REVIEW
OF
LITERATURE
2. REVIEW OF LITERATURE

2.1 PEPTIC ULCER DISEASES AND ANTIULCER PLANTS

2.1.1 Anatomical considerations of stomach

Stomach is a J shaped enlargement of the GI tract and the most dilated part of the alimentary canal, situated between the oesophagus and the small intestine. It lies directly under the diaphragm in the epigastric, umbilical and left hypochondric regions of the abdomen.

Stomach is divided into four main areas:

Cardia: It surrounds the superior opening of the stomach.

Fundus: The rounded portion above and to the left of the cardia is the fundus.

Body: Below the fundus the large central portion of the stomach is body.

Pylorus: The inferior region of the stomach that connects to the duodenum divides into two parts, pyloric antrum and pyloric canal (pylorus). The pylorus communicates with the duodenum of the small intestine via a sphincter called the pyloric sphincter.

Histology of Stomach

The wall of the gastrointestinal tract, especially from the oesophagus to the anal canal, has the same basic arrangement of the tissues. The four layers of the tract from the inside to outside are the mucosa, submucosa, muscularis and serosa. The stomach wall is composed of the same basic layers as the rest of the GI tract, with certain modifications.

1. Mucosal layer:

The mucosa reveals a layer of simple columnar epithelium (surface mucous cells) containing many narrow channels called the gastric pits, that extends down in the lamina propria. At the bottom of the pits lies the opening of the gastric glands. The glands contain four types of the secretory cells.

(1) Chief cells (Zymogenic cells, Peptic cells) secret pepsinogen

(2) Parietal (oxyntic) cells secret HCl

(3) Mucous cells secret mucous and pepsinogen
(4) Enteroendocrine cells (G cells) secret gastrin
(5) Enterochromaffin cells secret serotonin

2. Submucosal layer:
The submucosa of the stomach is composed of areolar connective tissue, which connects the mucosa to the muscularis.

3. Muscular layer:
The muscularis has three layers of the smooth muscle: an outer longitudinal layer, a middle circular layer, and an inner oblique layer. The oblique layer is limited mostly to the body of the stomach. This arrangement of fibres allows the stomach to churn food, break it into small particles, mix it with gastric juice and pass it to the duodenum.

2.1.2 Physiology and regulation of gastric acid secretion

Stomach secretes about 2.5 litres of gastric juice daily. Parietal cells of oxyntic gland secrete hydrochloric acid. Gastric secretion can be classified in 3 phases known as cephalic phase, gastric phase and intestinal phase according to location of the afferent stimuli initiating the response.

1. Cephalic phase: Afferent impulses initiated by taste, thought and smell of food, hospitality etc. are relayed through vagal efferent fibres to stomach. Even emotional factors can influence gastric secretion through these pathway. Stimulation of specific areas in frontal cortex and anterior hypothalamus also results in gastric secretion.

2. Gastric phase: This phase is brought about by the mechanical stimuli like distension of the stomach with food and chemical mechanism operating through amino acids and other products of digestion. These stimuli act on the receptors in mucosa and stomach wall initiating local neuronal reflexes which involve the same postganglionic cholinergic neurons that are stimulated by vagal preganglionic fibres. There is release of gastrin from gastrin secreting G cells of pyloric mucosa caused by neurons and a direct stimulant effect on the acid secreting parietal cells by the products of digestion. As acid secretion proceeds pH falls and gastrin secretion is inhibited.
3. Intestinal phase: The digestion products of proteins on entering the duodenum may still influence the secretory activity of stomach. This effect may be due to a hormone like bombesin released from duodenum or may be due to another peptide, enterooxytin. The sequence of intracellular chemical reaction leads to secretion of gastric acid. Some chemical mediators that interact with parietal cells initiate the chemical reactions via the release of 'second intracellular messengers'.

The three major pathways regulate gastric acid secretion.
1. Neuronal stimulation: via acetylcholine, released from vagus nerve
2. Endocrine stimulation: via gastrin, released from G cells.
3. Paracrine stimulation: via histamine, released from mast cells.

Acetylcholine, Gastrin and Histamine act on Muscarinic receptor, Gastrin receptor and H₂ receptor respectively. These receptors are present on the basolateral membrane of the parietal cells. Acetylcholine, released by postganglionic nerves near the muscarinic receptor on the parietal cell, increases HCL secretion by increasing the permeability of the parietal cell to extracellular calcium. Gastrin reaches its gastrin receptors situated on parietal cells via blood (endocrine effect). Baudiere⁴⁶ has suggested that acetylcholine and perhaps gastrin activates phospholipase C to release inositol phosphate from membrane phospholipids, which then releases intracellular calcium. Histamine diffuses into the H₂ receptor after local release from the mast cells⁴⁷. When histamine binds to the H₂ receptor on the parietal cell, it increases the affinity of a GTP regulatory protein for cytosolic GTP which then activates adenylate cyclase, converting cytosolic ATP to c-AMP. Increase in cellular c-AMP levels and free cytosolic calcium result in the activation of one or more protein kinases and in the phosphorylation of a variety of proteins that activates the intracellular secretory canaliculi and proton pump.

The canaliculi becomes externalized after fusing to the apical membrane, forming long microvilli opening into the lumen. The increase in second messengers induces the movement of a H⁺ - K⁺ - ATPase from the tubulovesicles into the secretory canaliculi. This enzyme promotes electrogenic entry of potassium and chloride.
The mechanism of HCl secretion by parietal cell is such that hydrogen are generated within the parietal cell from H₂O; the corresponding hydroxyl ions are combined with CO₂ under the action of carbonic anhydrase to form HCO₃⁻ ions, which are then exchanged for Cl⁻ ions at the basolateral membrane of the parietal cell. Chloride ions entering the parietal cell in exchange for HCO₃⁻ are transported into the secretory canaliculus along with K⁺ ions via Cl⁻ and K⁺ conductance pathways closely associated with H⁺ - K⁺ - ATPase. H⁺ ions are exchanged for the K⁺ ions on a 1:1 baiss, a transport process catalysed by H⁺ - K⁺ - ATPase and involving a phosphorylated intermediate protein. Thus, the net result is secretion of H⁺ and Cl⁻ at concentrations of 160mM, whereas K⁺ ions are primarily recycled rather than secreted. As the apical membrane of the parietal cell and other gastric epithelial cells is very impermeable to H⁺, most acid secreted by parietal cells remains in the gastric lumen rather than diffusing back into the tissue.

Besides the endogenous stimulants of the acid secretion (histamine, gastrin, acetylcholine and calcium), two additional neuropeptides enkephalin and bombesin have been reported to increase acid secretion in humans when given parenterally⁴⁸. Several endogenous substances are capable of reducing acid secretion when infused intravenously. These include prostaglandin E₂, several peptides like secretin, somatostatin, glucagon, GIP, neurotensin, calcitonin gene related peptide, thyrotropin releasing hormone, peptide YY, enterogastrone and orogastron and dopamine, magnesium and zinc ions.

2.1.3 Pathophysiology of peptic ulcer diseases

Peptic ulcer is a recurrent disease, which includes ulceration at any site in the gastrointestinal tract where mucosal cells (parietal cell) secret hydrochloric acid. This disease affect large populations in all geographical regions. Although acid is thought to be the most important cause of ulcerogenesis, mucosal defence is also considered to be a dominant factor.
Types of peptic ulcer disease:

1. Gastric ulcer
   The primary event in the pathogenesis of gastric ulcer is considered to be the altered mucosal resistance with consequent damage by acid, pepsin and other destructive agents. Pathophysiological abnormalities found in gastric ulcer patients include:
   a. Gastric motility and emptying defects
   b. Duodenogastric reflux, bile reflux due to pylorus defects.
   c. Gastritis
   d. Mucosal ischemia
   e. Altered bicarbonate production

2. Duodenal ulcers
   Patients with duodenal ulcers have one or more of the following physiological defects. These defects include:
   a. Increased number of parietal cells
   b. Increased parietal cell sensitivity to gastrin
   c. Increased basal and stimulated secretory rates of acids and pepsin
   d. Increased meal stimulated gastrin release
   e. Increased serum pepsinogen concentration
   f. Increased rate of gastric emptying
   g. Decreased acid-induced inhibition of gastrin release of acid secretion
   h. Impaired bicarbonate secretion in pancreatic juice. Hence failure to buffer gastric acid secretion
   i. Impaired duodenal mucosal defence.

The factors that contribute to the development of peptic ulcer disease are classified as under[^49].
A. DEFENSIVE FACTORS

1. Gastric mucosal barrier
   a. Pre-epithelial factors
      Mucus
      Bicarbonate
   b. Epithelial factors
      Chemical agents
      Hydrophobic cell membranes
      Rapid cell turnover
      Restitution of epithelium
   c. Sub-epithelial factors
      Blood flow
      Angiogenesis

2. Prostaglandins

3. Others
   Secretin
   Somatostatin
   Growth factors

B. AGGRESSIVE FACTORS

1. Endogenous factors
   Gastric acid secretion
   Pepsin secretion

2. Exogenous factors
   NSAIDS
   Cortisteroids
   Alcohol
   Cigarette smoking
   Diet
   H.pylori infection
   Caffeine
   Oxygen free radicals

Besides these local factors of GI tract, general factors like vagal effects, hormonal effects (Histamine, Noradrenaline), insufficient circulation, shock, general ischaemia etc can also become a part of pathogenesis of peptic ulcer disease.

Constitutional and environmental factors like sex, age, temperament, family history, social class, geographical difference occupation etc. can also be a cause of peptic ulcer disease.
(A) DEFENSIVE FACTORS

1. Gastric mucosal barrier
(a) Pre-epithelial factors

Mucus and Bicarbonate

Mucus is secreted by surface epithelial cells, goblet cells and submucosal Brunner’s glands. Bicarbonate ions are also secreted and are trapped into the mucus, creating a gradient of pH from 1-2 in the lumen to 6-7 at the mucosal surface. The mucus and bicarbonate protect the mucosa from the gastric juice. Locally produced prostaglandins stimulate the secretion of both mucus and bicarbonate.

The mucus of gastric juice occurs in two forms, visible mucus and dissolved mucus. The later is secreted directly into the lumen or may be derived from the mucus gel by proteolytic degradation or mechanical shearing during digestion.\textsuperscript{50} Bicarbonate secretion is stimulated by acid, PG-E\textsubscript{2}, c-AMP, a newly characterized peptide Guanilyl, via c-GMP\textsuperscript{51} and other mucosal protectants. Mucus contribute significantly to cytoprotection by

(i) Lubrication and mechanical protection.

The mucus gel covers the entire surface of the gastroduodenal mucosa, lubricating it and providing first line defense against noxious gastric contents. A dynamic balance exists between its production on one hand and degradation by pepsin on other hand\textsuperscript{52}.

(ii) Mixing barrier

Mucus being readily permeable to H\textsuperscript{+} ions, prevents the relatively small amount of bicarbonate ions from mixing with the bulk of H\textsuperscript{+} ions in the lumen thus confining the neutralization and ensuring pH gradient across the mucus layer\textsuperscript{53}

(iii) Prevention of back diffusion of pepsin and pepsinogen activation

Mucus by phenomenon of phase separation, attenuates back diffusion of macromolecules like pepsin from gastric juice. Mucus also transports pepsinogen and prevents its activation into pepsin.
(iv) Repair of superficial mucosal damage
Damage to surface cells, leads to a rapid release of large amount of mucus and plasma proteins, which together with the cellular debris form a coating over the damaged area, providing a favourable environment for repair and restitution\textsuperscript{54}.

(v) Antibacterial activity
Identification of bacteria in human stomach in gastritis indicates that normal gastric mucus may have antibacterial activity.

Reduction of biosynthesis of gastric sulfated mucin following acid hypersecretion may be responsible for the formation of gastric ulcer\textsuperscript{55}. Human gastrointestinal mucins and milk proteins inhibit H.Pylori sialic acid specific haemagglutination suggesting their possible role in the prevention of H.pylori infection\textsuperscript{56}.

(b) Epithelial factors:
Chemical agents, hydrophobic cell membrane, lipid cell turnover and process of restitution

This mechanism include chemical groups (sulphydryl compounds) which fight against oxidative stress as well as hydrophobic cell membrane, lipid cell turnover and process of restitution are also important in maintaining the epithelial cell layer\textsuperscript{57}.

Non – protein sulphydryl compounds (SC) are present in high concentration in gastric epithelium. Reduced glutathione, a major component of SC is capable of binding reactive free radicals which accumulate during tissue ischaemia and injury induced by noxious agents like ethanol. Reduced glutathione induces gastric mucosal protection by increasing SC levels which are involved in prostaglandin synthesis and PG receptor activation. They may also directly influence membrane permeability, cell release and effects of mediators likely to be involved in inducing mucosal damage\textsuperscript{58}.

Stomach wall also possesses hydrophobicity inspite of its hydrophilic mucoid layer. This is due to the surface active phospholipids (SAP) present as the intergranular matrix of unsecreted mucus which provides major resistance to
hydrogen diffusing from the lumen of stomach to the vital organelles of surface mucus cells. This protective mechanism can be reduced by decreasing the number of SAP by strong solvents like ethanol\textsuperscript{59}. Stress ulcers are associated with a change in the lipid profile of gastric mucosa\textsuperscript{60} while each of the barrier breakers display greater affinity for SAP. Bile salts chemically complex with SAP while NSAIDs inhibit the production of PG controlling SAP synthesis\textsuperscript{61}. Following extensive damage of the surface epithelial cells, repair occurs within a few hours by the process of restitution. Restitution involves morphological healing\textsuperscript{62} accompanied by physiological return of function characterized by concomitant flux of bicarbonate ions across the epithelium. The process is inhibited by luminal pH below 4\textsuperscript{63} and augmented by high bicarbonate ions. PGs do not appear to be involved in restitution\textsuperscript{64}.

(c ) Sub-epithelial factors

**Bloodflow and angiogenesis**

Blood flow enhances the mucosal defense by delivering tissue oxygenation and nutrient. An important factor in the relationship between mucosal blood flow, tissue integrity and mucosal defense is the maintenance of intramucosal acid–base neutrality\textsuperscript{65}. Undamaged mucosal epithelial layer permits minimal hydrogen ions to back diffuse into the lumen at pH 2 or above, the bicarbonate and mucus adequately buffer such back diffusion\textsuperscript{50, 66}. Local or systemic infusion of the low molecular weight phospholipid, platelet activity factor which reduces mucosal blood flow, cause hemorrhagic erosions in the gastric mucosa\textsuperscript{67, 68}.

Angiogenesis is the formation and growth of new capillary blood vessels, in many physiological conditions such as wound healing and amniotic development. Both growth factors and inhibitors are involved in the regulation of vascular growth\textsuperscript{69, 70, 71, 72}.  

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2. Prostaglandins

Endogenous prostaglandins (PGs) occur in the mucus membrane of fundus and body of stomach. They exhibit marked anti-secretory activity against all types of secretagogues except c-AMP. The term "Cytoprotection was initially coined to describe the ability of PGs to augment gastroduodenal mucosal injury, independent of acid secretion inhibition. The potential mechanisms involved in prostaglandin mucosal resistance are multiple, including

- Stimulation of secretion of mucus and bicarbonate
- Increasing mucosal blood flow
- Strengthening of gastric mucosal barrier, decreasing gastric motility, increasing the release of endogenous mediator of gastric cytoprotection like sulfydryls and epidermal growth factor
- Scavenging free radical
- Decreasing release of endogenous mediators of gastric injury – vasoactive amines and leukotrienes and stimulation of cellular growth and repair.

3. Others

Secretin, somatostatin and Epidermal growth factor

Secretin, a gastrointestinal hormone released from mucosal cells of the duodenum, stimulates pancreatic secretion and bile flow. It inhibits gastric acid secretion and motility. It also increases pepsin secretion.

Somatostatin, present in gastric mucosa, pancreatic islets and in nerves of GIT inhibits gastric secretion and motility.

Epidermal growth factor, shown to be identical to urogastrone is now designated as URD / EGF. EGF promotes wound healing and accelerates peptic ulcer healing. It is a potent inhibitor of gastric secretion.
(B) AGGRESSIVE FACTORS

Aggressive factors that damage the mucosa of the gastrointestinal tract may originate endogenously or exogenously.

1. Endogenous factors

**Gastric acid secretion and pepsin secretion**

Schewartz\(^81\) formed the dictum "no acid no ulcer" and even today the antisecretory drugs like H\(_2\) blockers and proton pump inhibitors are leading the market. The acid base status of the gastroduodenal mucosa is an important determinant of mucosal susceptibility to ulceration. The acid gradient is created by H\(^+\), K\(^+\) - ATPase which maintains the H\(^+\) gradient at a cell lumen ratio of 1:2,000,000. In duodenal ulcer, the rate of HCl secretion in the stomach is much higher than normal. But in gastric ulcer, the rate of acid secretion is either normal or less than normal\(^82\). Endogenous substances like Histamine (H\(_2\) – receptor) and Acetylcholine (muscarinic receptor) interact with parietal cell receptors, stimulating the H\(^+\) / K\(^+\) ATPase\(^83\).

Pepsin is a proteolytic enzyme, which has little digestive power without acid. The optimum pH for pepsin activity is 1.8 to 3.5 and beyond pH 5, it is almost inactive. In gastric and duodenal ulcer patients, there is greater proportion of pepsin than in normal subjects. This results into digestion of mucus more rapidly\(^84\).

2. Exogenous factors

**NSAIDs**

NSAIDs induce gastric damage due to inhibition of Cox-1, responsible for prostaglandin synthesis. Traditional NSAIDs delay healing of peptic ulcers by decreasing epithelial cell proliferation in ulcer margin, decreasing angiogenesis in ulcer bed and slowing maturation of the granulation tissue\(^85\). Proton pump inhibitors protect against NSAIDs induced ulcer\(^86\). There is possibility of inter-relationships between H.pylori and NSAIDs in the pathogenesis of gastric and duodenal erosions\(^87\). Platelet derived growth factor reverses the effect induced by NSAIDs on ulcer healing\(^88\).
Corticosteroids

Corticosteroids decrease the mucosal barrier and increase acidity. Steroids reduce the rate of shedding of gastric mucosal cells by decreasing the rate of cell renewal. Steroids potentiate the development of ulcers from other causes (e.g., aspirin injection) also imply that they impair normal defense mechanism.

Alcohol

Ethanol rapidly penetrates the gastric mucosa and causes cell and plasma damage that results in increased membrane permeability leading to intracellular accumulation of sodium and water. When the increased membrane permeability fails to maintain electrolyte balance between intracellular and extracellular compartment, the massive intracellular accumulation of calcium represents a major step in pathogenesis of gastric mucosal injury. Ethanol produces damage to gastric mucosa by increasing gastric acid secretion and gastric mucosal damage is also attributed to free radical damage which results in lipid peroxidation products. Mast cell degranulation also occurs in ethanol induced gastric damage. Ethanol administration markedly delayed the gastric emptying.

Smoking

Smoking actually increases the incidence of peptic ulcer disease and it also slows down the rate of healing. Numerous mechanism have been proposed to explain the effect of smoking on peptic ulcer. It decreases gastric mucosal blood flow and inhibits gastric mucous secretion, gastric prostaglandin secretion, salivary epidermal growth factor secretion, duodenal mucosal bicarbonate secretion and pancreatic bicarbonate secretion.

Helicobacter pylori infection

Today over 50% of the world population is chronically infected by this pathogen. H. pylori is a gram negative, spiral shaped organism, which colonize on the surface of gastric antrum. Its strong urease property causes the release of ammonia which provides the environment of increased pH, enabling the organism to survive.
in highly acidic gastric atmosphere. H. pylori was first detected in gastric mucosa and then in faeces, saliva, dental plaques and also in drinking water. H. pylori is present in 90 - 95% of patients with gastric ulcer. There are more chances of dyspepsia, peptic ulcers and erosions in patients on long term NSAIDs when H. pylori is present than when it is absent. Degenerative changes are mediated by both direct (bacterial toxin) and indirect (inflammatory response) mechanisms.

Diet

Epidemiological evidence implicates dietary factors in the geographical distribution of duodenal ulceration among people on impoverished diets particularly when polished rice forms the main component. In a study in India, people suffering from duodenal ulcer, derived symptom relief by supplementation of their diet with fresh rice bran. This observation was confirmed in the rat model in which fresh rice bran and rice bran oil were found to be protective against ulceration. On storage rice bran and its oil lost their protective properties and became actively ulcerogenic. It was considered possible that on storage lipid peroxidation of unsaturated fatty acids in oil gave rise to cytotoxic ketoaldehydes. Support of this proposal was obtained by the demonstration that cysteine suppressed the ulceration induced by stored rice bran oil.

Caffeine

Caffeine acts synergistically with histamine (not pentagastrin) to stimulate gastric acid secretion. It also enhances the secretion of pepsin.

Free radicals

A free radical is a reactive molecule, most often an oxygen molecule with a missing electron that damages other molecules in our body by stealing electrons from them. Free radicals may be formed from electromagnetic radiation, exogenous compounds or normal metabolic pathway. Free radicals react with almost every known biological molecule in their vicinity and damage protein, causes breakdown of DNA strands and initiates peroxidation of various molecules. The hydroxyl radical is most reactive of all and may be considered the ultimate...
damaging species whenever superoxide is formed. The ever growing significance of antioxidant nutrients such as alpha tocopherol, beta carotene and ascorbic acid has come to light\textsuperscript{106}.

2.1.4 Therapy of peptic ulcer disease

The lifetime prevalence of peptic ulcer disease is approximately 10% and some physician estimate that 50% of healthy individuals experience heart burn on a daily basis. The pathophysiology of acid – peptic disease may be thought of as an imbalance between aggressive factors (acid, pepsin, H.pylori infection) and local mucosal defenses – the secretion of bicarbonate, mucus and prostaglandins. The goal of therapy for ulcers are relief from pain, promotion of healing, prevention of recurrence, avoidance of ulcer perforation, gastric obstruction etc.

Classification of antiulcer agents

1. Drugs with acid neutralizing activity

   Antacids

   They are weak bases, react with gastric hydrochloric acid to form salt and water and thereby diminish quantity of free hydrochloric acid in stomach. Effect of antacids is transient.

   e.g. Magnesium oxide and hydroxide
   
   Magnesium carbonate
   Magnesium trisilicate
   Aluminium hydroxide
   Sodium carbonate

2. Drugs with antisecretory activity

   (A) Proton pump inhibitors (PPI)

      (a) Reversible proton pump inhibitors (RPPI)

      Eg. : Imidazopyridien SCH 28080.

      It is not used clinically as it is hepatotoxic.
Acyn quinoline SK and F 96067.
It is a weak base, has shorter duration of action than Omeprazole.
Analogue of SCH 28080 under clinical investigation is SK & F 97574 has a longer duration of action than SK & F 96067.

(b) Irreversible proton pump inhibitors
Eg.: Substituted benzimidazoles like Omeprazole, Lansoprazole, Pantoprazole, Rebaprazole, Laminoprazole.
These compounds cause 100% inhibition of acid secretion but has no effect on bicarbonate secretion.

(B) H₂ receptor antagonist
Eg.: Cimetidine, Ranitidine Famotidine, Nizatidine, Ebritidine, Roxatidine.
The H₂ receptor antagonists inhibit gastric acid secretion elicited by histamine and gastrin. They inhibit 80% acid secretion and also pepsin secretion falls.

(C) Antimuscarinic agents
Eg.: Pirenzepine, Telenzepine.
These agents have not proved successful in the therapy of peptic ulcer because of unwanted effects of general antimuscarinic blockade. They reduce basal acid secretion and stimulated acid secretion to a lesser extent. They do not reduce food stimulated secretion.

(D) Histidine decarboxylase inhibition
Eg.: Epicatechin, Toxifen, Amentoflavon.
These agents reduce the histamine content of fundus and atrum by inhibiting H⁺-K⁺ ATPase.

(E) Cholecystokinin antagonist
Eg.: Proglumide, Loxyglumide.
They act by competitive blocking the gastric receptors.
3. Mucoprotective agents

(A) Prostaglandin analogues
   Eg. Misoprostol, Riprostil, Arboproctic, Enprostil

(B) Bismuth compound
   Eg. Colloidal bismuth subcitrate – tripotassium dicitrato bismuthate, Bismuth subsalicylate, Bismuth subgallate, Bismuth subnitrate

(C) Sucralfate

(D) Carbenoxolone

4. Anti H. pylori drugs

Dual Therapy:
* Tripotassium dicitratobismuthate + Metronidazole
* Ranitidin bismuth citrate + Clarithromycin

Triple Therapy:
* Omeprazole + Clarithromycin + Amoxycillin
* Omeprazole + Amoxycillin + Plaunotol
* Lanzoprazole + Amoxycillin + Clarithromycin

Quadruple therapy:
* Omeprazole + Colloidal bismuth subcitrate + Tetracycline + Metranidazole
* Omeprazole + Amoxycillin + Clarithromycin + Metranidazole

2.1.5 Plant drugs with antiulcer activity

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<th>Active principle or extract</th>
<th>Models used</th>
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<td>Amphipterygium adstringens</td>
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<td>Ethanol¹⁰⁹</td>
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<td>4</td>
<td>Aglaia roxburghiana</td>
<td>Aerial parts and fruits</td>
<td>Ethanol extract</td>
<td>Aspirin and pylorus ligation&lt;sup&gt;112&lt;/sup&gt;</td>
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<td>Musa sapientum L. var. paradisiaca (Plantain banana)</td>
<td>Unripe fruit (pulp)</td>
<td>Flavanoid – leucocyanidin</td>
<td>Aspirin&lt;sup&gt;113&lt;/sup&gt;,&lt;sup&gt;117&lt;/sup&gt;, phenyl butazone&lt;sup&gt;114&lt;/sup&gt;, restraint and prednizolone&lt;sup&gt;115&lt;/sup&gt;, histamine&lt;sup&gt;116&lt;/sup&gt;.</td>
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<td>19</td>
<td>Emblica officinalis</td>
<td>Fruit</td>
<td>Methanol extract (Ethyl Acetate fraction)</td>
<td>H&lt;sup&gt;+&lt;/sup&gt;K&lt;sup&gt;+&lt;/sup&gt;ATPase inhibitory activity&lt;sup&gt;132&lt;/sup&gt;</td>
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<tr>
<td>20</td>
<td>Zingiber officinale Rosc. (Ginger)</td>
<td>Rhizome</td>
<td>6-gingesulfonic acid, 6-gingerol, 6-shogaol</td>
<td>Aspirin, indomethacin, stress&lt;sup&gt;133,134&lt;/sup&gt;</td>
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<tr>
<td>21</td>
<td>Croton cajucara</td>
<td>Whole plant</td>
<td>Trans-de-hydrocrotonin</td>
<td>Ethanol, restraint stress, pylorus ligation&lt;sup&gt;135&lt;/sup&gt;</td>
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<td>22</td>
<td>Hymenocardia acida Tul.</td>
<td>Stem bark</td>
<td>Aqueous extract : glycosides, tannins, saponins</td>
<td>Indomethacin, serotonin, cold restraint stress&lt;sup&gt;136&lt;/sup&gt;</td>
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<td>23</td>
<td>Aframomum melegueta</td>
<td>Whole plant</td>
<td>Ethanol extract</td>
<td>Pylorus ligation, hypothermic restraint stress, indomethacin, cysteamine&lt;sup&gt;137&lt;/sup&gt;</td>
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<th>No.</th>
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<th>Active principle or extract</th>
<th>Models used</th>
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<tr>
<td>24</td>
<td>Parkia biglandulosa</td>
<td>Dried pulp of pods</td>
<td>Aqueous extract</td>
<td>Pylorus ligation, aspirin, ethanol&lt;sup&gt;138&lt;/sup&gt;</td>
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<tr>
<td>25</td>
<td>Rhamnus triquerta</td>
<td>Rhizomes and roots</td>
<td>Emodin</td>
<td>Restrain stress, pylorus ligation and aspirin&lt;sup&gt;139&lt;/sup&gt;</td>
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<td>26</td>
<td>Seleginella bryopteris</td>
<td>Aerial parts</td>
<td>Ethanol extract</td>
<td>Restrain stress&lt;sup&gt;140&lt;/sup&gt;</td>
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<td>27</td>
<td>Tetrapleura tetraptera and Taverniera abyssinica</td>
<td>Aerial parts</td>
<td>Aqueous extract</td>
<td>HCl – ethanol&lt;sup&gt;141&lt;/sup&gt;</td>
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<td>28</td>
<td>Picrasma quassinoides</td>
<td>Wood</td>
<td>Methanol and chloroform extract</td>
<td>Aspirin&lt;sup&gt;142&lt;/sup&gt;</td>
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<td>29</td>
<td>Aralia elata</td>
<td>Root bark</td>
<td>Butanol extract</td>
<td>HCl – ethanol&lt;sup&gt;143&lt;/sup&gt;</td>
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<td>30</td>
<td>Trianthema pentadra</td>
<td>Herb</td>
<td>Methanol extract</td>
<td>Aspirin&lt;sup&gt;144&lt;/sup&gt;</td>
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<td>31</td>
<td>Camellia sinensis</td>
<td>Leaves</td>
<td>Hot water extract</td>
<td>Cold restraint stress&lt;sup&gt;145&lt;/sup&gt;</td>
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</table>
2.2 LIVER DISORDERS AND ANTIHEPATOTOXIC PLANTS

2.2.1 Anatomical considerations of liver

Liver is the largest solid organ in the body and one of the most complex, constituting about 2% of the mass of the body. It is enclosed in a connective sheath known as Glisson's capsule and it contains four main components, namely.

1. hepatocytes or the parenchymal cells constitute about 60% of the liver
2. reticulo endothelial cells (Kupffer cells)
3. biliary tracts
4. blood vessels

On histological examination, the liver appears to be composed of radical columns of cells arranged in lobules around a central efferent vein. At the periphery of the lobules lie portal tracts, each containing a small branch of the hepatic artery and of the portal vein and a small bile duct. Between the columns of liver cells are sinusoids lined with cells of the reticulo-endothelial system known as Kupffer cells. Small bile canaliculi lie between the liver cells, forming a network which opens eventually into the interlobular ducts situated in the portal tracts.

From the portal vein and from the hepatic artery in the portal tract, blood passes into the sinusoids and reaches the central vein, which drains into the hepatic veins. Mixing of portal venous and hepatic arterial blood appears to occur in the sinusoids. When the normal architecture of the liver, including presinusoidal sphincter on the arterioles, is damaged by disease, direct transmission of the high arterial pressure to the portal system may be partly responsible for the portal venous hypertension found in such conditions.

Bile, secreted by the liver cells, passes, in reverse direction to the blood flow, through canaliculi to the periphery of the lobule. There, the bile ducts are lined with cuboidal epithelium and gradually become larger as they progress to the porta hepatis. Ultimately the common hepatic duct is formed by the union of the ducts from the right and left lobes of the liver, and this, with the cystic duct from the gall – blader, forms the common bile duct. This usually traverses the substance of the head of the
pancreas, where it is joined, in the majority of cases, by the pancreatic duct. The united ducts then open into the second part of the duodenum through the ampulla of Vater, the opening being controlled by the sphincter of Oddi.

2.2.2 Metabolic activities of the liver

Liver cells perform many functions of liver. It plays an important role in the maintenance of internal environment through its multiple diverse functions. It is involved in the intermediatory metabolism of proteins, fats and carbohydrates and in the synthesis of number of plasma proteins, such as albumin, fibrinogen and clotting factors in the production of varied enzymes and formation and excretion of bile.

(a) Carbohydrate Metabolism

Liver is an important organ in the body for the maintenance of a normal concentration of blood glucose. It is able to covert glucose, fructose, galactose, glycerol, certain amino acid residues, and 2- and 3-carbon compound (e.g. lactate, pyruvate and oxalo-acetate) to glycogen. In hypoglycaemia it hydrolysates stored glycogen to glucose. These mechanisms are intrinsic functions of the organ but they are influenced by many extrahepatic factors, e.g. insulin, adrenalin, thyroxine, cortisol and glucagon.

(b) Protein Metabolism

Liver is the most important site of deamination of amino acids, as a preliminary step in their interconversion and oxidation. Urea synthesis from the amino groups made available by this process occurs solely in the organ. Plasma albumin, prothrombin, fibrinogen and the other clotting factors V, VIII, IX and X are synthesized perhaps exclusively in the parenchymal cells of the liver. Alfa and beta globulins are mainly formed in the liver, while gama globulin is formed by cells of the reticulo-endothelial system. As a result of these synthesis, the protein pattern of the plasma is to a large extent determined by liver function.
(c) Lipid Metabolism

Liver plays an important part in fat metabolism. Fats are oxidized in the liver as far as the four carbon chain stage (ketone bodies) is concerned. The amount of this oxidation depends, *inter alia*, upon the availability of carbohydrate and is greatly increased when sugar is absent as in fasting or when there is difficulty in its use as in diabetes mellitus. The ketone bodies themselves do not appear to be oxidized in the liver and are liberated into the blood stream for peripheral oxidation. Triglycerides are formed in the liver and synthesis of phospholipid from fatty acid, glycerol, phosphate and a nitrogenous base, e.g. choline, also occurs largely in the liver. Cholesterol is synthesized in the liver and is also esterified there. Cholesterol and triglycerides circulate in the blood as lipoproteins; not only is the liver an important source of these complexes which maintain lipid in colloidal solution, but it also contains an enzyme which can break the lipid-protein bond. Bile salts, the breakdown products of cholesterol, are synthesized in the liver cells and in turn facilitate the excretion of cholesterol in the bile.

(d) Vitamin Metabolism

Liver is directly or indirectly concerned with the metabolism of many vitamins. Fat-soluble vitamins depend to some extent for their absorption upon a normal biliary secretion. Vitamin K is required by the hepatic cells for the production of prothrombin and factor VII. Liver contains enzymes and prosthetic groups. The phosphorylation of thiamine, which is a necessary preliminary to its function as a coenzyme, the methylation of nicotinic acid and the 25-hydroxylation of vitamin D also occurs in the liver.

(e) Inactivation of Hormones

Oestrogens, corticosteroids and other steroid hormones are conjugated in the liver with glucuronic acid and excreted in the urine, though other modes of inactivation also occur. Thyroxine and vasopressin are probably inactivated in the liver, but the mechanisms are unknown.
(f) **Detoxification of Drugs**

Liver plays a vital role in the detoxification of drugs as well as endogenous hormones. This is achieved by enzyme systems of broad specificity located on the endoplasmic reticulum (microsomal enzymes). At these sites the drugs are rendered more water soluble and can then be excreted in the bile and urine. Alkaloids such as morphine or atropine are partly destroyed in the liver, ammonia is converted to urea, barbiturates undergo oxidation of their side chain and are rendered pharmacologically inert. Conjugation with glucuronic acid occurs with salicylates, morphine and chloral hydrate, and these conjugates are less active than their precursors.

(g) **Biliary Excretion**

Bile is produced by the liver and passes through the intrahepatic biliary channels to the common hepatic duct and then to the gall-bladder. The main constituents apart from water and inorganic slats are bilirubin, bile acids, cholesterol, alkaline phosphatase and mucin.

1) **Bilirubin**

Haemoglobin is broken down by reticulo-endothelial cells mainly in the spleen, liver and bone marrow. The bile pigment, bilirubin, is derived from the non-iron-containing residue of haemoglobin after the separation from globin. A small amount of bilirubin is derived from other haem-containing compounds such as haemoglobin precursors in the bone marrow, myoglobin and the cytochromes. In the blood this unconjugated bilirubin (prehepatic bilirubin) is bound to plasma albumin and as a consequence, does not pass readily through the glomerulus of the kidney into the urine. Unconjugated bilirubin is actively transported from the blood to the bile by the liver cells and during its passage it is separated from its protein and is conjugated with glucuronic acid. Conjugation occurs in the microsomes of the liver cells by the activity of glucuronyl transferase and renders the pigment water-soluble so that it becomes capable of being more freely excreted in the urine. This compound is called conjugated bilirubin.
In the small intestine conjugated bilirubin is metabolized by bacteria to a series of isomers of stercobilinogen which on oxidation form the main faecal pigment stercobilin. The bulk of these pigment is excreted in the stool (250 mg/day) but some is reabsorbed from the gut. Most of this is excreted by the liver cells into the intestine and a small part is excreted in the urine (2-4 mg/day) where it is called urobilinogen. Urobilinogen and its oxidation product urobilin are chemically identical with stercobilinogen and stercobilin, respectively.

2) Excretion of Bile Acids and Cholesterol

Bile acids are the breakdown products of cholesterol. They are synthesized in the liver and conjugated with glycine and taurine to form bile salts which are secreted directly into the bile. Here they may form micelles when in sufficient concentration and these micelles, which also contain phospholipid, permit the solubilisation of cholesterol although its biliary concentration far exceeds its aqueous solubility in a simple solution. An alteration of these solutes in bile is now recognized as a major factor in the precipitation of cholesterol and provides the nidus for gall-stone formation. In the lumen of the proximal small intestine bile salts are essential for the solubilisation of the products of fat digestion. About 90 per cent of the bile salts are reabsorbed from the distal ileum and return to be reexcreted by the liver. Only a small amount (300 mg) of bile salts escapes daily into the colon. In the colon the bile salts have a cathartic action due to interference with the resorption of electrolytes and water. In addition to a troublesome diarrhoea there is also steatorrhea since the liver cannot compensate for the increased loss of bile salt.

3) Excretion of Enzymes

The serum alkaline phosphatase is derived mainly from the intrahepatic biliary system and the level tends to rise when there is obstruction to biliary excretion. An isoenzyme produced by the osteoblasts accounts for a variable proportion of alkaline phosphatase activity in growing children and in disease of bone. In about 50 per cent of healthy individuals there is in the serum a small amount of alkaline phosphatase which is produced by the intestinal mucosa. Yet another isoenzyme is produced by the placenta and accounts for some of the serum alkaline phosphatase activity in pregnancy. Various malignant tumours, e.g. of lungs and
pancreas, have been shown to produce alkaline phosphatase which has similar physico-chemical properties to the placental isoenzyme.

Hence, any injury to liver or impairment of its function has grave implication for the health of the affected person. Every year about 18,000 people are reported to die due to liver cirrhosis caused by hepatitis\textsuperscript{146,147}. Although viral infection is one of the main causes of hepatic injury, xenobiotics, excessive drug therapy, environment pollutants and chronic alcohol ingestion can also cause severe liver injury. Since it plays a central role in processing, metabolizing and disposition of foreign chemicals, it is susceptible to their injurious effects.

2.2.3 Diseases of liver

1. Viral hepatitis:

This infection is caused either by hepatitis virus A or by hepatitis virus B. Former is spread through food and water and later by administration of blood and blood products. During the cause of viral hepatitis, serum levels of liver enzymes especially GPT and GOT is raised. Also bilirubin concentration in plasma raises.

2. Hepatic failure

Acute failure in a healthy individual may be produced by poisoning with a hepatotoxic substance. Severe hepatic failure is symptomised by muscle tremors, exaggerated planter reflexes, muscle spasticity, convulsions and finally death supervenes.

3. Fatty liver:

The amount of fat in hepatocytes may be considerably increased if fat metabolism is impaired (eg. In diabetes) or if the proportion of fat in the diet is excessive, particularly when there is deficiency of choline and methionine.

4. Cirrhosis:

This liver disorder is characterized by loss of hepatocytes and their replacement by fibrous connective tissue. The case of cirrhosis include viral hepatitis, biliary obstruction, hepatotoxic agents, malnutrition and congestive heart failure.
2.2.4 Hepatotoxic agents and drugs

Liver is the chief organ engaged in the process of detoxification to defend and protect the body against many harmful effects. If the liver is incapable of detoxifying a poisonous compound, it fixes the unwarranted substance to itself thus protecting the more vital organs, that is why, such extensive reserve power is conferred on the liver to compensate for any possible damage to itself in the arduous fight against harm, especially in the process of fixation of poison. In fixing the poison to itself, the liver undergoes vicarious suffering and degeneration.

Hepatotoxic agents and drugs can cause direct damage to the liver or interferer with its function.\textsuperscript{148}

1. By causing hepatitis, necrosis with jaundice, haemorrhagic manifestation or hepatic coma.
   e.g. Carbon tetrachloride, benzene, quinoline derivatives, phynytin, isoniazide etc.

2. By causing hepatic fibrosis or metabolite 6-mercaptopurine cholestasis and hepatic necrosis
   e.g. Paracetamol, salicylates and tetracyclines.

3. By causing obstructive jaundice with intra-hepatic biliary obstruction
   e.g. Chlorpromazine, thio-uracils, para amino salicylic acid and methimazole

4. Inteference with bilirubin metabolism and excretion
   e.g. Androgens and anabolic steroids like Methyl estosterone, oxymetholone, stanozolol

5. Membrane specific toxins wherein the specific toxic effect on hepatocytes membrane leads to death of hepatocytes
   e.g. Peptide toxins – amanitine and phalloidin

Phosphorous and arsenicals cause both acute and chronic cirrhotic changes in the liver. Bile acids, e.g. Cheno-de-oxy cholic acid affect liver function by competitive inhibition of microsomal enzymes and by their detergent effect resulting in the
hypoactive endoplasmic reticulum. This impairs metabolism of exogenous compounds like bile acids resulting in hepatocellular necrosis.

The liver damage may manifest as demonstrated below:

- **Causative agent**
  - Recovery
  - **Acute hepatitis** → Death
    (necrosis, steatosis, inflammation)
  - Recovery
  - **Chronic hepatitis**
    (necrosis, inflammation, fibrosis)
  - **Cirrhosis** → Death

Plants containing pyrrolizidine alkaloids are also reported to cause hepatotoxicity.
- e.g. Symphytum officinale.
- Symphytum xuplandium.
- Tussilago farfara.
- Petasites japonicum.

### 2.2.5 Therapeutic approaches and targeted objectives

**Therapeutic Approaches and Targeted objectives – Hepatitis B**

Persistent hepatitis B virus infection may be controlled by the following therapeutic approaches until resistance develops\(^{149}\).

**Chemotherapy (Nucleoside analogues)**
- Lamivudine
- Pencyclovir
- Combination: Lamivudine + Pencyclovir
Hepatitis B vaccine

Modern era of vaccinology began in 1950. Its pursuit has been based largely on breakthroughs in cell culture, bacterial polysaccharide chemistry, molecular biology and immunology. Hepatitis B vaccine is a sterile suspension containing purified virus manufactured by recombinant DNA technology. Hepatitis B vaccine prevents both hepatitis B viral (HBV) infection and those diseases related to HBV infection. It is used for active immunization against hepatitis infections. The discovery of antigen of hepatitis B virus in the blood of human infection carriers opened the door to a hepatitis B vaccine. Probes were carried out to explore purification, yield, inactivation, safety, and efficacy of a possible hepatitis B vaccine. In 1980, a high level protective efficacy of the vaccine was proved, first in Chimpanzee challenge studies and then in controlled clinical trials in man. The vaccine was proved safe and highly protective and was licenced for general use.

2.2.6 Plants with antihepatotoxic principles

Though liver diseases are among the important diseases affecting mankind, no remedy is available for majority of them at present. Treatment options for common liver diseases such as cirrhosis, fatty liver and chronic hepatitis are problematic. The effectiveness of treatments such as interferon, colchicines, penicillamine and corticosteroids are inconsistent at best and the incidence of side effects profound. All too often, the treatment is worse that the disease. Physicians and patients are in need of effective therapeutic agents with a low incidence of side effects. Plants potentially
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constitute such a group. Number of medicinal preparations have been advocated in traditional system of medicine, especially in Ayurveda for treating liver disorders. In recent years many researchers have examined the effects of plants used traditionally by indigenous healers and herbalists to support liver function and treat diseases of the liver. Basic scientific research has uncovered the mechanisms by which some plants afford their therapeutic effects as well as reaffirmed the effectiveness of certain plants or plant extracts in clinical studies. However, there is paucity of reviews on medicinal plants possessing hepatoprotective activity. Hence it was though worthwhile to collect and enumerate data on medicinal plants possessing hepatoprotective activity so that it could serve as a source of information to provide an idea about the current trends in research on plants possessing hepatoprotective activity. Silybum marianum (milk thistle), Picrorhiza kurrao (Kutkin), Curcuma longa (turmeric), Camellia sinensis (green tea), Chelidonium majus (greater celendine), Glycyrrhiza glabra (licorice) and Allium sativa (garlic) are among the handful of plants which have been fairly well researched.

Following table exhibits a number of plant drugs with hepatoprotective activity\textsuperscript{155,156}.

<table>
<thead>
<tr>
<th>No.</th>
<th>Plants</th>
<th>Part of plant used</th>
<th>Active principle or extract</th>
<th>Models used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Silybum marianum,</td>
<td>Seed</td>
<td>Flavanolignans</td>
<td>Carbon tetrachloride\textsuperscript{157}, thioacetamide\textsuperscript{158}, galactosamine\textsuperscript{159}, thallium\textsuperscript{160}, lead and cadmium poisoning\textsuperscript{161}, plasmodium berghei infection in mastomys\textsuperscript{162}</td>
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<td></td>
<td></td>
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<td>Silymarin and Silybin</td>
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<td>2.</td>
<td>Picrorhiza kurrao</td>
<td>Roots and rhizomes</td>
<td>Iridoid glycosides, Picrosides I, II, III and Kutkoside</td>
<td>Amanita poisoning\textsuperscript{163,164}, Carbon tetrachloride\textsuperscript{165,166,167}, galactosamine\textsuperscript{166,168,170}, ethanol\textsuperscript{171}, aflatoxin B1\textsuperscript{172}, acetaminophen\textsuperscript{173}, thioacetamide\textsuperscript{174}, oxytetracycline\textsuperscript{176} and monocrotaline\textsuperscript{176}</td>
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<tr>
<td>No.</td>
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<td>Part of plant used</td>
<td>Active principle or extract</td>
<td>Models used</td>
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<td>3.</td>
<td>Andrographis paniculata</td>
<td>Aerial parts</td>
<td>Diterpenoid lactone, Adrographolide</td>
<td>Carbon tetrachloride, ethanol, galactosamine, infective hepatitis</td>
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<td>4.</td>
<td>Phyllanthus niruri</td>
<td>Aerial parts including roots</td>
<td>Phyllanthin and hypophyllanthin</td>
<td>Carbotetracloride and D-galactosamine, hepatitis B virus</td>
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<td>5.</td>
<td>Glycyrrhiza glabra</td>
<td>Roots</td>
<td>Glycyrrhizin and glycyrrhetinic acid</td>
<td>Carbon tetrachloride, D-galactosamine</td>
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<td>6.</td>
<td>Panax ginseng</td>
<td>Roots</td>
<td>Oleanane type saponin ginsenoside Ro</td>
<td>Carbon tetrachloride, galactosamine, ( \alpha )-naphthyl isothiocyanate (ANIT)</td>
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<td>7.</td>
<td>Lawsonia alba</td>
<td>Bark</td>
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<td>Carbon tetrachloride</td>
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<td>8.</td>
<td>Gentiana macrophylla</td>
<td>Roots</td>
<td>Secoirridoid gentiopicroside</td>
<td>Carbon tetrachloride, Lipopoly schararide (LPS) or bacillus calmette – Guerin (BCG)</td>
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<td>10.</td>
<td>Lycium chinense</td>
<td>Fruits</td>
<td>Zeaxanthin, Zeaxanthin palmitate</td>
<td>Carbon tetrachloride</td>
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<td>11.</td>
<td>Cochlospermum tinctorium</td>
<td>Rhizome</td>
<td>Flavonoids, triterpene and apocardeooids</td>
<td>Aflatoxin B, carbon tetrachloride</td>
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<td>12</td>
<td>Curcuma longa</td>
<td>Rhizomes</td>
<td>Curcumin</td>
<td>Carbon tetrachloride&lt;sup&gt;203, 204&lt;/sup&gt;, galactosamine&lt;sup&gt;205&lt;/sup&gt;, pentobarbital, 1-chloro-2-4-dinitrobenzene, 7-4-hydroxy nonen&lt;sup&gt;206&lt;/sup&gt;, paracetamol&lt;sup&gt;207&lt;/sup&gt;, aflatoxin B&lt;sup&gt;208, 209&lt;/sup&gt;</td>
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<td>Camellia sinensis</td>
<td>Leaves</td>
<td>Polyphenol epigallocatechin gallate</td>
<td>2-nitropropane&lt;sup&gt;210&lt;/sup&gt;, alcohol&lt;sup&gt;211&lt;/sup&gt;, galactosamine&lt;sup&gt;212&lt;/sup&gt;, 1,4-naphthoquinone&lt;sup&gt;213&lt;/sup&gt;</td>
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<td>14</td>
<td>Acacia catechu</td>
<td>Heart wood</td>
<td>Cyanidanol</td>
<td>Carbon tetrachloride&lt;sup&gt;216&lt;/sup&gt;</td>
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<td>Allium sativum</td>
<td>Bulbs</td>
<td>S.allyl mercapto cysteine</td>
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<td>Withania coagulens</td>
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<td>Withanolide F</td>
<td>Carbon tetrachloride&lt;sup&gt;218&lt;/sup&gt;</td>
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<td>Boerhavia diffusa</td>
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<td>Boerhavia repanda</td>
<td>Roots</td>
<td>Petrol ether, chloroform and methanol extract</td>
<td>Carbon tetrachloride, galactosamine and paracetamol&lt;sup&gt;220&lt;/sup&gt;</td>
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<td>Butea monosperma</td>
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<td>Isobutrin and butrin</td>
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<td>Withania somnifera</td>
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<td>Calotropis gigantean</td>
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<td>Carbon tetrachloride&lt;sup&gt;223&lt;/sup&gt;</td>
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<td>Carbon tetrachloride&lt;sup&gt;223&lt;/sup&gt;</td>
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<td>Indigofera tinctoria</td>
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<td>Alcohol extract</td>
<td>Carbon tetrachloride&lt;sup&gt;227,228&lt;/sup&gt;</td>
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<td>Sambuculin A and Alpha &amp; Beta amyrin</td>
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<td>Desozy prodophyllotoxin</td>
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2.3 PATHOPHYSIOLOGY OF DIARRHOEA AND PLANT DRUGS

2.3.1 Intestinal Physiology

Diarrhoea is the too frequent passage of faeces which is characterized by an abnormal increase in stool frequency, weight or liquidity. Diarrhoea ranges from a mild and socially inconvenient illness to a major cause of death and malnutrition among children in developing countries; acute diarrhoea causes 4-5 million deaths throughout the world annually. Watery diarrhoea results from disordered water and electrolyte transport in the small intestine. Intestinal transport mechanisms are also the basis for the management of diarrhoea through oral fluid therapy and feeding. Drugs have a place in its management but the first priority of therapy is to preserve fluid and electrolyte balance because diarrhoea involves both an increase in the motility of the gastrointestinal tract and a decrease in the absorption of fluid and thus a loss of electrolytes (particularly sodium) and water. The condition is often assumed to be infectious, but it may be caused by anxiety, food, drugs, microbial or other toxins.\(^{239}\)

Normal intestinal fluid balance

Normally, absorption and secretion of water and electrolytes occur throughout the intestine. For example, a healthy adult takes in less than two litres of fluid each day. Saliva and secretions from the stomach, pancreas, and liver add about seven litres, making a total of about nine litres that enter the small intestine every day. There, water and electrolytes are simultaneously absorbed by the villi and secreted by the crypts of the bowel epithelium. This causes a two-directional flow of water and electrolytes between the intestinal lumen and the blood. Since fluid absorption normally is greater than fluid secretion, the net result is fluid absorption. Usually, more than 90% of the fluid entering the small intestine is absorbed, so that about one litre reaches the large intestine. There, further absorption occurs, only 100 to 200 millilitres of water being excreted each day in formed stools. Any change in the two-directional flow of water and electrolytes in the small intestine (i.e., increased secretion, decreased absorption, or both) results in either reduced net absorption or...
net secretion and causes an increased volume of fluid to enter the large intestine. When this exceeds its limited absorptive capacity, diarrhoea occurs.

**Intestinal absorption of water and electrolytes**

Absorption of water from the small intestine is caused by osmotic gradients that are created when solutes (particularly sodium) are actively absorbed from the bowel lumen by the villous epithelial cells. There are several mechanisms whereby sodium is absorbed in the small intestine. To enter the epithelial cells, sodium is linked to the absorption of chloride, or absorbed directly as sodium ion, or exchanged for hydrogen ion, or linked to the absorption of organic materials such as glucose or certain amino acids. The addition of glucose to an electrolyte solution can increase sodium absorption in the intestine as much as threefold.

After being absorbed, sodium is transported out of the epithelial cells by an ion pump referred to as Na⁺K⁺ ATPase. This transfers sodium into the extracellular fluid (ECF), which elevates its osmolality and causes water and other electrolytes to flow passively from the bowel lumen through intercellular channels and into the ECF. This process maintains an osmotic balance between fluid in the bowel and ECF in the intestinal tissue.

**Intestinal secretion of water and electrolytes**

Secretion of water and electrolytes normally occurs in the crypts of the small bowel epithelium where NaCl is transported from ECF into the epithelial cell across its basolateral membrane. The sodium is then pumped back into the ECF by Na⁺K⁺ ATPase. At the same time, secretory stimuli increase the ability of chloride to pass through the luminal membrane of the crypt cells, allowing that ion to enter the bowel lumen. This movement of chloride ion creates an osmotic gradient that causes water and other electrolytes to flow passively from the ECF into the bowel lumen through the intercellular channels.
2.3.2 Mechanisms of watery diarrhoea

Diarrhoea being infectious is often caused by enteropathogens (protozoa, bacteria, virus) and parasites. They reach the small intestine, where the proliferation takes place. On attaining considerable strength, the pathogen starts interfering in the cell function of the intestine, which results into the inflammation of the intestine (enteritis). Sometimes the intestine loses its tonicity and normal peristaltic movement by which the gas produced in the digestive procedure does not get cleared becomes the cause of flatulence, which is commonly known as gastro-enteritis. All those factors become responsible for treating less osmotic pressure, lesser the osmotic pressure poor is the absorption, ultimately leads to diarrhoea. This type of diarrhoea is generally termed as inflammatory diarrhoea and osmotic diarrhoea.

Sometimes, high proliferation of the pathogen and parasite leads to the sloughing (cast off) of mucous and epithelial layer of the intestine, which are seen normally in the faeces. The epithelial and mucous layer sloughing leads to pitecheal haemorrhages in the intestine and turry coloured blood is seen in the stool termed as inflammatory diarrhoea. Diarrhoea has many diverse causes but there are two principal mechanisms by which watery diarrhoea occurs. (i) secretion (i.e. maldigestive) and (ii) osmotic imbalance (i.e. malabsorptive). Inflammatory states and deranged intestinal motility due to intestinal infections can cause diarrhoea by both mechanisms, secretory diarrhoea being more common and both may occur in a single individual.

Secretory diarrhoea

Secretory diarrhoea is caused by the abnormal secretion of fluid (water and salts) into the small bowel. This occurs when the absorption of sodium by the villi is impaired while the secretion of chloride in the crypts continues or is increased. Net fluid secretion results and leads to the loss of water and salts from the body as watery stools; this causes dehydration. In infectious diarrhoea, these changes may result from the action on the bowel mucosa of bacterial toxins, such as those of *Escherichia*
coli and *Vibrio cholerae* or of viruses, such as rotavirus; other mechanisms may also be important.

**Osmotic diarrhoea**

The small bowel mucosa is a porous epithelium; water and salts move across it rapidly to maintain osmotic balance between the bowel contents and the blood. Under these conditions, diarrhoea can occur when a poorly absorbed, osmotically active substance is ingested. If the substance is taken as an isotonic solution, the water and solute will simply pass through the gut unabsorbed, causing diarrhoea. Purgatives, such as magnesium sulfate, work by this principle. The same process may occur when the solute is lactose (in children with lactase deficiency) or glucose (in children with glucose malabsorption); both conditions are occasional complications of enteric infections. If the poorly absorbed substance is taken as a hypertonic solution, water (and some electrolytes) will move from the ECF into the gut lumen, until the osmolality of the intestinal contents equals that of ECF and blood. This increases the volume of the stool and, more importantly, causes dehydration owing to the loss of body water. Because the loss of body water is greater than the loss of sodium chloride, hypernatraemia also develops.

Most commonly, diarrhoea is caused by use of laxatives or stool softeners. These may be poorly absorbed sugars such as lactulose and sorbitol that are fermented by intestinal bacteria in the colon or poorly absorbed salts of magnesium (sulphate, oxide or hydroxide) or sodium (sulfate or citrate) ions. Other commonly used laxatives which cause diarrhoea include ricinoleic acid, phenolphthalein, dioctyl sodium sulfosuccinate and senna. In such drug induced diarrhoea, the diarrhoea that ensues is characterized by a stool osmolality higher than that of plasma.

The most serious drug induced diarrhoeal state is antibiotic related pseudomembranous colitis due to *Clostridium difficile*, the antibiotics most frequently implicated are ampicillin or amoxicillin, clindamycin and cephalosporins. *Escherichia coli* or *Vibrio cholera* infections cause diarrhoea through an enterotoxin that causes net excretion of chloride by the enterocyte.
2.3.3 Consequences of watery diarrhoea

Diarrhoea stool contains large amounts of sodium, chloride, potassium, and bicarbonate. All the acute effects of watery diarrhoea result from the loss of water and electrolytes from the body in liquid stool. Additional amount of water and electrolytes are lost when there is vomiting, and water losses are also increased by fever. These losses cause dehydration (due to the loss of water and sodium chloride), metabolic acidosis (due to the loss of bicarbonate), and potassium depletion. Among these, dehydration is the most dangerous because it can cause decreased blood volume (hypovolaemia), cardiovascular collapse, and death if not treated promptly. Three types of dehydration are considered below.
Isotonic dehydration

This is the type of dehydration most frequently caused by diarrhoea. It occurs when the net losses of water and sodium are in the same proportion as normally found in the ECF. The principal features of isotonic dehydration are:

- there is a balanced deficit of water and sodium;
- serum sodium concentration is normal (130-150 mmol/l);
- serum osmolality is normal (275-295 mOsmol/l);
- hypovolaemia occurs as a result of a substantial loss of extracellular fluid.

Isotonic dehydration is manifested first by thirst, and subsequently by decreased skin turgor, tachycardia, dry mucous membranes, sunken eyes, lack of tears, a sunken anterior fontanelle in infants, and oliguria. The physical signs of isotonic dehydration begin to appear when the fluid deficit approaches 5% of body weight and worsen as the deficit increases. As the fluid deficit approaches 10% of body weight, dehydration becomes severe and anuria, hypotension, a feeble and very rapid radial pulse, cool and moist extremities, diminished consciousness, and other signs of hypovolaemic shock appear. A fluid deficit that exceeds 10% of body weight leads rapidly to death from circulatory collapse.

Hypertonic (hypernatraemic) dehydration

Some children with diarrhoea, especially young infants, develop hypernatraemic dehydration. This reflects a net loss of water in excess of sodium, when compared with the proportion normally found in ECF and blood. It usually results from the ingestion during diarrhoea of fluids that are hypertonic (owing to their content of sodium, sugar, or other osmotically active solutes, such as lactose in whole cow’s milk) and not efficiently absorbed, and an insufficient intake of water or other low-solute drinks. The hypertonic fluids create an osmotic gradient that causes a flow of water from ECF into the intestine, leading to a decrease in the ECF volume and an increase in sodium concentration within the ECF. The principal features of hypernatraemic dehydration are:

- there is a deficit of water and sodium, but the deficit of water is greater;
- serum sodium concentration is elevated (>150 mmol/l);
• serum osmolality is elevated (>295 mOsmol/l);
• thirst is severe and out of proportion to the apparent degree of dehydration; the child is very irritable;
• seizures may occur, especially when the serum sodium concentration exceeds 165 mmol/l.

Hypotonic (hyponatraemic) dehydration

Children with diarrhoea who drink large amounts of water or other hypotonic fluids containing very low concentrations of salt and other solutes, or who receive intravenous infusions of 50% glucose in water, may develop hyponatraemia. This occurs because water is absorbed from the gut while the loss of salt (NaCl) continues, causing net losses of sodium in excess of water. The principal features of hyponatraemic dehydration are:

• there is a deficit of water and sodium, but the deficit of sodium is greater;
• serum sodium concentration is low (<130 mmol/l);
• serum osmolality is low (<275 mOsmol/l);
• the child is lethargic; infrequently, there are seizures.

Base-deficit acidosis (metabolic acidosis)

During diarrhoea, a large amount of bicarbonate may be lost in the stool. If the kidneys continue to function normally, much of the lost bicarbonate is replaced by the kidneys and a serious base deficit does not develop. However, this compensating mechanism fails when renal function deteriorates, as happens when there is poor renal blood flow due to hypovolaemia. Then, base deficit and acidosis develop rapidly. Acidosis also results from excessive production of lactic acid when patients have hypovolaemic shock. The features of base-deficit acidosis include:

• the serum bicarbonate concentration is reduced - it may be less than 10 mmol/l;
• arterial pH is reduced - it may be less than 7.10;
• breathing becomes deep and rapid, which helps to raise arterial pH by causing a compensating respiratory alkalosis;

• there is increased vomiting.

Potassium depletion

Patients with diarrhoea often develop potassium depletion owing to large faecal losses of this ion; these losses are greatest in infants and can be especially dangerous in malnourished children, who are frequently potassium-deficient before diarrhoea starts. When potassium and bicarbonate are lost together, hypokalaemia does not usually develop. This is because the metabolic acidosis that results from the loss of bicarbonate causes potassium to move from ICF to ECF in exchange for hydrogen ion, thus keeping the serum potassium level in a normal or even elevated range. However, when metabolic acidosis is corrected by giving bicarbonate, this shift is rapidly reversed, and serious hypokalaemia can develop. This can be prevented by replacing potassium and correcting the base deficit at the same time. The signs of hypokalaemia may include:

• general muscular weakness;
• cardiac arrhythmias;
• paralytic ileus, especially when drugs are taken that also affect peristalsis (such as opiates).

2.3.4 Treatment of diarrhoea

Following are the approaches or suggested line of treatment of diarrhoea.

(I) Rehydration therapy:

The goal in managing diarrhoeal dehydration is rapidly to correct fluid and electrolyte deficits (termed "rehydration therapy") and then to replace further fluid and electrolyte losses as they occur until diarrhoea stops (termed "maintenance therapy"). Fluid losses can be replaced either orally or intravenously; the latter route is usually needed only for initial rehydration of patients with severe dehydration.
(a) Oral rehydration therapy (ORT)

ORT is based on the principle that intestinal absorption of sodium (and thus of other electrolytes and water) is enhanced by the active absorption of certain food molecules such as glucose (which is derived from the breakdown of sucrose or cooked starches) or l-amino acids (which are derived from the breakdown of proteins and peptides). Fortunately, this process continues to function during secretory diarrhoea, whereas most other pathways of intestinal absorption of sodium are impaired. Thus, if patients with secretory diarrhoea drink an isotonic salt solution that contains no source of glucose or amino acids, sodium is not absorbed and the fluid remains in the gut, ultimately adding to the volume of stool passed by the patient. However, when an isotonic solution of glucose and salt is given, glucose-linked sodium absorption occurs and this is accompanied by the absorption of water and other electrolytes. This process can correct existing deficits of water and electrolytes and replace further faecal losses in most patients with secretory diarrhoea, irrespective of the cause of diarrhoea or the age of the patient.

(b) Oral rehydration salts (ORS)

The principles underlying ORT have been applied to the development of a balanced mixture of glucose and electrolytes for use in treating and preventing dehydration, potassium depletion, and base deficit due to diarrhoea. To attain the latter two objectives, salts of potassium and citrate (or bicarbonate) have been included, in addition to sodium chloride. This mixture of salts and glucose is termed oral rehydration salts (ORS); when ORS is dissolved in water, the mixture is called ORS solution.

The later takes advantage of glucose coupled sodium uptake and solvent drag in the small intestine which results in absorption of sodium and free water even in case of bacterial toxin induced secretory diarrhoea245.

The world Health Organisation has recommended an oral rehydration solution containing 90 mEq/l of sodium, 90 mEq/l of glucose, 20 mEq/l of potassium, 80 mEq/l
of chloride and 30 mEq / l of bicarbonate. The use of trisodium citrate, dihydrate is preferred, since this gives ORS packets longer shelf life.

(II) The use of antiinfective agents:

Campylobacter for eg. is the commonest bacterial organism causing gastroenteritis in UK and severe cases may require erythromycin. Chemotherapy may be necessary in some types of enteritis like typhoid, cholera, amoebic dysentery.

(III) The use of non-antimicrobial antidiarrhoeal agents:

These include

- Antimotility agents like opiates (codeine, diphenoxylate and loperamide), which allows time for more water to be absorbed.
- Adsorbents which increase the viscosity of gut contents directly. This includes kaolin, pectin, chalk, charcoal, methyl cellulose and magnesium aluminium silicate.
- Agents which modify fluid and electrolyte transport such as Non-steroidal anti-inflammatory agents such as aspirin and indomethacin, Bismuth salicylate and phenothiazines.

2.3.5 Andiarrhoeal Plant Drugs

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<th>Plants</th>
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<th>Active principle or extract</th>
<th>Model used</th>
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<td>Artemisia absinthium</td>
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<td>Berberine and crude extract</td>
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<td>Crude extract</td>
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<td>Mangifera indica</td>
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<td>Egletes viscose</td>
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<td>Tetramethoxy flavone</td>
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2.4 ANTIMICROBIALS OF PLANT ORIGIN

2.4.1 Introduction

Infectious diseases account for approximately one half of all deaths in tropical countries. In industrialized nations, despite the progress made in the understanding of microbiology and their control, incidents of epidemics due to drug resistant microorganisms and the emergence of hitherto unknown disease causing microbes pose enormous public health concerns.

Perhaps it is not surprising to see that infectious disease mortality rates are actually increasing in developed countries such as the United States. Death from infectious disease, ranked 5th in 1981, has become the 3rd leading cause of death in 1992, an increase of 58%. It is estimated that infectious disease is the underlying cause of death in 8% of the death occurring in the US. The increases are attributed to increase in respiratory tract infections and HIV/AIDS. Other contributing factors are an increase in antibiotic resistance in nosocomial and community acquired infections.

2.4.2 Historic use of plants as antimicrobials

Much of the exploration and utilization of natural products as antimicrobials arise from microbial sources. It was the discovery of penicillin that led to later discoveries of antibiotics such as streptomycin, aureomycin and chloromycetin. Though most of the clinically used antibiotics are produced by soil micro-organisms or fungi, higher plants have also been a source of antibiotics. Historically, plants have provided a source of inspiration of novel drug compounds, as plant derived medicines have made large contributions to human and well-being. Their role is two fold in the development of new drugs: (1) they may become the base for the development of a medicine, a natural blueprint for the development of new drugs, or (2) a phytomedicine to be used for the treatment of disease. There are numerous illustrations of plant derived drugs. Some of the selected examples include the isoquinoline alkaloid emetine obtained from the underground part of Cephalis ipecacuanha, and related species, has been used for many years as an amoebicidal drug as well as for the treatment of abscesses due
to the spread of Escherichia histolytica infections. Another important drug of plant origin with a long history of use, is quinine. This alkaloid occurs naturally in the bark of Cinchona tree. Apart from its continued usefulness in the treatment of malaria, it can be also used to relieve nocturnal leg cramps.

2.4.3 Present use of plants as antimicrobials

It is estimated that today, plant materials are present in, or have provided the models for 50% Western drugs. Many commercially proven drugs used in modern medicine were initially used in crude form in traditional or folk healing practices, or for other purposes that suggested potentially useful biological activity. Phytomedicines derived from plants have shown great promise in the treatment of intractable infectious diseases including opportunistic AIDS infections. Plants containing protoberberines and related alkaloids, picralime type indole alkaloids and garcinia biflavonones used in traditional African system of medicine have been found to be active against a wide variety of micro-organisms.

Higher plants have made important contributions in the areas beyond antiinfectives such as cancer therapies. Early examples includes the antileukaemic alkaloids vinblastine and vincristine, both obtained from Madagascan periwinkle (Catharanthus roseus / Vinca rosea). Other cancer therapeutic agents include taxol, homoharringtonine and several derivatives of Camptothein. For example, a well known benzylisoquinoline alkaloid papavarine has been shown to have a potent inhibitory effect on the replication of several viruses including cytomegalovirus, measles and HIV. Most recently, three new atropisomeric naphthylisoquinoline alkaloid dimmers, michellamines A, B and C were isolated from a newly described species tropical liana Ancistrocladus korupensis from the rainforest of Cameroon. These three compounds showed potential anti- HIV with michellamine – B being the most potent and abundant member of the series. These compounds are capable of complete inhibition of the cytopathic effects of HIV – I and HIV 2 on human lymphoblastoid target cell in vitro.
Plant based antimicrobials have enormous therapeutic potential. They represent a vast untapped source for medicine. The primary benefits of using plant derived medicines are that they are not only effective in the treatment of infectious diseases but they are relatively safer by simultaneously mitigating many of the side effects that are often associated with synthetic alternatives, offering profound therapeutic benefits and are more affordable. They are effective, yet gentle. Phytomedicines usually have multiple effects on the body. Many plants have tropisms to specific organs or systems in the body. Their actions often act beyond the symptomatic treatment of disease. For example Hycdrastis canadensis not only has antimicrobial activity, but also increases blood supply to the spleen, promoting optimal activity of the spleen to release mediating compounds.$^{283}$

### 2.4.4 Major classes of antimicrobial compounds from plants$^{284}$

<table>
<thead>
<tr>
<th>Class</th>
<th>Subclass</th>
<th>Example</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenolics</td>
<td>Simple phenols</td>
<td>Catechol</td>
<td>Substrate deprivation$^{285}$, Membrane disruption$^{286}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epicatechin</td>
<td></td>
</tr>
<tr>
<td>Quinones</td>
<td></td>
<td>Hypericin</td>
<td>Bind to adhesins, complex with cell wall, inactivate enzymes$^{287,288}$</td>
</tr>
<tr>
<td>Flavonoids</td>
<td></td>
<td>Chrysin</td>
<td>Bind to adhesins$^{289,290}$</td>
</tr>
<tr>
<td>Flavones</td>
<td></td>
<td>Abyssinone</td>
<td>Inactivate enzymes$^{291,292}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibit HIV reverse transcriptase$^{293}$</td>
</tr>
<tr>
<td>Tannins</td>
<td>Ellagitans</td>
<td></td>
<td>Bind to proteins and adhesins$^{294,295,296}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enzyme inhibition$^{297,298,299}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Substrate deprivation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Complex with cell wall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Membrane disruption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Metal ion complexation</td>
</tr>
</tbody>
</table>
### Simple phenols and phenolic acids

Cinnamic and caffeic acids are common representatives of a wide group of phenyl propane – derived compounds. The common herbs tarragon (Artemisia dracunculus) and thyme (Thymus vulgaris) both contain caffeic acid which is effective against virus\(^3\), bacteria\(^4\) and fungi\(^5\). Catechol and pyrogallon both are hydroxylated phenols shown to be toxic to microorganisms\(^6,7\). Phenolic compounds possessing a 3- side chain and containing no oxygen are classified as essential oils and often cited as antimicrobial as well eg. Eugenol of clove oil is considered bacteriostatic against both fungi\(^8\) and bacteria\(^4\).

### Quinones

Quinones are aromatic compounds with two ketone substitutions. They are ubiquitous in nature and are characteristically highly reactive. Kazmi\(^9\) described an anthraquinone from Cassia italica, a Pakistani tree which was bacteriostatic for...
Bacillus anthrax, Corynebacterium pseudodiphthericum and Pseudomonas aeruginosa and bactericidal for Pseudomonas pseudomalliae. Hypericin, an anthraquinone form St. John’s wort (hypericum perforatum) has received much attention lately as antidepressant. It is reported to have general antimicrobial properties287.

Flavones, flavonoids and flavonols

Flavones are phenolic structures containing one carbonyl group. Addition of a 3-hydroxyl group yields a flavonol. Flavonoids are also hydroxylated phenolic compounds but occurs as a C6-C3 unit linked to an aromatic ring. Since they are known to be synthesized by plants in response to microbial infection317 it should not be surprising that they have been found in vitro to be effective antimicrobial substances against a wide array of microorganisms.

Catechins, the most reduced form of the C6-C3 unit in flavonoid compounds have been researched extensively due to their occurrence in green teas. It was noticed some time ago that teas exerted antimicrobial activity318 and they contain a mixture of catechin compounds. These compounds inhibited in vitro vibrio cholerea319, streptococcus mutans320-323. Shigella324 and other bacteria and microorganisms322,314. Catechins inactivated Cholera toxin in Vibrio319 and inhibited isolated bacterial glycosyltransferases in mutants325. When the rats were fed a diet containing 0.1% tea catechins, fissure caries (caused by S.mutans) was reduced by 40 %326.

Flavonoids also exhibit inhibitory effects against multiple viruses. Numerous studies have documented the effectiveness of flavonoids such as swertifranceside327, glycyrrhizin328 against HIV. Flavone derivatives are inhibitory to respiratory syncytial virus (RSV)329,330. Kaul331 has provided summary of the activities and modes of action of quercetin, naringin, hesperidin and catechin in invitro cell culture monolayers.

An Isoflavone found in a west African legume, alpinumisoflavone prevents schistosomal infection when applied topically289. Phloretin, found in certain apples may have activity against a variety of microorganisms332. Galangin, trihydroxy flavone from Helichysum ureonitens shows wide range of activity against gram positive
bacteria as well as fungi\textsuperscript{333} and viruses, particularly HSV – I and Coxsackie B virus, type I\textsuperscript{309}.

**Tannins**

Tannins are polymeric phenolic substances capable of tanning leather or precipitating gelatin from solution, a property known as astringency. Their molecular weight range from 500 to 3000\textsuperscript{297} and are found in almost every plant part; bark, wood, leaves, fruits and roots\textsuperscript{295}. Tannins are either hydrolysable or condensed Tannins. Hydrolysable tannins are multiple esters of gallic acid with D – glucose. Condense tannins also called proanthocyanidins, derived from flavonoid monomers. Many human physiological activities such as stimulation of phagocytic cells, host mediated tumor activity and a wide range of anti-infective actions have been assignd to tannins\textsuperscript{297}. There is also evidence for direct inactivation of microorganisms: low tannin concentrations modify the morphology of germ tubes of Crinipellis perniclosa\textsuperscript{298}. Tannins in plants inhibit insect growth\textsuperscript{294} and disrupt the digestive events in ruminal animals\textsuperscript{299}.

Scalbert\textsuperscript{295} has reviewed the antimicrobial properties of tannins in 1991 and listed 33 studies which had documented the inhibitory activities of tannins. According to these studies, tannins can be toxic to filamentous fungi, yeast and bacteria. Condensed tannins have been determined to prevent growth and protease activity of ruminal bacteria\textsuperscript{334}.

**Coumarins**

Coumarins are phenolic substances made of fused benzene and pyrone rings\textsuperscript{335}. They are responsible for the characteristic odour of hay. As of 1996, at least 1,300 had been identified\textsuperscript{301}. Warfarin, a particularly well known courmarin used as oral anticoagulant and as rodenticide\textsuperscript{302} have shown antiviral effects\textsuperscript{336}. Coumarin was also found in vitro to inhibit Candida albicans\textsuperscript{337}. Hydroxycinnamic acids related to coumarins, inhibit gram positive bacteria\textsuperscript{338}. Also phytoalexins, hydroxylated derivatives of coumarins, produced in carrots in response to fungal infection are presumed to have antifungal action\textsuperscript{301}.
Terpenoids and Essential oils:

The fragrance of plants is carried in the so called Quinta essentia or essential oil fraction. These oils are secondary metabolites that are highly enriched in compounds based on an isoprene structure. They are called terpene (C₅H₈). Where these compounds contain additional elements, usually oxygen, they are termed as terpenoids. Examples of common terpenoids are methanol and camphor (monoterpenes) and farnesol and artemisin (sesquiterpenoids). Artemisin and its derivative arteether, also known as quinghaosu, find current use as antimalarials.

Terpenes or Terpenoids are active against bacteria, fungi, viruses and protozoa. In 1977 it was reported that 60% of essential oil derivatives examined to date were inhibitory to fungi while 30% inhibited bacteria.

Capsaicin, a terpenoid constituent has clearly inhibited growth of various bacteria to differing extents. Although possibly detrimental to the human gastric mucosa, capsaicin is also bactericidal to Helicobacter pylori. Another hot tasting diterpene aframodiol from Cameroonian spice is a broad spectrum antifungal. The ethanol soluble fraction of purple prairie clover yield a terpenoid petalostemumol, which showed excellent activity against Bacillus subtilis and Staphylococcus aureus. The latex of carica papaya was found to be bacteriostatic to Bacillus subtilis, Enterobacter cloacae, Escherichia coli, Salmonella typhi, Staphylococcus aureus and Proteus vulgaris.

Alkaloids:

Heterocyclic nitrogen compounds are called alkaloids. The first medicinally useful example of an alkaloid was morphine. Diterpenoid alkaloids commonly isolated from the plants of Ranunculaceae or butter cup family are commonly found to have antimicrobial properties. Solamargine, a glycoalkaloid from the berries of solanum is useful in HIV infections associated with AIDS. Berberine again is an important representative of alkaloid group potentially effective against trypanosomes and plasmodia.
Lectins and polypeptides

Peptides are inhibitory to microorganisms was first reported in 1942\textsuperscript{368}. Inhibition of bacteria and fungi by these macro-molecules from herbaceous Amaranthus has long been known\textsuperscript{369}. Thionins are peptides commonly found in barley and wheat\textsuperscript{370,371}. They are toxic to yeast, gram negative and gram positive bacteria\textsuperscript{372}. Fabatin, 47 residue peptide from fava beans, structurally related to thionins inhibits E.coli, P. aeruginosa and Enterococcus hirae\textsuperscript{310}. The larger lactin molecules, which included mannose specific lectins from several plants\textsuperscript{373}, are inhibitory to viral proliferation (HIV)\textsuperscript{374,375,376}.

Mixtures

The chewing stick is widely used in African countries as an oral hygiene aid (in place of a toothbrush)\textsuperscript{377}. Crude extract of chewing stick of one such specie, Serindeia werneckeii, inhibited the periodontal pathogens Romanus gingivatis and Bacteroides melaninogenicus\textsuperscript{378}. The active component of the Nigerian chewing stick (Fagara zanthoxyloides) was found to consist of various alkaloids\textsuperscript{379}. Whether these compounds, long utilized in developing countries, might find use in the Western world is not yet known.

Other compounds

Many phytochemicals not mentioned above have been found to exert antimicrobial properties. It should be mentioned, however that there are reports of antimicrobial properties associated with polyamines (in particular spermidine)\textsuperscript{380}, isothiocyanates\textsuperscript{381,382}, thiosulfinates\textsuperscript{383} and glucosides\textsuperscript{384,385}.

Polyacetylenes deserve special mention. Estevez – Braun isolated a C\textsubscript{17} polyacetylene from Bupleurum salicifolicum, a plant native to Canary islands. The compound, \(8\text{-heptadeca-2(z), 9(z)diene-4,6-diynyl-1,8-diol} \) was inhibitory to S.aureus and B. subtilis, but not to yeasts and gram negative bacteria\textsuperscript{386}.
Much has been written about the antimicrobial effects of cranberry juice. In 1990, researchers found that the monosaccharide fructose present in cranberry and blueberry juices competitively inhibited the absorption of pathogenic urinary tract epithelial cells, acting as an analogue for mannose\textsuperscript{387}. Clinical studies have borne out the protective effects of cranberry juice\textsuperscript{388}. Many fruits contain fructose, however, and researchers are now seeking a second active compound from cranberry juice which contributes to the antimicrobial properties of this juice\textsuperscript{387}.

### 2.4.5 Plant products as antimicrobial agents

<table>
<thead>
<tr>
<th>Common name</th>
<th>Scientific name</th>
<th>Compound</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe</td>
<td>Aloe barbadensis</td>
<td>Latex</td>
<td>Corynebacterium, Salmonella, Streptococcus and S. aureus \textsuperscript{389}</td>
</tr>
<tr>
<td></td>
<td>Aloe vera</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aloe</td>
<td>Aloe barbadensis</td>
<td>Latex</td>
<td>Corynebacterium, Salmonella, Streptococcus and S. aureus \textsuperscript{389}</td>
</tr>
<tr>
<td></td>
<td>Aloe vera</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apple</td>
<td>Malus sylvestris</td>
<td>Phloretin</td>
<td>General\textsuperscript{332}</td>
</tr>
<tr>
<td>Bael</td>
<td>Aegle marmelos</td>
<td>Terpenoid</td>
<td>Fungi\textsuperscript{390}</td>
</tr>
<tr>
<td>Barbery</td>
<td>Berberis vulgaris</td>
<td>Berberine</td>
<td>Bacteria, protozoa\textsuperscript{366,367}</td>
</tr>
<tr>
<td>Basil</td>
<td>Oscimum basilicum,</td>
<td>Terpenoids</td>
<td>Salmonella bacteria\textsuperscript{391}</td>
</tr>
<tr>
<td>Black pepper</td>
<td>Piper nigrum</td>
<td>Piperine</td>
<td>Fungi, E.coli, Lactobacillus\textsuperscript{359}</td>
</tr>
<tr>
<td>Blueberry</td>
<td>Vaccinium spp.</td>
<td>Fructose</td>
<td>E.coli\textsuperscript{387}</td>
</tr>
<tr>
<td>Caraway</td>
<td>Carum carvi</td>
<td>Coumarins</td>
<td>Bacteria, Fungi, Virus\textsuperscript{300,336,392,393}</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Matricaria chamomilla</td>
<td>Anthemic acid</td>
<td>M. tuberculosis, S.aureus, S.typhimurium &amp; helminths\textsuperscript{300,392,393}</td>
</tr>
<tr>
<td>Chili pepper</td>
<td>Capsicum annum</td>
<td>Capsaicin</td>
<td>Bacteria\textsuperscript{304,365}</td>
</tr>
<tr>
<td>Cranberry</td>
<td>Vaccinium spp.</td>
<td>Fructose</td>
<td>Bacteria\textsuperscript{388,394,395}</td>
</tr>
<tr>
<td>Common name</td>
<td>Scientific name</td>
<td>Compound</td>
<td>Activity</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Echinacea</td>
<td>E. augustifolia</td>
<td>Echinoside</td>
<td>General$^{395}$</td>
</tr>
<tr>
<td>Garlic</td>
<td>Allium sativum</td>
<td>Allicin</td>
<td>General$^{397,400}$</td>
</tr>
<tr>
<td>Goldenseal</td>
<td>Hydrastis canadensis</td>
<td>Berbaine, hydrastine</td>
<td>Bacteria, Giardia duodenale, trypanosomes$^{307}$</td>
</tr>
<tr>
<td>Grape fruit peel</td>
<td>Citrus paradisa</td>
<td>Terpenoid</td>
<td>Fungi$^{401}$</td>
</tr>
<tr>
<td>Green tea</td>
<td>Camellia sinensis</td>
<td>Catechin</td>
<td>General, Shigella vibrio, S. mutans, Viruses$^{286,302,324,326}$</td>
</tr>
<tr>
<td>Lemon balm</td>
<td>Melissia officinalis</td>
<td>Tannins</td>
<td>Viruses$^{313}$</td>
</tr>
<tr>
<td>Olive oil</td>
<td>Olea europaea</td>
<td>Hexanal (aldehyde)</td>
<td>General$^{402}$</td>
</tr>
<tr>
<td>Onion</td>
<td>Allium cepa</td>
<td>Allicin</td>
<td>Bacteria, Candida$^{403}$</td>
</tr>
<tr>
<td>Orangepeel</td>
<td>Citrus sinensis</td>
<td>Terpenoid</td>
<td>Fungi$^{401}$</td>
</tr>
<tr>
<td>Oregon grape</td>
<td>Mahonia aquifolia</td>
<td>Berberine</td>
<td>General, plasmodium$^{307,366}$</td>
</tr>
<tr>
<td>Tarragon</td>
<td>Artemisia dracunculus</td>
<td>Kaffeic acid, Tannins</td>
<td>Virus helminths$^{313}$</td>
</tr>
<tr>
<td>Cashew</td>
<td>Anacardium pulsatilla</td>
<td>Polyphenols</td>
<td>Bacteria and fungi$^{404}$</td>
</tr>
<tr>
<td>Ashwagandha</td>
<td>Withania somnifera</td>
<td>Withaferin A</td>
<td>Gram positive, Gram negative, fungi$^{405}$, Mycobacterium tuberculosis$^{406}$</td>
</tr>
</tbody>
</table>

2.4.6 Plant with promising antiinfective activity

Plants containing protoberberines and related biflavones used in traditional African system of medicine have been found to be active against a wide variety of microorganisms. Many medicinal plants of Africa have been investigated for their chemical components and some of the isolated compounds have been shown to possess interesting biological activity$^{407}$. Some of these plants are discussed below.
**Garcinia kola**, bitter kola (Guttiferae)

*Garcinia kola*, is found in moist forest and grows as a medium size tree, it is cultivated and distributed throughout west and central Africa. Medicinal uses include, purgative, antiparasitic, antimicrobial. The seeds are used in the treatment of bronchitis and throat infections. They are also used to prevent and relieve colic, cure head or chest colds and relieve cough. Also the plant is used for the treatment of liver disorders and as a chewing stick408.

The constituents include—biflavonoids, xanthones and benzophenones. The antimicrobial properties of this plant are attributed to the benzophenone, flavanones. This plant has shown both anti-inflammatory, antimicrobial and antiviral properties. Studies show very good antimicrobial and antiviral properties. In addition, the plant possesses antidiabetic, and antihepatotoxic activities408.

**Aframomum melegueta** (Zingiberaceae) Grains of Paradise

This is a spicy edible fruit that is cultivated and occurs throughout the tropics. It is a perennial herb. The medicinal uses of *Aframomum* include aphrodisiac, measles, and leprosy, taken for excessive lactation and post partem hemorrhage, purgative, galactogogue and anthelmintic, and hemostatic agent. The constituents are essential oils—such as gingerol, shagaol, paradol. Studies show antimicrobial and antifungal activity and effective against schistosomes408.

**Xylopia aethiopica**, Ethiopian Pepper (Abbibaceae)

An evergreen, aromatic tree growing up to 20 m high with peppery fruit. It is native to the lowland rainforest and moist fringe forest in the savanna zones of in Africa. Medicinal uses of the plant are, as a carminative, as a cough remedy, and as a post partum tonic and lactation aid. Other uses are stomachache, bronchitis, biliousness and dysentery. It is also used externally as a poultice for headache and neuralgia. It is used with lemon grass for female hygiene. It is high in copper, manganese, and zinc409.
Key constituents are diterpenic and xylopic acid. In studies, the fruit as an extracts has been shown to be active as an antimicrobial against gram positive and negative bacteria. Though it has not been shown to be effective against *E. coli*. Xylopic acid has also demonstrated activity against *Candida albicans*. 

**Cryptolepis sanguinolenta** Lindl. Schltr. (Periplocaceae)

A shrub that grows in the rainforest and the deciduous belt forest, found in the west coast of Africa. Its main medicinal use is for the treatment of fevers. It is used for urinary tract infections, especially *Candida*. Other uses are inflammatory conditions, malaria, hypertension, microbial infections and inflammatory conditions, stomach aches colic.

Active principals identified are indo quinoline alkaloids. Studies show inhibition against gram negative bacteria and yeast. Additionally studies have shown this plant to have bactericidal activity. Clinical studies have shown extracts of the plant were effective in parasitemia. Recent in vitro study shows activity against bacteria specifically, enteric pathogens, most notably *E. coli* (but also staphylococcus, *C. coli*, *C. jejuni,* pseudomonous, salmonella, shigella, streptococcus, and vibrio) and some activity against *candida*. It has shown histamine antagonism, hypotensive, and vasodilatory activities. In addition it has demonstrative antihyperglycemic properties.

**Chasmanthera dependens** Hoschst (Menispermaceae)

A woody climber that grows wild in forest margins and savanna. The plant is cultivated. It is used medicinally for venereal disease, topically on sprained joints and bruises and as a general tonic for physical and nervous debilities. The constituents include berberine type alkaloids, palmatine, colombamine, and jateorhizine. Studies show that the berberine sulfate in the plant inhibits lieshmania.

**Nauclea latifolia** Smith (Rubiaceae)

It is a shrub or small spreading tree that is a widely distributed savanna plant. It is found in the forest and fringe tropical forest. Medicinal uses are as a tonic and fever
medicine, chewing stick, toothaches, dental caries, septic mouth and malaria., diarrhea and dysentery\textsuperscript{414}.

Key constituents are indole-quinolizidine alkaloids and glycoalkaloids and sapponins. There are studies showing the root has antibacterial activity against gram positive and negative bacteria and antifungal activity\textsuperscript{408}. It is most effective against Corynebacterium\textit{diphtheriae}, \textit{Streptobacillis} sp., \textit{Streptococcus} sp., \textit{Neisseria} sp., \textit{Pseudomonas aeruginosa}, \textit{Salmonella} sp.\textsuperscript{415}.

\textit{Araliopsis tabouensis} (Rutaceae)

It is a large evergreen tree found throughout west tropical Africa. Its medicinal use is for the treatment of sexually transmitted diseases. The bark infusion is drunk for gonorrhea in the Ivory coast\textsuperscript{416}. Its major constituents are alkaloids. Seven alkaloids have been isolated from the root and stem bark\textsuperscript{417}.

Many of the plants presented here show very promising activity in the area of antimicrobial agents, warranting further investigation.