- 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 phytoconstituents with hepatoprotective 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 of any substance. For the in vivo models. The dose of a known hepatotoxin like CCl₄, 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 pyruvate transaminase (SGPT) or by recording the increase in hesobarbital sluptum or by histological examination of liver. In vitro models employing primary cultured...
Phenoxy propanoids

Phenols

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

\[
\begin{align*}
&\text{MeO} \\
&\text{RO} \\
&\text{CH}_2\text{CH} = \text{C} \\
&\text{H} \\
R = \text{H} \text{ in Eugenol} ; R = \text{Ac} \text{ in Acetyleneugenol}
\end{align*}
\]

Phenolic compounds from two Arnica spices have been shown to be useful for treating CCl₄ induced toxic symptoms in rats. The activity of serum enzymes was restored and the level of SGOT was reduced by the seventh day and the activities of SGPT and alkaline phosphatase normalized. The Arnica treatment also restored the bile forming function of liver and improved the secretion of cholates and bilirubin and the excretion of cholestrol.

*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, coumarin-3-carboxylic acid and dicoumarol were shown to stimulate choleresis in rats.

Isofraxidin, scopoletin and umbelliferone 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**

![Diagram of Silybin](image)

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.*

examined the antihepatotoxic effects of flavnolignans and related constituents from *S. marianum* using CCl₄ and D-gal N induced cytotoxicity in primary cultured rat hepatocytes as model systems.

A series of lignans have been isolated from well-known Chinese traditional drugs *Schizandra Chinensis* and *S. sphenanthera* (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

![Schizantherine A structure](image)

Desoxypodophyllotoxin, a lignan, has been isolated from the leaves of *Thujaopsis 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*, *Foeniculum vulgare*, *Apium graveolens* and *Petroselinum sativam* all belonging to the family Umbelliferae.

**Terpenoids**

**Monoterpenoids**

(+)-Borneol, a bicyclic monoterpneoid, or its esters with fatty acids of dicarboxylic acids, were reported to be choleretics. One of the major sources of this constituent is *Dryobalanops aromatica* (Dipterocarpaceae)
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.

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

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

**Papyriogenin**

![Diagram of Papyriogenin]

**Carotenoids**

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

**Crocin**

![Diagram of Crocin]

**Glycosides**

**Iridoid glycosides**

Extracts of *Picorrhiza kurroa* (Scrophulariaceae) popularly known in India as Kutaki have shown marked protective action on liver against CCl₄ intoxicated rats. Iridoid glycosides like picroside I and picroside II isolated from this species showed protective effects against liver intoxication of mice with CCl₄. Geniposide 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 jasminoides (Rubiaceae) and from the seeds of Plantago asiatica (Plantaginaceae). Acubin and iridoid glycoside, isolated from both leaves and seeds of Plantago 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

\[
\text{H} \quad \text{H} \quad \text{H} \quad \text{COOH} \\
\text{HOH}_2\text{C} \quad \text{H} \quad \text{Me}
\]

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\textsubscript{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 peroxides⁹ in the liver of rats fed with peroxidized oil.

**Piceid**

![Chemical structure of 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.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Plant name</th>
<th>Flavonoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Helichrysum arenarium</em> (compositae)</td>
<td>Flamin, quercetin, kaempferol, narringenin and isohelichrysin</td>
</tr>
<tr>
<td>2.</td>
<td><em>Artemisia capillaris</em> (compositae)</td>
<td>Eupatolin, arcapallin, capillartemisin A, capillartemisin B</td>
</tr>
<tr>
<td>3.</td>
<td><em>Tageles patula</em> (compositae)</td>
<td>Patuletin</td>
</tr>
<tr>
<td>4.</td>
<td><em>Euphorbia stepposa</em> (Euphorbiaceae)</td>
<td>Kaempferol-3-rhamnoglucoside, Quercetin-3-rhamnoglucoside, stepposide, steppogenin-7-β-D-glucopyranoside, robidnol-3-gallate</td>
</tr>
<tr>
<td>5.</td>
<td><em>Cercis siliquastrum</em> (Leguminoseae)</td>
<td>Myricitoside (C)</td>
</tr>
<tr>
<td>7.</td>
<td><em>Scrophalaria grossheimi</em> (scrophulariaceae)</td>
<td>5,7,3 –Trimetoxy-4’ flavone</td>
</tr>
<tr>
<td>8.</td>
<td><em>Mentha pieperata</em> (Labiatae)</td>
<td>Mixed flavonoids</td>
</tr>
<tr>
<td>9.</td>
<td><em>Stachys recta</em> (Labiatae)</td>
<td>Stachyrin</td>
</tr>
</tbody>
</table>

Cont…
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Plant name</th>
<th>Flavonoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.</td>
<td><em>Canscora decussala</em> (Gentianaceae)</td>
<td>Mangiferin</td>
</tr>
<tr>
<td>11.</td>
<td>Embryos of cereals, vegetable oils (palm, olive, etc.)</td>
<td>$\alpha$-Tocopherol (Vitamin E)</td>
</tr>
</tbody>
</table>

**Quercetin**

![Quercetin structure]

The flavonoids in plants such as *Colinium goggyria*, *Anemone hepatica* (Ranunculaceae), *Convallaria majalis* (Liliaceae) and *Omonus arvenis* (Leguminosae) were found to have hepatoprotective activity\textsuperscript{10}.

**Organic acids and lipids**\textsuperscript{11-13}

1. Artichoke extract - Monocaffeoylquinic derivatives
2. *Cynara scolymus* (Leguminosae) - Glycolic acid, glyceric acid, cynarin: 1,5-dicaffeoylquinic acid
3. *Coffea* (Rubiaceae) – Chlorogenic acid
4. *Curcuma longa* (Zingiberaeae) – Hydroferulic acid, dihydrocholic acid
5. *Linum usitatissimum* (Linaceae) - Arachidonic acid, linoleic acid
6. Vitamin B\textsubscript{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**

(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) *Aristolochia clementis* (Aristolochiaceae) – Pilocarpine

**Boldine**

![Boldine](image)

**Xanthines**

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

![Xanthines](image)
Theophylline
Fruran derivative

Atractylochin, a furan derivative, has choleretic effect.

\[
\begin{array}{c}
\text{O} \\
\text{CH} & \text{CH} & \text{C} & \text{C} & \text{C} & \text{C} & \text{C} & \text{C} \\
\text{H} & & & & & & & \text{Me}
\end{array}
\]

Atractylochin

Plants and their constituents having hepatoprotective activity.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Plant constituent</th>
<th>Name of the plant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Andrographolide</td>
<td>Andrographis Paniculata</td>
</tr>
<tr>
<td>2.</td>
<td>Silybin</td>
<td>Silybum marianum</td>
</tr>
<tr>
<td>3.</td>
<td>Picroside I</td>
<td>Picrorhiza kurroa</td>
</tr>
<tr>
<td>4.</td>
<td>Picroside II</td>
<td>Picrorhiza kurroa</td>
</tr>
<tr>
<td>5.</td>
<td>Kutkoside</td>
<td>Picrorhiza kurroa</td>
</tr>
<tr>
<td>6.</td>
<td>Gomishins</td>
<td>Schizandra chinensis</td>
</tr>
<tr>
<td>7.</td>
<td>Schisandrin A</td>
<td>Schizandra chinensis</td>
</tr>
<tr>
<td>8.</td>
<td>Glycrrhin A</td>
<td>Glycyrrhiza glabra</td>
</tr>
<tr>
<td>9.</td>
<td>Glycyrrhetinic acid</td>
<td>Glycyrrhiza glabra</td>
</tr>
<tr>
<td>10.</td>
<td>Saikosaponins</td>
<td>Bupleurum falcatum</td>
</tr>
<tr>
<td>11.</td>
<td>Sarmentosins</td>
<td>Sedum sarmetosum</td>
</tr>
<tr>
<td>12.</td>
<td>Wuweizisu C</td>
<td>Schizandra chinensis</td>
</tr>
<tr>
<td>13.</td>
<td>Catechin</td>
<td>Ancardium occidentalis</td>
</tr>
<tr>
<td>14.</td>
<td>Ursolic acid</td>
<td>Eucalyptus Spp</td>
</tr>
<tr>
<td>15.</td>
<td>Curcumin</td>
<td>Curcuma longa</td>
</tr>
<tr>
<td>16.</td>
<td>Fumaric acid</td>
<td>Sida cordifolia</td>
</tr>
</tbody>
</table>

Mechanism of hepatoprotective action

The inhibition of HBV by Phyllanthus amarus in \textit{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\textsuperscript{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.

**REFERENCES**


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