REVIEW ARTICLE

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# Naturally Occurring Iridoids with Pharmacological Activity

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**Iridoids, a widely distributed class of natural products have shown encouraging biological activities including hepatoprotective, anticancer, immunostimulant, and antileishmanial. The present review describes the recent reports on the promising biological activities of iridoids isolated from plant sources.**

IRIDOIDS are a group of highly functionalised monoterpenoids usually but not invariably as glycosides with cyclopenta [c] pyran skeleton. They represent a large and still expanding group of natural constituents. The name "iridoid" was probably derived from the compounds such as iridomyrcetin, iridolactone and iridoidal, isolated from a genus of ants knows as *iridomyrex*. These compounds are responsible for defensive secretion of ants[1]. Sometimes they referred to as "pseudoindicans" due to blue colouration developed on hydrolysis. Although iridoids were isolated in the latter part of the nineteenth century, the basic skeleton of these compounds was first proposed by Halpern and Schmid in 1958 based on their investigations on structure elucidation of plumieride[2]. More than 600 iridoids have so far been isolated from different plant families such as Acanthaceae, Alangiaceae, Bignoniaceae, Buddlujaceae, Caprifoliaceae, Ericaceae, Fouquieriaceae, Gentianaceae, Gesneriaceae, Golgulariaceae, Hydrangeaceae, Loasaceae, Loganiaceae, Labiatae, Lamiaceae, Lentibulariaceae, Myoproceae, Olaceae, Orobanchaceae, Pedaliaceae, Plantaginaceae, Retziaceae, Rubiaceae, Saxifragaceae and Verbanaceae. They could be classified in eleven structural types[3] : (A) Eight carbon basic skeleton, (B) Nine carbon basic skeleton, (C) Ten carbon basic skeleton, (D) Iridoid aglycones, (E) Simple Secoiridoid glycoside, (F) Secoiridoid glycosides: terpene conjugated, (G) Secoiridoid glycosides: Phenolic conjugated, (H) Bisglycosidic iridoids and secoiridoids (I) Nonglycosidic iridoids: Plumeria type, (J) Nonglycosidic iridoids: Valeriana type, (K) Nonglycosidic iridoids: Miscellaneous.

Iridoids have long been studied as biosynthetic precursors of indole alkaloids. However, in recent years they have been shown to be an important biologically active plant constituents and some of the compounds are in clinical trials. Earlier reviews on iridoids[3-12] dealt mostly on their isolations, structure elucidations, biosyntheses and distribution in different plant families. In this review an attempt has been made to compile recent reports and research on biological activities of iridoids isolated from plant sources (Table-1).

## KUTKIN AND PICROLIV:

The bitter glycoside, kutkin, isolated from the roots of *Picrorrhiza kurrooa* Benth[13] was shown to be a mixed crystal of two glycosides kutkoside (1) and picroside-1(2) in the ratio of 1:2 and a small amount of other minor iridoid glycosides[14]. It could not be resolved into its constituents by repeated fractional crystallization[14]. It showed significant hepatoprotective activity in hepatic damage induced by galactosamine in rats and Plasmodium berghei (mastomys)[15]. It demonstrated significant antiinflammatory activity in a variety of test models which include adjuvant-induced and formaldehyde arthritis in rats and mice,

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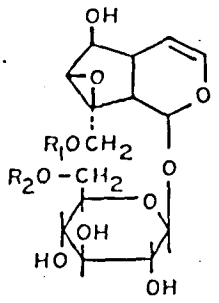
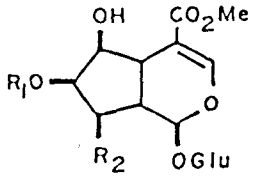


(1) $R_1$ = vanilloyl, $R_2$ = H

(2) $R_1$ = H, $R_2$ = cinnamoyl.

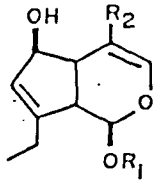


(3) $R_1$ = p-methoxycinnamoyl, $R_2$ = Me.

(4) $R_1$ = caffeoyl, $R_2$ = $CH_2OH$.

(5) $R_1$ = coumaroyl, $R_2$ = Me.

(6) $R_1$ = H, $R_2$ = Me.

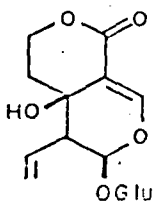


(9) $R_1$ = Glu, $R_2$ = H.

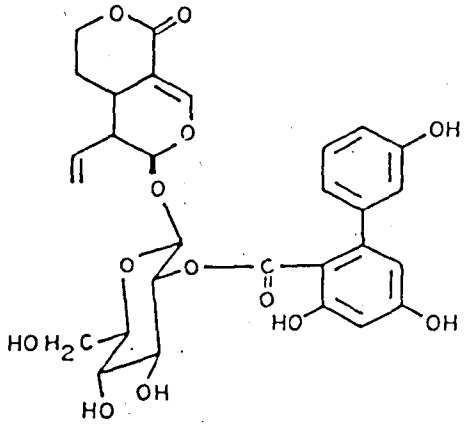
(10) $R_1$ = Glu, $R_2$ = $CO_2CH_3$.

(11) $R_1$ = H, $R_2$ = H.

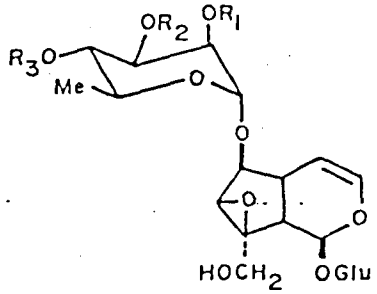
(12) $R_1$ = H, $R_2$ = $CO_2CH_3$.



(7)



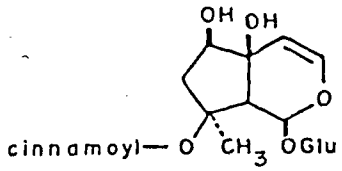
(8)



(13) $R_1$ = $R_2$ = Ac, $R_3$ = p-methoxycinnamoyl.

(14) $R_1$ = $R_2$ = cinnamoyl, $R_3$ = Ac.

(15) $R_1$ = $R_3$ = H, $R_2$ = p-methoxycinnamoyl.



(16)

**Fig. 1: Bioactive iridoids from medicinal plants**

**Table 1 : Biological Activity of iridoids**

| Iridoids | Source | Activity |
|---|---|---|
| 1. Kutkoside (1) | Picrorrhiza kurrooa | hepatoprotective, antiinflammatory immunostimulant |
| 2. Picroside-1 (2) | | |
| 3. Arbortristoside A (3) | Nyctanthes arbortristis | antileishmanial, antiviral, immunostimulant, anticancer |
| 4. Arbortristoside B (4) | | anticancer |
| 5. Arbortristoside C (5) | | antiviral, immunostimulant, anticancer |
| 6. 6 - Hydroxyloganin (6) | | antileishmanial |
| 7. Swertiamarin (7) | Swertia japonica | antispastic |
| 8. Amarogentin (8) | Swertia japonica, S. chirata | hepatoprotective, antiulcer, antileishmanial |
| 9. Aucubin (9) | Aucuba japonica | antimicrobial |
| 10. Aglycone of scandoside methylester (12) | Hedyotis colymbosa | antitumor |
| 11. Scropoliosode A (13) | | |
| 12. Koelzioside (14) | | |
| 13. 6-0-(3"-0-p methoxycinnamoyl) - ∝-L-rhamnopyranosylcatapol | Scrophularia koelzii | hepatoprotective, immunostimulant |
| 14. Harpagoside (16) | | |

carageenan-induced oedema in rats and mice, dextran-induced oedema in rats, acetic acid-induced vascular permeability in mice leucocyte migration in rats. It failed to exhibit any analgesic, antipyretic and ulcerogenic effects[16,17]. Picroliv, a standardised fraction isolated from the ethanol extract of roots and rhizome of *Picrorrhiza kurrooa* containing kutkoside (1) and picroside-I (2) as major constituents displayed a strong hepatoprotective activity in several models of liver damage[18-20]. It exhibited strong immunostimulant activity and was shown to enhance the nonspecific immune response as characterised by an increase in macrophage migration index, [$^{14}$C]-glucosamine uptake, phagocytosis of [$^{14}$C]-leucine labelled *Eschericha Coli*, chemiluminescence of peritoneal macrophages and higher uptake of [$^{3}$H]-thymidine in the lymphocytes of the treated mice[21].

## ARBORTRISTOSIDES:

Arbortristosides A(3), B(4), C(5) and 6β-hydroxyloganin (6) isolated from the seeds of the Nyctanthus arbortristis L (oleaceae)[22,23] exhibited antileishmanial activity both in vitro (against amastigotes in macrophage cultures) and *in vivo* (in hamsters) test systems[23]. Arbortristoside A (3) showed significant antileishmanial activity *in vivo* (79.68±21.68%)[24]. Arbortristoside A (3) and C(5) displayed antiviral activity against encephalomyocardic virus (EMCV) and semiliko forest virus (SFV) with an increase in average survival time of injected animals[25]. The iridoids (3 and 5) showed inhibition in the anti PCA test and exhibited a significant immunostimulant activity as indicated by increase in macrophage migration index, haemagglutination titre and plaque forming cells in mice[25]. Arbortristosides A (3) and B (4) were found to have anticancer activity against cholanthrene-induced fibrosarcoma[26].

## SWERTIAMARIN:

Swertiamarin (7) isolated from *Swertia japonica* showed sedative effect in mice, pigeons and rabbits and induced sleep in mice injected with subthreshold dose of phenobarbital[27]. It markedly inhibited contraction of isolated duodenal and uterine smooth muscles of rats and rabbits. Acetylcholine, barium chloride or histamine-induced ideal spasm in guinea pig was antagonised by swertiamarin. It also antagonised pituirin and acetylcholine-induced excitation of rabbit small intestine and uterus. It has very low toxicity and is a safe and effective antispastic agent[28].

## AMAROGENTIN:

Amarogentin (8) isolated from *Swertia chirata*[29], *Swertia japonica*[30], exhibited significant hepatoprotective activity[31] and prevented gastric ulcer formation to a great extent when administered orally to the rats[32]. It has been shown to possess significant antileishmanial activity *in vitro* and *in vivo* (Hamster)*. It is a newly recognised inhibitor of type I DNA topoisomerase from Leishmania and exerts its effect by interaction with the enzyme preventing binary complex formation[33].

## AUCUBIN AND SCANDOSIDE METHYLESTER:

Aucubin (9) isolated from *Aucuba japonica* ThunB showed antimicrobial activity against *Staphylococcus aureus* in the presence of β-glucosidase (an effect equivalent to that of 600 I.U. of Penicillin)[34]. Scandoside methylester (11) was isolated from *Hedyotis colymbosa* Lam; the aglycones of aucubin (10) and of scandoside methylester (12) both showed potent antitumor activities[35]. This iridoid (12) was moderately active against L1210 leukemia but was remarkably active against Ehrlich ascites carcinoma in mice, Meth A and sarcoma 180 (ascities form) and was more potent than 5-fluorouracil[36].

## SCROPOLIOSIDE A, KOELZIOSIDE, HARPAGOSIDE AND 6-0(3"-0-p- METHOXY CINNAMOYL)-∝-L RHAMNOPYRANOSYLCATALPOL:

Scropolioside A (13), koelzioside (14), 6-0-(3"-0-p-methoxycinnamoyl)-∝-L-rhamnopyranosylcatalpol (15) and harpagoside (16) isolated from *Scrophularia koelzii* showed significant protection of rat liver against thioacetamide-induced toxicity[37]. Scropolioside A (13) was shown to induce maximum hepatoprotection. Immunostimultant response was observed with all the four iridoids with harpagoside exhibiting maximum response[38].

Iridoids represent a large and expanding group of bioactive natural constituents. It is surprising that such a large and important class of natural product has so far failed to attract much interest of any but a few biochemists and pharmacologists. The controlled clinical experiments on some iridoids such as picroliv and kutkin have been reported. However, more biochemical information on the properties of iridoids in animal cells are needed to fulfill a serious investigation of the therapeutic possibilities of this class of natural products, iridoids.

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