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A Review of Iridoid Glycosides Content and Their Biological Properties from Genus Citharexylum

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Abstract

Citharexylum is a genus of flowering plants that belongs to Verbenaceae family. Various species of genus Citharexylum are cultivated as ornamentals. The species have various potent pharmacological and biological activities such as antioxidant, antidiabetic, antibacterial, anticancer and antipyretic activities. The Citharexylum botanical genus is a rich source of iridoid glycosides. All of the iridoids isolated from Citharexylum species have a- mono-glucosidic structure. The activity of iridoids glycosides from Citharexylum species such as antinociceptive, antimicrobial, anti-schistosomal, cytotoxic, anticancer, hepatoprotective, nephroprotective, antispasmodic, muscle relaxation, antidiabetic, antiallergic, immunomodultory, antityrosinase and anticholinesterase was discussed. The structure-activity relationships as anti-inflammatory and antioxidant agents were illustrated. The study extended to the application of plants with a high content of iridoid glycosides as well as the further search and future perspective. This review provides an exhaustive compilation of the iridoid glycosides-containing species of Citharexylum along with conjectures regarding potential biological activities, particularly those related to antioxidant and anti-inflammatory properties. To our knowledge, this is the first review on the iridoid glycosides content and their biological properties from genus Citharexylum from the period 1983 till 2024.

Keywords: *Citharexylum*; iridoid glycosides; biological activities; anti-inflammatory; antioxidant, structure-activity relationship, future prospective.

1. Introduction

Nature provides a vast array of metabolites with diverse range of biological activities. One important class of secondary metabolites present in some animals and plants are iridoids [1, 2]. They are class of compounds provided by nature with wide range of biological activities [1]. Iridoids have broad classes of skeleton of cyclopenta[c]pyran monoterpenoids represented in iridane (cis-2-oxabicyclo [4.3.0]nonane). Iridoid glycosides are the iridoids that often bound to glucose in plants. Most iridoids are prevalent in the dicotyledonous plants of important families, particularly in the Verbenaceae, Lamiaceae, Rubiaceae, Plantaginaceae and Loganiaceae that represent the classical sympetalous order of families [3], while they are not detected in other families.

Although iridoids were first isolated in the 1800s from plants, the research work that led to elucidation of the structures of this group was carried out in 1950s on iridodial that had been isolated from the common Australian ants, species of Iridomyrmex. The name given to these compounds was later adapted to refer to the structural class [4], most members of which have been isolated from plants. Iridoid glycosides were not considered particularly important as a pharmacologically active class of compounds, for a long time [4]. Iridoids have been long utilized in traditional medicines used as tonics, sedatives, febrifuges, antiarthritic, hypotensive, cough medicines, antipyretics, antidiabetics, for treatment of wounds, tumors, and for skin disorders [5].

Many members of the family Verbenaceae are known to contain iridoids. Verbenaceae contains 100 genera and nearly 3000 species with immense importance for aromatic and medicinal purposes as

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well as ornamental forage resources [6]. *Citharexylum* genus belongs to this family and includes about 115 species [7, 8]. *Citharexylum* plants are commonly known as zitherwoods or fiddlewoods, since their wood is used in the sounding boards of string instruments [9]. The name of *Citharexylum* is derived from the Greek words; *kithara*, that means "lyre" and *xylon* that means "wood," and referring to the usage of their wood in the sounding boards of string instruments [9]. *Citharexylum* genus has revealed good biological effects, such as gastroprotective, anti-inflammatory, hypoglycemic, radical scavenging, antipyretic, anticancer and antimicrobial activities [8, 10-13].

During the last few years, a number of bioactive iridoid glycosides have been discovered in the genus *Citharexylum* [13]. The main activities related to the iridoids as bioactive secondary metabolites isolated from *Citharexylum*, are antioxidant and anti-inflammatory. Extensive research on these metabolites has demonstrated various activities, including hypolipidemic [14], hypoglycemic [5], cardioprotective, neuroprotective [5], antimalarial, antitumor, antiviral, antibacterial [14], antiallergic, antispasmodic, purgative and immunomodulation [1, 14].

This review will pay close attention to the biological and pharmacological properties of iridoids from genus *Citharexylum*. Furthermore, providing an overview of the most known iridoid-containing *Citharexylum* for which different activities have been demonstrated *in vitro* and/or *in vivo*, especially the antioxidant and anti-inflammatory properties.

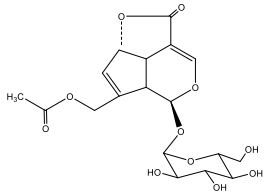
2. The basic nucleus of iridoid glycosides

Iridoids, a group of monoterpenes that are found as glycoside compounds in the plant material, are characterized by the existence of a cyclopentanoid residue in their skeleton [15]. Due to advances in phytochemical research over the last decade, unique classes of iridoid glycosides with exceptional activities and distinct structures have been discovered [1, 2]. The classification of iridoids can be divided into two categories: non-glycosidic iridoids and iridoid glycosides based on the presence or absence of intramolecular glycosidic bonds.. Iridoid glycosides are further subdivided into secoiridoids and carbocyclic iridoids. The metabolites of iridoid glycosides such as aucubin and catalpol showed neuroprotective, and anti-inflammatory activities [15]. The main basic nucleus of iridoid glycosides are the acetal derivatives of iridodials and are classified as monoterpenoids [16]. They are distinguished chemically by a six-membered ring that has oxygen bonded to a cyclopentane ring.

The iridane skeleton arises by the ten-oxogeranial cyclisation biosynthesized from geraniol to give iridodial by the 10-hydroxygeraniol. The later iridodial is oxidized to iridotrial. Oxidation, glycosylation and methylation convert iridotrial to the nucleus of iridoids. Four main groups (secoiridoids, the glycosides of iridoid, and simple or non-glycosylated iridoids) are the most common classification of iridoids among many other different classifications proposed. Almost all iridoids and secoiridoids are glycosides [3]. A glycosidic linkage that was usually formed at the aglycone C-11 or the hydroxyl of C-1 has connected to the iridoid glycoside. Two types of the iridoids could be divided to; iridoid glycosides such as deacetylasperulosidic acid, geniposide, loganin, and acetylbarlerin and secoiridoid glycosides such as gentiopicroside, swertiamarine, qinjiaoside B, qinjiaoside A, and oleuropein, as well as the sweroside, according to the integrity of the cyclopentane unit. Iridoids are organic compounds that tend to react with sugars forming glycosides, as the 1-OH group in iridoids can be unstable. Besides the glycosidic iridoids, there exist unglycosylated iridoids called non-glycosidic iridoids, such as valtrate and acevaltrate, and bis-iridoids, like sylvestroside I, cantleyoside, laciniatoside I, and laciniatoside II. All these iridoids can be found in nature. [17] are present in nature as well. These kinds of compounds have a wide range of physiological functions and are employed as agents with antipyretic and sedating activities [16].

2.1. Iridoid glycosides

Glycosides are the most common form of iridoids to which glucose is attached at the hydroxyl group at position C-1 [18]. The iridoid glycosides at C-1 are polyglycosides formed which are polyhydroxyl linked, and the majority are β-D-glucosides. Asperuloside is one of the uncommon new structures that have been discovered among the isolated rare iridoid glycosides. Asperuloside has a ketone functional group at C-6 [18]. This compound was isolated from the stems and roots of *Ronabea emetica.* Asperuloside is characterized by the anti-inflammatory activity as it suppresses mitogen-activated protein kinase and nuclear factor kappa B (NF-κB) signaling pathways. It inhibits inducible nitric oxide synthase, prostaglandin E2 (PGE2), nitric oxide, interleukin 6 and tumor necrosis factor alpha (TNF-α) production in LPS-induced mouse leukaemic monocyte macrophages (RAW 264.7) cells [19].



Asperuloside

The 2D structures of iridoid glycosides are presented in a study by López-López [20]. These iridoids have a glucose moiety at C-1, except spinomannoside (**6**) (Figure 1). Instead of the glucosyl group at C-1, the compound (**6**) contains a mannosyl group. The 5-deoxypulchelloside (**1**) lacks the double bond in C-7/C-8, it has two extra hydroxyl groups at C-7 and C-6. Additionally it at C-8 it has a methyl instead of the hydroxymethyl group. Pulchelloside I (**2**), in addition to these structural differences also presents an extra hydroxyl at C-5 (Figure 1). The iridoid glycosides, 5-deoxypulchelloside I (**1**), lamiide (**3**), and spinomannoside (**6**), have been identified in the flowers of C. *spinosum* [21]. These compounds have anti-cholinesterase, anti-tyrosinase, and cytotoxic activities with variable degree that may be attributed to the chemical structure [21]. Spinomannoside (**6**), which is structurally very similar to 5-deoxypulchelloside (**1**), contains a mannose at C-1 instead of the glucose. Lamiide (**3**) presents a hydroxyl at C-8, C-7, and C-5, lacks the double bond in C-8/C-7, and has a methyl group instead of the hydroxymethyl at C-8 (Figure 1).

2.2. The main isolated iridoid glycosides from Citharexylum *species*

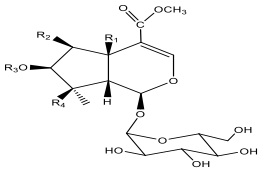
Several iridoid glycosides were isolated from different species of *Citharexylum* (Figure 1 and Table 1). 5-Deoxypulchelloside I (**1**), pulchelloside I (**2**), and lamiide (**3**) are the main isolated iridoids from most species of *Citharexylum*. The iridoids of lamiide type have been isolated such as 5-deoxypulchelloside I (**1**), lamiide (**3**), 7-ß-O-acetate of lamiide (**4**) and lamiidoside (**12**), along with a series of iridoids glycosides such as pulchelloside I (**2**), 8-epiloganin (**7**), duranterectoside C (**14**), durantoside I (**16**) which were also isolated and identified using spectroscopic means [21-24]. Some of these iridoid glycosides were reported as biologically active compounds with antityrosinase activity such as 5-deoxy pulchelloside (**1**), lamiide (**3**), phlomiol (**5**), lamidoside (**12**), and durantoside I (**16**) [21]. - Caudatosides A-F (**19**-**24**), and 5-deoxypulchelloside I (**1**), were isolated from the fruits of *Citharexylum caudatum* [26]. 5-Deoxypulchelloside I (**1**) was also isolated from the leaves of *C. fruticosum* [27].

3. Biological activities

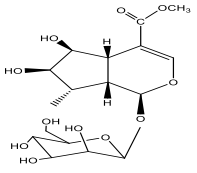
Iridoid glycosides widely exist in plants of many families with a wide variety of biological activities such as sedative, hypotensive, antitussive and antipyretic activities [32]. This review summarizes the pharmacological properties of different Citharexylum species that have high iridoid glycosides content. Iridoids have immuno-modulating, anti-inflammatory, neuroprotective, cardioprotective, hepatoprotective, anticancer, antimicrobial, antioxidant, hypolipidaemic, choleretic, hypoglycaemic, purgative and antispasmodic activities that were revealed by *in vitro* and *in vivo* studies [33].

3.1. Structure-activity relationships

Analysis of molecular similarities is important in drug discovery because it helps to identify new drug candidates based on the functional and/or structural similarity with other drugs [20]. A model of the quantitative structure activity relationships (QSAR) that has an acceptable ability to predict biological activity was designed by López-López et al. [20]. According to the squared regression coefficient, the QSAR model displays the predictive and the descriptive ability of QSAR model. Lamiide (**3**) was the outlier of the correlation prediction, since the polar surface area (PSA) of (**3**) was higher than the PSA value for other similar iridoids.



	R_1	R_2	R_3	R_4
1	H	OH	H	H
2	OH	OH	H	H
3	OH	H	H	OH
4	OH	H	CH_3CO	OH
5	OH	OH	OH	OH



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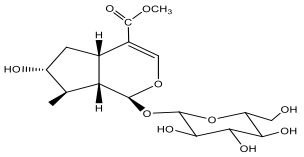

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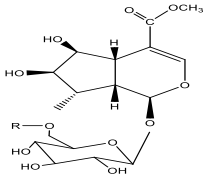
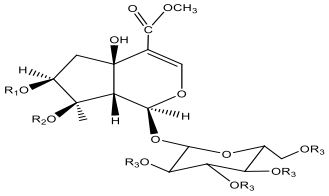
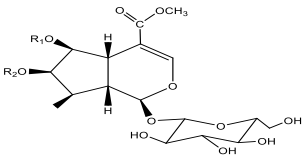


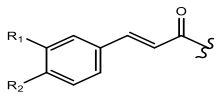
	R
8	Vanilloyl
9	Syringoyl
10	Feruloyl
11	Sinapoyl



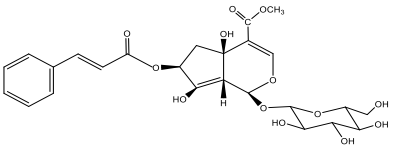
	R_1	R_2	R_3
12	Cou *Z*	H	H
13	Cou *E*	H	H
14	Cin *E*	H	H
15	$CouCH_3$	H	H
16	Cin *Z*	H	H
17	Cin *α*	Ac	H
18	Cin*β*	Ac	Ac



	R_1	R_2
19	Cin *Z*	H
20	H	Cin *Z*
21	Cou *Z*	H
22	H	Cou *Z*
23	Caf *Z*	H
24	H	Caf *Z*



	R_1	R_2
Cin	H	H
Cou	H	OH
Caf	OH	OH



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Cou= Coumaric acid, Cin= Cinnamic acid, Caf= caffeic acid, *Z= trans, E= Cis*

Figure 1. Iridoid glycosides isolated from *Citharexylum* species

Table 1. Iridoid glycosides isolated from *Citharexylum* species

No. of compounds	Compound	Species	Extract/fraction (s)	Organ (s)	Country	References
1	5-Deoxypulchelloside I	*C. fruticosum*	Methanol	Leaves	India	[26]
		C. caudatum	Acetone	Fruits	America	[22]
		C. quadrsangulare	Ethyl acetate	Leaves	Egypt	[11]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
2	Pulchelloside I	*C. spinosum*	*n*-Butanol	Flowers	Tunisia	[24]
3	Lamiide	*C. fruticosum*	Methanol	Leaves	India	[26]
		C. quadrangulare	Methanol	Leaves	Egypt	[21]
		C. quadrangulare	Methanol	Aerial parts	Egypt	[28]
		C. spinosum	Methanol	Aerial parts	Egypt	[23]
		C. quadrangulare	Ethyl acetate	Leaves	Egypt	[11]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
4	Lamiide 7-*β*-*O*-Acetate	*C. spinosum*	Methanol	Aerial parts	Egypt	[23]
5	Phlomiol	*C. fruticosum*	Methanol	Leaves	India	[26]
		C. quadrangulare	Methanol	Leaves	Egypt	[21]
6	Spinomannoside	*C. spinosum*	*n*-Butanol	Flowers	Tunisia	[24]
7	8-Epiloganin	*C. spinosum*	Methanol	Aerial parts	Egypt	[23]
8	Tunispinoside A	*C. spinosum*	Ethyl acetate	Trunk bark	Tunisia	[29]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
9	Tunispinoside B	*C. spinosum*	Ethyl acetate	Trunk bark	Tunisia	[29]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
10	Tunispinoside C	*C. spinosum*	Ethyl acetate	Trunk bark	Tunisia	[29]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
11	Tunispinoside D	*C. spinosum*	Ethyl acetate	Trunk bark	Tunisia	[29]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
12	Lamiidoside	*C. fruticosum*	Methanol	Leaves	India	[26]
		C. quadrangulare	Methanol	Leaves	Egypt	[21]
		C. spinosum	Methanol	Aerial parts	Egypt	[23]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
13	Duranterectoside B	*C. quadrangulare*	Ethyl acetate	Leaves	Egypt	[11]
14	Duranterectoside C	*C. spinosum*	Methanol	Aerial parts	Egypt	[23]
15	Durantoside II	*C. fruticosum*	Methanol	Leaves	India	[26, 30]
16	Durantoside I	*C. fruticosum*	Methanol	Leaves	India	[26, 30]
		C. quadrangulare	Methanol	Leaves	Egypt	[21]
		C. quadrangulare	Ethyl acetate	Leaves	Egypt	[11]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
17	Durantoside I monoacetate	*C. spinosum*	Ethyl acetate	Flowers	Tunisia	[31]
18	Durantoside I tetraacetate	*C. spinosum*	Ethyl acetate	Flowers	Tunisia	[31]
19	Caudatoside A	*C. caudatum*	Acetone	Fruits	America	[22]
20	Caudatoside B	*C. caudatum*	Acetone	Fruits	America	[22]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
21	Caudatoside C	*C. caudatum*	Acetone	Fruits	America	[22]
22	Caudatoside D	*C. caudatum*	Acetone	Fruits	America	[22]
23	Caudatoside E	*C. caudatum*	Acetone	Fruits	America	[22]
		C. spinosum	*n*-Butanol	Flowers	Tunisia	[24]
24	Caudatoside F	*C. caudatum*	Acetone	Fruits	America	[22]
25	Spinoside	*C. spinosum*	Ethyl acetate	Flowers	Tunisia	[31]

Pulchelloside I (**1**) and lamiide (**3**), although they have the same number and type of substituents, the conformation of the glucose increased the area in (**3**). This was noteworthy showed how the iridoids's conformation affected their shape and size, as is noted in the volume, ovality, and area values [20]. The QSAR model indicates the influence of the dipole moment on the activity of the iridoids. The difference of the polar surface area of the iridoids, the solubility of the iridoids in water, and the difference in the polarizability of the iridoid glycosides are relevant for the biological activity [20]. The glycosides of iridoid are generally not doing work directly in the blood. They work in the stomach acid, digestive system enzymes, intestinal membrane enzymes, intestinal bacteria [19]. Chemical structures of some iridoid glucosides commonly found in Verbenaceae are the C4-carboxy-iridoids and C4-decarboxylated iridoids [20]. The compounds change into another structure and then play different biological role [19, 20].

The silyl-tert-butyl diphenylsilyl compound of durantoside I (**16**) analogue has the cinnamate group at carbon 7 were less cytotoxic than the compound devoid of the cinnamate group under the structural comparison of these compounds [34].

3.1.1. Anti-inflammatory and antinociceptive activities

Many different disorders can cause inflammation, such as inflammatory bowel syndrome, Alzheimer's disease, atherosclerosis, and arthritis [19]. Non-steroidal anti-inflammatory drugs like paracetamol, aspirin, ibuprofen and indomethacin along with corticosteroids like prednisone, are commonly used for treatment modalities. Because they are not selective for the cyclooxygenase enzymes linked to inflammation, these may have a variety of adverse effects, and that they may be very expensive. Therefore, the hunt for secure and potent anti-inflammatory compounds derived from natural sources as safe and effective agents is still ongoing research [3].

Many of iridoid glycosides group of these cyclic monoterpenoid phytochemicals possess significant pharmacological and biological activities and are found in a number of folk medicinal plants [35].

These ethnobotanicals have a long history of traditional use due to their use in treatment of inflammation. Osteoarthritis has traditionally been classified as a noninflammatory arthritis and is a much more complex disease with inflammatory mediators released by cartilage. A structurally related compound to 8-*epi*-loganin (**7**), loganin has ameliorated cartilage degeneration and osteoarthritis development in an osteoarthritis mouse model through inhibition of NF-κB activity and pyroptosis in chondrocytes [36].

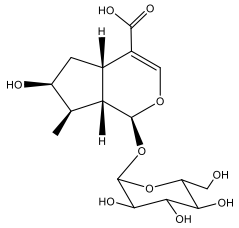
The anti-inflammatory activity of iridoids has been demonstrated by inhibiting TNF-α production in RAW 264.7 cells [37].

The aqueous fraction of *C. quadrangulare* Jacq possessed the most significant anti-inflammatory activity compared with the extracts of petroleum ether, chloroform and ethyl acetate while it was more vigorous than indomethacin reference drug by showing significant decreasing of paw edema [11]. Many iridoid glycosides could exert as inhibitors of oxidative stress, metabolic dysfunctions, inflammatory cytokines *via* regulation of histone acetylation state and cellular redox balance [38-40]. Lamiide (**3**), loganic acid, 8-epi-7-deoxyloganic acid, morroniside are examples of such bioactive iridoids.

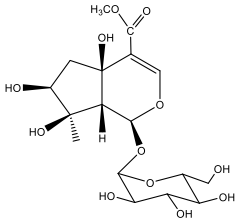
8-Epiloganin (**7**) was isolated from the aerial parts of *C. spinosum* [23] and reported to inhibit the release of pro-inflammatory cytokines induced by lipopolysaccharide in RAW264.7, namely, tumor necrosis factor-α and interleukin-1β. The underlying mechanism of the anti-inflammatory action of that 8-epiloganin is associated with downregulation of nuclear factor-κB [40]. Lamiide (**3**) was estimated for its anti-inflammatory activity in the brain phospholipid and carrageenan-induced paw edema (of rat) assays [41].

Prior to carrageenan injection (30 min) pretreatment of lamiide (**3**, 12.5-100 mg/kg) to rats was demonstrated to reduce the paw edema volume dose-dependently. It deduced the paw edema volume by 78 and 64% comparing to the control group (at 100 and 50 mg/kg), respectively. ED_{50} value was 62.3±0.2 mg/kg. In the rat brain phospholipid assay, lamiide (**3**) demonstrated phospholipid peroxidation inhibition (IC_{50} of 0.93 ± 0.01 mM). Lamiide (**3**) may exert its anti-inflammatory effect through its antioxidant activity *via* scavenging free radicals from the lipid membrane [41]. Lamiide (**3**) inhibited soybean 5-lipoxygenase *in vitro* [20].

The anti-inflammatory activity of twelve iridoid glucosides including lamiide (**3**) in carrageenan-induced mouse paw edema and the induced mouse ear edema by their tissue plasminogen activity (TPA) evaluated by Recio et al. [43]. Of many iridoid glucosides such as lamiide (**3**) and loganic acid showed anti-inflammatory activity in the models of mouse ear edema induced by TPA and mouse paw edema induced by carrageenan models. The authors hypothesized that a double bond (between C-8 and C-7, ethylene group) in the iridoid glucoside structure has an important role on anti-inflammatory activity [43].



Loganic acid

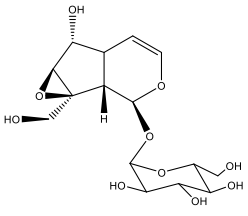


Lamiide **(3)**

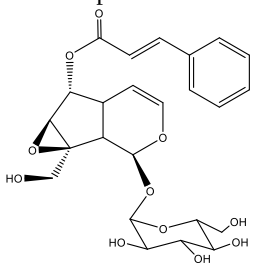
Lamiide (**3**) has the capacity to prevent membrane lipid peroxidation at IC_{50} value of 0.929± 0.01 mM, and it inhibited phospholipid peroxidation. It is well-known that the incubation of phospholipids with Fe^{+2} (at 37 °C), they naturally undergo non-enzymatic oxidation. The inhibition percentage of lamiide (**3**) was 71 and 57% inhibition at 1.40 and 1.20 mM, respectively. The value of Trolox C, used as the positive control, was 45% (100 µM). Through the presence of lamiide (**3**) with its free radical scavenging activity, the anti-inflammatory properties could be related to its presence [41]. The potential application of iridoid glycosides as organically produced medications for illnesses associated with inflammation has been highlighted by many studies [14, 40].

3.1.2. Structure-activity relationships as anti-inflammatory agents

Several structure-activity relationships were deduced from many studies on the iridoid glycosides as anti-inflammatory agents [41, 43]. The iridoids capacity to inhibit inflammatory responses depends on the existence of a hydroxyl group in position C-10 of the iridoid skeleton and an electron-withdrawing group in position 11 (C=O) [44]. These compounds might enhance the reduction of pro-inflammatory mediators like chemokines, cytokines, reactive oxygen species (ROS), and prostaglandins [44, 45]. The anti-inflammatory activity of the iridoid glycoside catalpol has increased by cinnamoyl group substitution at position six of the parent molecule



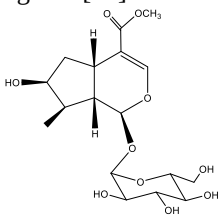
Catalpol



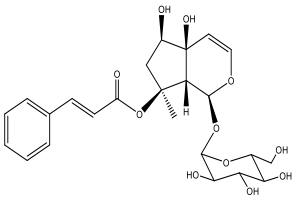
6-*O*-Cinnamoyl catalpol

The anti-inflammatory benefits of iridoids are linked to their antioxidant properties [46]. These characteristics have the ability to shield tissues and cells from oxidative stress and inflammation-induced apoptosis. The iridoids structure may have an impact on their capacity to treat inflammation. Iridoids can protect the cells from harm and modulate the inflammatory response due to their structure. Future investigations prior to developing iridoids were suggested as medicinal substances to treat illnesses associated with inflammation [45].

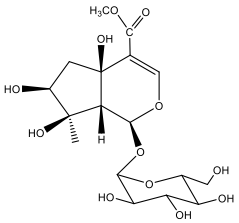
The topical activity decreases if a hydroxyl function is introduced. Hence lamiide (**3**) and harpagoside are less effective topically than the iridoid glycoside loganin [43].



Loganin



Harpagoside

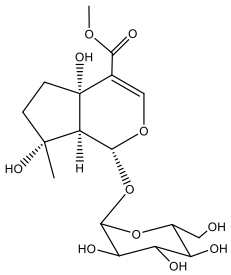


Lamiide (**3**)

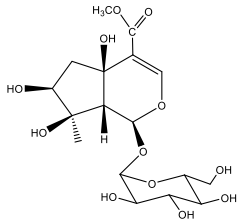
The topical activity increases with the conversion of a -COOH moiety to its -COOMe analogue. The hydroxyl substitution at C-5, methyl substitution of carboxyl C-11, and unsaturation at C-7/C-8 (ethylene group) are the other positive characteristics for topical activity. The ethylene group between C-8 and C-7 is the most positive characteristic for anti-inflammatory activity [43].

However, harpagoside and lamiide (**3**) are less effective - than loganin, - both compounds displayed significant anti-inflammatory activity at 10 mg/kg in acetic acid-induced writhing test [4]. Lamiide (**3**) which is devoid of the C_7-OH group was reported to possess dose-dependent anti-inflammatory activity against carrageenan-induced oedema. Certain iridoid glycosides could significantly inhibit cyclooxygenase-2 (COX-2) activity and its chemical structure was comparable to PGE2 and other selective COX-2 inhibitors, like celecoxib [47]. These substances possess two adjacent side-chains

with a pentanomic ring and the similarity may cause the binding to the COX-2 enzyme and also they showed marginal inhibition activity against macrophages respiratory burst [47]. The iridoid ipolamiide, a structurally related compound to lamiide (**3**) which is devoid of the C_7-OH group, possess dose-dependent anti-inflammatory activity (79%) towards carrageenan-induced oedema under comparable experimental conditions and dosage levels [41] Ipolamiide selectively inhibits neutrophil influx and inhibits total leukocyte accumulation 24 h after the intrathoracic injection of carrageenan. Ipolamiide was isolated from the ethanolic extract of *Stachytarpheta cayennensis* leaves (Verbenaceae) [41].



Ipolamiide



Lamiide (**3**)

3.2. Antioxidant activity

Antioxidants are defined as the substances that are present at low concentrations compared to those of an oxidizable substrate which significantly delays or prevents oxidation of that substrate, in the biological systems [48]. Researchers have looked into the potential of antioxidants to prevent diseases like Alzheimer's disease, cancer, cataracts, and rheumatoid arthritis, stroke. Preservation of food and cosmetics are examples of uses of antioxidants in the industry [48].

Khan and Siddique [49] evaluated the antioxidant activity of *C. spinosum* leaves chloroform extract in rats (at the doses of 100 and 200 mg/kg). The activity level of antioxidant enzymes and non-enzymatic antioxidant glutathione (GSH) contents were increased while lipid peroxidation (TBARS) was decreased, dose dependently with chloroform extract. In addition, the decrease in body and increase in kidney weight induced with CCl_4 was restored with chloroform etract of *C. spinosum*.

Barizão et al. [8] determined the antioxidant capacity of *C. solanaceum* different parts of fruits (seed and pulp + skin ethanol extracts). Both ethanol extracts showed scavenging capacity for the reactive nitrogen species (RNS) and ROS however, the scavenging capacity for the RNS was higher than for the ROS. Ajaib et al. [50] analysed the antioxidant activity of *C. spinosum* different parts by using techniques including; 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) free radical scavenging activity, metal chelating activity and 2,2'-azino-*bis*(3-ethylbenzothiazoline-6-sulfonic acid. The pancreatic lipase and antioxidant parameters were strongly influenced by total content iridoids [51].

Iridoids exhibited many physiological and biological activities [31]. They were identified in *C. solanaceum*. The lamiide (**3**) showed moderate antioxidant activity using ferric reducing antioxidant power [42].

3.2.1. Structure-activity relationships as antioxidant agents

Duranterectoside B (**13**) and duranterectoside C (**14**) are examples of such iridoid glycosides class isolated from *C. spinosum* (aerial parts and flowers) [11, 23]. Duraterectoside A, lamiidoside (**12**), and durantoside II (**15**) are examples of the main reported iridoid glycosides with antioxidant activities [52]. The iridoid glycosides, duranterectosides A, - B (**13**), -C (**14**), and -D, along with durantosides I (**16**) and II (**15**), and lamiidoside (**12**) were also evaluated for their antioxidant activities. All the investigated iridoid glycosides showed potent antioxidative scavenging activity by four different methods [52]. The half maximal inhibitory concentration values in the range 17.21-4.07 µM for the $^{\bullet}OH$ radical inhibitory activity test, 0.719-0.481 mM against DPPH radicals, 18.94-3.39 µM in the peroxynitrite ($ONOO^{-}$) scavenging activity test, and 97.37-43.3 µM in the total ROS inhibitory activity test [52]. Duranterectoside reported the strongest scavenging potential with IC_{50} values of; 3.39 ± 0.02 µM, 43.30 ± 0.05, 4.07 ± 0.03, 0.481 ± 0.06 mM for the $ONOO^{-}$ scavenging activity test, total ROS inhibitory activity, hydroxyl radical ($^{\bullet}OH$) inhibitory activity test, and the DPPH radicals, respectively.

3.3. Antimicrobial activity

Flower essential oil and extracts of *C. spinosum* exhibited antioxidant and antibacterial activities [10, 53, 54].). *C. spinosum* L. is ornamental shrub used as antimicrobial and for the treatment of asthma [55]. This plant had some biological isolated compounds, such as 5-deoxypulchelloside (**1**), 8-epiloganin (**7**), lamiidoside (**12**), and duranterectoside C (**14**) [21, 23, 55]. Patra [35] has reported the antimicrobial

properties of different classes of phytochemicals including the iridoids. Different parts of *C. spinosum* were evaluated for their antimicrobial potential by agar well diffusion method [50]. The maximum antibacterial effect was exhibited by methanol bark extract (44.5 ± 0.5 mm) against *Staphylococcus aureus*. The chloroform extract of leaves reported minimum activity (10.5 ± 0.5 mm).

El Ayeb-Zakhama et al. [56] evaluated the antifungal activity of *C. quadrangulare* Jacq. The organic and aqueous extracts can be considered as antifungal against the fungal diseases of crops [56]. Kamal et al. [57] determined the antimicrobial activity of *C. spinosum* extracts (80% aqueous, methanol and chloroform). The authors mentioned that both antifungal and antibacterial activity of *C. spinosum* leaf and bark extract was estimated by poisoned food technique and agar well diffusion [58] where, leaf extract showed remarkable antibacterial activity than bark extract. The *n*-hexane oily extract (HeOE) from *C. spinosum* wood and chloroform leaf extract of *C. spinosum* was assayed for its antibacterial activity by using minimum inhibitory concentration (MIC) and inhibition zones [27, 59]. The HeOE showed an inhibition zone value of 10 mm against the growth of *Pectobacterium carotovorum* subsp. *carotovorum* at 4000 µg/ml [27]. While *C. spinosum* chloroform extract showed the highest activity against *Escherichia coli* (10.6±0. 58 mm) and *Pectobacterium atrosepticum* (13.6±0. 58 mm) [59]. At a low concentration (8 µg/ml) of the methanolic extract of *C. spinosum* wood showed a powerful inhibition against the endophytic fungus *Paecilomyces variotii* growth [60].

Several Verbenoideae have durantosides (**15** and **16**), lamiide (**3**) and/or ipolamiide as common content and attributed to the activities of many species of Verbenaceae plants such as *Clerodendrum inerme, Gmelina arborea, Gmelina philippensis, Holmskioldia sanguinea, Lantana camara, Nyctanthes arbortristis, Premna odorata, Premna japonica*, and *Stachytarpheta urticaefolia*. Five active antimicrobial iridoid glycosides such as 5-deoxy pulchelloside (**1**), lamiide (**3**), phlomiol (**5**), lamidoside (**12**), and durantoside I (**16**) are isolated from *Citharexylum quadrangular*e. The antibacterial iridoid glucosides, pulchelloside I (**2**) and phlomiol (**5**) exhibited moderate antibacterial activity [61]. Pulchelloside I (**2**) displayed antibacterial activity against nine of twelve different strains tested and was the most active iridoid glycosides [61]. Moreover, the most noteworthy antimicrobial activity of compound (**2**) was against penicillin-resistant *E. coli*, *Bacillus cereus*, *Staphylococcus aureus* and *Proteus mirabilis* with an MIC value of 0.05 mg/ml.

3.4. Anti-schistosomal activity

The parasitic disease bilharzia, snail fever, or human schistosomiasis is brought on the infection by the worm belong to *Schistosoma* genus [62]. Snails of freshwater release parasites in water due to the infection with different species of *Schistosoma* and the contamination of water in bathing or drinking, these parasites colonize in human blood vessels after entering the human body [62]. The most common symptoms of this infection are bloody stool, blood in urine, fever, diarrhea, gland enlargement, and abdominal pain. Prolonged infections causes kidney failure and liver damage. Only praziquantel, the isoquinolinone drug, is widely used for treatment of this dangerous disease [62]. Previous studies have been performed to find effective compounds from of *C. quadrangulare* that can suppress the infection of *S. mansoni* [63, 64]. El-Naggar [53] illustrated the possible mechanism for anti-schistosomal effect of *C. quadrangulare* extract by its content of active constituents that may directly affect the schistosomal vitality at different stages and the adult female worms.

Iridoids have been reported to have an effective molluscicidal activity [65]. They exhibited strong activity against *Lymnaea natalensis*, *Biomphalaria pfeifferi, Bulinus rohlfsii*, and *B. globusus*, the species of fresh water snails, with range of 1.3-5.3 mg/l for the LD_{90} values. *B. rohlfsii* and *B. globusus* were the intermediate hosts of *S. haematobium* [62]. In addition, iridoids showed moderate molluscicidal activity against *Bulinus africanus* snails [66].

3.5. Cytotoxic and anticancer activity

The therapeutic potentials of iridoid glycosides against cancer have been highlighted by different studies [20, 67]. The roles of these compounds at each stage of cancer development, such as epithelial mesenchymal transition, proliferation, invasion, angiogenesis, and migration were reported. The exploration of iridoid glycosides as anticancer agents represents evolving and dynamic field within tumour research [20]. While challenges exist, the multifaceted pharmacological activities of iridoid glycosides make them promising candidates for potential development into therapeutics of cancer and further investigation. The cytotoxicity of lamiide (**3**) against HepG-2 and Ca co2 cancer cells indicated a low cytotoxicity (IC_{50} values of < 100 µg/ml) [20]. To lamiide (**3**), two structurally related compounds, the iridoid glycosides ipolamiide and β-hydroxyipolamiide were investigated for their anti-angiogenic effects. The effect was confirmed in chick chorioallantoic membrane and zebrafish embryo assays [67]. This is a supporting evidence for the

potential of these compounds to inhibit tumor angiogenesis [67].

Phlomiol (**5**) was isolated from the methanol extract of leaves *C. fruticosum* collected from India [26] and from *C. quadrangulare* collected from Egypt [21]. The antitumor effect (*in vivo* and *in vitro* study) of phlomiol (**5**) on H22 and S180 human tumour cells proliferation was evaluated [26, 68]. Mice were administered various doses of phlomiol (**5**) for 14 days after transplantation with dose-dependent manner of activity ($P < 0.05$, r = 0.989). Inhibition of the proliferation was exerted by phlomiol (**5**, 100-50 $mg.L^{-1}$) against the investigated tumour cells. The activity of this compound (10, 5, 2.5 $mg.kg^{-1}$) were 74.5%-35.0 % and 65.0%-28.5% with H22 and S180 respectively. The activity of phlomiol (**5**) could relate to inhibition of proliferation as well as enhancing the function of immune system.

The antitumor activity of phlomiol (**5**) was confirmed by the study of Xie et al. [68].

Durantoside I (**16**) was obtained from the dried leaves and flowers of *C. spinosum*. Apisornopas et al. [69] estimated the cytotoxicity against several cancer cell lines of synthesized iridoid glycoside derivatives from durantoside I (**16**). The derivatives synthesis was carried out through modifying a sugar moiety by acetylation or silylation and/or the removal of cinnamate group at C-7 position. The results showed the removal of cinnamate group or addition of alkylsilane to durantoside I (**16)** improved anticancer effects more than those of the natural parent compound did [69].

Saidi et al. [21] investigated the anticancer properties of the iridoid glycosides (tunispinosides A-D; **8-11**) isolated from *C. spinosum*. The cytotoxic results revealed that, these compounds encouraged a cytotoxic effect against HeLa cells. In addition, they possessed cytotoxic property towards the human lung cancer (A549) cell line with IC_{50} values; 188.23 ± 3.88 and 197.00 ± 4.25 µg/ml, respectively. All investigated compounds exhibited weak toxicity against L929 cell line (IC_{50} > 500 µM). Moreover, the biological estimations exhibited the cytotoxic effects of iridoid glycosides towards HeLa with IC_{50} values 25.00 ± 1.00 µM, [29].

The values of IC_{50} (µM) against cervical cancer HeLa cells were 25.22, 31.96, 38.89, and 42.47 for the iridoid glycosides of pulchelloside (**2**), lamiide (**3**), spinomannoside (**6**) and 5-deoxypulchelloside (**1**), respectively [20]. However, these iridoid glycosides have a similar cytotoxic activity against the HeLa cell line.

Tenfen et al. [12] evaluated the cytotoxic effects of *C. myrianthum* Cham leaves. The potential cytotoxic effects of different extracts of *C. myrianthum* Cham were reported. The methanolic and dichloromethane fraction reduced cell viability of the two cancer cell lines (colorectal adenocarcinoma and non-small lung cancer cells). The authors added that, the effect of 100 $\mu g.ml^{-1}$ concentration reduced 50% of cell viability in both cancer cell lines.

3.6. Hepatoprotective activity

Khalifa et al. [21] mentioned the hepatoprotective effect of *C. quadrangulare*. The aqueous ethanolic (70%) extract at concentration of 20 and 40 mg exhibited hepatoprotective activity. Bioactive natural products with antioxidant activities can ameliorate or reduce inflammatory changes following an acute liver injury and showed cytokine expressions in the hepatic tissue of the treated mice [70, 71]. The hepatoprotective role of iridoid fractions from different plants belong to Verbenaceae against alpha-amanitin or CCl_4 induced fibrosis in rats was tested [72].

The fraction containing pulchelloside (**2**) prevented the manifestation of the hepatotoxic effect of CCl_4. The fraction rather quickly eliminated developing intoxication effect. This activity as hepatoprotective was confirmed to be effective and exceeds the known drug carsil [72].

Lamiide (**3**) and ipolamiide (devoid of –OH group of lamiide) are chemically of related structures of simple C-10 iridoid glycosides in *Citharexylum* species [20]. The two iridoid glycosides could ameliorate liver injury by decreasing oxidative damage and inhibiting the production of proinflammatory kinases and other were having hepatoprotective activity against the damage induced in HepG2 cells by ethanol [2]. The suggested mechanism of iridoid glycosides activity was the suppression of the pathways of STAT3 and NF-κB signalling [73]. The treatment of mice by iridoid glycosides reduced the level of liver enzymes (alanine aminotransferase, aspartate aminotransferase), TNF-α, malondialdehyde formation and expression of pro-inflammatory factors, as well as elevated superoxide dismutase and glutathione activity in the liver following an acute liver injury [74].

3.7. Nephroprotective activity

Nephropathy is rising from the exposure of kidneys to oxidative stress [38, 75]. Natural products with antioxidant activities can ameliorate the oxidative damage-induced nephrotoxicity by stimulation the signaling pathway of the nuclear factor erythroid 2-related factor 2 and suppressing oxidative stress [75, 76].

Khan and Siddique [49] suggested that methanol and chloroform extracts of *C. spinosum* have significant

nephroprotective properties by restoring the concentration of serum and urine markers in rats. Iridoids are lipophilic compounds [1, 77].

3.8. Neurprotective activity

They considered as prospective avenues for neurodegenerative disease treatment and have properties of endogenous neurotrophic factors.

8-*epi*-Loganin (**7**) was isolated from the flowers and aerial parts of *C. spinosum* [23]. Habtemariam [77] has demonstrated the important role of glucagon-like peptide 1 receptor (GLP-1R) and insulin-like growth factor 1 receptor (IGF-1R) in the mechanisms of neuroprotection role of iridoid glycosides. The author reported the protective effects of them against Parkinson's disease mimetic toxin 1-methyl-4-phenylpyridinium (MPP^+). An enhancement of the neurotrophic signals expression through up regulating the expressions of IGF-1R, GLP-1R, p-Akt and tyrosine hydroxylase. To reduce MPP^+-induced neuron damage, it can up-regulate GAP43, down-regulate membrane-rhoA/ROCK2/p-LIMK/p-cofilin and reduce the production of MPP^+-induced ROS. The experiment of Tseng et al. [78] showed that, iridoids could activate IGF-1R/GLP-1R, enhance neurotrophic signals, alleviate MPP^+ induced death and apoptosis, and inhibit RhoA/ROCK pathway neuron damage, and other mechanisms to achieve neuroprotective effect.

3.9. Antispasmodic and muscle relaxation activity

Kotapati et al. [79] estimated the methanolic extract of *C. serratum* leaves for its muscle relaxation and anxiolytic activity. The methanolic extract exhibited significant anxiolytic and muscle relaxation activity in all the employed experimental models when compared with standard treatment group [79].

On isolated guinea pig ileum, the iridoid loganin showed moderate relaxant activity by inhibiting the electrically induced contraction in a dose-dependent manner (with ED_{50} value of 100 µM) [80]. This inhibition happened 2-4 minutes after the compound was administered, and it lasted for 15 minutes. Iridoids exhibit their spasmolytic and relaxant effects by interaction with *β*-adrenergic system [14]. The main purpose of these compounds is as bronchodilators in pulmonary disorders and treatment of asthma. Thus, iridoids may be effective in treatment of asthma and menstrual disorders [14].

Smooth muscle-relaxant, spasmolytic or antispasmodic activity of the drugs are effective to suppress the muscle spasms of uterine, intestine, stomach, and other tissues to ameliorate disorders of menstrual, and bronchial as well as intestinal motility impairment [81]. Antispasmodic drugs act as antihistaminic, calcium antagonists, anti-*α*-adrenergic and anticholinergic agents for their spasmolytic activities. Through up-regulation of T-type calcium channels, iridoid glycosides were reported as new class of antispasmodic agents have been developed to improve colonic motility [14].

3.10. Antidiabetic activity

Mohammed et al. [11] found that, the ethyl acetate fraction of *C. spinosum* exhibited a significant hypoglycemic effect on hyperglycemic alloxaned rats where, it decreased the elevated level of glucose to 219 mg/dl. 8-*epi*-Loganin (**7**) was isolated from the aerial parts of *C. spinosum* [23]. A structurally related iridoid glycoside loganin decreased inflammation in type 2 diabetic db/db mice and renal and hepatic glucolipotoxicity [82, 83]. The compound showed good impact on anxiety- and depression-like behaviors and pro-inflammatory cytokines in male diabetic rats. The positive effect of this compound on antioxidant enzymes is most probably due to the well-known antioxidant, which scavenges the free radicals generated during diabetes [82].

The iridoid glycosides such as morroniside and loganin have effectively reduced hyperglycemia and had an impact on the accumulation of renal advanced glycation end-product including *N*ε-(carboxymethyl)lysine and *N*ε-(carboxyethyl)lysine [84]. Anti-diabetic effect of iridoid glycosides might achieve by inhibiting the phosphorylase of glycogen [85]. Harpagoside-B and scropolioside-D2 have been reported to exhibit hypoglycemic activity in fasting, normal, and alloxanized rats [84, 85]. Iridoid glycosides can improve the hyperglycemia and hyperlipidemia of high-fat diet-streptozotocin-induced diabetic mice through the phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt/PKB) signaling pathway, thereforetiridoid glycosides might be a potential medicine or functional food for type 2 diabetes mellitus remedies [86]. Aucubin is like all iridoids, has a cyclopentan-[C]-pyran skeleton and is a monoterpenoid based compound [84]. Presence of cyclopentanepyran rings in the structure of loganin, morroniside, and loganic acid categorizes them under iridoid class. This class exhibited protective effects against diabetic complications associated with inflammation caused by oxidative stress, advanced glycation end product formation and abnormal metabolic states [82]. Oxidative stress, dyslipidemia and hyperglycemia were ameliorated in both the hepatic and serum tissue. This effect was produced through augmentation of the oxidized to decreased glutathione ratio (kidney and liver), ROS (kidney, liver, and serum), as well as a decrease in thiobarbituric acid-reactive substances (kidney and liver).

A structurally related iridoid glycosides exhibited significant antidiabetic activity with range of EC_{50} values of 2.54-70.43 µM. Iridoid glycosides successfully decreased the hyperglycemic state and affected renal advanced glycation end-product (AGE) accumulation, such as N(epsilon)-(carboxyethyl)lysine and N(epsilon)-(carboxymethyl)lysine, while low molecular weight polyphenol fractions could reduce renal lipid peroxidation, the receptor for AGE, and inducible nitric oxide synthase. [84]. The iridoid glycosides have anti-diabetic effect by inhibiting the phosphorylase of glycogen and play an important role in preventing and/or postponing the occurrence of diabetic kidney disease, according to the previous studies [86]. 8-*epi*-Loganin (**7**) isolated from *C. spinosum* is structurally related to loganin which has been reported to exert a potent lipid-regulatory effect in the liver of type 2 diabetic mice by adjusting lipid metabolism associated genes [82].

3.11. Antiallergic activity

Numerous prevalent allergic diseases like bronchial asthma, anaphylaxis, allergic rhinitis, chronic urticaria, hypersensitivity pneumonitis and atopic and contact dermatitis, are developed from both genetic and environmental factors [14].

The aerial parts of *C. spinosum* L (methanol extract) possessed antiallergic properties [87]. The methanol extract have reported to exhibit antiallergic activity by inhibition of *β*-hexosaminidase enzyme production without affecting the viability of cell. The iridoid aucubin is used in the alleviation of chronic allergic inflammatory disease. Loganin, catalpol, and secoxyloganin, that having occupied at C-8 with sp(3) atom, were showed an allergy-preventive effect. While other iridoids having a double bond at C-8 and C-7 such as geniposide, asperuloside, and aucubin did not show any allergy-preventive activity [11, 21].

Iridoid glycosides exhibited their anti-allergic activity *via* inhibiting mast cells and passive cutaneous anaphylaxis degranulation in rats. Disodium cromoglycate was used as positive control to compare their activities [88].

Iridoid glucosides were used in traditional medicine for treatment of asthma, cough, and bronchitis [89].

3.12. Immunomodultory activity

Citharexylum species such as *C. spinosum* and *C. caudatum* contain many types of iridoids [22, 29]. The iridoid-rich extract fraction has been discovered to be immunostimulant at both the humoral and cellular levels [1]. An iridoid mixture from *C. quadrangulare* leaves inhibited serine proteinase and elastase activity with percentage of 31% at a concentration 15 µg [28]. An immunomodulatory effect of the mixtures; iridoid glycosides and iridoid glycosides-treated *S. mansoni* worm homogenate was evaluated by measuring the levels of immunoglobulin G (IgG) and immunoglobulin M (IgM) against *E. coli* lysates (ECL), solube *S. mansoni* worm antigenic preparation and cancer bladder homogenates as antigens by ELISA [90]. Immunizations with iridoid mixture treated homogenate resulted in significantly elevated ($P < 0.05$) IgM and IgG levels against the 3 used antigens in comparison with sera from control mice.

Loganin, the strucrully related to the isolated compound 8-*epi*-Loganin (**7**) from *C. spinosum* (aerial parts and flowers) [23], was one of the main iridoid that showed significant improvement effects on depression [91].

Ghisalberti [92] hypothesized that, iridoid glycoside can be best regarded as pro-drugs as immunomodulators and adaptogens. Abd-Alla et al. [93] suggested that iridoid glycosides ameleorated anxiety and depression-like behaviour in line with what was described by adaptogens and immunomodulators.

3.13. Antityrosinase and anticholinesterase activity

Anticholinesterase (AChE) is one of the targets of most of the clinically used drugs for the treatment of dementia [94]. The enzyme AChE is the key enzyme in the hydrolysis of the neurotransmitter acetylcholine and is also the target of most of the clinically used drugs for the treatment of Al-zheimer disease [19]. A previous study evaluated the anti-cholinesterase activity of *C. spinosum* leaves as well as the determination of the antioxidant and anti-inflammatory [95]. The investigations of Saidi et al. [21, 24] revealed the isolation of many compounds from *C. spinosum* included tunispinosides A-D (**19**-**22**) with antityrosinase activity at a concentration of 100 µM. *C. spinosum* exhibited antityrosinase properties [21]. The authors estimated these properties by using the extracts of flowers and trunk bark of the plant along with many isolated compounds. The ethyl acetate extract of the trunk bark demonstrated the highest antityrosinase activity at a concentration of 100µg/ml (55.0±1.8 %). While the same extract revealed highest AChE effect at IC_{50} value of 99.97±3.01 µg/ml [21]. In addition, the iridoid glycosides (**1**, **2**, **3**, **6**, **12**, **16**, **20** and **23**) had a significant anticholinesterase activity with IC_{50} values ranged from 17.19 ± 1.02 to 52.24 ± 2.50 µM [21]. Some hydrophilic and polar secondary metabolites of *C. spinosum* have a strong tyrosinase inhibitory potential [21].

The iridoid glycosides *viz*. 5-deoxypulchelloside I (**1**), pulchelloside I (**2**), lamiide (**3**), 7-*β*-*O*-acetyl lamiide (**4**), phlomiol (**5**), spinomannoside (**6**), 8-*epi*-loganin (**7**), lamidoside (**12**), duranterectoside B (**13**), duranterectoside C (**14**), durantoside I (**16**) and caudatosides B (**20**) and E (**23**) as well as spinoside (**25**) are examples of such iridoids class isolated from *C. spinosum* (aerial parts and flowers) [11, 23, 24, 31, 57]. The findings of Saidi et al. [21] mentioned that, the antityrosinase activity of isolated iridoids from *C. spinosum* relied on the position and nature of phenylpropanoid moiety on the iridoid aglycone, which have potential effects.

4. Application of plants with high content of iridoid glycosides

An iridoid glycosides-rich fraction, has the two iridoids pulchelloside (**2**) and phlomiol (**5**) as main constituents, was investigated for its anti-inflammatory activity [97]. The treatment with this fraction and piroxicam ointments (after 14 days of treatment) showed that all groups reported significant improvement comparing to control groups. The ointment of iridoid glycosides fraction (5%) motified better initial therapeutic effect than piroxicam ointment (5%). The fraction was suitable for topical applications as effective and a secure adjunctive treatment for inflammatory diseases, as established by this clinical trial [97].

5. Further search and future perspective

A comprehensive search of the literature on iridoid glycosides was carried out regarding *Citharexylum* genus using scientific databases like Scifinder, Scopus, Pubmed, Science-direct, Google Scholar and Google as well as the ethnobotanical textbooks. Search papers that contain iridoid glycosides in *Citharexylum* genus, iridoids of species in the genus *Citharexylum* were used. The search still limited to publications accessible online from 1983 to 2024.

Despite the achievements in the phytochemical studies of *Citharexylum* genus, there are some unclarified notifications as following:

Firstly, *Citharexylum* species are vastly used in folk medicine in many countries. However, more attention should be paid to the iridoids content of this genus due to its limitless medicinal properties.

Secondly, although *Citharexylum* genus includes about 105 species, literature mentioned the iridoid glycosides content of few species such as *C. spinosum*, *C. solanumaceum* and *C. caudatum*.

Thirdly, the chemical classes of iridoid glycosides are vastly distributed in different *Citharexylum* species. Their chemical classes that seek more studies are also obvious.

By using bioactivity guided isolation strategies, it may be possible that more biologically active iridoid glycosides could be identified.

Fourthly, the most common use of *Citharexylum* is as anti-inflammatory, antioxidant and antimicrobial agents. However, further *in vivo* investigations should be carried out to evaluate this genus and address this research gap.

Fifthly, lamiide (**3**) and its acetate form; 7-*ß*-*O*-acetate (**4**) of lamiide as well as lamiidoside (**12**) have been isolated from *Citharexylum* species. Additionally, the chemical structure *of* lamiide type iridoid glycoside is unique to *Citharexylum* and the iridoid glycosides are famous for their valuable pharmacological activities. Thus, more studies are needed for precise the identification and isolation of further lamiide-type iridoids by in-depth exploration techniques.

Sixthly, the presented data in this review state all the reported pharmacological and phytochemical studies and extensively focus only on some classes of iridoid glycosides in certain species, mainly the *C. spinosum*. However, the majority of iridoid glycosides contents of *Citharexylum* species still need more extensive future investigation.

The metabolites of iridoid glycosides are characteristic of the Citharexylum botanical genus and the Verbenaceae botanical family and are characterized by their anti-inflammatory and antioxidant activities. These metabolites present anti-inflammatory activity that may be beneficial in the treatment of inflammation and play a role as antioxidants, as proven *in vivo* through metabolomic approaches. The potential therapeutic applications of *Citharexylum* species for infectious lesions and skin inflammations caused by allergic reactions were still need further investigation.

6. Conclusions

The present review gives a good- resolution picture about the iridoid glycosides content of *Citharexylum* genus, the most studied species, iridoid glycosides as the main active compounds and their reported biological properties. Anti-inflammatory and antioxidant effects of *Citharexylum* species as well as their ability to improve inflammatory-related diseases (*i.e.* cancer, diabetes, hepatic disorder, etc.) are the main biological properties demonstrated which are proposed to be related to the iridoids content. Due to the significant functionality of iridoids content, the incorporation of *Citharexylum* extracts and /or the bioactive iridoids into natural-based drugs is a promising practice for nutraceuticals development. In addition, the current review produces suggestions for some iridoids of *Citharexylum* species that need more pharmacological, phytochemical investigations and

more stringent studies focusing on the safety, efficacy and mechanism of action of these compounds.

There is still limited research on the toxicological profiles and pharmacokinetics, although iridoid glycosides have shown promising pharmacological activities. Additionally, there is a deficiency in uniformity concerning the genus *Citharexylum* sources of these iridoid glycosides because of several factors, including plant species, geographical location, harvesting time, and isolation technique. Several iridoid glycosides have good availability as synthetic compounds by the aid of commercial pharmaceutical companies, which have contributed to the growth of research. This was evident by decreasing the time needed for a lengthy and difficult extraction process.

Recent research has led to recommendations for increased use of iridoid glycosides-containing plants in inflammation-related diseases, especially in arthritis. This recommendation relies on their iridoid glycosides content. To fully understand the underlying molecular mechanisms of iridoid glycosides and determine their pharmacological safety profile, more research is required. This will help develop iridoid glycosides as a therapeutic alternative agent against diseases related to inflammation and oxidation-related diseases.

The collected data mentioned more than 70% of iridoids from Verbenaceae were identified and isolated from *C. spinosum*. The activities against many diseases especially the inflammation for iridoids were reported. The glycosides of C-9 iridoids are classified as the major class that represents more than 80% of all iridoids. Future investigations are suggested regarding the structure activity relationship of iridoids, their molecular mechanism of action, toxicity, effective doses and clinical effects to promote the iridoids usage from *Citharexylum* as a new source of therapeutic medications.

7. Conflicts of interest

There are no conflicts to declare.

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