture has been presented in Fig. 2.5.
Fig. 2.6: Photograph of *O. bracteatum* plant.

According to “The Ayurvedic Pharmacopoeia of India (R)” the description of the plant has been provided as follows:

**2.5.2.2: a) Macroscopic:**

*Stem* - Cut pieces available in 5-9 cm long and 3.2 to 4.7 cm in dia., flattened, erect, stout; rough due to white, hard, hispid hairs and cicatrices, and longitudinal wrinkles; colour greenish-yellow; fracture, short; odour and taste not characteristic.

*Leaf* - Lanceolate to ovate-lanceolate, 12-30 cm long, 1.5-3.5 cm broad, acuminate tubercle-based hispid hairs present on both surfaces; greenish to light yellow on top and white beneath.

**b) Microscopic:**

*Stem* - Shows single-layered epidermis, covered with thick cuticle, some epidermal cells elongate to form long, warty, tubercle-based unicellular hairs, cortex differentiated in two
zones, 5-7 layered outer collenchyma, 3-4 layered inner parenchymatous cells, consisting of thin-walled, round to oval cells; phloem composed of usual elements; phloem fibres absent; xylem consisting of usual elements, vessels mostly solitary or rarely 2-3 in groups having spiral thickening, and fibres and tracheids having blunt tips and simple pits; xylem ray not distinct: pith consisting of round, thin-walled, parenchymatous cells.

**Leaf** - Midrib-single layered epidermis with thick cuticle and long warty, tubercle-based unicellular hairs present on both surfaces followed by 5-7 layers of collenchymatous and 3-4 layers parenchymatous cortical cells; vascular bundle situated centrally.

**Lamina** - isobilateral, single layered epidermis on either surface covered with thick cuticle, long warty, tubercle-based, simple, unicellular hairs present on both surfaces; palisade 2 layered, and spongy parenchyma 8-10 layered, stomata paracytic.

**Powder** - Greenish-brown; shows groups of oval to polygonal, thin-walled straight epidermal cells; spiral vessels; a few fibres entire or in pieces, elongated with blunt tips; long warty, tubercle-based unicellular hairs and a few paracytic stomata.

### 2.5.2.3. Chemical constituents

The literature survey revealed that very little phytochemical work has been carried out on the *O. bracteatum*. The plant contains some naphthaquinones, alkaloids and phenolic compounds. Alkannins and shikonins are chiral-pairs of naturally occurring isohexenynaphthazarins, found in the external layer of the roots of many species that belongs mainly to the *Onosma* of the *Boraginaceae* family (El-shazly *et al.*, 2003). Furthermore, nine minor alkaloids were identified on the basis of mass spectral data and/or Kovats retention indices (Shu, 2003). When roots of *Onosma argentatum* Hub. Mor. were extracted with n-hexane-dichloromethane mixture (1:1), subjected to silica gel column chromatography and elution was performed with a n-hexane-ethyl acetate mixture with gradient elution, deoxyshikonin, acetyl shikonin, 3-hydroxy-isovaleryl shikonin, 5,8-O-dimethyl acetyl shikonin were obtained (Reidl, 1978). The *O. bracteatum* and *Onosma thracicum* exhibits oleic and α-linolenic acids quantified at higher levels in endemic *O. bracteatum* while other fatty acids and α-tocopherol were observed at higher
concentrations in *O. thracicum*. The study of Onosmaechioides C. B. Clarke non Linn showed an alkannin or shikonin content with naphthoquinone derivatives i.e. deoxyalkannin or deoxyshikonin and 5, 8-dihydroxy-2-(4-methyl-6-oxo-5, 6-dihydro-2H-pyran-2-yl (1-4)- naphthoquinone and arnebin-6. Volatile components obtained by hydrodistillation from the aerial parts (leaves and flowers) of *O. echioides* L. var. columnae Lacaita were investigated by gas chromatography and gas chromatography-MS where 64 volatile components were identified, hexadecanoic acid and phytol were predominant in the flower oils while phytol and hexahydrofarnesyl acetone were the major components in the leaf oils. Alkanes, fatty acids and aldehydes constituted the major fraction in the flower oils while oxygenated diterpenes and ketones were predominant in the leaf oils (Nasir, 1989; Stearn, 1993).

Onosmins A and B have been isolated from *Onosma hispidum* Wall. ex G. Don and their structures were established as 2-[(4-methylbenzyl) amino] benzoic acid and methyl 2-[(4-methylbenzyl) amino] benzoate through spectroscopic studies, including 2D-NMR. The known compounds are apigenin, 6, 4'-dimethoxy-3, 5, 7-trihydroxy-flavone, 6, 7-dimethoxy-3, 5,4' trihydroxy-flavone and apigenin 7-O-beta-D-glucoside are also reported from this species. In 2006, from its ethanolic extract of root bark, isolation of 4-hydroxy-3-methoxy cinnamic acid (ferulic acid) and 4-hydroxy-3-methoxy benzoic acid (vanillic acid) was performed. Hispidone, a new flavanone has been isolated and assigned the structure (2S)-5, 2'- dihydroxy-7, 4', 5' trimethoxy-flavanone by spectroscopic methods and in addition to this benzoic acid and 4-hydroxy benzoic acid are also reported from this species (Kolarcik et al., 2010).

*Onosma paniculata* is reported to contain several shikonin derivatives like β-hydroxyisovalerylshikonin, acetylshikonin, dimethylacrylshikonin and a mixture of α-methylbutyrylshikonin and is oval erylshikonin. Onosma confertum W.W. Smith, Onosmahookerii Clarke var. longiflorum Duthie, O. hookerii Clarke and Onosma waltonii Duthic and these six species of Onosma are also used by peoples of Tibet and Yunnan, which contains various types and considerable amounts of naphthaquinones (Mehrabian et al., 2011).
2.5.2.4. **Traditional or folklore uses** (Qureshi and Qaiser, 1987)

The plant is used as a tonic, demulcent, diuretic and spasmolytic. Its flowers is useful in rheumatism, alterative, diuretic, syphilis, stimulants and cardiac tonic, leprosy and with heart diseases and is used as therapeutic plant recognized traditionally in Ayurveda for the dealing of asthma as well bronchitis. The root is extensively used for coloring purposes. Bruised roots of Ratanjot are applied externally to cutaneous eruptions. It yields a dye which is used for coloring silk or wool. Plant is used in rheumatism, syphilis and leprosy, useful for relieving of excessive thirst and restlessness in febrile excitement, in relieving heart palpitation, irritation of the bladder and stomach.

The effect of *O. bracteatum* Wall extract on degranulation of rat peritoneal mast cells and cell inhibitory effect in immunologically induced degranulation of mast cells was found significant. The hydro-alcoholic extract of this plant used in asthma as it stabilizes the mast cell activity, rheumatoid arthritis and showed a significant role in the marked reduction of bronchial hyper-responsiveness on decreasing the infiltration of the eosinophils and the neutrophils in rodents. This plant is also used in the Unani system of medicine for stress, disturbances of the body homeostasis or with the disturbances of the normal body physiology such as psychological (behavioral changes), immunological and hormonal imbalances which causes the pathogenesis of certain chronic diseases such as Alzheimer's disease, Parkinson's disease, hypertension, weakness of the immune system of the human body, asthma, diabetes, heart ailments, cancer, antioxidant with wound healing activity.

In addition according to Unani system of medicine and as Sedge in the Middle East, *O. bracteatum* Wall., known as Gaozabanis traditionally used as a tonic that helps in building the body's immune resistance with regulation of urine output. It has also been reported to be used in the treatment of asthma, bronchitis, tonic, alterative, demulcent, diuretic and spasmolytic. A decoction is used in the treatment of syphilis, rheumatism, leprosy, restlessness in febrile excitement, relieving excessive thirst, useful in irritation of the bladder, palpitation of the heart, stomach and strangury, also folk medicine for the
treatment of the wound and skin diseases. As a formulation, the plant parts are used as chief adjuvant

**Table 2.2: Traditional remedies against cough and asthmatic disorders** (Mali, Dhake, 2013, Aqel. 1991, Akiba *et al.*, 1979).

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Plant</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Acacia leucophloea</em> (Roxb.) Willd. (Mimosaceae), Aniyar / Runjdo</td>
<td>The stem bark is kept in mouth for 3 - 4 times a day for the quick relief of cough.</td>
</tr>
<tr>
<td>2</td>
<td><em>Acacia nilotica</em> (L.) Del. subsp. <em>Indica</em> (Bth.) Brenan (Mimosaceae), Baval</td>
<td>The stem bark powder is given orally at bed time for 10 - 12 days regularly to cure asthma.</td>
</tr>
<tr>
<td>3</td>
<td><em>Achyranthes aspera</em> L. (Amaranthaceae), Anghedi</td>
<td>The powdered seeds given with honey or jaggery in the morning are useful in asthma. The ash of the whole plant is mixed with honey and given 3 - 4 times a day for 8 - 10 days regularly to cure cough and asthma.</td>
</tr>
<tr>
<td>4</td>
<td><em>Adhatoda vasaca</em> (L.) Nees (Acanthaceae), Ardusi</td>
<td>The juice of fresh leaves mixed with honey or fresh leaves boiled with ginger (<em>Zingiber officinale</em>) and the decoction is given twice a day for 7 - 10 days as excellent cough remedies for chronic bronchitis and asthma. The dried leaves, smoked as cigarette, give much relief in asthma.</td>
</tr>
<tr>
<td>5</td>
<td><em>Ailanthus excels</em> Roxb. (Simaroubaceae), Arduso</td>
<td>The decoction of stem bark and leaves are given for 12 - 15 days for the treatment of chronic bronchitis and asthma.</td>
</tr>
<tr>
<td>6</td>
<td><em>Alangium salvifolium</em> (L.f.) Wang. (Alangiaceae), Aankol</td>
<td>The infusion of root bark is useful in cough disorders.</td>
</tr>
<tr>
<td>7</td>
<td><em>Anisomeles indica</em> (L.) O.Ktze. (Lamiaceae), Chodharo</td>
<td>The ash of whole plant is mixed with powdered l in di piper (<em>Piper longum</em>) and honey and then the mixture is given orally at bed time to reduce the cough.</td>
</tr>
<tr>
<td>8</td>
<td><em>Anogeissus latifolia</em> (Roxb.) Wall.ex Bedd. (Combretaceae), Dhav</td>
<td>The stem bark is kept in mouth for 3 - 4 times a day to cure cough.</td>
</tr>
<tr>
<td>9</td>
<td><em>Aristolochia indica</em> L. (Aristolochiaceae), Vasar</td>
<td>The paste of fresh root is applied over chest to cure cough in children.</td>
</tr>
<tr>
<td>No.</td>
<td>Plant Name</td>
<td>Part Used</td>
</tr>
<tr>
<td>-----</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>10</td>
<td>Barleriaprionitis L. (Acanthaceae), Pilokantaselio</td>
<td>Leaves</td>
</tr>
<tr>
<td>11</td>
<td>Bauhinia racemosa Lam. (Caesalpiniaceae), Setri</td>
<td>Leaves</td>
</tr>
<tr>
<td>12</td>
<td>Buteamonosperma (Lam.) Taub. (Papilionaceae), Khakhro</td>
<td>Flowers</td>
</tr>
<tr>
<td>13</td>
<td>Calotropisprocera (Ait.) R.Br. (Asclepiadaceae), Aakdo</td>
<td>Flowers</td>
</tr>
<tr>
<td>14</td>
<td>Capparis decidua (Forsk.) Edgew. (Capparaceae), Kerdo</td>
<td>Root</td>
</tr>
<tr>
<td>15</td>
<td>Cassia tota L. (Caesalpiniaceae), Puvadiyo</td>
<td>Seeds</td>
</tr>
<tr>
<td>16</td>
<td>Celosia argentea L. (Amaranthaceae), Lapdi</td>
<td>Whole Plant</td>
</tr>
<tr>
<td>17</td>
<td>Clerodendrum multiflorum (Burm.f.) O.Ktze. (Verbenaceae), Arni</td>
<td>Leaves</td>
</tr>
<tr>
<td>18</td>
<td>Curcuma longa L. (Zingiberaceae), Haldar</td>
<td>Rhizome</td>
</tr>
<tr>
<td>19</td>
<td>Cynodon dactylon (L.) Pers. (Poaceae), Dharo</td>
<td>Juice</td>
</tr>
<tr>
<td>20</td>
<td>Daturainnoxia Mill. (Solanaceae), Dhaturo</td>
<td>Leaves</td>
</tr>
<tr>
<td>21</td>
<td>Emblica officinalis Gaertn. (Euphorbiaceae), Aamla</td>
<td>Fruit</td>
</tr>
<tr>
<td>22</td>
<td>Euphorbia hirta L. (Euphorbiaceae),</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plant Name</td>
<td>Use</td>
</tr>
<tr>
<td>---</td>
<td>------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>23</td>
<td><em>Ficus racemosa</em> L. (Moraceae), Umro</td>
<td>The dried ripe fruits are mixed with jiggery and kept for 10 days. This preparation is given orally to treat asthma.</td>
</tr>
<tr>
<td>24</td>
<td><em>Gmelina arborea</em> Roxb. (Verbenaceae), Sivan</td>
<td>The leaves powder mixed with honey and given orally for 3-4 times a day for complete cure of cough.</td>
</tr>
<tr>
<td>25</td>
<td><em>Hemidesmus indicus</em> (L.) Schult. (Asclepiadaceae), Upalsali</td>
<td>The decoction of root is mixed with sugar and milk. The preparation is given twice a day especially against cough and cold in children.</td>
</tr>
<tr>
<td>26</td>
<td><em>Holarrhena antidysenterica</em> (Heyne ex Roth) Wall. (Apocynaceae), Kudo</td>
<td>The root powder of the plant is mixed with root powder of sag (<em>Tectona grandis</em>) and boiled in water. The decoction is given orally once a day for 10-15 days against asthma.</td>
</tr>
<tr>
<td>27</td>
<td><em>Holostemma annulare</em> (Roxb.) Schum. (Asclepiadaceae), Shirdodi</td>
<td>The flowers are generally given orally for 7 days against cough and asthma for quick relief.</td>
</tr>
<tr>
<td>28</td>
<td><em>Lawsonia inermis</em> L. (Lythraceae), Mendi</td>
<td>The leaves juice mixed with water and sugar, which is given orally for the treatment of asthma.</td>
</tr>
<tr>
<td>29</td>
<td><em>Leptadenia reticulata</em> (Retz.) Wt. &amp; Arn. (Asclepiadaceae), Kharkhodi</td>
<td>The leaves juice mixed with honey and given orally against cough.</td>
</tr>
<tr>
<td>30</td>
<td><em>Leucas cephalotus</em> (Lamiaceae), Kubo</td>
<td>The leaves juice is given orally for 10 days to cure chronic cough.</td>
</tr>
<tr>
<td>31</td>
<td><em>Madhuca indica</em> Gmel. (Sapotaceae), Mahudo</td>
<td>The extract of the flowers is given orally for 7 days to cure cough.</td>
</tr>
<tr>
<td>32</td>
<td><em>Maerua blongifolia</em> (Forsk.) A. Rich. (Capparaceae), Dholohemkand</td>
<td>The root crushed into the paste and applied over the chest of children to relieve the pain due to cough and cold.</td>
</tr>
<tr>
<td>33</td>
<td><em>Mimosa hamata</em> Willd. (Mimosaceae), Kaibaval</td>
<td>The ash of flowers and fruits mixed with honey and given orally twice a day against cough till relief.</td>
</tr>
<tr>
<td>34</td>
<td><em>Neuracanthus sphaerostachyus</em> (Nees) Dalz. (Acanthaceae), Ganthel</td>
<td>The ash of whole plant is mixed with either jaggery or honey and given orally 2-3 times a day to cure cough and asthma.</td>
</tr>
<tr>
<td>35</td>
<td><em>Pergulariadaemia</em> (Forsk.) Chiov. (Asclepiadaceae), Chamardudheli</td>
<td>The leaves of the plant mixed with the seeds of ajma (<em>Trachyspernumammmi</em>) are boiled with water and this extract is given orally for 7 days for quick relief against cough and asthma.</td>
</tr>
<tr>
<td>36</td>
<td><em>Punicagranatum</em> L. (Punicaceae), Dadam</td>
<td>The bark (rind) of fruit is kept in mouth 3 - 4 times a day and the juice is swallowed to cure cough.</td>
</tr>
<tr>
<td>37</td>
<td><em>Pupalialappacea</em> (L.) Juss. (Amaranthaceae), Gadarzipto</td>
<td>The root extract is given orally against congested cough.</td>
</tr>
<tr>
<td>38</td>
<td><em>Solanum indicum</em> L. (Solanaceae), Jangliringni</td>
<td>The dried leaves and fruits are mixed and smoked through Chilam (smoking pipe) to cure cough and asthma. The root powder is boiled with water and given orally to cure asthma and other respiratory complaints.</td>
</tr>
<tr>
<td>39</td>
<td><em>Sphaeranthus indicus</em> L. (Asteraceae), Gorakhmundi</td>
<td>The juice of the whole plant is warmed and mixed with powdered black pepper (<em>Piper nigrum</em>) and then given orally to cure cough.</td>
</tr>
<tr>
<td>40</td>
<td><em>Tecomaundulata</em> (Sm.) Seem (Bignoniacese), Ragatrohido</td>
<td>The stem bark powder boiled with milk is given orally against asthma for quick relief.</td>
</tr>
<tr>
<td>41</td>
<td><em>Terminalia arjuna</em> (Roxb. ex DC.) Wt. &amp; Arn. (Combretaceae), Arjunsadad</td>
<td>The decoction of stem bark is given orally to cure cough problems.</td>
</tr>
<tr>
<td>42</td>
<td><em>Terminalia bellirica</em> (Gaertn.) Roxb. (Combretaceae), Baheda</td>
<td>The cortical part of dried fruit is kept into the mouth 3-4 times a day to cure cough.</td>
</tr>
<tr>
<td>43</td>
<td><em>Terminalia crenulata</em> Roth. (Combretaceae), Sadad</td>
<td>The decoction of stem bark is given orally generally 1-2 tablespoon a day to cure cough problems till relief.</td>
</tr>
<tr>
<td>44</td>
<td><em>Trachysper mumammi</em> (L.) Spr. (Apiaceae), Ajmo</td>
<td>The paste of seeds is largely applied over chest to relief pain in bronchitis and other problems of chest in children.</td>
</tr>
<tr>
<td>45</td>
<td><em>Tylophora indica</em> (Burm.f.) Merr. (Asclepiadaceae), Damvel</td>
<td>The juice of fresh root bark and leaves mixed with water and given orally against asthma, till relief.</td>
</tr>
<tr>
<td>46</td>
<td><em>Urariapicta</em> (Jacq.) Desv. (Papilionaceae), Pilosamervo</td>
<td>The ash of whole plant or leaves mixed with honey and given orally 2 - 3 times a day against cough.</td>
</tr>
<tr>
<td>47</td>
<td><em>Urginea indica</em> L. (Liliaceae), Pankando</td>
<td>Very limited amount of crushed bulbs are given orally twice a day to reduce the stickiness of the</td>
</tr>
</tbody>
</table>
mucus in cough and bronchitis.

48  Vitexnegundo L. (Verbenaceae), Nagod  The leaves powder is mixed with jaggery and then it is given orally to cure cough.

49  Vitextrifolia L. (Verbenaceae), Nagod  The dried leaves are smoked to treat cough and asthma.

50  Zingiber officinale L. (Zingiberaceae), Aadu  The dried rhizome (Sunth) powder is used as medicine for chest diseases. The fresh juice of the rhizome is mixed with honey and given orally for 7 - 10 days to cure dry cough.

2.6. Synthetic compounds

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds. However, flavonoids are a group of chemical moieties of the compounds whose structure is based on C_{6}-C_{3}-C_{6} i.e. two phenyl rings are attached through a propane bridge. Flavonoids are a family of plant compounds with a similar flavone backbone composed of two aromatic rings and an oxygen heterocycle attached (Neunhoeffer, 1984). They exhibit diverse type of properties that are beneficial for human health via interacting with a number of cellular targets involved in critical cell signalling pathways in the body. Flavonoids can be classified into various classes i.e. Flavonols (Quercetin, Kaempferol), Flavones (Luteolin, Apigenin), Flavanones (Hesperetin), Flavonoid Glycosides (Rutin), Flavonolignans (silibinin), Flavans (Catechin, Epicatechin), Isoflavones (Genistein, Daidzein), Anthocyanidins (Cyanidin, Delphinidin), Aurones (Leptosidin, Aureusidin), Leuco-anthocyanidins (Teracacidin), Neoflavonoids (Coutareagenin, Dalbergin), Chalcones (Detty, 1988). Research in the field of flavonoids has increased since the French paradox concept was formulated by French epidemiologists in the 1980s, i.e., lower cardiovascular mortality rate observed in Mediterranean populations in association with red wine consumption and a high saturated fat intake. Flavonoids are components of a wide variety of edible plants, fruits, vegetables and of beverages such as tea, coffee, beer, and wine. So, *in vitro* inhibition of LDL oxidation by flavonoids derived from red wine was well documented and demonstrated.

Several beneficial properties of flavonoids have since been ascertained as information. Recent studies have shown the positive effect of flavones on disease related to oxidative
stress, such as atherosclerosis, diabetes, cancer, Alzheimer’s disease, etc. Some of the flavones of natural origin like Naringenin, Gingko flavone glycosides, and synthetic origin like Flavopiridol are presently available in the market as presented in Fig. 1.

![Chemical structure of flavone derived marketed compounds](image)

**Fig. 2.7**: Chemical structure of flavone derived marketed compounds.

Flavone is a class of flavonoids based on the backbone of 2-phenylchromen-4-one. It has three-ring skeletons with three functional groups, including hydroxy, carbonyl and conjugated double bond; consequently they give typical reactions of all three functional groups as shown in Fig 2. Flavones are colourless to yellow crystalline substances, soluble in water and ethanol. They give yellow colour solution when dissolve in alkali. Flavones are moderate to strong oxygen bases, and are soluble in acids due to the formation of oxonium salts having pKa values ranging from 0.8-2.45. Flavones have structure with its C-O-C bond angle 120.9°. Flavones can react in several ways, including
reduction reactions, degradation in the presence of base, oxidation, rearrangement, substitution, addition, condensation, reaction with organometallic reagents.

Fig. 2.8: The structure of flavone ring system.

Several synthetic methods have been developed and modified to get products of high yield, purity and of the desired quality. Flavones can be synthesized by various synthetic schemes like Claisen-Schmidt condensation (Sashidhara et al., 2012), Baker-Venkatraman-rearrangement (Mahal and Venkataraman et al., 1934; Baker, 1933), Ionic Liquid Promoted synthesis (Sarda et al., 2006), Allan-Robinson (Allan and Robinson et al., 1924), Vilsmeier-Haack reaction (Su et al., 2009), Wittig reaction, Fries rearrangement and modified Schotten-Baumann reaction. Now days, most of the flavones are synthesized based on the Baker - Venkataraman method. It involves the conversion of o-hydroxy acetophenone into phenolic ester, which undergoes an intramolecular Claisen condensation in the presence of a base to form β-di-ketone, which is cyclized to flavones by anacid-catalyzed cyclo dehydration (Scheme 1 and 2).

Traditionally, flavones were synthesized with Baker-Venkatraman-rearrangement but these reactions undergo the use of strong bases, acids, long reaction time and low yields consequently Sashidhara et al. reported expedient, simplistic and alternate synthesis of medicinally important flavones in which 2-hydroxychalcones resulting from condensation between acetophenones and salicylaldehyde, undergo oxidative cyclization on heating in the presence of catalytic iodine and generating diversified flavones under solvent-free environmental friendly conditions (Sashidhara et al., 2012). (Scheme 3)
Cotelle *et al.* reported that 2',3',4'-trihydroxyflavone exhibit interesting antioxidant properties expressed either by the capacity to scavenge free radicals or to competitively inhibit xanthine oxidase (Cotelle *et al.*, 1996). Reported SAR studies of antioxidant activities of flavones derivatives indicate that three structural features are essential for antioxidant activity are: the catechol group (3', 4'-OH) in the B-ring, the C2=C3 double bond in the C-ring, that enables the conjugation of the B-ring to the 4-oxo group, and the 3- and 5-OH groups together with the 4-oxo group (Fig. 3). A 2,3-double bond in conjugation with 4-keto functional group provides electron delocalization from the ring B and the electron-donating groups on the ring B reduce the O–H bond dissociation energy, thus these important groups or features impart radical scavenging properties to flavones. Hydroxyl group on the ring A appears to be of lower importance. Flavones also have the capability to form chelates with oxidizing metal ions and prevent various redox reactions, thus imparting antioxidant effects (Fig. 4).

![Figure 3](image1.png)  ![Figure 4](image2.png)

The 5-hydroxyl group in association with the 4-keto and catecholic hydroxyl groups chelates catalytically active metal ions involved in redox reactions, which may prevent the formation of oxidizing species (Kandaswami *et al.*, 1993). The most detrimental of the reactive oxygen species is the hydroxyl radical, which may induce lipid peroxidation generated in the Fenton reaction (Fig. 5) (Mattson 2001., Fu *et al.*, 1998). Hydroxyl groups on the B-ring donate hydrogen and an electron to hydroxyl, peroxyl, and peroxynitrite radicals, stabilizing them and giving rise to a relatively stable flavone radical (Pietta, 2000) as shown below: (Fig. 6)

\[
\text{Fe}^{2+} \rightarrow \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{HO}^+ + \text{OH}^- \\
\text{O}^{2-} + \text{H}_2\text{O}_2 \rightarrow \text{O}_2 + \text{OH}^- + \text{HO}^-
\]
In the treatment of AD, various flavones were used as adjuvant with some active moieties like tacrine due to their antioxidant activity. In that context, a new family of tacrine-4-oxo-4H-chromenehybrids has been designed, synthesized, and evaluated biologically for Alzheimer’s disease (AD), by Fernandez-Bachiller et al. The tacrine fragment with cholinesterase inhibitory activity and the flavone scaffold with free radical scavenging and β-secretase (BACE-1) inhibitory activities, the hybrids were found to be more potent than the parent inhibitor, tacrine as well as apigenin. Among all the hybrids, compound (Fig. 7) showed potent combined inhibition of BACE-1 and ChEs, as well as good antioxidant and CNS permeable properties (Fernandez–Bachiller et al., 2012).
Fig. 7
Flavones scaffold can be termed ‘skeleton key’ as it is an important core in many compounds acting at different targets to elicit varied pharmacological properties with various substitution patterns. It is the diversity of this structure that gives flavones wide range of biological activity. Inflammation has foremost role in several disease conditions like Asthma, atherosclerosis, Alzheimer’s disease, rheumatoid arthritis, diabetes mellitus, carcinoma, Crohn’s disease, gout, multiple sclerosis, osteoarthritis, psoriasis, bacterial or viral infections etc (Medzhitov ,2010; Grivennikov et al., 2010). Different inflammatory mediators involved in these conditions are plasma proteases, prostaglandins, leukotrienes, histamine, serotonin, nitric oxide, interleukins (IL-1 to IL-16), iNOS production, tumor necrosis factor-a (TNF-α), and chemokines (Nathan ,2002; Cronstein et al.,1995, Feghali and Wright, 1997). Tradionally, extracts of different plants have been used to treat acute and chronic inflammation. Variety of natural products (Fig. 8) as synthetic flavones has been reported to bind with various protein kinases directly and alter their phosphorylation state that regulates multiple cell signalling pathways. Therefore, revealing flavones can have excellent therapeutic value in the treatment of inflammatory and autoimmune diseases (Hou and Kumamoto,2010).

![Leutonin](Leutonin.png) ![Apigenin](Apigenin.png)

**Fig. 8**
Flavones have been reported to have an inhibitory effect on FcεRI receptor expression, anti-histaminic activity and leukotriene antagonism. Flavones also exhibit leukotriene antagonism. The leukotrienes cause constriction of the pulmonary airways and small blood vessels, so involved in asthma and vasospasmic diseases (Wu and Kover ,1989). Numerous carboxy flavones significantly modulate the action of leukotrienes. The presence of nitrogen atom in substituent group is essential for leukotriene antagonistic
activity (Fig. 9). However, Hatnapure et al., synthesized 6-methoxy-2-(piperazin-1-yl)-4H-chromen-4-one and 5,7-dimethoxy-2-(piperazin-1-ylmethyl)-4H-chromen-4-one derivatives and screened for their pro-inflammatory cytokines (TNF-α and IL-6) and antimicrobial activity. Compounds (Fig. 10) found to have promising anti-inflammatory activity (up to 65-87% TNF-α and 70-93% IL-6 inhibitory activity) at concentration of 10 μM with reference to standard dexamethasone (71% TNF-α and 84% IL-6 inhibitory activities at 1 μM), while some compounds found potent antimicrobial agent showing even 2-2.5-fold more potency than that of standard ciprofloxacin and miconazole at the same MIC value of 10 μg/mL. The presence of highly electron rich group such as OMe, pyrimidyl, morpholine on piperazine as well as homologation of chromone and piperazine moiety have strong relevance to the anti-inflammatory activity while the amino alkyl, cyano or alkenylalkyl group either on piperazine or chromone found to be effective potent antimicrobial agents (Hatnapure et al., 2012). 2-(2-Phenylethyl) chromone derivatives namely, congeners isolated from the resin deposited wood of Aquilariasinensis (Lour.) Gilg by Tu et al., and screened for their anti-inflammatory activity (Fig. 11).
Histamine is an intercellular chemical messenger and plays a critical role in several diverse physiological processes. Four human G-protein coupled histamine receptor subtypes (H1-4) are currently recognized to mediate various actions of monoamine histamine. Among the four subtypes, the histamine H1 receptor has been an attractive target for drug discovery for several years and H1 receptor antagonist have proved to be effective therapeutic agents for respiratory distress, thus contributing to an important
class of drugs today (Saxena et al., 2006). A series of 2-phenyl-4H-chromen-4-one analogues was evaluated for the H1 antihistaminic activity computational method. Compounds shown in Fig. 12 exhibited highest antihistaminic activity (Dave and Rahatgaonkar, 2009).

In addition, the protective role flavones have been used for many years in traditional medicine to treat infectious diseases (Abram et al., 1986). However, many research groups have reported flavones possessing antifungal, antiviral, and antibacterial activity of new compounds bearing the same ring skeleton. Nitrogen-containing flavones have been reported to have considerable antimicrobial activity.

![Fig. 12](image-url)