# CHAPTER - 2

# REVIEW OF LITERATURE

## 2.1. Kaempferia species

*Kaempferia rotunda* belongs to the family Zingiberaceae. Members of the Zingiberaceae are famous for their use as spices or as medicinal herbs; well-known examples include the rhizomes of *Zingiber officinale* (ginger) or *Curcuma longa* (turmeric)[1,2]. Rhizomes of *C. longa* or of *Kaempferia pandurata* are important in the folk medicine of South East Asia as antiseptics for wounds or as expectorants[3-7]. Rhizomes of several species from the Zingiberaeeae, however, also contain insecticidal constituents. Dried and powdered rhizomes of *C. longa,* for example, have been reported to act against storage-pest insects, such as *Tribolium castaneum*[8]. Recently, we could show that the sesquiterpene, xanthorrhizol, as well as other sesquiterpenes that are present in rhizomes of *Curcuma xanthorrhiza* or C. *zedoaria,* which are insecticidal towards larvae of the vigorous pest insect, *Spodoptera littoralis,* when applied topically via the larval integument[9]. The 50 species of the genus *Kaempferia* are nearly stemless herbs with thick, aromatic rhizomes. Most *Kaempferia* have silver to purple feather pattern in the middle of the upper side of the leaf radiating outwards with various green shades. Many, of the *Kaempferia* spp. produce small white, pink or orange flowers. *Kaempferia rotunda* has proven to be one of the *Kaempferia* for landscape planting[10].

### 2.1.1. *Kaempferia rotunda* Linn.

#### 2.1.1.1. Synonyms of the plant

Hindi- Bhuichampa; Beng.- Bhuichampa; Mar- Bhuichampa; Oriya-Bhuinchampa; Tel.- Bhuchampakamu; Nep.- Bhuichampa; Lepcha– Ribrip; Eng- Black horm; Guj- Bhuichampo.

#### 2.1.1.2. Distribution

The plant is found to be distributed throughout India in the hilly regions, at elevation ranging from 3000 to 5000 ft[11,12].

#### 2.1.1.3. Description of different parts of plant

*Kaempferia rotunda* Linn. belonging to the family Zingiberaceae is an aromatic herb with tuberous root-stalk and very short stem. Leaves are simple, few, erect, oblong or ovate-lanceolate, acuminate, 30cm long, 10cm wide, variegated green above and tinged with

**Fig.1.1. *Kaempferia rotunda* Linn.**

**Fig.1.2. Rhizomes with flower of *K. rotunda* Linn.**

purple below. Flowers are fragrant, white, tip purple or lilac arranged in crowded spikes opening successively. The plant produces a subglobose tuberous rhizome from which many roots bearing small oblong or rounded tubers arise[13]. The description of the plant is also undertaken by Gamble, Kirtikar and Basu[14,15].

**2.1.1.4. Pharmacological and phytochemical aspects of *K. rotunda* and allied species**

The ethnopharmacological studies showed that the rhizomes of *K.rotunda* are widely used as a local application for tumours, swellings and wounds. The roots have a hot ginger-like taste. They are also given in gastric complaints[16]. They help to remove blood clots and other purulent matter in the body. The juice of the rhizomes is given in dropsical affections of hands, feet, and of effusions in joints. In Ayurveda, the improvement formulations using the herb are *Chyavanaprasam, Asokarishtam, Baladthatryaditailam, Kalyanakaghritham* etc. It also improves complexion and cures burning sensation, mental disorders and insomnia[17]. The rhizomes are useful in vitiated conditions of vata and kapha, gastropathy, dropsy, inflammations, wound, ulcers, blood clots, tumours and cancerous swelling[18,19]. The decoction is applied with much benefit to wounds with coagulated blood and with any purulent matter. The rhizomes contain crotepoxide and β-sitosterol[20]. Rastogi and Asolkar *et. al.*[21,22] also reported crotepoxide in rhizomes. Rhizome contains essential oil, which gives a compound with melting point 149°C, which yielded benzoic acid on hydrolysis.

Chang *et.al.* reported that the extracts of Chinese medicinal herb belongstoZingeberaceae family having an effect of anti inflammatory and antioxidant[23].

Habsah *et. al.* screened dichloromethane and methanol extracts of 13 Zingiberaceae species from the Alpinia, Costus and Zingiber genera for antimicrobial and antioxidant activities. The antimicrobial activity of most of the extracts was antibacterial with only the methanol extract of *Costus discolor* showing very potent antifungal activity against only *Aspergillus ochraceous* (MID, 15.6μg/disc). All the extracts showed strong antioxidant activity comparable with or higher that of alpha-tocopherol[24].

Somchit *et. al.* evaluated the anti- pyretic activities (25, 50 and 100mg/kg) by using Brewers yeast induced pyrexia in rats and analgesic activities (25, 50 and 100mg/kg) by using acetic acid-induced writhing in mice of aqueous and ethanol extracts of *Zingiber zerumbet* rhizomes. Both the extracts showed significant anti-pyretic activities in Brewers

yeast induced pyrexia in rats through out the observation period of 8h. The ethanol extracts of the rhizomes how ever significantly decreased the writhing movements in mice in acetic acid induced writhing test[25].

Suvara *et. al.* showed the rhizomes of *Kaempferia parviflora* (Zingiberaceae) have been used in Thai traditional medicine for health promotion and for the treatment of digestive disorders and gastric ulcer. The data demonstrated that KP has a great potential for a supplemental use in vascular endothelial health promotion[26].

Mohsen *et. al.* studied the effects of hydroalcoholic extract of ginger on an acute model of duodenal ulcer induced by cysteamine orally (350 & 700mg/kg) and intraperitoneally (350mg/kg). It has concluded that ginger hydroalcoholic extract was effective to protect against duodenal ulceration and for i.p. injection as well as chronic administration, the efficacy was comparable with ranitidine[27].

Mahmood *et. al.* studied the effects of methanolic extract of the rhizomes of *Zingiber officinale* in rats for their ability to inhibit gastric lesions induced by ethanol. Animals pre-treated with ginger root extract significantly inhibited gastric lesions compared to control rats .The root extract at a dose of 1000mg/kg orally exert highly significant cytoprotection against ethanol-induced gastric lesions compared to 500mg/kg.This cytoprotection was accompanied with increase in mucus synthesis by gastric mucosa grossly when compared with control rats .These observation strongly suggested the cytoprotective effect of the ginger extract against ethanol-induced gastric ulcer in rats[28].

Shanbhag *et. al.* studied the wound healing effect of alcoholic extract of *Kaempferia galanga* and its effect in dexamethasone suppressed wound healing in Wistar rats. Three wound models viz. incision, excision and dead space wounds were used in this study. The parameters studied were breaking strength in case of incision wounds, epithelialization and wound contraction in case of excision wound and granulation tissue dry weight, breaking strength and hydroxyproline content in case of dead space wound. The dexamethasone treated group showed a significant ($P<0.001$) reduction in the wound breaking strength when compared to control group in incision type of wound model. Coadministration of *K. galanga* with dexamethasone had significantly ($P<0.001$) increased the breaking strength of dexamethasone treated group.In excision wound model, the percentage of the wound contraction was significantly ($P<0.05$) increased by

*K. galanga* only on 16th day and also it reversed the dexamethasone suppressed wound contraction on the 16 day. *K. galanga* significantly ($P<0.001$) reduced the time required for epithelialization and reversed the epithelialization delaying effect of dexamethasone significantly ($P<0.001$)[29].

Indrayan *et. al.* compared 'Kasthuri' and 'Rajani' varieties of medicinal and ornamental plant *Kaempferia galanga* differ morphologically. The essential oils from their rhizomes have remarkably different specific gravities, refractive indices, saponification and iodine values and in their chemical compositions. A total no. of 58 and 56 compounds have been identified in 'Kasthuri' and 'Rajani', respectively. 13 compounds are identified in the rhizome oil of 'Kasthuri' that are not present in the rhizome oil of 'Rajani' and another 11 compounds identified in 'Rajani' oil are not present in 'Kasthuri' oil. 45 compounds have been found common in both oils but their percentages differ in the two varieties[30].

Sirirugsa *et. al.* reported tuber and rhizome of *Kaempferia galanga* are used as a remedy for toothache or a wash for dandruff or scabson the head. It is stimulant, stomachic, and carminative. The rhizome is externally used to treat abdominal pain, swelling and muscular rheumatism. The tuber of *Kaempferia rotunda* is used to treat abdominal illness, gastric complaints. The rhizome is used to treat stomachache and is also used for cosmetics. The leaves are used as body lotion[31].

Nicolo *et. al.* studied plants of 27 families including Zingiberaceae, encompassing 75 species, have been selected on the basis of medicinal folklore in a broad screening programme for their anti-inflammatory activity, using carrageen in foot oedema in rats. Only 4 species including Zingiberace were very active, inhibiting carrageen in foot oedema by 42 to 74%, but overall 72% exhibited some anti-inflammatory activity[32].

Decoction of *K. galanga* used in the inflammed parts to reduce swelling. The leaves are used in sore eyes, sore throat, swellings, rheumatism and fever[33]. The essential oils of *K. galanga* root and rhizome showed antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*[34].

## 2.2. Eupatorium species

*Eupatorium cannabinum* belongs to the family Compositae (Asteraceae) is one of the largest and most diverse families of flowering plants, comprising one-tenth of all known

angiosperm species. It is characterized by the compound inflorescence that has the appearance of a single "composite" flower from which it derives its name. The Compositae is divided into two major subfamilies and one minor subfamily with 12 to 18 tribes, 1,100 to 2,000 genera and 20,000 or more species[35-38]. The family is a rich source of powerful insecticides and industrial chemicals, e.g., pyrethrum (*Chrysanthemum*) and rubber (guayule). Several species are grown as medicinal and culinary herbs. *Echinacea* and others may be sources of biologically active compounds with medical or nutritional benefits. The Compositae also includes several detrimental weeds (dandelion, ragweed, and thistle). Lettuce and sunflower are the best genetically characterized members of this family[39].

The genus Eupatorium is made up of more than 500 species Worldwide. They are mostly herbaceous perennials, some shrubs and rarely annuals. Various species of Eupatorium are reputed to be of medicinal value in the United States and other parts of the World. *Eupatorium purpureum* used for its tonic, astrigents and diuretic properties. *E. agerrratoides* is also used as an antispasmodic, diurectic and diaphoretic. *E. aromaticum* and *E. incarnatum* which have gained much reputation in diseases connected with inflammation and irritability of the bladder. The leaves of *Eupatorium glutinosum* employed as styptics. *E. cannabinum* used as purgative and for other purposes. *E. ayapana* is used as an antidote to the bites of venomous reptiles. *E. nervosum* is very efficacious in cholera, typhoid fevers, small pox[40,41].

**Fig.1.2. *Eupatorium cannabinum* Linn.**

### 2.2.1. *Eupatorium cannabinum* Linn.

#### 2.2.1.1. Synonyms of the Plant

Nepali – Banamara; Lepcha - Nam nong; English - Hemp agrimony.

#### 2.2.1.2. Distribution

The plant is found to be distributed throughout India. It is abundant in temperate Himalayas at altitudes of 3, 000-11,000 ft.[42].

#### 2.2.1.3. Description of dfferent parts of plant

The Hemp Agrimony, *Eupatorium cannabinum*, belongs to the great composite order of handsome, tall-growing perennial herb. The root-stock is woody and from it raises the erect round stems, growing from 2-5 feet high with short branches springing from the axils of the leaves, which are placed on it in pairs. The stems are reddish in colour, covered with downy hair and are woody below. They have a pleasant aromatic smell when cut. The root-leaves are on long stalks, but the stem-leaves have only very short root-stalks. They are divided to their base into three, more rarely five, lance-shaped toothed lobes, the middle lobe much larger than the others, the general form of the leaf being similar to that of the Hemp (hence both the English name and the Latin specific name, derived from *cannabis*, hemp). In small plants the leaves are sometimes undivided. They have a bitter taste, and their pungent smell is reminiscent of an umbelliferous rather than of a composite plant. All the leaves bear distinct, short hairs, and are sparingly sprinkled with small inconspicuous, resinous dots. Recently the plant has been found of use as an immune system stimulant, helping to maintain resistance to acute viral and other infections[43].

#### 2.2.1.4. Pharmacological and phytochemical aspects of *E. cannabinum* and allied species

Traditionally the tribals of Sikkim Himalayan used juice of *Eupatorium cannabinum* leaves as an antiseptic and curing of wounds. *Eupatorium cannabinum* traditionally reported that it will stop the bleeding both externally and internally making it excellent for use against ulcers[44,45]. Leaves are kept with children suffering from smallpox probably to reduce virulence of infection. Chloroform extracts of leaves of plant exhibited *in vitro* antimicrobial activity against *Bacillus subtilis*, *Escherichia coli*,

*Staphylococcus aureus* and *Aspergillius niger*[46]. The leaves contain a volatile oil (with α-terpinene, p-cymene, thymol and anazulene), which acts on the kidneys, and likewise some tannin and a bitter chemical principle which cut short the chill of intermittent fever. The Hemp agrimony contains flavonoids, pyrrolizidine alkaloids; polysachharides and p-cymene which is antiviral. It also contains eupatoriopicrin (sesquiterpene lactones) having anti cancer properties & inhibits cellular growth. The polysachharides stimulate the immune system[47].

It is used as cathartic, diuretic and anti-scorbutic and blood purifier. A homoeopathic tincture is prepared, given in frequent small well-diluted doses with water, for influenza, or for a similar feverish chill, and a tea made with boiling water poured on the dry leaves give prompt relief if taken hot at the onset of a bilious catarrh or of influenza[48].

Hemp agrimony has been employed chiefly as a detoxifying herb for fevers, colds, flu and other viral conditions. It also stimulates the removal of waste products via the kidneys. Due to its content of alkaloids; the plant should only be used under professional supervision[49]. The roots are diaphoretic, laxative and tonic. A homeopathic remedy is made from the leave is used in the treatment of influenza and feverish chills and also for disorders of the liver, spleen and gall bladder[50]. The leaves and flowering tops are, cholagogue, diuretic, emetic, expectorant, febrifuge, purgative and tonic[51-53]. The plant has a long history of use as a gentle laxative that does not provoke irritation though excessive doses cause purging and vomiting. Recent research has shown that the plant might have anti-tumour activity[54].

Rao *et. al.* reported the ethanolic extracts of *E. capillifolium* showed activity against *Bacillus subtilis* grown in a chemically defined medium but not in a complex natural medium[55].

Woerdenbag *et.al.* showed Eupatoriopicrin (EUP), a sesquiterpene lactone from *Eupatorium cannabinum* L. possesses cytostatic activity. This was demonstrated for FIO 26 cells *in vitro* with the aid of a clonogenic assay and *in vivo* by tumour growth delay in FIO 26 and Lewis lung tumour-bearing mice. *In vitro* the IC50 for 1 h exposure to EUP was 1.5 microgram/ml (4.1 nmol/ml)[56].

Phan *et. al. reported E. odoratum* showed significant inhibition of collagen gel contraction. Synergistic properties may contribute to wound-healing mechanisms[57].

Habtemariam *et.al* isolated. 5-acetyl-6-hydroxy-2,3-dihydro-cis-2-isopropenyl-3-tiglinoyloxy benzofuran from *E. purpureum*, which dose dependently inhibited inflammation in rat paw by carrageenan and is a potent inhibitor of some beta 1 and beta 2 integrin-mediated cell adhesions[58].

Urzua *et. al.* showed the antimicrobial testing of resinous exudate of *E. salvia* against five gram-negative and five gram-positive bacteria and found that the acetate of 7-hydroxy-8(17)-labden-15-oic acid to be the major active component[59].

Clavin *et. al.* reported that infusions of *E. laevigatum* produced a 46.6% reduction of stretches in acetic acid induced writhing test and showed no antinociceptive effects in hot plate test suggesting analgesic activity mechanism is unrelated to interaction with opioid systems[60].

Miraldi *et. al.* investigated the traditional ethnobotany and ethnomedicine of West Azerbaijan (Iran) including compositae family. In this region medicinal plants are often the only easily accessible health care alternative for most of the population in rural areas and in fact folk herbal medicine is the most used remedy to cure common diseases. They presented the most frequently used native species and the most common preparations made from them, in order to preserve the plant popular knowledge, which has traditionally been only an oral one[61].

Gupta *et. al.* reported petroleum ether and methanolic extracts of leaves of *Eupatorium ayapana* were tested for their antimicrobial activity. The petroleum ether extract showed higher antibacterial and antifungal activity than the methanolic extract[62].

Hesham *et. al.* isolated new diterpene glucoside 3,15-dihydroxy-*ent*-labd-7-en-17-oic acid 3-*O*-β-D-glucoside (**1**) and its aglycone (**2**) from *Eupatorium glutinosum*. The structures were determined by IR, one- and two-dimensional NMR, high-resolution MS, chemical transformations, and comparison of spectroscopic data with closely related diterpenes. Crude extracts showed antimicrobial and cytotoxic activities, but compounds 1 and 2 showed only antimicrobial activity. These results support the vernacular medicinal use of the plant as an antimicrobial[63].

Rios *et. al.* isolated two new benzofurane compounds, in addition to espeletone encecalinol beta-sitosterol and stigmasterol were isolated from *Eupatorium*

*aschenbornianum* which showed antimicrobial activities against *T. mentagrophytes* and *T. rubrum*[64].

*Baccharis teindalensis* (compositae) is a herbal plant which is widely used in folk medicine in Ecuador as an antiinflammatory, analgesic and antimicrobial remedy. Vidari *et. al.* evaluated the antidiarrhoeic and antiulcer activities of this extract in different mouse models. The ethanol extract of *B. teindalensis* showed antidiarrhoeic activity against the castor oil induced diarrhoea, at all doses tested. Furthermore, the ethanol extract induced a significant increase in myeloperoxidase activity as an index of the neutrophilic infiltration ($p<0.05$ vs control) and the higher dose of this extract (100 mg/kg) inhibited it in a remarkable way ($p<0.001$). These results confirm the gastrointestinal protection afforded by *B. teindalensis* and suggest that the antiulcer effect could be partially due to its antiinflammatory properties[65].

*Calendula officinalis* L. belongs to the Asteraceae family has long been used in topical applications, to treat skin ulcers, infected wounds, diaper rash, eczema, varicose veins, hemorrhoids, periodontitis and conjunctivitis. Reepithelizing and wound healing activityis one of the most extensively used actions of calendula. Creams containing calendula floral extract 5% in combination with alantoin, promoted remarkable epithelization in rat experimental models, with especial intensity on the metabolism of glycoproteins and collagen fibres during tissue regeneration. Alonso *et. al.* suggested that the water extracts of calendula flowers, applied on skin wounds, play a role as microvascularization inducing agents, thus contributing to speed up healing[66].

Albuquerque *et. al.* identified 12 compounds when the essential oils from leaves and roots of *Eupatorium betonicaeforme* were analyzed by GC-MS. The essential oil from roots and 2,2-dimethyl-6-vinylchroman-4-one (10.3-25.5%) can considered as natural larvicidal agents[67].

*Lactuca sativa* is a member of Compositae family. In folk medicine of Iran, the seeds of this plant were used for relieving of inflammation and osteodynia. Sayyah *et. al.* evaluated the anti-nociceptive and anti-inflammatory activities of crude methanol/petroleum ether (70/30, v/v) extract of the seeds. The extract exhibited a time- and dose-dependent analgesic effect in formalin test and also a dose-dependent anti-inflammatory activity in a carrageenan model of inflammation[68].

Suksamram *et. al.* isolated & identified flavanones, 2 chalcones & 2 flavones from flowers of *Eupatorium odoratum*. Isosakuranetin exhibited antimicobacterial activity, acacetin showed moderate cytotoxicity against NCI-H187 cells whereas luteolin exhibited moderate toxicity[69].

Maher *et. al.* proved that the ethyl acetate extract of the whole aerial parts of *Varthemia iphionoides* (Compositae) have a pronounced antibacterial activity. The compound sesquiterpene, selina-4,11(13)-dien-3-on-12-oic acid isolated from ethyl acetate extract exhibited potent antimicrobial activity against six bacterial species (*Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli*, *Bacillus cereus* and *Salmonella enteritides*). The minimum inhibitory concentrations (MICs) of this compound which was determined by the agar dilution method ranged between 250 and 500 μg/ml[70].

Chomnawang *et.al.* studied 13 medicinal plants, amongst them *Eupatorium odoratum*, *Garcinia mangostana*, and *Barleria lupulina* had strong inhibitory effects against growth of *Propionibacterium* a pus-forming bacteria triggering an inflammation in acne[71].

Dabaghi *et. al.* tested flavonoids of the leaves of *Eupatorium litoralle* for oxidative metabolism of isolated rat liver mitochondria. It revealed that hispidulin as an uncoupler of oxidative phosphorylation with distinct prooxidant and antioxidant properties when compared to eupafolin[72].

Muschietti *et. al.* presented methanol extracts from 11 Argentine medicinal plants. When the extracts assayed *in vitro* for antifungal activity against yeasts, hialohyphomycetes & dermatophytes, strongest effect was presented by *Eupatorium buniifolium* and *Terminalia triflora*[73].

Sasikumar *et. al.* studied antibacterial screening of petroleum ether, chloroform, ethyl acetate, methanol and aqueous extracts of *Eupatorium glandulosum* leaves which exhibited a broad spectrum of inhibitory activity against Gram (+) and Gram (-) pathogenic bacteria[74].

Shen *et. al.* studied Eupaheliangolide A, 3-epi-heliangin and heliangin of *Eupatorium kiirunense* exhibited cytotoxicity against human oral epidermoid (KB), cervical epitheloid (Hela) and liver (hepa59T/VGH) carcinoma cells[75].

Dubey *et. al.* screened essential oils extracted from 17 higher plants belonging to different families against *Botryodiplodia theobromae* and *Colletotrichum gloeosporioides* causing stem end rot disease and anthracnose disease in mango respectively. The essential oil of *Eupatorium cannabinum* was found to be fungitoxic in nature against both the mango-rotting fungi. *Eupatorium* oil was standardized through physico-chemical and fungitoxic properties. The oil showed a broad fungitoxic spectrum and was recorded to be more efficient than some synthetic fungicides. The oil also showed an inhibitory effect on pectinase and cellulase enzymes. The $LD_{50}$ of *Eupatorium* oil was found to be 22.01 ml/kg body weight on mammalian mice[76].

Judzentiene A isolated Germacrene D, Neryl acetate, neryl isobutyrate and β-Bisabolene from the essential oils of *Eupatorium cannabinum* L.[77].

Mullika *et. al.* investigated the activity of Thai medicinal plants on inflammation caused by *Propionibacterium acnes* in terms of free radical scavenging and cytokine reducing properties. *P. acnes* have been recognized as pus-forming bacteria triggering an inflammation in acne. Antioxidant activity was determined by DPPH scavenging and NBT reduction assay. The result showed that *Garcinia mangostana* possessed the most significant antioxidant activity and reduced reactive oxygen species production. *Eupatorium odoratum*, and *Senna alata* had a moderate antioxidant effect[78].

Clavin *et. al.* isolated and identified three anti-inflammatory compounds: nepetin, jaceosidin and hispidulin from *Eupatorium arnottianum* Griseb. dichloromethane extract. Nepetin reduced the TPA mouse ear edema by 46.9%; and jaceosidin by 23.2%. All these compounds are reported for the first time in this species. The finding of topical antiinflammatory activity exerted by *Eupatorium arnottianum* extract and the identification of active principles could support the use of this plant for the treatment of inflammatory affections[79].

Several species of the genus Tanacetum are traditionally used in a variety of health conditions including pain, inflammation, respiratory and gastrointestinal disorders. In the current investigation, Ishfaq *et. al.* evaluated the plant extract of *T. artemisioides* and some of its pure compounds (flavonoids) for analgesic, anti-inflammatory and calcium antagonist effects in various *in-vivo* and *in vitro* studies. Moreover the findings support

the traditional reputation of the genus Tanacetum for its therapeutic benefits in pain and inflammatory conditions[80].

Maria *et. al.* collected the information to cover the most recent developments in the ethnopharmacology, pharmacology and phytochemistry of this genus *Baccharis* genus (Compositae) which is an important source of natural medicinal products.. This review describes its traditional and folkloric uses, phyto-constituents and pharmacological of the prominent species of the genus *Baccharis*. Flavonoids and other phenolic compounds, diterpenoids and volatile constituents have been reported as the major phyto-constituents of the *Baccharis* species. Pharmacological studies are mainly based on the anti-inflammatory, antioxidant, antimicrobial, the treatment of wounds and ulcers, fever, gastrointestinal illnesses, as spasmolytics, diuretics and analgesics, and in the treatment of diabetes and bacterial/fungal infections[81].

## 2.3 Antioxidants from herbal sources

Reactive oxygen species (ROS), which consist of free radicals such as superoxide anion ($O_2^{\cdot}$) and hydroxyl ($HO^{\cdot}$) radicals and non-free radical species such as $H_2O_2$ and singled oxygen ($^1O_2$), are different forms of activated oxygen[82]. ROS are produced by all aerobic organisms and can easily react with most biological molecules including proteins, lipids, lipoproteins and DNA. *In vivo*, some of these ROS play positive roles in cell physiology; however, they may also cause great damage to cell membranes and DNA, inducing oxidation that causes membrane lipid peroxidation, decreased membrane fluidity, and DNA mutations leading to cancer, degenerative, and other diseases. Thus ample generation of ROS proceed to a variety of athophysiological disorders such as arthritis, diabetes, inflammation, cancer and genotoxicity[83-87]. Free radicals due to environmental pollutants, radiation, chemicals, toxins, deep fried and spicy foods as well as physical stress, cause depletion of immune system antioxidants, change in gene expression and induce abnormal proteins. Oxidation process is one of the most important routes for producing free radicals in food, drugs and even living systems. Catalase and hydroperoxidase enzymes convert hydrogen peroxide and hydroperoxides to non radical forms and function as natural antioxidants in human body. Due to depletion of immune system natural antioxidants in different maladies, consuming antioxidants as free radical

scavengers may be necessary[88]. Therefore, living organisms possess a number of protective mechanisms against the oxidative stress and toxic effects of ROS.

Antioxidants regulate various oxidative reactions naturally occurring in tissues and are evaluated as potential anti-aging agents. Hence, antioxidants can terminate or retard the oxidation process by scavenging free radicals, chelating free catalytic metals and also by acting as electron donors. Antioxidants have been widely used as food additives to provide protection from oxidative degradation of foods and oils. Hence, antioxidants are used to protect food quality mainly by the prevention of oxidative deterioration of constituents of lipids. The most extensively used synthetic antioxidants are propylgallate (PG), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and *tert*-butylhydroquinone (TBHQ). However BHT and BHA have been suspected of being responsible for liver damage and carcinogenesis[89,90]. Natural antioxidants are able to protect from ROS as well as other free radicals and retard the progress of many chronic diseases and lipid oxidative rancidity in foods[91]. Polyphenols are widely distributed in plants and phenolic antioxidants have been found to act as free radical scavengers as well as metal chelators[92]. It has also been reported that some types of polyphenols such as catechin, epicatechin, epigallocatechin, catechin gallate, epicatechin gallate and epigallocatechin gallate are present in the seaweeds like *Halimeda* algae[93].

Naturally occurring antioxidants in leafy vegetables and seeds, such as ascorbic acid, vitamin E and phenolic compounds, possess the ability to reduce the oxidative damage associated with many diseases, including cancer, cardiovascular disease, cataracts, atherosclerosis, diabetes, arthritis, immune deficiency diseases and aging[94]. Antioxidants are important in the prevention of human diseases. Antioxidant compounds may function as free radical scavengers, complexers of pro-oxidant metals, reducing agents and quenchers of singlet oxygen formation[95]. Antioxidants are often used in oils and fatty foods to retard their autoxidation[96].

Antioxidants are also important to the food industry. Manufacturers have strived to produce high quality food with superior texture, color, flavor and nutritional values in the shelf life period. However, many foods are subject to many factors that lead to the quality deterioration.

Among these undesirable factors, lipid autooxidation is one of the most concerned. The need of protecting food against oxidative degradation has prompted the wide usage of food additives.

Many studies have been shown that the presence of natural antioxidants from various aromatic and medicinal plants is closely related to the reduction of chronic diseases such as DNA damage, mutagenesis, and carcinogenesis[97]. Therefore, there has been a growing interest in research concerning alternative antioxidant active compounds, including plant extracts and essential oils that are relatively less damaging to the mammalian health and environment.

The antioxidative potential of methanol extract of *Ecklonia cava* was evaluated by using 1,1-diphenyl-2-picrylhydrazyl (DPPH), superoxide anion, hydrogen peroxide, hydroxyl radical, nitric oxide, ferrous ion chelating, reducing power and lipid peroxidation inhibition assays. The methanol extract showed significant ($p<0.05$) activities in all antioxidant assays and contained a high level of total phenolic conten[98].

Antioxidant activities of the extracts of *Teucrium* species were evaluated using three complementary *in vitro* assays: inhibition of DPPH radical, inhibition of hydroxyl radicals and protection of carotene-linoleic acid model system. It has seen that *Teucrium* species possess free radical and hydroxyl radical scavenging activity as well as antioxidant activity *in vitro*[99].

Potential antioxidative activities of enzymatic extracts from seven species of brown seaweeds were evaluated using four different reactive oxygen species (ROS) scavenging assays containing DPPH free radical, superoxide anion, hydroxyl radical and hydrogen peroxide scavenging assay. The enzymatic extracts exhibited more prominent effects in hydrogen peroxide scavenging activity compared to the other scavenging activities[100].

Total phenol contents and radical scavenging activity of the water extract of *Acanthopanax senticosus* extracts was determined for antioxidant activity. *A. senticosus* showed significant antioxidant activity and protective effect against oxidative DNA damage[101].

By using DPPH radical scavenging assay the antioxidant activity of crude methanol extracts from the leaves, flowers and pods of *Cassia alata* L has been investigated and it

has been found that the leaf extract exhibited a stronger antioxidant activity than the extracts from the flowers and pods[102].

The antioxidant potency of cultivated fruit-bodies of *Cordyceps militaris* L. was investigated by employing DPPH free radical scavenging, hydroxyl radical eliminating, iron chelating, inhibition of linoleic acid, lipid peroxidation and reducing power. The aqueous extract of *C. militaris* fruit-bodies shows a significant scavenging effect on DPPH, eliminating the capability on hydroxyl radicals and the chelating effect on ferrous iron and also shows positive results of inhibiting linoleic acid lipid peroxidation and reducing power[103].

The antioxidant effects, the levels of total phenol and contents of volatile oils and plant extracts *Rosmarinus officinalis* were determined in eight various Rosemary clones. Antioxidant acitvities and the total phenol contents were measured by spectophotometric method as well as the volatile oil content of the fresh plants with gas chromatograph it indicates that the antioxidant capacity of volatile oils and plant extracts closely related to the total phenol contents[104].

The methanolic crude extracts of 12 traditionally used Indian medicinal plants were screened for their antioxidant and free radical scavenging properties. The antioxidant activity of *Lawsonia inermis* was the strongest, followed in descending order by *Ocimum sanctum, Cichorium intybus, Piper cubeba, Punica granatum, Allium sativum, Delonix regia, Terminalia chebula, Terminalia ellerica, Mangifera indica, Camellia sinensis,* and *Trigonella foenum-graecum*[105].

The antioxidant properties of ethanol extract a *Ptychopetalum olacoides* was evaluated by using various *in vitro* systems. Extract acted as a scavenger of nitrogen oxides as well as superoxide generated by the xanthine-xanthine oxidase system. The extract also showed a high antioxidant capacity using a luminol chemiluminescence derived from a thermolabile diazocompound[108].

## 2.4. Wound healing agents from herbal source

Wounds occur as a result of physical injuries that break and expose the skin epidermal and dermal layers, causing damage to the blood vessels and leading eventually to bleeding. Wound healing is a complex sequence of events intiated by the stimulus of

injury to tissues. These events involve four main processes: coagulation, inflammation and debridement of wound, epithelia repairs and tissue remodeling and collagen deposition[107]. It is known that any agent that accelerates one or two of the above events is a promoter of wound healing[108]. Medicinal plant extracts, decoctions and concotions have been in use traditionally to treat various skin lesions (burns and wounds), and these plants have demonstrated wound healing properties in various animal models[109-111].

Wound healing consists of an orderly progression of events that establish the integrity of the damaged tissue. The process of wound healing is essential to prevent the invasion of damaged tissue by pathogens and to partially or completely reform the damaged tissue. The healing involves different phases, including inflammation, granulation, fibrogenesis, neo-vascularization, wound contraction and epithelialization[112]. The process of wound healing is promoted by several natural and plant products, which are composed of active principles like flavonoids, triterpenes, alkaloids, tannins and other biomolecules. These agents usually influence one or more phases of the healing process. The wound healing properties of *Aloe vera*[113], *Centella asiatica*[114], *Tridax procumbens*[115] and curcumin[116] have been reported and experimentally studied on various animal models.

Normal wound healing response begins the moment the tissue is injured. Wound healing is the process of repair that follows injury to the skin and other soft tissues. Following injury, an inflammatory response occurs and the cells below the dermis begin to increase collagen production. Later, the epithelial tissue is regenerated[117].

*Ayurveda*, the Indian traditional system of medicine, is based on empirical knowledge of the observations and the experience over millennia[118]. Healing of wounds is an important area of clinical medicine explained in most of the Ayurvedic texts since about 5000 BC under the heading "*Vranaropaka*." The wound as a medical problem was first discussed by Maharshi Agnibesha in *Agnibesha Samhita* (later known as Charaka *Samhita*) as Vrana[119] Maharshi Sushruta in *Sushruta Samhita*[120] elaborated on the subject.

Wound healing occupies an important field of research in modern biomedical sciences. The detailed pathophysiology of wounds is better understood following the establishment of the theory of a cell signal cascade system involved in the formation of new tissues repairing the wound. Modern biomedical scientists are now trying to develop suitable wound healing drug, corroborating the activity with cell signal triggering properties.

According to the Ayurveda, *Vrana* (wounds or ulcers) is the discontinuation of lining membrane that after healing leaves a scar for life[121] closely resembling the modern definition. Similarly, inflammation is considered to be an early phase in the pathogenesis of wounds termed *Vranashotha*. Different types of wounds as mentioned in Ayurveda may be endogenous in origin due to a defect in human functional units, such as *Vata* (nerve impulses), *Pitta* (enzymes and hormones), and *Kapha* (body fluids), or exogenous due to trauma, such as *Chinna* (cut wound), *Bhinna* (perforated wound), *Viddha* (punctured wound), *Kshata* (lacerated wound), *Picchita* (contusion), and *Ghrista* (abrasion wound[122]. These steps have striking similarities with wounds described in modern medicine[123,124]. In modern medicine, it is understood that there are certain essential polypeptides of the low concentration present in animal serum that control cell proliferation. These are called growth factors. Growth factors act by autocrine, paracrine and endocrine-signaling systems. There are several growth factors, which help in the healing of wounds in different ways. Platelet-derived growth factor is responsible for stimulation of connective tissue proliferation, epidermal growth factor mainly stimulates cutaneous tissue proliferation, and fibroblast growth factor stimulates many cell types with special references to fibroblast cells. Transforming growth factor, on the other hand, inhibits excess growth of some cell types[125]. However, a recent study reveals that some of these growth factors may have serious untoward effects such as carcinogenesis[126]. Classical management of wounds according to *Sushruta Samhita* follows 60 therapeutic steps, starting with an aseptic dressing of the affected part and ending with the rehabilitation of the normal structure and function[127]. These therapeutic measures were aimed not only to accelerate the healing process but also to maintain the quality and aesthetics of the healing. As described in different Ayurvedic classics like *Charaka Samhita* (ca. 5000 BC), *Sushruta Samhita* (ca. 1000 BC), *Astamga Hridaya* (ca. AD 600)[128] *Bhavaprakash Nighantu* (ca. AD 1500)[129], *Dhanwantari Nighantu* (ca. AD 1800)[130] and *Ayurveda Siksha* (AD 20th century)[131].

**Table 1: Ayurvedic *Vranaropaka* (wound healing) drugs of plant origin[118-120, 128-131]**

| Sl. No | Botanical name | Family | Parts used for wound healing |
|---|---|---|---|
| 01 | *Abies webbiana* Linn. | Pinaceae | Leaves |
| 02 | *Acorus calamus* Linn. | Araceae | Rhizome |
| 03 | *Achyranthus aspera* Linn | Amaranthaceae | Whole plant |
| 04 | *Adiantum lunulatum* Burm. | Polypodiaceae | Leaves |
| 05 | *Albizzia lebbeck* Benth. | Leguminosae | Stem bark |
| 06 | *Alstonia scholaris* | Apocyanaceae | Leaves |
| 07 | *Andropogon muricantus* Retz. | Graminae | Root |
| 08 | *Anogeissus latifolia* Wall. | Combretaceae | Stem bark |
| 09 | *Boerhaavia diffusa* Linn. | Nyctaginaceae | Whole plant |
| 10 | *Balanites roxburghii* Planch. | Simaronbaceae | Stem bark |
| 11 | *Cedrus deodara* Roxb. Loud. | Anonaceae | Leaves |
| 12 | *Coleus vettiveroides* Benth. | Labiatae | Whole plant |
| 13 | *Crocus sativus* Linn. | Iridaceae | Flower |
| 14 | *Curcuma longa* Linn. | Zingiberaceae | Rhizome |
| 15 | *Curcuma zedoria* Rosc. | Zingiberaceae | Tuber |
| 16 | *Cynodon dactylon* Linn. | Gramineae | Whole plant |
| 17 | *Datura fastuosa* Linn. | Solanaceae | Leaves |
| 18 | *Desmodium gangeticum* D.C | Leguminosae | Whole plant |
| 19 | *Dolichos biflorus* Linn. | Leguminosae | Seed |
| 20 | *Eclipta alba* Hassk.2 Keshuta | Compositae | Root |
| 21 | *Emblica officinalis* Linn. | Euphorbiaceae | Fruit, leaves |
| 22 | *Euphorbia thymifolia* R.Br. | Euphorbiaceae | Whole plant |
| 23 | *Ficus racemosa* Linn. | Moraceae | Leaves |

| | | | |
|---|---|---|---|
| 24 | *Ficus bengalensis* Linn. | Moraceae | Stem bark |
| 25 | *Gymnema sylvestre* R.Br. | Asclepiadaceae | Leaves |
| 26 | *Heliotropium indicum* Linn. | Boraginaceae | Leaves |
| 27 | *Hordeum vulgare* Linn. | Gramineae | Grain |
| 28 | *Iris germanica* Linn. | Irideae | Stem |
| 29 | *Jasminum sambac* Ait. | Oleaceae | Leaves |
| 30 | *Lens culinaris* Linn. | Leguminosae | Leaves |
| 31 | *Mimosa pudica* Linn. | Mimosoidae | Whole plant |
| 32 | *Mertynia diandra* Glox. | Mertyneaceae | Fruit, flower |
| 33 | *Nerium indicum* Mill. | Apocyanaceae | Root |
| 34 | *Oledelandia biflora* Linn. | Rubiaceae | Whole plant |
| 35 | *Pisum sativum* Linn. | Verbenaceae | Leaves |
| 36 | *Psoralia corylifolia* Linn. | Leguminosae | Seeds |
| 37 | *Rannunculus scleratus* Linn. | Rannunculaceae | Whole plant |
| 38 | *Saraca indica* Linn. | Leguminoae | Stem bark |
| 39 | *Swertia chirata* Buch.Ham3 Chireta | Gentianaceae | Stems, leaves |
| 40 | *Terminalia chebula* Retz. | Combretaceae | Fruits |
| 41 | *Tinospora tomentosa* Colebr. | Menispermaceae | Stem |
| 42 | *Tricosanthes dioica* Roxb. | Cucurbitaceae | Leaves, stem bark |
| 43 | *Vitex negundo* Linn. | Verbenaceae | Leaves |
| 44 | *Vateria indica* Linn. | Dipterocarpaceae | Latex |
| 45 | *Wedelia calendulacea* Less. | Compositae | Leaves |
| 46 | *Woodfordia fruticosa* Kurz. | Lytheraceae | Flower |
| 47 | *Zingiber officinale* Rosc. | Zingiberaceae | Rhizome |

Folk medicine practitioners in Peru employ plant preparations as wound-healing agents. The results of a scientific evaluation of the wound-healing activity of nine plants, *Peperomia galioides, Mentzelia cordifolia, Mutisia acuminata, Himatanthus sucuuba, Spondias mombin, Eleutherine bulbosa, Muehlenbeckia tamnifolia, Anredera diffusa and Jatropha curcas* were studied for wound healing activity on superficial and internal wounds (gastric ulcers). Significant wound-healing activity was detected in *Peperomia galioides, Anredera diffusa* and *Jatropha curcas*[132].

Aloe vera improves wound healing and inhibits inflammation. Since mannose-6-phosphate is the major sugar in the Aloe gel, Davis *et. al.* examined the possibility of its being an active growth substance and concluded that the mice receiving 300mg/kg of mannose-6-phosphate had improved wound healing.and anti-inflammatory activity[133].

Wound healing potential of different extracts of leaves of *Lawsonia alba* Lam. was evaluated by Mandawgade *et. al.* on the rat excision and incision wound models. The oral administration of ethanol extract of *Lawsonia alba* Lam. leaves exhibited significant healing response in both the wound models[134].

*Chandanadi yamak* was tested in male Wistar rats by two wound models. Incision wounds for tensile strength and excision wounds for wound contraction were employed along with histopathological evaluation. The application of the test formulation alone promoted wound contraction and reduced the time for wound closure showing healing potential comparable to marketed framycetin sulphate cream (1% W/W)[135].

A methanol extract of *L. lavandulaefolia* was examined for its wound healing activity both in the form of an ointment as well as an injection in two types of wound model in rats:

(i) the excision wound model
(ii) the incision wound model.

Both the injection and the ointment of the methanol extract of the plant material produced a significant response in both of the wound types tested. The results were also comparable to those of a standard drug, nitrofurazone, in terms of wound contracting ability, wound closure time, tensile strength and regeneration of tissues at the wound site[136].

## 2.5. Anti ulcer agents from herbal source

Gastric ulceration occurs due to imbalances between offensive and defensive factors of the gastric mucosa. The antiulcerogenic activity of many plant products is reported to an increase in mucosal defensive factors rather than decrease in the offensive factors[137].

A number of antiulcer drugs like gastric antisecretory drug H-2 receptor antagonists, antimuscarinic agents, proton pump inhibitors, mucosal protective agents–carbenoxolone sodium, sucralfate and prostaglandin analogues are available which are shown to have side effects and limitations[138]. There are several herbal ayurvedic preparations which have a protective effect against drug-induced gastric mucosal injury[139]. Constituents of ambrex are *Withania somnifera* roots (6%), *Orchis mascula* root (10%), *Cycas circinalis* male cone (25%), *Shorea robusta* resin (10%) and *Amber fossil* resin (15%). Individual components have been suggested to exhibit several properties like antistress' antidepressant, antioxidant, immunomodulatory[140], antitumor[141] (*Withania somnifera*), antihyperdipsia[142] (*Cycas circinalis*) antidiarrheal, antidysentery[143] (*Orchis mascula*), antibacterial[144], antiulcer[145] (*Shorea robusta*), antiseptic and antispasmodic activities[146].

Gastric ulceration is believed to be the result of constant confrontation in the stomach and upper small bowel between acid-pepsin aggression and mucosal defense. The regulation of mucosal microcirculation is intimately involved in the maintenance of gastric integrity and endogenous nitric oxide (NO) has been established to have a role in this regulation[147,148]. Reduced glutathione is also important for mucosal integrity since depletion of GSH from the gastric mucosa by electrophilic compounds induces macroscopic mucosal ulceration[149,150].

Peptic ulcer therapy has undergone many strides over the past few years and a number of drugs are now available for treatment. These drugs are broadly classified into two, those that decrease or counter acid pepsin secretion and those that afford cytoprotection by virtue of their effects on mucosal defensive factors. These drugs act by different mechanisms. Most of the commonly used drugs such as H2 blockers (ranitidine, famotidine *etc*), M-1 blockers (pirenzepine, telenzepine etc), proton pump inhibitors (omeprazole, lansaprazole *etc*), decrease secretion of acid while, drugs like sucralfate and carbenoxolone promote mucosal defenses. Of late the role of these drugs on the defensive factors is gaining importance. It is now assumed that these drugs ultimately balance the

aggressive factors (acid, pepsin, *H. pylori*, bile salts) and defensive factors (mucin secretion, cellular mucus, bicarbonate secretion, mucosal blood flow and cell turnover)[151]. Although these drugs have brought about remarkable changes in ulcer therapy, the efficacy of these drugs is still debatable. Reports on clinical evaluation of these drugs show that there are incidences of relapses and adverse effects and danger of drug interactions during ulcer therapy. Hence, the search for an ideal anti-ulcer drug continues and has also been extended to herbal drugs in search for new and novel molecules, which afford better protection and decrease the incidence of relapse.

Numerous plants and herbs are used to treat gastrointestinal disorders in traditional medicine. There has been renewed interest in identifying new antiulcer drugs from natural sources[152]. Before introduction of potent antiulcerogenic agents, i.e. H2 receptor antagonists, proton pump inhibitors, etc. plant remedies were widely employed for the treatment of various symptoms of peptic ulcer[153].

In Ayurveda, peptic ulcer mostly refers to *Amlapitta* or *Parinamasula. Amlapitta* is a disease of the gastrointestinal tract, especially of the stomach. It has not been described as an independent disease in major Ayurvedic texts, but has been mentioned in short in *Kashyapa* samhita. *Amlapitta* literally means, pitta leading to sour taste. Apart from the stress laid on food habits and personal hygiene, some herbal drugs have also been mentioned. Modern medicine has not adequately evaluated the usefulness of these drugs in ulcer therapy, although studies have been reported. Some active constituents have also been isolated from these potential anti- plantain banana (*Musa sapientum* var. paradisiaca), *Tamrabhasma* (an indigenous preparation of copper), ginger (*Zingiber officinale*) and satavari (*Asparagus racemosus*) and give an overview on other potential anti-ulcerogenic drugs[154].

Suba *et.al.* evaluated the gastric cytoprotective activity of the methanol extract of aerial parts of the plant *Barleria lupulina* Linn. in albino rats using various models of ulcers such as drug induced ulcers, restraint ulcers, duodenal ulcers and pylorus ligated ulcers. The study suggested that the methanol extract of aerial parts of *Barleria lupulina* Linn. showed protective effect against experimental gastric and duodenal ulcers[155].

Saha *et. al.* examined effects of the flavonoid rich fraction of the stem bark of *Manilkara hexandra* by indomethacin+pylorus ligated gastric ulcers in experimental animals. Oral

administration of the ethyl acetate extract inhibited the formation of gastric lesions induced by ethanol in a dose dependent manner[156].

Butanol fraction of *G. pentaphyllum was* evaluated for its anti-gastric ulcer activity using experimental models. Oral administration of the plant extract at 200 and 400 mg/kg body wt. significantly inhibited gastric ulcer formation induced by indomethacin. The findings indicate that the butanol fraction of *G. pentaphyllum* possesses gastroprotective potential related to the preservation of gastric mucus synthesis and secretion[157].

Anti-ulcer effect of *Salvia leriifolia* leaf extracts was studied in mice. Gastric mucosal lesions were induced by oral administration of HCl/ethanol to mice. The oral administration of aqueous and ethanolic extract significantly inhibited the development of ulcer. At repetitive doses, the oral administration of aqueous and maceration extracts before the nercotizing agents significantly inhibited the lesion. The results suggest that *S. leriifolia* leaf extracts have effective anti-ulcer activity in mice[158].

The antiulcer activity of a hydro-ethanolic extract prepared from the stems of *Kielmeyera coriacea* Mart. (Guttiferae) was evaluated in rats employing the ethanol-acid, acute stress and Indomethacin models to induce experimental gastric ulcers. Treatment with *K. coriacea* hydro-ethanolic extract provided significant antiulcer protection in the ethanol-acid and Indomethacin models, but not in the acute stress model. These results suggested that the *K. coriacea* hydro-ethanolic extract increased resistance to necrotizing agents, providing a direct, protective effect on the gastric mucosa[159].

The aqueous and ethanolic extracts of *Portulaca oleracea* were studied in mice for their ability to inhibit gastric lesions induced by HCl or absolute ethanol. In addition, their effects on gastric acid secretion were measured. Both extracts showed a dose-dependent reduction in severity of ulcers. The highest dose of extracts exerted similar activity to sucralfate. The oral and intraperitoneal administration of extracts reduced the gastric acidity in pylorus-ligated mice. These results suggest that *Portulaca oleracea* has gastroprotective action and validates its use in folk medicine for gastrointestinal diseases[160].

The anti-ulcerogenic potential of the methanol extract of *Ocimum suave* was investigated using four methods of gastric lesion induction in experimental Wistar rats; HCl/ethanol-induced gastric lesions, absolute ethanol-induced gastric lesions, indomethacin-

HCl/ethanol-induced gastric lesions and pylorus ligation-induced gastric lesions. Administration of the extract of *Ocimum suave* to the rats by oral route prevented the formation of acute gastric lesions induced using the four experimental techniques[161].

Evaluation of ethanolic extract of *Kaempferia parviflora* for its anti-gastric ulcer activity by experimental models has been observed. Oral administration of the extract at 30, 60 and 120 mg/kg significantly inhibited gastric ulcer formation induced by indomethacin, HCl/EtOH and water immersion restraint-stress in rats. In pylorus-ligated rats, pretreatment with the extract had no effect on gastric volume, pH and acidity output. The findings indicate that the ethanolic extract of *Kaempferia parviflora* possesses gastroprotective potential which is related partly to preservation of gastric mucus secretion and unrelated to the inhibition of gastric acid secretion[162].

The majority of *Ethiopian population* relies on traditional remedies and some of which may also have nutritional value. *Trigonella foenum-gracum* infusion and *Linum usitatissimum* water extract are used to manage peptic ulcer. Mequanente *et. al.* showed that both aqueous *T. foenum-gracum* and *L. usitatissimum* seed extracts reduced the ulcer index and ulcer number of ethanol induced lesions ($P<0.001$)[163].

A methanolic fraction from an extract of *Bryophyllum pinnatum* leaves was found to possess significant anti-ulcer activity in nine different experimental animal models. Premedication tests in rats revealed that the extract possessed significant protective action against the gastric lesions induced by aspirin, indomethacin, serotonin, reserpine, stress and ethanol. Significant protection with extract treatment was observed to occur for aspirin-induced ulcer in pylorus-ligated rats and for histamine-induced duodenal lesions in guinea pigs. Significant enhancement of the healing process was also found to occur in acetic acid-induced chronic gastric lesions in rats[164].

Ethanol extracts of *Terminaliapallida brandis* was evaluated for its anti-ulcer activity against drug-induced ulcers, histamine-induced ulcers in Swiss albino rats. The extracts at the doses of 250 and 500 mg/kg per os (p.o.) exhibited significant protection against ulcers produced by indomethacin, histamine and the effect was comparable to that of the reference drug famotidine orally[165].

## 2.6. Anti-inflammatory agents from herbal source

Inflammation is the defensive mechanism of tissue to any injury which may be caused by injection of chemical/physical agents but may lead to development of inflammatory bowl disease[166]. It involves pain, heat, redness, swelling and loss of function of effected parts. Various therapeutic approaches are available for reducing long term inflammatory response. These anti- inflammatory agents exert various effects that result in reduction in the number and activity of immune system cells. Several natural products are being used as good anti-inflammatory agents without the risk of side effects from the time immemorial.

Inflammation is generally considered as an essentially protective response to tissue injury caused by noxious physical, chemical or microbiological stimulus. It is a complex process involving various mediators, such as prostaglandins, leukotrienes and platelet activating factor[167]. The major macrophage derived inflammatory mediators such as proinflammatory cytokines, tumour necrosis factor-a (TNF- a) and the reactive free radical nitric oxide (NO) synthesized by inducible NO synthase (iNOS), contribute to the development of inflammatory diseases[168], thus, inhibition of the excessive production of TNF-a and/or NO could be employed as criteria to evaluate potential anti-inflammatory compounds. The current management of inflammatory diseases is limited to the use of anti-inflammatory drugs whose chronic administration is associated with several adverse effects. Plant-derived products are slowly emerging as a viable alternative because they are cheap, abundantly available and relatively less toxic.

Medicinal plants with anti-inflammatory activity are considerably employed in the traditional treatment of several disorders of inflammation. The inflammatory response involves a complex array of enzyme activation mediator release; fluid extravasations, cell migration, tissue breakdown and repair[169], which are aimed at host defense and usually activated in most disease conditions. These different reactions in the inflammatory response cascade are therapeutic targets which anti-inflammatory agents including medicinal plants interfere with to suppress exacerbated inflammatory responses usually invoked in such disorders as rheumatoid arthritis, in infection or injury. Inhibition of the synthesis of pro-inflammatory prostaglandins is one of such therapeutic targets to which some of the potent anti-inflammatory agents of clinical relevance (e.g. NSAIDs) owe

their activity. Several anti-inflammatory medicinal plants have also demonstrated the ability to inhibit the synthesis[170-172].

Medicinal plants are believed to be an important source of new chemical substances with potential therapeutic effects[173,174]. The research for plants with alleged folkloric used as pain relievers, anti-inflammatory agents, should therefore be viewed as a fruitful and logical research strategy in the search for new analgesic and anti-inflammatory drugs[175].

The rhizome extract of *Zingiber officinale* was investigated for anti-inflammatory and analgesic properties in albino rats and Swiss mice respectively. The extract produced significantly ($P<0.05$) inhibition of the carrageenan induced rat paw edema and a reduction in the number of writhing induced by acetic acid in mice. It has shown that rhizome extract of *Z. officinale* possesses anti-inflammatory and analgesic agents[176].

Anti-inflammatory activity of the ethanolic extract of the leaves of *Morus indica* Linn. was studied in Wistar rats using the carrageenan induced left hind paw edema, carrageenan induced pleurisy model. The ethanolic extract inhibited carrageenan induced rat paw edema. It has indicated that the ethanolic extract produced significant ($p<0.05$) anti-inflammatory activity when compared with the standard and untreated control[177].

The hydroalcoholic extract of *Plumbago capensis* showed a maximum inhibitory action on carrageenan induced paw edema and inhibited the leukocyte migration in a dose dependent manner. The anti-inflammatory activity observed was compared to the standard non-steroidal anti-inflammatory drug indomethacin. *Plumbago capensis* has shown significant anti-inflammatory activity with potential constituents targeting different components of inflammatory process[178].

Anti-inflammatory activity of the ethanolic extract of the orange tubular calyx of *N. arbor-tristis* and petroleum ether extract of root bark of *O. echioides* was studied in albino rats of Wistar strain using the carrageenan induced paw edema model. The results indicated that all the extract produced significant ($p< 0.05$) anti-inflammatory activity when compared with the standard drug (diclofenac sodium) and untreated control[179].

The effect of alcoholic extracts of leaf from *Araucaria bidwillii* was evaluated in experimental models of pain and inflammation. The alcoholic extracts of *A. bidwillii* showed significant inhibition in carrageenan and serotonin induced hind paw oedema. It

has suggested that the anti-inflammatory and analgesic effect of the extracts as claimed in folklore medicine[180].

The anti-inflammatory and antinociceptive properties of total methanolic extracts of the flowering aerial parts of two *Stachys* species in rat were investigated by carrageenan-induced paw edema and formalin test. Methanolic extracts of *Stachys schtschegleevii* and *Stachys balansae* have analgesic and anti-inflammatory effects in formalin test and carrageenan-induced paw edema[181].

The methanol extract of *Alangium salvifolium* plant roots has been studied for analgesic and anti-inflammatory activities in animal models. The methanol extract produced significant dose-dependent inhibition of carrageenan induced rat paw edema and marked analgesic activity[182].

*Teucrium stocksianum* species was studied using carrageenan induced rat paw edema, cotton-pellet method, and by topical application of the extract on edema. *T. stocksianum* showed significant analgesic and anti-inflammatory activities in all the models studied. Topical application of the extract was also shown to be anti-inflammatory. Results support the traditional use of the plant in the treatment of painful, inflammatory conditions[183].

## 2.7. Analgesic and Anti pyretic agents from herbal source

Pain is an unpleasant sensory experience which is essential for survival considerably. It has two components i.e. sensory experience and emotional or psychological component. Pain sensitivity varies from person to person. Pain can be classified as superficial (cutaneous) or deep (visceral). The superficial pain is usually sharp pricking and has quick response of sudden onset, while deep pain is dull and lasting. Since pain is both sensory and emotional, drugs may act as painkillers by altering either of these two aspects. The peripheral pain reception at the nerve endings can be interrupted by salicylates, the neuronal conduction is suspectible to local anasthetics and both opoid and non opoids can interfere with central integration of sensory and emotional components of pain.

An analgesic may be defined as a drug bringing about insensibility to pain without loss of consciousness. They are broadly of two types: narcotics and non-narcotic. Non-narcotics, which has three important properties namely analgesic, antipyretic and anti-inflammtory. Among the non-narcotic analgesic salicylates and para-amino phenol derivatives are used

for analgesic and antipyretic purposes. Narcotics can modify pain perception at the CNS[184,185].

The management and treatment of pain is probably one of the most common and yet the most difficult aspects of medicinal practice. Analgesic therapy is currently dominated by two major classes of analgesic drugs; namely opioids and non steroidal anti-inflammatory drugs (NSAIDs). Both classes of analgesic drugs produce serious side effects, such as gastrointestinal disturbances, renal damages with NSAIDs, respiratory depression and possibly dependence with opioids[186,187]. It is obvious that the design of analgesic agents with fewer side effects is desirable. One of the ways to achive this aim is the use of medicinal plants which are a rich source of potentially effective novel compounds.

Medicinal herbs have been used as a form of therapy for the relief of pain throughout history. The treatment of rheumatic disorder is an area in which the practitioners of traditional medicine enjoy patronage and success. Natural products in general and medicinal plants in particular, are believed to be an important source of new chemical substances with potential therapeutic efficacy[188]. Taking into account the most important analgesic prototypes (e.g. salicylic acid and morphine) were originally derived from the plant sources, the study of plant species traditionally used as pain killers should still be seen as a fruitful research strategy in the search of new analgesic and anti-inflammatory drugs. Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical diseases, though relatively little knowledge about their mode of action is available. There is a growing interest in the pharmacological evaluation of various plants used in Indian traditional systems of medicine[189].

Regulation of body temperature requires a delicate balance between the production and loss of heat and the hypothalamus regulate the set point at which body temperature is maintained[190]. In pyrexia (fever) the hypothalamic thermostat is disturbed and set for a high temperature[191]. Antipyretics are remedial agents that lower the elevated temperature of the body.They exert their action on the heat regulating centre in the hypothalamus[192]. Salicylates act centrally and reset this mechanism at the normal level and there by bring down the temperature; they donot show any demonstrable antipyretic activity in a normal individual.

Salicylates, paracetamol and other antipyretics act by inhibiting brain prostaglandin (PG) synthesis and release. They reduce heat production but increase dissipation of heat mainly by producing cutaneous vasodialation. Accompanying sweating assists the reduction of body temperature[193]. The screening of natural products has led to the discovery of somany potent antipyretic drugs.

Gupta *et. al.* investigated the methanol extract of *Caesalpinia bonducella* leaves for anti-inflammatory, analgesic and antipyretic activity by carrageenan induced edema, hot plate ,acetic acid induced writhing methods and Yeast-induced hyperpyrexia respectively. This study exhibited that the methanol extracts of leaves of *C. bonducella* possess anti-inflammatory, analgesic and antipyretic activities[194].

Amabeoku *et. al.* investigated analgesic and antipyretic activities of water extracts of *Dodonaea angustifolia* L. and *Salvia africana-lutea* L. by using acetic acid and hot plate induced writhing tests, and lipopolysaccharide (LP) induced pyrexia test in mice and rats. *D. angustifolia* and *S. africana-lutea* significantly inhibited acetic acid-induced writhing and also significantly delayed the time of reaction of mice to thermal stimulation produced by the hot plate. *D. angustifolia* and *S. africana-lutea* significantly reduced fever induced by LP[195].

Mutalik *et. al.* reported preliminary phytochemical screening of the dry residue of *S. melongena* which showed the presence of flavonoids, alkaloids, tannins and steroids produced significant analgesic and antipyretic effect in a dose dependent manner[196].

Oral administration of the aqueous extract of the stem of *Urtica macrorrhiza* reduced the number of writhings and stretchings induced by acetic acid and decreased licking activity of the late phase in formalin test and it suppressed Yeast-induced fever in rats at doses of 200 and 400 mg/kg[197].

## 2.8. Antimicrobial agents from herbal source

Antimicrobials are substances used in the treatment of infectious diseases that selectively suppress the infecting microorganism without significantly affecting the host. They affect microbial cells by interfering with one or more following process. Inhibition of cellwall synthesis leading to loss of viability and cell lysis, interfering with cell membrane function leading to leakage of intracellular compounds, inhibits protein synthesis, interfering with DNA-RNA synthesis, interfering with ignition complex and causing misleading of m-RNA, inhibition of viral DNA polymerase inhibiting the metabolism[198].

Antimicrobial agent include antibiotics which is defined as a chemical compound derived from or produced by living organisms which is capable, in small concentrations of inhibiting the growth of micro-organisms[199]. This definition limited antibiotics to substances produced by microorganisms but the definition could now be extended to include similar substances present in higher plants. Plants have many ways of generating antibacterial compounds to protect them against pathogens[200]. External plant surfaces are often protected by biopolymers e.g. waxes and fatty acid esters such as cutin and suberin. In addition, external tissues can be rich in phenolic compounds, alkaloids, diterpenoids, steroid glycoalkaloids and other compounds, which inhibit the development of fungi and bacteria[201]. Cell walls of at least some monocotyledons also contain antimicrobial proteins, referred to as thionins[202].

The use of medicinal plants and their extracts for the cure of localized and specific human infections is an age-old practice from time immemorial. As early as 1630, Europeans used natural quinine from the bark of cinchona tree to treat malaria; a dreaded disease caused by a protozoan parasite *Plasodium* species[203]. Numerous studies have been performed throughout the globe in search of newer antimicrobial agents and most of those studies are directed towards the microbes. A number of studies showed that the antimicrobial principles could also available from marine algae and higher plants, particularly among angiosperms[204]. The antimicrobial compounds isolated from higher plants are different in chemical structures. They may be flavonoids, essential oils, alkaloids, anthraquinones, triterpenoids, etc. One approach that has been used for the discovery of antimicrobial agents from higher plants is based on the evaluation of the medicinal plant extracts[205,206].

Herbal medicine is used to treat various infectious diseases, in most of the world's cultures, offering enormous prospects for discovering new drugs in popular medicine. Focusing attention on the plants medicinally used by indigenous people is the most efficient way to identify plants that may contain bioactive substances[207]. Considering the enormous variety of higher plant species, their potential as new drug sources has not been completely explored. Only 17% of this plant group has been systematically studied in the discovery of biologically active compounds[208]. Plants have been traditionally used for the treatment of diseases of different etiology. Plant extracts are used, for instance, as a source of medicinal agents to cure urinary tract infections, cervicitis, vaginitis,

gastrointestinal disorders and skin infections, such as herpes simplex virus[209]. Diseases caused by protozoa are responsible for considerable mortality in the tropical and subtropical countries. New drugs are now required for amoebiasis, leishmaniosis, malaria and trypanosomiasis treatment. The crisis of reemerging infectious diseases and the resistance of many pathogens for current drugs have been widely recognized as serious and of immediate concern. In addition, the compounds used in parasitic illness treatment, such as benznidazole, nifurtimox pentavalent antimonials, melarsoprol and pentamidine, are highly toxic, expensive and require long-term treatments[210-212]. The number of drugs available for human and animal trypanosomiases treatment is limited now a day. Effective drugs are urgently needed as therapeutical alternatives for antiprotozoa chemotherapy, and the higher plants are a potential source of new antiprotozoal drugs.

Even though pharmaceutical industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased. For a long period of time, plants have been a valuable source of natural products for maintaining human health, especially in the last decade, with more intensive studies for natural therapies. The use of plant compounds for pharmaceutical purposes has gradually increased. According to World Health Organization[213] medicinal plants would be the best source to obtain a variety of drugs. About 80% of individuals from developed countries use traditional medicine, which has compounds derived from medicinal plants. Therefore, such plants should be investigated to better understand their properties, safety and efficacy[214]. The use of both plant extracts and phytochemicals, with known antimicrobial properties, can be of great significance in therapeutic treatment. In the last few years, a no. of studies have been conducted in different countries to prove such efficiency[215-221].

Many plants have been used because of their antimicrobial traits, which are due to compounds synthesized in the secondary metabolism of the plant. These products are known by their active substances, for example, the phenolic compounds of plants have been investigated by a number of researchers world wide, especially in Latin America. In Argentina, a research tested 122 known plant species used for therapeutic treatments[222].

Ahmed *et. al.* studied the antibacterial activities of the chloroform and water extracts of *Ferula persica* Var. roots by the disc diffusion method.They reported that the chloroform extract of *F. persica* roots showed antibacterial activity; where as the water extract of the

roots at the concentrations that tested did not show any activity against *B. subtillis*, *B. cereus*, *E. coli*, *K. ponumoniae*, *S. typhi*, *S. aureus*, and *S. epidermilis*[223].

The water and ethanol extracts of the stem bark of two Nigerian medicinal plants, *Alstonia boonei* and *Morinda lucida*, were tested on clinical isolates of two Gram-positive and five Gram-negative bacteria. Ethanol extract of *A. boonei* was not active against any of the bacterial tested while the aqueous extracts of stem barks of *A. boonei, M. lucida and* ethanol extracts of stem bark of *M. lucida* showed antibacterial activity[224].

Bactericidal and antifungal assays were done using extracts derived from. *Zanthoxylum chalybeum* and *Warburgi ugandensis* by agar well diffusion, disc diffusion and colony count assays. *W. ugandensis* water extracts elicited antibacterial activity against both *Escherischia coli* and *Staphylococcus aureus* in the agar well assay. *Warburgia ugandensis* water extracts also showed antifungal activity against *Candida albicans*. However, *Z. chalybeum* extracts showed neither antifungal nor antibacterial activities[225].

Single or combined extracts of black thyme, fennel, sage, wild tea and wild mint were used to evaluate *in vitro* antibacterial activity against common pathogenic and lactic acid bacteria. The combined plant extracts (1:1 ratio) provided an entire antibacterial effect against pathogenic bacteria compared to the single plant extracts. The combined plant extracts with moderate inhibitory effects against both pathogenic and lactic acid bacteria could be sufficiently optimal when considering a natural feed additive to improve animal's gut health[226].

The acetone and alcoholic extracts of the leaves of *Cassia alata* showed significant *in vitro* antibacterial activity against *Staphylococcus aureus*, coagulase positive *Staphylococcus aureus, Bacillus sublitis, Bacillus cereus, Bacillus stearothermophilus, Escherichia coli, Salmonella typhi* and *Salmonella dysentriae*. In addition, the alcoholic extract also inhibited growth of *Klebsiellae pneumoniae* whereas the acetone extract inhibited the growth of *Vibro cholera*[227]. Alcoholic extract of dry nuts of *Semecarpus anacardium* showed bactericidal activity *in vitro* against three Gram-negative strains (*Escherichia coli, Salmonella typhi* and *Proteus vulgaris*) and two Gram-positive strains (*Staphylococcus aureus* and *Corynbacterium diphtheriae*). Subsequent studies have shown that the alcoholic extracts of different parts of the plant (leaves, twings, and green fruit) also possess antibacterial properties, especially the leaf extract. No dermatoxic effect (irritant property) was observed in the mouse skin irritant assay[228].

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