CHAPTER -2

REVIEW OF LITERATURE
2. REVIEW OF LITERATURE

2.1 PEPTIC ULCER

Peptic ulcer represents a major health problem, both in terms of morbidity and mortality. Research advances during the last few years have offered new insight in the therapy and prevention of gastroduodenal ulceration by measures directed at strengthening the mucosal defence system rather than by attenuating the aggressive acid-pepsin factors held responsible for the induction of ulcers. The rise in gastric acidity and peptic activity are usually a manifestation of a physiological disturbance affecting one or more mechanisms which normally regulate gastric secretion. Neurotransmitters or hormones that directly stimulate secretion of hydrochloric acid and pepsin by the gastric glands are acetylcholine, gastrin and histamine. In addition there are other factors which play an important role in the manifestation of peptic ulcers. Activity of the gastric secretory cells has been found to be stimulated by caffeine, alcohol, hydroalcoholic acid, sodium chloride, non-steroidal anti-inflammatory drugs (NSAIDs) and stress. There are two major components to the ulcerogenic effects of NSAIDs in the stomach, namely their topical irritant effects on the epithelium and their ability to suppress prostaglandin synthesis. The ability of NSAIDs to cause gastric damage correlates well with the ability to suppress gastric prostaglandin synthesis. There is also a time and dose dependency of both suppression of gastric prostaglandin synthesis and ulcerogenic activity.

Several components of gastric mucosal defense are influenced or mediated by prostaglandin, including mucus and bicarbonate secretion, blood flow, epithelial cell turnover and repair, and immunocyte function. Therefore, it is possible that inhibition of prostaglandin synthesis leads to a reduction in the ability of the gastric mucosa to
defend itself against luminal irritants. Several other endogenous substances such as nitric oxide, polypeptides such as substance P and endothelin, autacoid comprising platelet activating factor, leukotrienes, serotonin, histamine and reactive oxygen species have also been found to play an important role in the gastroduodenal lesion.

The precise biochemical changes during ulcer generation are not clear yet, although various hypotheses have been proposed from time to time. Increased gastric motility (Garrick et al., 1986), vagal overactivity (Cho et al., 1976), mast cell degranulation (Cho et al., 1979), decreased gastric mucosal blood flow (Hase and Moss, 1973; Kitagawa et al., 1979) and decreased prostaglandin level (Miller et al., 1987) during stress condition are thought to be involved in ulcer generation. Similarly, role of oxygen derived free radicals have been shown to play a role in experimental gastric damage induced by ischemia and reperfusion (Perry et al., 1986), hemorrhagic shock (Itoh and Guth, 1985) and ethanol administration (Mizui and Doteuchi, 1986). _Helicobacter pylori_ a pathogen is now known to be the most common and important causes of gastric ulcer in humans, exhibits active inflammation with epithelial damage accompanied by neutrophil migration.

For several decades, the adage, “no acid – no ulcer” has dominated the pharmacological basis of ulcer therapy, and the drugs used, reduced acid secretion. Not all patients, however, with gastric or duodenal ulcer have high acid secretion.

In fact, only 30%-40% of cases with duodenal ulcer have hypersecretion of gastric acid in patients with gastric ulcer, acid secretion is either normal or low. In these cases, decreased mucosal resistance might be the dominant factor. Peptic ulceration results from an imbalance between acid-pepsin secretion and mucosal
resistance. Since gastric acid is one of the major aggressive factor contributing to peptic ulcer disease, the reduction of gastric acid either by surgical or pharmacological intervention has been used to promote ulcer healing. Surgical treatment of peptic ulceration is usually either by vagotomy or removal of the diseased portion of the stomach.

More recently the role of mucosal factors in peptic ulceration has received considerable attention and the term “cytoprotection” has been introduced to encompass the physiological processes which protect gastric mucosa from acid-pepsin digestion. Most of these cytoprotective mechanisms are related, at least in part, to endogenous prostaglandin secretion. The usual medical treatment for peptic ulcer is either by the inhibition of acid secretion or by neutralization of the acid. The neutralization of gastric acid can be done by antacid administration but their effectiveness is only for a brief period. Muscarinic antagonists such as atropine or pirenzipine are effective inhibitors of acid production. The histamine H2-receptor antagonist cimetidine, ranitidine and famotidine act as potent inhibitors (70-80%) of secretion. Complete inhibition of parietal cells acid secretion by receptor antagonist is difficult because of complexity of known receptors on parietal cells and a variety of second messenger signaling system coupled to these receptors which involve adenylate cyclase coupled with histamine receptor and intracellular Ca²⁺ with acetylcholine receptors. Thus, the most successful and desirable therapy is to inhibit the enzyme responsible for acid secretion. Gastric H⁺-K⁺ ATPase of the parietal cell is the H⁺ ion pump responsible for acid secretion in the stomach and has been identified as a pharmacological target for the development of drug to treat ulcers. Long lasting
inhibition of the $\text{H}^+\text{-K}^+$ ATPase by drugs such as omeprazole, lansoprazole and timoprazole has been shown effective in the treatment of peptic ulcer disease. However, such agents irreversibly inactivate the ATPase and the return of acid secretion following such inhibition requires \textit{denovo} synthesis of new pump. This is the drawback of such type of inhibitors, because acid secretion is only achieved when new ion pumps are synthesized. This can be overcome by the use of reversible inhibitors of $\text{H}^+\text{-K}^+$ ATPase which may allow greater control over the duration of suppression of acid secretion. Other drugs, such as prostaglandins, carbenoxolone and sucralfate stimulate mucus production. The negative charge conferred on mucus, particularly by its sulphate radicals, has resulted into the development of new compound like the basic aluminum sucrose, octasulfate (sucralfate), which has properties similar to mucus. Thus, sucralfate and other cytoprotective drugs are effective in the management of peptic ulcer disease by their predominant actions on mucosal defensive factor.

Ulcers are local defects on the surface of an organ produced by inflammation. Common sites for ulceration are the stomach, duodenum, intestinal ulcers in typhoid fever, intestinal tuberculosis, bacillary and amoebic dysentery, ulcer of legs due to varicose veins etc. Peptic ulcers are very common. Doctors say that in the United States, almost one in every 10 people will get an ulcer at some time during their lives.

Peptic ulcer arises from an imbalance between damaging factors within the lumen and protective mechanisms within the mucosa of the stomach and duodenum. They occur most commonly (98-99%) in either the duodenum or the stomach in the ratio of 4:1. Each of the two main types may be acute or chronic.
Acute peptic ulcer or stress ulcers are multiple, small mucosal erosions, seen most commonly in the stomach but occasionally involving the duodenum. It is not clear how the mucosal erosion occur in the stress ulcers because actual hypersecretion of gastric acid is demonstrable in only Cushing’s ulcers occurring from intracranial conditions such as due to brain trauma, intracranial surgery and brain tumours.

Chronic peptic ulcers (Gastric and duodenal ulcers), the two major of ‘peptic ulcer disease’ of the upper gastrointestinal tract in which the acid-pepsin secretion is implicated in their pathogenesis. Peptic ulcers are common in the present-day life of the industrialized and civilized world.

Gastric and duodenal ulcers represent two distinct diseases as far as their etiology, pathogenesis and clinical features are concerned. However, pathological finding in both are similar and quite diagnostic.

**Anatomy of an ulcer**

The lining of the stomach and small intestine are protected by a self-lubricating mucous layer. If mucous layer is absent, gastric acid (hydrochloric acid) would not only digest your food, but your stomach and intestine as well. But, if this protective lining is compromised, that’s exactly what begins to happen.

An ulcer can be thought of as a lesion or sore that forms along the stomach or intestinal wall where it can corrode muscle and blood vessels and cause bleeding, evidenced blood in the stool. If this process is allowed to continue, bacteria and partially digested material can eventually leak into the abdominal cavity causing inflammation and severe pain. A perforated ulcer of this type usually requires
immediate surgery. Ulcers can also occur in the duodenum and can restrict or block
the intestinal opening, a condition that also demands immediate attention.

Surprisingly, ulcers do not always produce symptoms. But, the most common
symptom reported is burning pain between the breast bone and navel, usually
occurring shortly after a meal or when the stomach is empty. An accurate diagnosis
may involve an upper GI series or X-rays of the esophagus, stomach and duodenum
after drinking a barium cocktail. Other measures include blood and stomach tissue
tests to determine if H. pylori are present.

2.2 CAUSES OF ULCER

2.2.1 Helicobacter pylori gastritis

About 15-20% cases infected with H. pylori never develop duodenal ulcer in
their life time while gastric colonization by H. pylori never develops ulceration and
remain asymptomatic. However, there is an evidence to suggest that increased density
of H. pylori in the antrum is associated with greater likelihood of development of
duodenal ulcer. H. pylori can be identified in mucosal samples by histologic
examination, culture, increased activity, and serology (IgG and IgA antibodies to H.
pylori).

2.2.2 Acid-pepsin secretion

There is conclusive evidence that some level of acid-pepsin secretion is essential
for the development of duodenal as well as gastric ulcer. Peptic ulcer never occurs in
association with pernicious anaemia in which there are no acid and pepsin-secreting
parietal and chief cells respectively.
2.2.3 Mucus secretions

Any condition that decreases the quantity or quality of normal protective mucus ‘barrier’ predisposes to the development of ulcer.

2.2.4 Gastritis

Some degree of gastritis is always present in the region of gastric ulcer, though it is not clear whether it is the cause or the effect of ulcer. Besides, the population distribution pattern of gastric ulcer is similar to that of chronic gastritis.

2.2.5 Local irritants

Pyloric antrum and lesser curvature of the stomach is the site most exposed for longer periods to local irritants and thus are the common sites for occurrence of gastric ulcers. Some of the local irritating substances implicated in the etiology of peptic ulcers are heavily spiced foods, alcohol, cigarette smoking, unbuffered aspirin, non-steroidal anti-inflammatory drugs etc.

2.2.6 Dietary factors

Nutritional deficiencies have been regarded as etiologic factor in peptic ulcer e.g. occurrence of gastric ulcer in poor socioeconomic strata, higher incidence of duodenal ulcer in part of South India. However, malnutrition does not appear to have any causative role in peptic ulceration in European countries and the U.S.

2.2.7 Psychological factors

Psychological stress, anxiety, fatigue and ulcer-type personality may exacerbate as well as predispose to peptic ulcer disease.
2.2.8 Genetic factors

People with blood group O appear to be more prone to develop peptic ulcers than those with other blood groups. Genetic influences appear to have greater role in duodenal ulcers as evidenced by their occurrence in families, monozygotic twins and association with HLA-B5 antigen.

2.2.9 Hormonal factors

Secretion of certain hormones by tumours is associated with peptic ulceration e.g. elaboration of gastrin by islet-cell tumour in Zollinger-Ellison syndrome, endocrine secretion in hyperplasia and adenomas of parathyroid glands, adrenal cortex and anterior pituitary.

2.2.10 Miscellaneous

Duodenal ulcers have been observed to occur in association with various other conditions such as alcoholic cirrhosis, chronic renal failure, hyperparathyroidism, chronic obstructive pulmonary disease and chronic pancreatitis.

2.2.11 Endogenous mediators

Several endogenous mediators or substance have been identified and reported to be involved in the induction of gastrointestinal lesions. These have been found to be including lipid metabolites, neuropeptides, biogenic amines, reactive oxygen species and free radicals (Elasbech and Weiss., 1988).

2.2.11.1 Platelet-Activating Factor (PAF)

PAF is one of the most potent ulcerogen (Rosam et al., 1986). The mechanism involved in PAF induced ulceration is due to the sequestration of neutrophil
aggregates in stomach, vasoconstriction, generation of free radicals and release of lysosomal enzymes (Mcmanus et al., 1980; Wallace and Whittle, 1986).

### 2.2.11.2 Thromboxane A2 (TXA2) and Leukotriens (LTC4/D4)

They are derived from arachidonic acid through the action of enzyme cyclooxygenase and lipoxygenase. Vasoconstriction may be causative factor in the TXA₂ mediated gastric mucosal ulceration which predisposes the mucosa to disruption by local irritants. Leukotrienes induce vasoconstriction in the vascular bed in the rat submucosa that leads to tissue necrosis in the stomach (Wallace and Whittle, 1985). Leukotrienes also stimulate pepsinogen secretion from gastric chief cells (Fiorucci et al., 1995). Involvement of leukotrienes in stress induced (Ogle and Cho, 1989) and ethanol induced (Wallace et al., 1989) ulcer by decrease in blood flow and increase in reactive oxygen species (Peskar et al, 1991; Vaananen et al., 1992) has been reported.

### 2.2.11.3 Histamine

Histamine is present in large quantities, about 40 micrograms per wet weight, in the oxyntic mucosa of humans and other mammals (Reite et al., 1972; Troidl et al., 1975). Histamine has been found in the gastric wall and it is powerful stimulant for gastric secretion (Black et al., 1972). However, excessive release of histamine by histamine release or by injection of aqueous solution of histamine produces gastric and duodenal ulcer (Shayer et al., 1974). Histamine is involved in the other type of ulceration because blocking of histamine receptors prevents reserpine, steroid and NSAIDs induced gastric ulcer in human and experimental animals (Lau and Ogle, 1981). Histamine blockers such as Ranitidine have been reported to prevent psychological, stress-induced gastric ulceration (Cho and Ogle, 1978, 1979).
2.2.11.4 Serotonin (5-Hydroxytryptamine, 5HT)

Over 90% endogenous 5-hydroxytryptamine is found in the gastrointestinal tract. 5-HT is stored in endocrine cells and enteric neurons in the gut. It is established that 5-HT possess ulcer producing properties. Serotonin has been shown to be involved in the ethanol and reserpine induces ulceration. These ulcerogens release 5-HT from gastric mucosa which causes reduction in gastric blood flow and mucus depletion.

2.2.11.5 Free Radicals

Reactive oxygen species (ROS) such as superoxide anion (O$_2^-$), hydrogen peroxide (H$_2$O$_2$) and hydroxyl radical (OH$^-$) have emerged as highly toxic agents responsible for a wide variety of tissue damage (Halliwell et al., 1990). The involvement of these ROS in the pathogenesis of gastric ulceration was first evident from the studies on ischemia-reoxygenation–induced gastric mucosal injury (Itoh et al., 1985, Perry et al., 1996). A growing body of experimental and clinical evidence suggests that gastric mucosal damage by ethanol (Mizui et al., 1986, Szelenyl et al., 1988, Pihan et al., 1987). Non-steroidal anti-inflammatory drugs (Vaananenn et al., 1991, Yoshikawa et al., 1993) and by Helicobacter pylori (Davies et al., 1994) is mediated through the ROS (Phull et al., 1995). Moreover, ROS may play an important role in gastric ulceration induced by several kinds of stress (Yoshikawa et al., 1987, Salim et al., 1990). The pathogenesis of gastric mucosal lesions by water-immersion restraint stress and burn shock in rat is associated with increased lipid peroxidation (Yoshikawa et al., 1987, Yoshikawa et al., 1986). Systemic administration of
glutathione or superoxide dismutase prevents water-immersion stress-induced ulceration (Hirota et al., 1989, Hirota et al., 1990).

2.3 Gastric Mucosal Defense Mechanisms

2.3.1 Mucus bicarbonate barrier

Peptic ulcers are not solely induced by the offensive factor of the acid and pepsin but the breakdown of mucosal resistance is also considered as an important factor making the stomach susceptible for ulcer (Goel and Bhattacharya, 1991).

The entire surface of the gastric mucosa is covered by a continuous layer of mucus gel, which has a variable thickness of less than 500 µm (Allen et al., 1993). Both the surface mucus cells and the mucus neck cells in the upper part of the gland secrete mucus. Mucus is released predominantly by the process of exocytosis. Mucus consist of about 1% by weight salt and other dialysable components, 0.5-1% free protein and a similar quantum of carbohydrate rich glycoprotein and 95% or more water. The glycoprotein component of mucus is responsible for the characteristic viscous gel forming property, believed to be important for the functional role of mucus.

Mucus and bicarbonate secretion (Allen & Garner, 1980) complement each other and little protection can be afforded by either if functioning in isolation. Secretion of alkali by surface epithelial cells into the unstirred mucus layer thereby forming a pH gradient offers better protection than alone (Williams and Turnberg, 1981). Recent studies suggest that vagal cholinergic stimulation and luminal acid control gastric bicarbonate secretion (Fandriks and Jonson, 1990). The protective zone produced by
bicarbonate transport into the mucus gel is termed as ‘mucus-bicarbonate barrier’ offering gastroprotection against damaging factors (Wallace et al., 1992).

2.3.2 Gastric mucosal renewal and restitution

The rapid proliferation of gastric mucosa plays an important role in mucosal protection during normal state and following mucosal damage. After mucosal damage, the undifferentiated neck cells proliferate, towards the lumen and differentiate into surface epithelial cells. The proliferation of gastric mucosal cell is the intrinsic property to fight against any damage. Following extensive damage of the surface epithelial cells, repair occurs within a few hours, through a process called restitution which is not due to cell proliferation. This restitution process is augmented by high bicarbonate concentration and PGs do not appear to be involved in restitution (Goel and Bhattacharya, 1991).

2.3.3 Epidermal Growth Factors (EGF)

EGF is the most studied growth factor found in abundance in human salivary glands, bruneers glands and pancreas. Considerable evidence has revealed the secretion of various growth factors into the gastrointestinal lumen (Konturek et al., 1984). The presence of EGF like immunoreactivity in lumen gastric secretion has been recently demonstrated (Konturek et al., 1981). Thus EGF is secreted in gastric, duodenal and possibly, in small intestinal secretion and involved in the pathogenesis and healing of gastroduodenal ulcers in humans.

2.3.4 Mucosal and sub mucosal blood flow

Mucosal blood flow constituents an important line of mucosal defense. It play a vital role in protecting the mucosa by delivering oxygen, nutrients and bicarbonate to
the cells and removing hydrogen ion that has penetrated the mucus-bicarbonate and epithelial barrier. Prostaglandins appear to be important in regulating mucosal blood flow because in NSAIDs induced ulcer decrease in gastric mucosal blood flow has been observed (Kitahora and Guth, 1987; Goel and Bhattacharya, 1991).

2.3.5 Endogenous prostaglandins

Prostaglandins (PGs) are synthesized in large amounts by the gastric and intestinal mucosa. The PGE and PGI series of PGs have been shown to protect the deeper mucosal cells from the experimental necrotic damage (Miller et al., 1983) and some studies also suggest that a deficiency in prostaglandin production may contribute to ulcer formation (Dajani et al., 1986).

PGs increase gastric mucosal blood flow, mucus and bicarbonate secretion strengthens the mucus bicarbonate barrier. Since PGs protects the gastric mucosa by influencing all aspects of cytoprotective mechanism. Any drug (NSAIDs) or abnormal physiological (Stress) or pathological (H. pylori) condition which inhibits prostaglandin biosynthesis, is expected to cause gastric damage (Goel and Bhattacharya, 1991).

2.3.6 Sulphydryl compounds (SC)

Non-protein sulphydryl compounds are present in high concentration in the gastric epithelium. The major component of SC is reduced glutathione (Karmeli et al., 1996) which is capable of binding to reactive free radicals which are generated during tissue ischemia and injury induced by noxious agent like ethanol (Avila et al., 1996). The precise role of SC in gastroduodenal cytoprotection remains unclear, but they
appear to be involved that the blocking agent can reduce the cytoprotection effect of PGs in stomach (Karmeli et al., 1996).

2.3.7 Endogenous antioxidants

Antioxidants are defined as “any substance that even when present at low concentration compared with those of an oxidizable substrate, significantly delays or prevent oxidation of that substrate”. Uncontrolled oxidation in aerobic organisms produces oxidative stress, cell damage and eventually cell death.

These free radical scavenging enzymes are first line defense against oxidative injury within the cell and are known as preventive antioxidant. They remove the reactants involved in inhibition of the free chain reaction (Buettner et al., 1993).

Many plant secondary metabolites act as potent antioxidants. Natural antioxidant defense have shown that free radical scavenger/antioxidant such as SOD, Catalase, Vitamin E, Vitamin C, Vitamin A, Glutathione reduce the mucosal injury induced by different mediators (Sharma and Gupta, 1997).

2.3.8 Nitric oxide (NO)

It is well reported that NO formed by constitutive enzyme plays an important role in the modulation of gastric mucosal integrity by interacting with sensory neuropeptides and endogenous prostaglandins (Takeuchi et al., 1995).

Nitric oxide also inhibits the pentagastrin induced acid secretion in rats (Esplugues et al., 1993). Mucin secretion by rat gastric cells has been found to be stimulated by nitric oxide and c-GMP.
2.4 TREATMENT OF ULCER

2.4.1 Antacids

Antacids are now prescribed mainly for symptomatic relief and widely accepted for self-medication. They are used to produce relief to the gastric pain associated with hyperchlorhydria. The majority of antacids are based on combination of calcium, aluminium and magnesium all of which cause side effects. At low dose, antacids are ineffective in neutralizing acid in the stomach, extremely high doses of antacids are required to completely neutralize the excess acid in stomach (Berstad et al., 1982; Ippoleti et al., 1983; Kumar et al., 1984). However, long term uses of these antacids have been shown to produce significant mucosal protection (Goel and Bhattacharya, 1991).

Antacids are used in combination to give both immediate and sustained action to minimize undesirable effects by using a lower dose of each component and to use one component to antagonize side effects of another (e.g. laxation versus constipation). The most common combination is that of Al (OH)$_3$ and Mg (OH)$_2$.

2.4.2 Histamine H$_2$-receptor antagonist

The introduction of H$_2$-receptor antagonist in the mid 1972s by Black and his colleagues constituted a major breakthrough in the drug treatment of peptic ulcers. H$_2$-receptor antagonists can competitively inhibit histamine action at all H$_2$-receptor but their main clinical use is as inhibitors of gastric acid secretion (Lundell et al., 1975; Feldman and Burton, 1990). H$_2$-receptor antagonist also decreases gastric volume and pepsin concentration in the gastric content. H$_2$-receptor antagonist inhibits gastric acid secretion elicited by histamine or by gastrin in a dose dependent and
competitive manner. These agents decrease both basal and food stimulated acid secretion by 90% or more. H2-receptor antagonist also decreases intrinsic factor secretion from parietal cells. The most commonly used drugs are cimetidine (Shrees and Roberts, 1981) and ranitidine (Woodings et al., 1980; Shree and Roberts, 1981). Newer H2-receptor antagonist, such as nizatidine, and famotidine (Orr et al., 1988; Langtry et al., 1989) are also available. Recently, roxatidine and loxatidine have been shown to be devoid of such adverse effects and more potent and longer acting.

2.4.3 Muscarinic antagonists

Muscarinic antagonists reduce basal secretion of gastric acid by 40-50%. However, stimulated secretion is inhibited to a lesser extent. Vagal stimulation produces an increased secretion of histamine and gastric acid that can be blocked by either nicotine or muscarinic antagonist (pirenzepine) (Del-Tacca et al., 1989). Moreover, cholinergic agonist can exert powerful stimulatory effects on acid secretion in presence of H2-antagonist through interaction with muscarinic receptor on the parietal cells. Selective antagonists of M1 receptors are as effective as atropine or other nonselective muscarinic antagonists, but they are less likely to produce the adverse effects that are characteristic of cholinergic blockade (e.g. dry mouth, tachycardia). Two such drugs currently in clinical trail in the United States are pirenzepine and telenzepine.

The potent blocking effects of pirenzepine are unexplained because the type of muscarinic receptor on the endocrine cells has not been defined and pirenzepine is less effective than cimetidine in reducing acid secretion.
2.4.4 Proton pump inhibitors

The ultimate mediators of acid secretion is the H⁺-K⁺ATPase enzyme (proton pump) found in the smooth membrane structure in the parietal cell called tubulo-vesicles as long as the cell is not secreting acid. As acid secretion increases, it transfers progressively to the microvilli of the secretory canaliculus of the cell. This transformation is due to change in level of c-AMP or (Ca²⁺) in the cell. H⁺-K⁺ATPase consist of α and β-subunits. The a-subunit is 1034 amino acid containing catalytic subunit with a molecular mass of 114 KDa. A-subunit contains the phosphorylation site, ATP binding site and binding site for proton pump inhibitor. The 291 aminoacids containing b-subunit is glycoprotein with a molecular mass of 60-80 KDa. One of the roles of b-subunit is to stabilize the a-subunit in the membrane (Sachs and Shin, 1995).

A strict relationship between inhibition of acid secretion and block of H⁺-K⁺ATPase by omeprazole has also been demonstrated. The mechanism of inhibition has also been extensively studied. The inhibition is due to irreversible interaction of the active compound with the SH group of H⁺-K⁺ATPase forming a disulphide bond (Im et al., 1985). Similar to omeprazole other substituted benzimidazole such as timoprazole and picoprazole also inhibit acid secretion (Sewing et al., 1984). Their efficacy and mechanism of action have been studied, but omeprazole was found to be more potent than other two compounds. Reported side effects include headache, diarrhea, skin rash and reversible abnormalities in biochemical liver function tests.

The long term use of omeprazole results in complete inhibition of H⁺-K⁺ATPase enzyme. Omeprazole produces gastric carcinoma when given long-term, probably due to complete acid inhibition which stimulates gastrin production causing hyperplasia.
(Larsson et al., 1986). Prolonged treatment with in patients Omeprazole results in achlorhydria (blocked in acid secretion) and hypergastrinemia (Lamberts et al., 1993).

2.4.5 Cytoprotective drugs

2.4.5.1 Misoprostol and Enprostil

PGE$_2$ and PGI$_2$, the predominant prostaglandins synthesized by the gastric mucosa, inhibit the secretion of acid and stimulate the secretion of mucus and bicarbonate. Misoprostol (analog of PGE$_1$) inhibit gastric acid secretion by inhibiting the histamine-mediated stimulation of the parietal cell. Currently misoprostol is used to prevent gastric ulceration in patients who use large doses of Aspirin-like drugs for the treatment of arthritis (Roth et al., 1989; Penney et al., 1994). Effective oral doses of misoprotol and related agents cause diarrhea and some abdominal cramping. Misoprostol and enprostil cause abdominal pain and diarrhea as well as bleeding in the first trimester of pregnancy (Levis et al., 1992).

2.4.5.2 Sucralfate

Nagashima and Yoshida (1979) reported that sucralfate is clinically effective in healing of gastric and duodenal ulcers and has no systemic side effects. Sucralfate is also effective as a prophylactic treatment, preventing peptic ulcer recurrence and preventing stress ulceration in critically ill patients. Sucralfate is a complex of aluminium hydroxide and sulphate sucrose which promote healing of ulcers. It is thought to be act by coating the ulcer surface, by binding to the positively charged exposed protein molecules. Sucralfate a non absorbable aluminium salt of sucrose octasulfate, served as reference compound. The drug sucralfate is claimed to inhibit
peptic activity. It has got specific affinity for ulcer and protects the ulcer as natural mucus dose (Libeskind et al., 1982; Lichtenberger et al., 1983).

2.4.5.3 Tripotassium dicitrate bismuthate

It has been used clinically in duodenal ulcers refractory to cimetidine. Unfortunately, it is uncertain how it works. Although it does adhere to the raw surface of an ulcer (Koo et al., 1982), this ‘Band-Aid’ action seems unlikely to protect from acid and peptic attack. Under the influence of bismuth, the microvilli of epithelium cell in the duodenal mucosa return to their normal height whereas cimetidine has no such action. It is a bismuth chelate which promotes the healing of peptic ulcers. It is possible that bismuth has a role in the maintenance of mucosal repair and a short course of treatment may provide depot of bismuth, which gives some months of protection against relapse (Pounder et al., 1984). It may act by coating the ulcer and protecting the ulcer and protecting it in particular it absorbs pepsin. It also acts as bactericidal against H.pylori.

2.4.5.4 Deglycyrrhinizes liquorice (DGL) and Carbenoxolone

DGL differs from pure liquorice-containing products and indeed, carbenoxolone in having a sufficiently low glycyrrhizinic acid content to render it free of the potential side-effects of carbenoxolone. The evidence for a beneficial effect of maintenance carbenoxolone is weak. In addition, in the latter study, hypertension and hypokalaemia were found in 27% and 15% respectively in patients over the age of 60.
Oxidative stress and free radicals

2.5 Oxidative stress

Oxidative stress is caused by an imbalance between the production of reactive oxygen and antioxidant defense systems to readily detoxify the reactive intermediates or easily repair the resulting damage. All forms of life maintain a reducing environment within their cells. This reducing environment is preserved by enzymes that maintain the reduced state through a constant input of metabolic energy. Disturbances in this normal redox state can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids and DNA.

The role of free radicals has been implicated in the causation of several diseases such as liver cirrhosis, atherosclerosis, cancer, aging, arthritis, diabetes, etc (Halliwell et al., 1994) and the compounds that can scavenge free radicals have great potential in ameliorating these disease processes. Reactive oxygen and nitrogen free radicals include superoxide (O$_2^-$), hydroxyl (OH), peroxyl (RO$_2$•), alkoxy (RO•), hydroperoxyl (HO$_2$•), nitric oxide (NO) and nitrogen dioxide (•NO$_2$) radicals. Oxygen and nitrogen free radicals can be converted to other non-radical reactive species, such as hydrogen peroxide (H$_2$O$_2$), hypochlorous acid (HOCl) and peroxynitrite (ONOO$^-$). The reactive oxygen species (ROS) are continuously produced during normal physiologic events and are removed by antioxidant defense mechanisms. There is a balance between the generation of ROS and inactivation of ROS by the antioxidant system in organisms.
Under pathological conditions, the imbalance between ROS and antioxidant defense mechanisms leads to oxidative modification in cellular membrane or intracellular molecules. Consequently, antioxidants that can neutralize direct ROS attacks and terminate free radical-mediated oxidative reaction would have beneficial effect in protecting the human body from various diseases (Havsteen, 1983). The removal of these free radicals is achieved through enzymatic and non-enzymatic antioxidant reactions. Antioxidants (e.g., glutathione, arginine, citrulline, taurine, creatine, selenium, zinc, vitamin E, vitamin C, vitamin A) and antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase, glutathione S-transferase) exert synergistic actions in scavenging free radicals.

2.6 Free radicals

Oxygen derived free radicals have been implicated in the pathogenesis of many diseases in many species. Oxygen radical are capable of damaging, reversibly or irreversibly the compounds of all biochemical classes including nucleic acids, proteins, free amino acids, lipids, lipoproteins, carbohydrates and connective tissue macromolecules. These species may have an impact on such cell activities as membrane function, metabolism, and gene expression in the biological system; the oxidant of substrates is mainly affected by free radical such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). Free radicals are species containing one or more unpaired electrons and are capable of independent existence. These are normal products of cellular aerobic metabolism. Superoxide (O₂⁻) and hydroxyl (OH⁻) species are the predominant cellular free radicals. Hydrogen peroxide (H₂O₂) and peroxynitrite...
(ONOO') although not themselves free radicals contribute to the cellular redox state. Collectively these molecules are referred as reactive oxygen species (ROS). The major sources of ROS are mitochondrial oxidative metabolism, enzymatic reaction involving mixed-function oxidases and auto-oxidation of small molecules (Perry et al., 1986; Itoh and Guth., 1985).

Free radicals are defined as chemical species possessing unpaired electrons in their outer orbit which are generally very reactive. If free radicals react with a nonradical, another free radical must be produced. This implication is reflected continuously in cells either during phagocytosis or pathological conditions. The most important reactant in free radical biochemistry in the aerobic cells is oxygen and its radical derivative O$_2^-$ and OH, H$_2$O$_2$ and transition metals (Fe$^{2+}$, Cu$^+$) (Cheeseman and Slater, 1993). Reduction of oxygen by the transfer of a single electron produces superoxide radicals

$$O_2 + e^- \rightarrow O_2^-$$

Superoxide radicals can react with nitric oxide to generate peroxynitrite

$$O_2^- + NO \rightarrow ONOO^-$$

A two electron reduction of oxygen yields H$_2$O$_2$ and is often generated in biological systems via the dismutation of superoxide.

H$_2$O$_2$ is not a free radical but falls into the category of reactive oxygen species (ROS) that indicates not only oxygen free radicals but also non-radical oxygen derivatives that are involved in oxygen radical production. H$_2$O$_2$ is an important compound in free radical biochemistry because it can rather easily be broken-down.
particularly in the presence of transition metal ions, to produce that most reactive and
damaging oxygen free radical, the hydroxyl radical OH.

\[ \text{H}_2\text{O}_2 + \text{Fe}^{2+} \rightarrow \text{OH} + \text{OH}^- + \text{Fe}^{3+} \]

This ion catalyzed (Fe$^{2+}$) reaction is known as Fenton reaction. The non-
catalyzed Haber-Weise is the reaction of superoxide directly with H$_2$O$_2$.

\[ \text{O}^- + \text{H}_2\text{O}_2 \rightarrow \text{OH} + \text{OH}^- + \text{O}_2 \]

The spontaneous reaction is less likely in biological system due to low steady
state and concentration of the reactants. The auto-oxidation of reduced transition metal
can also generate superoxide.

\[ \text{Fe}^{2+} + \text{O}_2 \rightarrow \text{Fe}^{3+} + \text{O}_2^- \]
\[ \text{Cu}^+ + \text{O}_2 \rightarrow \text{Cu}^{2+} + \text{O}_2^- \]

The hydroxyl radicals are capable of reversibly or irreversibly damaging
compounds of all biochemical classes, including nucleic acid, protein, and free amino
acids, lipids, lipoprotein, carbohydrates and connective tissue macromolecules. These
species may have impact on such cell activities as membrane function, metabolism
and gene expression. The role of oxygen derived free radicals has been demonstrated
in acute and chronic ulceration (Del Saldato et al., 1985; Bast et al., 1991; Freeman
and Crapo., 1982). Involvement of neutrophil in ulcer has been implicated in different
models of gastrointestinal mucosal injury such as colitis, ischemia (Perry et al., 1986),
reperfusion (Grisham et al., 1990) stress (Das et al., 1997) and ethanol (Mizui and
Doteuchi., 1986) induced ischemia/reperfusion and ethanol induced injury to the
gastric and intestinal mucosa are substantially ameliorated in neutropenic animals
(Tepperman and Soper, 1994).it is also widely accepted that oxygen derived free
radical result in the lipid peroxidation and damage of cellular membrane with the release of intracellular component e.g. lysosomal enzymes leading to further tissue damage.

Another hypothesis is that free radicals particularly hydroxyl radical causes degradation of hyaluronic acid, the principle component of the epithelial basement membrane, and thus promote mucosal damage. The body has an effective mechanism to prevent and neutralize the free radical induced damage. It is done by a set of endogenous antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, glucose oxidase and catalase. They help in maintaining the balance between the reactive oxygen species generation and its eradication.

2.7 Anti-oxidant Defense Mechanisms

The cell is able to handle and survive the continuous production of ROS because of the existence of a delicate balance between cellular systems that generate the various oxidants and those that maintain the antioxidant defense mechanisms. Oxidative stress occurs when the homeostatic balance between the pro oxidant and the antioxidant capacities in biological system is disturbed and the redox state becomes more pro-oxidizing (Matsuo and Kaneko 2000).

Cellular antioxidant defense is classified into two categories: enzymatic and non-enzymatic. Primary antioxidant enzymes include SOD, catalase (CAT) and glutathione peroxidase (GPX). Non-enzymatic antioxidants such as ubiquinol, vitamin E, vitamin C and β–carotene directly scavenge ROS. In addition, thiol-containing antioxidants such as reduced glutathione (GSH) and other low molecular weight thiols
play an important role in maintaining substrate levels for GPX and keep protein thiol groups, vitamin E and vitamin C in reduced states.

SOD converts superoxide radical to hydrogen peroxide. Mammalian species contain three types of SOD. Manganese-containing SOD (Mn-SOD) is mitochondrial in origin while a majority of copper- and zinc-containing SOD (Cu, Zn-SOD) is cytosolic. The extra cellular SOD (Ec-SOD) constitutes the iron-containing enzymes (Fe-SOD) and those belong to the Cu, Zn-SOD family. In mammals, the highest SOD activity is found in liver, followed by kidney, brain, adrenal gland and heart. The distribution of SOD activity in the cell varies from tissue to tissue. In rat liver, about 90% of SOD activity is attributed to Cu, Zn-SOD, whereas in the myocardium, the contribution of Mn-SOD is higher, ranging from 15 to 20% (Ji and Hollander 2000).

CAT is a heme protein which catalyzes the decomposition of hydrogen peroxide to water and oxygen molecule. CAT is located primarily in the organelle called peroxisome. It, however, is present only at a very low concentration in myocardium, whereas GPX is present in a significant amount (Ji and Hollander 2000).

GPX is a selenium-containing enzyme that catalyzes the reduction of hydrogen peroxide and organic hydroperoxide into water and corresponding alcohol at the expense of GSH, which is oxidized glutathione (GSSG). Reduction of GSSG is catalyzed by glutathione reductase, a flavin-containing enzyme, wherein reduced nicotinamide adenine dinucleotide phosphate (NADPH) is used as the reducing power. GPX is located both in the cytosol and mitochondrial matrix of the cell. The activity of GPX is highest in liver and erythrocytes. The brain, kidney and heart also possess moderate activity of GPX (Ji and Hollander 2000). Recently, a membrane-associated
phospholipid hydroperoxide glutathione peroxidase which possesses high peroxidase activity towards phospholipid and cholesterol hydroperoxides but low activity towards hydrogen peroxide has been identified (Thomas et al., 1990).

2.8 Diabetes mellitus

The word diabetes is derived from the Greek word that means “to siphon or drain off”, the most obvious sign of diabetes being excessive urination. “Mellitus” comes from a Latin word that means “Sweet”.

Diabetes is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin. This results primarily in elevated fasting and postprandial blood glucose levels. If this imbalanced homeostasis does not return to normalcy and continues for a protracted period of time, it leads to hyperglycemia that in due course turns into a syndrome called diabetes mellitus.

In 1921, Dr. Frederick G. Banting and a medical student, Charles H. Best, took fluid from animal pancreases, purified it and injected it into Leonard Thompson, a 11-year-old boy suffering from severe diabetes. Leonard was barely alive and weighed only 75 pounds. But after injections of the fluid, his blood sugar levels went down, he was able to eat more normal diet, he gained weight, and he lived to be an adult. The magic ingredient in that fluid was “Insulin”.

Unfortunately, as people with diabetes mellitus started living longer, doctors noticed that they tended to develop diseases of the eyes, kidneys, nerves, and blood vessels. Doctors began to suspect that these problems might be due to high levels of sugar in the blood.
Diabetes mellitus is a heterogeneous metabolic disorder characterized by chronic hyperglycemia with derangement of principal metabolic fuels such as carbohydrate, protein and fat metabolisms caused by the relative or absolute lack of insulin and/or secretion. The syndrome had a particular predilection for micro vascular complications (nephropathy, retinopathy and neuropathy) and increased tendency for macro-vascular complications (peripheral vascular disease, cerebrovascular disease and coronary artery disease) (Rubin et al., 1994). In a nutshell diabetes is defined as a metabolic cum vascular disorder. Diabetes is the single most important metabolic disease, widely recognized as one of the leading causes of death and disability worldwide (Songer et al., 1995; Zimmet et al., 1999).

Complications of diabetes mellitus are acute complications and chronic complications. Acute complications mainly include ketoacidosis and ketoacidotic coma. Chronic complications are further divided into microvascular and macrovascular complications. Micro vascular complications are coronary artery disease, diabetic cardiomyopathy & peripheral vascular disease.

### 2.8.1 A rising global burden

Diabetes mellitus (predominantly type II) is a major and growing health problem in almost all countries. Globally, the prevalence of diabetes in adults aged over 20 years was estimated to be 4% in 1995 and is projected to rise to 5.5% by 2025. Over the same period, the number of people with diabetes will increase from 135 million people to 300 million people, about 75% of whom will live in developing countries. In the western pacific region, the current number of people with diabetes is estimated to be 30 million. This will rise to at least 55 million adults by 2025. Of these
38 million will be in China and 9 million in Japan. The prevalence of diabetes exceeds 8% in 12 countries and areas of the region and in some Pacific Island countries it exceeds 20%. In countries where lifestyle changes began only recently (e.g. Cambodia, Vietnam) diabetes prevalence is relatively low, but there are signs that this is changing, in these countries rapid increases in prevalence can be anticipated unless urgent preventive action is taken.

The number of people with diabetes will more than double over the next 25 years, to reach a total of 366 million by 2030. Most of this increase to occur at a result of a 150% rise in developing countries. These projections of the number of the people with diabetes in 2030 take into account trends in urbanization—the fact that people are moving from rural areas to cities, particularly in developing countries. This affects the number of people with diabetics, because people living in cities in developing countries tend to be less physically active and have higher levels of overweight and obesity than people in rural areas. In fact, current trends in obesity suggest that these projections are conservative and that the increase in the prevalence of diabetes may be even greater. In developing countries it is people in the middle, productive years of their lives that are particularly affected by diabetes. In these countries all three quarters of all the people with diabetes are under 65 years old and 25% of all adults with diabetes are younger than 44. In developed countries, more than half of all people with diabetes are older than 65, and only 8% of adults with diabetes are younger than 44.

The Pacific island countries exhibit some of the highest recorded prevalence’s of diabetes globally. Other countries in the Asian parts of the region are undergoing emerging epidemics of the disease. In 2000, 3.2 million people died from
complications associated with diabetes. In countries with high diabetes prevalence, such as those in the pacific and the Middle East, as many as one in four deaths in adults aged between 35 and 64 years is due to diabetes. Diabetes has become the one of the major causes of premature illness and death in most countries; mainly through the increased risk of cardiovascular disease (CVD). Cardiovascular disease is responsible for the 50%-80% of deaths in people with diabetes. Diabetes is the leading cause of blindness, amputation and kidney failure. These complications account for much of the social and financial burdens of diabetes. Although diabetes is sometimes considered a condition of developed nations, the loss of life from premature death among persons with diabetes is greatest in developing countries. The burden of premature death from diabetes is similar to that of HIV/AIDS, yet the problem is largely unrecognized.

The prevalence of diabetes is rising rapidly especially in the urban population in India. Since 1971-2000, a 10 fold increase has been observed (from 1.2% to 12.1%). It has remained an urban phenomenon so far and all the previous epidemiological studies have illustrated a 4 fold difference in the prevalence of diabetes between the urban and rural population. National urban diabetes survey in 2000 by a group of doctors found that Hyderabad topping the list (16.6% of its population) followed by Chennai (13.5%), Bangalore (12.4%), Kolkata (11.7%), Delhi (11.6%) and Mumbai (9.3%). The incidence in most metros and cities in India presently is 10-15%. No wonder India is the diabetic capital of the world.
2.8.2 Classification of Diabetes mellitus

The etiologic classification of Diabetes Mellitus currently recommended by WHO and the ADA is presented as:

1. Type I Diabetes mellitus (β-cell destruction usually leading to absolute insulin deficiency).
   A. Autoimmune
   B. Idiopathic
2. Type II Diabetes mellitus
3. Other Specific types
   A. Genetic defects of β-cell function
   B. Genetic defects in insulin action
   C. Diseases of the exocrine pancreas
   D. Endocrinopathies
   E. Drug- or chemical-induced diabetes
   F. Infections
   G. Uncommon forms of immune-mediated diabetes
   H. Other genetic syndromes sometimes associated with diabetes
4. Gestational diabetes

2.8.2.1 Type I Diabetes mellitus

Type I Diabetes is the form of disease due primarily to β-cell destruction. This usually leads to type of diabetes in which insulin is required for survival. Type I Diabetes usually is characterized by the presence of anti-GAD, anti-islet cell, or anti-insulin antibodies, which reflect the autoimmune process that have led to β-cell
destruction. Individuals who have one of more of these antibodies can be subclassified as having type IA, immune-mediated type I diabetes.

Type IA diabetes shows strong associations with specific haplotypes or alleles at the DQ-A and DQ-B loci of the human leukocyte antigen (HLA) complex. The rate of \( \beta \)-cell destruction is quite variable, being rapid in some individuals, especially in infants and children, and slower in adults. Some have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia or ketoacidosis and others, particularly adults, may retain some residual \( \beta \)-cell function for many years and have some-times been termed as having “latent autoimmune diabetes.”

Type IB or idiopathic, diabetes is characterized by low insulin and c-peptide levels similar to those in Type IA. Such patients are prone to ketoacidosis, although they have no clinical evidence of autoimmune antibodies.

2.8.2.2 Type II Diabetes Mellitus

Type II diabetes is the most common form of diabetes formerly known as non-insulin dependent diabetes (NIDDM), sometimes referred to as adult-onset DM, usually begins after age 40 as a multifactorial disease that may involve improper insulin secretion, malfunctioning insulin and/or insulin resistance in peripheral tissues, either of which may be the predominant feature. Ketoacidosis seldom occurs spontaneously but can arise with stress associated with another illness such as infection.

The pancreas plays a primary role in the metabolism of glucose by secreting the hormones insulin and glucagon. The islets of langerhans secrete insulin and glucagon directly into the blood. Inadequate secretion of insulin, inadequate structure or
function of insulin or its receptors results in impaired metabolism of glucose, carbohydrates, proteins and fats and this is characterized by hyperglycemia and glycosuria. Hyperglycemia is the most frequently observed sign of diabetes and is considered the etiologic source of diabetic complications.

**Causes of Type II Diabetes mellitus**

- Over weight (obesity) which also leads to insulin resistance
- Family history with Type II diabetes
- Have high blood pressure
- Over 65-74 years of age
- Women may develops type 2 diabetes during pregnancy
- Childhood obesity
- A very high cholesterol and triglyceride levels

**Common symptoms of Type II diabetes**

- Frequent urination (polyuria) and dehydration
- Excessive thirst (polydipsia)
- Extreme hunger (polyphagia)
- Unexplained weight loss
- Increased fatigue
- Numbness or tingling in hands or feet
- Dry, itchy skin
- Slow-healing sores
- Red, swollen or tender gums or gingivitis
- Frequent infections, including urinary tract infections and yeast infections
- Blurry vision
- Dizziness
- Irritability

2.8.2.3 Treatment

The various strategies for the treatment of diabetes are as follows:
2.9 *Ficus racemosa* Linn. (Unripe fruits)

**Family** : Moraceae

**Botanical synonyms** : Ficus glomerata Roxb. Ficus semicostata F.M.

**Common names** :

Hindi : Gular
Sanskrit : Udumbara
English : Cluster fig
Tamil : Atti
Telugu : Atti, bodda
Gujrati : Umbar, umar
Bengali : Dumar, yajnadumbar

**Description**

A medium-sized to large evergreen or occasionally deciduous tree up to 18 m tall, often with an irregular, shabby crown. Barks are smooth, pinkish-brown to reddish-gray, coarsely flaky on older trees; latex copious, cream-buff in color. Young shoots and figs finely white-hairy, turning glabrous. Leaves alternate, glabrous, 6-9 cm long and 3.2-8.5 cm wide, ovate-oblong or elliptic-lanceolate, margins entire, tapering to a bluntly pointed apex, base acute or rounded, 3-nerved; petioles 1.3-3.8 cm long; stipules 2 cm long, pubescent. Receptacles (figs) subglobos, dence tomentose, 1.5-4 cm across, dull reddish when ripe, borne in large clusters on short, leafless, warty, branches arising from the trunk and older branches.
**Distribution**

Found throughout of India to an elevation of about 2000 m in evergreen forests and along the banks of streams in moist ravines in deciduous forests. Also found in Srilanka, Pakistan, southern China to New Guinea and northern Queensland, Australia.

**Traditional Uses**

The milky juice (latex) from the plant is reportedly used for treating piles and diarrhea and externally for healing of wounds. Fruits are used as a stomachic & carminative to relieve dysentery, diarrhoea & for treatment of diabetes. Roots are used in cases of dysentery & diabetes. Barks are used in cases of dysentery. In Mumbai, the sap of this plant is a popular remedy for mums & other inflammatory enlargement. It is also used in treatment of skeletal fracture in Srilanka (Ram et al., 1960).

**Phytochemical constituents**

The plant of *Ficus racemosa* Linn contains glycoside, tetracyclictriterpene glauanol. Fruits contain Glauanol. Leaves, Barks, Heartwood contains tetra cyclic triterpene glauanol acetate characterized as 13α, 14β, 17β, 20 αH-lanosta-8, 22 diene-3β-acetate. Stems bark contain Leucoanthrocyanin, tannin, Leucocyanidin -3-o-β-D-glycopyranoside & Leucopelaronidin-3-o-α-L-rhamnopyranoside,Ceryl behenate, Lupeol & Alpha-amyrin acetate (Ram et al., 1960).

**Past studies on biological activities of Ficus Racemosa**

Hepatoprotective activity of *Ficus racemosa* leaves in rats by including chronic liver damage by subcutaneous injection of 50% v/v carbon tetrachloride in liquid paraffin at a dose of 3mL/kg on alternate days for a period of 4 weeks. The biochemical parameters SGOT, SGPT, serum bilirubin and alkaline phosphatase were estimated to
assess the liver function. The activity of extract was also comparable to a standard liver tonic (Neutrosec) (Subhash et al., 1999).

Anti-inflammatory activity of the petroleum ether extract of the leaves of *Ficus racemosa* Linn. in carrageenin, serotonin, histamine & dextran induced hind paw edema in rat’s models. The extract at doses of 200 and 400 mg/kg has been found to possess significant anti-inflammatory activity on the tested experimental models. The effect produced by the extract was comparable to that of phenylbutazone, a prototype of a non-steroidal anti-inflammatory agent (Mandal et al., 2000).

Anti-bacterial activity of *Ficus racemosa* Linn. Leaf extract against *Escherichia coli* ATCC 10536, *Bacillus pumilis* ATCC 14884, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 25619 and *Staphylococcus aureus* ATCC 29737. The effects produced by the extract were significant and were compared with chloramphenicol. The petroleum ether extract was most effective against the tested organisms (Subhas et al., 2000).

Hypoglycemic activity of methanolic extract of the stem bark of *Ficus racemosa* Linn. (MEBFR) both in normal and alloxan-induced diabetic rats. The MEBFR at the doses examined (200 and 400mg/kg p.o.) exhibited significant hypoglycemic activity in both model. The activity was also comparable to that of the effect produced by a standard ant diabetic agent, glibenclamide 10mg/kg body weight (Rao et al., 2002).

Anti-pyretic effect of a methanolic extract of stem bark of *Ficus racemosa* Linn. (MEFR) on normal body temperature & yeast induced pyrexia in albino rats. A yeast suspension (10 ml/kg body weight) increased rectal temperature 19 h after subcutaneous injection. The MEFR, at doses of 100, 200 and 300mg/kg body weight p.o., showed
significant dose-dependent reduction in normal body temperature and yeast-provoked elevated temperature. The anti-pyretic effect of MEFR was comparable to that of paracetamol (150 mg/kg body weight, p.o.), a standard anti-pyretic agent (Bhaskara et al., 2002).

Anti-tussive potential of methanolic extract of stem bark of *Ficus racemosa* Linn. Reported that methanolic extract of *Ficus racemosa* Linn. (MEFR) was tested for its antitussive potential against a cough induced model by sulphur dioxide gas in mice. The antitussive activity of the extract was comparable to that of codeine phosphate (10mg), a standard antitussive agent. The extract exhibited maximum inhibition of 56.9% at a dose of 200mg/kg (p.o.) 90 min after administration (Rao et al., 2003).

SriLankan traditional practitioners claimed as an anti-diuretic effect of the decoction of the bark of *Ficus racemosa* Linn. in rats using three doses (250, 500 and 1000 mg/kg) following oral administration. The reference drug used was ADH. The result demonstrated both the low and high doses of decoction and ADH significantly impaired the total urine output. The decoction-induced anti diuresis had a rapid onset (within 1 h), peaked at 3 h and lasted throughout the study period (5 h). The anti-diuretic potential of decoction was about 50% lower than that of ADH. The decoction caused a reduction in urinary Na⁺ level and Na⁺/K⁺ ratio and an increase in urinary osmolarity indicating multiple mechanisms of action (Ratnasooriya et al., 2003).

A new anti-inflammatory glycoside from ethanolic extract of *Ficus racemosa* Linn bark showed potent inhibitory activity against COX-1 & 5-LOX in-vitro with IC₅₀ values of 90 and 18 µM. Racemosic acid also demonstrated a strong antioxidant activity to scavenge ABTS free radical cations with IC₅₀ values of 19 µM. In addition, cytotoxic
effects of the extract of Ficus racemosa were investigated in-vitro using the ATP-based luminescence assay and result showed no cytotoxicity on the cell lines skin fibroblast (IBR3), human caucasian hepatocyte carcinoma (Hep G2) and human Caucasian promyelocytic leukemia (HL-60). (Rachel et al., 2004).

Potential antifilarial activity of alcoholic & aqueous extract of the fruit of *Ficus racemosa* Linn. on spontaneous movements of both the whole worm & nerve muscle preparation of Cervi & on the survival of microfilaria in-vitro (250 – 350 mg/kg) Alcoholic as well as aqueous extract caused inhibition of spontaneous motility of whole worm and nerve muscle preparation of *Setaria Cervi* characterized by increase in amplitude and tone of contraction (Vandana et al., 2005).

Potential beneficial effect of *Ficus racemosa* extract on KBrO₃-mediated renal oxidative stress and cell promotion response in rats. KBrO₃ (125 mg/kg body weight, intraperitoneally) enhanced lipid peroxidation, xanthine oxidase, gamma-glutamyl transpeptidase and hydrogen peroxide (H₂O₂) generation with reduction in renal glutathione content and antioxidant enzymes. KBrO₃ treatment also induced tumor promotion markers, viz., ornithine decarboxylase activity and thymidine [3H] incorporation into renal DNA. A sharp elevation in the levels of blood urea nitrogen and serum creatinine has also been observed. Treatment of rats orally with *Ficus racemosa* extract (200 mg/kg body weight and 400 mg/kg body weight) resulted in a significant decrease in xanthine oxidase, lipid per oxidation, gamma-glut amyl transpeptidase and H₂O₂ (Khan et al., 2005).

Chemo-preventive effect of *Ficus racemosa* extract against Fe-NTA-induced (Ferric nitrilotriacetate) renal oxidative stress, hyper-proliferation response and renal carcinogenesis in rats. Fe-NTA (9 mg/kg body wt., intraperitoneally) enhances renal lipid
peroxidation, xanthine oxidase, gamma-glutamyl transpeptidase and hydrogen peroxide generation with reduction in renal glutathione content, antioxidant enzymes. Treatments of rats orally with *Ficus racemosa* extract (200 and 400 mg/kg body wt.) resulted in significant decrease in gamma-glutamyl transpeptidase, lipid peroxidation, xanthine oxidase hydrogen peroxide, blood urea nitrogen, serum creatinine, renal ODC activity, DNA synthesis and incidence of tumors. *Ficus racemosa* extract is a potent chemopreventive agent and suppresses Fe-NTA-induced renal carcinogenesis and oxidative damage response in wistar rats (Khan *et al.*, 2005).

Gastro protective effect of 50% ethanolic extract of *Ficus glomerata* fruit (FGE) was studied in different ulcer models in rats. FGE showed dose dependent inhibition of ulcer index in pylorus ligation, ethanol and cold restraint stress induced ulcers. FGE prevents the oxidative damage of gastric mucosa by blocking lipid peroxidation and by significant decrease in superoxide dismutase (Rao *et al.*, 2008).

Plants with anti-ulcer activity

Ulcer is most common disease throughout the world. Although ulcer is one of the oldest known diseases of mankind and affects a large population of the world, no substantial progress has been made in achieving a permanent cure. The search of screening and development of drugs for anti-ulcer activity has been an unending problem. There is much hope of finding active anti-ulcer compound from indigenous plants as these are still used in therapeutic despite the progress made in conventional chemistry and pharmacology for producing effective drugs. Since there are number of reports of plants with anti-ulcer activity and also since reviews on plants having anti-ulcer activity are tabulated in table- 1.
Table no: 1 Indian medicinal plants reported for its ulcer protective activity

<table>
<thead>
<tr>
<th>S.No</th>
<th>Plant Name (Family)</th>
<th>Part used</th>
<th>Extract</th>
<th>Experimental model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Aegle marmelos</em> (Rutaceae)</td>
<td>Unripe fruit</td>
<td>Ethanolic</td>
<td>Hypothermic restraint stress, absolute ethanol, and indomethacin</td>
<td>Dhuley <em>et al.</em>, (2004)</td>
</tr>
<tr>
<td>2</td>
<td><em>Anogeissus latifolia</em> (Combretaceae)</td>
<td>Bark</td>
<td>50% aqueous alcoholic</td>
<td>Aspirin, cold-resistant stress, pylorus ligated and ethanol</td>
<td>Govindarajan <em>et al.</em>, (2006) (In press)</td>
</tr>
<tr>
<td>5</td>
<td><em>Centella asiatica</em> (Umbelliferae)</td>
<td>Whole plant</td>
<td>Juice</td>
<td>Cold restraint stress, indomethacin, ethanol, pylorus ligation, acetic acid</td>
<td>Sairam <em>et al.</em>, (2001)</td>
</tr>
<tr>
<td>6</td>
<td><em>Curcuma longa</em> (Zingiberaceae)</td>
<td>Rhizomes</td>
<td>Ethanol and ethyl acetate</td>
<td>Pylorus-ligation</td>
<td>Kim <em>et al.</em>, (2005)</td>
</tr>
<tr>
<td>7</td>
<td><em>Desmodium gangeticum</em> (Leguminosae)</td>
<td>Leaves</td>
<td>Ethanolic</td>
<td>Ethanol, pylorus ligation, aspirin &amp; cold-resistant stress</td>
<td>Dharmani <em>et al.</em>, (2005)</td>
</tr>
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</tr>
<tr>
<td>11</td>
<td><em>Nigella sativa</em> L (Ranunculaceae)</td>
<td>Seeds</td>
<td>oil</td>
<td>ethanol</td>
<td>Kanter et al., (2005)</td>
</tr>
<tr>
<td>15</td>
<td><em>Solanum nigrum</em> (Solanaceae)</td>
<td>fruit</td>
<td>Ethanolic</td>
<td>Cold restraint stress, aspirin, ethanol, pylorus ligation</td>
<td>Jainu et al., (2006)</td>
</tr>
</tbody>
</table>
2.10 *Aegle Marmelos*

**Classification**

Kingdom : Plantae  
Division : Magnoliophyta  
Class : Magnoliopsida  
Sub class : Rosidae  
Order : Sapindales  
Family : Rutaceae  
Genus : *Aegle*  
Species : *marmelos*

**Common name**

Botanical name : *Aegle marmelos*  
English name : Wood apple  
Hindi name : Bael  
Ayurvedic name : Jamber kul

**History**

This is sacred tree amongst the Hindus, its leaves being used in the worship of Lord Shiva. On this account it is found to be cultivated everywhere in Hindu’s gardens. It is considered sacrilegious to destroy it; enormous quantities of leaves are gathered for use in the temple at certain seasons. In ancient Sanskrit poems it is frequently considered to be very auspicious. The baton of the Vaishya or the third caste of Hindus is obtained from this tree. The fruit is the subject of several solar-phallic myths. Hindu physician regard the unripe or half ripe fruit as astringent, digestive and stomachic and prescribed in diarrhea and dysentery. The dried pulp of the fruit is called as Velva pushbike in Sanskrit. The root bark is used as a remedy in hypochondrisis, melancholia and palpitation of the heart.
**Parts Used:** Root and Leaves

**Description**

The bael fruit tree is slow-growing, of medium size, up to 40 or 50 ft (12-15 m) tall with short trunk, thick, soft, flaking bark, and spreading, sometimes spiny branches, the lower ones drooping. Young suckers bear many stiff, straight spines. A clear, gummy sap, resembling gum arabic, exudes from wounded branches and hangs down in long strands, becoming gradually solid. It is sweet at first taste and then irritating to the throat. The deciduous, alternate leaves, borne singly or in 2's or 3's, are composed of 3 to 5 oval, pointed, shallowly toothed leaflets, 1 1/2 to 4 in (4-10 cm) long, 3/4 to 2 in (2-5 cm) wide, the terminal one with a long petiole. New foliage is glossy and pinkish-maroon. Mature leaves emit a disagreeable odor when bruised. Fragrant flowers, in clusters of 4 to 7 along the young branch lets, have 4 recurved, fleshy petals, green outside, yellowish inside, and 50 or more greenish-yellow stamens. The fruit, round, pyriform, oval, or oblong, 2 to 8 in (5-20 cm) in diameter, may have a thin, hard, woody shell or a more or less soft rind, gray-green until the fruit is fully ripe, when it turns yellowish. It is dotted with aromatic, minute oil glands. Inside, there is a hard central core and 8 to 20 faintly defined triangular segments, with thin, dark-orange walls, filled with aromatic, pale-orange, pasty, sweet, resinous, more or less astringent, pulp. Embedded in the pulp are 10 to 15 seeds, flattened-oblong, about 3/8 in (1 cm) long, bearing woolly hairs and each enclosed in a sac of adhesive, transparent mucilage that solidifies on drying.

**Origin and Distribution**

The tree grows wild in dry forests on hills and plains of central and southern India and Burma, Pakistan and Bangladesh, also in mixed deciduous and dry dipterocarp
forests of former French Indochina. Mention has been found in writings dating back to 800 B.C. It is cultivated throughout India, mainly in temple gardens, because of its status as a sacred tree; also in Ceylon and northern Malaya, the drier areas of Java, and to a limited extent on northern Luzon in the Philippine Islands where it first fruited in 1914. It is grown in some Egyptian gardens, and in Surinam and Trinidad. Seeds were sent from Lahore to Dr. Walter T. Swingle in 1909 (P.I. No. 24450). Specimens have been maintained in citrus collections in Florida and in agriculture research stations but the tree have never been grown for its fruit in this state except by Dr. David Fairchild at his home, the "Kampong", in Coconut Grove, after he acquired a taste for it, served with jaggery (palm sugar), in Ceylon

**Botanical Description**

Deciduous tree, up to 12 to 20 m high, armed; main trunk about 30 cm across; spine 2 to 3 cm long. Leaves pinnately trifoliate, dimorphic; leaflets ovate-elliptic to elliptic-lanceolate, terminal ones about 13 x 6.5 cm and lateral about 7 x 4 cm, apex blunt, base oblique, margin shallowly crenate-serrate, lateral sessile and terminal stalked; petioles slender, about 6 cm long, glabrous. Flowers in axillary and terminal racemose or cymose, greenish-white, fragrant; pedicels 2 to 4 mm long, densely puberulent. Calyx cupular with 5 small deltoid or suborbicular teeth, finely puberulent. Petals greenish-white, 4-5, ovate-oblong, glabrous. Fruits subglobose, 5 to 10 cm across; pericarp hard, woody, grey or yellowish; many seeded. Seeds oblong, flattened, embedded in a sweet, thick, orange or flesh-coloured mucilaginous pulp.

**Flowering & Fruiting:** March – December
Climate

The bael fruit tree is a subtropical species. In the Punjab, it grows up to an altitude of 4,000ft (1,200 m) where the temperature rises to 120º F (48.89º C) in the shade in summer and descends to 20º F (-6.67º C) in the winter, and prolonged droughts occur. It will not fruit where there is no long, dry season, as in southern Malaya.

Soil

The bael fruit is said to do best on rich, well-drained soil, but it has grown well and fruited on the oolitic limestone of southern Florida. It grows well in swampy, alkaline or stony soils, grows luxuriantly in the soils having pH range from 5 to 8. In India it has the reputation of thriving where other fruit trees cannot survive.

Varieties

One esteemed large cultivar with thin rind and few seeds are known as 'Kaghzi'. Dr. LB. Singh and co-workers at the Horticultural Research Institute, Saharanpur, India, surveyed bael fruit trees in Uttar Padesh, screened about 100 seedlings, selected as the most promising for commercial planting: 'Mitzapuri', 'Darogaji', 'Ojha', 'Rampuri', 'Azamati', 'Khamaria'. Rated the best was 'Mitzapuri', with very thin rind, breakable with slight pressure of the thumb, pulp of fine texture, free of gum, of excellent flavor, and containing few seeds.

There is extreme variability of 24 cultivars collected in Agra, Calcutta, Delhi and Varanasi. He decided that selections should be made for high sugar content and low levels of mucilage, tannin and other phenolics.
Only the small, hard-shelled type is known in Florida and this has to be sawed open, cracked with a hammer, or flung forcefully against a rock. Fruits of this type are standard for medicinal uses rather than for consuming as normal food.

**Propagation**

The bael fruit is commonly grown from seed in nurseries and transplanted into the field. Seedlings show great variation in form, size, texture of rind, quantity and quality of pulp and number of seeds. The flavor ranges from disagreeable to pleasant. Therefore, superior types must be multiplied vegetatively. L.B. Singh achieved 80% to 95% success in 1954 when he budded 1-month-old shoots onto 2-year-old seedling bael rootstocks in the month of June. Experimental shield-budding onto related species of *Afraegle* and onto *Swinglea glutinosa* Merr. has been successful. Occasionally, air-layers or root cuttings have been used for propagation.

**Pests and Diseases**

The bael fruit seems to be relatively free from pests and diseases except for the fungi causing deterioration in storage.

**Uses**

Bael fruits may be cut in half, or the soft types broken open, and the pulp, dressed with palm sugar, eaten for breakfast, as is a common practice in Indonesia. The pulp is often processed as nectar or "squash" (diluted nectar). A popular drink (called "sherbet" in India) is made by beating the seeded pulp together with milk and sugar. A beverage is also made by combining bael fruit pulp with that of tamarind. These drinks are consumed perhaps less as food or refreshment than for their medicinal effects.

Mature but still unripe fruits are made into jam, with the addition of citric acid. The pulp is also converted into marmalade or syrup, likewise for both food and
therapeutic use, the marmalade being eaten at breakfast by those convalescing from diarrhea and dysentery. A firm jelly is made from the pulp alone, or, better still, combined with guava to modify the astringent flavor. The pulp is also pickled.

Bael pulp is steeped in water, strained, preserved with 350 ppm S0₂, blended with 30% sugar, then dehydrated for 15 hrs at 120º F (48.89º C) and pulverized. The powder is enriched with 66 mg per 100 g ascorbic acid and can be stored for 3 months for use in making cold drinks ("squashes"). A confection, bael fruit toffee, is prepared by combining the pulp with sugar, glucose, skim milk powder and hydrogenated fat. Indian food technologists view the prospects for expanded bael fruit processing as highly promising.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Component</th>
<th>Food value per 100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Water</td>
<td>54.96-61.5g</td>
</tr>
<tr>
<td>2.</td>
<td>Protein</td>
<td>1.8-2.62g</td>
</tr>
<tr>
<td>3.</td>
<td>Fat</td>
<td>0.2-0.39g</td>
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<tr>
<td>4.</td>
<td>Carbohydrates</td>
<td>28.11-31.8g</td>
</tr>
<tr>
<td>5.</td>
<td>Ascorbic Acid</td>
<td>8-60 mg</td>
</tr>
<tr>
<td>6.</td>
<td>Thiamine</td>
<td>0.13 mg</td>
</tr>
<tr>
<td>7.</td>
<td>Riboflavin</td>
<td>1.19 mg</td>
</tr>
</tbody>
</table>

*Fresh bael fruit, as analyzed in India and in the Philippines.

The pulp also contains a balsam-like substance, and 2 furocoumarins-psoralen and marmelosin (C₁₃H₁₂O₃), highest in the pulp of the large, cultivated forms. There is as
much as 9% tannin in the pulp of wild fruits, less in the cultivated types. The rind contains up to 20%. Tannin is also present in the leaves, as is skimmianine. The essential oil of the leaves contains \( d \)-limonene, 56% \( a \)-d-fellandrene, cineol, citronellal, citral; 17% \( p \)-cymene, 5% cumin aldehyde. The leaves contain the alkaloids \( O \)-(3, 3-dimethylallyl)-halfordinol, \( N \)-2-ethoxy-2-(4-methoxyphenyl) ethylcinnamamide, \( N \)-2-methoxy-2-[4-(3’, 3’-dimethyloxy) phenyll] ethylcinnamide, and \( N \)-2-methoxy-2-(4-methoxyphenyl)-ethylcinnamamide.

**Toxicity**

The leaves are said to cause abortion and sterility in women. The bark is used as a fish poison in the Celebes. Tannin ingested frequently and in quantity over a long period of time, is antinutrient and carcinogenic.

**Constituents of Bael**

The Bael tree is one of the most useful medicinal plants of India. Its medicinal properties have been described in the ancient medical treatise in Sanskrit, *Charaka Samhita*. All the parts of this tree including stem, bark, root, leaves and fruit at all stages of maturity has medicinal virtues and has been used as traditional medicine for a long time. The pulp also contains a balsam-like substance and 2 furocoumarins-psoralen and marmelosin \( (C_{13}H_{12}O_{3}) \), highest in the pulp of the large, cultivated forms. The root and leaves contain Umbeliferone, \( \beta \)-Sitosterol, Stigmasterol. The fruit, roots and leaves have antibiotic activity. The root, leaves and bark are used in treating snakebite. Chemical studies have revealed the following properties in the roots: psoralen, xanthotoxin, \( O \)-methylscopoletin, scopoletin, tembamide and skimming.
Main constituents of Bael:

2 furocoumarins-psoralen, marmelosin, skimmianine, d-phellandrene, cineol, citronellal, citral, O-(3,3-dimethylallyl)-halfordinol, N-2-ethoxy-2-(4-methoxyphenyl) fagarine and skimmianine, psoralen, xanthotoxin, O-methylscopoletin, scopoletin, tembamide, and skimmianine also decursinol, haplopine and aegelinol. Root extract included auraptene, umbelliferone, marmin, lupeol, skimmianine. Leaves contain rutacine (apparently identical to skimmianine) and aegelin.

Umbelliferone or 7-hydroxycoumarin is a widespread natural product of the coumimic family. It occurs in many familiar plants from the Apiciceae (Umbelliferae) and Rutaceae family such as carrot, coriander and bael. It is a yellowish-white crystalline solid which has a slight solubility in hot water, but high solubility in ethanol. It absorbs ultraviolet light strongly at several wavelengths (Joule et al., 1995).

Gallic acid is an organic acid, also known as 3, 4; 5-trihydroxybenzoic acid. Gallic acid is commonly used in the pharmaceutical industry. It is used as a standard for determining the phenol content of various analytes by the Folin-Ciocalteau assay; results are reported in gallic acid equivalents. Gallic acid seems to have anti-fungal and anti-viral properties. Gallic acid acts as an antioxidant and helps to protect our cells against oxidative damage.
Medicinal Uses

The fresh ripe pulp of the higher quality cultivars, and the "sherbet" made from it, are taken for their mild laxative, tonic and digestive effects. A decoction of the unripe fruit, with fennel and ginger, is prescribed in cases of hemorrhoids. It has been surmised that the psoralen in the pulp increases tolerance of sunlight and aids in the maintaining of normal skin color. It is employed in the treatment of leucoderma. Marmelosin derived from the pulp is given as a laxative and diuretic. In large doses, it lowers the rate of respiration, depresses heart action and causes sleepiness.

For medicinal use, the young fruits, while still tender, are commonly sliced horizontally and sun-dried and sold in local markets. They are much exported to Malaya and Europe. Because of the astringency, especially of the wild fruits, the unripe bael is most prized as a means of halting diarrhea and dysentery, which are prevalent in India in the summer months. Bael fruit was resorted to by the Portuguese in the East Indies in the 1500's and by the British colonials in later times.

Bitter, light-yellow oil extracted from the seeds is given in 1.5 g doses as a purgative. It contains 15.6% palmitic acid, 8.3% stearic acid, 28.7% linoleic and 7.6% linolenic acid. The seed residue contains 70% protein.

The bitter, pungent leaf juice, mixed with honey, is given to allay catarrh and fever. With black pepper added, it is taken to relieve jaundice and constipation accompanied by edema. The leaf decoction is said to alleviate asthma. A hot poultice of the leaves is considered an effective treatment for ophthalmia and various inflammations, also febrile delirium and acute bronchitis.

A decoction of the flowers is used as eye lotion and given as an antiemetic. The bark contains tannin and the cournarin, aegelinol; also the furocourmarin, marmesin;
umbelliferone, a hydroxy coumarin; and the alkaloids, fagarine and skimmianine. The bark decoction is administered in cases of malaria. Decoctions of the root are taken to relieve palpitations of the heart, indigestion, and bowel inflammations; also to overcome vomiting.

The fruit, roots and leaves have antibiotic activity. The root, leaves and bark are used in treating snakebite. Chemical studies have revealed the following properties in the roots: psoralen, xanthotoxin, O-methylscopoletin, scopoletin, tembamide, and skimmin; also decursinol, haplopine and aegelinol, in the root bark.

**Past studies on biological activities of Aegle marmelos**

The antifungal activity of essential oil isolated from the leaves of bael (*Aegle marmelos* (L.) Correa ex Roxb. Rutaceae) has been evaluated using spore germination assay. The oil exhibited variable efficacy against different fungal isolates and 100% inhibition of spore germination of all the fungi tested was observed at 500 ppm. However, the most resistant fungus, *Fusarium udum* was inhibited 80% at 400 ppm. Kinetic studies showed concentration as well as time dependent complex inhibition of spore germination by the essential oil (Rana *et al.*, 1997).

Design of *Peumus boldus* tablets by direct compression of a novel dry plant extract using common excipients. The formulation containing dry plant extract of Pb (170 mg), Avicel PH101 (112 mg), Lactose CD (112) and magnesium stearate (6 mg), compressed at 1000 mPa. It was concluded that the compressed tablet formulation showed the best pharmaceutical performance (Santiago Palma *et al.*, 2002).

The hypoglycemic effect of the water extract of the fruits of *Aegle marmelos* was examined in streptozotocin-induced diabetic Wistar rats. Oral administration of the water
extract (125 and 250 mg/kg) twice a day for 4 weeks resulted in significant reductions in blood glucose, plasma thiobarbituric acid reactive substances, hydro peroxides, ceruloplasmin and α-tocopherol and a significant elevation in plasma reduced glutathione and VitaminC in diabetic rats. The effect of the extract at a dose of 250 mg/kg was more effective than glibenclamide in restoring the values of these parameters. The results of this study clearly show the hypoglycaemic activity of the fruit extract (Kamalakkannan et al., 2003).

Analgesic, anti-inflammatory and anti-ulcer effects of unripe fruits of 50% ethanol extract of *Aegle marmelos* were examined. *Aegle marmelos* (50-200 mg/kg) has showed the significant analgesic and anti-inflammatory activities. *Aegle marmelos* showed a significant and dose dependent gastric ulcer protection in indomethacin induced ulcers also (Rao et al., 2003).

Hypoglycemic and antioxidant effect of aqueous extract of *Aegle marmelos* leaves (AML) have been evaluated in diabetic rats. The study showed a significant hypoglycemic effect in the dose of 500 mg/kg body weight once daily. AML has decreased the malondialdehyde (MDA) levels and increased glutathione (GSH). This indicates the *in-vivo* anti-oxidant activity of AML. Hence, the hypoglycemic and anti-oxidant effects of AML have been demonstrated (Sharmila et al., 2004).

The effect of the alcoholic extract of the leaves of *Aegle marmelos* Corr. on guinea pig isolated ileum and tracheal chain was investigated. The results showed that alcoholic extract of this plant produced a positive relaxant effect in isolated guinea pig ileum and tracheal chain. Because the alcoholic extracts elicited the antagonistic effect against histamine and also relaxed the histamine-induced contractions, it can be
concluded that relaxations induced by *Aegle marmelos* in both guinea pig ileum and tracheal chain were due to the depression of H₁-receptors (Arul *et al.*, 2004).

The serial extracts of the leaves of *Aegle marmelos* Corr. were investigated for anti-inflammatory property. The analgesic and anti-pyretic properties were also evaluated. The most of the extracts derived from the plant *Aegle marmelos* caused a significant inhibition of the carrageenan-induced paw oedema and cotton-pellet granuloma in rats. The extracts also produced marked analgesic activity by reduction the early and late phases of paw licking in mice. A significant reduction in hyperpyrexia in rats was also produced by the most of the extracts. This study was established anti-inflammatory, antinociceptive and antipyretic activities of the leaves of *Aegle marmelos* (Veerappan *et al.*, 2005).

Dried root powder of *Rhinacanthus nasutus*, were extracted with methanol (MeOH) in a Soxhlet apparatus and made into 2 formulations of tablet containing the extract at 5% and 10% concentration. Due to the viscous and poor flow properties of the crude MeOH extract obtained, a wet granulation method was conducted in developing the tablets. Lactose was used as filler. Polyvinyl pyrrolidone (PVP) K30 (15% w/w solution in alcohol) was used as the binding agent, while stearic acid (2% w/w) was used as a lubricant. Both formulas of prepared tablets had a smooth shiny surface with a round shape. It was reported that physical properties of the tablets, such as weight variation, friability and disintegration time, met the requirements of the USP XX standard (Yupha *et al.*, 2006).

Hypoglycemic and anti-hyperglycemic activity of *Aegle marmelos* seed extract in normal and diabetic rats have been studied. The aqueous extract of *Aegle marmelos* seeds
was administered orally at different doses (100, 250 and 500 mg/kg) to normal as well as sub (fasting blood glucose (FBG) normal; glucose tolerance abnormal) and mild (FBG 120–250 mg/dl) diabetic rats. The dose of 250 mg/kg was found to be most effective dose and it decreases blood glucose level (BGL) by 35.1% in normal healthy rats after 6 h of administration. These results clearly indicate that aqueous seed extract of *Aegle marmelos* possess anti-diabetic and hypolipidemic effects in diabetic rats (Achyut *et al.*, 2006).

Analgesic activity of methanol extract of *Aegle marmelos* leaves has been reported. The results of the study indicated that the methanol extract of the *Aegle marmelos* leaves significantly reduced the writhing induced by acetic acid. The extract at dose levels of 200 and 300 mg/kg showed significant analgesic activity in the tail flick test. It was concluded that the extract possesses both peripheral and central analgesic activities in mice (Shankarnath *et al.*, 2007).

Anti-hyperglycemic and anti-dyslipidemic activities are attributed to an alkaloidal-amide, Aegeline 2, which was isolated from the leaves of *Aegle marmelos* and this was clearly evidenced by lowering the blood glucose levels by 12.9% and 16.9% at 5 and 24 h, respectively, in sucrose challenged streptozotocin induced diabetic rats (STZ-S) model at the dose of 100 mg/kg, b.w. Aegeline 2 has also significantly decreased the plasma triglyceride (Tg) levels by 55% (*P* < 0.001), total cholesterol (TC) by 24% and free fatty acids (FFA) by 24%, accompanied with increase in HDL-C by 28% and HDL-C/TC ratio by 66% in dyslipidemic hamster model at the dose of 50 mg/kg body weight (Narender *et al.*, 2007).

*In-vivo* anti-fertility activity of *A. marmelos* leaf extract was investigated on the reproductive system of male albino rats. The study inferred that the leaf extract of *Aegle*
marmelos (AMLEt) suppresses fertility in male rats. Complete recovery of fertility was observed following the withdrawal of drug. Absence of any deleterious effect on the vital organs points to the safe use of the extract. It was concluded that suppression of fertility in male albino rats following the administration of 50% ethanolic extract of Aegle marmelos (Chauhan et al., 2007).

The hepatoprotective effect of bael leaves (Aegle marmelos) in alcohol induced liver injury in albino rats was investigated. The results were compared with the standard herbal drug silymarin (133.04 µg/g tissue). The experimental results indicate that, the Bael leaves have excellent hepatoprotective effect (Vinodhini et al., 2007).

The study was designed to elucidate the toxicity of the widely used plant Aegle marmelos in rats. Alcoholic, total aqueous, whole aqueous and methanolic extracts isolated from the leaves of Aegle marmelos have been studied for their possible toxic effects. Based on the results of the acute toxicity studies, it was concluded that a dose of 1000 mg/kg body wt of all the extracts of Aegle marmelos given interperitoneally appeared to be non-toxic. The dose of 1000 mg/kg body wt for acute intraperitoneal toxicity is generally considered to be very high and the LD50 values of all the Aegle marmelos extracts showed a broad therapeutic window and high therapeutic index value. Thus Aegle marmelos leaf extracts have a high margin of safety (Veerappan et al., 2007).

Anti-diabetic activity of leaf and callus extracts of Aegle marmelos (the bael tree) has been reported in streptozotocin induced diabetic rabbits. The present study was undertaken to find the extent to which calluses obtained from leaf explant of Aegle marmelos has a potential for application in diabetes management compared to the ordinary plant material. Treatment using extracts from both leaf and callus produced
significant decreases in blood sugar level in diabetic rabbits. Among the various extracts, the methanol extracts of the leaf and callus brought about the maximum anti-diabetic effect. The study revealed that the *in vitro* callus culture of *Aegle marmelos* has as much potential in diabetes management as the original leaf extract (Sevugan *et al.*, 2008).

The extracts of the stem bark of *Alstonia boonei*, an important antimalarial herb, was formulated into tablet dosage form. Tablets were formulated using direct compression and wet granulation methods. The mechanical properties of the tablets were assessed using crushing strength and friability and the crushing strength: friability ratio (CSFR) while drug release properties were evaluated using disintegration and dissolution times. There were statistically significant (*p*<0.01) differences in the CSFR values and drug release properties of A. boonei tablets prepared by both methods (Majekodunmi *et al.*, 2008).

*In-vitro* anti-fertility activity of *Aegle marmelos* on human sperm motility was investigated. In this study, various concentrations of the ethanol extracts of leaves of *Aegle marmelos* were evaluated for their *in-vitro* effect on sperm motility. It was found that the extracts had a considerable effect on the motility of sperm (Remya *et al.*, 2009).

Immunomodulatory action of methanolic extract of *Aegle marmelos* fruit (FEAM) was investigated in experimental model of immunity. It was concluded that FEAM possesses potential for augmenting immune activity by cellular and humoral mediated mechanisms more at low dose (100 mg/kg) than high dose (500 mg/kg) (Phatru *et al.*, 2010).

Antioxidant activity, quantitative estimation of phenols and flavonoids in different parts of *Aegle marmelos* were evaluated. The effectiveness of radical scavenging activity
of leaves extract was about 10 times greater than reference antioxidant butylated hydroxy toluene (BHT). The greater amount of phenolic compounds leads to more powerful radical scavenging effect as shown by methanolic extract of *Aegle marmelos* leaves (Nadeem *et al.*, 2010).

Formulation and evaluation of herbal tablets containing *ipomoeadigitata linn.* extract have been studied. A solid pharmaceutical dosage formulation using a novel dry plant extract (tuberous roots) using various excipients viz., carbopol, ethylcellulose, MCC, dibasic calcium phosphate and PEG-4000 by direct compression method, the compressed tablets were evaluated for the weight variation, friability, hardness and disintegration time. Then, it was reported that the formulation has shown statically significant anti-diabetic activity (Margret Chandira *et al.*, 2010).

The extract of the stem bark of *G. parvifolia* as tablet dosage form was performed by use of formulation using dry and wet methods and compared in respect to characteristics like hardness test, weight uniformity test, friability test, disintegration time and dissolution test and other properties. Results showed that it is better to use wet method for granulation to produce ideal tablet dosage form (Faizatun *et al.*, 2010).
Table no: 3  Plants investigated for its antioxidant activity

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Plant name</th>
<th>Family</th>
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