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- A BRIEF REVIEW

PHYTOCONSTITUENTS WITH HEPATOPROTECTIVE ACTIVITY

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ABSTRACT

Liver plays a vital role in metabolism and excretion. Liver ailments needs to be treated with utmost care. In India, there are about 100 medicinal plants used in 33 herbal formulations. These hepatoprotective plants have the phytoconstituents such as phenyl compounds, coumarins, essential oils, monoterpenoids, diterpenoids, triterpenoids, steroids, alkaloids and other nitrogenous compounds. A brief review of phytoconstitments with hapatoprotective activity has been reported.

Key words: Hepatoprotective plants, Phytoconstituents, Terpenoids, Phenyl compounds.

INTRODUCTION

Natural products and plants as liver protecting drugs

The successful therapy of liver depends on identification of pathogens and elaboration of suitable models for hepatic injuries *in vivo* and *in vitro* test model systems are available to screen the antihepatotoxic activity[1] of any substance. For the *in vivo* models. The dose of a known hepatotoxin like CCl_4, D-galactosamine (D-gal N), alcohol, thioacetamide etc., which produces a marked and measurable effect, is administered to the animal. The magnitude of toxic effect is measured by some suitable parameters e.g., by determining the activity of serum glutamate oxalacetate transaminase (SGOT) and serum glutamate pyruviate transaminase (SGPT) or by recording the increase in hesobarbital sluptum or by histological examination of liver. *In vitro* models employing primary cultured

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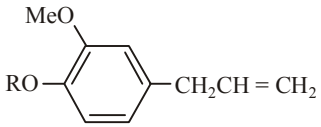
hepatocytes and using CCl_4 or D-Gal N or ethanol as toxins have been devised. Phytoconstituents with elucidated structures or otherwise have been classified under appropriate chemical groups.

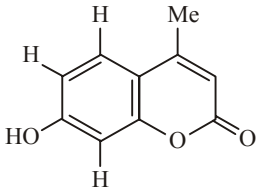
Phenyl propanoids

Phenols

The acetone extract of *Syzygium aromaticum* (Myrtaceae) as well as eugenol and acetyleugenol from the same plant exhibited cholagogue activity in experimental animals.



R = H in Eugenol ; R = Ac in Acetyleugenol



4-Methylumbelliserone

Phenolic compounds from two Arnica spices have been shown to be useful for treating CCl_4 induced toxic symptoms in rats. The activity of seurm enzymes was restored and the level of SGOT was reduced by the seventh day and the activites of SGPT and alkaline phosphatase normalized. The Arnica treatment also restored the bile forming function of liver and improved the secretion of cholates and bilerubin and the excretion of cholestrol.[2]

Cichorium intybus (compositae) popularly known as chicory and polyphenolic compounds from Gurinea charcoviensis have been shown to exert cholagogue effect.

There are a number of coumarin derivatives viz 7-hydroxy, 7-s- hydroxy, 4-hydroxy, 4,7-dihydroxy and 4,7-dimethyl-5-hydroxy coumarin[3], coumarin-3-carboxylic acid and dicoumarol were shown to stimulate choleresis in rats.

Isofraxidin, scopoletin and mumbeliferone were the coumarin derivatives isolated from *Artemisia abrotanum* (compositae).

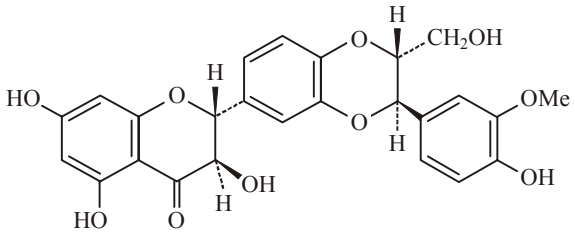
A hydroxyl group, which can be mainly converted into a glucronate is necessary in exerting a strong choleretic action. On the basis of these studies, the choleritic mechanism of coumarin derivatives is considered to be based on an active excretion of water.

Umbelliferone, methyl umbelliferone and esculatain are some of the coumarin derivatives. The presence of a hydroxyl or ether group at C-6 in these derivatives caused no marked changes in activity. The compounds with a hydroxyl group at C-7 exerted high activity and methylation of C-7 hydroxyl group diminished the activity.

Lignans

Silymarin obtained from the seeds of *Silybrun marianum* (compositae) is the most thoroughly investigated. Silymarin posses antihepato toxic activity. Silymarin is a mixture of isomeric flavolignans- silybin, silydianin and silychristen.

Silybin



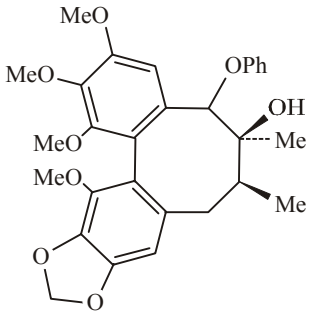
The protective effect of silymarin is brought by competitively blocking the binding of phalloidin to receptors on the hepatocyte membrane surface and hindering α-amanitin to penetrate through the membrane into the cell nucleus. *In vitro* studies conducted with nuclei and nucleoli from rat liver point to another mechanism for the protective action of silymarin.

Hikino *et al.*[2] examined the antihepatotoxic effects of flavnolignans and related constituents from *S. marianum* using CCl_4 and D-gal N induced cytotoxicity in primary cultured rat hepatocytes as model systems.

A series of lignans[4] have been isolated from well-known Chinese traditional drugs *Schizandra Chinensis* and *S. spheranthera* (Magnoliaceae). These are dibenzo cyclooctane derivatives and include schizandrins, schizantherins, wuweizins and gomisins.

Schizantherin A, Schizantherin B, Schizantherin C and Schizanterin D isolated from fruits of *S. sphenanthera* have been found to lower the SGPT level of the chronic viral hepatitis patients.

Schizantherine A



Desoxypodophyllotoxin, a lignan, has been isolated from the leaves of *Thujopsis dolabrata* (Cupversaceae).

Essential oils

Liver histology, liver metabolic and serum enzyme studies showed that essential oil of *Baechea fratescens* (Myrtaceae) known in China as Gang Song protected mice against liver damage.

Rose oil from different species of the genus Rosa (Rosaceae) increased the secretion of bile fluid and major organic components of bile. Dill oil obtained from the fruits of *Anethum graveolens* (umbelliferae) increased the secretion of the lipid complex by 15 % choleric acid by 26 % and the amount of bile by 11.1 %.

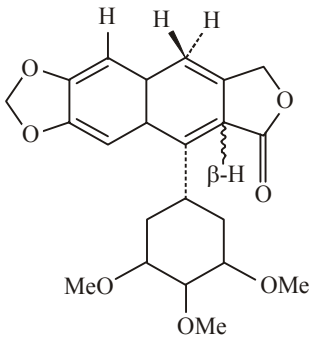
The essential oils from *Perovskia abrotanoids*, *Salvia rhytidea*, *Ziziphro afghanica* and *Origanum glaucum* all belonging to family Labiatae had a marked choleretic activity in rats.

Regeneration of liver increased significantly by s.c. injection of oils of *Pimpinetta anisum*, *Foenuculum vulgdre*, *Apium graveolens* and *Petroselinum sativam* all belonging to the family Umbelliferae.

Terpenoids

Monoterpenoids

(+) Borneol, a bicyclic monoterpenoid, or its esters with fatty acids of dicarboxylic acids, were reported to be cholertics[5]. One of the major sources of this constituent is *Dryobalanops aromatica* (Dipterocarpaceae)



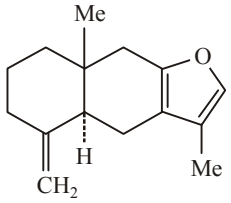
(+) -Borneol

Sesquiterpenoids

Extracts of various samples of the crude drug prepared from the rhizomes of *Atracylodes macrophala* and *A. Lancae* (compositae) exhibited antihepatoxic activity. The major sesquiterpenoid active components atractylon, β-eudemol and hinesol exhibited significant liver protecting effect[6].

The effect of sesquiterpenoid and related compounds of the root of *Lindera strychinifolia* (Lauraceae) was studied. The significant observation was that lindstrem, a main sesquiterpenoid constituent of the plant, suppressed SGPT and SGOT levels from increase due to the administration of hepato toxins.

Atractylon



Diterpenoids

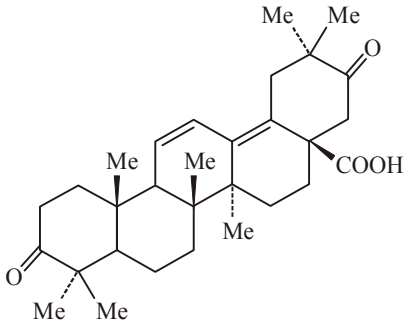
Aqueous extract of the plant *Andrographis paniculata* (Acanthaceae) popularly known in India as Kalmegh contains a diterpenoid adrographolide.

Triterpenoids

Antihepatotoxic effects of papyriogenins and their glycosides, isolated from the leaves of *Tetrapanax papyriferum* (Araliaceae) were studied. Papyriogenin A, Papyriogenin B, Papyriogenin C, Propapyriogenin A, 11-dehydro propapyriogenin A, 16-episkogenin C and propapyriogenin A were the chemical constituents (triterpenoids) of this plant.

The antihepatotoxic action of curcurbitiacin B, which usually occurs in *Cucurbita pepo* (Cucurbitaceae) and curcurbitacin E commonly occurring in *Ecbalium elaterium* (Cucurbitaceae) were studied by Chinese workers. Zygophillin, a bitter principle and quinovic acid, a triterpene compound both of which are water insoluble and isolated from *Zygophyllum coccineum* (Zygophillaceae) had anti-inflammatory and choleretic activity in experimental animals. Development of experimental cirrhosis in rats was shown to be prevented by glycyrrizin and glycyrrhetic acid the constituents of *Glycyrrhiza glabra* (Leguminosae).

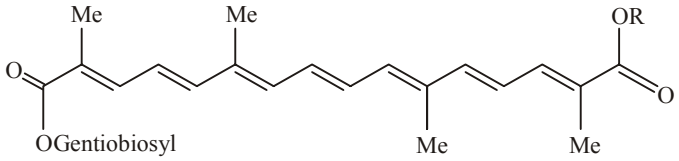
Papyriogenin



Carotenoids

Crocin and crocetin isolated from the fruits of *Gardenia florida* (Rubiaceae), when administered into rabbits, increased the bile secretion[7].

Crocin



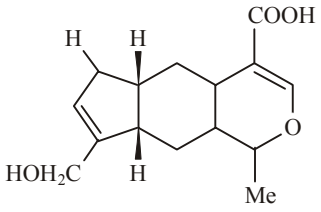
Glycosides

Iridoid glycosides

Extracts of *Picorrhiza kurroa* (Scrophulariaceae) popularly known in India as Kutaki have shown marked protective action on liver against CCl_4 intoxicated rats. Iridoid glycosides like picroside I and picroside II isolated from this species showed protective effects against liver intoxication of mice with CCl_4. Geniposide[8] is the primary pharmacologically active component isolated from the alcoholic extract of *Gardenia*

jasminoides (Rubiaceae) fruits. A choleretic geniposidic acid aclycone was isolated from the fruits of *Gardenia jasminoids* (Rubiaceae) and from the seeds of *Piantago asiatica* (Plantaginaceae). Acubin and iridoid glycoside, isolated from both leaves and seeds of *Plantoago asiatica* showed potent liver protecting activity. Aglycone of loganin and iridoid glycoside, isolated from the methanolic extract of *Patrinia villosa* (Valerianaceae) roots showed choleretic activity. Similar activity has been observed in syringopicroside isolated from the leaves of *Syringa oblata* (Oleaceae).

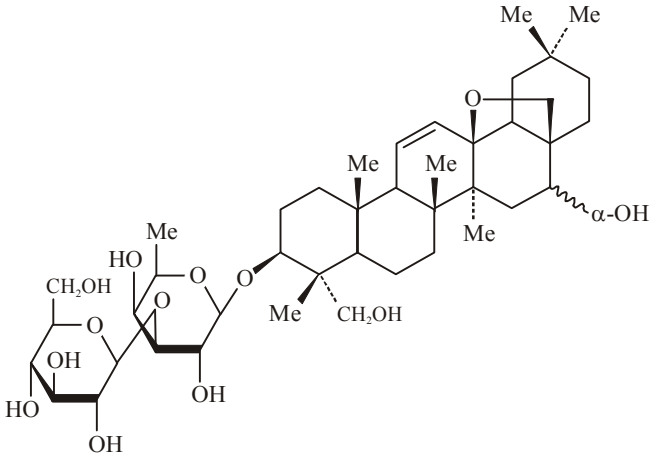
Aclycone



Saponins

The beans of *Glycine max* (Leguminosae) Daizu in Japanese was found to contain various saponins. The oleanene type triterpenes in oligoglycosides of these soyasaponins are known to have a glucurnide linkage. Saikosaponin D and saikosamponin A from *B. falcatum* show interesting results on liver functions. The saponins of the gypsogenic series have been isolated from *Dianthus superbus* (Caryophyllaceae) and *Ginseng* (Arleaceae) were proved to be effective orally to decrease the elevated SGOT and SGPT levels in CCl_4 intoxicated rabbits.

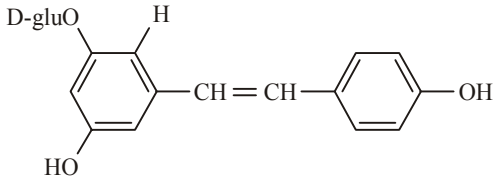
Saikosaponin



Other glycosides

Piceid, 2,3,5,4′-tetrahydroxystilbene-2-O-D-glucoside obtained from roots of *Polygonum cuspidatum* and *P. multiflorum* (Polygonaceae) partly inhibited the deposition of lipid peroxides[9] in the liver of rats fed with peroxidized oil.

Piceid



Flavonoids

A series of experimental investigations made the way for the discovery of catechin type drugs. Catechin belongs to flavonoid group of compounds.

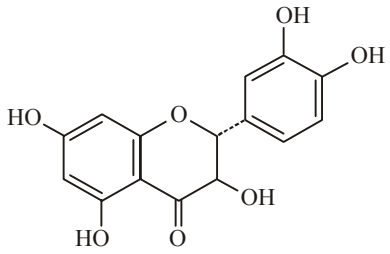
The following flavonoid compounds were found to have curative effect on liver.

S. No.	Plant name	Flavonoid
1.	*Helichrysum arenarium* (compositae)	Flamin, quercetin, kaempferol, narringenin and isohelichrysin
2.	*Artemisia capillaris* (compositae)	Eupatolin, arcapallin, capillartemisin A, capillartemisin B
3.	*Tageles patula* (compositae)	Patuletin
4.	*Euphorbia stepposa* (Euphorbiaceae)	Kaempferol-3-rhamnogluscoside Quercetin- 3-rhamnoglucoside, stepposide, steppogenin-7-β-D-glucopyranoside, robidnol-3-gallate
5.	*Cercis siliquastrum* (Leguminoseae)	Myricitoside (C)
6.	*Reseda luteola* (Resedaceae)	Luteolin - glucoside
7.	*Scrophalaria grossheimi* (scrophulariaceae)	5,7,3 –Trimetoxy-4′ flavone
7.	*Scrophalaria grossheimi* (scrophulariaceae)	5,7,3 –Trimetoxy-4′ flavone
8.	*Mentha pieperata* (Labiatae)	Mixed flavonoids
9.	*Stachys recta* (Labiatae)	Stachyrin

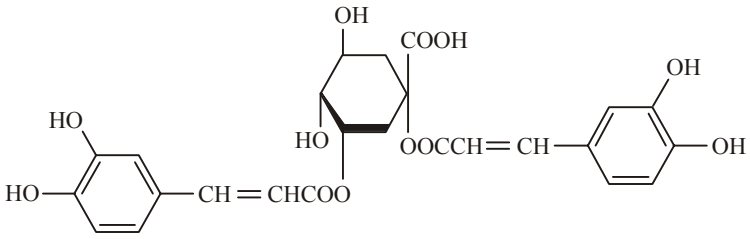
Cont…

S. No.	Plant name	Flavonoid
10.	*Canscora decussala* (Gentianaceae)	Mangiferin
11.	Embryos of cereals, vegetable oils (palm, olive, etc.)	α-Tocopherol (Vitamin E)

Quercetin



Synarin



The flavonoids in plants such as *Colinium goggyria*, *Anemone hepatica* (Ranumculaceae), *Convallaria majalis* (Liliaceae) and *Omonus arvenis* (Leguminosae) were found to have hepatoproective activity[10].

Organic acids and lipids[11-13]

(i) Artichoke extract - Monocafeolyquinic derivatives

(ii) *Cynara scolymus* (Leguminosae) - Glycolic acid, glyceric acid, cynarin: 1,5-dicaffeolylquinic acid

(iii) *Coffea* (Rubiaceae) – Chlorogenic acid

(iv) *Curcuma longa* (Zingiberaeae) – Hydroferulic acid, dihydrocholic acid

(v) *Linum usitatissimum* (Linaceae) - Arachidonic acid, linoleic acid

(vi) Vitamin B_{12} - Pangamic acid

Comparative choleretic activity of phenol carboxylic acids has been determined and it was found to be in the following order: Ferulic acid > Caffeic acid > Isochloroginic acid > Trimethoxycinnamic acid > Cholrogenic acid > Cyanarin > Neochorogenic acid > Quinic acid.

Nitrogenous compounds

Alkaloids[15]

(i) *Peumus boldus* (Monimlaceae) – Alcoholic extract- Isoquinoline alkaloid boldine

(ii) *Fumeria* (Fumaniaceae) – Protopine

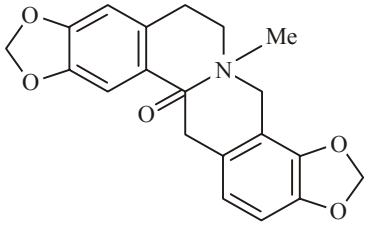
(iii) *Beriberis vulgaris* (Berberidaceae) – Berberine, columabmine, oxycathine, berbamine and yatroricine.

(iv) Solanaceous plants – Atropine, a tropan alkaloid

(v) *Rauwolfia* (apocyanceae) – Indole alkaloid reserpine

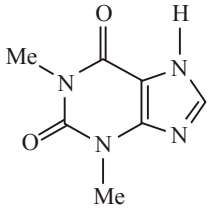
(vi) *Aristoclochia clementis* (Aristolochiaceae) – Pilocarpine

Boldine



Xanthines

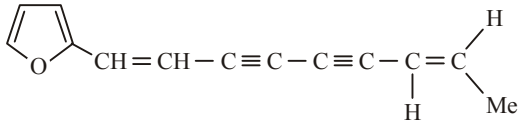
Caffeine in *Coffea* (Rubiaceae) and *Theasinesis* (Ternstroeminaceae) increases bile secrtion in mice, rats and pigs. Theophylline produced a choleretic effect.



Theophylline

Fruran derivative

Atractylodin, a furan derivative, has choleretic effect.



Atractylodin

Plants and their constituents having hepatoprotective activity.

S. No.	Plant constituent	Name of the plant
1.	Androgrpholide	*Andrograhis Paniculata*
2.	Silybin	*Silybum marianum*
3.	Picroside I	*Picrorhiza kurroa*
4.	Picroside II	*Picrohiza kurroa*
5.	Kutkoside	*Picrohiza kurroa*
6.	Gomishins	*Schizandra chinensis*
7.	Schisandrin A	*Schizandra chinensis*
8.	Glycrrhizin	*Glycyrrhiza glabra*
9.	Glycyrrhetinic acid	*Glycyrrhiza glabra*
10.	Saikosaponins	*Bupleurum falcatum*
11.	Sarmentosins	*Sedum sarmetosum*
12.	Wuweizisu C	*Schizandra chinensis*
13.	Catechin	*Ancardium occidentalis*
14.	Ursolic acid	*Eucalyptus Spp*
15.	Curcumin	*Curcuma longa*
16.	Fumaric acid	*Sida cordifolia*

Mechanism of hepatoprotective action

The inhibition of HBV by *Phyllanthus* amarus in *in vitro* studies gave an idea about the mechanism of hepatoprotective action. Elimination of the virus from the serum, interruption of the interaction between HBV enhancer I and cellular transcription factors,

disruption of HBV polymeric activity and mRNA transcription and replication by the active principle of the plant are the various steps of hepatoprotective action.

The factors like variations[16] in the plant material, period and place of collection of plants, age of plants and part of plants used do affect the hepatoprotective action.

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