Hepatoprotective Activity of Selected Bangladeshi Medicinal Plants and Their Isolated Compounds

A Review Submitted

By

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Examination Roll No. MS-090713

Session: 2009-10

Submitted To

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Khulna-9208, Bangladesh
August, 2014

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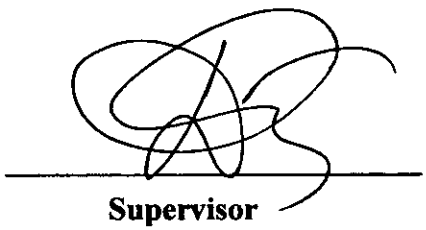

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Dedicated to

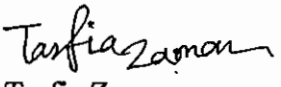
My Beloved Family

TITLE

Hepatoprotective Activity of Selected Bangladeshi Medicinal Plants and Their Isolated Compounds (A review)

Declaration

This thesis reports the orginal research work of the author, except as otherwise stated. The material presented has not been submitted either in whole or in part for a degree from this or any other university. The findings of the research has not been/will not be published anywhere without the the concurrences of the concerned supervisor. Legal action would be taken in any case of infringement regarding the declaration.



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MS-090713

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Abstract

The scientific basis for the statement that the plants and their active compounds play a promising role in the prevention of the diseases is continuously advancing. The present review is aimed at compiling data on promising medicinal plants of Bangn labesh that have been tested in hepatotoxicity models using the modern scientific system along with their chemical constituents having hepatoprotective potential. Six plants namely *Alocasia indica* (Mankachu), *Andrographis paniculata* (Kalmegh), *Eclipta alba (Bhringraj / Kalokeshi), Elephantopus scaber* (Gojialata), *Ipomoea aquatic* (Kolmi Shak) and *Wedelia chinensis* (Keshraj) have been enlisted with highest hepatoprotective activity reported in published literature. Terpenoids, alkaloids, phytosterols, phenolic acids and flavonoids are the major chemical classes of the compounds with hepatoprotective activity that have been reported from those plants. Thus, this review summarizes the contemporary research on Babgladeshi medicinal plants focusing on hepatoprotective activity and form a platform for future endevour in the said direction.

ACKNOWLEDGEMENT

At the very beginning, I offer my deepest gratitude to the almighty Allah for all his merciful blessings bestowed upon me. Allah, to whom all praises, goes for enabling me to complete my review work.

I am very grateful to our honorable teacher and supervisor Dr. Kazi Md. Didarul Islam, Associate Professor, Biotechnology and Genetic Engineering Discipline, Khulna University, Khulna, for his systematic supervision, literature support and valuable suggestions throughout the whole period of this work. I am also grateful to all of the teachers of Biotechnology and Genetic Engineering Discipline, Khulna University for their assistance & encouragement to perform the review work.

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The author

August, 2014

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List of Abbreviation

AST	Asparate aminotransferase
ALT	Alkaline aminotransferase
ALP	Alanine phosphates
DBL	Direct bilirubin
GS-MS	Gas chromatography-mass spectrometry
HPLC	High performance liquid chromatography
KC	Kuffer cells
NK	Natural killer cells
PCM	Paracetamol
ROS	Reactive Oxygen Species
SOD	Superoxide dismutase
TAA	Thioacetamide
TBL	Total bilirubin
TNF	Tumor Necrosis Factor

Chapter One

Introduction

Introduction

The liver is the largest glandular and vital organ in the body and the chief site for intense metabolism and excretion. Liver carry outs numerous number of vital functions in human body system and among these functions, three have been known as the most important ones, clearance of damaged red blood cells and bacteria by phagocytosis, remove and excrete body wastes and hormones as well as drugs and other foreign substances, and synthesize plasma proteins, including those necessary for blood clotting. [Kelly 2008] [Tortora et al. 2008]. So it has a surprising role in the maintenance, performance and regulating homeostasis of the body. It is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction [Ward 1999]. The other functions of the liver are carbohydrate, protein and fat metabolism, detoxification, secretion of bile and storage of vitamin. Thus, to maintain a healthy liver is a crucial factor for overall health and well being. But it is continuously and variedly exposed to environmental toxins and abused by poor drug habits and alcohol and prescribed and over-the-counter drug which can eventually lead to various liver ailments like hepatitis, cirrhosis and alcoholic liver disease. [Sharma et al. 1991] [Subramonium et al. 1999]

Thus liver diseases are some of the fatal disease in the world today. They pose a serious challenge to international public health. Liver is prone to many diseases because of its multidimensional functions. The most common diseases includes infections such as hepatitis A, B, C, E, alcohol damage, fatty liver, cirrhosis, cancer, and drug damages (especially by acetaminophen and cancer drugs). However, liver has a great capacity to regenerate and has a large reserve capacity. In most cases, the liver only produces symptoms after an extensive damage. Necrosis and apoptosis are the two forms of cell death have become well defined [Reed 2000]. Hepatocytes death is the main feature of most liver diseases [Bilodeau 2003]. Hepatic injury is caused by hepatocytes death and can be identified when there is an increase of more than three times of normal serum transaminase enzymes (AST, ALT and ALP).

Liver disorders are one of the foremost health concerns in human due to various chemicals (carbon tetrachloride, D-galactosamine, thioacetamide, ethanol) including therapeutic agents

(acetaminophen and chemotherapeutic drugs), alcohol and other environmental toxins that can produce hepatotoxicity which may lead to death [Victor 2006].

Chemical induced liver damage:

Chemicals that cause liver injury are termed hepatotoxins, and more than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to liver which may be manifest by abnormal liver enzyme tests. Certain medicinal agents when taken in overdoses and sometimes even when introduced within therapeutic ranges may injure the organ. Other chemical agents such as those used in laboratories and industries, natural chemicals (e.g. microcystins) and herbal remedies can also induce hepatotoxicity.

Numerous mechanisms may be cited to be responsible for either inducing hepatic injury or worsening the damage process. Although the exact mechanism of hepatic injury remains largely unknown, it appears to involve 2 pathways—direct hepatotoxicity and adverse immune reactions. In most instances, hepatic injury is initiated by the bioactivation of drugs to chemically reactive metabolites, which have the ability to interact with cellular macromolecules such as proteins, lipids, and nucleic acids, leading to protein dysfunction, lipid peroxidation, DNA damage, and oxidative stress [Lynch et al. 2007]. Additionally, these reactive metabolites may induce disruption of ionic gradients and intracellular calcium stores, resulting in mitochondrial dysfunction and loss of energy production. Its dysfunction releases excessive amount of oxidants which in turn injures hepatic cells. Activation of some enzymes in the cytochrome P-450 system such as CYP2E1 also leads to oxidative stress. Injury to hepatocyte and bile duct cells lead to accumulation of bile acid inside liver. This promotes further liver damage. This impairment of cellular function can culminate in cell death and possible liver failure [Blazka et al. 1995]. Hepatic cellular dysfunction and death also have the ability to initiate immunological reactions, including both innate and adaptive immune responses. Stress and damage to hepatocytes result in the release of signals that stimulate activation of other cells, particularly those of the innate immune system, including Kupffer cells (KC), natural killer (NK) cells, and NKT cells. These cells contribute to the progression of liver injury by producing proinflammatory mediators and secreting chemokines to further recruit inflammatory cells to the liver. It has been demonstrated that various inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ,

and interleukin (IL)-1β, produced during hepatic injury are involved in promoting tissue damage [Bourdi et al. 2002]. However, innate immune cells are also the main source of IL-10, IL-6, and certain prostaglandins, all of which have been shown to play a hepatoprotective role [Rubinstein et al. 1986]. Thus, it is the delicate balance of inflammatory and hepatoprotective mediators produced after activation of the innate immune system that determines an individual's susceptibility and adaptation to hepatic injury.

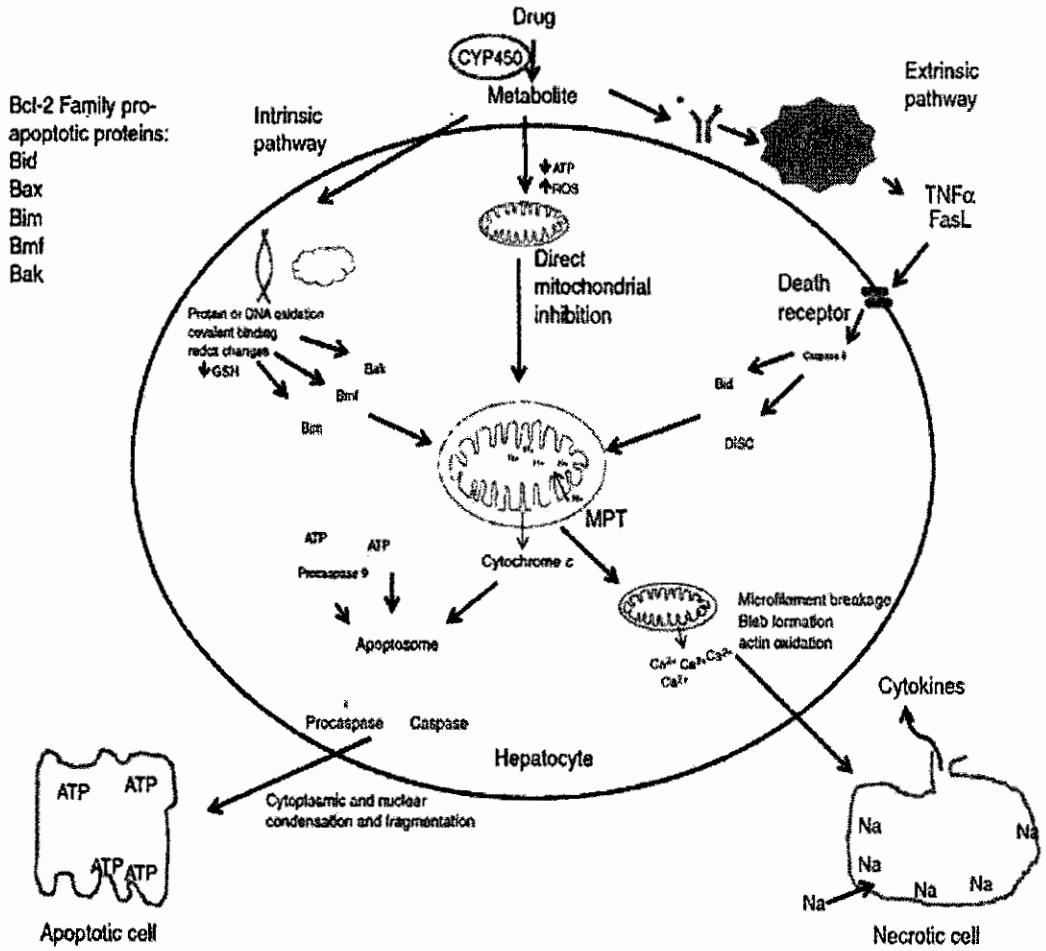


Figure 1. Biochemical mechanisms of chemical induced liver injury.

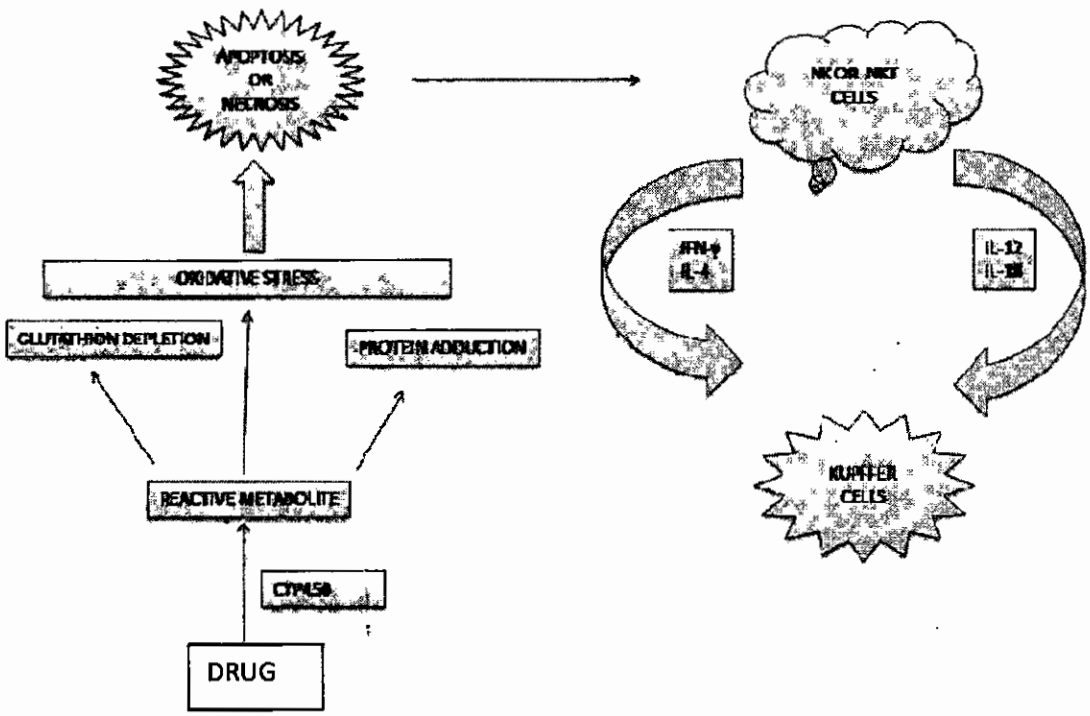


Figure 2. Mechanism of hepatic injury.

Alcohol induced liver damage:

Alcohol is a well-known hepatotoxicity that is widely used to induce toxic liver injury in a range of laboratory animals. Damage by alcohol is regarded as the analogue of liver damage caused by a variety of hepatotoxicity in human. Alcohol results an increase in the release of endotoxin from gut bacteria and membrane permeability of the gut to endotoxin, or both. Elevated levels of endotoxin activate Kupffer cells to release substances such as eicosanoids, TNF-alpha, prostaglandins and free radicals. Prostaglandins increase oxygen uptake and most likely are responsible for the hypermetabolic state in the liver. The increase in oxygen demand leads to hypoxia in the liver, and on reperfusion, alpha-hydroxyethyl free radicals are formed which lead to tissue damage in oxygen-poor pericentral regions of the liver lobule [Thurman 2009]. When

alcohol is consumed chronically, it eventually results in liver scarring or what is known as cirrhosis or end-stage alcoholic liver disease [Longstreth et al. 2009].

Hepatoprotective

Hepatoprotectives are a class of therapeutic agents that includes synthetic as well as natural product which offer protection to liver from damage or help in regeneration of hepatic cells. [Handa 1991]

The hepatoprotective agents act through various mechanisms to protect against various deleterious effects. By involving through one or more mechanisms, they act on the hepatocytes/liver directly or indirectly and help in proper functioning. The mechanisms include (a) an increase in antioxidant level/decrease in oxidants (ROS formation), (b) inhibition of cytochrome P450s, (c) increase and decrease level of Liver enzymes, (d) reduced peroxidation / Lipid peroxidation (MDA), and (e) increasein level of glutathione or reducing equivalents.

(a) Increase in antioxidant level / decrease in antioxidants (ROS formation)

Antioxidants are substances that at relatively low concentrations are able to compete with other oxidizable substrates and, thus, to significantly delay or inhibit the oxidation of these substrates. Thus, these antioxidant molecules in cells can act either by free radical neutralization or by inhibiting their formation (Halliwelland Gutteridge, 1989). Several enzymes are present, which help in facilitating protection from oxidants by inhibiting/neutralizing the ROS formation like superoxide dismutase (SOD), Catalase, Peroxidases (Glutathione peroxidases) [Singh et al. 2011]. Antoxidant enzymes also help by detoxifying lipid peroxidation products (glutathione Stransferases,glutathione peroxidases and ascorbateperoxidase). A network of low molecular weight antioxidants (ascorbate, glutathione, etc.) along with enzymes (mono dihydro ascorbate reductase, dehydroascorbate reductase and glutathione reductase) is needed for the regeneration of the active forms of the antioxidants [Droge, 2002 and Kumar Vivek et al. 2011].

(b) Inhibition of cytochrome P450

The cytochrome p 450 system is actively involved in metabolism of many drugs and xenobiotics and help in their elimination from the body. This enzyme is poly- morphic in nature of different forms involved in drug metabolism. Cytochrome P450s are generally located in the endoplasmic reticulum (ER) and with the help of coenzyme, NADPH reductase catalyzes the two elec-tron reduction of molecular O2 to H2O. The most com- mon reaction catalyzed by cytochromes P450 is a monooxygenase reaction, e.g., insertion of one atom of oxygen into an organic substrate (RH) while the other oxygen atom is reduced to water [Sigel et al. 2007].

Cytochrome p450 (CYP1A1) is present in the mito-chondria of liver tissue. The enzyme is targeted to the mitochondria by proteolysis of cryptic MT-targeting signals, which remove a certain number of amino acids from the NH2 terminus, thus producing two alternative truncated isoforms of mitochondrial CYP1A1 (mt1A1) [Tsatsakis et al. 2009]. The active site of cytochrome P450 contains a haem iron center. The iron is tethered to the P450 protein via a thiolate ligand derived from a cysteine residue. This cysteine and several flanking residues are highly conserved in known CYPs. Because of the vast variety of reactions catalyzed by CYPs, the activities and properties of the many CYPs differ in many aspects [Meunier et al. 2004]. However, CYP450s and other enzymes can also bioactivate chemicals, converting them to reactive products that modify cellular constituents and produce damage [Guengerich et al. 2005 and Guengerich, 2006]. In contrast to the P450s involved in sterol metabolism in normal physiological condition, the levels of the xeno- biotic-metabolizing CYP450s vary widely, and individuals can be completely lacking these because of muta- tion. In an individual deficient of the particular CYP450 (poor metabolizer), limited metabolism of the particular drug will result in the toxic accumulation of the drug or its metabolites [Kuntze 1989; Rofiee et al. 2011].

(c) Increase and decrease level of Liver enzymes

Hepatic cells participate in metabolic activities and contain a variety of enzymes. In tissue, separate aminotransferase (AST) and alkaline aminotransferase (ALT) were found to be in

higher concentrations in acytoplasm, and AST exists in mitochondria. In liver injury, transport function of the hepatocytes gets disturbed, resulting in the leakage of plasma membrane and thereby causing an increased enzyme level in serum. The elevated activities of these enzymes are in- dicative of cellular leakage and the functional integrity of the cell membranes in liver. ALP is excreted by liver via bile in the liver injury due to hepatotoxins, which results in a defective excretion of bile by the liver and is reflected in their increased levels in serum [Tatiya et al. 2012]. Hepatotoxins produce varying degrees of damage to the liver. They may produce a variety of morphological changes, which may be typical of the various agents. Liver damage is usually associated with elevation in the serum levels of many biochemical markers such as AST, ALT, ALP, bilirubin, triglycerides and cholesterol [Peter et al 2010]. CCl_4 is commonly used to induce hepatotoxicity in animal models.Metabolic processes convert CCl_4 into the trichloromethyl radical (CCl_3-) which interacts with O_2 to yield the highly reactive trichloromethylperoxy radical CCl_3O_2]. Both radicals are capable of binding to proteins and lipids or abstracting a hydrogen atom from unsaturated lipids, which induces lipid peroxidation and leads to changes in the endoplasmic reticulum reduction in protein synthesis, and elevation of serum transaminase enzyme levels. The significant increase in the serum marker enzymes viz, AST, ALT and ALP and decrease in the level of albumin and total protein has been observed in CCl_4 treated rats.

(d) Reduced peroxidation / Lipid peroxidation (MDA)

The massive production of reactive species may lead to depletion of protective physiological moieties glutathione, tocopherols, etc. The depletion of these low molecular weight antioxidants further propagate the peroxidation and alkylation causing the chain reactionto proceed and finally damage to the membrane function and structure [Baheti et al. 2006]. One of the end products formed following membrane damage is malondialdehyde (MDA) and their increased in level suggests enhanced lipid peroxidation, which may lead to tissue damage and may be as a consequence or failure of antioxidant defense mechanisms to prevent the formation of excessive free radicals [Dash et al. 2007].

(e) Increase in level of glutathione and reducing equivaleents

The glutathione protects hepatocytes by combining with the reactive metabolite of paracetamol thus preventing their covalent binding to liver proteins. The non-enzymic antioxidant, glutathione is one of the most abundant tripeptides present in the liver. Its functions are mainly concerned with the removal of free radical species such as hydrogen peroxide, superoxide radicals, alkoxy radicals, and maintenance of membrane protein thiols and as a substrate for glutathione peroxidase and GST [Dash et al. 2007; Balasubramanian, 2011; Das et al. 2012]. Drugs act through various mechanisms and maintain the functionality of important organ.

Liver diseases in Bangladesh

Liver diseases are an important and largely neglected health issue in low and middle income countries, which carry the highest burden. The number of people suffering from liver disease in Bangladesh is increasing at an alarming rate. According to the latest WHO data published in April 2011 liver disease death in Bangladesh reached 15,290 or 1.60% of total deaths. The age adjusted Death Rate is 14.80 per 100,000 of population ranks Bangladesh #60 in the world [http://www.worldlifeexpectancy.com].

In 2012, President of Bangladesh Hepatology Society, was quoted as saying by leading English newspaper; the cause of the 43 percent cases admitted to hospitals with acute hepatitis and jaundice was hepatitis E virus, 22 percent cases by hepatitis B, 8 percent was hepatitis A and 3 percent was hepatitis C. Hepatitis-B virus causes about 41 percent of liver cirrhosis and 25 percent of liver cancer in the country. Though the vaccine of hepatitis-B is very effective to prevent the virus, very few people take the vaccine for lack of awareness. He further said in 80 percent cases, hepatitis-B is not curable and prevention is the best way to combat the disease. But hepatitis-C can be cured through early diagnosis and treatment. Though hepatitis-A and E viruses are not so malignant, hepatitis-B and C pose serious threats to human health, stressing the need to be cautious during blood transfusion and using syringe and needles [http://english.peopledaily.com].

Evidence-based medicinal evaluation for liver treatment

In spite of the tremendous advances made in allopathic medicine, no effective hepatoprotective medicine is available. Even available synthetic drugs to treat liver disorders in also cause further damage to the liver. Conventional drugs are sometimes inadequate and can have serious adverse effects, to create a demand to develop new drugs. The modern medicine has little to offer for alleviation of hepatic ailments whereas most important representatives are of phytoconstituents. Herbal medicines are in great demand in the developed as well as developing countries for primary healthcare because of their wide biological and medicinal activities, higher safety margins and lesser costs [Chattopadhyay et al. 2007]. The 21st century has seen a paradigm shift towards therapeutic evaluation of herbal products in liver diseases by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation.

The nature has bestowed some plants with the property to prevent, treat and cure hepatic disturbances with interception of fewer side effects. Hepatoprotectives are a class of therapeutic agents that includes synthetic as well as natural product which offer protection to liver from damage or help in regeneration of hepatic cells. Medicinal herbs are significant source of hepatoprotective drugs. It has been reported that about 170 phytoconstituents isolated from 110 plants belonging to 55 families do possess hepatoprotective activity [Handa 1991]. Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, curcuminoids, lignans, essential oils and terpenoids. Clinical research has also shown that herbals have genuine utility in the treatment of liver diseases. Only a small portion of hepatoprotective plants as well as formulations used in traditional medicine are pharmacologically evaluated for its efficacy [Hikino et al. 1988].

Bangladesh has a rich tradition of alternative medicinal practices, which include homeopathy, Ayurvedic, Unani, and folk medicine. The latter is practiced by folk medicinal practitioners known commonly as Kavirajes, who rely almost exclusively on medicinal plants for treatment of various ailments. The mode of plant usage is simple, being decoctions, pastes or macerations of

whole plant or plant parts followed by topical or oral administration. Villages form the primary unit of human habitation in the country and most of the people are relay on Kavirajes for primary health care. Maximum people in Bangladesh depend on the traditional medicine for the treatment of jaundice or other liver diseses, because they get effective results from Kaviraje's treatment than the allopathic medicine.

Chapter Two

Methodology

Methodology

For the present review first of all we have enlisted a group of Bangladeshi medicinal plants those are traditionally being used against various liver diseases. The traditional medicine refers to a broad range of ancient natural health care practices including folk/tribal practices as well as Homeopathy, Ayurveda, Siddha, and Unani. In Bangladesh, folk medicinal practitionars known commonly as Kaviraj who rely almost exclusively on medicinal plants for treatment of various ailments. Intended for these purpose we conducted practitioners documents, books and web based information those are available for medicinal plants and their activities. From these recourses we have selected plants with hepatoprotective activity which have the highest number of citation or reference of usage.

After preliminary selection we have selected ten Bangladeshi medicinal plants those have reported hepatoprotective activity. In this regard we considered published research article, herbal drug directory and authentic web based information. The literature search was conducted in Pubmed database (19__-2014), focused on language literature in English. We read more than 30 full articles and a total of 80 peer-reviewed papers focused on hepatoprotective activity of Bangladeshi medicinal plants and their derivative compounds.

Subsequently we studied their botanical and taxonomical description, traditional uses, herbal and Unani formulation. Following the investigation of the reported activity of those plants we focused on their isolated chemical compounds and their classes. At that time we specified the compounds those have hepatoprotective potential.

Flow chart of the review

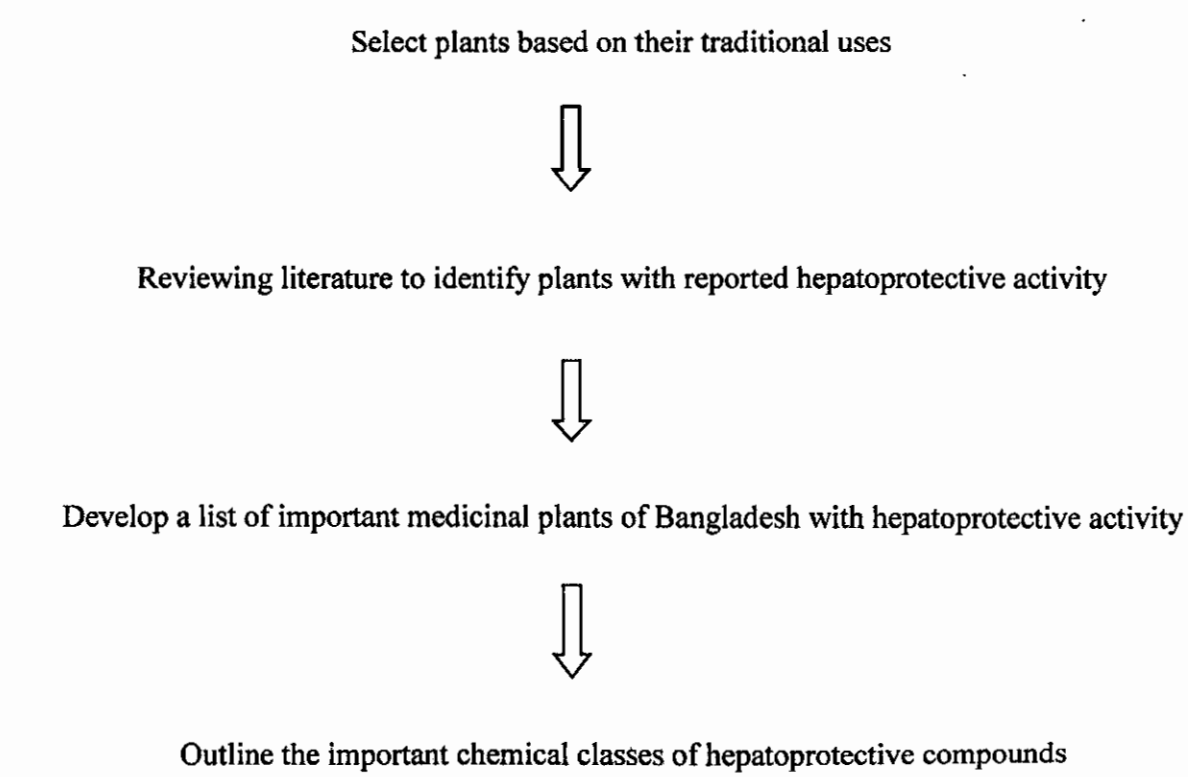


Figure 3. Flow chart of the review.

***Alocasia indica* (Mankachu)**

Figure 4. *Alocasia indica*

Alocasia indica (synonym: *Alocasia macrorrhizos)* is a species of flowering plant in the arum family, Araceae. It is a very robust evergreen herb, the thick, sculpted, glossy green leaves are held upright on dramatically rigid stems, growing up from 2 to 5 m in height under favorable conditions. It is commonly known as Mankachu in Bengali and Giant Taro or Elephant Ear Taro in English, distributed throughout Bangladesh and other parts of Asia. Commonly found growing around human settlements and Tropical humid forest. The plant has been used as folk medicine in different districts of Bangladesh. The tuber part of the plant is edible and is also used as a common vegetable that is easily, available and cheap. *A. indica* is very famous among general people due to being an enriched source of minerals and protein. It has been traditionally used for the treatment of jaundice, diabetes, constipation, prevent iron deficiency, to enhance eye sight, whole plant is utilized for pus in the ears. Stem juice is applied to prevent edema, pain, and bleeding from cuts and wounds [Mollik et al. 2010, M Rahmatullah et al. 2010, MR Haque et al. 2010, Al-Mahmud et al. 2011, Rahmatullah et al. 2009].

The edible tuber part of the plant is a very common vegetable among Asian people though maximum focus of research was done with the non-edible leaf part of the plant. It is experimentally reported that the leaf extract possesses hepatoprotective, antioxidant, antimicrobial, antifungal, anti-nociceptive, anti-inflammatory and antiprotozoal activities [Wahid et al. 2010, Mulla et al. 2010, WA Mulla et al. 2009, Patil et al. 2011, Mulla et al. 2009].

Mullah et al. (2009) reported that hydroalcoholic extract of *A. indica* leaves (250 and 500 mg/kg) effectively inhibited CCl_4 and paracetamol induced changes in the serum marker enzymes in a dose-dependent manner as compared to the normal and standard drug silymarin-treated groups .Hepatic steatosis, fatty infiltration, hydrophic degeneration and necrosis observed in CCl_4 and paracetamol- treated groups were completely absent in histology of the liver section of the animals treated with the extracts. CCl_4 and paracetamol (PCM) induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (381.23± 23.08 U/L), AST (650.56± 28.12 U/L) and ALP (745.23± 39.45 U/L) were observed significantly indicating acute hepatocellular damage and biliary obstruction. Treatment with *A. indica* (500 mg/kg) resulted in significant reduction in serum marker enzymes ALT (21.34± 3.06 U/L), AST (167.23± 12.67 U/L) and ALP (458.56± 22.08 U/L) similar to silymerin treated group which seems to offer the protection and maintain the functional integrity of hepatic cells. Histological examination of the liver tissue from CCl_4 and PCM treated animals revealed that CCl_4 and PCM had produced profound inflamation, severe congestion of blood vessels, mild hydropic degeneration, pyknosis of nucleus congestion especially in the sinusoids and occasional necrosis. Pre treatment of animals with silymerin, *A. indica* (250 mg/kg) and *A. indica* (500 mg/kg) reduced the inflammation, degenerative changes and steatosis. The results suggest that the hydroalcoholic extract of leaves of *A. Indica* possess significant potential as hepatoprotective agent [Mulla et al. 2011].

The priliminary phytochemical investigation of the hydroalcoholic extract of *A. indica* leaves showed that it contains flavinoids, cyanogenic glycosides, citric acid, ascorbic acid and polyphenolic compounds. *A. indica* contains chief constituents of alocasin, flavonoids and glycosides. Hepatoprotective potential of hydroalcoholic extract of *A. indica* may be due to the presence of alocasin, flavinoids other polyphenolic moieties present in it [Wahid A Mullah et al. 2009, Prajapati et al. 2009].

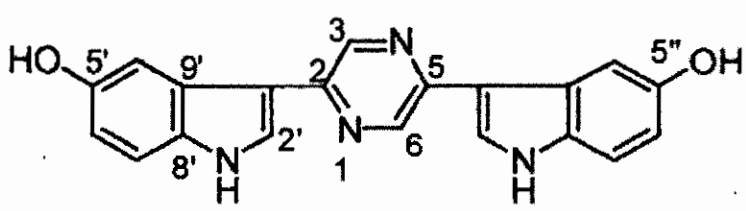


Figure 5. The structure of Alocasin.

As leaves are enormously used in folk medicine, scientists were interested to investigate their potentiality. But recently some researchers were interested the tuber part of *A. indica*.

Khowala et al. (2014) investigate the in vivo hepatoprotective activity of *A. indica* tuber using Gas Chromatography-Mass Spectrometry (GC-MS) analysis of ethanolic extract. In their experiment, the liver toxicity was induced by the administration of CCl_4. In vivo experiment showed that serum markers of ALT and AST level increased 2 fold and 1.7 fold by CCl_4 administered group as compared to normal group. Treatment with ethanolic extract at concentration of 200 mg/kg/day displayed the recovery percentage of serum ALT by 65.32% and AST by 77.36% when compared to CCl_4 treated group. CCl_4 induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (47.66±2.74 U/L) and AST (44.33±4.46 U/L) were observed significantly indicating acute hepatocellular damage. Treatment with *A. indica* (200 mg/kg body wt) significantly reduced the serum marker enzymes ALT (31.83±1.57 U/L) and AST (29.5±1.52 U/L) similar to control group ALT (22.66±1.78 U/L) and AST (25.16±1.64 U/L).

Khowala et al. (2014) also showed the presence of sixteen bioactive compounds in *A. indica* tuber ethanolic extract by GC-MS. Their results demonstrated that the ethanolic extract of the tuber contained higher concentrations of flavonoids and phenolic compounds. GCMS analysis of the ethanolic extract identified ß-Hydroxyque brachamine ($C_{19}H_{26}N_2O$) 1.9%; Gibb-3ene-1, 10-dicarboxylic acid, 2, 4 a-dihydroxy -1 methyl-8methylene, 14a-lactone, 10methyl ester ($C_{20}H_{24}O_5$) 3.8%; Butanoic acid, 4, 4 dithiobis ($C_8H_{16}N_2O_4S_2$) 2.6%; 5-(P-Aminophenyl)-4-(o-tolyl)-2 thiazolamine ($C_{16}H_{15}N_3S$) 8.4%; 3H-1,4-Benzodiazepine-2-amine,7chloro-N-methyl-5-phenyl,4-oxide ($C_{16}H_{14}CLN_3O$) 4.7%; 10, 12, 14 Nonacosatriynoic acid (C_{23} H_{46} O_2) 15.3%; Androst-4-en-11-ol-3, 17-dione, 9-thiocyanato ($C_{20}H_{25}NO_3S$) 16.0%; Estra-1, 3, 5 (10)-trien-17-one, 3hydroxy-6-methoxy, o-methyloxime, (6á) ($C_{20}H_{27}NO_3$) 29.5%, 17 alpha-ethynyl-17 beta-hydroxy-6beta methoxy -3 alpha, 5 cyclo-5 alpha-androstan-19-oic acid ($C_{22}H_{30}O_4$); 1H indole, 3 benzyl -2-phenyl ($C_{21}H_{17}N$) and 1H indole, 5 methyl-2, 3 diphenyl ($C_{21}H_{17}N$). Ethanolic extract of A. indica possess three major bioactive compounds of which 10,12,14-Nonacosatriynoic acid (peak area 15.3%) and Androst-4-en-11-ol3,17-dione,9-thiocyanato (peak area 16%) were found as essential oil whereas the major peak 29.5 % Estra-1,3,5(10)-trien-17one, 3-hydroxy-6-methoxy,o-methyloxime was a phytosterol [Nguyen et al. 2004].

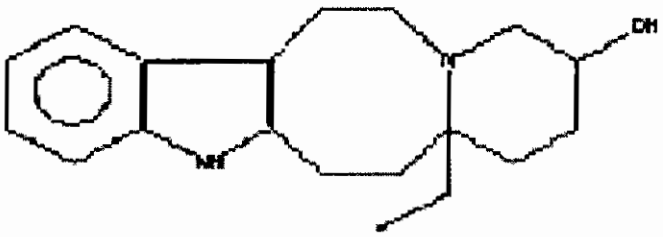


Figure 6. ß-Hydroxyque brachamine ($C_{19}H_{26}N_2O$)

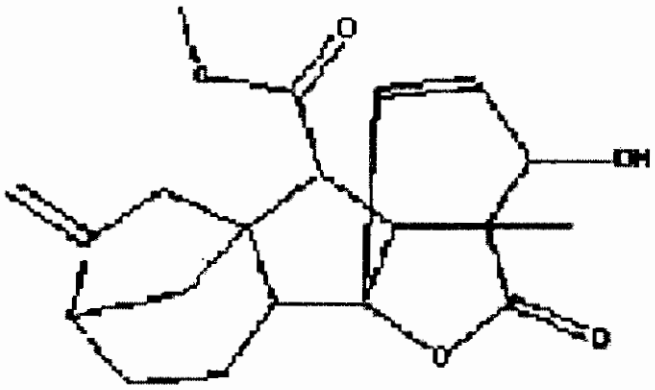


Figure 7. Gibb-3ene-1, 10-dicarboxylic acid, 2, 4 a-dihydroxy -1 methyl-8methylene, 14a-lactone, 10methyl ester ($C_{20}H_{24}O_5$).

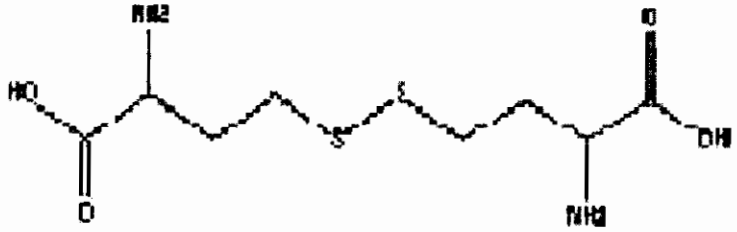


Figure 8. Butanoic acid, 4, 4 dithiobis ($C_8H_{16}N_2O_4S_2$)

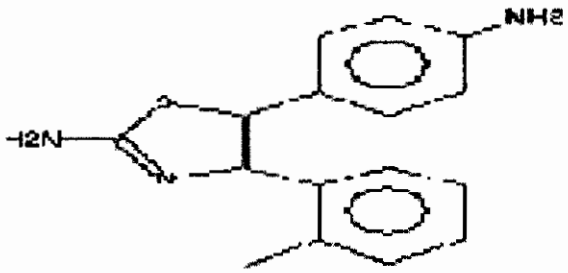


Figure 9. 5-(P-Aminophenyl)-4-(o-tolyl)-2 thiazolamine ($C_{16}H_{15}N_3S$)

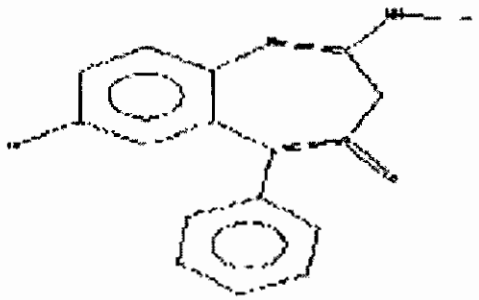


Figure10. 3H-1,4-Benzodiazepine-2-amine,7chloro-N-methyl-5-phenyl,4-oxide ($C_{16}H_{14}CLN_3O$)

Figure 11. 10, 12, 14 Nonacosatriynoic acid (C_{23} H_{46} O_2)

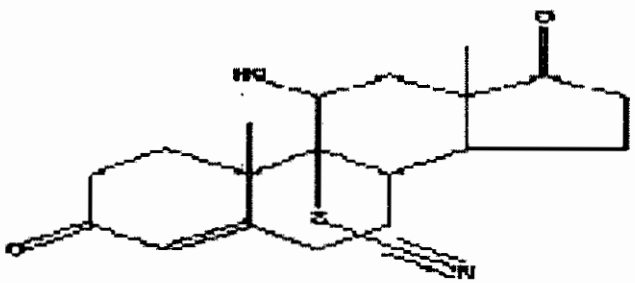


Figure 12. : Androst-4-en-11-ol-3, 17-dione, 9-thiocyanato ($C_{20}H_{25}NO_3S$)

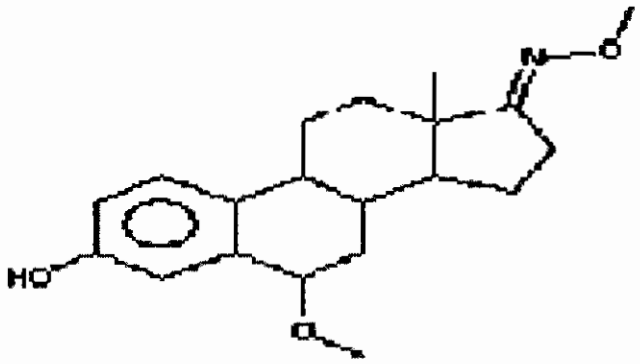


Figure 13. Estra-1, 3, 5 (10)-trien-17-one, 3hydroxy-6-methoxy, o-methyloxime, (6á) ($C_{20}H_{27}NO_3$)

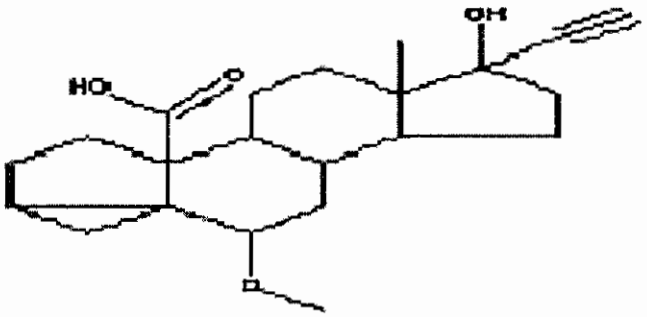


Figure 14. 17 alpha-ethynyl-17 beta-hydroxy-6beta methoxy -3 alpha, 5 cyclo-5 alpha-androstan-19-oic acid ($C_{22}H_{30}O_4$).

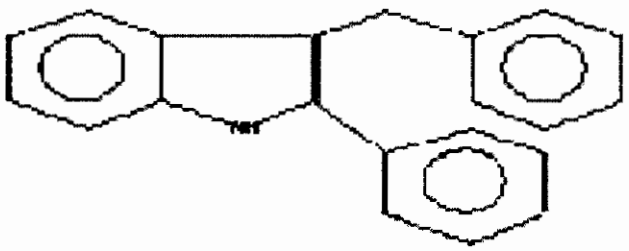


Figure 15. 1H indole, 3 benzyl -2-phenyl ($C_{21}H_{17}N$)

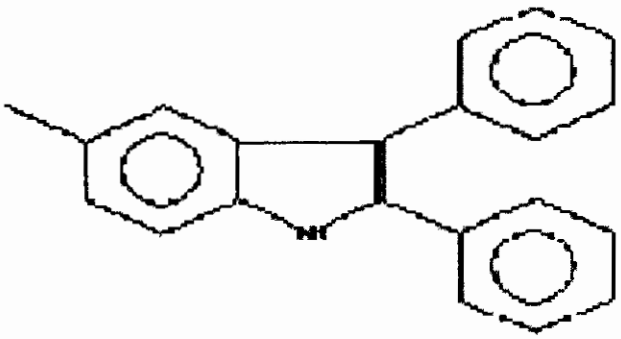


Figure 16. 1H indole, 5 methyl-2, 3 diphenyl ($C_{21}H_{17}N$)

Essential oils have been used medicinally in history and their fundamental Medical applications proposed by those who sell medicinal oils range from skin treatments to remedies for cancer and often are based solely on historical accounts of use of essential oils for these purposes. Modern works are preferred to discuss specific compounds of less "essential oils" as a class. Plant-derived essential oils class compounds have gained attention for biological roles due to their higher bioavailability. Recently, some essential oils extracted from plants have been reported to have antioxidant effects through scavenging radicals and inducing antioxidant enzymes, so they have also possibility to show hepatoprotective effect [Ortet et al. 2011, Sharififar et al. 2011, Kim et al. 2011, Campelo et al. 2011].

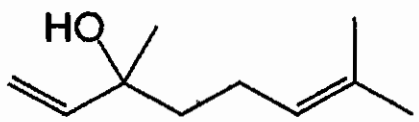


Figure 17. Basic structure of essential oil.

Valan et al. (2010) demonstrated that the essential oil protected mice against liver damage and also increased the secretion of bile fluid. The essential oil had a marked choleretic activity in rats [Valan et al. 2010].

Hawary et al. (2013) investigated the hepatoprotective activity of the plant derived essential oils compounds. Activity was assessed by measuring liver-related biochemical parameters following CCl4-induced hepatotoxicity *in vivo*. Administration of the oils at the same dose of standard led to a decrease in all of the parameters that were elevated by CCl_4. Based on their results, it can be concluded that the plant derived essential oils seem to have hepatoprotective activity in rats [Hawary et al. 2013].

Above discussion we have proposed that the hepatoprotective potential of ethanolic extract of *A. indica* tuber may be due to the presence of 10, 12, 14-Nonacosatriynoic acid and Androst-4-en-11-ol-3, 17-dione, 9-thiocyanato as a class of essential oil.

Andrographis paniculata (Kalmegh)

Figure 18. *Andrographis paniculata*

Andrographis paniculata commonly known as king of bitters is an annual herbaceous plant in the family Acanthaceae. As an Ayurveda herb it is known as Kalmegh or Kalamegha, meaning "dark cloud". It can be found in a variety of habitats, such as plains, hillsides, coastlines, and disturbed and cultivated areas such as roadsides, farms, and wastelands. In Bangladesh it mainly found in Chittagong and Chittagong hill tract. *A. paniculata* grows erect to a height of 30–110 cm in moist, shady places. The slender stem is dark green, the lance-shaped leaves, small pinkish flowers are borne in spreading racemes, and the fruit is a capsule around 2 centimeters long and a few millimeters wide and contains many yellow-brown seeds. The genus *Andrographis* consists of 28 species, of which *A. paniculata* is the most popular due to its medicinal properties [Wikipedia, the free encyclopedia.htm].

It has been used as medicinal herbs for centuries in several traditional systems of medicine all over the world. It is extensively used as home remedy for various diseases in Indian sub-continent traditional system as well as in tribal medicine in Bangladesh and some other countries for multiple clinical applications. *A. peniculata* was recommended in Charaka Samhita dating back to 175 BC for the treatment of Jaundice along with other plants in polyherbal preparations. It has also been used traditionally for sluggish liver as an antidote in case of colic dysentery and dyspepsia [Mishra et al. 2010].

A. paniculata has been used in Asia to treat variety of chronic and infectious diseases [Alpha Omega Labs, 2008]. It has been traditionally used as a remedy against diabetes [Norhaida et al.

1994], hypertension [Ahmad et al. 1993], inflammation [Patarapanich et al. 2007] and cobra bite [Selvanayagam et al. 1994]. Extensive research revealed that *A. paniculata* has a surprisingly broad range of pharmacological effects and some of them are extremely beneficial and include hepatoprotective [Handa et al. 1990], anticancer [Kumar et al. 2004], anti HIV [Chang et al. 1988], anti AIDS [Stephen et al. 2000] and immunostimulatory [Puri et al. 1993]. Other pharmacological effects include; antimalarial [Misra et al. 1992], antityphoid [Sabu et al. 2006], antiviral [Wiart et al. 2005], antibacterial [Mishra et al. 2009], antidiarrhoeal [Gupta et al. 1993], antipyretic [Vedavathy et al. 1991], anti-inflammatory [Chang et al.1986], antidiabetic [Zhang et al. 2000], antithrombotic [Yeung et al. 1987], cardiovascular [Tan et al. 2004], antivenom [Chang et al. 1986], antifertility [Sakila et al. 2009] and psychopharmacological activity [Mandal et al. 2001]. *A. paniculata* may be a promising treatment for the alleviation of subjective symptoms of respiratory tract infections [Coon et al. 2004]. It may also be beneficial for those with chronic fatigue syndrome and fibromyalgia [Khan et al. 2007].

Sivaraj et al. (2011) investigated the protective effect of the leaf extract of *Andrographis paniculata* against ethanol induced liver toxicity in male albino rats. The liver toxicity was induced by the administration of ethanol to the animals at the optimum dosage of 7.9g/kg body wt., orally for 45 days. After induction of liver toxicity the aqueous plant extract of *A. paniculata* was administered to the animal 250 mg/kg body wt., for 45 days. The liver toxicity and protective effect of the plant extract was assessed by the estimation of liver marker enzymes like ALT, AST, ALP, Bilirubin and liver histopathological studies. In this investigation, the marker enzymes were significantly elevated in ethanol treated animals, when compared to levels in normal animals. When the plant extract *A.paniculata* was administered to the animals the liver marker enzymes like ALT, AST, ALP, bilirubin were significantly reduced by 42.59%, 30.87%, 42.03% and 28.33% respectively, when compared to the levels in ethanol fed control groups. Then they compared to the standard drug silymarin- treated groups in a dose-dependent manner. Ethanol induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (107±2.04 IU/l/min/mg), AST (217.3±6.02 IU/l/min/mg), ALP (426.1±4.44 IU/l/min/mg) and Bilirubin (0.60±0.02 mg/dl) were observed significantly indicating acute hepatocellular damage. A significant reduction in serum marker enzymes ALT (61.42±1.81 IU/l/min/mg), AST (150±3.78 IU/l/min/mg), ALP (247±5.861 IU/l/min/mg) and bilirubin (0.43±0.01 IU/l/min/mg)

were observed in the treatment group receiving *A.paniculata* extract 250 mg/kg similar to silymerin treated group ALT (59.78±1.67 IU/l/min/mg), AST (150±3.20 IU/l/min/mg), ALP (240±4.96 IU/l/min/mg) and Bilirubin (0.43±0.01 IU/l/min/mg) which seems to offer the repair the hepatic injury and/or restore the cellular permeability [Sivaraj et al. 2011].

Nasir et al. (2013) also investigated the hepatoprotective effect of the aqueous leaf extract of *A. paniculata* against CCl_4 – induced hepatic injury in rats. Significant ($P<0.05$) increase of serum levels of ALT, AST, ALP, total bilirubin (TBL), direct bilirubin (DBL) in CCl_4 intoxicated rats were restored to normal levels when treated with the extract and CCl_4. The liver toxicity and protective effect of the plant extract was assessed by the estimation of liver marker enzymes like ALT, AST and bilirubin level studies. The liver toxicity was induced by the administration of 30% carbon tetrachloride in liquid paraffin (1ml/kg body weight, *i.p.*) for four days. CCl_4 induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (14.66 ± 0.29U/L), AST (14.06 ± 0.38U/L) and TBL (21.87± 0.20 U/L) were observed. Treatment with *A. paniculata* (300 mg/kg body wt) a significant reduction in serum marker enzymes ALT (10.05 ± 0.33 U/L), AST (10.26 ± 0.56 U/L) and TBL (14.58 ± 0.21 U/L) similar to silymerin treated group ALT (9.38 ± 0.22U/L), AST (9.94 ± 0.42 U/L) and TBL (14.43±0.13U/L). The study demonstrated that *A. paniculata* possesses significant hepatoprotective effects [Nasir et al. 2013].

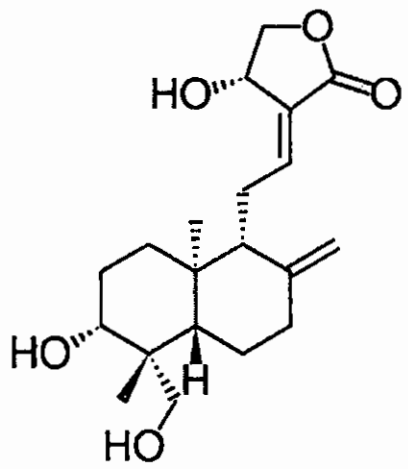
Jayavelu et al. (2013) reported the hepatoprotective effect of the aqueous leaf extract of *A. paniculata* against paracetamol (PCM) induced hepatic injury in *Wistar albino* rats. The activities of serum marker enzymes of the liver like ALT, AST, ALP and bilirubin were increased by the administration of paracetamol (500 mg/kg body weight). These activities were found to be reduced after the administration of plant extracts in the toxicity induced groups. The results of the experiment show that the levels of marker enzymes were high in paracetamol induced group (ALT-110.37%, AST- 81.22%, ALP-113.68% and bilirubin-338.04%) when compared to the normal. The plant extracts show a better reduction of liver marker enzymes (ALT- 18.41%, AST- 26.34%, ALP- 31.39% and bilirubin-29.28%) when compared with PCM toxicated rats. PCM induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (102.56±0.004 IU/l/min/mg), AST (122.36±3.16 IU/l/min/mg), ALP

(152.38±0.44 IU/l/min/mg) and Bilirubin (4.03±0.001 mg/dl) were observed significantly indicating acute hepatocellular damage. When treated with *A. paniculata (*500mg/kg body wt) a significant reduction in serum marker enzymes ALT (83.67±0.065 IU/l/min/mg), AST (90.12±0.05 IU/l/min/mg), ALP (104.54±1.24 IU/l/min/mg) and Bilirubin (2.85±0.18 IU/l/min/mg) were observed similar to standard (Liv.52) treated group ALT (58.23±1.15 IU/l/min/mg), AST (75.21±0.04 IU/l/min/mg), ALP (80.01±0.15 IU/l/min/mg) and Bilirubin (1.01±0.048 IU/l/min/mg). This study showed that the extracts of *A. paniculata* could play a significant role to protect and cure the liver cells against paracetamol induced toxicity [Jayavelu et al.2013].

Cheung et al. (2010) reported that *A.paniculata* contains diterpenes, lactones and flavonoids. Flavonoids mainly exist in the root, but also can be isolated from the leaves. The leaves contain two bitter lactone andrographolides, and kalmeghin. Active compounds extracted with ethanol or methanol from the whole plant, leaf and stem of *A. paniculata* include over 20 diterpenoids and over 10 flavonoids [Cheung et al. 2010, Matsuda et al. 1994, Pholphana et al. 2004].

By studied **Rao et al. 2004, Xu et al. 2010 and Cheung et al. 2001** their literature we observed that the major constituents of *A.paniculata* are diterpenoids, flavonoids and polyphenols [Rao et al. 2004, Xu et al. 2010, Cheung et al. 2001].

Andrographolide ($C_{20}H_{30}O_5$) is the major diterpenoid in *A. paniculata*, making up about 4%, 0.8~1.2% and 0.5~6% in dried whole plant, stem and leaf extracts respectively [Burgos et al. 1997, Reddy et al. 2003]. Andrographolide is a labdane diterpenoid, Labdane is a natural bicyclic diterpene. It is a colorless and extremely bitter substance.



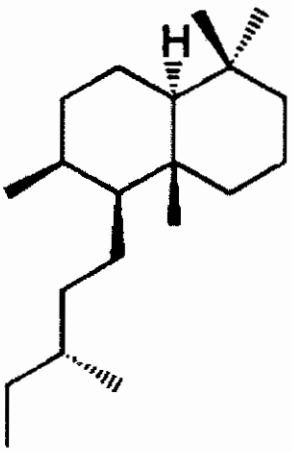


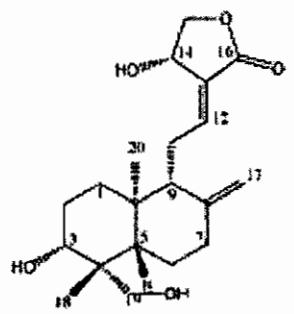
Figure 19. Andrographolide ($C_{20}H_{30}O_5$)

Figure 20. The structure of labdane diterpene

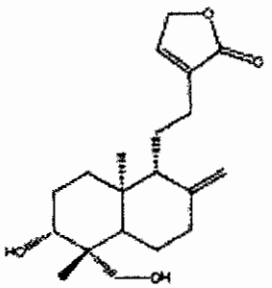
Among the andrographolide analogues, 14-deoxy-11,12-didehydroandrographolide is immunostimulatory, anti-infective and anti-atherosclerotic; neoandrographolide is anti-inflammatory, anti-infective and anti-hepatotoxic; 14-deoxyandrographolide is immunomodulatory and anti-atherosclerotic. Among the less abundant compounds from *A. paniculata*, andrograpanin is both anti-inflammatory and anti-infective; 14-deoxy-14,15-dehydroandrographolide is anti-inflammatory; isoandrographolide, 3,19-isopropylideneandrographolide and 14-acetylandrographolide are tumor suppressive; arabinogalactan proteins are anti-hepatotoxic [Das et al. 2009, Kapil et al. 1993].

Kapil et al. (1993) showed that pre-treatment of mice with andrographolide, andrographiside and neoandrographolide alleviated hepatotoxicity induced by intoxication of carbon tetrachloride (CCl_4) or tert-butylhydroperoxide (tBHP) in mice [Singha et al., 2007]. The glucoside groups in andrographolid and neoandrographolide were suggested to act as strong antioxidants. The *A. paniculata* aqueous extract and andrographolide decreased oxidative stress in isolated rat lymphocytes exposed to nicotine [Akowuah et al. 2009]. Arabinogalactan, another aqueous component of the *A. paniculata*, Tris-buffer extract and andrographolide minimized the toxicity in pre-treated mice [Jaruchotikamol et al. 2007]. Oral treatment of rats with the *A. paniculata* methanol extract followed by CCl_4 administration restored plasma lipid peroxidation, ALT and AST [Chatuphonprasert et al. 2009]. Andrographolide significantly induced the expression of

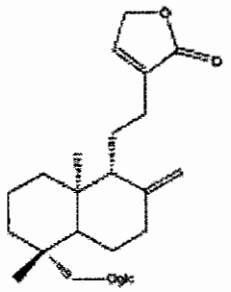
CYP1A1 and CYP1A2 mRNAs in a concentration-dependent manner, and synergistically induced CYP1A1 expression with the typical CYP1A inducers [Pekthong et al. 2007, Pekthong et al. 2009]. In addition, the *A. paniculata* 60% ethanol extract or andrographolide may cause herb-drug interactions through CYP3A and CYP2C9 inhibition *in vitro* or CYP2C11 inhibition *in vivo* [Chang et al. 2008, Fernandez et al. 2006]. Induction of drug-metabolizing enzymes is considered to be an adaptive response to a cytotoxic environment. The *A. paniculata* ethanol extract, EtOAc extract and andrographolide induce the expression of the pi class of glutathione S-transferase, a phase II biotransformation enzymes involved in detoxification of various classes of environmental carcinogens, in rat primary hepatocytes [Heim et al. 2002]. A recent study showed that this induction by andrographolide was suppressed by the increase of cAMP or cAMP analogues [Hollman et al. 1999].



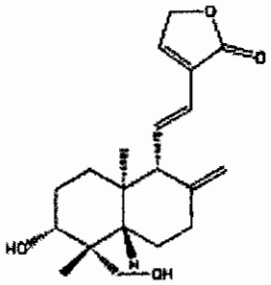
andrographolide



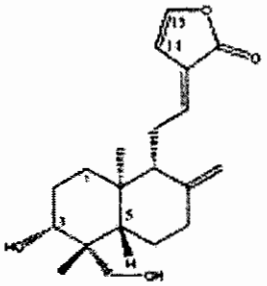
14-deoxyandrographolide



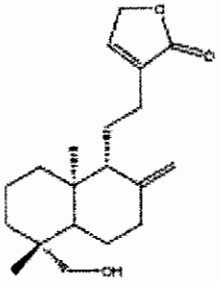
neoandrographolide



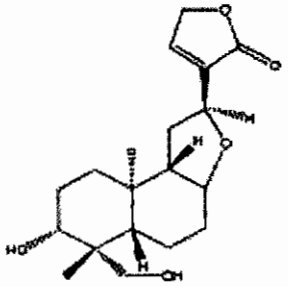
14-deoxy-11,12-didehydro-andrographolide



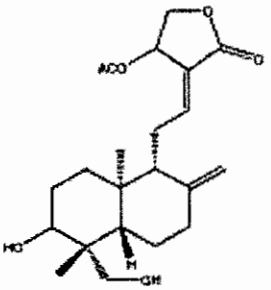
14-deoxy-14,15-didehydro-andrographolide



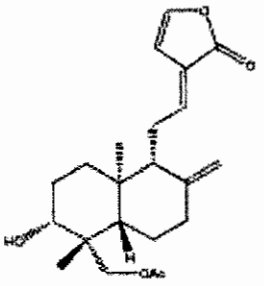
andrograpanin



isoandrographolide



14-acetylandrographolide



19-*O*-acetylanhydroandrographolide

Figure 21. Structures of andrographolide **compounds isolated from** *A. paniculata.*

Active compounds extracted with ethanol or methanol from the whole plant of *A. paniculata* over ten flavonoids has been isolated.

Flavonoids are low molecular weight bioactive polyphenols those are widely distributed among the plant kingdom [Heim et al. 2002, Peterson et al. 1998, Tsuchiya et al. 2010]. Flavonoids are secondary metabolites characterised by flavan nucleus and C6-C8-C6 carbon-skeleton. These are group of structurally related compounds with a chromane-type skelton having phenyl substituent in C2-C3 position [Rijke et al. 2006, Cushnie et al. 2005, Tsuchiya et al. 2010].

The basic structural feature of flavonoid is 2-phenyl-benzo-γ-pyrane nucleus consisting of two benzene rings (A and B) linked through a heterocyclic pyran ring (C) as shown in fig (I)[Cook et al. 1996].

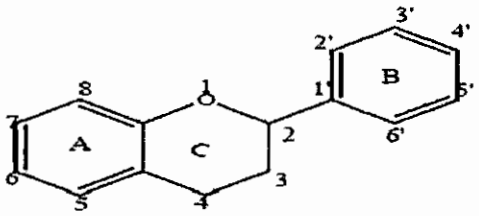


Figure 22. The basic structure of flavonoid.

Flavonoids differ in their arrangement of hydroxyl, methoxy and glycosidic side groups and in the conjunction between A and B rings. A variation in C ring provides division of subclasses. According to their molecular structure, they are divided into the following eight classes [Rijke et al. 2006].

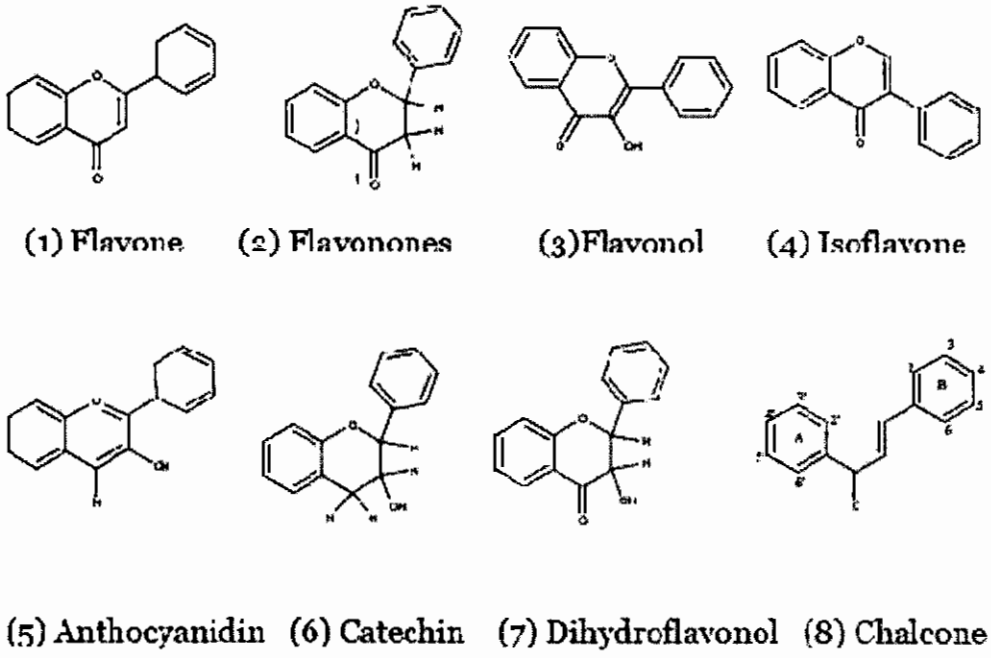
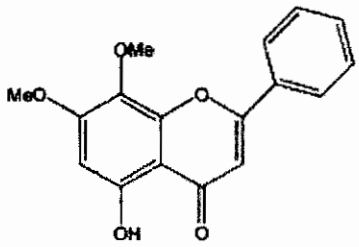


Figure 23. Chemical structure of different types of flavonoids.

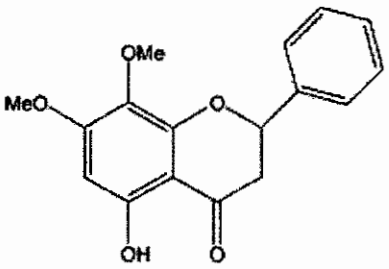
In plants, flavonoids are often present as O-glycosides or C-glycosides. The O-glycosides possess sugar substituent bound to –OH of aglycone, usually at position 3 or 7, whereas, C-glycosides possess sugar groups bound to Carbon of aglycone usually 6-C or 8-C [Reddy et al. 2003].

Flavonoids bind to subunit of DNA-dependent RNA polymerase I, thus activating the enzyme. As a result, protein synthesis gets increased leading to regeneration and production of hepatocytes [Kuroyanagi et al. 1987].

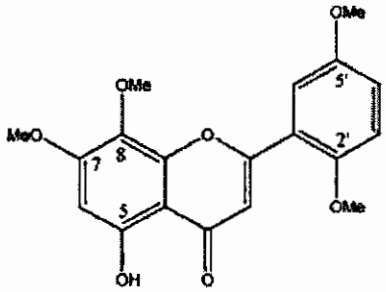
From ethyl acetate ($EtOA_C$)-soluble fraction of the ethanol or methanol extract of *A. paniculata*, 5-hydroxy-7,8-dimethoxyflavone, 5-hydroxy-7,8,2',5'-tetramethoxyflavone, 5-hydroxy-7,8,2',3'-tetramethoxyflavone, 5-hydroxy-7,8,2'-trimethoxyflavone, 7-*O*-methylwogonin and 2'-methyl ether were isolated as the main flavonoids [Chao et al. 2010, Radhika et al. 2010].



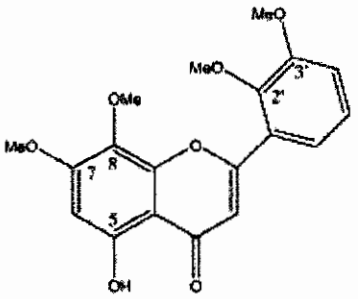
5-hydroxy-7,8-dimethoxyflavone



5-hydroxy-7,8-dimethoxyflavanone



5-hydroxy-7,8,2',5'-tetramethoxyflavone



5-hydroxy-7,8,2',3'-tetramethoxyflavone

Figure 24. Structures and bioactivities of flavonoids isolated from *A. paniculata*.

***Eclipta alba* (*Bhringraj* / Kalokeshi)**

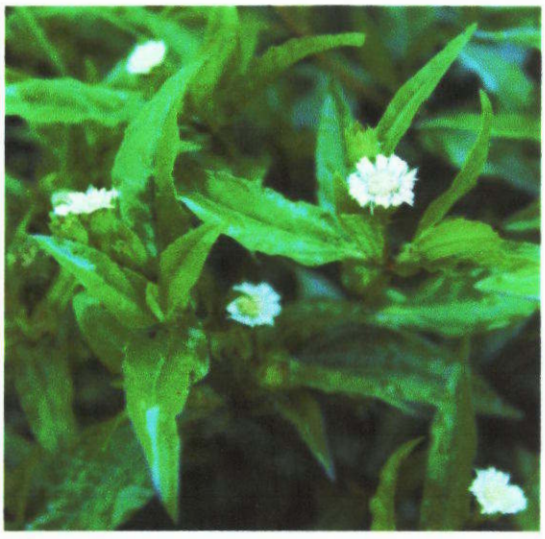


Figure 25. *Eclipta alba*

Eclipta alba (syn. *Eclipta prostrata.*) commonly known as false daisy, *yerba de tago*, and *bhringraj*, is a species of plant in the family Asteraceae. Other common name is Kalokeshi. This species grows commonly in moist places as a weed in warm temperate to tropical areas worldwide. It is valuable due to its medicinal importance, mainly used as hepatoprotective and hair tonic in Ayurveda. It is widely distributed throughout Bangladesh, India, China, Thailand, and Brazil [Wikipedia]. This plant has cylindrical, grayish roots. The solitary flower heads are 6–8 mm in diameter, with white florets. The achenes are compressed and narrowly winged. It is an annual, erect or prostate entirely pubescent herb, often rooting at nodes with opposite, sessile, usually oblong, 2.5-7.5 cm long leaves with appressed hairs [Chopra et al. 1956]. According to Ayurvedic philosophy *E.alba* is bitter; alterative and anthelmintic. It is useful in inflammations, hernia, eye diseases, bronchitis, asthma, leucoderma, anemia, heart and skin diseases, right blindness, syphilis etc. It is reported as beneficial for complexion, hair, eyes, and teeth. Expressed juice of *E. alba* mixed with goat's milk is used in frontal sinusitis and nasal cattarh in children [Council of Scientific and Industrial Research, New Delhi, 1952]. The plant is used as an antidote for snake bites in Korea [Medicinal Plants in the Republic of Korea. World Health Organization, Manila. 1987] . The plant juice, mixed with an aromatic (essential oil), is used in the treatment of catarrhal problems and jaundice. The leaves are used in the treatment of scorpion stings [Medicinal Plants of Nepal Dept. of Medicinal Plants. Nepal: 1993]. It is

experimentally reported that the plant extract possesses Hypolipdimeic effect [Zhang et al. 2001, Tabassum et al. 2004], Anti aggressive effect [Lobo et al. 2008], Analgesic effect [Sawant et al. 2004], Anti-inflammatory effect, Antimicrobial effect [Arunachalam et al. 2009], Antimalarial effect [Bapna et al. 2007], Antihyperglycemic effect [Ananthi et al. 2003], Hypolipdimeic effect [Kumari et al. 2006, Kim et al. 2008], Neuropharmacological effects [Thakur et al. 2005], Hair growth promoting effects [Datta et al. 2009], Effect on proteolytic and hemorrhagic activities [Samiulla et al. 2003], Effect on osteoblast differentiation [Lee et al. 2008].

Lal et al. (2010) reported that the hepatoprotective activity on methanolic extract and sub fractions of leaves and the chloroform extract and sub fractions of roots of *Eclipta alba* was carried out using carbon tetrachloride- induced liver damage and Lysosomal enzymes level in wistar albino rats. Significant ($P<0.05$) increase of serum levels of alanine aminotransferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP) and bilirubin in CCl_4 intoxicated rats were restored to normal levels when treated with the extract and CCl4. The liver toxicity and protective effect of the plant extract was assessed by the estimation of liver marker enzymes like ALT, AST, ALP and Bilirubin level studies. The liver toxicity was induced by the administration CCl_4 (10 mg/per kg i.p). CCl_4 induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (412.7±15.8 U/L), AST (210.0±26.0 U/L), ALP (195.4±18.5 U/I) and TBL (0.97±0.04 U/L) were observed. Treated with chloroformic root *E. alba extract* (200 mg/kg body wt) a moderate reduction in serum marker enzymes ALT (374.0±21.0U/L), AST (128.0±23.0U/L), ALP (126.0±21.0U/L) and TBL (0.79±0.06 U/L) whereas silymerin (100ml/kg) treated group ALT (210.7±4.4U/L), AST (97.0±25.0U/L) ALP (86.6±17.0 U/L) and TBL (0.40±0.06U/L). Then treated with methanolic leaves *E. alba* extract (200 mg/kg body wt) a significant reduction in serum marker enzymes ALT (290.0±5.5U/L), AST (106.7 ± 17.5U/L), ALP (119.0 ± 23.0U/L) and TBL (0.77±0.05U/L) similar to silymerin (100ml/kg) treated group ALT (210.7±4.4U/L), AST (97.0±25.0U/L) ALP (86.6±17.0 U/L) and TBL (0.40±0.06U/L). The study demonstrated that methanolic leaves *E. alba* extract possesses significant hepatoprotective effects [Lal et al. 2010].

Saxena et al. (1993) proposed that Ethanol/water *E. alba* extract significantly counteracted CCl4-induced inhibition of the hepatic microsomal drug metabolizing enzymes. The loss of

hepatic lysosomal acid phosphatase and alkaline phosphatase by CCl_4 was significantly restored by ethanol/water extract [Saxena et al. 1993].

Tabassum et al. (2004) reported that the treatment with 50% ethanol extract of *E.alba* (100 and 250mg/100g body weight) was found to protect the mice from hepato-toxic action of paracetamol as evidenced by significant reduction in the elevated serum transaminase levels. Histopathological studies showed marked reduction in fatty degeneration and centri zonal necrosis in animals receiving different doses of *E.alba* along with paracetamol as compared to the control group [Tabassum et al. 2004].

Phytochemical studies on *Eclipta* revealed the presence of Alkaloids including ecliptine and nicotine from the whole plant [Pal et al. 1943, Khargava et al. 1974, Sikroria et al. 1982]. Bio-active steroidal alkaloids, verazine, 20-epi-3-dehydroxy-3-oxo-5, 6-dihydro-4, 5-dehydroverazine ecliptalbine, (20R)-4s-hydroxyverazine, 4s-hydroxyverazine, (20R)-25s-hydroxyverazine and 25s-hydroxyverazine has been identified from the methanolic extract [Kader et al. 1998].

The major coumestan isolated from the dried leaves of *Eclipta alba* includes wedelolactone ($C_{16}H_{10}O_7$) and desmethylwedelolactone. Coumestan forms the central core of a variety of natural compounds known collectively as coumestans. Coumestans, including a coumestrol and phytoestrogen are found in a variety of plants. Wedelolactone (1,8,9-trihydroxy-3-methoxy-6H-1-benzofuro 3,2-c chromen-6-one) is an organic chemical compound classified as a coumestan, [Prakash et al., 2008] coumestans are oxidation products of pterocarpan that are similar to coumarin. Pterocarpans are derivatives of isoflavonoids, which is a group of compounds that can be described as benzo-pyrano-furano-benzenes. Wedelolactone derivatives include dimethylewedelolactone-7-glucoside and nor-wedelolactone isodemethylwedelolactone, and strychnolactone have been reported from by percolation and hot extraction of *E.alba* whole plant [Zhang et al., 2001]. Wedelolactone and desmethylwedelolactone are major components; showed dose-dependent significant activity in preventing CC14 induced liver injury [Singh et al. 2001].

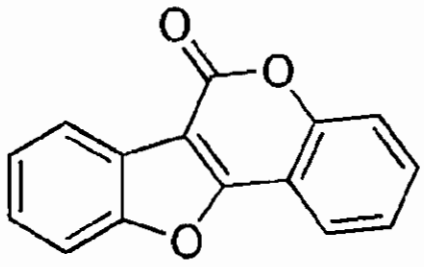


Figure 26. Structure of coumestan

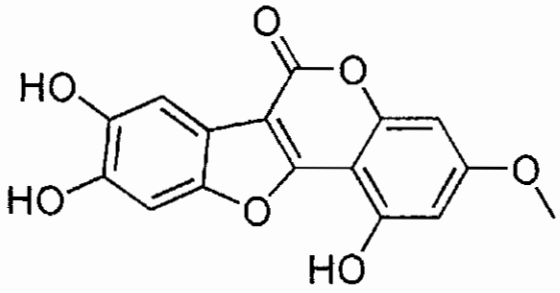


Figure 27. Structure of wedelolactone

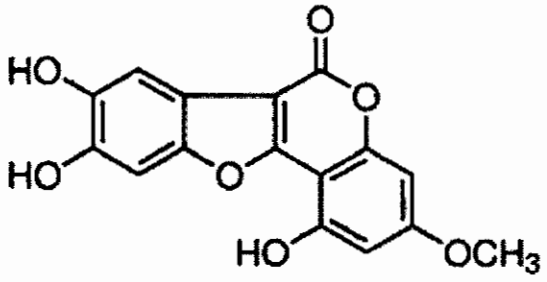


Figure 27. Structure of desmethylwedelolactone

Many Hydrocarbons like Ddithienylacetylene ester [Jain et al. 1999], ecliptal or α-terthienyl aldehyde [Das et al. 1991], α-terthienyl-methanol [Han et al. 1998], and α-formylterthienyl [Zhang et al. 1997] were isolated from *E. alba*.

Whole plant is said to have many Triterpenene like saponin, eclalbatin, together with α-amyrin, β-amyrin, ursolic acid, oleanolic acid and wedelic acid. Ecliptasaponin C and D, new triterpenoid glucosides, have been isolated from the whole plant of *E. alba*. From the whole parts of six new oleanane triterpene glycosides, eclalbasaponins I-VI have been isolated [Yahara et al. 2006].

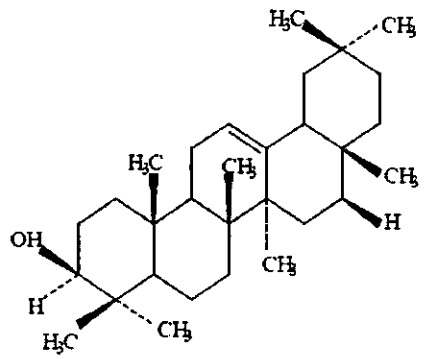


Figure 28. Structure of α-amyrin

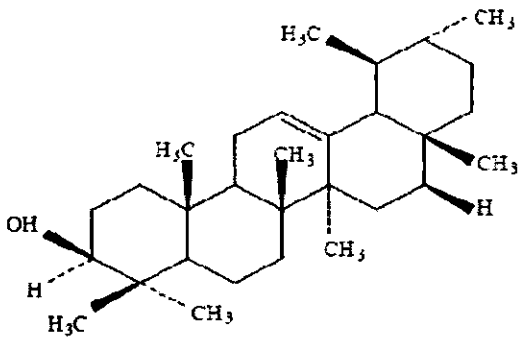


Figure 29. Structure of β-amyrin

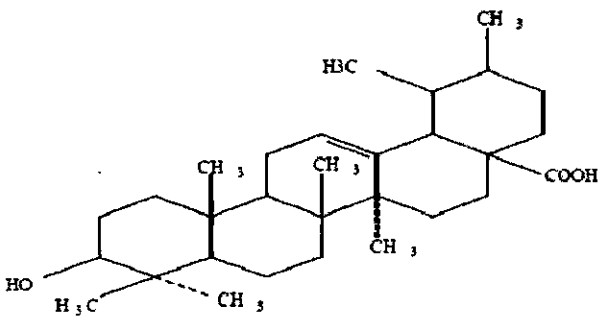


Figure 30. Structure of ursolic acid

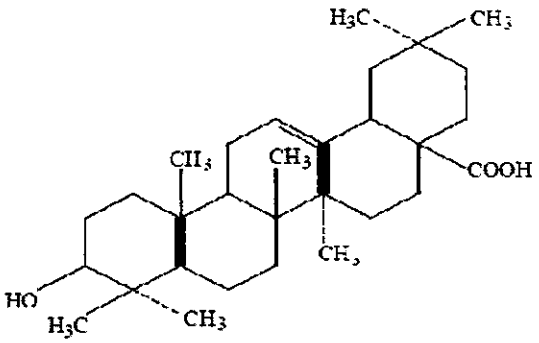


Figure 31. Structure of oleanolic acid

Polyacetylenic thiopenes 5'- senecioyloxymethylene-2-(4-isovaleroxybut-3-ynyl) dithiophene, 5'-tigloyloxymethylene -2-(4-isovaleroxybut-3-ynyl) dithiophene have been reported form the plant. The roots contain polyacetylene substituted thiophenes [Singh et al. 1988].

The aerial parts of the plant have been reported to contain phytosterol; β glucoside of phytosterol, daucosterol and stigmasterol-3-O-glucoside [Zhang et al. 1997]. The whole plant contains stigmasterol [Han et al. 1998] and β-sitosterol [Zhang et al. 2001].

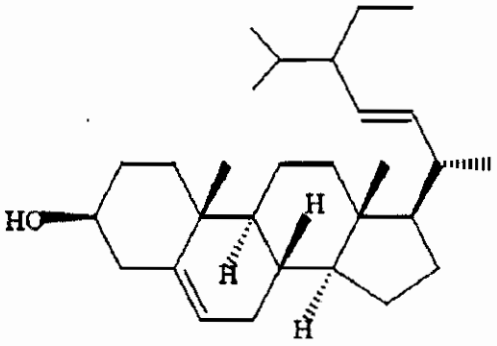


Figure 32. Structure of stigmasterol

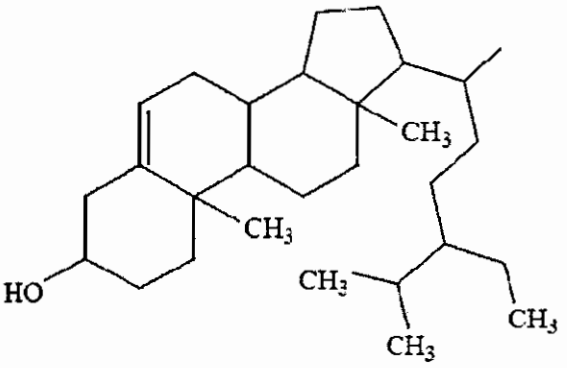


Figure 33. Structure of β-sitosterol

Flavonoids like apigenin, luteolin and luteolin-7-glucoside were isolated from *E. alba*.[28]

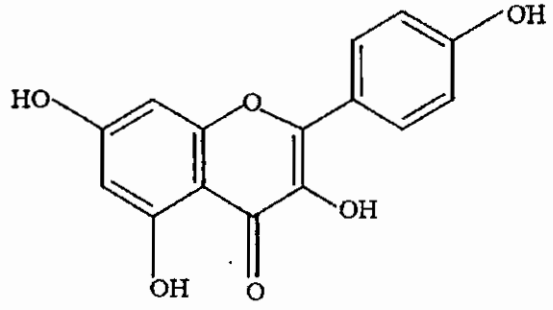


Figure 34. Structure of apigenin

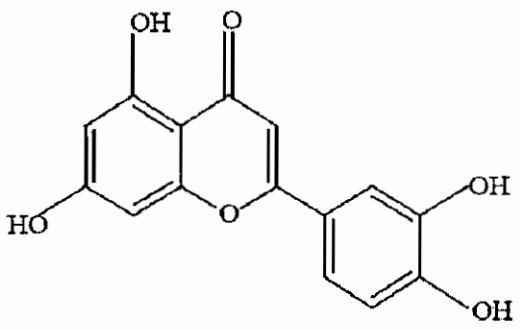


Figure 35. Structure of luteolin

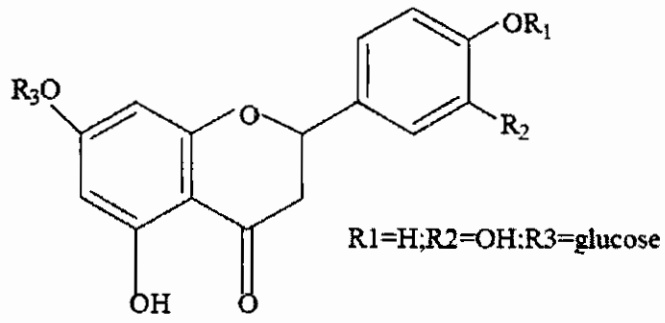


Figure 36. Structure of luteolin-7-glucoside

Nonacosanol, stearic acid, lacceroic acid and 3, 4-dihydoxy benzoic acids were also isolated [Zhang et al. 2001].

***Elephantopus scaber* (Gojialata)**

Figure 37. *Elephantopus scaber*

Elephantopus scaber is a species of flowering plant in the Asteraceae family. It is found in Indian Subcontinent, Southeast Asia, Tropical Africa, Eastern Asia and Australia. The plant is popularly known as Elephant's foot in English and Gojialata in Bangla. The herb is an erect and hairy with a height of 30-60 cm. Leaves are mostly in basal rosette and 10-25 cm in length. Stem usually dichotomously branched and flowering heads are borne in clusters at the ends of the branches. The flowering heads are numerous, sessile and forming a large terminal inflorescence comprising about four violet flowers [Wikipedia, the free encyclopedia.htm]. In the traditional medicine, the medical attribution of this species has been known for a long time. As per the traditional claims, the roots were used as antipyretic, cardiotonic and diuretic. [Nadakarni et al.1954]. The whole plant of *Elephantopus scaber* has been used in Bangladesh folk medicine for the treatment of pneumonia [Lin et al. 1992], nephritis [Lin et al. 1992], hepatitis [Lin et al. 1995], chronic arthritis [Tsai et al. 1999], tumor [Xu et al. 2006], and diabetes [Daisy et al. 2009]. Decoction of roots and leaves is used as emollient and given in dysuria, diarrhea, dysentery and in stomachic pain [Kiritikar et al. 1991]. The aqueous extract of leaves is applied externally to treat eczema and ulcers [Chopra et al. 1956]. The pharmacological properties of the leaf extracts have been evaluated for hepatoprotective properties [Lin et al. 1995], diuretic [Poli et al. 1992] and anti-inflammatory [Tsai et al. 1992].

Sheba et al. (2012) observed that the hepatoprotective activity of methanolic extract of Elephantopus scaber root against CCl_4 induced liver damage in rats. The in vivo hepatoprotective activity was studied by estimating AST, ALT and ALP levels and by histopathological examination in CCl_4 toxicity induced experimental rats. Methanolic extract of Elephantopus scaber root at doses of 75mg and 150mg/kg body weight significantly reduced the levels of AST, ALT and ALP. Histopathological changes induced by CCl_4 were reduced by the treatment of methanolic extract of Elephantopus scaber root. The level of these enzymes was significantly increased (P: 0.05) compared to vehicle control after the injection of CCl_4. Treatment with curcumin at a dose of 75 mg/kg body weight, methanolic extract of Elephantopus scaber root at a dose of 75 mg/kg and150 mg/kg body weight showed significant decrease ($P \leq 0.05$) compared to toxic control, with a protection of 81%, 59%, 66% in the level of ALT, 84%, 50%, 66% in the level of AST and 68%, 42%, 54% in the level of ALP. The elevation of these liver marker enzymes and the decrease of protein and albumin caused by the CCl4 induced liver damage is significantly decreased by the administration of the methanolic extract of Elephantopus scaber root. Curcumin also showed better protection towards CCl4 induced liver damage [Kannakuzhiyil et al. 2012].

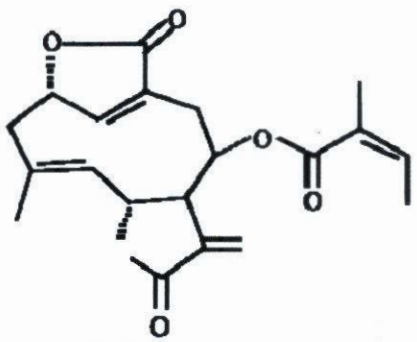
Rajesh and Latha (2001) has studied the efficacy of roots of *Elephantopus scaber* to prevent carbon tetrachloride (CCI4)-induced chronic liver dysfunction in the rats by determining different biochemical markers such as aspartate aminotrasferase (AST), alanine aminotrasferase (ALT), alkaline phosphatase (ALP) and also protein in serum and total lipid, cholesterol and phospholipids in tissues. The liver toxicity was induced by the administration of O. 1 ml of CCl_4 in groundnut oil (1:1v/v) per 100 g body weight of rats. CCl_4 induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (69.44±2.45 U/L), AST (29.17±1.02 U/L) and ALP (390.50± 13.73) were observed. Treatment with *E. scaber* (250 mg/kg body wt) a significant reduction in serum marker enzymes ALT (43.33±2.21 U/L), AST (16.66±0.86 U/L) and ALP (159.75±8.00 U/L) compare to control group ALT (27.78±0.70 U/L), AST (*16.66±0.42*U/L) and ALP (88.75±2.24U/L). From the results, it can be concluded that root powder of *E. seaber* prevents hepatic injury induced by $CC1_4$ in rats by decrease in the activities of these enzymes [Rajesh et al. 2001].

Ganga *et al.* (2012) observed that oral administration of different fractions (hexane, methyl acetate, methanol and ethanol) of *E. scaber* in different doses (125, 250 and 500 mg kg^{-1}) showed anti-hepatotoxic activities against carbon tetrachloride (CCl_4) induced hepatic damage in rats. CCl_4 induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (141.00± 1.88 U/L), AST (194.33± 2.73 U/L), ALP (471.50 ± 12.16 U/L) and total bilirubin (0.27 ± 0.0 mg/dl) were observed. Standard group Silymarin (50mg/kg) showed ALT (60.83 ±1.08 U/L), AST (102.50± 1.61 U/L), ALP (245.33 ±2.70 U/L) and total bilirubin (0.17 ± 0.01 mg/dl). The effect of *Elephantopus scaber* hexane fraction (500mg/kg) on CCl_4-treated induced alterations in serum hepatic enzymes ALT (102.56±0.91 U/L), AST (143.22±0.32 U/L), ALP (316.23±1.19 U/L) and total bilirubin (0.21 ± 0.02 mg/dl) were showed. The effect of *Elephantopus scaber* Ethyl acetate fraction (500mg/kg) on CCl_4-treated induced alterations in serum hepatic enzymes ALT (101.89±0.86 U/L), AST (142.04±0.45 U/L), ALP (315.69±0.96 U/L) and total bilirubin (0.21 ± 0.00 mg/dl) were showed. The effect of *Elephantopus scaber* Ethanol fraction (500mg/kg) on CCl_4-treated induced alterations in serum hepatic enzymes ALT (90.07±0.55 U/L), AST (124.95±0.17 U/L), ALP (298.96±0.46 U/L) and total bilirubin (0.19±0.00 mg/dl) were showed and Methanol fraction (500mg/kg) showed ALT (92.97±0.37 U/L), AST (128.74±0.43 U/L), ALP (301.81±0.29 U/L) and total bilirubin (0.19±0.00 mg/dl). The study demonstrated that ethanol fraction showed better activity compared with other fractions [Ganga et al. 2012].

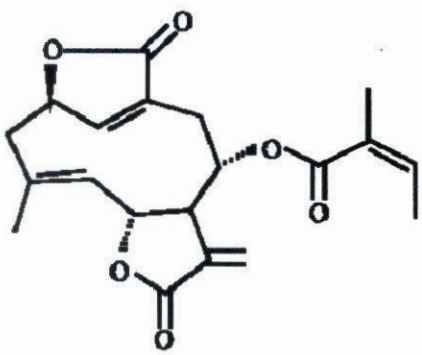
Ho et al. (2012) reported that the protective effect of *Elephantopus scaber* on the ethanol-induced liver damage in mice. They were observed accelerating serum biochemical profiles (including AST, ALT, ALP and total bilirubin) associated with fat drop and necrotic body in the liver section were observed in the mice treated with ethanol [100 μL of ethanol (50% v/v)]. Ethanol induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (172.2 ± 2.9U/L), AST (902.8 ± 16.7 U/L), ALP (118.0 ± 3.0 U/L) and total bilirubin (228.0 ± 19.2 mmol/L) were observed. Treatment with *E. scaber* ethanol extract (5000/30 mg/kg body wt) a significant reduction in serum marker enzymes ALT (69.7 ± 5.6 U/L), AST (348.2 ± 6.3 U/L), ALP (90.7 ± 13.3 U/L) and total bilirubin (136.3 ± 42.8 mmol/L) compare to control group ALT (81.9 ± 17.8 U/L), AST (187.4 ± 26.3 U/L), ALP (84.0 ± 10.9 U/L) and total bilirubin (177.6 ± 21.2 mmol/L) [Rahim et al.2012].

Phytochemical analysis revealed that the plant is a rich source of terpenoids and flavonoids. The isolated compounds have known for diverse biological functions such as antidiabetic, antibacterial, anticancer, antioxidant and hepatoprotective effects. Major chemical constituents of *Elephantopus scaber* are sesquiterpene lactones, phenolic acids and flavonoids.

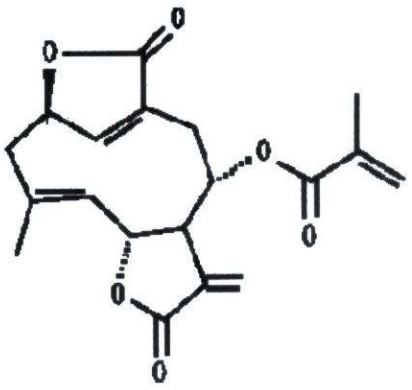
The sesquiterpenoids are C15 compounds formed by the assembly of three isoprenoid units. Their structure may be linear, monocyclic or bicyclic. They constitute a very large group of secondary metabolites, the characteristics of the Compositae family. Based on their carbocyclic skeletons, sesquiterpene lactones can be classified into four major groups: Germacranolides, guaianolides, pseudoguaianolides and eudesmanolides. All sesquiterpene lactones contain a-methylene y-lactone ring either cis or trans-fused to the C_6-C_7 or C_8-C_7 position of the carboxylic skeleton. Pharmacological activities of sesquiterpene lactones include antimicrobial, antiviral, anti-inflammatory, anti-tumor and hepatoprotective [Picman et al. 1986, Juliana et al. 2013]. Most of the research work carried out on this plant, has focused on sesquiterpenelactones. The major sesquiterpene lactones isolated from *E. scaber* are shown here:



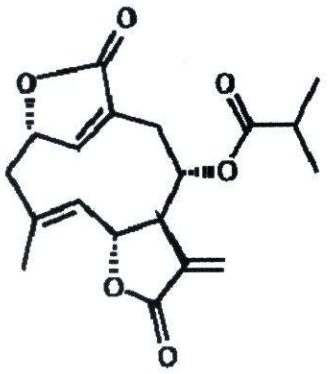
Scabertopin



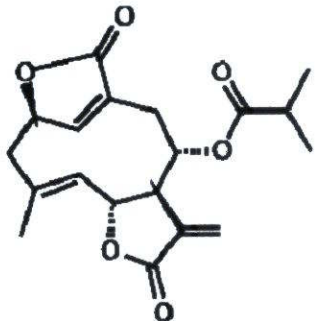
Isoscabertopin



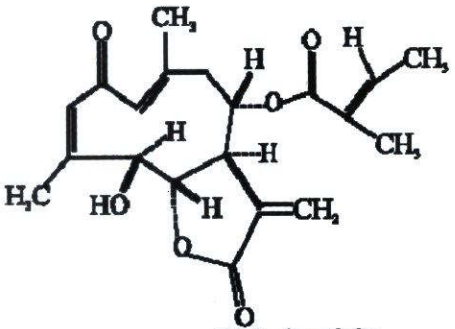
Deoxyelephantopin



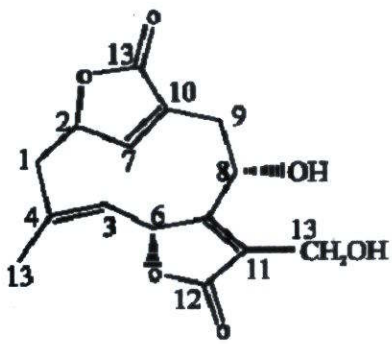
iso-17, 19-dihydrodeoxyelephantopin



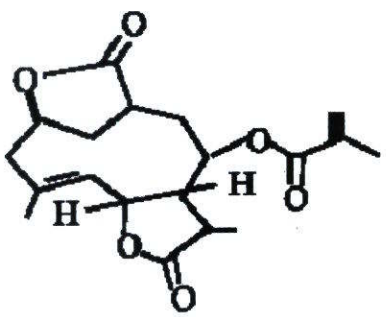
17, 19-dihydrodeoxyelephantopin



Molephantinin



Scabertopinol



11, 13-dihydrodeoxyelephantopin

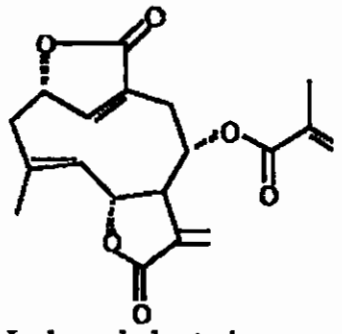
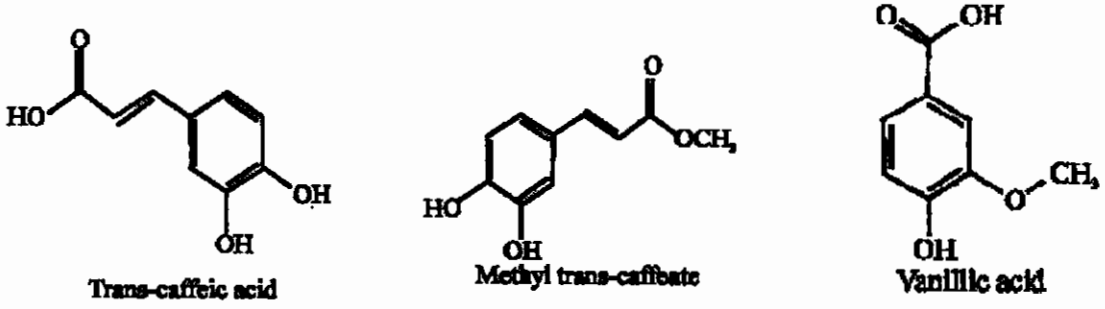
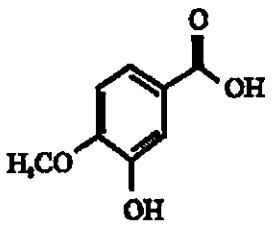


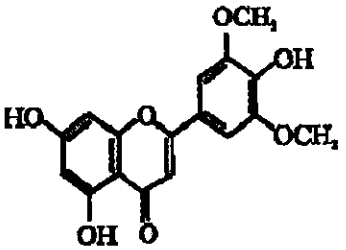
Figure 38. Bioactive sesquiterpene lactones from *E. scaber*

Phenolic acids and flavonoids were isolated from different fractions of whole plant *E. scaber*. Phenolic compounds 3,4- dihydroxy benzaldehyde, p- coumaric acid, vanillic acid, syringic acid, isovanillic acid, p- hydroxybenzoic acid, ferulic acid, 3-methoxy-4-hydroxyl cinnamic aldehyde, tricin, syringic acid, E-3-(3-ethoxy-4hydroxyphenyl) acrylic acid, 2-hydroxybenzolate acid were purified from the ethanol fraction of the plant [Hisharn et al. 1992, Chang et al. 2012, Zhang et al. 2011]. Flavonoid a glycoside luteolin and flavonoid glycosides luteolin-7 Oglucuronide 6"-methyl ester and luteolin-4-0- -D glucoside were identified along with three polyphenols trans-p-coumari acid, methyl trans-caffeate, trans-caffeic acid from methanol extract of aerial part of *E. scaber* [Chang et al. 2012].

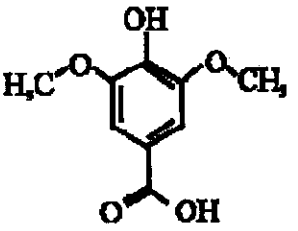




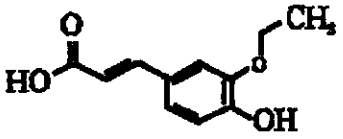
ISovanillic acid



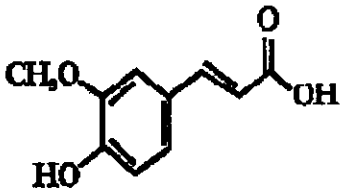
Tricin



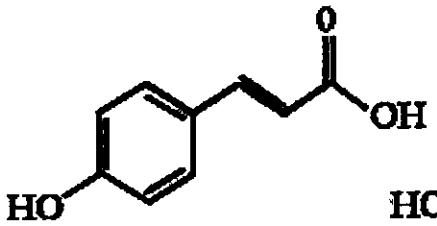
Syringic acid



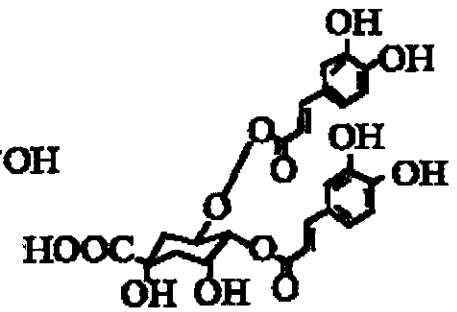
E-3-(3-ethoxy-4-hydroxypenyl acrylic acid



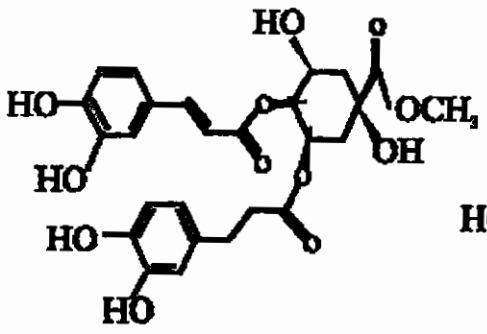
Ferulic acid



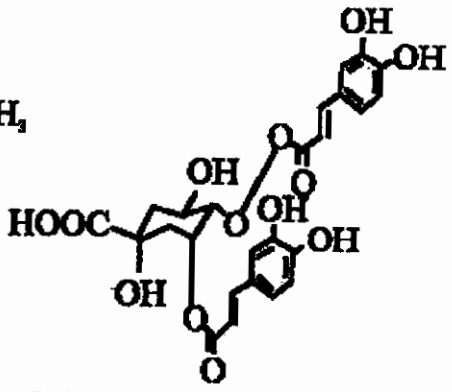
Trans-p coumaric acid



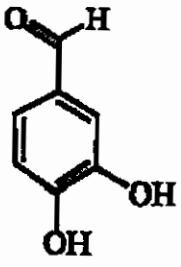
4, 5-di-o-caffeoyl quinic acid



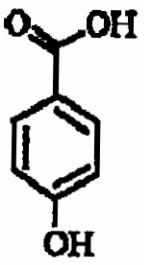
3,4-di-o-caffeoyl quinic acid methyl ester



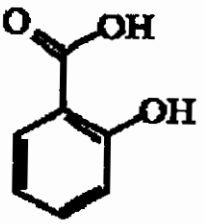
3,4-di-o-caffeoyl quinic acid



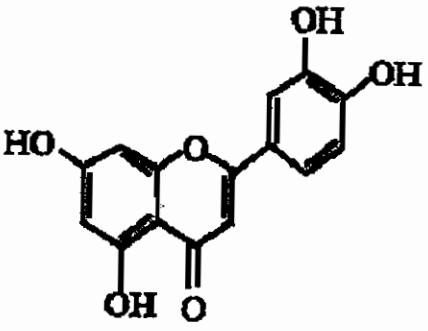
3,4-dihydroxybenzaldehyde



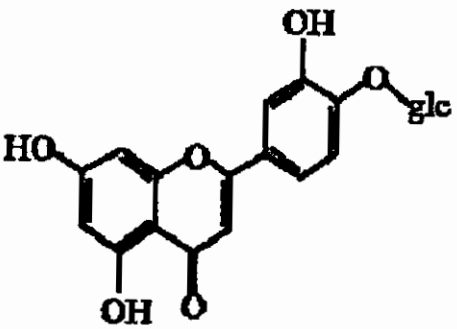
4 hydroxybenzaldehyde



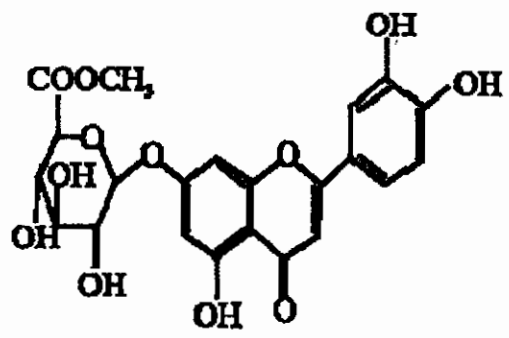
Salicylic acid



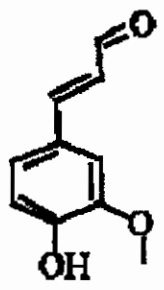
Luteolin



Luteolin 4-O-β-D glucoside



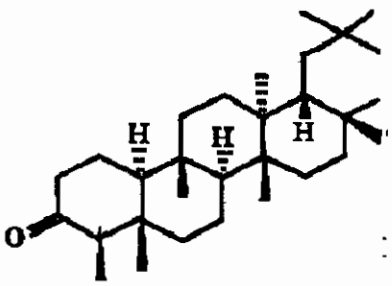
Luteolin 7-O-glucuronide
6" methyl ester



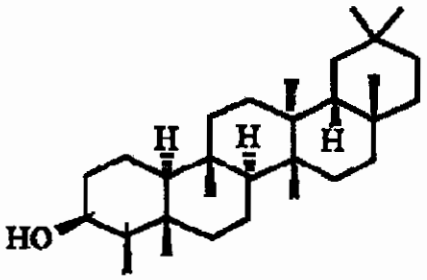
3 methoxy 4-hydroxy
cinnamaldehyde

Figure 39. Some phenolic acids and flavonoids isolated from *E. scaber.*

A number of triterpenes and steroids have been isolated from *E. scaber* [Santhosh et al. 2012].



Friedelin



Epifriedlinol

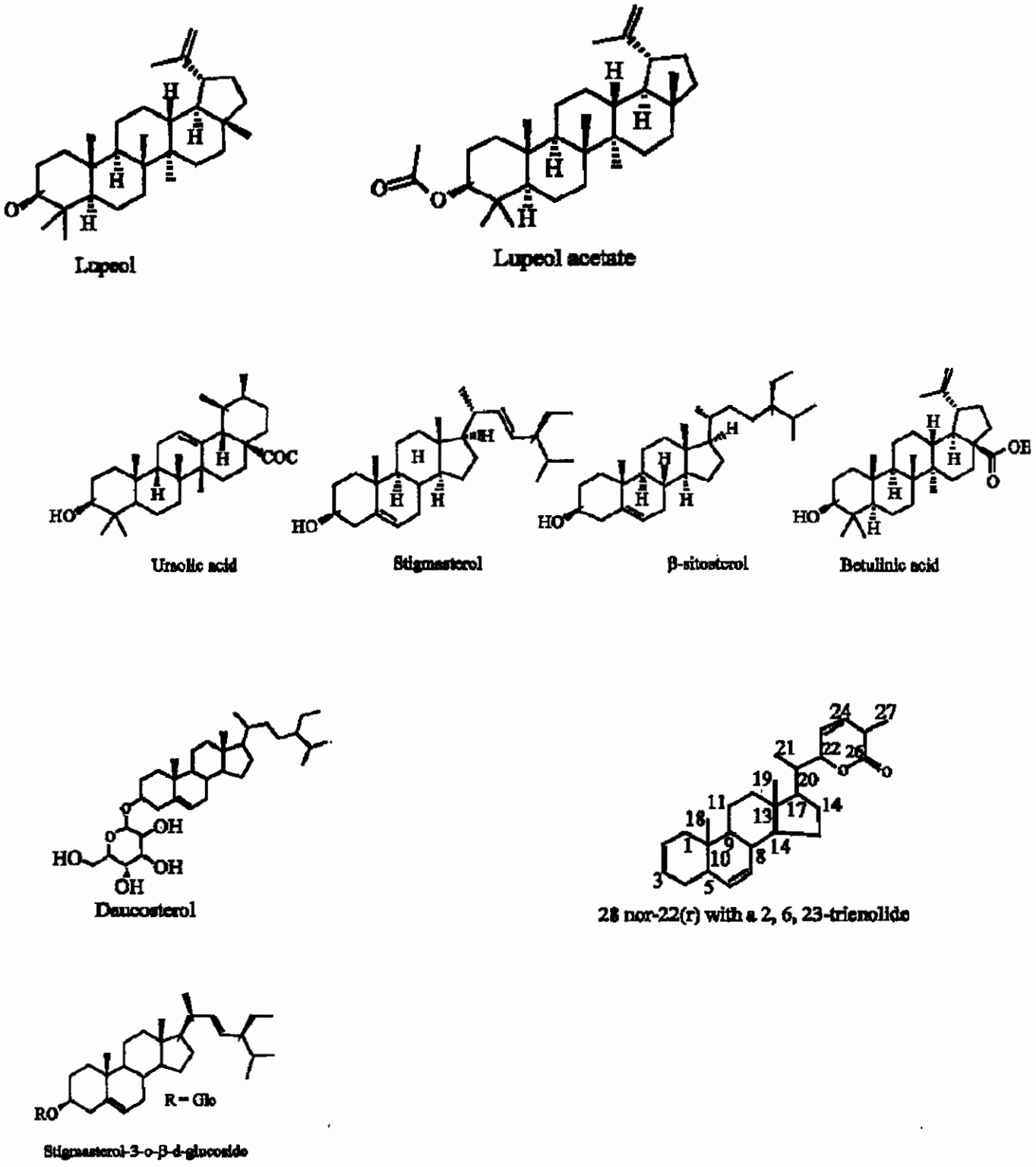
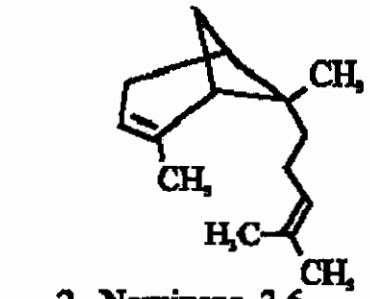
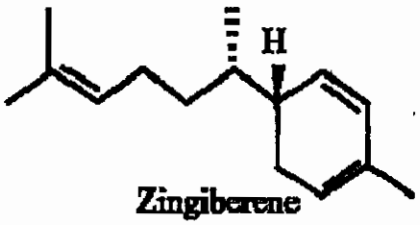


Figure 40. Chemical structures of bioactive triterpenoids and steroids from *E. scaber.*

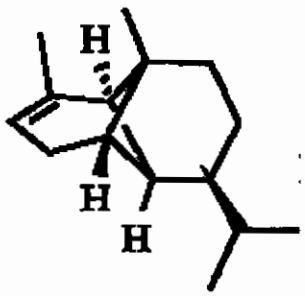
An essential oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants. Other constituents include essential oils, salt and minerals.



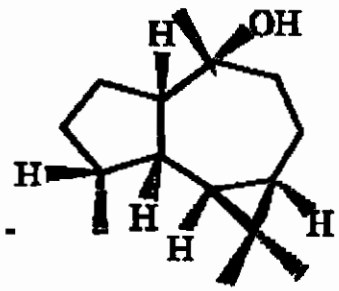
2, -Norpinene, 2,6-dimethyl-6-(4-methyl-3-pentenyl)



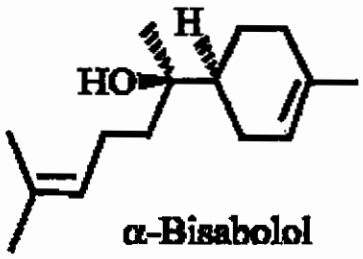
Zingiberene



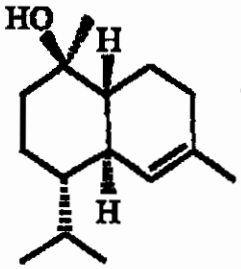
Copaene



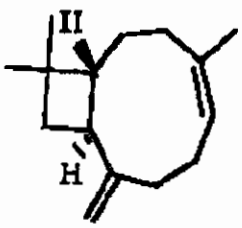
Ledol



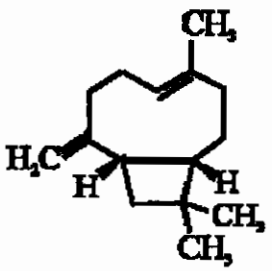
α-Bisabolol



α-Cadinol



Isocaryophyllene



Caryophyllene

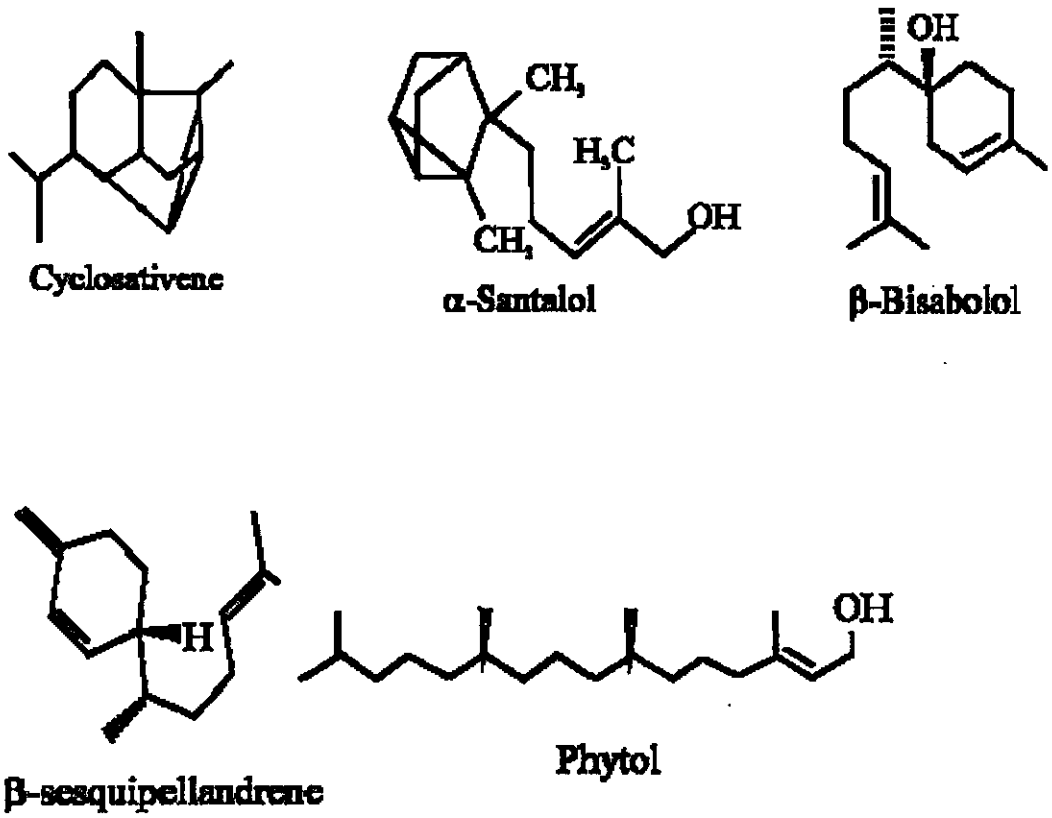


Figure 41. Chemical structures of selected components of essential oils.

Sesquiterpenoid, phenolic and flavonoid compounds are responsible for hepatoprotective potentiality of *E. scaber.*

***Ipomoea aquatic* (Kolmi Shak)**

Figure 42. *Ipomoea aquatic*

Ipomoea aquatic, of Convolvulaceae family is a semi aquatic, tropical plant grown as a vegetable for its tender shoots and leaves. It is found throughout the tropical and subtropical regions of the world, although it is not known where it originated, but it is found throughout of Bangladesh. It is known as kalmi shak in Bengali, water spinach or river spinach in English ["Adobong Kangkong (River Spinach) Recipe" 2014]. *I. aquatica* flourishes naturally require little, if any, care. It grows in water or on moist soil along the margins of stagnant streams, fresh water ponds, ditches, marshes and wet rice fields; sometimes found floating on water bodies. Its stems are 2–3 metres (7–10 ft) or more long, rooting at the nodes, and they are hollow and can float. The leaves vary from typically sagittate (arrow head-shaped) to lanceolate, 5–15 cm (2–6 in) long and 2–8 cm (0.8–3 in) broad. The flowers are trumpet-shaped, 3–5 cm (1–2 in) in diameter, and usually white or pale purple in color with a mauve centre. It occurs both in wild and cultivated state and is easily propagated either by planting cuttings of the stem shoots that will root along nodes or planting the seeds from flowers that produce seed pods. It is one of the most popular green leafy vegetable. [http://www.curiousgardener.com/2011, "Kangkungking.com" 2014] Green leafy vegetables form a rich source of dietary fibres, nutraceuticals and vitamins, including A, B, C, E, and "U" (S-methyl methionine), riboflavin, folic acid, and minerals, eg calcium, iron and

phosphorus and is used to treat gastric and intestinal disorders. [Watt et al. 1972, Westphal et al. 1993]

In traditional medicine (Ayurveda), the extracts of leaves of *I. aquatica* are orally administered to alleviate the disorders like jaundice and nervous debility. This plant is used medicinally in Southeastern Asia. It is effectively used against nosebleed and high blood pressure [Duke et al. 1985, Perry et al. 1980]. The juice of *I. aquatica* is used as emetic in cases of opium and arsenic poisoning [Chopra et al. 1956]. Dried juice has purgative properties [Nadkarni et al.1954]. Leaves and stems are said to be cooling. In Assam, the plant is given for nervous and general debility. It is used also for piles as anthelmentic, used in leucoderma, leprosy, jaundice and liver complaints [Nadkarni et al.1954]. This plant is supposed to possess an insulin-like principle according to indigenous medicine in Sri Lanka [Jayaweera et al. 1982]. The medicinal uses of hitherto report includes: effect on liver diseases [Badruzzaman et al.1992, Nadkarni et al. 1954] eye diseases [Jain et al. 1981], constipation [Samuelsson et al. 1992] and the inhibition of prostaglandin synthesis [Tseng et a. 1992].

Mackeen *et al.* (1997), demonstrated moderate antinematodal activity of *I. aquatica* against pine wood nematode, *Bursaphelenchus xylophilus*. [Mackeen et al. 1997]. The aqueous extract of this plant also possess hypoglycemic effect [Malalavidhane et al. 2000]. This plant also possesses **antioxidant activity** [Prasad et al. 2004, Prasad et al. 2005]. This plant also shows moderate anticancer activity against Vero, Hep-2 and A-549 cancer cell lines [Prasad et al. 2005].

Alkiyumi et al. (2012) reported that ethanol extract of *I. aquatica* against liver damage were evaluated in thioacetamide (TAA)-induced chronic hepatotoxicity in rats with a dose-dependent manner as compared to the normal and standard drug silymarin- treated groups hepatic steatosis. Thioacetamide (TAA), which has been used in the present study, is a well-established tool to induce hepatotoxicity in experimental animal models [Mangipudy et al. 1995, Dorğru et al.2001]. TAA is able to produce different grades of hepatic damage, including centrilobular necrosis [Ledda-Columbano et al. 1991], inflammation and suppression of anti-oxidant activity [Mangipudy et al. 1995]. In the current study the hepatic damage occurred was assessed by measuring serum levels of specific liver enzymes such as ALP, ALT, AST and bilirubin. Even though these enzymes were found to be elevated in the TAA treated group of animals due to the

leakage of the enzymes from liver as a result of tissue damage, the plant extract treatment was found to significantly ($p < 0.001$) restore the enzyme levels both at 250 and 500 mg/kg. These results were well compared with the standard drug, silymarin. In most instances, the serum bilirubin levels must be elevated in hepatic jaundice [Dorğru-Abbasoğlu et al.2001]. We have observed a similar trend in the elevation of serum billurubin level during TAA traement, and concurrent reduction with the plant extract. It is well known that following cellular damage the capacity to synthesize proteins is reduced, and as the extent of damage increases, the levels of these proteins in the plasma will tend to decrease [Ledda-Columbano et al. 1991]. A similar observation was seen in our studies, where the total protein and total albumin levels in the serum were markedly decreased, but as seen in the silymarin treated group, the plant extract also restored these levels of protein to normal signifying a return from the abnormal state to normal. Thioacetamide induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (160.8 ± 0.4 IU/L), AST (221.63 ± 1.45 IU/L) and ALP (234.1 ± 0.28 IU/L) were observed significantly indicating acute hepatocellular damage and biliary obstruction. Treated with *I. aquatica* (500 mg/kg) a significant reduction in serum marker enzymes ALT (39.85 ± 0.33 IU/L), AST (63.73 ± 0.30 IU/L) and ALP (77.8 ± 0.46 U/L) similar to silymerin treated group which seems to offer the protection and maintain the functional integrity of hepatic cells. Histological examination of the liver tissue from thioacetamide treated animals revealed that thioacetamide had produced profound inflamation, severe congestion of blood vessels, mild hydropic degeneration, pyknosis of nucleus congestion especially in the sinusoids and occasional necrosis. Pre treatment of animals with Silymerin, *I. aquatica* (250 mg/kg) and *I. aquatica* (500 mg/kg) reduced the inflammation, degenerative changes and steatosis. [Salim et al. 2012]

Sivaraman et al (2014), isolated two major phytoconstituents from the hydro alcoholic leaves extract of *Ipomoea aquatica* have been identified as Flavonoid derivative such as quercetin and the phenolic acid such as chlorogenic acid. In their experiment, the first compound isolated as a yellow amorphous powder with melting point 310° C has a molecular formula of C15H10O7 based on the Mass spectrum. λ max from UV spectrum indicated the presence of conjugation and two chromophores which is a specific character of flavonoids. The data correlates the structure of the isolated compound is a flavonoid with phenyl group. The complete spectral detail of the compound they concluded that the proposed structure was identified as Quercetin (compound with flavonol skeleton ring) **[Sivaraman et al 2014]**. Quercetin is believed to protect against

several degenerative diseases by preventing lipid peroxidation. Quercetin is considered to be a strong antioxidant due to its ability to scavenge free radicals and bind transition metal ions. These properties of quercetin allow it to inhibit lipid peroxidation. [Hollman et al. 1997, Sakanashi et al. 2008] Quercetin, being a major constituent of the flavonoid from *Ipomoea Aquatica* plant, which fighting several chronic degenerative diseases. [Bouktaib et al. 2002]

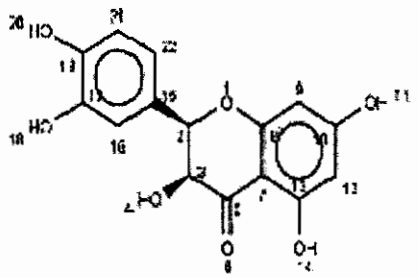


Figure 43. The structure of Quercetin

The second compound isolated as a white amorphous powder with melting point 207° C. has a molecular formula of C16H18O9 based on the Mass spectrum. λ max from UV spectrum of isolated chlorogenic acid and standard appears very similar. From the correlation of all data's it was concluded that the isolated compound shows the presence of phenolic acid group such as chlorogenic acid [Sivaraman et al 2014]. It was reported that chlorogenic acid possesses hepato protective activity [Basnet et al. 1996]. It also strongly inhibits lipid peroxidation [Born et al. 1996].From the literature it was also concluded that the compund chlorogenic acid has anti-hyperlipidemic [Yuchi et al. 1986] and anti-ulcer activities [Pisha et al. 1994].

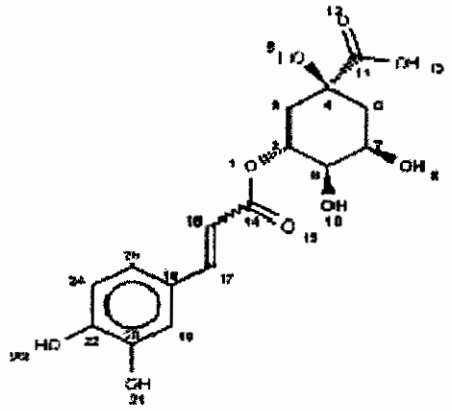


Figure 44. The structure of chlorogenic acid

Sivaraman et al 2013, reported that the Chlorogenic acid, Beta carotene, Quercetin and Beta sitosterol are the major chemical constituents of *I. aquatic* [Sivaraman1 et al. 2013].

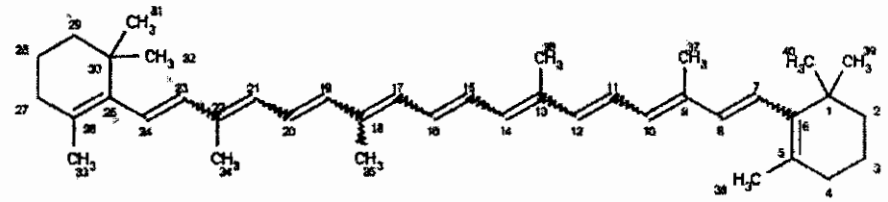


Figure 45. The structure of β-carotene

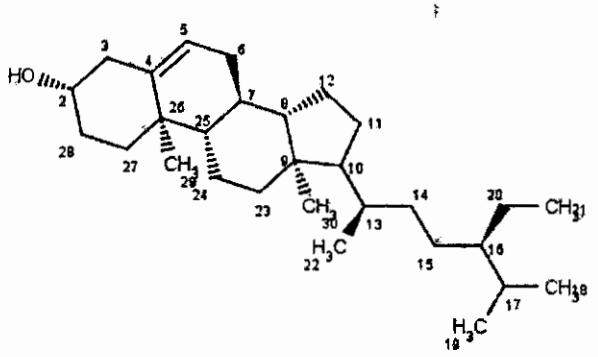


Figure 46. The structure of β- sitosterol

Ortaliza *et al.* 1969 estimated the carotene contents and its availability of *I. aquatica* [Ortaliza et al. 1969]. The effects of *I. aquatica* on cholesterol metabolism in rats were studied by Chen *et al.* 1991. They characterized the major carotenoids in water convolvulus (*Ipomoea aquatica*) by open-column, thin layer and high performance liquid chromatography. Comparing the absorption spectra and retention time with reference standards the compounds were identified as β-carotene, cryptoxanthin, lutein, lutein epoxide, violoxanthin and neoxanthin [Chen et al. 1991]. Carotenoids and chlorophylls in *I. aquatica* were determined by Chen and Chen (1992) using liquid chromatography. These carotenes and chlorophylls were analyzed by High Performance Liquid Chromatography (HPLC). Fourteen peaks were detected in HPLC, of which 12 pigments were identified. These pigments include neoxanthin, violaxanthin, cryptoxanthin, lutein epoxide, lutein, cis-lutein, chlorophyll b, chlorophyll b^1, chlorophyll a, β-carotene and cis β-carotene. These samples were then compared with standards by thin layer chromatography [Chen et al. 1991]. Wills and Rangga 1996, analyzed carotene contents of *I. aquatica* by reverse phase HPLC and gradient elution. The carotenes identified were zeaxanthin, lutein, anthraxanthin, flavoxanthin, auroxanthin, luteoxanthin, neoxanthin, β-carotene, violoxanthin, cryptoxanthin, neoxanthin and neoxanthin b. These samples were compared to standards and identified. [Wills et al. 1996]. Provitamin A and carotenoids from *I. aquatica* of different maturity and origin were investigated by Hulshof *et al.* 1997 [Hulshof et al. 1997]. The carotene contents were different

when collected from different places. Also, the carotene content of mature plant was high compared to that of young plants. Provitamin A carotenoid content of *I. aquatica* at different maturity and origin was reported by Paul *et al.* 1997 [Paul *et al.* 1997].

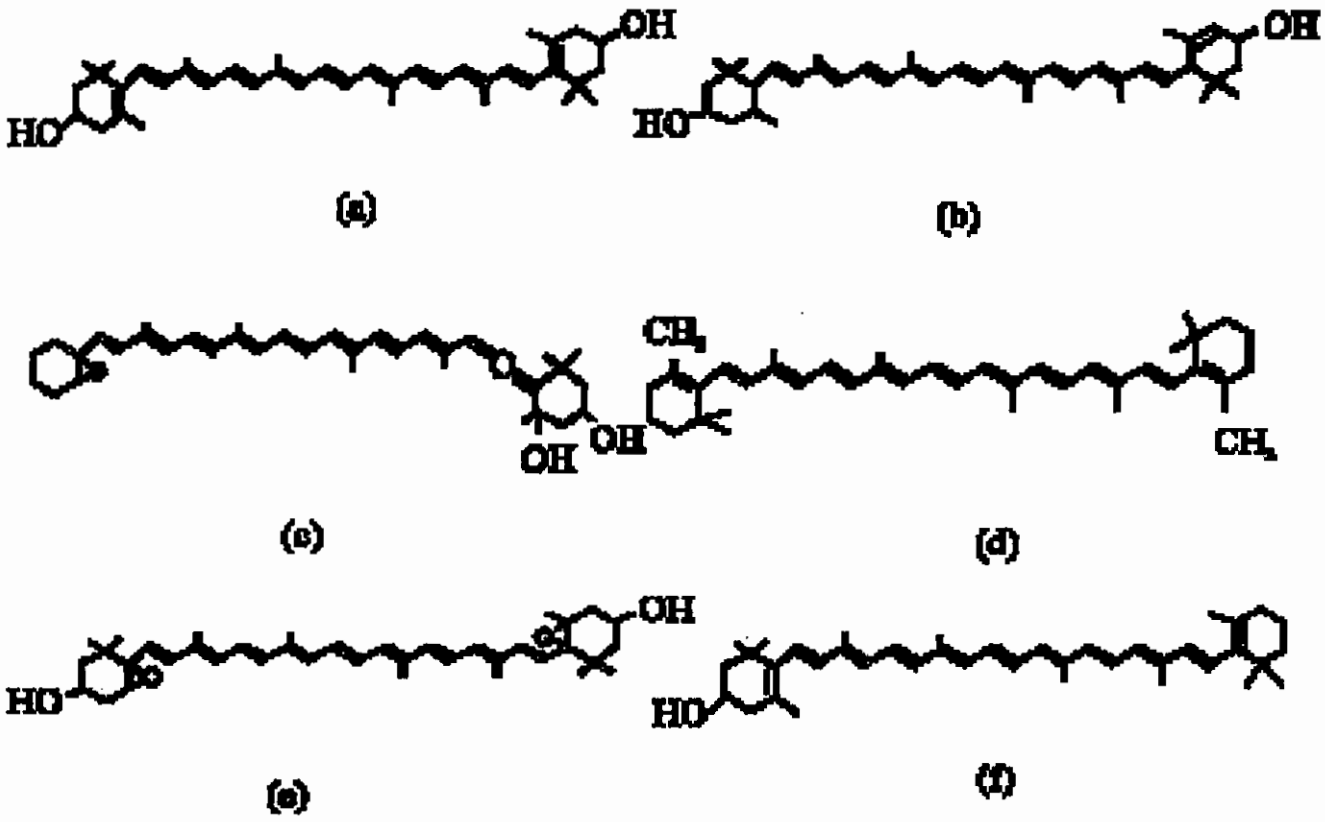


Figure 47. Carotene from Ipomoea aquatica (a) Zeaxanthin, (b) Lutein, (c) Neoxanthin, (d) β-carotene, (e) Violoxanthin and (f) Cryptoxanthin.

Daniel (1989) estimated the polyphenol contents of *I. aquatica* and identified Flavonoid: quercetin 3'-methyl ether, quercetin 4'-methyl ether and anthocyanins [Daniel et al. 1989].

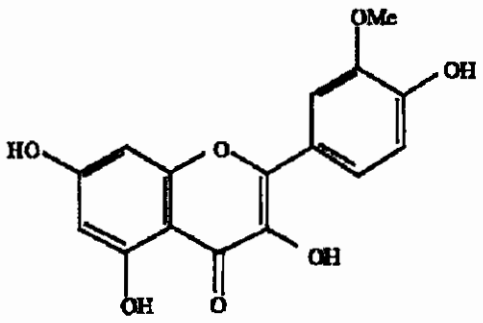


Figure 48. Quercetin 3'-methyl ether

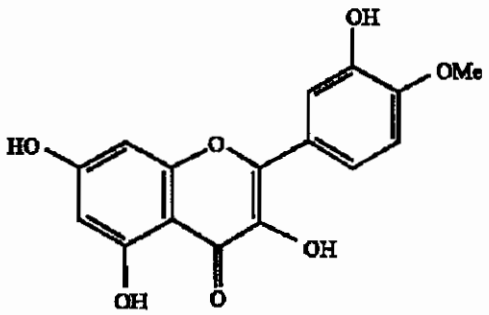


Figure 49. Quercetin 4'-methyl ether

Flavonoid contents of *I. aquatica* like mycertin, quercetin, luteolin and apigenin content were identified by Chu *et al.* 2000. [42] Prasad *et al.* 2005 isolated a 7-O-β-D-glucopyranosyl-dihydroquercetin-3-O-α-D-glucopyranoside and it was characterized using UV, MS and NMR data [Prasad et al. 2005].

***Wedelia chinensis* (Keshraj)**

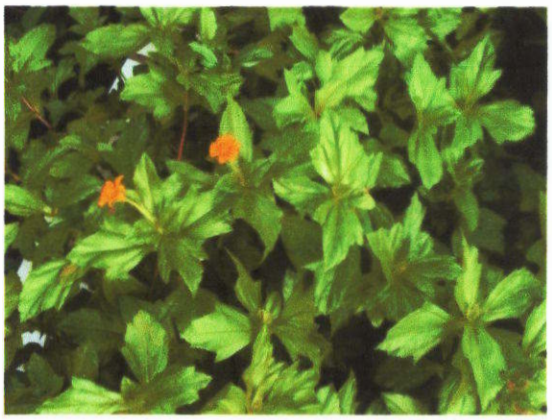


Figure 50. *Wedelia chinensis*

The flowering plant *Wedelia chinensis* (Synonyms: *W. calendulacea*) belonging to family Asteraceae (sunflower family). The name of the genus honours German physician Georg Wolfgang Wedel [Wikipedia, the free encyclopedia.htm]. It is a perennial herb, is one of the most commonly occurring plants in Bangladesh. In Bengali it is known as Kesraj or Bhimra and one of the most commonly occurring plants in Bangladesh. The plant is also distributed throughout India in wet places and coastal areas [Nomani et al. 2013]. It is scabrous procumbent perennial soft herb with high camphor like odour and has a gorgeous growth. [Martin et al. 2003] It is a perennial herb of 0.3-0.9 m high, stem procumbent at base and rooting at lower nodes .Leaves are opposite, subsessile, 2.5-7.5 by 1-2.8 cm lanceolate-oblong, entire or irregularly cenate-serate , scabrous with short white hairs and base tapering. Heads of flowers, 2-3.2 cm diameter, solitary, peduncles 2.5-15cm long erect, slender, slightly thickened beneath the heads [Kirthikar et al. 2006]. *Wedelia chinensis* is a drug of natural origin (herbal medicine) and is most popular herbal medicine used in various system of traditional medicine. The literature reveals that various parts of *Wedelia chinensis* have been used as folklore medicine for treating various ailments like hepatoprotective efficacy, cholagouge, jaundice, diarrhoea, couch, cephalahagia, diphtheria and pertussis [A Dictionary Indian Raw Materials and Industrial Products, 2005]. The decoction of the plant is used a deosurbent and is given in uterine haemorrhage and menorrhagia. Leaves are supposed to work as tonic which is useful in cough, cephalagia, skin disease and alopecia. Infusion of the plant is given in Indo China for treating

swelling of abdomen. Decoction of the plant was extensively used by the tribes to reduce the mental tension and also to induce sleep and the plant affects CNS [Suresh et al. 2010] *Wedelia chinensis* is very specific in treating viral hepatitis. Traditionally the fruit, leaves and stem are used in child birth and in treatment of bites and stings, fever and infection. Leaves are used to treat the kidney dysfunction cold, wound and amenorrhea [Mathew et al. 1983]. The plant is astringent, bitter, acrid, thermogenic, anti-inflammatory, vulnery, ophthalmic, cardiotonic, anthelmintic, diuretic, aphrodisiac, sudorific, febrifuge and trichogenousand is useful in vitiated conditions of Kapha and Vata,inflammation, elephhanmtiasis, otalgia, cephalagia,wounds, ulcers, nyctalopia, dysopia, hepatosplenomagaly,colic, dyapepsia, helminthiasis, strangury, anaemia.Sminal weakness, fever, baldness and graying of hair [Chopra et al. 1956, Arya Vaidya Sala: Orient langman Limited; 1983]. Traditionally the fruits, leaves and stem are used inchildbirth and in the treatment of bites and stings, fever andinfection. The leaves are used in the treatment of kidneydysfunction, cold, wounds and amenorrhea [Mathew et al. 1983]. *W. chinensis* is a very useful herbal medicinal plant. Its leaves can be used in treatment of dermatological disorders, cough,headache, hair loss, lice, strengthening the nervous system, lack of blood, digestive system disorders. The leaves are used in dyeing grey hair and in promoting the growth of hair. They are considered tonic, alternative, and useful in coughs, cephalalgia, skin diseases, and alopecia. The juice of the leaves is much used as a snuff in cephalalgia. The seeds and flowers, as well as the leaves, are used in decoction, in the quantity of half of teacupful twice daily as deobstruent. In decoction, the plant is used in uterinehaemorrhage and menorrhagia. W. chinensis using home remedy Osteochondritis dissecans, Multiple sclerosis, Juvenile arthritis, Gouty arthritis, Rheumatic fever, etc. leaves extracts are a natural alternative to commonly usedanti-inflammatory drugs like Dolonex (Piroxicam), Brufen (Ibuprofen) and Voveran etc. *W. chinensis* leaves extract can be used with confidence for treating Rheumatic fever [Meena et al. 2011]. Extensive research revealed that *W. chinensis* has a surprisingly broad range of pharmacological effects and they are extremely beneficial and include hepatoprotective [Linn et al. 1994, Garima et al. 2009, Wagner et al. 1986, Abdul et al. 2012], wound healing [Mishra et al. 2009, Prakash et al. 2008, Verma et al. 2008, Raja rt al. 2003], anticancer [Gupta et al. 2007], Immunostimulant [Prakash et al. 2008, Govindachari et al. 1985], CNS depressant [Prakash et al. 2008, Suresh et al. 2010], antioxidant [Kataki et al. 2012], adaptogenic and antistress [Verma et al. 2009], sedative [Prakash et al. 2008,], anti-osteoporotic [Shirwaikar et al. 2006],

chemopreventive [Haldar et al. 2011], analgesic and anti-inflammatory [Kobori et al. 2004, Sureshkumar et al. 2006], androgen suppressing activity [Lin et al. 2007], anthelmintic and febrifuge anticonvulsant [Mishra et al. 2011], anti-ulcerogenic and mucosal protective agent [Tuticorin et al. 1992], antibacterial and antimicrobial [Mottakin et al. 2004, Manjamalai et al. 2010], insecticidal [Pang et al. 2000].

Mishra et al. (2009) reported that the hepatoprotective effect of alcoholic and aqueous extract of whole plant of *Wedelia chinensis.* That was monitored by estimating the serum marker enzymes of the liver like alanine aminotransferase (ALT), asparate aminotransferase (AST), alanine phosphates (ALP), total bilirubin (TBL) and liver weight of albino rat. The activities of serum marker enzymes increased by the administration of CCl4 (0.5 ml/kg b.w.). CCl_4 induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (218.23±3.04 IU/L), AST (227.3±3.04 IU/L) ALP (27.46±4.03 IU/L) and TBL (8.96±0.41U/L) were observed. Treated with *Wedelia chinensis* ethanolic extract (500 mg/kg body wt) showed a significant reduction in serum marker enzymes ALT (37.08±1.68 IU/L), AST (37.08±1.68 IU/L), ALP (7.16±0.14 IU/L) and TBL (0.43±0.02 IU/L); and aqueous extract (500 mg/kg body wt) also showed a significant reduction in serum marker enzymes ALT (38.4±2.10 IU/L), AST (43.6±0.95 IU/L), ALP (7.72±0.38 IU/L) and TBL (0.43±0.005 IU/L) similar to silymerin treated group ALT (36.5±1.73 IU/L), AST (39.6±0.95 IU/L), ALP (6.74±0.39 IU/L) and TBL (0.42±0.02 IU/L). The study demonstrated that *W. chinensis* possesses significant hepatoprotective effects [Garima et al. 2009].

Emmanuel et al. (2001) reported that the hepatoprotective effect of the methanolic leaf extract of *Wedelia chinensis* against Paracetamol (PCM) induced hepatic injury in *Wistar albino* rats. The activities of serum marker enzymes of the liver like alanine aminotransferase (ALT), asparate aminotransferase (AST) and alanine phosphates (ALP) were increased by the administration of Paracetamol. These activities were found to be reduced after the administration of plant extracts in the toxicity induced groups. PCM induced intoxication in normal rats elevated the levels of serum marker enzymes ALT (2.94±0.2 IU/l/min/mg), AST (5.54±0.43 IU/l/min/mg) and ALP (6.15±0.46 IU/l/min/mg) were observed significantly indicating acute hepatocellular damage. Treated with *W. chinensis* (250mg/kg body wt) a significant reduction in

serum marker enzymes ALT (1.49±0.18 IU/l/min/mg), AST (1.05±0.09 IU/l/min/mg) and ALP (3.85±0.28 IU/l/min/mg) compare to control group ALT (1.35±0.10 IU/l/min/mg), AST (0.73±0.06 IU/l/min/mg) and ALP (3.55±0.28 IU/l/min/mg). This study showed that the extracts of *A. paniculata* could play a significant role to protect and cure the liver cells against paracetamol induced toxicity. [Emmanuel et al. 2001]

Extensive studies have been carried out on W. chinensis. Chemical components isolated from the plant are as follows: The expressed juice of the herb contained an oil-solubleblack dye, 11.2; tannin, 220; carotene, 1.14; Chlorophyll, 3.75; Saponin (contradictory report), 500; phytosterol, 3.75;waxy compound, 29.7; resin, 44; chloroform extract(resinous mass), 27; gum, 80; total sugar, 1 040 mg/100 g juice. There are many investigations showed the presence of an alkaloid in the stems, leaves and flowers. The leaves contain isoflavanoids and wedelolactone (I) (0.05%). The latter is the lactone of 5:6-dihydroxy-2-(2:6-dihydroxy4-methoxyphenyl) benzofuron-3-corboxylic acid andanalogous in structure to coumestrol an estrogen fromclover A dictionary Indian Raw Materials and Industrial Products, The Wealth of India, RawMaterials, Council of Scientific and Industrial Research, 2005, Govindchari et al. 1956, Govindchari et al. 1957, Govindchari et al. 1961].

Lin et al. (2007) reported four anti-proliferative phyto-compounds in *Wedelia chinensis*, including indole-3-carboxylaldehyde, wedelolactone, luteolin and apigenin. [Feng et al. 2007]

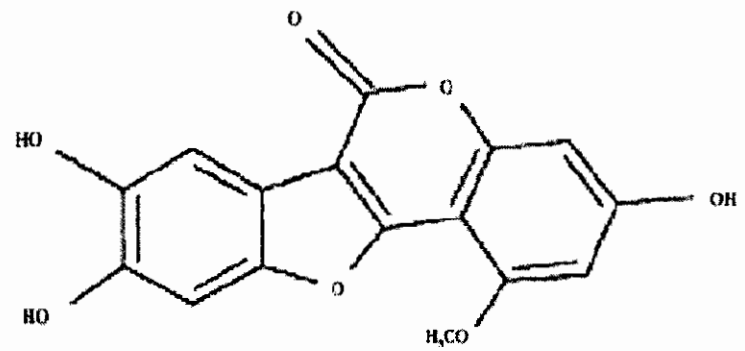


Figure 51. The structure of wedelolactone

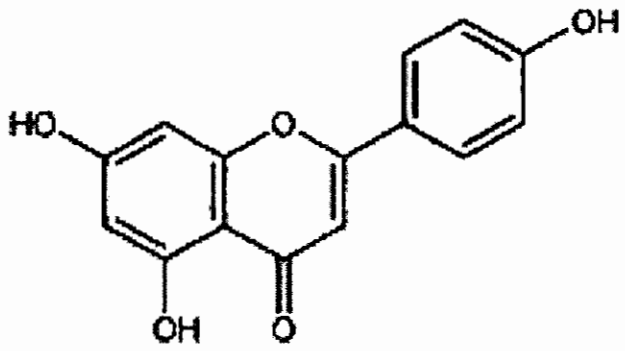


Figure 52. The structure of apigenin

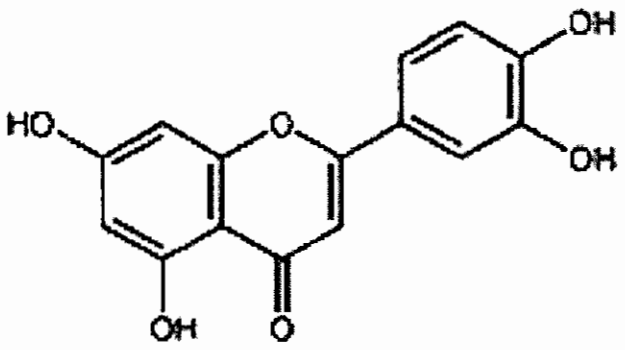


Figure 53. The structure of luteolin

The leaves contain isoflavonoids and bisdesmosidicoleanolic acid saponins[Khare et al. 2007, Masoodi et al. 2011]. Norwedelolactone has also been isolated from alcoholic extract of leaves [Bhargava et al. 1970].

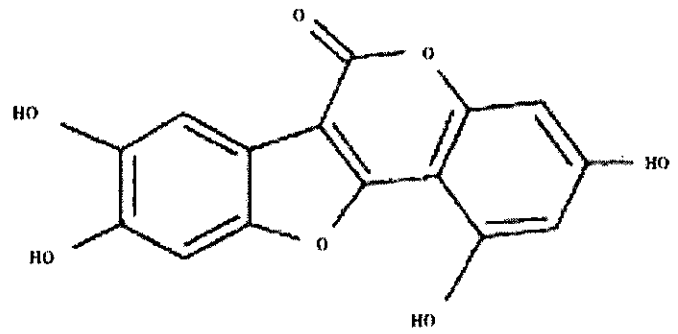


Figure 54. Structure of Norwedelolactone

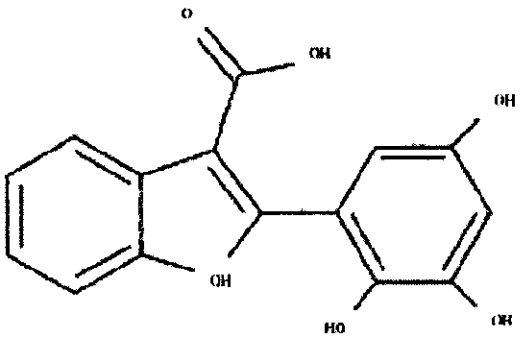


Figure 55. Structure of Norwedelic acid

Norwedelic acid (5, 6-dihydroxy-2 (2', 4', 6'-trihydroxyphenyl)-benzofuran-3-carboxylic acid) [Masoodi et al. 2011].

Triterpenoid saponin: bisdesmodic-osidic oleanolic acid saponins have been isolated from fresh leaves of this plant, of the three saponins one is a new bisdesmisidicoleanolic acid saponin, which have been identified as. -D-glucopyranosyl-3-o-[o-.-D-xylopyranosyl-(1.2).-D Glucuronopyranosyl] oleanolate ,. -D-glucopyranosyl 3.-[(o-.-D-xylopyranosyl-(1.)-(pD-glucuronopyranosyl)]-olean-12-en-28 oate) [Masoodi et al. 2011, CSIR. A dictionary Indian Raw Materials and Industrial Products, The Wealth of India, Raw Materials. New Delhi: Council of Scientific and Industrial Research, First supplement series; 2004].

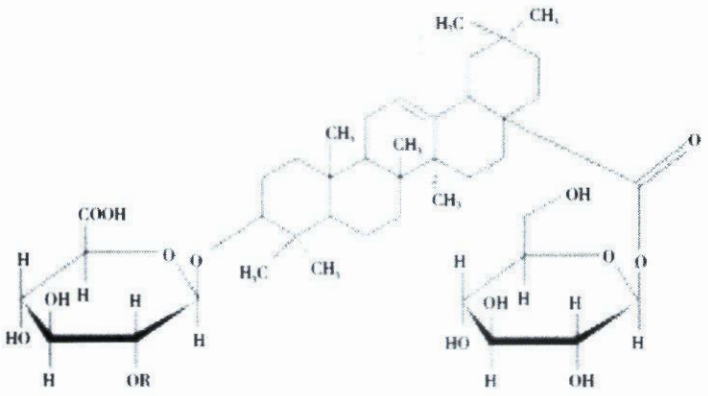


Figure 56. The structure of terpenoid saponin

The active fraction of the methanolic extract of the herb contained fatty acids, melissic and lignoceric acid,stigmasterol and stigmasteryl glucoside, Kauren diterpenes(-) kaur-16-en-19-oic acid and a mixture of the three esters, 3α-angeloyloxy-3α-triglinoyloxy and 3-senecioyloxy-kaur-16-en-19-oic acid [Haider et al. 2003].

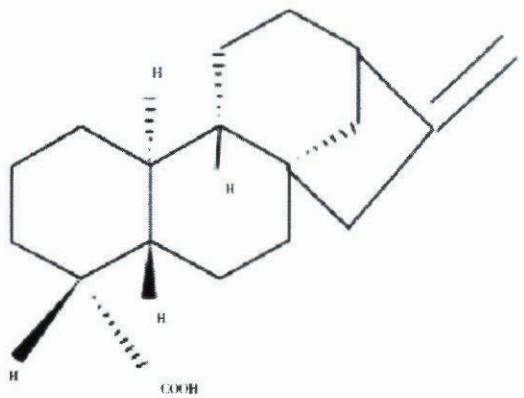


Figure 57. The structure of Kauren diterpenes(-) kaur-16-en-19-oic acid

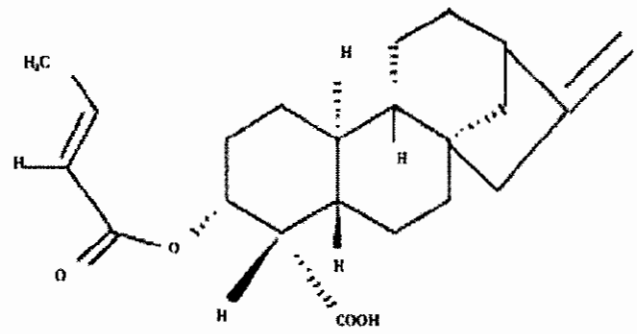


Figure 58. The structure of 3α-triglinoyloxy-kaur-16-en-19-oic acid.

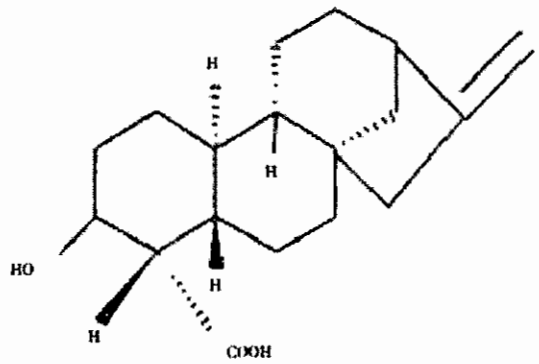


Figure 59. The structure of 3α-angeloyloxy- kaur-16-en-19-oic acid

The essential oil of the aerial parts of the W. chinensis Merrill was analyzed by GC and GC/MS. Nineteen compounds have been identified accounting for 94% of the oil. It was made up of mainly monoterpenes hydrocarbons (50.6%), sesquiterpenes hydrocarbons (22.5%), oxygenated sesquiterpenes (20.3%) with only small amounts ofoxygenated monoterpenes (0.7%). The main constituents were found to be.-pinene (21.7%), spathulenol (20.3%) and limonene (14.3%) [Garg et al. 2005].

The herb is said to possess properties and main active constituents coumestans, i.e., wedelolactone and Norwedelolactone [Wagner et al. 1986]. Mainly these constituents showed hepatoprotective activity [Sing et al. 2001].

Chapter Three

Discussion

Discussion

In this review article, an attempt has been made to compile some hepatoprotective medicinal plants from Bangladesh and their bioactive compounds, also searching a specific compound from each plant, which has hepatoprotective potential. This review focus on numbers of plants was selected based on their reported hepatoprotective activity and their bio-active compounds, which validate their use in the folk medicinal system of Bangladesh. These plants are available in all over Bangladesh.

10, 12, 14-Nonacosatriynoic acid and Androst-4-en-11-ol-3, 17-dione, 9-thiocyanato as a class of essential oil isolated from ethanolic extract of *Alocasia indica* tuber belonging to Araceae family, both compounds are responsible for hepatoprotective potentiality.

Andrographolide as a class of diterpenoid and flavonoid compounds in *Andrographis paniculata, reduces hepatotoxicity in mice. Andrographis paniculata belong to* Acanthaceae *family.*

Wedelolactone and desmethylwedelolactone as a class of coumestans are derivatives of isoflavonoids. These are major components in leaves of *Eclipta alba* (family: Asteraceae) showed hepatoprotective activity.

Sesquiterpenoid, phenolic and flavonoid compounds are responsible for hepatoprotective potentiality of *E. scaber* in the Asteraceae family.

Chlorogenic acid possesses hepatoprotective activity isolated from *Ipomoea aquatica* in the family Convolvulaceae.

Wedelolactone and Norwedelolactone as a class of coumestans are derivatives of isoflavonoids showed hepatoprotective activity, isolated from *Wedelia chinensis* (family: Asteraceae).

Above discussion we recognize that mostly flavonoid group compounds are responsible for hepatoprotection and most of the plants are belong to Asteraceae family.

Presented review suggests that biologically active molecules or compounds derived from these plant extracts may serve as an effective and targeted hepatoprotective drugs.

Elephantopus scaber	Gojialata	Asteraceae	whole plant	Used for the treatment of pneumonia, chronic arthritis, nephritis, hepatitis, tumor and diabetes. Decoction of roots and leaves is used as emollient and given in dysuria, diarrhea, dysentery and in stomachic pain. Leaves are applied externally to treat eczema and ulcers.	Lin et al.(1992) Daisy et al.(2009) Tsai et al.(1999) Xu et al.(2006) Lin et al.(1995) Kiritikar et al.(1991) Chopra et al.(1956)
Ipomoea aquatic	Kalmi shak	Convolvulaceae	whole plant	To alleviate the disorders like jaundice and nervous debility. Used against nosebleed and high blood pressure and as emetic in cases of opium and arsenic poisoning. Given for nervous and general debility. Used in leucoderma, leprosy, jaundice and liver complaints.	Duke (1985) Perry (1980) Chopra (1956) Nadkarni (1954)

Wedelia chinensis	Kesraj	Asteraceae	whole plant	Treating various ailments like hepatoprotective efficacy, cholagouge, jaundice, diarrhoea, couch, cephalahagia, diphtheria, skin disease, alopecia.and pertussis. It is very specific in treating viral hepatitis. The fruit, leaves and stem are used in child and in treatment of bites and stings, fever and infection. Leaves are used in dyeing grey hair and in promoting the growth of hair.	The Wealth of India (2005, 567-568). Suresh (2010) Chopra (1956) Mathew (1983) Indian Medicinal Plants-A Compendium of 500 species. (1983)

Table 2: Hepatoprotective activity (Percent reduction) of selected plants:

Plant Name	Used part & solvent extraction	Toxic chemicals	Dose	Parameters in serum % reduction				References
				ALT	AST	ALP	TB	
Alocasia indica	leaves hydroalcoholic extract	CCl_4 and Paracetamol (PCM)	Ektract (500mg/kg) Extract (500mg/kg)	5.59% 23.0%	25.70% 27.46%	61.53% 46.59%		**Mullah et al. 2009**
	Tuber Ethanolic extract	CCl_4	Extract (200mg/kg)	66.78%	66.54%			**Khowala et al. 2014**
Andrographis paniculata	Leaves Aqueous extract	Ethanol	Extract (250mg/kg)	57.40%	48.32%	57.96%	71.66%	**Sivaraj et al. 2011**
	Leaves Aqueous extract	CCl_4	Extract (300mg/kg)	68.55%	72.97%		66.66%	**Nasir et al. 2013**
	Leaves Aqueous extract	PMC	Extract (500mg/kg)	81.55%	73.65%	68.60%	70.71%	**Jayavelu et al. 2013**
Eclipta elba	Leaves Methanolic extract	CCl_4	Extract (200mg/kg)	70.26%	50.80%	60.90%	79.38%	**Lal et al. 2010**
	Root Chloroformic extract	CCl_4	Extract (200mg/kg)	90.62%	60.95%	64.48%	81.44%	

Elephantopus scaber	Roots Methanolic extract	CCl_4	Extract (75mg/kg) Extract (150mg/kg)	41% 34%	50% 34%	58% 46%		**Sheba et al. 2012**
	Roots	CCl_4	Extract (250mg/kg)	62.39%	57.11%	40.90%		**Rajesh and Latha 2001**
	Different fractions Hexane Ethyl acetate Ethanol Methanol	CCl_4	Extract (500mg/kg)	 72.73% 72.26% 63.87% 65.93%	 73.69% 73.09% 64.29% 66.24%	 67.06% 66.95% 63.40% 64.01%	 77% 77% 70.37% 70.47%	**Ganga et al. 2012**
	Whole plant Ethanol	Ethanol		40.47%	38.56%	76.86%	59.78%	**Ho et al. 2012**
Ipomoea aquatica	Whole plant Ethanol	Thioacetamide	Extract (500mg/kg)	24.78%	28.75%	33.23%		**Alkiyumi et al. 2012**
Wedelia chinensis	Whole plant Alcoholic & Aqueous extract	CCl_4	Ethanolic extract (500mg/kg) Aqueous extract (500mg/kg)	16.99% 17.59%	16.31% 19.19%	26.07% 28.11%	4.79% 4.68%	**Mishra et al. 2009**

	Leaves Methanolic extract	PCM	Extract (250mg/kg)	50.68%	18.95%	62.60%		**Emmanue et al. 2001**

Table 3: Isolated compounds from selected plants:

Plant Name	Used part	Isolated Compounds	Compound responsible for hepatoprotective activity	References
Alocasia indica	Leaves Hydroalcoholic extract Tuber Ethanolic extract	flavinoids, cynogenetic glycosides, citric acid, ascorbic acid, polyphenolic compounds. ß-Hydroxyque brachamine ($C_{19}H_{26}N_2O$); Gibb-3ene-1, 10-dicarboxylic acid, 2, 4 a-dihydroxy -1 methyl-8methylene, 14a-lactone, 10methyl ester ($C_{20}H_{24}O_5$); Butanoic acid, 4, 4 dithiobis ($C_8H_{16}N_2O_4S_2$); 5-(P-Aminophenyl)-4-(o-tolyl)-2 thiazolamine ($C_{16}H_{15}N_3S$); 3H-1,4-Benzodiazepine-2-amine,7chloro-N-methyl-5-phenyl,4-oxide ($C_{16}H_{14}CLN_3O$); 10, 12, 14 Nonacosatriynoic acid (C_{23} H_{46} O_2); Androst-4-en-11-ol-3, 17-dione, 9-thiocyanato ($C_{20}H_{25}NO_3S$); Estra-1, 3, 5 (10)-trien-17-one, 3hydroxy-6-methoxy, o-methyloxime, (6á) ($C_{20}H_{27}NO_3$); 17 alpha-ethynyl-17 beta-hydroxy-6beta methoxy -3 alpha, 5 cyclo-5 alpha-androstan-19-oic acid ($C_{22}H_{30}O_4$); 1H indole, 3 benzyl -2-phenyl ($C_{21}H_{17}N$) and 1H indole, 5 methyl-2, 3 diphenyl ($C_{21}H_{17}N$).	alocasin, flavinoids and polyphenolic compounds. 10, 12, 14-Nonacosatriynoic acid and Androst-4-en-11-ol-3, 17-dione, 9-thiocyanato as a class of essential oil.	**Tien et al. 2004** **Khowala et al. 2014**

Andrographis paniculata	Whole plant Ethanol or Methanol extract	Diterpenoids, Flavonoids and Polyphenols. Diterpenoids: Andrographolide ($C_{20}H_{30}O_5$); 14-deoxy-11, 12-didehydroandrographolide; neoandrographolide; 14-deoxyandrographolide; andrograpanin; isoandrographolide, 3, 19-isopropylideneandrographolide; 14-acetylandrographolide and arabinogalactan proteins.	Andrographolide, Neoandrographolide, Arabinogalactan proteins and Flavonoids	**Rao et al. 2004, Xu et al. 2010 and Cheung et al. 2001**
	Whole plant Ethanol or Methanol extract	Flavonoids: 5-hydroxy-7,8-dimethoxyflavone; 5-hydroxy-7,8,2',5'-tetramethoxyflavone; 5-hydroxy-7,8,2',3'-tetramethoxyflavone; 5-hydroxy-7,8,2'-trimethoxyflavone; 7-*O*-methylwogonin and 2'-methyl ether.		**Chao et al. 2010** **Radhika et al. 2010**

Eclipta alba	Whole plant Methanolic extract	Alkaloids: ecliptine and nicotine. Steroidal alkaloids, verazine, 20-epi-3-dehydroxy-3-oxo-5, 6-dihydro-4, 5-dehydroverazine ecliptalbine, (20R)-4s-hydroxyverazine, 4s-hydroxyverazine, (20R)-25s-hydroxyverazine and 25s-hydroxyverazine.		**Kader et al. 1998**
	Leaves	Coumestan: wedelolactone ($C_{16}H_{10}O_7$) and desmethylwedelolactone.	Wedelolactone and desmethylwedelolactone	**Sing et al. 2001**
	Whole plant	Triterpenene: saponin, eclalbatin, together with α-amyrin, β-amyrin, ursolic acid, oleanolic acid and wedelic acid. Ecliptasaponin C and D, new triterpenoid glucosides, oleanane triterpene glycosides and eclalbasaponins I-VI.		**Yahara et al. 2007**
	Whole plant and Roots	Polyacetylenic thiopenes 5'-senecioyloxymethylene-2-(4-isovaleroxybut-3-ynyl) dithiophene, 5'-tigloyloxymethylene -2-(4-isovaleroxybut-3-ynyl)		**Singh et al. 1988**

		dithiophene and polyacetylene substituted thiophenes.		**Zhang et al 1997**
	Aerial parts	Phytosterol; β glucoside of phytosterol, daucosterol and stigmasterol-3-O-glucoside.		**Zhang et al. 2001 and Han et al. 1998**
	Whole plant	Stigmasterol and β-sitosterol Flavonoids like apigenin, luteolin and luteolin-7-glucoside; Nonacosanol, stearic acid, lacceroic acid and 3, 4-dihydoxy benzoic acid.		
Elephantopus scaber		Terpenoids, sesquiterpene lactones, phenolic acids and flavonoids. Sesquiterpenoids: scabertopin; isocabertopin; deoxyelephantopin; iso-17,19-dihydrodeoxyelephantopin; molephantinin; scabertopinol; 11,13-dihydrodeoxyelephantopin; isodeoxyelephantopin.	Sesquiterpene lactones, Phenolic acids and Flavonoids.	**Picman et al. 1986** **Juliana et al. 2013**
	whole plant ethanol fraction	Phenolic compounds: 3,4-dihydroxy benzaldehyde, p- coumaric acid, vanillic acid, syringic acid,		**Hisharn et al. 1992.** **Zhang et al. 2011**

		isovanillic acid, p-hydroxybenzoic acid, ferulic acid, 3-methoxy-4-hydroxyl cinnamic aldehyde, tricin, syringic acid, E-3-(3-ethoxy-4hydroxyphenyl) acrylic acid, 2-hydroxybenzolate acid.		**Chang et al. 2012**
	Aerial part Mthanol fraction	Flavonoid a glycoside luteolin and flavonoid glycosides luteolin-7 Oglucuronide 6"-methyl ester and luteolin-4-0- -D glucoside were identified along with three polyphenols trans-p-coumari acid, methyl trans-caffeate, trans-caffeic acid		**Chang et al. 2012**
Ipomoea aquatic	Whole plant	Flavonoid: Quercetin; quercetin 3'-methyl ether, quercetin 4'-methyl ether and anthocyanins.		**Daniel et al. 1989** **Sivaraman et al 2014**
		Phenolic compound: Chlorogenic acid.	Chlorogenic acid	**Basnet et al. 1996**
		Carotenoids: zeaxanthin, lutein, anthraxanthin, flavoxanthin, auroxanthin, luteoxanthin, neoxanthin, β-carotene, violoxanthin, cryptoxanthin, neoxanthin and neoxanthin b.		**Ortaliza *et al.* 1969** **Wills et al. 1996**

Wedelia chinensis		indole-3-carboxylaldehyde, wedelolactone, luteolin and apigenin.	Norwedelolactone and Norwedelic acid.	**Lin et al 2007**
	Leaves	Isoflavonoids and bisdesmosidicoleanolic acid saponins		**Masoodi et al. 2011**
	Leaves Alcoholic extract	Norwedelolactone and Norwedelic acid		**Bhargava et al. 1970**
	Fresh leaves	Triterpenoid saponin: bisdesmodic-osidic oleanolic acid saponins as. -D-glucopyranosyl-3-o-[o-.-D-xylopyranosyl-(1.2).-D Glucuronopyranosyl] oleanolate, -D-glucopyranosyl 3.-[(o-.-D-xylopyranosyl-(1.)-(pD-glucuronopyranosyl)]-olean-12-en-28 oate).		**Masoodi et al. 2011**

	Methanolic extract	Fatty acids, melissic and lignoceric acid,stigmasterol and stigmasteryl glucoside, Kauren diterpenes(-) kaur-16-en-19-oic acid and a mixture of the three esters, 3α-angeloyloxy-3α-triglinoyloxy and 3-senecioyloxy-kaur-16-en-19-oic acid		**Haider et al. 2003**

Chapter Four

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