INTRODUCTION

The liver is the second largest and one of the most essential organs which is located within the lower part of the rib-cage on the right hand side of the body. It has a huge variety of functions in the body and is the only organ that can repair and re-grow itself after damage. It is a seat of metabolism which is responsible for performing many functions in the body. Bile juice produced by liver gets secreted in the intestines which is required for the fat digestion body. It also works as a guard by keeping check on the cholesterol levels in the blood stream. It also produces certain proteins that are very much required for performing ware and tear function in the body. It also works as an energy store of the body thus providing energy when required in emergency conditions.

ANATOMY AND PHYSIOLOGY OF LIVER

The liver is a fairly large organ that consistently lies in the right upper part of the abdomen. From front it has a roughly triangular shape. It stretches from the right upper abdomen across the mid line to halfway across the left upper abdomen (left lobe) and from the right upper abdomen to halfway down the flank on the right (right lobe). Above the liver sits the right diaphragm and the right lung, and below the liver is the intestines. The gall bladder nestles directly below the liver and is attached to it. The gall bladder stores bile from the liver to be squirted into the first part of the small bowel (duodenum) when fat enters the intestine, to help emulsify the fat for absorption.
A large portion of the output of the heart (about one-third) flows to the digestive system. This blood returns, rich with nutrients and digestive impurities, to the liver through the veins of the portal circulatory system. The liver vascular system is expandable and compressible, and can store large quantities of blood. It normally contains about one-tenth of the blood volume in the body, but can, under certain diseased conditions, expand to hold up to a fourth of the body’s blood. Under conditions of stress, on the other hand, its
veins can contract so it holds only a thirtieth of the body’s’ blood. Thus the liver blood volume can potentially vary by a factor of more than seven. About three-fourths of the blood coming into the liver comes from venous circulation; only about a fourth comes directly from the heart through the arteries. Arterial blood is moved under force, being pumped by the heart, normally under pressure ten to fifteen times that of the blood in the portal veins. Thus most of the blood in the liver is not moved through it by arterial pressure and has a natural tendency to stagnate.

The liver is also extremely permeable to fluids, such that they flow freely into its lymphatic system; the lymph derived from the liver accounts for from one-half to two-thirds of the total lymph in the body. Finally, the liver secretes bile into the small intestine, after storage in the gall bladder. Bile helps to digest fat and is a key player in the symphonic action of the enzymes and hormones that coordinate digestion. Thus the liver is an expandable and contractible reservoir of blood, lymph, and bile. Because it has only weak arterial circulation, these fluids have a tendency to become stagnant and the liver to become congested.

**FUNCTIONS OF LIVER**

The liver has multiple functions. The liver processes all the blood leaving the stomach and intestines. It breaks down the nutrients and drugs in the blood into forms that are easier for the rest of the body to use or excrete. Amongst other important functions, the liver is responsible for eliminating and detoxifying the poisons that enter our blood stream.
The liver is also very important in the digestion of food and produces bile which is essential in the breakdown of fats, thereby preventing obesity - one of the biggest contributors to bad health. It also regulates blood sugar and stores any excess sugar in a useful ‘quick-release’ form for when it is needed. The liver clears the blood of old red blood cells, bacteria and other infectious organisms as well as ingested toxins including alcohol. It is responsible for producing a large number of different proteins including hormones and blood clotting factors and is the organ which stores Vitamin A, D, E and K.

The functioning of liver does not really decrease with age so, in the absence of disease, the liver should work optimally right into very old age - helping to keep all body systems functioning normally and supporting overall vitality and protection from illness. The maintenance of optimal liver functioning is therefore of vital importance in the quest for holistic health In traditional Chinese medicine, for example, a healthy liver is seen as the most critical element in the body's ability to fight disease and function optimally.

LIVER DISEASES

Environmental pollution, fast foods, drugs, alcohol and sedentary lifestyles all contribute to sluggish and diseased livers. The result of a diseased liver are depressed immune systems, constant fatigue, obesity, sluggish digestive systems, allergies, respiratory ailments, and unhealthy skin among many other health problems. Alcohol and many pharmaceutical drugs can affect the metabolism of the liver, and if this continues for long periods of
time, health will be endangered. A common sign of a damaged liver is jaundice, a yellowness of the eyes and skin.

There are many diseases that may affect the liver and they include:

- Liver cancer
- Fatty liver
- Wilson’s disease
- Hepatitis
- Hemochromatosis
- Cirrhosis

Like other parts of our body, cancer can affect the liver. Cancer of the liver (primary hepatocellular carcinoma or cholangiocarcinoma and metastatic cancers, usually from other parts of the gastrointestinal tract.

Fatty liver is termed if lipids account for more than 5 percent of its weight. The mechanisms for the development of fatty liver are varied. A reduction in the hepatic oxidation of fatty acids as a result of mitochondrial dysfunction can lead to micro vesicular steatosis. Another mechanism is related to an imbalance between fat uptake and secretion, with high insulin-to-glucagon ratio status leading to macro vesicular steatosis.

Wilson's disease, a hereditary disease which causes the body to retain copper.
Hepatitis, inflammation of the liver, caused mainly by various viruses like hepatitis A, hepatitis B and hepatitis C but also by some poisons, autoimmunity or hereditary conditions.

Hepatitis A or infectious jaundice is caused by a picornavirus transmitted by the fecal-oral route. It causes an acute form of hepatitis and does not have a chronic stage. Worldwide, hepatitis B is another major cause of cirrhosis and hepatocellular carcinoma. Many patients with hepatitis B virus infection fail standard therapy. Hepatitis C virus infection is the leading cause of chronic liver disease and the reason for 30 to 35 percent of liver transplantations (Knolle et al., 1998; Zein et al., 1996).

Haemochromatosis, a hereditary disease causing the accumulation of iron in the body, eventually leading to liver damage.

Cirrhosis is the formation of fibrous tissue in the liver, replacing dead liver cells. The death of the liver cells can for example be caused by viral hepatitis, alcoholism or contact with other liver-toxic chemicals.

In some liver diseases, such as primary biliary cirrhosis, treatment can slow but not stop the progression of liver injury (Poupon et al., 1991). Although each form of liver disease has a distinct natural history, most forms progress slowly from hepatitis to cirrhosis, often over 20 to 40 years (Propst et al., 1995).
Symptoms of a diseased liver

The external signs include a coated tongue, bad breath, skin rashes, itchy skin, excessive sweating, offensive body odour, dark circles under the eyes, red swollen and itchy eyes, acne rosacea, brownish spots and blemishes on the skin, flushed facial appearance or excessive facial blood vessels. Other symptoms include jaundice, dark urine, pale stool, bone loss, easy bleeding, itching, small, spider-like blood vessels visible in the skin, enlarged spleen, and fluid in the abdominal cavity, chills, pain from the biliary tract or pancreas, and an enlarged gallbladder. The symptoms related to liver dysfunction include both physical signs and a variety of symptoms related to digestive problems, blood sugar problems, immune disorders, abnormal absorption of fats, and metabolism problems.

EVALUATION OF DRUG TOXICITY

Most ingested substances are metabolized and chemically altered as they pass through the liver. The liver is vulnerable to injury from some medications, vitamins and herbal remedies (Speeg and Bay, 1995). Prescription and over-the-counter arthritis and pain medications are widely used. Nonsteroidal anti-inflammatory drugs (NSAIDs), which are taken to alleviate headache and a variety of pain symptoms, can cause idiosyncratic liver toxicity. Fatalities associated with NSAID use have been reported (Carson and Willett, 1993). In one study, the use of ibuprofen was associated with a more than 20-fold increase in liver function values in three patients with hepatitis C virus infection (Riley and Smith, 1998). Acetaminophen has
predictable hepatotoxicity and affects the liver in a dose dependent manner. However, acetaminophen hepatotoxicity has been reported with dosages of less than 4 g per day, usually in association with starvation or alcohol ingestion (Zimmerman and Maddrey, 1995).

**HERBAL MEDICINES**

Herbal drugs have become increasingly popular and their use is widespread.

Ayurveda is accepted to be the oldest treatise on medical system, which came into existence in about 900 BC. The word Ayurveda derived from ‘Ayur’ meaning life and ‘veda’ meaning science.

Herbal medicines are prepared from a variety of plant materials—leaves, stems, roots, bark and so on. They usually contain many biologically active ingredients and are used primarily for treating mild or chronic ailments. Naturopathic medicine, traditional Chinese medicine and Ayurvedic medicine all differ in how diseases are diagnosed and which herbal remedies are prescribed. Out of these, the Chinese herbal medicine or the Traditional Chinese Medicine (TCM) has a potential usage similar to the Indian system of medicine.

‘Ethanopharmacology’ have been recently defined as “the interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by man”. The objectives of ehanopharmacology are to rescue and document an important cultural heritage
before it is lost, and to investigate and evaluate the agents employed. Thus, it plays an immense role in evaluation of natural products and more particularly the herbal drugs from traditional and folklore resources. The random screening of plants for food and medicine by our prehistoric ancestors is probably the basis of the botanical pharmacopoeia that exists in virtually all cultures. What of the future for plant based agents? There are many possibilities for research, but priority should be given to tropical infectious and chronic diseases for which current mediations have severe drawbacks, and to the scientific appraisal of plant-based remedies that might be safer, cheaper, and less toxic for self-medication than existing prescription medicines. Man and perhaps some of his closer relatives, has always made use of plants to treat illness, and many of these remedies have real beneficial effects. Licensing regulations and pharmacovigilance regarding herbal products are still incomplete and clear cut proof of their efficacy in liver diseases is sparse.

There is clearly a need for greater education of patients and doctors about herbal therapy, for legislation to control the quality of herbal preparations, and in particular for further randomized controlled trials to establish the value and safety of such preparations in Hepatic disorders.

**EXPERIMENTAL HEPATOTOXICITY IN RATS**

**Carbon tetrachloride- induced hepatotoxicity**

Animal studies have revealed that carbon tetra chloride is metabolized in the liver by cytochrome P-450 (Sipes *et al.*, 1977). One of the resulting
products of the metabolic activity is believed to be a trichloromethyl radical that leads to the formation of chloroform, hexachloroethane, carbon monoxide, trichloromethanol, phosgene and carbon dioxide. The radical is thought to induce lipid peroxidation resulting in membrane destruction and the loss of organelle and cell function (Rao and Recknagel, 1968).

**Free radicals and hepatotoxicity**

The cytochrome p-450 system is encased in phospholipids membrane rich in polyenoic fatty acid. Hence these polyenoic fatty acids are the most likely immediate target for the initial lipid peroxidative attack to occur. The organic fatty acid radical rearranges, yielding organic peroxy and hydroxyl peroxy radicals. The radical destroy the cytochrome p-450 hemoprotein, thus compromising the mixed-function oxygenase activity. The rapid decomposition of the endoplasmic reticulum and its function is a direct result of this lipid peroxidative process (Zangar *et al.*, 2000).

Trichloromethyl free radicals can react with sulphydryl groups, such as glutathione (GSH) and protein thiols, and the covalent binding of the trichloromethyl free radicals to the cell proteins is considered to be the initial step in a chain of events that eventually lead to membrane lipid peroxidation and finally to cell necrosis (Recknagel *et al.*, 1991). Several mechanisms have been proposed for CCl₄ induced fatty liver and necrosis. Important mechanisms include damage to endoplasmic reticulum, mitochondria lysosomes, disturbances in hepatocellular calcium homeostasis, and lipid peroxidation. All are mediated by free radicals. Lipid peroxidation may be
looked upon as occurring in two steps. Some toxic event initiates lipid peroxidation and organic free radical generated by the initiation process serve to propagate the reaction.

**MECHANISM OF LIPID PEROXIDATION**

The steps involved in lipid peroxidation are described below and shown schematically (Anjali et al., 2001).

**Initiation**

\[ \text{H}_2\text{O} \longrightarrow \text{HO}^\bullet, \text{H}^\bullet, \text{e}_{\text{aq}}^-, \text{O}_2^\bullet, \text{H}_2\text{O}_2 \]

\[ \text{LH}^+\text{OH} \longrightarrow \text{L}^\bullet + \text{H}_2\text{O} \]

**Propagation**

\[ \text{L}^\bullet + \text{O}_2 \longrightarrow \text{LOO}^\bullet \]

\[ \text{LOO}^\bullet + \text{LH} \longrightarrow \text{LOOH} + \text{L}^\bullet \]

**Termination**

\[ \text{L}^\bullet + \text{L} \longrightarrow \text{L-L} \]

\[ \text{LOO}^\bullet + \text{LOO}^- \longrightarrow \text{LOOH} + \text{O}_2 \]

\[ \text{LOO}^\bullet + \text{L}^\bullet \longrightarrow \text{LOOL} \]

Malondialdehyde is the major reactive aldehyde resulting from the peroxidation of biological membrane polyunsaturated fatty acid (PUFA). Thus MDA is used as an indicator of tissue damage and reacts with thiobarbituric acid and produce red colored products.
Mechanism of lipid peroxidation

Hepatotoxicity following acute exposure to CCl₄ is manifested as necrosis and inflammation mainly in the centrilobular areas of the rodent liver (Germano et al., 2001).
The covalent binding of the radical to cell components initiates the inhibition of lipoprotein secretion and thus steatosis, whereas reaction with oxygen, to form $^\cdot$CCl₃ initiates lipid peroxidation. The latter process results in loss of calcium homeostasis and, ultimately, apoptosis and cell death. The massive production of reactive species may lead to depletion of protective physiological moieties (glutathione and $\alpha$-tocopherol, etc.), ensuing widespread propagation of the alkylation as well as peroxidation, causing damage to the macromolecules in vital biomembranes (Aldridge, 1981). The reactive species mediated hepatotoxicity can be effectively managed upon administration of such agents possessing anti-oxidants (Attri et al., 2000), free radical scavengers (Sadanobu et al., 1999) and anti-lipid peroxidation (Lim et al., 2000).

Based on a pharmacokinetic model developed by (Paustenbach et al., 1988) about 4% of the carbon tetrachloride that is metabolized is converted to and excreted as carbon dioxide. The remaining metabolic products may bind to proteins, lipids and DNA. The liver and kidney are target organs for carbon tetrachloride toxicity. The severity of the effects on the liver depends on a number of factors such as species susceptibility, route and mode of exposure, diet or co-exposure to other compounds, in particular ethanol. Furthermore, it appears that pretreatment with various compounds, such as phenobarbital and vitamin A, enhances hepatotoxicity, while other compounds, such as vitamin E, reduce the hepatotoxic action of carbon tetrachloride.
REFERENCE DRUG

Silimarın

Silimarın is widely used as a standard hepatoprotective drug in many liver disorders. The main effects of silymarin are the membrane stabilising and antioxidant effects, it is able to help the liver cell regeneration, it can decrease the inflammatory reaction, inhibit the fibrosis in the liver and the long administration of silymarin significantly increased the survival time of patients with alcohol-induced liver cirrhosis (Fehér and Lengyel, 2008; Müzes et al., 1990) reported the antioxidant, antiperoxidative effects might be important factors in the mechanism of hepatoprotective action of silymarin.

Silymarin prevents to a considerable degree the increase of the serum enzymes (GOT, GPT, MDH, SDH, ICDH, AP) activity caused by a D-galactosamine injury, enhances the metabolic conversion of the UDP-hexosamine into UDP-acetyhexosamine in the liver and hastens the normalizing of the UDP-glucuronic acid content in the liver of rats (Tyutyulkova et al., 1981). Silymarin corrected the altered immunoreactions and the decreased superoxide-dismutase (SOD) activity of erythrocytes and lymphocytes in patients with alcoholic liver cirrhoses. The scavenger effect of silymarin was demonstrated in the sub cellular fractions of liver cells in animal experiments (Feher et al., 1989).

ECLIPTA ALBA

_Eclipta alba_ Hassk. (Bhingaraja and Fam: Compositae) is a perennial shrub, has a short, flat or round stem, deep brown in color which grows
widely in moist tropical countries. Different uses have been reported for this shrub. It is used as alterative, anthelmintic, expectorant, antipyretic, antiasthmatic, tonic, deobstruent in hepatic and spleen enlargement, in skin diseases and as a substitute for Taraxacum (a popular liver tonic). It is good for the diseases of spleen, stomatitis, toothache, hemicrania, fever, pain in liver and cures vertigo (Yunani). Its juice in combination with honey is administered for Catarrh and Jaundice (Chopra et al., 1996). *Eclipta alba* is an indigenous medicinal plant, has a folk (Siddha and Ayurvedha) reputation popularly used for the inflammation, anthelmintic, astringent, deobstruent and hepatoprotective effect (Bhattachary et al., 1997).

**Synonyms**

- *Eclipta erecta*
- *Eclipta prostrata*
- *Verbesina alba*
- *Verbesina prostrata*
**Figure 2. Eclipta alba**

<table>
<thead>
<tr>
<th><strong>Kingdom</strong></th>
<th>Plantae</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td><strong>Class</strong></td>
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<tr>
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<td>Eclipta</td>
</tr>
<tr>
<td><strong>Species</strong></td>
<td><em>Eclipta alba</em></td>
</tr>
</tbody>
</table>

**Vernacular names**

<table>
<thead>
<tr>
<th><strong>Latin</strong></th>
<th><em>Eclipta alba</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sanskrit</strong></td>
<td>Bhringaraja</td>
</tr>
<tr>
<td><strong>English</strong></td>
<td>Traling Eclipta</td>
</tr>
</tbody>
</table>
**Pharmacognostic characteristics**

Trailing *Eclipta* is a small, erect or prostate many branched and a coarsely haired annual herb. It grows up to 20 cm in height. It has a round, feeble stem, simple eclipitis hairy leaves, variable in shape, bright green in color with very small flowers, called florets. The leaf epidermis is composed of single layer of parenchymal cells with characteristic non-glandular trichomes, on both surfaces. In transaction, the stem is circular in outline with a ring of collateral endarch vascular bundles of varying sizes and central parenchymatous pith. The root has a diarch structure with normal and secondary growth.

The plant grows all over India, especially, in moist places, up to an elevation of about 800 meters. An erect annual grows 10-15 cm in height, with flat or round, blackish-chocolaty, much branched, pubescent stems. The leaves are opposite, serrate, 3-5 cm long and blackish-green in color. The flowers are small penny-sized, white, on a long stalk. The fruits are many seeded and the seeds are black, resemble cumin seeds. The plant flowers in September and fruits in November. Ayurvedic texts describe three varieties of bhringaraja according to colors of flowers viz. white, yellow and blue. The white variety is commonly used.
**Phyto Chemical constituents of *Eclipta alba***

It contains a large amount of resin and an alkaloid principle ecliptine. The presence of reducing sugar and steroids in the seeds has been observed. A number of compounds had been isolated from the plant. Wedelolactone, chemically described as 7-methoxy-5,11,12-trihydroxy-coumestan (Zhang and Guo, 2001) is basically a furanocoumarin, previously reported as responsible for the hepatoprotective activity. Literature survey revealed that HPLC and UV spectrophotometry (Das *et al.*, 1990) methods had been reported for the estimation of wedelolactone in a methanol extract of *Eclipta alba*. Wedelolactone consist of heterocyclic fused ring, which is responsible for fluorescent behavior. Wedelolactone possesses a wide range of biological activities and is used for the treatment of hepatitis and cirrhosis (Wagner *et al.*, 1986).

![wedelolactone](image1.png)  
*Figure 3. Major chemical constituents of *Eclipta alba*.*
Medicinal properties and uses

Juice of the leaves is a hepato tonic and deobstruent. Root is a tonic. The herb is used in hepatic and spleen enlargements and in skin diseases. Fresh juice obtained from leaves is given in fever, liver disorders and rheumatism. A paste of the herb mixed with sesame oil is used over glandular swellings, elephantiasis and skin diseases. In Gujarat district and Punjab, it is used externally for ulcers and as an antiseptic for wounds in cattle. Recently Chandra et al. (1987 have observed a significant anti-inflammatory activity of the powder in rats. It has been reported to be useful in liver ailments (Handa et al., 1986) and has been shown to possess hepatoprotective activity against carbon-tetrachloride induced liver cell damage in animals. The plant is an active ingredient of many herbal formulations prescribed for liver ailments and shows effect on liver cell generation. There are also reports of clinical improvement in the treatment of infective hepatitis (Dixit and Achar, 1979). Eclipta alba leaves showed antihyperglycemic activity (Ananthi et al., 2003). The roots of Eclipta alba were found effective in wound healing (Patil et al., 2004). In vivo hepatoprotective activity of alcoholic extract (Saxena et al., 1993; Singh et al., 2001) and analgesic study of total alkaloids of Eclipta alba were also reported (Sawant et al., 2004).

Ayurvedic Properties

Bhringaraja is bitter in taste, pungent in the post digestive effect and has hot potency (virya). It alleviates kapha and vata dosas. It possesses light (laghu) and dry (roksa) attributes. It is a rejuvenator, tonic and beneficial to eyes, hair and the skin (Kaiyadeva Nighantu)
*Piper longum*

*Piper* species are widely distributed in the tropical and subtropical regions of the world and have multiple applications in different folk medicines. In traditional Chinese medicine, many species are used to treat inflammatory diseases. The Chinese Pharmacopoeia contains three monographs: *Piper nigrum* (“Hujiao”), *Piper longum* (“Bibo”) and *Piper kadsura* (“Haifengteng”). In addition, several other *Piper* species are commonly found in China. *Piper longum* fruits are ovoid, yellowish orange, minute, and drupe and are sunk in the fleshy spike. The spikes are red when ripe. Odour is aromatic and the taste is pungent.

<table>
<thead>
<tr>
<th><strong>Botanical Name</strong></th>
<th><em>Piper longum</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common Name</strong></td>
<td>Long Pepper, Pipli</td>
</tr>
<tr>
<td><strong>Part Used</strong></td>
<td>Fruit, Root, Stem</td>
</tr>
<tr>
<td><strong>Habitat</strong></td>
<td>Most deciduous to evergreen forests</td>
</tr>
<tr>
<td><strong>Product offered</strong></td>
<td>Seeds, Roots, Fruit, Stem</td>
</tr>
<tr>
<td><strong>Kingdom</strong></td>
<td>Plantae</td>
</tr>
<tr>
<td><strong>Division</strong></td>
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<td><strong>Order</strong></td>
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</tr>
<tr>
<td><strong>Species</strong></td>
<td><em>P. longum</em></td>
</tr>
</tbody>
</table>
Vernacular names

Hindi, Punjabi : Pipul, Pipli, Piplamul
Bengali : Pipli, Piplamore (root)
Gujarati : Pipli
Kannada : Hippali, Hippalibali, Kuna
Malayalam : Tippali, Pippali
Marathi : Pimpli
Oriya : Pippoli
Sanskrit : Pippali
Sindhi : Pipli
Tamil : Thippali
Telugu : Tippili, Pippallu
Urdu : Pipul, Pipli.
Pharmacognostic characteristics

Pepper long is the dried fruit of *Piper longum*, which is a slender, aromatic plant with creeping jointed stems and perennial woody roots. Leaves numerous, lower one broadly ovate, very cordate with broad rounded lobes at base, upper one oblong–oval, cordate at the base, all sub acute, entire glabrous thin, bullate with reticulate venation.

Phytochemical constituents

The fruits contain 1% volatile oil, resin, alkaloids piperine and piperlonguminine, isobutyldeca-trans-2-trans-4-dienamide and a terpenoid substance. Roots contain piperine, piperiongumine. Dihydrostigmasterol has been isolated. It contains aromatic oil, an alkaloid and pipalartine. Besides this it contains sesamin and piplasterol. The root contains pipperin, pippalartin, pipperleguminin, sterols and glycosides.

Medicinal properties and uses

Aromatic, stimulant, carminative, good for constipation, for gonorrhea, paralysis of the tongue, advised in diarrhea, cholera, scarlatina, Chronic Malaria and Viral hepatitis. *Piper Longum* is most commonly used to treat respiratory infections such as stomach ache, bronchitis, diseases of the spleen, cough, tumors, and asthma. When applied topically, it soothes and relieves muscular pains and inflammation. In Ayurvedic medicine, it is said to be a good rejuvenator. *Piper longum* helps to stimulate the appetite and it dispels gas from the intestines. An infusion of *Piper longum* root is used after birth to
induce the expulsion of the placenta. It is used as sedative in insomnia and epilepsy. Also as cholagogue in obstruction of bile duct and gall bladder.

Activity-guided fractionation of a methylene chloride soluble extract led to the isolation of three known piperine-related compounds, methylpiperate (1), guineensine (2), and piperlonguminine (3) of these, methylpiperate (1) and guineensine (2) showed significant MAO inhibitory activities (Lee et al., 2008).

Examination on the effects of several extracts of *Piper longum* L. on rabbit platelet function showed Thromboxane A(2) receptor agonist U46619 caused rabbit platelet aggregation, which was potently inhibited by the ethanol or butanol extract of *Piper longum* L. These results suggest that *Piper longum* L. contains a constituent(s) that inhibits platelet aggregation as a non-competitive thromboxane A(2) receptor antagonist (Iwashita et al., 2007). Amides of known structures that contain four subtypes of amides were rapidly determined, and novel amides were also identified for *Piper longum*. Forty-two amides were rapidly identified, of which 22 were found in this plant for the first time and 9 were new compounds (Sun et al., 2007).

Pullela *et al.* (2006) employed a systematic bioassay guided fractionation method and isolated pipataline, pellitorine, sesamin, brachystamide B and guineensine as active principles. A reversed-phase high-performance liquid chromatography method was developed to quantify these active principles in the plant material, which can serve as an effective quality control tool. The extract of *P. longum* at non-toxic concentrations
(10 microg/ml, 5 microg/ml, 1 microg/ml) inhibited the VEGF-induced vessel sprouting in rat aortic ring assay. Moreover, *P. longum* was able to inhibit the VEGF-induced proliferation, cell migration and capillary-like tube formation of primary cultured human endothelial cells. Hence, the observed antiangiogenic activity of the plant *P. longum* is related to the regulation of these cytokines and growth factors in angiogenesis-induced animals (Sunila and Kuttan, 2006).

Piperine has been shown to enhance the bio-availability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics, due to its easy partitioning and increasing permeability. Piperine was evaluated and found to exert significant protection against tertiary butyl hydroperoxide and carbon tetrachloride induced hepatotoxicity, by reducing both in vitro and in vivo lipid peroxidation. Methyl piperine significantly inhibited the elevation of total serum cholesterol, and the total cholesterol to HDL-cholesterol ratio, in rats fed with a high cholesterol diet. *Piper longum* Linn, an important medicinal plant belonging to the family piperaceae has been used in traditional medicine by people in Asia and Pacific islands especially in Indian medicine (Guido and David, 1998).

*Piper longum* is a component of medicines reported as good remedy for treating gonorrhea, menstrual pain, tuberculosis, sleeping problems, respiratory tract infections, chronic gut related pain and arthritic conditions (Singh *et al.*, 1992).
*Piper longum* possessed a demonstrable immunostimulatory activity, both specific and nonspecific, as evident from the standard test parameters such as haemagglutination titre (HA), plaque forming cell (PFC) counts, macrophage migration index (MMI) and phagocytic index (Tripathi *et al.*, 1999). Three isolates of black pepper were active against Gram-positive bacteria and moderately active against Gram-negative bacteria. Each isolate was highly active against at least one particular species of bacteria; *Piper longum*inine (1) against *Bacillus subtilis*, piperine (2) against *Staphylococcus aureus* and pellitorine (3) against *Bacillus sphaericus* (Srinivasa Reddy *et al.*, 2001).