CHAPTER - 1

INTRODUCTION
On the earth, plants occupy a unique position since they are the foundation for life. They are the main producers in all food chains. The plants directly supply 90% of human calorific intake and about 80% of protein intake. Plants and herbs are being used widely as an important medicinal foundation of medicine for time immemorial. Around 80% of Indian population lives in small and remote villages where per capita income is very meager and not able to afford the allopathic medicines which are costlier. India is foundation of wealth for a hugenumeral of herbs with curative properties, and they are picking for the traditional medicinal methods. Therefore, it is imperative that this great natural resource be used and augmented in accordance with the development of technology and the requirements of the humans. The current era sets the goal of side effect free treatment by way of neutraceuticals.

The traditional medicine has gained global interest as a number of plants have been quoted in curing diseases successfully. The people of Asia used medicinal plants as an integral part of the ethnobotanical aspects for centuries. The allopathic medicine has evolved from tribe medicine and traditional system only after systematic chemical and pharmaceutical screening. Advanced microbial and chemical methods can use to synthesize medicinal and aromatic compounds, but in many cases it is very much expensive. Though, the use of synthetic compounds leads to a decline in the use of plants or its parts in modern medicine. However, synthetic medicine develops undesirable effects due to which, people are more favorable to use natural compounds obtained from plants.

It is estimated that 20,000 plants species were used for medicinal purposes. Approximately out of 120 plant species, 74% of species derived drugs was found as a result of chemical studies to isolate the active chemical moiety which was responsible for their medicinal use. The temperate, tropical and subtropical species were included in Asiatic flora, which provide systems for plants or plant parts based drugs and these systems work as vital part in the healthcare systems of many countries in Asia. Asia’s 80% population are still depending on traditional and folk remedies for day-to-day medical needs.

More than 70% of India’s populations still use the traditional herbal medicine (Vaidya and Devasagayam, 2007). Phytochemical analysis of plants crude drugs for the management of cancer, yielding a number of active chemical with antitumor activity. Plants from many families have proven to accumulate alkaloids, which have anti-HIV
activity. It has been reported several plant-derived drugs and aromatic compounds including anti-malarial agent from *Artemisia annua* and forskolin from roots of Coleus, which is used as an anticoagulant in reducing intraocular pressure in cases of glaucoma. Forskolin also serves as an aid to nerve regeneration following trauma (Hussain, 1993).

### 1.1. IMPORTANCE OF FRUITS, VEGETABLES AND MEDICINAL PLANTS

The term vegetables were at first utilized for a couple of plant or its part, now the term for some nourishment plants and their eatable parts. There is no agreeable natural contrast among leafy foods. Various vegetables comprise a greater amount of water which makes vegetable little in calories. Vegetables consist of vitamins, fibers, calcium, potassium and iron. Beets like peas, lentils, beans, and so on are a commendable origin of starches while likewise having protein content high. High protein and fat weight control plans for weight decrease are the converse of wellbeing consuming practice.

Carbs show in plant with low rate of fats constituents are considered as vitality establishments that are standard for human absorption framework. Sugar introduce in vegetables and apples and oranges is not "awful" as glucose present in products of the soil was the principle vitality source. The thing in abundance amount is terrible for human health, however, the right amount and type of food at the right time and place are the right nutrition.

Whole, if not more, nourishment is conceivable from vegetables only. Many persons will be unconscious that vegetable sustenances have enough protein to keep up sports bodies construct. The power of the strong elephant originates from the vegetables, plants and herbs. Also, the non vegetarians gets his protein from flora through the creatures that are devoured. A blend of rice and vegetables would provide for one enough protein. Possibly Vitamin D and B12 are not delivered in full extent from vegetables. Combination of rice with legumes raises the uptake of protein.

Phytochemicals are the chemicals constituents that are available in vegetables and fruits. It is nowadays thought that these elements have the capability to neutralize the oxidants formed in cells of our body due to digestion, constructing the faster age of cells (Hegde, 2001).
Human foodstuff decisions and consuming examples have been determined by impulse and budgetary status and have been preferential by the advancement of foodstuffs all the more on their expense, taste, and not as much of for their nutrition. The differences in human dietary examples around the globe has been well known and reported, regardless examples related with a lower hazard of ceaseless maladies, including basic structures of tumor that have additionally been illustrious in literature. In examining these different patterns, continuous admission of products of the soil, vegetables, entire grains and proteins of plant in examination with the run of the classic American diet exhibited noticeably compact danger of malignant like diseases, heart infection and some incessant maladies of maturing.

Epidemiological literatures and nutrition knowledge simply characterized these intake configurations as high-fiber low-fat dietary supplements. These easy terms directed to the thought that the fiber or the herbal supplements could repeat the aids of the well dietary outlines and unnoticed the aids of nutrients present in vegetables, at the same time likewise the wellbeing of the dietary modality in general.

As an consequence of idea, nourishing design reflected its profits over a sole part, researches directed to investigate a solitary segment of the eating methodology in a given populace while all the other variables were kept steady. Be that as it may, separated unadulterated synthetic substance might drop their bioactivity or might not act in the equivalent way as they do at what time devoured from the sustenances. The expected profits were not understood for fiber supplementation (Alberts et al., 2000).

However, overall investigations recommend a few growths of air digestive expanse, nutritive admissions of 500 - 700 g of foods grown from the ground for every day is connected with a 50 % diminish in danger. An eating regimen rich in plant root nourishments gives crucial vitamins and minerals alongside more or less 25,000 phytochemicals which can't be given by an unique Western example which will be focused around sugar, salt, oils and refined grains.

Conventional plant-based nourishment in different nations may be rich in a large number of these phytoconstituents (Rao, 2003). Late writing of current seeker gatherer individuals have demonstrated that these populaces consume more than 800 diverse mixtures of plant-based nourishments, however when they migrated into town and begins
consuming supposed road sustenances because of which they start to create nourishing insufficiencies (Lee, 1995).

India has an ancient heritage (Sharma and Deshwal, 2011) of traditional medication. The Indian materia medica provides data on the urban myths drills and customary parts of remedially vital naturally occurring harvests. Indian old-style medication are centered on Siddha, Unani and Ayurveda systems. The valuation of these crude drugs obtained from plant origin is mainly in view of pharmacological, phytochemical, and unified methods including different instrumental strategies, for example, microscopy, chromatography and others. All these traditional Indian medicinal systems are unique, but there is a common cord in their general practice and fundamental principles.

With the rising interest worldwide in tolerating and examining conventional frameworks of prescription and abusing their potential uses focused around different human services techniques, the assessment of the rich society of customary medication is fundamental. The government of different countries and the private sector are exploring all the potentials for the perfect assessment of these systems in order to successfully adopt the therapeutic approaches available in original systems of medicine and help in producing relevant data which permits the use of such products on the national healthcare program (Mukherjee, 2001).

In recent times, natural products are becoming vital part of medicinal system because there is now concern over noxiousness and side effects of modern drugs. There is also a realization that natural medicines are safer and allopathic drugs are often ineffective in several ailments. Medicinal plants had existed even before human beings made their presence on the earth. Man’s existence has been made possible on earth only due to the important role played by the plant kingdom in sustaining life. Since the first light of culture, in increase to food crops, man cultivated medicinal herbs for his medical needs. Botanicals have been used to ameliorate human suffering since antiquity.

Even today the active principles derived from botanical form a major component of the therapeutic armamentarium, as about 130 pure chemical entities extracted from about 100 species being accepted as medicine curing of diverse diseases throughout the world. Most of them have been developed on the basic information obtained from the traditional herbal
medicinal systems of the west. On the other hand, Ayurveda, the Indian system of medicine remains largely unexplored even through medicinal plants have continued to be an area of major scientific research to discover new therapeutic molecules which can further be used as templates for the development of new therapeutic improved drugs.

Many renowned drug houses have launched very active programs of mechanism based natural product discovery research. In one such program, more than 61,000 primary screening assays in 21 different mechanisms based assay system yielded less than 0.03 % true leads. The bulk screening of herbs or trees for novel chemical entities is very costly as well as exhaustive with low-cost effectiveness. It is well-understood that specialized biological screening based on traditional use is more economical and effective.

In Ayurvedic texts, there is an exhaustive description of herbs and their clinical uses which can be further explored using modern scientific methods to establish their therapeutic usefulness and detect the wonder molecules. Ayurveda, thus, has an important role in bioprospecting of further medicine. Possibly because of different therapeutic principles, many difficulties are faced during this process of drug development, which can be adequately overcome by an appropriate correlation of principles for diagnosis and treatment of both the systems of medicine. This in turn depends on an appropriate interpretation of ayurvedic texts in contrast to mere translation in different languages (Arora and Kumar, 2002).

Notwithstanding, there are numerous limits in regards to wellbeing and viability of formulations containing herbal extract. The knowledge about active substance of herbal products are not well-documented. Data on danger and unfavorable impact of these details are needing. The pharmacokinetics and pharmacodynamic data is not accessible for herbal formulations. Pack inserts providing details regarding safety and warning are not mandatory for the sale of herbal formulations, which are available as over the counter preparations.

The lay public should know the risk of untested and unregulated remedies. Selection of plant or herbs material grounded on the eminence, standardization of strategies for preparation, authorization of regulation in regards to proper names are assessed, which will enhance the quality and worthiness of readiness with natural constituents as restorative operators. Writing and information available in journals and on the website are other measures to assist research in this field (Kuruvilla, 2002).
1.2. IMPORTANCE AND SCOPE OF HERBAL MEDICINE

We can certainly assume that the healing properties of some plants were discovered by primeval humans fairly early, and they learned how to use them. People gained valuable experiences by collecting and using medicinal plants and handed down their knowledge to their generations. One of the first written records concerning curative drugs and narcotic substances was found on a clay tablet in Assyrian cuneiform script dating back to 2,700 BC. The tablet mentions a brown drug, daughter of the poppy, meaning opium. In ancient Egypt, medical science and the use of medicinal substances have an age old tradition. The Egyptian Pharmacopoeia always had a supply of medications of plant and animal, as well as mineral origins. There were 25 types of medicinal plants, as basic nutritional and medicinal plants, onion, garlic, lettuce, lentils, olives and caraway were used (Gupta and Chitme, 2000).

The knowledge of Indian physicians is documented by the so-called Bower manuscript found in the ruins of MINGSI in 1889, central Asia. The document and its author praise the garlic as a panacea claiming it to prolong life to 100 years. In ancient Chinese pharmacology and herbal medicine the most extensive fields of medicine, they contained 8160 prescriptions for the use of various drugs, with instructions on how to use, how to collect and prepare various drugs from medicinal plants.

Ayurveda has well-known treaties known as Charak Samhita and Susrut Samhita, the oldest and very first written document of Ayurveda (900 BC). It describes 341 preparation of plants as medication and more importantly classify these in terms of physiological activity. The traditional medicine used in India known popularly as the Indian medicine system includes Unani, Siddha, and Ayurveda Naturopathy.

Herbal therapy gives logic means for curing of many internal ailments which are considered to be obstinate and incurable in other medicinal systems. It lays a countlesstransaction of prominence on maintenance of specific progressive health. It therefore points at both the prevention and cure of diseases. Natural therapy (Thaibinh, 1998) also studies the basic human nature and natural stuffs like hunger, thirst, sleep, sex, etc. It delivers a disciplined, disease free life and will give a holistic approach to the therapy.
What is Herbs and Herbal Medicine?

Medicinal herb or herb have various implications, but in this framework, it refers to "unpolished pharmacologically active substance of plant source applied for the management of disease, often long-lasting nature, or to attain the situation of better fitness." Herbal or natural formulations called "phytopharmaceuticals" or "phytomedicines" are the formulations made from diverse plant portions. They are available in different types of formulations such as solid dosage forms (tablet, capsule), semisolids (Creams and ointments), elixir, powder, extract, tincture, cream, and parenteral. Natural products in the unpolished state are also used in treatment.

A single isolated pharmacologically active substance obtained from plant sources such as reserpine is not considered as herbal medication. Herbal medicines are not incorporated with homeopathic products. Samuel Hanemann, a German physician, discovered homeopathic medicine in the 18th century, which also utilizes medicinal plants and other plant products. This is based upon the "Law of similarity and dilutions."

There is a treasure of non-scientific plant-based medicine information which are easily accessible to the person. Access to this literature is important to the concerned person or pharmacist as a drug information provider. The pharmacist of different countries plays an important role in providing information about drug safety and effectiveness as compared with other health care personnel. In the event that the herb is utilized as a remedial operator, it ought to be considered as a medication (Thaibinh, 1998).

The term “traditional medicine” have several definitions and interpretations. The most comprehensive is the one where the WHO has defined it as a total of all the knowledge and practices which are help in diagnosis and prevention of diseases as well as the elimination of mental, social, physical imbalance, which trust only on practical involvement and notes handed down from one generation to another in the form of writing or verbally (Thaibinh, 1998).

The traditional medication is generally picking up ubiquity over allopathic pharmaceutical due to the accompanying reasons:

1. Climbing expenses of restorative forethought.
2. As these are from characteristic root, they are free from reactions.
3. It gets to the root drive and gets rid of it so that the disease does not come once more.
4. Therapy for many stubborn ailments.
5. Easy obtainability of medicines from natural foundations.

Herbal Therapy Scope and Need

Nowadays, humans worried about lifestyle sicknesses like sorrow, disease and heart inconveniences brought on flawed sustenance and anxiety. Since these infections have a mental or passionate segment, there is a developing conviction that allopathy is generally not able to treat, its compromises is interim easing from indications (Gupta and Chitme, 2000). A conventional Indian polish held that certain medications ought to be formed through the expansion of picking substance that improves the bioavailability of the drug. Two Indian modern biology labs have recently confirmed the bioavailability enhancing ability of piperine molecule, the active component of pepper.

A hostile to tuberculosis drug rifampicin must be given at a higher measurement than needed so as to repay misfortunes happened on the route to the required site. Detailing of piperine molecule with rifampicin spare the counter impacts of the drug. The R&D department of various herbal industries investing on research and development of OTC therapies (Thaibinh, 1998).

Side Effects of Herbals

Little is thought about wellbeing of phytomedicines. Literature reported a number of reactions. Anyhow as a rule, reactions gone unreported in light of the fact that natural medication help generally is embraced toward oneself and frequently disregarded by medicinal experts amid the patient forethought. Distinguishing the unfriendly impacts is further eased off on the grounds that it is unrealistic dependably to survey the nature of certain home grown therapeutic items (Dandagi et al., 2008).

Interactions between Allopathic -Herbal medicine

The potential danger of home grown medicine interfacing with recommended allopathic medications was likewise a stress with the expanded utilization of phytomedicines.
Recently, a few communications have drawn the consideration of the wellbeing group. A probable interaction stated by Janetzky and Morreale between ginseng and warfarin drug with plentiful well known drug reactions.

A clinically huge connection in the middle of warfarin and natural pharmaceutical which contains roots of *S. miltiorrhiza* creating coagulating anomalies. A randomized, hybrid study led on eight subjects showed that there are no noteworthy pharmacokinetic interfaces among the Levofloxacin drug and selected traditional herbal drugs. Terminal elimination half-life or renal clearance, plasma absorption and AUC of levofloxacin does not reflect any differences as compared with the herbal drugs (Dandagi et al., 2008).

**Adulteration of Herbal Medicine**

Standardized products of herbal origin are getting to be dynamically accessible the business. In few portions of the globe where government models and quality control are not upheld, debasement and defilement cause security and in addition adequacy issues. The vicinity of adulterants, for example, mercury, lead or arsenic in home grown medication can result in critical lethality. About 23.7% of traditional Chinese medicines collected over a period of one year from eight different Taiwan hospitals were jagged with hydrochlorothiazide, indomethacin, acetaminophen, caffeine like adulterants along with other drugs (Dandagi et al., 2008).

**Herbal Research**

Herbal remedies popularized because of their efficacy, easy obtainability, low price and somewhat being lacking of serious toxic effects. Natural products (crude drug extracts and pure compounds) derivative from developed floras, bugs or creatures, either marine or terrestrial origin. Many of traditional healing herbs were compound analysis prominent to the segregation of curable compounds. Starting from 1800 A.D., the isolation and characterization of herbal extracts became a major part of pharmacopoeias (Dandagi et al., 2008).

**Why Herbal Remedies?**

Herbal medicines or drug products are in boundless plea in un-industrialized, industrialized states for their chief health care systems in view of their broad organic exercises, higher wellbeing edges and lesser expenses. They give therapeutics in memory
loss, osteoporosis, immune disorders, etc. like age related disorders which are not curable with modern medicine is available. Government, public and academic curiosity in herbal treatments is rising because of toxicity figures and financial burden of medicine scheme (Handa, 1991).

**Current Scenario In Herbal Trade**

In world, India is one of the heading biodiversity focuses having in excess of 45,000 distinctive plant species. Around 20 thousand plants are known to have great therapeutic properties of which just around 7000 – 8000 are continuously utilized by customary restorative specialist. The Ayurvedic medicine system uses around seven hundred, Siddha around six hundred, Unani around seven hundred and modern medicine (Allopathy) about 30 plant species. Herbal technology is the biggest revenue earner in India after information technology.

Today WHO indorses and inspires the use of ancient herbal medications in National Health Care Programs because these drug is easily available at lesser charge and relatively safer. People’s trust in therapies is mirrored by an expecting Rs. 450 crores annual turnover of the herbal industry. Big and small pharmaceutical industries counting some multinational have attracted by healthy annual growth rate of 11 % and increasing export perspectives. Yet, due to lack of appropriate quality control measures, the present share of Indian crude drugs in the world trade is quite insignificant (0.045 %) (Palav and D'mello, 2006).

**Constraints on Herbal Trade**

The natural drug market in India is around one billion dollar and the export of unrefined medications is around 80 million$ in India. Lack of complete standardization is critical difficulties confronted by these formulations. Natural prescriptions were readied from materials of plant inception which are defenseless to tainting, decay and variety in arrangement of active constituents. Leading and important duty is the assortment of the correct kind of therapeutically efficacious plant solid (Tamizhmani et al., 2003).

**Necessary Steps For Promoting Herbal Drugs**

- New phytoconstituents i.e. isolation, purification and characterization.
- Use of newly isolated phytoconstituent for designing of equivalents with reduced toxicity or amended therapeutic action.
Management of phytoconstituents into medicinally important drugs (Bhanu et al., 2003, Tamizhmani et al., 2003).

Ethnopharmacological Approach To Herbal Drugs

The term ethnopharmacology refers the interdisciplinary scientific thought, observation, description and experimental examination of indigenous crude drugs and biological activities. Recent curiosity in ethnopharmacological information about shrub drugs has greatly increased for several reasons. Scientists showed that of 119 important plants derived drugs used in one or more countries, and 88 regarded as having been discovered as a result of being derived from a plant used in traditional medicine (de Smet, 1985).

Practical Aspects of Herbal Drug Discovery

The following outline characterizes a brief summary of the stages involved in the development of pure drug from a plant source.

- Collection and identification of the plant and deposition of voucher sample in local and major herbaria.

- A literature survey of the plant species selected for studies. Extraction with solvent and preparation of non-polar and polar extracts for initial biological testing.

- Evaluation of plant extract against a panel of biological test methods as exemplified by receptor binding, enzyme inhibition and/or cytotoxicity assays.

- Activity guided fractionation on the extract showing activity, by monitoring each chromatographic fraction with bioassay chosen from the panel available to the investigation.

- Structure elucidation of pure active isolate(s) using spectroscopic techniques and chemical methods, if necessary.

- Test each active compound (whether of novel or known chemical structure) in all biological test approaches available, in direction to conclude potency and selectivity of the medicine.
- Perform molecular modeling studies and prepare derivatives of the active compound of interest.
- When total synthesis is not practical, carry out large scale re-isolation of interesting, active compounds for toxicological, pharmacological and mutation studies.
- Clinical trials (phase I – III) (Bhanu et al., 2003).

**Future Prospects In Herbal Medicines**

Currently, scientific research on medicinal herbs or plants is continuing most intensely in research institutes, universities and pharmaceutical research laboratories as well as in the clinics of many developed countries. This research is oriented mainly into two directions.

Firstly, the active constituents of plants that have long been known for their therapeutic properties have been investigated and the second sphere of basic research has led to the detection of new varieties of medicinal plants or herbs and new crude drugs from the other remote areas of the world where fresh species with unknown substances still remain to be looked into it. Each and every traditional medicine, drugs of Ayurveda, Unani and Siddha need to be tested and validated scientifically.

CSIR, New Delhi, which was already involved in this field, validated about 350 formulations for different activities. This is a welcome trend since its attempt to marry traditional practice with modern knowledge for the betterment of health. World health organization has given emphasis to the confirm the quality control of herbs and herbal products by using modern analytical techniques.

Several countries have herbal pharmacopoeias and lay down monographs to maintain their quality (Dobriyal and Narayana, 1998).
**Phytochemistry-“An Emerging Trend”**

Plant-based drugs or drug products are constantly progressively favored in restorative science. Healing fragments of therapeutic plant, as well as the figure and measure of compound mixes delivered, utilizes for development and advancement. The helpful worth and pharmacological activity of the medication are because of the vicinity of certain compound constituents, for example, starches, subsidies of carbs, pectins, gums, adhesives, tannins, different manifestations of glycosides, phenolic mixes, lipids, altered and unpredictable oils and different sorts of alkaloids.

These phytoconstituents are of colossal vitality to the humankind. Phytochemical examination of plants or plant parts is a fascinating exploration territory, prompting the extraction and detachment of a few new mixes.
Despite the fact that the voluminous writing has gathered on optional results of the plant, almost no data is accessible on vicinity and pathways developing in dry zones. Information of concoction substances display in plants is attractive, not just for the disclosure of remedially dynamic operators, additionally on the grounds that such information may be paramount in finding new sources, for example, oils, gums, tannins and originators for the amalgamation of compound substances. Separated from that, learning of the concoction mixes of plants and herbs would be esteemed in finding the true estimation of folkloric cures (Naidu et al., 2011).

**Herbal Drug Market**

Commercially, plant derived medicine are worth about $ 40 billion worldwide out of which $14 billion a year only in the United States. The average turnover of Indian herbal medicine industry is about 2,300 crore against the pharmaceutical industry, which is turned about Rs.14, 500 crore with a growth rate of 15 %.

However to achieve the goal of the major exporter of herbal remedies several steps need to be taken:

a. Systematic study of world market demand and short listing of medicinal herbs with good potential.
b. The organized cultivation of medicinal herbs on a large scale.
c. Encouragement for agro based phytochemicals and pharmaceutical industries to manufacture value added herbal products.
d. Strict legislation to control quality and purity.
e. The upgradation of cultivation and collection process.
f. Documentation of research work and standardisation for quality (Mukherjee et al., 1998).

The increasing demand for herbal medicines inevitably led to the subject of obtaining and maintaining their quality and purity based on internationally recognized guidelines.

**Current Status of Standardization**
WHO has highlighted on the necessity to guarantee the quality of herbs and herbal preparations by using current techniques. Several pharmacopoeias like British Herbal Pharmacopoeia (BHP), Japanese Pharmacopoeia (JP), United States Pharmacopoeia (USP), British Herbal Compendium (BHP), German Commission E, etc. laydown monographs for herbs to maintain their quality. BHP contains 233 monographs and quality control tests, and Chinese Herbal Pharmacopoeia contain 1751 monographs of substances and articles, BHC contains 84 monographs of medicinal plants. German Commission E has 330 monographs for drugs used in German folk medicine.

Standardization by Marker Compound

The best tool developed for standardization is by chromatography. It describes the botanical identity and chemical sanctity of herb. One of such technique is marker compound testing and finger print 1010 analysis. Secondary metabolites present in the herb are considered as marker compounds. Different methods were used to investigate the marker compounds in medicinal herbs with the help of modern and sophisticated tools like HPTLC, HPLC, etc. (Dobriyal and Narayana, 1998). List of marker compounds for some herbs exposed below.

<table>
<thead>
<tr>
<th>Sr.no.</th>
<th>Name of Herb</th>
<th>Marker Compound</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td><em>Andrographis paniculata</em></td>
<td>Andrographolides</td>
</tr>
<tr>
<td>2.</td>
<td><em>Boerhaavia diffusa</em></td>
<td>Punarnovine</td>
</tr>
<tr>
<td>3.</td>
<td><em>Curcuma longa</em></td>
<td>Curcuminoids</td>
</tr>
<tr>
<td>4.</td>
<td><em>Eugenia caryophylata</em></td>
<td>Eugenol</td>
</tr>
<tr>
<td>5.</td>
<td><em>Glycyrrhiza glabra</em></td>
<td>Glycyrrhizin</td>
</tr>
<tr>
<td>6.</td>
<td><em>Withani somnifera</em></td>
<td>Withanolides</td>
</tr>
<tr>
<td>7.</td>
<td><em>Tinospora cardifolia</em></td>
<td>Giloin</td>
</tr>
<tr>
<td>8.</td>
<td><em>Piper longum</em></td>
<td>Piperine</td>
</tr>
<tr>
<td>9.</td>
<td><em>Ocimum basilicum</em></td>
<td>Eugenol</td>
</tr>
<tr>
<td>10.</td>
<td><em>Zingiber officinale</em></td>
<td>Gingerol</td>
</tr>
</tbody>
</table>

1.3. INTRODUCTION TO INFLAMMATION, PAIN AND FEVER

1.3.1. Inflammation:
Inflammation is one of the most important and very complex experiences. Pain has demarcated as an upsetting tactile and passionate familiarity connected with genuine harm, or depicted in standings of such injury. “Nociception can be defined as a response specific to potential tissue damage stimulation.” It is a mechanism whereby deleterious peripheral stimuli are pass on to the central nervous system.

Pain not always related with nociception, but it is a subjective experience. Inflammation may be acute or chronic type. Acute pain is commonly well accounted for in terms of nociception giving rise to an intense and unpleasant sensation. In contrast, most chronic pain states are related with irregularities of the normal physiological conduit, giving rise to an improved amount of pain related with a mild harmful stimulus (hyperalgesia), pain evoked by a non-toxic stimulus (allodynia), or impulsive spasms of pain with no precipitating stimulus.

The recent evidence suggests that the pain may be postulated to exist in three different groups of processes, each predominating in different painful disorders. These involve,

1. Nociceptive pain: Nociceptive pain may occur as a secondary phenomenon caused by a non-neurologic source of continuing noxious stimulation in the periphery.

2. Neuropathic pain: Neuropathic pain may be generated directly by the disordered or damaged nervous system. Neuropathic pain comprises of a number of very distinct subtypes, all of which are precipitated by neural injury. The important sub-types are:
   - Differentiate pain—that depends on the different function of the sympathetic nervous system and
   - Sympathetically maintained pain—that is related to the ongoing activity in a peripheral focus of aberrant neural activity (Rang et al., 2003).

3. Psychogenic pain: In case of psychogenic pain, the psychological factors play an important role in generating or magnifying the pain even when another identifiable neurologic or peripheral causes exist (Justins and Richardson, 1993).
Depending on the causes and duration, inflammation is classified as acute inflammation and chronic inflammation. Acute inflammation inflammation is of somewhat small period, lasting for a few hours to few weeks, and its main physical features are the edema (exudation of liquid and protein plasma) and the displacement of leukocytes. Chronic inflammation is generally of a longer period also is related histologically with the vicinity of macrophages and lymphocytes and the proliferation of small blood vessels and fibroblasts.

Cardinal signs of inflammation as postulated by Celsus in the first century A.D; are as follows.

- Redness (rubor): An intensely swollen tissue shows up red, e.g., skin influenced by sunburn, cellulite due to bacterial contamination or intense conjunctivitis. It is because of expansion of little veins inside the harmed region or part of the body.

- Heat (calor): Build in body temperature is seen just in fringe segments of the body, such as skin. It will be on account of hyperemia (expanded blood stream) through the locale, coming about in vascular development and the supply of fresh blood to the injured part. Systemic pyrexia results from a percentage of the synthetic go betweens of aggravation helps the nearby temperature of the body.

- Swelling (tumor): Edema consequences swelling, the accumulation of liquid in the extravascular region in the form of fluid exudates furthermore to a lesser degree, from the physical manifestation of the incendiary cells relocating into the affected part.

- Pain (dolor): Torment will be one of the best known characteristics of intense aggravation. It comes about mostly from the extending and specifically, structures discharge under weight in a sore pit of the body. The prostaglandins, bradykinin and serotonin, are a portion of the concoction arbiters of intense irritation which are known to impel aching.

- Function Loss: A well-known outcomes of aggravation, was further included by Virchow (1821-1902) to the list Celsus of drawn peculiarities. Pain inhibits the movement of moderately swollen part while severe swelling may cause the physical immobilization of the tissues (Underwood and Cross, 2009).
Screening Methods for Anti-Inflammatory action:

Anti-inflammatory action of a crude drug or compound is determined by observing specific suppression of the emblems of distinctive inflammatory reaction tempted experimentally in laboratory animals. To mimic this clinical condition, animal models of inflammation could be grouped into three categories viz. acute, subacute and chronic.

A. Acute inflammation models

1) Rat paw oedema
2) Mouse ear oedema
3) Ultraviolet light induced erythema
4) Chemical peritonitis (ascites)
5) Chemical pleurisy (pleural effusion)

B. Subacute inflammation models

1) Granuloma pouch
2) Cotton pellet granuloma

C. Chronic inflammatory models:

1) Adjuvant induced arthritis.

1.3.2. Pain:

Ingredients resulting from extraction of plants have utilized form the creation of phase for numerous resolutions comprising the management of aching. Till then, not a single chemical of plant origin was discovered and identified. Currently, tranquilize development has turned into a troublesome arena far past the utilization of solitary organically growing items. Nonetheless, regular items have ruled the medication business for a long time and a few advertised medications are focused around disengages.

There has late return in the investigation of regular items, particularly from the nutritive complement commerce. Management of the pain and the addiction of drug molecules research are now concentrating on the development of compound which are obtained from the natural sources. Lately, referents have been made from completely synthetic compounds and natural substances which are completely based on herbal pharmacophores, was introduced into the flea market.
The health areas and researchers still fight with contraindications summaries of these painkilling materials that are unwanted. Vagrant targets are additionally being explored for their possible functions in controlling of nuisance. The etiology of aching has turned out to be a compound arena, and as more classifications methods were discovered, more probable drug marks are being recognized. This investigation will play up a number of the most recent information of innovative, commonly determined mixes that have painkilling possessions.

Undesirable physical or passionate encounters are known as agony. Torment will be the most prominent basic cause that persons search out medicinal consideration. It was separated into two sorts, intense torment and ceaseless agony. Intense agony supports a cautioning framework to expel oneself from specific ache jolts. Unending ache indistinct spells and vague motives and appears to fill no agreeable need. Constant torment administration is chief issue due to accessible meds and their objectionable symptom. The symptoms of right now utilized torment prescriptions differ focused around the class of executor utilized. Then again, numerous restorative staff, will be concerned with enslavement, tolerance, gastrointestinal impacts, and misuse.

Latest clinical studies (Ballantyne and Mao, 2003) recommend that the correct utilization of agony treatment has an okay of delivering addicts and due to this recommending exertion appear to be evolving. Notwithstanding, we can separate physical torment into no less than four jolts bunches: mechanical, warm, substance.

The incitement of C-strands nerve endings or A-filaments initiation convey sterrible boosts. It ought to specify that inside provocative agony delivering components commonly determined mixes manner to build torment echelons. Nociceptors discovered in skin however likewise in further ranges. Signs communicated via receptors will be translated as ache in the cerebral focuses of mind. Torment possibly will emerge inprerequisite of boosts; was identified as ghost ache. The multifaceted association of torment and harm in fact marks view of ache, imperative examination concern.

As formerly specified, the cerebrum and spinal rope show a major part in focal torment systems. Then again, the learning of mind systems is still generally restricted. The dorsal horn of spinal rope was supplied with a few neurotransmitters comprising nitric
oxide, substance P, excitatory amino acids etc. It is flawless that anguish broadcast to cerebrum is beneath differing physical mechanism.

Without a doubt, this sorts troublesome test in revelation approaches to restrain torment perceptions deprived of bringing about reactions. It is exceptionally obvious that regular items stay, cherished birthplace of novel mixes to assist as pain relieving executors or atoms for advancement.

More exploration is led on characteristic items, certain that further various mixes found and innovative instruments of activity will clarified. With progresses ready in expository science and disconnection science, mixes of immaculate lipid environment found and will progress as of late instituted field of lipidomics.

There is abundant explanation behind energy for impending of regular items exploration, especially with the advancement of unique executors associate with pathways (nociceptive). Pharmacognosy and therapeutic science will graft nearly to guarantee that mixes of common source were investigated for their potential in the improvement of novel medication hopefuls.

Various methods to screen analgesics using different pain stimuli were summarized in table 2.

<table>
<thead>
<tr>
<th>Pain stimulus</th>
<th>Species</th>
<th>Methods</th>
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<tr>
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<td>Mouse / Rat</td>
<td>Hot plate methods</td>
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<td>Tail flick test</td>
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<td>Any</td>
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<td>Chemical Methods</td>
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<td>------------------</td>
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<td>------------------------------------------</td>
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<tr>
<td>Electrical Stimulation</td>
<td>Dog, Rabbit, Guinea Pig</td>
<td>Tooth pulp stimulation Mouse Pododolorimeter</td>
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1.3.3. Fever

Human temperature of body between 37.22°C and 40.57°C onward is known as pyrexia while rise of body temperature above 41.66°C is the hyperpyrexia. Imbalance of heat regulating mechanism responsible for the rise of body temperature. Toxins (pyrogens) act on WBC and produce endogenous pyrogen. It acts directly on anterior hypothalamus and the body temperature was elevated. Fever occurs due to any of the causes such as infections (e.g. pneumonia, typhoid, fever, etc.), injury to nervous centres, dehydration, tissue destruction, administration of some drugs, etc.

Puerperal pyrexia

Puerperal pyrexia is well-defined as the occurrence of fever in a mother greater than or equal to 38°C in the first fourteen days after giving birth. There are numerous causes of such a temperature, but in the days earlier to antibiotics, it was a signal which was very much feared as it had a very poor diagnosis (Ledger, 2003). These days, with quick recognition and management of the fundamental cause, the outcome is noticeably improved.

The indications with which the mother presents may well deliver some idea of where the source of the infection is, or there may be numerous symptoms raising to more than one system that will need a systematic method of determining the problem. Definite causes of puerperal pyrexia may consist of mastitis, genital region infection UTI, post-operative contagion and thrombosis. The symptoms are as follows:

*Urinary tract infection*

- Frequency, dysuria, haematuria
- Rigors from pyelonephritis
- 95% caused by E. coli, proteus, klebsiella.
Genital tract infection
- Tender bulky uterus
- Prolonged bleeding /pink or discoloured lochia
- Painful, inflamed perineum
- May be caused by E. coli, anaerobes, Gro Clostridium welchii (rare, but serious).

Mastitis
- Painful, hard, red breast +/- abscess
- Nipple trauma and cellulitis
- Usually caused by Staph.

Post-operative infection following caesarean section
- Painful, red suture line
- Deep tenderness on palpation
- Lochia pink /coloured.

Deep venous thrombosis
- Painful, swollen calf
- Caused by venous stasis.

Other infections of Pyrexia in a lately delivered mother can also be due to reasons common to all persons, such as viral infection chest infection, etc. The method used to screen anti-pyretic activity of drugs and plants extracts were discussed below

A) Yeast induced pyrexia:

The most extensively used method for evaluating the anti-pyretic activity of a compound involves-
1. Injecting subcutaneously or intraperitoneally into rats a small amount of 1 ml per 100 g b. wt. of aqueous suspension (20 %) of Brewer’s yeast.
2. Allowing the fever to become stabilized (7 - 24 h.).
3. Administering the test compound,
4. Record rectal temperature at different interval after drug administration for approximately 5 h. (Chitme et al., 2005).

**B) Other methods for anti-pyretic screening:**

Most of the other methods used to estimate the anti-pyretic action of drugs utilize bacterial pyrogens as the fever encouraging agents. In addition to rats, cats and rabbits are found to give satisfactory responses to such pyrogens. Intraventricular injection of human serum albumin and rabbit endogenous pyrogens produced dose-dependent fever in rabbits. Fever induced by intraventricular albumin was significantly suppressed by intraventricular injection of indomethacin. The infusion of E.coli lipopolysaccharides (LPs) 5 to 10 µg/kg i.v. produces fever and rectal temperature was measured at hourly intervals for 13 h.

This bon maxim from Osler shrewdly shades the billof apprehension felt by the individuals who go to hot patients at the bedside. Specialists still level headed discussion on the part or evaluation of sickness temperature, and iatrogenic fever encounters intermittent resurgence (Whitrow, 1990). As hero or reprobate, maybe no sign seen so dichotomously. These days fever is considered as patient uneasiness manifestation.

Between demonstrations of minding, fever reparable, along these lines it oftentimes treated. General expert since old times have utilized endless physical intends to lower body temperature (Mackowiak and Plaisacne, 1998). Applying *P. cinchona*as fever suppressing in 1600s, however, eighteenth eraproducing of cinchona made lack (Aronson, 1994) and hunt down choices.

Reverend Stone in 1763 educated, London Royal Society, about against pyretic impacts of "fever bark" from English willow (Aronson, 1994). Despite the fact that his discovering seemed fresh, it essentially settled known to antiquated Egyptians and Galen H.hundreds of years back (Mackowiak and Plaisacne, 1998).

Salicylic acid was initially arranged in the year 1838. The dynamic segment willow bark. An alternate subsidiary, acetylsalicylic acid (ibuprofen) were later blended in the year 1853 and made financially accessible as an hostile to pyretic in 1899 (Mackowiak and
Plaisacne, 1998). From that point forward, various antipyretic drugs brought into medical prescription.

The solution of paracetamol for the fever will be more later. Despite the fact that antecedents, for example, acetanilide and phenacetin were progressed in the second a large portion of the nineteenth century, the normal utilization of acetaminophen as an against pyretic and pain relieving did not happen until the 1950s. The antipyretic medications ordinarily utilized today incorporate acetaminophen, acetylsalicylic acid, and some other nonsteroidal calming medications (Nsauds).

The fundamental activity of antipyretics respites in capacity to stifle catalyst cox (cyclooxygenase) and upset the union of provocative pgs (Weissmann G, 1991). Late meets expectations on the instrument of hostile to pyretic activity of these medications uncover impacts autonomous restraint of cyclooxygenase.

Fever is incited as an auxiliary impact of disease, tissue harm, irritation, join dismissal, malaginancy or illness circumstances (Salawu et al., 2008). Natural shield of the body which make an atmosphere where irresistible go between or harmed tissue can't survive. Generally the sickness ridden or harmed tissue starts the higher establishment of genius incendiary arbiter's (cytokines) which build the prostaglandincombination close the hypothalamus territory and consequently initiating hypothalamus, raise temperature of body.

As the framework of regulation will be directed by a anxious criticism system, hence when temperature goes high, it extends the veins and expand perpiration to dimish fever, basically when the fever goes low hypothalamus secure within. Elevated temperature frequently climbs speedier malady development by expanding tissue drying out, catabolism, prevailing protests, amid seroconversion fallouts quicker ailment move. Most hostile to pyretic remedies impede the cyclooxygenase outflow, trim down lifted temperature by repressing Pge2.

Besides, manufactured executors for all time hinder cyclooxygenase-2 with high selectivity however will be harmful to liver, mind, glomeruli, center muscles, while regular cyclooxygenase-2 suppressor have lesser chose thru less reactions (Luo and BOHLIN,
Fever Pathogenesis

Several intermediary underlying fever have been keyed out in recent years as depicted in figure 2. The life-threatening "endogenous pyrogens" included in making an exceptionally managed provocative reaction to tissue trauma and toxicities will be polypeptide cytokines. Cytokines which are pyrogenic, like interleukin-1b and 6, tumor putrefaction component are those that demonstration specifically on the hypothalamus to influence a fever reaction (Luheshi, 1998). Pyrogens exogenous, such as bacterial superficial constituents, incite pyrexia generally viastimulus of cytokines. The bacterial external film lipopolysaccharide, regardless, will be able of working at the hypothalamus phase, in the same route as interleukin-1b (Dinarello et al., 1999).

These signs actuate the release of different arbiters, most strikingly prostaglandin E2, in the POAH region (Luo and BOHLIN, 2005). Pge2 will be gathered as proximal facilitator of response. Neurons comportment E-prostanoid adjust characteristic boot frequency in Pge2 reaction, conjuring height in temperature regulatory purpose of the body. There are 4 cell receptors Ep1 to Ep4 for Pge2. The specific receptor subtype included in pyrogenesis was obscure. While mice missing Ep3 (subtype receptor of neuronal Pge2) show an impeded febrile rejoinder to pyrogens. Ushikubi work appear to embroil receptor Ep4 (Oka et al., 2000).

The intracellular happenings which triggers fever after receptor coupling (Pge2-EP) among subjects are vague till time. Fever is firmly tweaked by the safe response. Incendiary jolts starting the era of propyretic messages exasperate the discharge of endogenous against pyretic components (Kluger et al., 1998).

Substances, for example, arginine vasopressin empowering glucocorticoids, and hormone act midway, incidentally repress pyrexia. The cytokine has a few mitigating properties, together with fever concealment (Pajkrt et al., 1997). In expansion, a course of lipid mixes distinguished epoxyeicosanoids created by assured P-450 compounds demonstrated noteworthy part avert the irritation and fever.
Identical to a biochemical response pathway, pyrexia itself appears to be equipped for countering the release of cytokines which are pyrogenic (Jiang et al., 1999). For outline, febrile temperatures upgrade TNF early discharge in endotoxin-tested wistar rodent, yet cutoff its delayed interpretation after both lipopolysaccharide infusion or bacterial contamination.

The figure 2 showed that infectious tissue invasion starts a provocative response and initiates leukocytes. The eruction of platelets hooked on swollen regions relies on upon sequencial interchange controlled by mixed bag bond atoms. Triggered leukocytes discharge the pyrogenic cytokines interleukin-1b and 6, tumor corruption element (TNF).

Hematogenous spreading permits these microbial waster to energize endothelial creation of pge inside focal sensory system. CNS Pge2 production triggered by fringe provocative signs which go along neural associations, (for example, the vagus nerve). Neurons present in the preoptic zone of the front hypothalamus demeanorprecise E-prostanoid coordinate febrile reaction next Pge indicator. It adjuststerminating recurrence neurons, comingabout inraised thermo-administrative customary socket.
The temperature of body by febrile customary point was arrived at through the managed inspiration of physiologic progressions and behavioral pointed at enhancing heat creation and diminishing heat scattering. Fever should upgrade the systemic and fringe provocative reaction to sulling partially by altering the statement of incendiary cytokines and expanding leukocyte capacity.