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1. DISEASE REVIEW

The gastro-intestinal tract has single contiguous layer of cells from lower esophageal sphincter to the anus that separate the inside of the body from the external environment. Separation is important, as there are wide varieties of environmental agents in the lumen of the bowel that can initiate or perpetuate mucosal inflammation if they cross the epithelial barrier. This simple maneuver of bypassing the epithelial barrier and placing luminal compounds directly into colonic wall initiated inflammatory diseases. The concept emerges that by simply abrogating epithelial barrier function, inflammatory disease can be induced in a susceptible host with features that are expressed both locally and systemically (Arrieta et al., 2006).

The delicate epithelial barrier is threatened by the effect of acid, bile salts, hydrolytic enzymes that are used for the digestion and microbial attachment and invasion. The potential for cumulative damage may explain why the epithelium is rapidly and continuously replaced throughout life (Bevins et al., 1999). The mucosa layer provided by the epithelial cells is postulated as "First line of defense" against mucosal injury. This layer of mucous along with the "Second line of defense", a healthy epithelial cells themselves, has been thought to play significant role in defense of the mucosa against injury and ulceration. The mucosa producing epithelial cell lining the gastric pits and surface of the mucosa are believed to supply mucous quite rapidly to produce a coat protecting the cells against injury (Lipkin M, 1971).

1.1. Gastric ulcer

The stomach has pivotal role in the digestive process, functioning both as reservoir and a mill by virtue of gastric glands secreting hydrochloride acid (HCl) and pepsin. Acidification of ingested food initiates the process of digestion by creating optimal condition for peptic digestion of proteins. Stimulation of gastric acid secretion during digestion involves cephalic, gastric and intestinal phase, which overlap in time and are modulated by complex neural and humoral interplay. Mucosal gastric glands produce gastric juice, the parietal cell being the predominant type having the ability to secret HCl. The other important type of cell is chief cell, which secret pepsinogen,
which is activated in to pepsin in the acidic medium of gastric juice, while the third cell, the mucous cells secret mucin. Both acid and pepsin have a proteolytic action on living tissues and are capable of auto digestion of gastro duodenal mucosa. However mucosal defense is incredibly efficient and can be effectively counter normal mechanical, chemical and thermal insults. The mechanism involved in mucosal protection and repair appears to be closely interrelated (Goel and Bhattacharya, 1991).

Gastric acid hyper secretion and gastro duodenal or gastro esophageal ulcers, due to stress are very common human sufferings today in the world of globalization. The pathophysiology of acid gastric diseases is attributed to the imbalance between aggressive factors (like acid, pepsin and *Helicobacter pylori* infection) and defensive factors (like secretion of mucous, bicarbonate and prostaglandin) (Jain *et al.*, 2007). Hyper secretion of acid is pathological condition, which occurs due to uncontrolled secretion of HCl from the parietal cells of the gastric mucosa through the H⁺-K⁺ ATPase proton pump. Hyper secretion of acid aggravates the gastro-duodenal ulcers by loss of gastro protection by various factors (Bandyopadhyay *et al.*, 2004). Calcium influx also seems to be playing an essential role in the stimulation-secretion coupling in mammalian oxyntic cells and has been considered as a serious contender for the development of various types of ulcers. Calcium channel blockers reported to inhibit the influx of calcium and also inhibited the histamine, gastrin, carbachol and cAMP induced stimulation of gastric acid secretion (Jain *et al.*, 1994).

*Helicobacter pylori* infection is the most common cause of peptic ulcer proved by isolation of *H. pylori* from stomach of patients with gastritis and peptic ulcer (Marshal and Warren, 1983). The protection afforded by the pre-epithelial, epithelial and sub-epithelial mechanism of the mucosa against aggressive factors assaults was termed as cytoprotection and its breakdown was envisaged as the major cause of peptic ulceration. However for optimum efficiency they require requisite nutritional support thus change in accustomed diet may also be contributory factor in the etiology of peptic ulcer (Goel and Bhattacharya, 1991). Gastric ulceration observed, after short term and long term administration of non steroidal anti-inflammatory drugs such as indomethacin, aspirin, paracetamol etc., in human and laboratory animals may be due to the deficiency of prostaglandin from the gastric mucosa resulting in to mucosal ulceration (Tanaka *et al.*, 2002).
Dopamine is present in large concentration in the gastro-intestinal mucosa, especially in the enterochromaffin like cells of gastric mucosa and gastric juice. It has been proposed that dopamine imbalance is one of the several factors that may contribute to the pathogenesis of gastric and duodenal ulcers (Desai et al., 1996).

The putative factors, which form counter part of the gastro-duodenal mucosal protective system and the drugs, which augment them are likely to be effective in peptic ulceration.

1.2. **Intestinal damage**

Epithelial lining of the intestine plays critical role to separate inside of the body from the external environment. It is not only play role as barrier function but also secret important product such as immunoglobulin, mucous, digestive enzymes, defensins and other antimicrobial products. Epithelial barrier is formed by the rigid lipid bilayer of the enterocyte brush border. In most of the cell membranes, this structure has appreciably solubility of lipid compounds but offer strong barrier to water soluble constituents. The enterocytes balance its dual function as both, an absorptive and barrier cell by embedding transport system with in this membrane for the water soluble compounds. The functional state of epithelial tight junction can be assessed by measuring the rate of movement of probes across the junction (Arrieta et al., 2006).

Epithelium is rapidly and continuously replaced through out life for epithelial renewal, stem cell proliferation and differentiation for normal functions of gastrointestinal tract. Proliferation of small intestinal epithelial cells occurs in the crypt cells. Crypt cells which rapidly regenerate and migrate to the villus tip lead to replacement of intestinal epithelium is completed with in 2 days in rats and 3 days in human (Bevins et al., 1999; Yuncu et al., 2004). The epithelial layer is structurally supported by the lamina propria, which contains blood vessels and nerves. The highly folded lamina propria forms finger and leaf shaped villi, which significantly enlarge the surface area of the small intestine. The area is further expanded by the apical brush border membrane of the enterocytes, which contains densely packed microvilli (Asperen et al., 1998). The brush border membrane lining enterocytes are highly specialized to perform varieties of function. It is involved in the digestion and
absorption of nutrients and thus play crucial role in the maintenance of the human health. The digestive enzymes such as lactase, sucrase, alkaline phosphatase, γ-glutamyl transpeptidase are located at the microvillus surface of the enterocytes where they mainly involved in the digestion and absorption. Impairment of these enzymes located at brush border membrane lead to nutritional alteration in the human body (Bhalla et al., 2004).

It has been recognized that non-steroidal anti-inflammatory drugs (NSAID) can damage not only the upper gut (stomach and duodenum) but also lower segment of the gastro-intestinal tract (Hawkey CJ, 2000). Methotrexate (MTX) is widely used as chemotherapeutic agents for the treatment of many cancers and also used as an anti-inflammatory and immunosuppressive agent. The malabsorption arising from anti-tumour drugs such as methotrexate may be due to damage to crypt cells and histological changes such as shortening of the structure of micro-villi. Methotrexate (MTX) and its breakdown products inhibit several enzymes in the metabolic pathway of folic acid. Cytotoxic and anti-proliferative effect of high dose of MTX is ascribed to inhibition of DNA, RNA and protein synthesis. Long-term low dose of MTX may lead to accumulation of adenosines, a lymphotoxic, immunosuppressive and anti-inflammatory autacoids (Tsurui et al., 1990; Rampton, 2001). One of the major side effects reported with the methotrexate therapy inhibition of intestinal epithelial proliferation and induction of apoptosis in the small intestine crypts (Taminiau et al., 1980). The side effects manifested as poor nutrient absorption due to decreased surface area, nausea, diarrhoea, stomatitis, gastro-intestinal ulceration and mucotitis. In addition, MTX depresses absorption of certain drugs, metabolic activity and active transport capacity of the intestinal mucosa. It also inhibits the small intestinal brush border membrane composition such as protein and lipid and change the physical structure of brush border membrane (Yamamoto et al., 1997).

1.3. Inflammatory bowel diseases (IBD)

The term inflammatory bowel diseases commonly used to describe the two idiopathic bowel diseases having many similarities but conditions usually have distinctive morphological appearance. These are,

1. Crohn’s disease
2. Ulcerative colitis
Inflammatory bowel disease is a common and chronic gastro-intestinal disorder characterized by intestinal inflammation and mucosal tissue damage initiated and perpetuated by deregulation immune response along with several intra and extra intestinal manifestation including environmental, genetic and auto immune phenomena (Jurjus et al., 2004). The IBD primarily affect the ileum or colon that is characterized by abnormal intestinal permeability. Ulcerative colitis is diffuse mucosal and sub mucosal disease involving only the colon while crohn’s disease is a chronic transmural disease causing inflammation in the segment of terminal ileum and/or colon or any segment of alimentary tract and characterized by pain and diarrhoea (Jagtap et al., 2004).

The gut inflammation in patients of IBD is associated with intestinal muscle dysfunction and increased mass of muscle cells and collagen in the intestinal wall (Meerveld et al., 2001). The involved regions of gut often exhibit an intense filtration of leucocytes (including granulocytes and lymphocytes), crypt cell hyperplasia and intestinal oedema. Prolonged or inadequate activation of the intestinal immune system plays an important role in the pathophysiology of chronic mucosal inflammation. Furthermore the extensive gut inflammation and tissue injury accompanying by infiltration of neutrophils, macrophages, lymphocytes and mast cells ultimately giving rise to mucosal disruption and ulceration (Fiocchi et al., 1998).

Infiltrated and activated neutrophils represent an important source of reactive oxygen and nitrogen species. These species are cytotoxic agents, including cellular oxidative stress by cross linking proteins, lipids and nucleic acid causing cellular dysfunction and damage (Holma et al., 2001). In addition to free radicals, neutrophils also release proteases and lipid mediators that can contribute to intestinal injury. Macrophages produce certain cytokines such as tumour necrosis factor (TNF-α) and interleukin-1 β and level of such cytokines are often increased in both animal models and patients with ulcerative colitis (Mustafa et al., 2006). In addition to cytokines, leucotrienes, thromboxane, platelet activating factors, nitric oxide are also released from the activated mucosal cells (Hagar et al., 2007).

Clinical features of ulcerative colitis are characterized by episode of diarrhoea with the passage of blood (rectal bleeding), malaise, anorexia, weight loss and chronic
relapsing course with abdominal pain. Macroscopic features show ulcer in sigmoid colon and rectum, mucosal granulomatous, swollen and hyperplasic mucosa, extensive muco-purulent discharge and hemorrhages. Microscopy shows mucosal injury in primary stage, congested and densely in-filtration of leucocytes in active stage, crypt abscesses and herniation of inflamed mucosa through the lamina muscularis mucosa in sever case.

1.4. Oxidants, antioxidants and gastro-intestinal tract

Recent evidences suggested that reactive oxygen species or pro-oxidants or oxidative stress is implicated in the etiopathogenesis of gastro-intestinal disorders. The chemical compounds and reactions capable of generating toxic reactive oxygen species/free radicals are referred as pro-oxidants. On the other end, compounds and reactions disposing or scavenging off this species, suppressing there formation and opposing there deleterious actions are called as anti-oxidants in normal cells. There is a balance between pro-oxidants and anti-oxidants, however, this balance shifted towards pro-oxidants when there is generation of free radicals or oxidative stress, which result in to serious cell damage (Peterhans, 1997; Repetto and Llesuy, 2002).

Free radicals defined as chemical species possessing an unpaired electron, which is formed by homolytic cleavages of a covalent bond of a molecule, by the loss of a single electron from a normal molecule or by the addition of a single electron to a normal molecule. This species may be either oxygen derived (ROS, reactive oxygen species) or Nitrogen derived (RNS, reactive nitrogen species). The five possible reactive oxygen metabolites species (ROMs) are; super-oxide anion (O2' ), Hydroperoxyl radical (HO2·), peroxy ion (HO2'), hydrogen peroxide (H2O2) and hydroxyl radical (OH).

Superoxide dismutase reduces O2' and H2O2 by its catalytic activity, while other anti-oxidative enzymes glutathione peroxidase and catalase convert H2O2 into H2O. However accumulation of O2 and H2O2 results in to formation of most reactive species OH in the presence of metal catalyst such as Cu+/Fe+, which oxidize lipids giving rise to lipid peroxidation (Green and Hill, 1984; Halliwell and Gutteridge, 1990; Chessman and Slater, 1993). Similarly, nitrogen derived oxygen species are mainly nitric oxide (NO), peroxy nitrite, nitrogen dioxide and dinitrogen trioxide.
The oxidant/free radicals are species with very short life, high reactivity and damaging activity towards macromolecules like proteins, DNA and lipids (Irshad and Chaudhary, 2002)

1.4.1. Oxidants and free radicals species

1.4.1.1. Super oxide anion (O$_2^-$)

Super oxide is the first reduction product of O$_2$. In aqueous solution, at neutral or slightly acidic pH, O$_2^-$ is relatively non reactive species and dismutase to H$_2$O$_2$. This reaction occurs spontaneously or it is catalyzed by intra cellular enzyme superoxide dismutase. The most important source of superoxide anion is oxidative enzyme, among which xanthine oxidase and NADPH/NADH oxidase are the most effective sources (Cross and Jones, 1991). The anion radical regulates metabolites capable of signaling and communicating important information to the cellular genetic machinery (McCord et al., 2000). Over production of O$_2^-$ take place in various chronic inflammatory diseases such as inflammatory bowel diseases (Villegas et al., 2001; Paola et al., 2005), induced by xenobiotic such as methotrexate, nonsteroidal anti-inflammatory drug such as aspirin, toxins, stress, tissue injury etc., (Parks, 1989; Peterhans, 1997; Bafna and Balaraman, 2005).

1.4.1.2. Hydrogen peroxide (H$_2$O$_2$)

Hydrogen peroxide is the most stable, least reactive and the most readily detected non radical oxygen species. H$_2$O$_2$ is the primary product of the reduction of O$_2^-$ by numerous oxidase localized in peroxisome (Oshino et al., 1973). H$_2$O$_2$ and peroxides like H$_2$O$_2$ are very sensitive to decomposition by the species that react with it and the reaction is catalyzed by redox active metal complexes. It is also involved in the generation of free radicals in the presence of transitional metal ion. H$_2$O$_2$ readily cross the cell membrane and attack different sites by converting into hydroxyl radical. The H$_2$O$_2$ is also indicated as the most effective species for cellular injury (Irshad and Chaudhary, 2002). The H$_2$O$_2$ is also considered as the primary source of mucosal injury in gastro-intestinal tract (Itoh and Guth, 1985) and involved as mediators of experimental and human IBD (Grisham, 1993).
1.4.1.3. Hydroxyl radical (OH)

Hydroxyl radical is highly reactive ROS. It can react with practically any molecule present in the cell. For this reason, it is short lived and due to unstability it does not diffuse through the cell. Hydroxyl radical produced by reaction of H$_2$O$_2$ and super oxide anion (Chessman et al., 1993) and lipid is very susceptible to OH attack and initiate lipid peroxidation. Amongst all the reactive oxygen species especially, hydroxyl radicals play a major role causing oxidative damage to mucosa in all most all type of ulcers (Bandyopathyay et al., 2002). Hydroxyl radical reported to mediate intestinal damage including inflammatory bowel disease (Grisham, 1993). The intestine is also well endowed with enzymes capable of producing such free radicals (Parks, 1989).

1.4.1.4. Malondialdehyde (MDA)

Malondialdehyde is the major reactive aldehyde resulting from the peroxidation of biological membrane polyunsaturated fatty acids. MDA is a secondary product of the lipid peroxidation and is used as an indicator of tissue damage by a series of chain reactions and important cause of destruction and damage to the cell membrane (Ohkawa et al., 1979). Available evidence suggests that stress significantly induced lipid peroxidation due to generation of ROS (Sairam et al., 2002). Increase in LPO level was observed in experimental ulcerative colitis which initiate vicious cycle that generate more and more ROMs resulted in to exhausted cellular antioxidants and favour the consequences for the development of inflammation (Paiva et al., 2004). It is also observed that LPO contributes to the development of methotrexate mediated tissue damage (Sener et al., 2006).

1.4.1.5. Nitric oxide (NO)

Nitric oxide and its derivatives produced in the inflamed tissue contribute to GI tract disorders. In the gastro-intestinal tract, NO can be either protective or deleterious in different disorders dependent on what type of NO synthase is responsible for pathological conditions. Constitutive NO (cNOS) is responsible for the production of NO in physiological and inducible NO (iNOS) in pathophysiological conditions. cNOS is cytoprotective by directly acting as an inducer of an defense response in the GI tract, while iNOS as an important inflammatory mediator and may contribute significantly in many GI tract disorders. More specifically, NO production
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has been shown to be increased in ulcerative colitis, crohn’s disease, toxic mega colon and diverticulitis. NO could react with peroxide anion to form more poisonous nitrite anion, which can disturb the function of inflammatory cells and further impair the colonic mucosa (Cho et al., 2001; Paola et al., 2005; Hagar et al., 2007).

1.4.1.6. Xanthine Oxidase (XO)

The xanthine oxidoreductase (XOR) system which consists of xanthine dehydrogenase and xanthine oxidase (XO) is the major biological sources of reactive oxygen species. The XOR system is predominately present as XDH in normal tissue and converted into free radical generating XO form in damaged tissue (Kale, 2003) and the rate of conversion in rat small intestine is the most rapid of all tissue studied in GI tract. It is postulated that xanthine oxidase would be capable of extensive damage to vascular endothelium and responsible for multiple tissue dysfunctions (Parks, 1989).

1.4.1.7. Myeloperoxidase (MPO)

Neutrophils contain high concentration of myeloperoxidase and its activity considered as biochemical marker of neutrophils infiltration in the inflammed gastrointestinal tissues (Krawisz et al., 1984; Mustafa et al., 2006). Neutrophils recruited in the tissue by local production of cytokines and can then contribute to tissue destruction by the production of reactive oxygen metabolites, granular enzymes and cytokines that further amplify the inflammatory response by their effect on macrophages and lymphocytes (Paola et al., 2005). Evidence suggests that myeloperoxidase level increase in intestine contributes to methotrexate induced oxidative organ injury (Sener et al., 2006). MPO level is also reported to be increased in acetic acid induced model of experimental colitis (Gonzalez et al., 1999; Medina et al., 2004; El-Medany et al., 2005).

1.4.2. Antioxidants

To counteract the harmful effect of ROS and RNS, antioxidant defense mechanisms operate to detoxify or scavenges these ROS and RNS. The antioxidant system comprises different types of functional components classified as first line, second line or third line of defenses. The first line of defense comprises preventive
antioxidants that act by quenching superoxide anions, conversion of $\text{H}_2\text{O}_2$ and sequestration of metal ions. The antioxidants belonging to this category are:

1.4.2.1. Superoxide dismutase (SOD)

SOD is most important enzyme found virtually in all aerobic organisms and act by quenching of superoxide anions which is active oxygen radical produced in different aerobic metabolism with subsequent oxidative stress. SOD is stress protein synthesized in response to oxidative stress. It also protect cell from damage caused by hydroxyl radicals generated by $\text{H}_2\text{O}_2$ decomposition by metal catalyst (Irshad and Chaudhary, 2002; Ray and Hussain, 2002). Superoxide anions produced in various models of gastric ulcers in rats catalyzed by dismutase by superoxide dismutase and provide protection to gastric mucosa (Tondon et al., 2004; Bafna and Balaraman, 2005). Available studies show that administration of superoxide dismutase mimetic agents may be beneficial for treatment of inflammatory bowel diseases (Cuzzocrea et al., 2001).

1.4.2.2. Glutathione peroxidase (GPx)

Glutathione peroxidase enzyme is well known first line defense against oxidative stress, which in turn requires glutathione as cofactor. GPx is selenium containing enzyme catalyses the oxidation of GSH to GSSG. This oxidation reaction occurs at the expense of $\text{H}_2\text{O}_2$ to water and oxygen. It also catalyzes the lipid hydroperoxide to water using reduced glutathione as substrate (Irshad and Chaudhary, 2002). It was observed that glutathione peroxidase level in gastric mucosa significantly decreased in ulcerated rats (Anandan et al., 1999).

1.4.2.3. Catalase

Catalase is tetrameric enzyme, present in most of the cells and act by catalyzing the decomposition of $\text{H}_2\text{O}_2$ to water and oxygen. It is localized mainly in the mitochondria and in sub cellular respiratory organelles (Pryor, 1986). Superoxide dismutase converts the reactive oxygen to $\text{H}_2\text{O}_2$, which if not scavenged by the catalase can by itself cause lipid peroxidation by increase in the generation of hydroxyl radical (Das et al., 1997). Therefore, ulcer protective effect, colitis protective activity could be best achieved by change in catalase and superoxide dismutase activity (Cuzzocrea et al., 2001; Sairam et al., 2002).
1.4.2.4. Glutathione (GSH)

Glutathione is an important constituent of intracellular protective mechanisms against a number of noxious stimuli, including oxidative stress. Additionally, GSH scavenges superoxide anion and protect protein thiol groups from oxidation. The GSH redox cycle catalyzed by the endogenous antioxidative enzymes such as glutathione peroxidase which reduces \( \text{H}_2\text{O}_2 \) and thus breaking chain reaction that leading from \( \text{O}^{-} \) to the highly reactive \( \text{OH} \) (Villegas et al., 2001). Previous report suggested significant reduction in the level of glutathione level in acetic acid induced experimental colitis (Millar et al., 1996; Sido et al., 1998) observed due to liberation of oxygen derived free radicals. The observed anti-gastric ulcer activity of *Emblica officinalis* has been attributed significant protection to glutathione level of gastric mucosa (Rajeshkumar et al., 2001).

The other antioxidants belonging to second line defense include vitamin A, vitamin C, vitamin E, uric acid, flavanoids and ubiquinol. The third lines of defense antioxidants are complex group of enzymes for repair of DNA, damaged protein, oxidized lipid and peroxides. These enzymes repair the damage to the biomolecules and reconstitute the damaged cell membranes. These enzymes are lipase, protease, DNA repair enzymes etc (Irashad and Chaudhary, 2002). Hence, drugs with multiple mechanism of protective action including antioxidants properties may be one way forward in minimizing tissue injury in various gastro-intestinal disorders.

1.5. The concept of Amlapitta and Grahani disease according to Ayurveda

Substances with bitter taste, cause burning sensation and which vitiate the pitta dosa, stress, alcoholic drinks and over eating resulted in to amlapitta (hyperacidity). It is manifested by fatigue without work, throat and heart burning sensation, dyspepsia and vomiting sensation (Sastri and Sastri, 1973).

According to Charaka, one of the three great triumvirates of Ayurveda, grahani (duodenum and upper part of intestine) is the vital organ situated above the umbilical region and in between Amasaya (stomach) and Pakvasaya (colon). It is considered as main seat of agni (enzymes responsible for digestion and metabolism) and is supported and nourished by the strength of agni. It plays an important role as to receive food and retain for proper digestion. Normally, it restrain the down ward
movement of undigested food and after digestion, it release the food through the sides of its lumen. The disease Grahani (malfunctioning of duodenum and upper part of intestine) is the leading digestive system disorder due to malfunction of agni (impairment of enzymes responsible for digestion and metabolism).

The impairment of agni is responsible for cause of vidaha of food (a part of which is digested and other part without digestion). The digested food and undigested food moves downward and this condition is called as grahani-gada (sprue syndrome). The symptoms of grahani disease are manifested by morbid thirst, feeling of laziness, diminution of strength, burning sensation, delay in digestion of food cause heaviness of body and hyper motility of the gut, resulting in frequent evacuation of the bowel (Sharma and Das, 1997).

1.6. Animal models for evaluating the drugs for gastro-intestinal cytoprotective activity

1.6.1. Animal models for Gastric ulcer

1.6.1.1. Pyloric ligation plus aspirin- induced gastric ulcer in rats

Aspirin suspension in 1% CMC in water administered in a dose of 200 mg/kg, orally once daily for three days (Jam et al., 1994). On third day, one hour after aspirin administration pylorus was ligated as per the method of Shay et al. (1945). After six hours the gastric wall showed ulcer with significant reduction in mucous content and mucin activity. Drugs which strengthening mucosal barrier or mucosal resistant factors significantly prevent the gastric mucosal damage in pyloric plus aspirin induced ulcer.

1.6.1.2. Stress-induced ulcer in rats

Gastro-intestinal erosion is one of the consistent finding in human and experimental animals subjected to different types of stress. Stress cause significant alteration in the anti-oxidant status followed by generation of free radicals, which play important role in stress induced ulcer.
a. **Water immersion induced ulcer**

The fasted rats were immersed to the level of xiphoid process in glass jar filled with water for 14 h at 25 ± 2 °C. The raised level of acid secretion and free radical generation may be important in aggravating process of gastric lesion during water immersion (Parmar and Jagruti, 1993).

b. **Cold and restrain ulcer**

The rats are immobilized in a stress cage and forced to remain in a cold room (4-6 °C) for 3 hours. The observed ulcer due to stress is both due to physiological and psychological factors (Parmar and Jagruti, 1993; Sairam et al., 2002).

1.6.1.3. **Ethanol- induced gastric mucosal damage**

Acute gastric ulceration induced by administration of absolute ethanol in dose of 5 ml/kg intra-gastrically to rats (Robert, 1979). Absolute ethanol induced lesion appears as blackish lesions grouped in patches of varying size, usually parallel to the major axis of the stomach.

1.6.1.4. **Acetic acid- induced chronic gastric ulcer in rats**

Chronicity of the experimental acetic-acid ulcer model in the rats uniquely resembles to the human peptic ulcer. 0.05 ml of 100 % acetic acid applied on the serosal surface of the stomach topically, using cylindrical mould for 60 s exposure followed by rinsing the acid with normal saline. It has been reported that back diffusion of HCl and increased capillary permeability induced by acetic acid was mainly due to release of histamine (Goswami et al., 1998).

1.6.2. **Animal models for Intestinal damage**

1. **Intestinal damage caused by anti-tumour drugs**

Anti-tumour drugs such as methotrexate (MTX), 5-flurouracil and cyclophosphamid are well known to cause serious damage of small intestinal, leading to malabsorption and diarrhoea (Horie et al., 1998).

a. **Methotrexate induced- small intestinal damage in rats**

Oral administration of methotrexate in dose of 10 mg/kg in saline for 3 days leads to impairment of intestinal constituents. MTX treatment caused decrease in the
protein and lipid content in the rat small intestinal homogenate as well as in the brush border preparation of the intestine (Tsurui et al., 1990). In other study oral administration of methotrexate in dose of 15 mg/kg for 4-5 days leads to increased permeation of non absorbable dye such as phenol red and fluorescence isothiocyanate dextran through intestine which showed that MTX treatment alter the intestinal permeability in rats (Nakamaru et al., 1998).

b. Intestinal basolateral membranes damage by CMF in rats

Rats injected with CMF (cyclophosphamide 10 mg, MTX 1 mg and 5-flourouracil 10 mg/kg) on day first and day 8 for six cycles intravenously with 14 days gap between each cycles showed increase in lipid peroxidation and damage of membrane structure associated with decreased basolateral ATPase activity. The metabolites of cyclophosphamide binds to the thiol group and reduce the level of glutathione and reduced glutathione. The CMF treatment also showed drastic change in membrane fluidity (Subramaniam et al., 1995).

2. Intestinal lesion caused by meloxicam and piroxicam in rats

Meloxicam is cyclooxygenase-2 inhibitor and piroxicam is cyclooxygenase-1 inhibitor nonsteroidal anti-inflammatory drugs (NSAID). Administration of meloxicam (7.5 mg or 15 mg/kg) and piroxicam (10 or 20 mg/kg) and again refed at 24 h cause intestinal lesion in rats. Several factors are likely to be involved in the intestinal lesion induced by NSAID. It has been emphasized that kinetic factors are important in the intestinal toxicity of these compounds and enterohepatic recirculation of NSAID promotes lesion formation in the small intestine of experimental animals (Villegas et al., 2001). Neutrophils appear to be main effector cells and the microbial invasion of mucosa may provide neutrophils chemo traction. These agents provoke a burst of reactive radical species generation.

1.6.3. Animal models for ulcerative colitis

1.6.3.1. Acetic acid- induced colitis

Epithelial or mucosal necrosis can be induced by luminal instillation of dilute acetic acid. In original description of the model, 0.5 ml of 10-50 % of acetic acid diluted with water was instilled in to rectum of Sprague-Dawley rats and after 10
second of surface contact the acidic solution was withdrawn and lumen flushed with three times with saline (MacPherson et al., 1978). In a later modification 1 ml of 4 % acetic acid was slowly infused 5 cm into the rectal lumen of a lightly anaesthetized rat. After 30 second of exposure, excess fluid was withdrawn and lumen flushed with phosphate buffer (Yamada et al., 1991). Many further modifications introduced and most subsequent studies have used 2 ml of 4 % acetic acid was slowly infused 8 cm into the rectal lumen for 10 s exposure because higher concentration and long exposure cause perforation (Galvez et al., 1997; Paiva et al., 2004). Acetic acid induced colitis is an easily inducible model of colitis and the similarities of the inflammatory mediators profile to colitis suggest that inflammatory phase resembles to acute human intestinal inflammation (Elson et al., 1995).

1.6.3.2. Trinitrobenzene sulfonic acid (TNBS)- induced colitis

Colitis would occur in mice or rats by treatment with TNBS enema after destruction of mucosal barrier with an ethanol enema. It was shown that 10 mg of TNBS in 0.25 ml of 50 % ethanol developed the ulcerative colitis in rats after 48 h (Galvez et al., 2006). In another method, 25 mg/rat in 0.8 ml of 50 % alcohol developed colitis in rats (Cozzocrea et al., 2001). Granulomas with infiltration of inflammatory cells were seen in the intestine of this model.

1.6.3.3. Indomethacin- induced enterocolitis

It was shown that indomethacin induces small intestinal and colonic ulceration in a dose dependent fashion in rodents. Epithelial damage is mediated by inhibition of synthesis of protective prostaglandins (Elson et al., 1995). It was observed that colitis was developed by injecting 7.5 mg/kg, sc on two consecutive days in rats (Jagtap et al., 2004).

1.6.3.4. Dextran sodium sulphate (DSS)- induced colitis

3.5 % of DSS (30-40 KDa molecular weight) dissolved in sterile water and mice were allowed to drink water *ad libitum* for 11 days caused ulcerative colitis (Siegmund et al., 2001). In another study, 5 % DSS in drinking water for 7 days in rat developed the colitis, which resulted in to overt inflammation in the mid distal rat colon that reminiscent of human IBD (Singh et al., 2004). DSS induced colitis
showed infiltration of inflammatory cells specially neutrophils, shortening of colon and significant reduction in prostaglandin-$E_2$.

1.6.3.5. Peptidoglycan-polysaccharides (PG-PS)-induced colitis

It is demonstrated that the nine intramural injection (subserosal) of the PG-PS made in to 5 cm segment of distal colon developed colitis manifested by significant increased myeloperoxidase activity and cytokines like IL-1β and TNF-α (Fitzpatrick et al., 2001).

2. CHURNA AND KWATH KALPANA REVIEW

In Ayurveda, great emphasis is given to obtain comprehensive knowledge on all aspects of drugs including identification, procurement, processing, preparation and application under a separate branch known as "Bhaishajya kalpana" (Pharmacy). Various types of basic preparations, conceptual background for their formulation has been dealt in great detail in Ayurvedic literature. The main aim is to provide highest quality drug preparations that are best suited for the treatment of a particular disease condition. Some of the important types of preparations used in Ayurvedic therapeutics are- churna (fine powder), kwath (filtered decoction), vati (tablets or pills), avaleha (extracts or electuary), asava or arista (medicated spirituous liquid) etc. Amongst this, churna and kwath are an important type of formulations. It forms a very large section in industries and in practice.

2.1. CHURNA

According to the ancient literature, Saranghadhara Samhita (Sarma and Tripathi, 1966), churna means nicely powdered dry drug that is filtered through a cloth. Rajaha or ksoda (powder) are synonyms explained for churna. According to Ayurvedic Formulary of India, churna is fine powder of single or mixture of two or more cleaned and dried drugs. The powder is fine of at least 80 mesh sieve. They retain potency for one year (Anonymous, 2003).

2.2. KWATH

Certain drugs or combination of drugs are made in to coarse powder (Javkut) and used for preparation of kasaya (decoction), hima (cold infusion), phanta (hot
infusion) etc., such powder called as kwath curma. Such preparation retains potency for one year (Anonymous, 2003). According to Saranghadhara Samhita (Sarma and Tripathi, 1966), one pala (48 g) of coarsely powdered drugs mix with 16 pala (768 g) of water. This mixture is to be boiled on low to medium heat up to 1/8th water remaining means two pala (96 g). Filter through cloth and used when it is warm.

Churna and kwath administered with different anupana according to disease condition. Anupan means vehicle taken along with drugs help to mix immediately in the stomach and fast assimilation of drugs result in to its better therapeutic effect. The types of materials used for anupana and in what quantity has been clearly mentioned in the classics. For example, jaggery is to be added to the powder, it should be taken in equal quantity and if sugar is to be taken, it should be taken in double quantity. Churna is administered with water or milk, then such liquid should be four times in proportion to churna in quantity. If kwath administered along with honey than quantity of honey should be 1/8th of the total dose of kwath in disease due to pitta dosa (Sarma and Tripathi, 1966).
3. DRUGS REVIEW

3.1. TRIPHALA CHURNA

Triphala is a traditional Ayurvedic herbal formulation, consisting of fine powder prepared by mixing equal proportion of dried pericarp of Haritaki (*Terminalia chebula* Retz.), Bibhitaka (*Terminalia belerica* (Gaertn) Roxb.) and Amalaki (*Emblica officinalis* Gaertn) fruits (Vaidya, 1968; Dwivedi, 1974; Murthy, 1998; Anonymous 2003). However, there are no clear cut guidelines with regards to the proportion of the three ingredients. Some use equal proportions and some authors prepare Triphala by mixing one parts of Haritaki, two parts of Bibhitaka and four parts of Amalaki (Sarma and Tripathi, 1966; Vaidya, 1968).

**Synonym:** Phalatrika, Vara

**Ayurvedic Properties**

<table>
<thead>
<tr>
<th>Rasa</th>
<th>Kasaya with other anu-rasa</th>
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<tr>
<td>Guna</td>
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<td>Madhura</td>
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<tr>
<td>Karma</td>
<td>Tridoshashamaka</td>
</tr>
</tbody>
</table>

**Pharmacological Review**

Triphala classified as an important medicine of the ‘Rasayana’ group and is believed to promote health, immunity and longevity and frequently used to treat chronic ulcer (Sandhya *et al.*, 2006a) and it is an antioxidant rich herbal formulation (Jeena *et al.*, 1995; Vaidya *et al.*, 1998).

The aqueous extract of Triphala is reported as anti-gastric ulcer and anti-peptic activity (Satyanarayanana *et al.*, 1994), to act as a good herbal radio protective agent against gamma radiation (Jageta *et al.*, 2002, Sandhya *et al.*, 2006b), to be cytotoxic to human breast cancer cell line and transplanted tumour in mice (Sandhya *et al.*, 2006a) and *in vitro* showed antioxidant activity against radiation induced strand break formation in plasmid DNA (pBR322) (Naik *et al.*, 2005).
The extracts of Triphala reported to exhibit antimutagenic activity (Kaur et al., 2002), reduce damage due to oxidative stress (Srikumar et al., 2006), to possess sustained anti-diabetic activity and to act as free radical scavengers (Sabu and Kuttan, 2002), cytotoxic and apoptotic agent against breast cancer cells and prostate cancer cells (Kaur et al., 2005) and in vitro to possess antibacterial activity against Salmonella typhia, Shigella dysenteriae, Vibrio cholerae, Staphylococcus aureus and Klebsiella aerogenes (Mehta et al., 1993).

The powder of Triphala reported as promising anti-inflammatory and anti-arthritic drug (Rasool and Sabina, 2007) and as potent and novel therapeutic agents for scavenging of nitric oxide (Jagetia et al., 2004), as a cardiotonic drug (Tariq et al., 1977) which is also prescribed for symptoms of inflammation, heat, infection, obesity, anaemia, fatigue, candida, poor digestion, assimilation, tuberculosis, pneumonia and AIDS (El-Mekkawey et al., 1995).

Clinical Studies

Triphala powder has been effective as laxative and used in management of hyperacidity and other gastric problems (Mukherjee et al., 2006) and to possess antibacterial activity against bacterial isolates from HIV infected patients (Srikumar et al., 2007). The decoction of Triphala is found to treat leucorrhea in women (Singh and Londhe, 1993). Triphala with Lauha bhasma and Glycercriza glabra showed significant increase in haemoglobin level in anaemic patients (Jha et al., 2006).

Therapeutic Uses

Triphala is traditionally been used as laxative in chronic constipation, colon cleansing, digestion problems and poor food assimilation. It also been used in cardiovascular diseases, high blood pressure, to reduce serum cholesterol, poor liver function, large intestine inflammation and ulcerative colitis (Anonymous, 1952; Mukherjee et al., 2006). In ancient text, it is classified as good rejuvenator, tonic, hair tonic, good for digestion, purgative, cure all diseases of eyes, heal ulcer, remove diseases of skin, fat, diabetes, blood and fever (Sarma and Tripathi, 1966; Murthy, 1998)
Formulations of Triphala used for hyperacidity according to Chakradatt (Tripathi, 1997) are,

3.1.1. **Chinnodbhavadi kwath:** Mix Triphala, stem of Guduchi (*Tinospora cordifolia* (Willd.) Miers.), stem bark of Neem (*Azadirachta indica* A. Juss.) and leaves of Patola (*Trichosanthes dioica* Roxb.) and prepare kwath. Cold kwath along with honey used for chronic hyperacidity.

3.1.2. **Triphala kalka:** New iron vessel pasted with the paste of Triphala and kept for one night. This paste along with honey and sugar candy used for hyperacidity.

3.1.3. **Phalatrikadi kwath:** Mix Triphala (Phalatnka), leaves of Patola and Katuki (*Picrorhiza kurroa* Royle ex Benth.) and prepare kwath. This kwath along with honey and sugar candy used for hyperacidity and fever.

3.1.4. **Chaturth patoladi kwath:** Mix Triphala, leaves of Patola and stem bark of Neem and prepare kwath. Cold kwath along with honey used for pain, burning sensation and other problems due to hyperacidity.

According to Carak Samhita (Sharma and Das, 1996):

1. Along with honey and ghee, if person can take one Harde after previous meal digested (means early morning), two Bibhutakas before meals and four Amlas after food for one year, then that person can live hundred years free from old ages and diseases.
2. New iron vessel should be pasted with the paste of Triphala and kept for 24 hours. This paste mix with honey and water and drink at morning for one year, then such person can live for hundred years free from old ages and diseases.

**Dose:** 3-6 g of the drug in powder form.

**Important formulations:**

Trihaladi Kwath, Trihaladi churna, Chinnodbhavadi kwath churna, Abhaya vatak, kansahartaki, Abhayavati, Triphaladi kshar, Phalanst, Phalatrikadyarst, Shiva guggulu, Triphaladi ghrita, Brahma rasayana
3.2. AMALAKI

The drugs consist of pericarp of dried mature fruits of *Emblica officinalis* Gaertn.

**Synonym:** *Phyllanthus emblica* Linn.

**Family:** Euphorbiaceae

**Vernacular names**

- Sanskrit: Amalaki, Dhatriphala, Amrithphala, Amalaka
- Assamese: Amlaku, Amlakhi, Amlakhu
- English: Emblic myrobalan
- Bengali: Amla, Dhatri
- Gujarati: Amla, Ambala
- Hindi: Amla, Aonla
- Kannad: Nellikai
- Malay: Nellikka
- Marathi: Amlaku, Amla, Ambal
- Telugu: Usrika, Usrikaya

**Habitat and Distribution**

Throughout tropical and subtropical India, found both in natural state in mixed deciduous forest of the country ascending to 1300 m. on hills; cultivated in gardens, home yards or grown as a road side tree. Mostly fruits are collected in winter season after ripening and in Kashmir in summer.

**Part Used:** Fruits, Seed, Bark and Leaves.

**Botanical Description**

3.2.1. Macroscopy profile

A small or medium sized, deciduous tree with smooth, greenish grey, exfoliating bark; Leaves sub sessile, closely set along the branchlets, dactichous, narrowly linear, obtuse, having appearance of pinnate leaves; Flowers greenish-yellow, in axillary fascicles on the leaf bearing branchlets, often naked portion below
the leaves with fibriate bracts at the base; Fruits fleshy, globose, with 6 obscure verticles furrows, pale yellow. Six seed trigonous.

Drug consists of curled pieces of pericarp of dried fruit occurring either as separated single segment or united as 3 or 4 segments; bulk colour grey to black, pieces showing a broad, highly shrivelled and wrinkled external surface with few whitish specks; texture rough, cartilaginous, tough; taste, sour and astringent.

3.2.2. Microscopy profile

Transverse section of fruit shows epicarp consisting tubular and polygonal in surface view; cuticle present; mesocarp cells tangentially elongated parechymatous and crushed, differentiated roughly into a peripheral 8 or 9 layers of tangentially elongated smaller cells, rest consisting of mostly isodiametric larger cells with walls showing irregular thickenings; ramified vascular elements occasionally present; stone cells present either isolated or in small groups towards endocarp, pitted vascular fibers, walls appearing serrated due to the pit canals leading into lumen.

3.2.3. Powder

Fine powder shows epidermis with uniformly thickened straight walled, isodiametric parenchyma cells with irregular thickened walls, occasionally short fibres and tracheids.

Ayurvedic Properties

- **Rasa**: Amla, Kasaya, Madhura, Tikta, Katu
- **Guna**: Ruksa, Laghu
- **Veerya**: Sita
- **Vipaka**: Madhura
- **Karma**: Tridoshashamaka, Rasayana, Vrasya, Caksusaya

Phytochemical Review

The fruit pulp contain moisture, protein, fat, mineral matter, crude fibre, carbohydrates, calcium, phosphorus, iron, nicotinic acid and probably the richest known natural source of vitamin C and pectin. The fruits, bark and leaves are rich in tannin; fruit contains two tannins, on hydrolysis one giving gallic acid, ellagic acid and glucose and the other giving ellagic acid and glucose. It also contains flavanoids
in different proportion, trigalloyl glucose, terchebine and corilagin (Rastogi and Mehrotra, 1990).

The other compound isolated as carotene and vitamin C by precipitation of tannin (Satyanarayana and Kadkol, 1963), phyllemblic acid and mucic acid (Rao and Siddiqui, 1964) and carbohydrates as a D-glucose, D-fructose and myo-inositol, pectin with D-galactoronic acid, D-arabinosyl, D-xylosyl, D-rhamnosyl, D-glucosyl, D-mannosyl and D-arabinosyl residues. (Khanna and Nag, 1972).

**Pharmacological Review**

Methanolic extract of *Emblica officinalis* reported to possess anti-ulcer and anti-secretory activity and also showed H⁺- K⁺-ATPase inhibitory activity in animal models (Mathew *et al*., 1995; Sairam *et al*., 2002). The extract also found effective for the reversal of dyslipidemia and intima media thickening and plaque formation in aorta in hypercholesterolaemic rabbits (Antony *et al*. 2006).

Ethanol extract of *Emblica officinalis* have been reported to possess antitussive activity (Nosal Ova *et al*., 2003), antisecretory, antiulcer and cytoprotective properties (Rajeshkumar *et al*., 2001; Al-Rehaily *et al*., 2002). The bioactive tannoid principles; an emblicanin-A and B and flavanoid from *Emblica officinalis* have been reported to exhibit antioxidant activity in rats (Bhattacharya *et al*., 2002; Anila and Vijayalakshmi, 2003). The flavonoids isolated from *Emblica officinalis* also exhibited highly potent hypolipidemic and hypoglycemic activities (Anila and Vijayalakshmi, 2000).

Aqueous extract of *Emblica officinalis* has been reported as antihepatocarcinogenic and hepatoprotective against CCL₄ damaged liver in rats (Jeena *et al*. 1999; Jeena *et al*., 2000) and cytotoxic to L-929 cells in culture and found to reduce ascites and solid tumours in mice indicated antitumour activity of extract (Jeena *et al*., 2001).

The extracts of *Emblica officinalis* also reported to exhibit potent antipyretic activity (Perianayagama *et al*., 2004), anti-inflammatory and antiarthritic activity (Ganju *et al*., 2004), potentiate adrenergic function thereby enabling body to recover
from stress (Rege et al., 1999), immunomodulatory activity (Sai Ram et al., 2002), radioprotective activity against sublethal gamma radiation (Singh et al., 2005) and ameliorate the deleterious effect of butter fat and beef fat in rats (Augusti et al., 2001). The churna has been proved to be useful remedy for management of alzheimer’s diseases (Vasudevan and Parle, 2007).

**Therapeutic Uses**

Used as Rasayana (Rejuvenatives), anti-diabetic and also used in blood disorders, burning sensation, acid gastritis, eye diseases, anaemia and gastric disorders.

**Dose:** 3-6 g of the drug in powder form.

**Important Formulations:**

Triphala churna, Chinnodbhavadi kwath churna, Chyavanprash, Dhatrilauha, Amalaki rasayana, Amlakyavaleha, Phalarishta.

### 3.3. BIBHITAKA

Drug consists of pericarp of dried ripe fruits of *Terminalia belerica* (Gaertn) Roxb.

**Synonym:** *Terminalia punetata* Roxb and *Myrobalanus belerica* B. Gaertn.

**Family:** Combretaceae

**Vernacular names**

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<td>Punjabi</td>
<td>Bahera, Balela, Bayrah</td>
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</table>
Habitat and Distribution:

The plant is common throughout India in the plain and lower hills chiefly in the deciduous forests, at 900 m elevation where the climate is not very dry.

Part Used: Fruit, Seed and Bark.

Botanical Description:

3.3.1. Macroscopy profile

A handsome tree with characteristic bark attaining a height up to 40 m, found in deciduous forests. Stems straight, frequently buttressed when large; Leaves petiolate, broadly elliptic, clustered towards the ends of branches; Flowers greenish yellow, in solitary, simple, axillary spikes. Fruits spherical to ovoid suddenly narrowed in to a very short stalk, fresh ripe fruits slightly silvery or with whitish shining pubescent surface; mature fruit grey to grayish brown with with slightly wrinkled appearance; obscurely 5 angled.

3.3.2. Microscopy profile

Transverse section of fruit shows an outer epicarp consisting of a layer of epidermis, most of epidermal cells elongate to form hair like protuberance with swollen base; composed of a zone of parenchymatous cells, slightly tangentially elongated and irregularly arranged, intermingled with stone cells of varying shape and size; elongated stone cells found towards periphery and spherical in the inner zone of mesocarp in groups of 3-10; mesocarp traversed in various directions by numerous vascular strands; bundles collateral, endarch; simple starch grains and some stone cells found in most of mesocarp cells, few peripheral layers devoid of starch grains; rosettes of calcium oxalate and stone cells present in parenchymatous cells; endosperm composed of stone cells running longitudinally as well as transversely.

Ayurvedic Properties

Rasa Kasaya
Guna Ruksa, Laghu
Veerya Usna
**Phytochemical Review**

*Terminalia bellerica* fruit contains 20 to 30% tannins; gallic acid, ellagic acid, ethyl gallate and chebulagic acid (Row et al., 1961; Row and Murthy, 1968). A new cardiac glycoside present as bellericanin and phillembin (Awasthy and Nath, 1968), thaninilignane 7-hydroxy-3′-4′ (methylenedioxy) flavane and anolignane B (Valsaraj et al., 1997) and new cardenolide, cannogenol 3-O-β-D-galactopyranosyl-(1→4)-O-α-L-rhamno-Pyranoside was isolated from the *Terminalia bellerica* (Yadav and Rathore, 2001).

Arjunenin and its glucoside, triterpenoid belleric acid and its glucoside; bellericoside have been defined as 2α, 2β, 23, 24-tetrahydroxy olean-12-en-28-oic acid and its β-D glucopyranosyl ester have been reported in fruits of *Terminalia bellerica* (Nandy et al., 1989).

**Pharmacological Review**

The fruit extract of *Terminalia bellerica* reported to protect myocardial necrosis (Tariq et al., 1977), to possess free radical scavenging activity (Palav and D’Mello, 2006) and activity for CCK and GABA receptors (Mishra, 1998). The extract also showed significant inhibitory activity on human immunodeficiency virus-1 (HIV) reverse transcriptase (El-Mekkaway et al., 1995).

Lignane isolated from *Terminalia bellerica* was shown to posses anti-HIV, antimalarial and antifungal activities (Valsaraj et al., 1997). Powdered drug of *Terminalia bellerica* fruit decreased liver and aorta cholesterol concentration in atherosclerotic rabbits (Shailaa et al., 1998).

The aqueous extract of *T. bellerica* reported as hypotensive, cardiac depressant, intestinal antispasmodic and CNS depressant effect (Kotangale et al., 2004) and ethanol extract of fruit and its active constituent’s gallic acid showed protection
against carbon tetra chloride induced liver and kidney damage (Anand et al., 2006; Jadon et al., 2007).

**Therapeutic Uses**

Fruit is used as an astringent, anthelmintic, laxative, useful in eye diseases, bronchitis, expectorant in cough, vomiting, in biliousness, in inflammatory effects of small intestine and throat.

**Dose:** 3-6 g. of the drug in powder form.

**Important Formulations**

Triphala churna, Chinnodbhavadi kwath churna, Triphaladi Taila, Lavangadi Vati, Phalatrikadi kwath, Talishadi churna, Bibhitaki kwath.

4. **HARITAKI**

Drugs consist of the pericarp of mature fruits of *Terminalia chebula* Retz.

**Synonym:** *Terminalia reticulata*

**Family:** Combretaceae

**Vernacular names**

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<td>Karaka, Karakkaya</td>
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</table>
Habitat and Distribution

The plant is found throughout India, chiefly in deciduous forests and areas of light rainfall, but occasionally also in slightly moist forests, up to about 1500 m elevation. Found abundantly in North India.

Part Used: Fruit and Seed

Botanical Description

3.4.1. Macroscopy profile

A moderate sized or large deciduous tree attaining 25-30 m height, a rounded crown and spreading branches. Bark is dark brown, often longitudinally cracked, exfoliating in woody scales; Leaves glabrous or nearly so when mature, not clustered, alternate or subopposite, elliptic, oblong, acute rounded or cordate at base with pair of large glands at the top of the petiole; Flowers yellowish white, in terminal spikes.

Intact fruits yellowish brown, ellipsoid, ovoid or obovoid, wrinkled and more or less 5 ribbed longitudinally. Basal portion is narrower and somewhat elongated on tapering. Taste astringent

3.4.2. Microscopy profile

Transverse section of pericarp shows epicarp consisting of one layer of epidermal cells, inner tangential and upper portions of radial wall thick; mesocarp, 2-3 layers of collenchyma, followed by a broad zone of parenchyma in which fibres and sclereids in group and vascular bundles scattered; fibres with peg like out growth and simple pitted walls; sclereids of various shapes and sizes but mostly elongated, tannins and raphides in parenchyma; endocarp consists of thick-walled sclereids of various shapes and sizes, mostly elongated; epidermal surface view reveal polygonal cells, uniformly thick-walled, several of them divided into two by a thin septa; starch grains simple rounded or oval in shape, measuring 2-7 μ. diameter, found plenty in almost all cells of mesocarp.
3.4.3. Powder

Brownish in color; under microscope shows a few fibres, vessels with simple pits and groups of sclereids.

Ayurvedic Properties

- **Rasa**: Kasaya, Katu, Tikta, Amla, Madhura
- **Guna**: Laghu, Ruksa
- **Veerya**: Usna
- **Vipaka**: Madhura
- **Karma**: Tridoshashamaka, Rasayana, Cakṣusaya, Dipana, Anulomana, Hradya, Medhya, Prameha.

Phytochemical Review

Fruits of *Terminalia chebula* contain tannins which on hydrolysis give chebulic acid and D-galloyl glucose (Anonymous, 1953). Fractionation of methanol extract of *Terminalia chebula* fruits led to the isolation of three hydrolyzed tannins and a related compound, gallic acid 1,2,3,4,6 penta-O-galloyl beta D-glucopyranose, chebulagic acid & chebulmic acid, as an active principles (Lee *et al.*, 1995). The Chromatographic fractionation of methanolic extract also yielded 2,4-chebulyl-β-D-glucopyranose (Saleem *et al.*, 2002).

The other compounds isolated and characterized as phenolic compounds; gallic acid and syringic acid (Bhaumik *et al.*, 1989), 1,6-di-O-galloyl-D-glucose, punicalagin, 3,4,6-tri-O-galloyl-D-glucose, casuarinin, chebulanin, corilagin, neochebulinic acid (Juang *et al.*, 2004; Juang and Sheu, 2005), punicalagin, terflavin & terchebulin with novel tetraphenyl carboxylic acid (terchebuhc acid) moiety (Lin *et al.*, 1990) from fruits of *Terminalia chebula*.

From leaves of *Terminalia chebula*, a new triterpene, 2-α-hydroxymicromeric acid, maslinic acid and 2-α-hydroxy ursolic acid (Singh, 1990), hydrolysable tannins terflavin B, C, and D, punicalagin and punicalin (Lin *et al.*, 1990) were isolated.
Pharmacological Review

The fruit pericarp of *Terminalia chebula* have shown cytoprotective activity to gastric mucosa (Dahanukar et al., 1983), cardioprotective activity (Reddy et al., 1990) and ameliorate the effect of isopreterenol induced damage (Suchalatha and Shyamaladevi, 2004; Suchalatha et al., 2005). Tannin fraction from the dried fruit pulp reported as antimutagenic potential (Kaur et al., 1998).

Methanolic extract of *Terminalia chebula* fruit and its phenolics chebulinic acid, tannic acid and ellagic acid showed most growth inhibitory effect on several malignant cell lines (Saleem et al., 2002) and prophylactic treatment with methanolic extract showed chemopreventive activity on nickel chloride induced renal oxidative stress and toxicity (Prasad et al., 2006). The aqueous methanolic extract is reported to have potent rat intestinal maltase inhibitory activity which suggested use of extract in managing type II diabetes mellitus (Gao et al., 2007).

Water extract of fruit of *Terminalia chebula* reported as inhibitor of urease activity of *Helicobacter Pylori* (Malekzadeh et al., 2001), strong anti-anaphylactic action (Shin et al., 2001), antihyperglycemic activity (Murli et al., 2004) and potent inhibitor of TBRAS formation as antioxidant drug (Naik et al., 2003; Naik et al., 2004; Lee et al., 2005) and gastric motility improving agent and useful alternative to prokinetic drugs (Tamhane et al., 1997).

Topical administration of an alcoholic extract of the leaves of *Terminalia chebula* shows healing of dermal wound (Suguna et al., 2002).

Therapeutic uses

The fruits are stomachic and carminative, tonic and alternative properties. It is also used in heart diseases, respiratory diseases, pain, fever, inflammation, piles, anaemia, diabetes and gastric disorders.

Dose: 3–6 g of the drug in powder form.
Important formulations

Abhayarista, Agastya haritaki rasayana, Citraka-haritaki, Chinnodbhavadi kwath churna, Dasamula haritaki, Brahma rasayana, Triphala churna, Triphaladi taila, Abhaya lavana, Pathyadi lepa.

5. GUDUCHI

The drug consists of dried mature pieces of stem of *Tinospora cordifolia* (Willd.) Miers ex Hook. F. & Thoms.

**Synonym:** *Menispermum cordifolium* Miers, *Cocculus cordifolia* Miers.

**Family:** Menispermaceae

**Vernacular names**

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**Habitat and distribution**

Found throughout tropical India, ascending to an altitude of 900 m from Kumaon eastward as well as southward up to Srilanka.

**Part used:** Stem and Root
Botanical Description

3.5.1. Macroscopy profile

A large glabrous climber shrub with succulent, corky, grooved stem; Flowers small, yellow or greenish yellow, appearing when the plant is leafless, in axillary and racemosa panicles; Male flowers clustered and Female flowers usually solitary.

Young stem green with smooth surface and swelling at nodes, old one shows a light brown surface marked with warty protuberance due to circular lenticels; Fruits ovoid to subglobosa, glossy, red, pea sized.

3.5.2. Microscopy profile

Transverse section of stem shows outer most layer of cork followed by 2-3 layers of chollenchymatous cortex and 4-6 layers of parenchymatous cortex, consisting of circular to isodiametric type of cells. Cortical cells are filled with plenty of starch grains and secretory cells. Pericyclic fibres are lignified containing single prism in each chamber. Vascular zone composed of 10-12 or more wedge strips of phloem. Medullary rays wide containing starch grains with concentric striation and central hilum. Pith large, thin walled cells with starch grains.

Ayurvedic Properties

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<thead>
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<th>Rasa</th>
<th>Tikta, Kasaya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guna</td>
<td>Laghu</td>
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<tr>
<td>Veerya</td>
<td>Usna</td>
</tr>
<tr>
<td>Vipaka</td>
<td>Madhura</td>
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<tr>
<td>Karma</td>
<td>Tridosasamaka, Balya, Dipana, Rasayana, Raktashodhaka, Jvaraghna</td>
</tr>
</tbody>
</table>

Phytochemical Review

Tinosponone and tinocordioside (Maurya et al., 1995), sesquiterpene glucoside tinocordifolioside (Maurya et al., 1997), sesquiterpene tmocordifolin (Maurya and Handa, 1998) have been isolated and reported from the stem of *Tinospora cordifolia*.

The new clerodone furano diterpene named columbin (Bhatt et al., 1988), tinosporaside (Khan et al., 1989), immunological active arabinolactone (Chuntalwar et
Review of Literature

al., 1999), cordioside, furano diterpene (Bhatt and Sabata, 1989), magnoflorine (Pachaly and Schneider, 2006) and several glycosides, alkaloids; Jetrorrhizine, palmitine, berberine, tembeterine, phenyl propene, disaccharides, cordifolioside A, B and C (Gangan et al., 1994; Maurya et al., 1995) have been isolated from *Tinospora cordifolia*.

Other compounds isolated as choline, tinosporic acid, tinosporal, tinosporone, 20-β-hydroxy ecdysone (Pathak et al., 1995), cordifolioside D & E and palmatoside C and F (Gangan et al., 1995; Gangan et al., 1996).

Pharmacological Review

Aqueous extract of *Tinospora cordifolia* reported to possess antiinflammatory, analgesic and antipyretic activity (Ikram et al., 1987) and radio protective activity against sub lethal dose of gamma radiation in mice (Pahadiya and Sharma, 2003). The aqueous extract also showed antiulcer, hypolipidemic, antidiabetic and antioxidant activity (Stanely and Menon, 1999; Stanely and Menon, 2003; Sarma et al., 2006).

Methanol, aqueous and methylene chloride extract of Guduchi reported to possess antineoplastic activity in-vitro and dichloromethane extract showed antineoplastic activity in-vivo in mice transplanted with Ehrlich ascites carcinoma (Jagetia et al., 1998; Jagetia and Rao, 2006). Methanol extract of stem also have shown anti-tumour activity (Mathew and Kuttan, 1999) and antifertility in male rats (Gupta and Sharma, 2003). Ethanol extract exhibited significant anti-stress activity in comparison to diazepam (Sarma et al., 1998).

Syringin and cordiol (Kapil and Sharma, 1997) and (1,4)-α-D-glucane (Nair et al., 2006) isolated from *Tinospora cordifolia* reported to activate the immune system of body. The water and ethanol extract of stem also found to possess immunomodulatory action and antianaemic activity against cyclophosphamide induced immunosuppression in mice (Manjrekara et al., 2000).

Therapeutic Uses

Used as tonic, immunomodulator, hepatoprotective, antidiabetic, antipyretic, anti-anaemic. It is also used in various skin diseases and jaundice. Freshly prepare
juice act as powerful diuretic. Starch obtained from stem and root used in chronic diarrhoea, dysentery, acid dyspepsia, intestinal irritability and tonic.

Dose: 3-6 g of drug in powder form.

Important Formulations

Chinnodbhavadi kwath churna, Amritarista, Guduchi taila, Guduchyadi Churna, Guduchi satva, Amrtottara kwath churna.

6. NEEM

The drug consists of stem bark of *Azadirachta indica* A. Juss.

Synonym: *Melia azadirachta* Linn.

Family: Meliaceae

Vernacular names

<table>
<thead>
<tr>
<th>Language</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Mahanim</td>
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<td>Nim, Nimgacha</td>
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<td>Gujarati</td>
<td>Kadvolimbdo, Limba</td>
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<td>Mal</td>
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<tr>
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<td>Balantanimba, Limba, Kadummba</td>
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<tr>
<td>Punjabi</td>
<td>Nimba, Bakam, Nim</td>
</tr>
<tr>
<td>Tamil</td>
<td>Veppai, Vembu, Veppam</td>
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<tr>
<td>Telugu</td>
<td>Vemu, Vepa</td>
</tr>
</tbody>
</table>

Habitat and Distribution

Occurring throughout India up to elevation of 900 m, found in deciduous forests, also widely cultivated.
Botanical Description

3.6.1. Macroscopy profile

A moderate sized to fairly large, evergreen tree attaining a height of 12-15 m with stout trunk and spreading branches. Leaves are alternate, imparipinnate, leaflets sub opposite, serrate, very unequal at base; Flowers white or pale yellow, hermaphrodite, in axillary panicles; Drupes green, turning yellow on ripening, oblong or ovoid oblong, one seeded.

The bark external surface is channelled, tough, fissured, rusty grey with a rough scaly surface. Internally bark is yellowish, laminated and coarsely fibrous and foliaceous. Odour- characteristics and taste bitter.

3.6.2. Microscopy profile

Bark shows outer exfoliating pieces hard, woody, considerably thick in older barks; almost entirely dead elements of secondary phloem, alternating with discontinues tangential bands of compressed cork tissue. The secondary phloem composed of several layers of stone cells together with collapsed phloem elements filled with brown content; in between the successive zones of cork tissue, 3-5 layers of fibre groups with thin walled and often collapsed phloem elements present. Each zone of cork tissue consists of several layers of regular thin walled cells with few compressed rows thick walled cells towards outer surface. Number of newly formed cork composed of thin walled rectangular cells with two layers of cork cambium below which zone secondary phloem present.

Secondary cortex is absent in most cases. Phloem of outer bark mostly collapsed with few large secretory cavities. Most of phloem parenchyma contains starch grains, prismatic crystals of calcium oxalate. Structures of bark vary accordingly gradual formation of secondary cork bands.

Ayurvedic Properties

<table>
<thead>
<tr>
<th>Rasa</th>
<th>Tikta</th>
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<tbody>
<tr>
<td>Guna</td>
<td>Laghu, Ruksa</td>
</tr>
<tr>
<td>Veerya</td>
<td>Sita</td>
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<tr>
<td>Vipaka</td>
<td>Katu</td>
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</tbody>
</table>
Phytochemical Review

The bark extracts rich in phenol, unsaturated sterols, triterpene and saponins (Subramanian and Lakshman, 1996). It also contains vanilic acid, catechol, campesterol, stigmasterol, sitosterol, β-amyrine, lupeol, nimbin, nimbidin, nimbinin, sugiol, kulinone, kulactone, kulalactone, methyl kulanate, 6-β-hydroxy-4-sigmasten-3-one and 6-β-hydroxy-4-campesten-3-one (Chatterjee and Pakrashi, 1997 and Sharma et al., 2000).

A number of phenolic diterpenoids, limonoids, c-secomeliacins, c-secolimonoids, polysaccharides such as arabinofucoglucanes and flucogalactoglucoarabinones (Fujikawa et al., 1982; Fujikawa et al., 1984; Devkumar and Sukh Dev, 1996) and other two new isomeric diterpenoids nimbinone and nimbimone and new ring c-seco-tetranortriterpenoid isonimbohde (Ara et al., 1988) have been isolated from stem bark of Azadirachta indica.

Other compounds isolated as gallic acid, (+) gallocatechin, (-) epicatechine, (+) catechin and epigallocatechin (Vander Nat et al., 1991).

Pharmacological review

Neem (Azadirachta indica) stem bark aqueous extract reported to possess potent anti-secretory and anti-ulcer effect in animal models without any significant adverse effect (Bandyopadhyay et al., 2002; Raji et al., 2004). The aqueous extract also showed strong anti-complement activity and inhibited the generation of chemiluminescence by activated human polymorphonuclear leucocytes (PMN) which indicated compound inhibit oxidative burst of PMN during inflammation (Vander Nat et al., 1987; Vander Nat et al., 1991) and enhances the immune response of Balb-c mice to sheep red blood cells in vivo (Njiro et al., 1999).

The chloroform extract and polysaccharides isolated from stem bark of Azadirachta indica reported to possess antiinflammatory activity in rats and mice (Fujikawa et al., 1984; Tidjan et al., 1989). The water soluble polysaccharides
isolated from stem bark showed strong anti-tumour activity in mice bearing sarcoma cells (Fujikawa et al., 1982). Phenolic compound from stem bark of *Azadirachta indica* produced antioxidant activity *in vitro* (Sultana et al., 2007).

The tablet suspension from the leaf and bark of *Azadirachta indica* showed anti-malarial activity against *Plamodium yelli nigeriensis* infection in mice (Isah et al., 2003). Ethanolic extract of stem bark of *Azadirachta indica* showed estrogenic activity in rats and also significantly increased ovarian wet weight and glycogen content (Bhargav and Prakash, 2001; Bhargav and Jain, 2005).

**Therapeutic Uses**

Useful in skin diseases, diabetes, itching, fever and malaria, burning sensation, ulcer, wound and inflammation, bleeding disorders, urinary discharge and also used as appetizer, anthelmintic and anti-periodic.

**Dose:** 2-4 g of drug in powder form.

**Important Formulations:**

Nimbadi kwath churna, Chinnodbhavadi kwath churna, Nimbadi churna, Panchanumba churna, Panchtikta guggulu ghrita, Pathyadi kwath churna, Sudersan churna.

7. **PATOLA**

The drug consists of dried leaves of *Trichosanthes dioica* Roxb.

**Family:** Cucurbitaceae

**Vernacular names**

<table>
<thead>
<tr>
<th>Sanskrit</th>
<th>Patola, Meki, Parvara, Parvagi</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Pointed gourd</td>
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<tr>
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<td>Patol, Potal</td>
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<td>Potala, Patal</td>
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<td>Hindi</td>
<td>Parwal, Parvar, Palval</td>
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<tr>
<td>Kannad</td>
<td>Kodupodavalu, kaadu-padavala</td>
</tr>
</tbody>
</table>
Review of Literature
Mai Patolam, Kattupatolam
Marathi Kadupadvala, Parvar, Palwal
Punjabi Palwal, Parwal
Tamil Pey-padal, Kombu-pudalai
Telugu Adavi-patola, Kommupotala

Habitat and Distribution
It is found wild in the plain of North India and extensively cultivated all over the warmer region of India for its fruits.

Part Used: Leaves, root, fruit

Botanical Description
3.7.1. Macroscopy profile
A dioecious climber with perennial root stock; Stem slender, angled, hispid, extensively climber, more or less scabrous and woolly; Tendrils usually forked. Leaves ovate oblong or cordate, acute, sinuate, dentate, not lobed, rigid and rough on both surfaces. Flowers dioecious, white; Male flowers racemed, woolly outside; Female flowers solitary. Fruits oblong or nearly spherical acute smooth, orange red when ripe.

3.7.2. Microscopy profile
TS of leaf show a broad elevation on the lower side and elevation on the upper side, and dorsiventral laminar extension. Upper and a lower epidermis bearing multicellular simple and glandular trichomes protect whole tissue. In the midrib region just below the both the epidermis there are few layers of collenchyma. In the center there is a crescent shaped vascular bundle formed by xylem and phloem and is protected by a pericycle formed by fibers only on the lower side. Vascular bundles are divided into 2 or 3 meristele in the center and a small one on the upper side. The lamina region shows upper and lower epidermis, a single layer of palisade below the former and 3 to 4 layers of mesophyll in the lower side with transversely running vascuatures. TS of petiole of the leaf shows irregularly oval to rectangular outline with 6 to 7 vascular bundles protected by pericycle in the outer side, epidermis is highly hairy shows collenchymatous hypodermis. There is pith in the center with few lignified pitted cells.
Ayurvedic Properties

Rasa  Tikta
Guna  Laghu, Snigdha
Veerya  Usna
Vipaka  Katu
Karma  Tridoshashamaka, Jvara, Daha, Aruchi, Arsa, Kriminasak, Vranshoth, Khalitya

Phytochemical Review

Leaves of patola contain moisture, proteins, fibres, carbohydrates, mineral matters, calcium and phosphorus (Anonymous, 1976) and cucurbita-5 and 24-dienol in mature plants. Fruits contain nicotinic acid, riboflavinbe, vitamine C, thiamine, 5-hydroxy tryptamine (Sharma et al., 2002).

Pharmacological Review

Ethanolic extract of Trichosanthes dioica Roxb. Plant and aerial part reported to posses significant lowering of blood sugar in fasted rats and depressed the peak value in glucose loaded single and long term fed rats (Chandrasekhar et al., 1989).

Therapeutic Uses

Tonic, febrifuge, antipyretic, antiulcer and anti-inflammatory, anti-gastritis, anti-diarrhoea. It is also used in bleeding disorders, skin diseases, piles and Jaundice.

Dose: 10- 20 ml of drug in form of juice and 50-100 ml in form of decoction.

Important Formulations

Patoladi kwath churna, Chinnodbhavadi kwath churna, Phalatrikadi kwath churna, Patolyadi lepa, Patolyadi kwath, Panchtukta ghrita, Nyagrodhadi churna, Patolyadi churna.

(References for general plant details- Refer bibliography)