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Therapeutic potentials of iridoids derived from Rubiaceae against in vitro and in vivo inflammation: A scoping review

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ABSTRACT

Acute inflammation may develop into chronic, life-threatening inflammation-related diseases if left untreated or if there are persistent triggering factors. Cancer, diabetes mellitus, stroke, cardiovascular diseases, and neurodegenerative disorders are some of the inflammation-related diseases affecting millions of people worldwide. Despite that, conventional medical therapy such as non-steroidal anti-inflammatory drugs (NSAIDs) is associated with serious adverse effects; hence, there is an urgent need for a newer and safer therapeutic alternative from natural sources. Iridoids are naturally occurring heterocyclic monoterpenoids commonly found in Rubiaceae plants. Plant extracts from the Rubiaceae family were demonstrated to have medicinal benefits against neurodegeneration, inflammation, oxidative stress, hyperglycaemia, and cancer. However, the therapeutic effects of natural iridoids derived from Rubiaceae as well as their prospective impacts on inflammation in vitro and in vivo have not been thoroughly explored. The databases of PubMed, Scopus, and Web of Science were searched for pertinent articles in accordance with PRISMA-ScR guidelines. A total of 31 pertinent articles from in vitro and in vivo studies on the anti-inflammatory potentials of iridoids from Rubiaceae were identified. According to current research, genipin, geniposide, and monotropein are the most researched iridoids from Rubiaceae that reduce inflammation. These iridoids primarily act by attenuating inflammatory cytokines and mediators via inhibition of the NF-κB signalling pathway in various disease models. A comprehensive overview of the current research on the anti-inflammatory properties of iridoids from the Rubiaceae family is presented in this review, highlighting the characteristics of the experimental models used as well as the mechanisms of action of these iridoids. To develop an alternative therapeutic agent from iridoids, more studies are needed to elucidate the effects and mechanism of action of iridoids in a wide variety of experimental models as well as in clinical studies pertaining to inflammation-related diseases.

1. Introduction

Inflammation plays a critical role in the pathogenesis of various metabolic and degenerative disorders, including hypertension, stroke, diabetes, cardiovascular disease, neurodegeneration, and cancer. It is suggested that chronic stress can promote persistent inflammation by activating various biomarkers related to stress and inflammation (Liu et al., 2017). These chronic stress and inflammation-related disorders pose substantial hazards to human health, with high morbidity and mortality rates. Diabetes, a chronic condition characterised by increased insulin resistance and hyperglycaemia, is the seventh greatest cause of mortality in the United States (American Diabetes Association, 2022). In addition, the World Stroke Organisation reported 12.2 million new stroke cases per year (World Stroke Organisation, 2022), with 19.05 million cardiovascular-related deaths globally (American Heart Association, 2022). These figures demonstrate that inflammation-related diseases have a substantial impact on human health, necessitating the need for early medical intervention as well as prophylactic management of

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potentially serious consequences.

Inflammation is a spectrum of immune responses directed against exogenous and/or endogenous stimuli that can cause severe harm or infection. It is a protective mechanism that occurs either retrospectively, after tissue damages have already occurred, or prospectively, when the virulence factor is recognised before tissue injury. Loss of regulation, function, or structure in a tissue system may elicit an inflammatory response. Under these circumstances, the inflammatory signalling pathways are activated via different inflammatory mediators and components to rapidly eliminate the triggering factors from the system and restore the homeostatic conditions (Medzhitov, 2021). Activation of inflammatory signalling pathways such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPK) during active inflammation results in high levels of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) in the system. Nitric oxide synthases (NOS) are enzymes that catalyse the conversion of L-arginine to NO radicals. Neuronal NOS (nNOS) and endothelial NOS (eNOS) are barely expressed under physiological conditions. In contrast, iNOS is a key enzyme highly expressed by macrophages during the inflammatory response that produces NO as an inflammatory mediator. Activated macrophages also secrete pro- and anti-inflammatory cytokines involved in the pathogenesis of numerous inflammatory disorders (Kamalian et al., 2020).

The NF-κB pathway is a canonical inflammatory signalling cascade that is activated through the recognition of pro-inflammatory cytokines, toll-like receptors (TLRs), oxygen radicals, and other microbial products. NF-κB is an essential transcription factor involved in tissue homeostasis, infection, inflammation, apoptosis, and autoimmunity. During the resting period, NF-κB remains inactive and binds to the inhibitor-kappa B (IκB) protein in the cytosol. When an insult occurs, the IκB kinase (IKK) becomes activated and targets the IκB for proteasomal degradation that results in the release of p65 and p50 subunits of NF-κB to the nucleus. The binding of these NF-κB subunits to the cellular genome induces the transcription of various inflammatory mediators implicated in the pathophysiology of numerous inflammation-related diseases. Tumour necrosis factor-alpha (TNF-α), IL-6, and IL-1β are some of the notable pro-inflammatory cytokines commonly measured in inflammatory research (Barnabei et al., 2021). Clinical manifestations of acute inflammation at this stage include redness, hotness, pain, swelling, and loss of function. Therefore, treating and managing acute inflammation at an early stage is of utmost importance, as the persistence of the triggering factors or failure of the immune system to eliminate them could lead to chronic systemic inflammation (Furman et al., 2019).

Several treatment strategies for targeting inflammation have been developed and are routinely used clinically. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most prescribed pain medications in clinical settings, accounting for 5 to 10 percent of prescriptions (Wongrakpanich et al., 2018). NSAIDs act by inhibiting cyclooxygenase (COX) and inhibiting prostaglandin production from arachidonic acid, an unsaturated fatty acid present in the lipid bilayer of the cell membrane. The anti-inflammatory effect of NSAIDs is due to the reduced production of prostaglandins that mediate the occurrence of oedema, fever, and pain (Ghlichloo & Gerriets, 2023). There are two major classes of NSAIDs, which are based on the drug's selectivity for COX isoenzymes. Nonselective NSAIDs block both COX-1 and COX-2, whereas selective NSAIDs only target COX-2. The non-selective NSAIDs, on the other hand, have substantial gastrointestinal effects due to the suppression of the physiologically protective prostaglandins. Gastric ulcers, perforations, and bleedings occur because of the defective gastric mucosal layer, caused by the uncoupling of mitochondrial oxidative phosphorylation, and increased intestinal permeability in chronic NSAID use (Bindu et al., 2020; Ghlichloo & Gerriets, 2023). It was also reported that regular consumption of NSAIDs among patients with renal damage, especially among those requiring dialysis, increased the risks of stroke and cardiovascular-related mortality by at least 1.3-fold and 4-fold, respectively (Hsu et al., 2017; Lai et al., 2019). Thus, safer therapeutic alternatives targeting inflammation are warranted to improve patients' health while reducing drug-related adverse effects.

For many centuries, humans have consumed natural products derived from plants and herbs as medicine. Plants remain significant sources of pharmacologically active compounds for diverse medicinal uses in treating different types of human diseases in the modern world. Plant-based medicines accounted for at least 11 percent of the total 252 essential medications listed by the World Health Organisation (WHO) (Sahoo et al., 2010). Rubiaceae are among the most researched plant families for their pharmacological properties and the isolation of natural bioactive compounds. In traditional African medicine, 99 genera and 318 species of Rubiaceae plants were used for their healing properties (Van Wyk, 2020). Rubiaceae are a madder family of flowering plants and shrubs that are also known as coffee or bedstraw plants. The Rubiaceae family has about 630 genera and 13,000 species that are usually found in warm tropical climates. Taxonomically, the Rubiaceae plants are classified into the Rubioideae, Cinchonoideae, Antirheoideae, and Ixoroideae subfamilies (Martins & Nunez, 2015). Phytochemical screenings have identified various bioactive compounds from Rubiaceae, including alkaloids, terpenes, tannins, flavonoids, iridoids, and sterols (Kala, 2015). Some of these isolated compounds were proven to exhibit important medicinal uses and were further developed for clinical use. For example, *Coffea arabica* is a well-known source of caffeine, which is a drug that stimulates the central nervous system by improving alertness and enhancing cognitive function. Caffeine is also used clinically as the treatment of migraine headaches in combination with ergotamine, as it possesses vasoconstricting properties. It has been shown that inducing cerebral vasoconstriction helps to reduce the symptoms of a migraine attack (Ngo & Tadi, 2023). In addition, the world's first antimalarial drug, quinine, was isolated from the Cinchona tree during the 17th century. Malaria is a parasitic fever caused by Plasmodium species that may be life-threatening if left untreated (Buck & Finnigan, 2023). The discovery of quinine marked the beginning of a pharmacotherapeutic approach to malaria. It was the first step towards developing newer synthetic antimalarial agents such as chloroquine and hydroxychloroquine, which remain important therapeutic drugs targeting several Plasmodium species to date (Achan et al., 2011). Both *Coffea arabica* and Cinchona are from the Rubiaceae subfamilies of Ixoroideae and Cinchonoideae, respectively.

Iridoids are cyclopentane pyran monoterpenes that are abundant in plants, such as Rubiaceae. Based on their chemical structures, iridoids are divided into iridoid glycosides, secoiridoid glycosides, non-glycosidic iridoids, and bis-iridoids. Naturally occurring iridoids isolated from plant sources have been shown to exert anti-tumour, antioxidative, hepatoprotective, neuroprotective, and anti-inflammatory effects in many preclinical studies (Wang et al., 2020). Several iridoids, namely lamiide, catalposide, loganin, swertiamarin, aucubin, harpagoside, harpagide, and catalpol, were isolated from different plant sources (Verbenaceae, Bignoniaceae, Gentianaceae, Eucommiaceae, Pedaliaceae, and Scrophulariaceae, respectively) and investigated for their potential anti-inflammatory activities in vitro and in vivo (Viljoen et al., 2012). However, limited research has been conducted on the pharmacological effects of iridoids derived from Rubiaceae, particularly on inflammation-related diseases.

There is evidence that iridoids have a structure–activity link with their anti- inflammatory properties. According to the findings by Carrillo-Ocampo et al. (2013), the ability of iridoids to inhibit inflammatory responses is dependent on the presence of an electron-withdrawing group in position 11 (C = O) and a hydroxyl group in position 10 of the iridoid skeleton. These molecules may improve the suppression of pro-inflammatory mediators such as cytokines, chemokines, prostaglandins, and reactive oxygen species (Carrillo-Ocampo et al., 2013). The anti-inflammatory activity of catalpol, an iridoid glycoside, was boosted when a cinnamoyl group was substituted for position 6 of the parent molecule (Danielewski et al., 2020). The results of another study by Thao et al. (2021) revealed that the anti-inflammatory benefits of iridoids and anthocyanins are connected to their antioxidant

Table 1
Primary and secondary review questions of this scoping review.

Primary review question	Which iridoids isolated from Rubiaceae plants have been studied for their anti-inflammatory properties in cell culture and/or animal studies?
Secondary review questions	1 Which experimental model has been used within the sources of evidence identified for the primary review question?
	2 What are the characteristics of the experimental design used in the studies?
	3 What parameters are being used (or considered) to measure the anti-inflammatory properties of iridoids from Rubiaceae in the studies?

Table 2
PCC statement of this scoping review.

Element	Description
Population	In vitro and in vivo models of inflammation.
Concept	Anti-inflammatory properties of bioactive iridoids.
Context	Iridoids isolated from Rubiaceae plants.

characteristics. These qualities can protect cells and tissues from oxidative damage and inflammation-induced apoptosis. The interaction between iridoids and anthocyanins had a synergistic impact on reducing inflammation and enhancing liver function (Thao et al., 2021). Because of this, the structure of iridoids may affect their ability to cure inflammation. Iridoids can modulate the inflammatory response and protect the cells from harm due to their structure. Hence, it is vital to comprehend the characteristics of the currently existing study to execute future investigations before developing iridoids as therapeutic agents targeting inflammation-related diseases.

The main goal of this scoping review was to look at the current evidence of in vitro and in vivo studies using iridoid compounds from Rubiaceae as a possible treatment for diseases that are caused by inflammation. The prospective research questions are presented in Table 1 as a guide for identifying research gaps and highlighting important characteristics of the studies selected for this review. In addition, Table 2 shows the PCC (Population, Concept, and Context) statement for this scoping review, which is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) guideline (Tricco et al., 2018).

2. Materials and methods

2.1. Systematic literature search

The current review adheres to the PRISMA-ScR checklist (Tricco et al., 2018; Peters et al., 2020). The literature search was conducted in English in May 2023 using PubMed, Scopus, and Web of Science databases. The search string (iridoid OR iridoids OR "iridoid lactone" OR "iridoid glycoside" OR "iridoid glucoside" OR secoiridoid) AND (Rubiaceae) AND (anti-inflammatory OR "anti-inflammatory effects" OR "anti-inflammatory activity" OR "anti-inflammatory properties" OR inflammation) AND ("cell culture" OR "in vitro" OR "mammalian cells" OR "in vivo" OR animal OR rats OR mice) were used for all three databases with no specific filters applied. Reference tracing was performed for all included full-text articles to ensure the inclusion of relevant articles in this review.

2.2. Inclusion criteria

All primary research articles discussing the anti-inflammatory properties of iridoids derived from Rubiaceae plants using cell culture and/or animal studies were included, but not limited to the type of cell line or animal. Studies using iridoids isolated from plant sources and purchased from chemical suppliers were considered. Studies using plant extracts or fractions of the plant extract as the treatment intervention were excluded. The studies were required to describe the parameters used to determine the anti-inflammatory properties of the investigated iridoid compound as part of the research outcomes. Articles that did not describe the source of the iridoid compound and did not discuss the inflammatory parameters as one of the research outcomes were omitted.

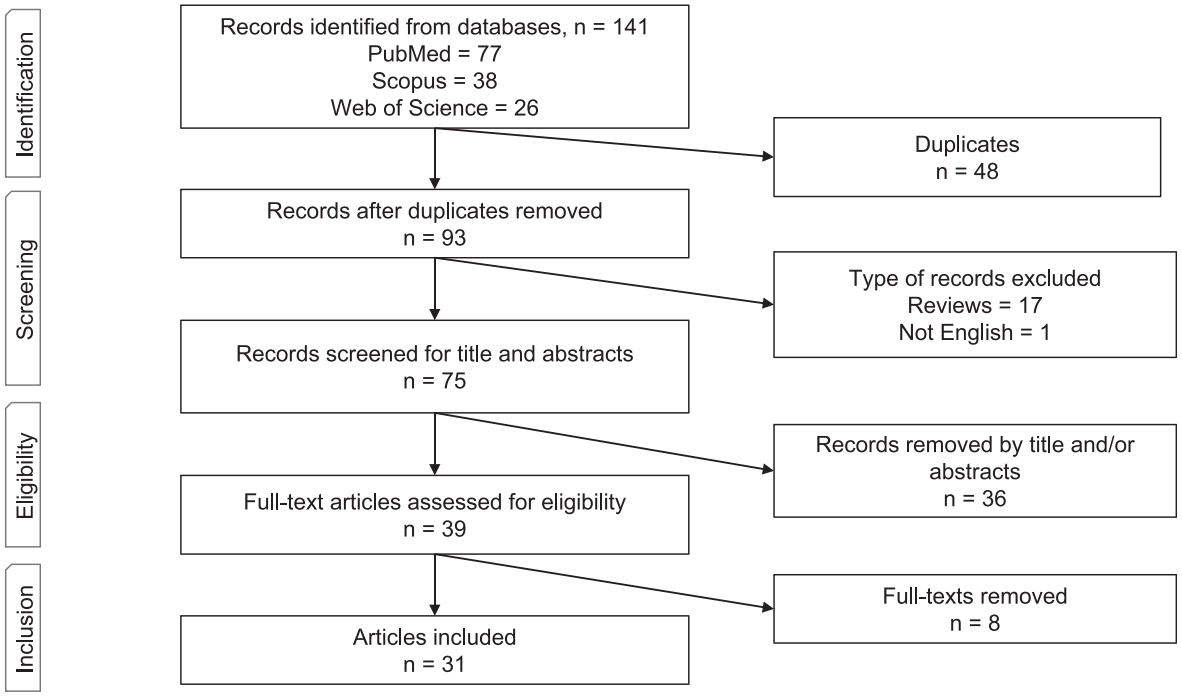

Fig. 1. PRISMA flowchart of the study selection process.

Table 3
Lists of excluded articles with respective treatment and plant source.

Reference	Treatment	Plant source
De Carvalho Junior et al. (2021)	Mixture of epi-geniposidic acid and geniposidic acid	*Psychotria suterella*
Hou et al. (2014)	Iridoid glycosides from *Paederia scandens* containing asperuloside, paederoside and scanderoside	*Paederia scandens*
Hu et al. (2019)	Total iridoid glycosides	*Gardenia jasminoides* Ellis
Karna et al. (2019)	Mixture of monotropein, astragalin and spiraeoside	*Morinda officinalis* How.
K.D. Li et al. (2019)	Genipin-tyroside derivant	*Gardenia jasminoides* Ellis
Liu et al. (2012)	Iridoid glycosides from *Paederia scandens* containing asperuloside, paederoside and scanderoside	*Paederia scandens*
Zhang et al. (2020)	Iridoid glycosides mixture containing deacetylasperulosidic acid and monotropein	*Morinda officinalis* How.
Zhu et al. (2012)	Iridoid glycosides from *Paederia scandens* containing asperuloside, paederoside and scanderoside	*Paederia scandens*

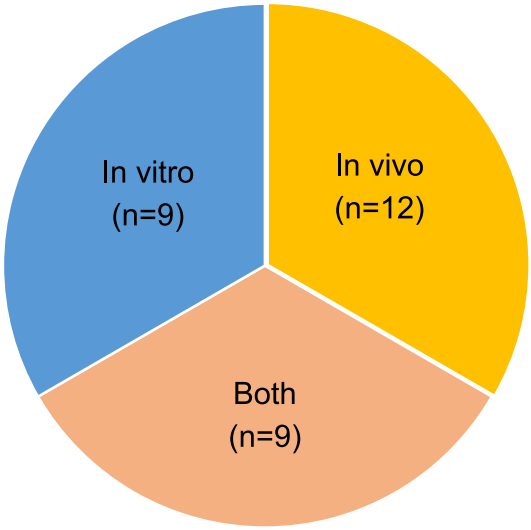

Fig. 2. Categories of the selected studies.

Review papers, conference abstracts, and other grey literature were disregarded.

2.3. Data extraction

The literature was organised according to the PRISMA flowchart using EndNote 20 (Clarivate, Philadelphia, USA). Two independent authors (AJ and MAZ) screened the titles and abstracts of the searched articles, followed by thorough assessments of the full texts according to the inclusion criteria. Any discrepancies in the inclusion of the articles were resolved by one-to-one discussion. Subsequently, AJ and MAZ independently performed data extraction using a standardised data extraction form to collect the following data: (1) name and source of the iridoid compound; (2) experimental model and study design; (3) inflammatory parameters; (4) result; and (5) conclusion.

3. Results

3.1. Study selection

The summary of the study selection process is presented in Fig. 1, according to the PRISMA flowchart. The literature search in PubMed, Scopus, and Web of Science yielded 141 articles. The citation manager software EndNote® 20 for the Windows version (Clarivate, Philadelphia, USA) was used to remove 48 duplicate articles. An article in a non-English language and 17 review articles were excluded. A total of 36 articles were further excluded based on the title and abstracts. Two independent reviewers assessed the remaining 39 articles thoroughly according to the inclusion criteria. Any disputes were resolved through one-on-one discussions between the reviewers. The final selection process resulted in 31 relevant primary research articles after the exclusion of eight articles. These eight articles were rejected because their treatments consisted of mixtures of iridoids instead of a single pure bioactive compound. The lists of rejected articles and the respective treatments used, as well as the plant source of the iridoids, are listed in Table 3.

3.2. Characteristics of the selected studies

The experimental categories of the included studies are illustrated in Fig. 2. Nine studies employed both in vitro and in vivo experimental models; nine studies used only in vitro models; and 12 studies used only in vivo models. Although a few studies reported utilising a combination of experimental models, including in silico, sections of the studies that are not relevant to the research question of this review were not taken into consideration when data extraction was performed.

Fig. 3 depicts the publication years of the relevant studies included in this review. The bar chart shows a chronological trend of the published studies from 2004 to 2023, with five published in 2019 and four in 2014. This graph depicts the trend of scientific interest in iridoids and inflammation research areas between 2014 and 2019.

There was a total of 31 studies from six countries: 18 from China (58.1%), seven from Korea (22.6%), two from Japan and Taiwan (6.5%), and one from Vietnam and Ghana (3.2%). The pie chart (Fig. 4) illustrates the percentage of the selected studies according to their country of origin. The results indicate that research studies on natural plants as potential sources of medicine are most prevalent in Asian countries, with no studies from the United States or Europe included in this review.

The main characteristics and research outcomes extracted from each of the relevant studies are summarised in tabular form. Table 4 gives an overview of the relevant in vitro studies of natural iridoids from Rubiaceae with potential anti-inflammatory activities, whereas Table 5 provides the research summary for the relevant in vivo studies.

Fig. 5 illustrates the number of studies published on iridoids investigated for their anti-inflammatory properties. Geniposide and genipin recorded the highest number of publications selected for this review, with ten and six studies, respectively. Three studies included both genipin and geniposide in their experiments, whereas another three studies used only monotropein as the treatment compound. Only one study was published for scandoside, geniposidic acid, genipin-1-β-$_D$-gentiobioside, officinaloside, deacetylasperulosidic acid, asperulosidic acid and obtucabarmates C, and neonacin and reticunin each. Two other studies reported newly isolated iridoids which are ML2-2, ML2-3, 2′-O-*cis*-coumaroylgardoside, and 6′-O-caffeoylioxide.

4. Discussion

4.1. Current research trend in iridoid studies against inflammation

The scientific interest in iridoids as natural remedies against inflammation has been most significant in Asian countries, as the published studies were reported from China, South Korea, Taiwan, and Japan. The reason could be due to the geographical distribution of Rubiaceae plants such as morinda and gardenia in Asian countries. Moreover, the increasing research interest in iridoids among Asian

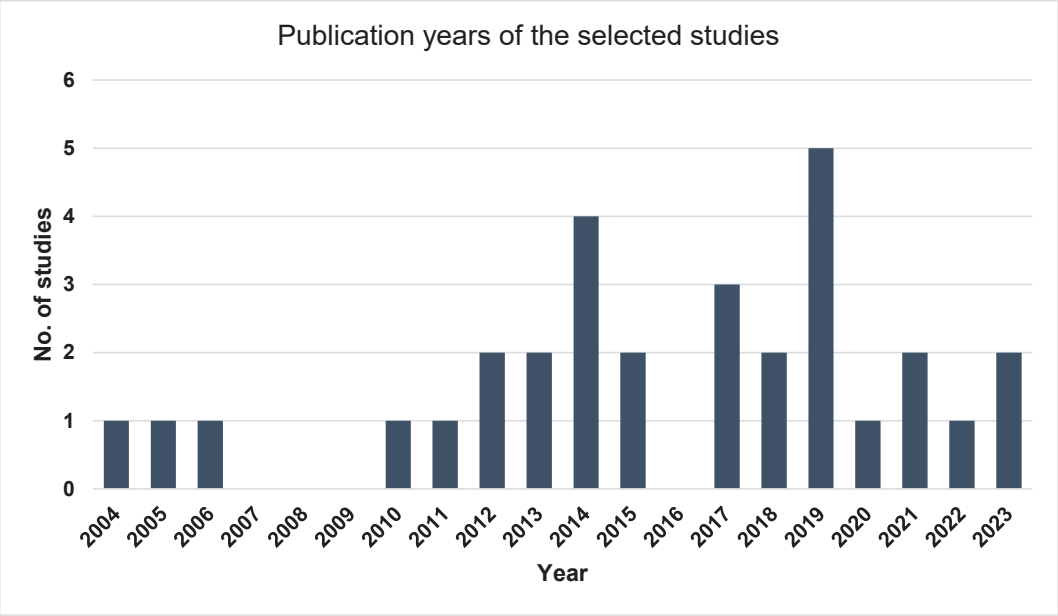

Fig. 3. Publication years of the selected studies.

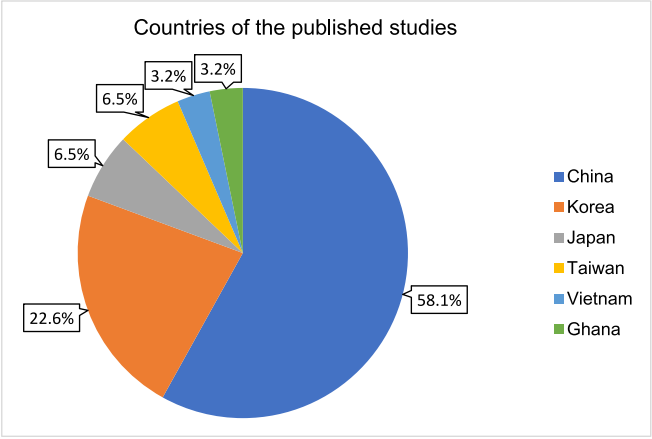

Fig. 4. Countries of the selected published studies.

researchers could also be due to the long history of the use of the plant sources of these iridoids as traditional medicine in Asian cultures for many centuries. *Morinda citrifolia* L. Rubiaceae is also called noni, nuna, Indian mulberry, mengkudu, or cheesefruit, according to the local populations. The noni plant typically grows in tropical regions with temperate climates, such as China, India, Vietnam, Malaysia, the Pacific Islands, and Australia (Bui et al., 2006). Nowadays, noni fruits are still widely consumed by the local communities as herbal supplementation in the form of seed oil as well as fruit flavourings in many food products (juice, jam, yoghurt, and ice cream) due to their nutritional values (Jahurul et al., 2021). Meanwhile, G*ardenia jasminoides* Ellis is a flowering plant commonly found in Southern China and Japan and is very commonly used in traditional Chinese medicine as well as in industrial applications for fabrics and dyes (Chen et al., 2020).

As most of the selected studies were conducted in China and Korea, we looked into the respective research groups and institutes to examine the research trend related to the iridoids study. Our data showed that most of the research was conducted in institutions related to traditional Chinese medicine (TCM). The TCM institutes involved are Guangzhou University of Chinese Medicine (Cai et al., 2021), Anhui University of Chinese Medicine (Chen et al., 2015; Wang et al., 2018), Jiangxi University of Traditional Chinese Medicine (C. Li et al., 2019), Nanjing University of Chinese Medicine (Li et al., 2021), and the Institute of Traditional Chinese Medicine & Natural Products, Jinan University (Li et al., 2020). Meanwhile, in Korea, two papers were published by a research group from the School of Pharmacy, Sungkyunkwan University (Kim et al., 2015; Kim et al., 2013) and another two from the College of Pharmacy, Sookmyung Women's University (Koo et al., 2006; Koo et al., 2004). This shows that research on iridoids has mainly been conducted by the same research groups throughout the years, which may be due to the challenges pertaining to the development of drugs from natural products. There are multiple steps involved in the natural product discovery process, including crude extraction from natural sources, identification of bioactive compounds, investigation of pharmacological effects, and toxicity studies (Atanasov et al., 2021). The process is often lengthy, requiring a lot of resources and expertise to finally produce a marketable drug that is safe and effective for human use. Besides that, the chemical structures of iridoids are quite complex, rendering their chemical synthesis quite challenging (Wang et al., 2020). In this review, the majority of acquired compounds were supplied by chemical companies based in China, Japan, and Taiwan. Therefore, we believe that the specific interest in Rubiaceae-derived iridoid compounds in inflammation research may be attributable to the commercial availability of the pure compounds in the Asian region, which allows researchers to bypass the complex steps of compound extraction and isolation from their respective plant sources.

Geniposide, genipin, and monotropein are the three iridoid compounds derived from Rubiaceae that are most investigated for their anti-inflammatory effects. The bioavailability of these compounds is a crucial factor in assessing their therapeutic efficacy in both in vitro and in vivo testing, which piques the interest of researchers in this field. Geniposide ($C_{17}H_{24}O_{10}$), also known as genipin-1-O-β-glucoside, is an iridoid glycoside isolated from *Gardenia jasminoides* Ellis. It is easily dissolved in polar solvents such as water and ethanol due to the presence of a glucose moiety in its chemical composition (Gao & Feng, 2022). Upon oral administration, geniposide reached its peak concentration in the liver and spleen after 30 min and in the brain and kidney after 2 h. The absolute bioavailability of geniposide in rats was reported to be 9.67% and its maximum tissue distribution was observed in the kidney. Other routes of administration, such as intramuscular and intranasal, resulted in greater bioavailability than oral administration by 72.69 and 49.54%,

Table 4
Summary of the effects of iridoids against induced inflammation in vitro.

Ref.	Compound	Source	Experimental model	Study design	Inflammatory parameter	Result	Conclusion
Araki et al. (2014)	Genipin	Purchased from Wako Chemical Co. (Osaka, Japan).	LPS-induced murine microglial (BV-2) cells.	Cells were pre-treated with genipin for 1 h followed by LPS stimulation at 0.1 μg/ml for 24 h.	NO production Gene expression of iNOS, COX-2, IL-1β and IL-6	Genipin (up to 50 μM) reduced LPS-induced NO production in BV-2 cells. Genipin at 6.25 and 50 μM reduced mRNA expression of iNOS, COX-2, IL-1β and IL-6 in LPS-induced BV-2 cells.	Genipin inhibited LPS-induced neuroinflammation in BV-2 cells.
Cai et al. (2021)	Officinaloside E Officinaloside F	Ethanolic extraction from the aerial parts of *Morinda officinalis How*.	LPS-induced murine macrophages (RAW 264.7) cells.	Pre-treatment for 1 h at a concentration range of 12.5, 25 and 50 μM followed by LPS stimulation at 100 ng/ml for 6 h or 18 h.	NO production Gene expression of iNOS, COX-2, TNF-α and IL-1β TNF-α, IL-1β and IL-6 levels Protein expression of iNOS and COX-2	Officinaloside E and F inhibited NO production in LPS-induced cells with IC_{50} of 26.7 and 31.85 μM, respectively. Officinaloside E and F dose-dependently reduced mRNA expression and protein levels of the inflammatory cytokines and enzymes.	Officinaloside E and F isolated from Morinda *officinalis* How showed significant anti-inflammatory effects against LPS possibly via COX-2 and iNOS proteins.
Chang et al. (2017)	Genipin	Purchased from Challenge Bioproducts Co. Ltd. (Taichung, Taiwan).	*H. pylori*-infected human gastric AGS cells	Cells were infected with *H. pylori* (MOI 100) and treated with genipin (up to 250 μM) for 6 h.	Virulence gene expression Bacterial adhesion and invasion assay Gene expression of IL-8 and IFN-γ	Genipin attenuated *vacA* and *cagA* expression and dose-dependently inhibited *H. pylori* adhesion and invasion in AGS cells. Genipin suppressed IL-8 and IFN-γ expression in infected AGS cells in a dose-dependent manner.	The antibacterial action of genipin against *H. pylori* infection in AGS cells could be due to its anti-inflammatory activity targeting the pro-inflammatory cytokines.
Chang et al. (2019)	Isoboonein	Methanolic extraction from stems of *Neonauclea reticulata*.	LPS-induced murine macrophages (RAW 264.7) cells.	Cells were treated with various concentrations of compounds (up to 1000 μg/ml) in the presence of LPS (100 ng/ml) for 24 h.	NO production	Isoboonein inhibited significant NO production ($p < 0.001$) at IC_{50} of 86.27 ± 3.45 μg/ml compared to indomethacin (positive control) with IC_{50} of 46.71 ± 3.14 μg/ml.	Isoboonein possess significant anti-inflammatory effects against LPS-stimulated NO production.
Fu et al. (2012)	Geniposide	Purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Jilin, China).	LPS-stimulated primary mouse macrophages. LPS-treated mTLR4 and mMD-2 co-transfected HEK293 cells.	Primary mouse macrophages or transfected HEK293 cells were treated with geniposide (up to 200 μg/ml) with and without LPS (1 μg/ml) for 24 h.	Levels of pro-inflammatory cytokines (IL-8, IL-6, IL-1β and TNF-α) Protein expression of NF-κB, MAPKs and TLR4	IL-8 level was reduced in geniposide-treated LPS-stimulated HEK293-TLR4/MD-2 cells in a dose-dependent manner. Geniposide dose-dependently reduced the levels of IL-6, IL-1β and TNF-α in LPS-stimulated mouse macrophages. Geniposide showed significant inhibition of NF-κB and MAPKs activation and IκB-α degradation. Geniposide attenuated TLR4 expression in LPS-stimulated cells.	Geniposide produced anti-inflammatory action against LPS by downregulating TLR4 expression.
He et al. (2018)	Scandoside	Ethanolic extraction of *Hedyotis diffusa Willd.*	LPS-induced RAW264.7 cells	Cells were pre-treated with scandoside (40, 80 and 160 μg/ml) for 1 h followed by LPS stimulation (50 ng/ml) for 24 h.	Levels of NO, PGE2, TNF-α and IL-6 Gene expression of TNF-α and IL-6 Gene and protein expression of iNOS and COX-2 Protein expression of IκB-α, p38, ERK1/2 and JNK (total and phosphorylated)	Scandoside reduced the levels of inflammatory mediators and cytokines in LPS-stimulated cells dose-dependently. Scandoside decreased mRNA levels of TNF-α, and IL-6 compared to LPS control. Scandoside inhibited LPS-induced iNOS and COX-2 expression at both gene and protein levels in a dose-dependent manner. Scandoside reduced LPS-stimulated IκB-α and JNK phosphorylation dose-dependently. Scandoside reduced LPS-stimulated p38 and ERK1/2 phosphorylation at 160 μg/ml.	Scandoside inhibited NF- κB and MAPK signalling pathways to produce its anti-inflammatory effect against LPS.

(*continued on next page*)

Table 4 (*continued*)

Ref.	Compound	Source	Experimental model	Study design	Inflammatory parameter	Result	Conclusion
Koo et al. (2004)	Genipin	Purchased from Wako, Japan.	LPS/IFN-γ induced murine macrophage RAW264.7 cells	Cells were treated with genipin (50 to 300 μM) with or without LPS (1 μg/ml) and/or IFN-γ (10 U/ml) for 24 h.	Nitrite level iNOS expression Expression of IκB-β and phospho-c-*Jun*	Genipin dose-dependently inhibits NO production and iNOS expression in LPS/IFN-γ induced cells. Genipin inhibited IκB-β degradation in LPS/ IFN-γ induced cells but not phospho-c-*Jun* level.	The anti-inflammatory activity of genipin against LPS/IFN-γ stimulated macrophages could be due to the inhibition of the NF-κB/iNOS pathway (instead of JNK/SAPK).
C. Li et al. (2019)	Geniposide Genipin	Compounds were purchased from Shanghai Yuanye Bio-Technology Co., Ltd. (Shanghai, China).	Rat liver BRL-3A cell line	Cells were treated with geniposide or genipin at various concentrations (100, 200, and 300 μg/ml) for 24 h.	Levels of NO, TNF-α and IL-6	Groups treated with genipin and geniposide (200 and 300 μg/ml) showed significantly elevated levels of NO, TNF-α and IL-6 compared to the control group. Low dose (100 μg/ml) genipin and geniposide increased TNF-α level but not IL-6 and NO.	Moderate and high doses of genipin and geniposide promoted the production of inflammatory cytokines in rat hepatocytes.
Li et al. (2020)	2′-O-*cis*-coumaroyl-gardoside 6′-O-caffeoylioxide	Isolated from 60% ethanolic extraction of the dried fruits of *Gardenia jasminoides Ellis*.	LPS-induced RAW264.7 cells	Cells were pre-treated with compound for 30 mins followed by induction with LPS (1 μg/ml) for 24 h with or without the compound.	PGE2 level	2′-O-*cis*-coumaroylgardoside and 6′-O-caffeoylioxide inhibited LPS-induced PGE2 expression in RAW264.7 cells at IC_{50} of 121.4 and 83.38 μM, respectively.	Newly isolated iridoid glycosides from *Gardenia jasminoides* showed inhibitory effects against PGE2 in murine macrophages.
Li et al. (2021)	Genipin-1-β-$_{D}$-gentiobioside	Purchased from Shanghai Ronghe Pharmaceutical Technology Development Co., Ltd (Shanghai, China).	High glucose-induced podocyte model with AMPK silencing.	Cells were treated with 20 μM genipin-1-β-$_{D}$-gentiobioside. Normal and untreated podocytes were included as negative control.	Protein expression of total and p-AMPK, SIRT1, NLRP3, p-NF-κB p65, ASC, cleaved caspase-1, GSDMD-N and cleaved IL-1β.	Cells treated with genipin-1-β-$_{D}$-gentiobioside showed: Increased AMPK, p-AMPK/AMPK and SIRT1 expressions. Reduced NLRP3, p-NF-κB p65, ASC, cleaved caspase-1, GSDMD-N and cleaved IL-1β expressions.	Genipin-1-β-$_{D}$-gentiobioside protects podocytes against high glucose-induced inflammation and injury by promoting the AMPK/SIRT1 pathway.
Lu et al. (2011)	Geniposide	Isolated from *Fructus gardeniae*	LPS-induced RAW 264.7 cells	Cells were pre-treated with various concentrations of geniposide or other compounds (baicalin, berberine, baicalein) or Huang-Lian-Jie-Du herbal decoctions for 2 h followed by stimulation with LPS (2 μg/ml) for 18 h.	Levels of NO, PGE2, IL-10, TNF-α and IL-6	Geniposide-treated cells showed dose-dependent inhibitory effects on the pro-inflammatory cytokines in RAW264.7 cells but not significantly when compared to other compounds and herbal decoctions.	Geniposide exerts minimal anti-inflammatory effects compared with the Huang-Lian-Jie-Du herbal decoctions that contain mixtures of iridoids, flavonoids and alkaloids.
Shan et al. (2023)	Geniposide	Purchased from Solarbio Co. (Beijing, China).	LPS-induced porcine intestinal epithelial IPEC-J2 cells	Cells were pre-treated with geniposide (0.1, 1 and 10 mmol/L) for 24 h followed by incubation with LPS (0.1 mg/ml) for 6 h.	Expressions of NF-κB-related proteins mRNA expression of p65, IKK, IκB, and COX-2	Geniposide (1 mmol/L) reduced the expressions of NF-κB-related proteins. Geniposide (1 mmol/L) restored the mRNA expression of p65, IKK, IκB, and COX-2 to normal levels.	Geniposide exerts inhibitory action against LPS-induced inflammation in porcine intestinal epithelial cells.
Shi et al. (2014)	Geniposide	Isolated from *Gardenia jasminoides*	Inflammation-induced RAW 264.7 cells	RAW264.7 cells and peritoneal macrophages using either stimulant: LPS (50 ng/ml), CpG DNA (20 μg/ml), Pam3CSK4 (10 μg/ml), Poly I:C (50 μg/ml), or MDP (50 μg/ml)	Levels of NO, PGE2, TNF-α and IL-6 mRNA expression of iNOS, COX-2, TNF-α and IL-6 Protein expression of iNOS, COX-2, IκB-α, p-IκB-α, p38, p-p38, Erk1/2, p-Erk1/2, SAPK/JNK, p-SAPK/JNK, MyD88, NF-κB p65, c-Jun	Geniposide inhibited LPS-induced NO and PGE2 production dose-dependently. Geniposide reduced the expression of inflammatory mediators induced by different stimulants. Geniposide inhibited p65 and c-Jun nuclear translocation dose-dependently against LPS stimulant.	Geniposide exerts anti-inflammatory activity against various stimulants targeting the NF-κB, MAPK and AP-1 signalling pathways.
Shin et al. (2013)	Monotropein	Methanolic extraction from the roots of *Morinda officinalis*	LPS-induced RAW 264.7 cells	Cells were treated with various concentrations of monotropein with or without LPS (1 μg/ml) for desired incubation period.	NO and PGE2 levels. Expression of iNOS, COX-2, TNF-α and IL-1β	Monotropein inhibited LPS-induced production of NO, PGE2. Monotropein reduced the expression of iNOS, COX-2, TNF-α and IL-1β in LPS-	Monotropein exerts anti-inflammatory activity via inhibition of NF-κB activation.

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Table 4 (*continued*)

Ref.	Compound	Source	Experimental model	Study design	Inflammatory parameter	Result	Conclusion
					Expression of NF-κB proteins	stimulated cells. Monotropein-treated LPS-induced cells showed reduced degradation of IκB-α and suppressed IKK activity.	
Tran et al. (2019)	Asperulosidic acid Obtucarbamates C	Ethanolic extraction from the aerial parts of *Psychotria prainii*	LPS-induced RAW 264.7 cells	Cells were pre-treated with compounds at various concentrations (up to 30 μM) for 30 min followed by LPS stimulation (30 μg/ml) for 24 h.	NO level	Asperulosidic acid and obtucarbamates C demonstrated significant inhibition of NO production with IC_{50} of 5.75 ± 0.85 and 6.92 ± 0.43 μM, respectively.	Iridoids isolated from the *Psychotria* exerted potential inhibitory activity against LPS-induced NO production in RAW264.7 cells.
Wang et al. (2014)	Monotropein	Isolated from *Morinda officinalis*	IL-1β-induced cultured rat chondrocytes	Cells were treated with 10 ng of IL-1β and monotropein (25, 50 and 100 μg/ml) for 48 h.	Gene and protein expressions of COX-2, COL2A1, MMP-3, MMP-13, caspase-3, and caspase-9	Monotropein counteracted the effects of IL-1β by increasing the expression of COL2A1 and reducing that of COX-2, MMP-3, MMP-13, caspase-3, and caspase-9.	Monotropein exerts anti-inflammatory, anti-apoptotoc and anti-catabolic effects in primary cultures of rat knee chondrocytes.
Wang et al (2018)	Geniposide	Purchased from the Guangxi Shanyun Biochemical Science and Technology Co. Ltd. (Guangxi, China)	TNF-α-induced miRNA-124a-transfected fibroblast-like synoviocytes (MH7A) in rheumatoid arthritis patients	Cells were transfected with miRNA-124a mimic or inhibitor for 24 h followed by treatment with 50 μM geniposide for another 24 h and stimulated with TNF-α (10 ng/ml) for additional 12 h.	Expression of Itgβ1, Ras, pERK1/2, ERK1/2 Levels of IL-4, TGF-β1, IL-1β, and IL-17	Geniposide attenuated the expressions of Itgβ1 and Ras/ERK1/2-related proteins while promoting the expression of miRNA-124a.The levels of anti-inflammatory cytokines (IL-4 and TGF-β1) were increased while that of pro-inflammatory cytokines (IL-1β and IL-17) were decreased in geniposide-treated group in presence of miRNA-124a mimic.	Geniposide exerts its anti-inflammatory effect by modulating miRNA-124a towards inhibition of Itgβ1/Ras-ERK1/2 signalling pathway.
Zheng et al. (2010)	Geniposide	Purchased from National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China)	LPS/lipid A/ IL-1β-stimulated RAW 264.7 cells	Depending on the types of assays, cells were stimulated with either LPS (100 ng/ml), lipid A (2 μg/ml) or IL-1β (50 ng/m) with simultaneous addition of geniposide at various concentrations for desired incubation period.	Levels of TNF-α and IL-6 mRNA expression of TNF-α and TLR4 Protein expression of p38 MAPK (total and phosphorylated)	Geniposide inhibited TNF-α mRNA expression, and TNF-α and IL-6 release from RAW264.7 cells stimulated by LPS and lipid A, not by IL-1β. Geniposide inhibited LPS-induced expression of TLR4. Geniposide suppressed the phosphorylation of p38 MAPK induced by LPS not by IL-1β.	The anti-inflammatory effects of geniposide could be due to its interaction with LPS.

Abbreviations: COX-2: cyclooxygenase-2; ERK: extracellular-signal-regulated kinase; IκB-α: inhibitor kappa B – alpha; IL: interleukin; iNOS: inducible nitric oxide synthase; Itgβ1: integrin beta 1; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MyD88: myeloid differentiation primary response 88; NF-KB: nuclear factor kappa B; NO: nitric oxide; PGE2: prostaglandin E2; SAPK/JNK: stress-activated protein kinases/jun amino-terminal kinases; TGF-β1: tumour growth factor – beta 1; TNF-α: tumour necrosis factor – alpha;

Table 5
Summary of the effects of iridoids against induced inflammation in vivo.

Ref.	Compound	Source	Experimental model	Study design	Inflammatory parameters	Results	Conclusion
Araki et al. (2014)	Genipin	Purchased from Wako Chemical Co. (Osaka, Japan).	LPS-induced sickness behaviour mice model.	Genipin (100 and 300 mg/kg) was given orally for 1 h before LPS (500 μg/kg) administration intraperitoneally for 2 h or 24 h.	Behavioural changes: immobility, social interaction, and locomotor activity.Expression of c-Fos (an indirect marker of neuronal activity). Gene expression of iNOS, COX-2, IL-1β and IL-6 in hypothalamus and amygdala.	Genipin (100 and 300 mg/kg) inhibited LPS-induced prolonged immobility. Genipin improved social interaction in LPS-induced mice treated with 100 mg/kg genipin (but not 300 mg/kg). No change in locomotion with or without genipin. Genipin (100 mg/kg) reduced c-Fos positive cells in LPS-induced mice in the hypothalamic paraventricular nucleus and central nucleus of the amygdala. Genipin (100 mg/kg) reduced gene expression of inflammation-related genes in the hypothalamus and amygdala of LPS-induced mice.	Genipin at 100 mg/kg showed inhibition of neuroinflammation in the hypothalamus and amygdala of LPS-induced sickness behaviour mice.
Chang et al. (2017)	Geniposide Genipin	Geniposide was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan), whereas genipin was purchased from Challenge Bioproducts Co. Ltd. (Taichung, Taiwan)	*Helicobacter pylori*-mediated inflammation in C57BL/6 mice.	Mice were infected with *H. pylori* 26695 at 1×10^9 CFU every other day for three times followed by daily oral administration of genipin (18 and 26 mg/kg/day) or geniposide (31 and 62 mg/kg/day) for 3 days.	Virulent gene expression Serum levels of IFN-γ and IL-1β Serum levels of IgA and IgM Gene expression of COX-2 in gastric tissue	Both compounds reduced *vacA* gene expression, not *cagA,* in the gastric tissue of infected mice. All treatment groups had reduced serum inflammatory cytokines except for IL-1β in those treated with 31 mg/kg/day of geniposide. All treatment groups showed reduced IgA and IgM levels except the group treated with low dose genipin (18 mg/kg/day). All treatment groups suppressed COX-2 gene expression in mice gastric tissue.	Genipin and geniposide inhibited *H. pylori* infection through their anti-inflammatory activity.
Chen et al. (2015)	Geniposide	Ethanolic extraction from the fruits of *Gardenia jasminoides* Ellis.	Adjuvant arthritis male Sprague-Dawley rats.	Freund's Complete Adjuvant (FCA) was used to induce arthritis in rats followed by intragastric administration of geniposide (30, 60 or 120 mg/kg) or control once daily from day 17 to day 24 post-immunisation. Rats were sacrificed on day 24 and knee synovial tissue was collected for examination and culture of fibroblast-like synoviocytes.	Paw swelling volume Arthritis index score HPE of ankle joint Levels of IL-1, IL-6, TNF-α, and IL-10 Protein expression of total and phosphorylated MKK-3/6, p38 and MAPKAP2	All treatment groups reduced paw swelling and arthritis systemic score from day 18 to day 24 post-immunisation. Geniposide-treated groups (60 and 120 mg/kg) suppressed histopathological inflammatory changes in the rats' ankle joints with minimal synovial hyperplasia. Cultured synoviocytes of rats treated with geniposide (60 and 120 mg/kg) showed significant reduction of IL-1, IL-6 and TNF-α and elevation of IL-10. All treatment groups showed significant reduction of phosphorylated MKK-3/6, p38	Geniposide produced an anti-inflammatory effect against adjuvant arthritis by targeting pro-inflammatory cytokines probably via the p38 MAPK pathway.

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Table 5 (*continued*)

Ref.	Compound	Source	Experimental model	Study design	Inflammatory parameters	Results	Conclusion
						and MAPKAP2, but not the total proteins.	
Chen et al. (2022)	Geniposide	Purchased from Chengdu Dicotyledon Chinese Medicine Resources Co., Ltd. (Chengdu, China).	Streptozotocin and high fat diet-induced diabetic wound model of Wistar rats.	Rats were treated with control or geniposide (200, 400 or 500 mg/kg) via oral gavage once daily for 7 days.	Blood glucose level Wound assessment HPE of skin lesion Levels of IL-1β, IL-6, TNF-α, and IL-10 in wound tissue	All treatment groups showed reduced blood glucose level on day 7 compared to control. Wound healing by occlusion was observed in geniposide-treated groups on day 3 and day 7. Geniposide-treated groups (400 and 500 mg/kg) showed minimal tissue infiltration with improved fibroblast proliferation. Levels of IL-1β, IL-6 and TNF-α in wound tissue of geniposide-treated rats were significantly attenuated whereas the level of IL-10 was elevated dose-dependently.	Geniposide exerts anti-diabetic effects and promotes wound healing via the modulation of inflammatory mediators.
Choi et al. (2005)	Monotropein	Methanolic extraction of the dried roots of *Morinda officinalis*.	Carrageenan-induced rat paw oedema	Rats were pre-treated with monotropein (20 or 30 mg/kg) or ibuprofen (positive control) orally for one week followed by injection of 1 % carrageenan solution of the hind paw.	Volume of paw oedema	Monotropein at 30 mg/kg decreased paw oedema volume by 39.6% at 3 h post-carrageenan induction which is comparable to that of ibuprofen (62%).	Monotropein exerts its-anti-inflammatory action by reducing acute paw oedema.
Fu et al. (2012)	Geniposide	Purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Jilin, China).	LPS-induced acute lung injury mice model	Mice were pre-treated with geniposide (50 mg/kg) or control via intraperitoneal injection followed by intranasal administration of LPS (10 μg in 50 μL PBS).	Inflammatory cell counts of BAL fluidCytokines level (IL-1β, IL-6 and TNF-α) of BAL fluid MPO activity in lung HPE of lung tissue	Geniposide (50 mg/kg)-treated group reduced the number of neutrophils and macrophages as well as the levels of IL-1β, IL-6 and TNF-α in BAL fluid compared to LPS control. Geniposide reduced lung myeloperoxidase activity compared to LPS control. Minimal inflammatory changes were observed in the lung tissue of LPS-induced mice treated with geniposide compared to the control.	Geniposide attenuated the inflammatory changes of acute lung injury in LPS-induced mice.
Kim et al. (2015)	Genipin	Purchased from Wako Pure Chemical Industries, Ltd. 81 (Osaka, Japan).	Cecal ligation and puncture (CLP) induced sepsis in male ICR mice	Mice were treated with genipin (1, 2.5 and 5 mg/kg) or control via intravenous injection at 0 h and 24 h after CLP surgical procedure.	Sepsis survival rate Total splenocyte count Splenic CD4+ and CD8+ lymphocyte population and apoptosis Splenic levels of IL-2, IFN-γ, IL-10, and IL-4	Genipin (2.5 mg/kg) significantly improved septic mice survival at day 7 compared to sham. Genipin inhibited the reduction of total splenocyte counts in CLP-induced mice. Genipin-treated CLP-induced mice showed elevated lymphocyte counts of CD4+ and CD8+ as well as reduced apoptosis. Genipin restored the levels of IL-2, IFN-γ, IL-10, and IL-4 to baseline in CLP mice.	Genipin acts as an immunosuppressant in the late phase of sepsis while preventing the occurrence of cytokine shift.

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Table 5 (*continued*)

Ref.	Compound	Source	Experimental model	Study design	Inflammatory parameters	Results	Conclusion
Kim et al. (2013)	Geniposidic acid	Methanolic extraction from the fruit of *Gardenia jasminoides Ellis.*	D-galactosamine and LPS-induced fulminant liver failure model	Male ICR mice were pre-treated with geniposidic acid (12.5, 25 and 50 mg/kg) or control intraperitoneally for 1 h followed by intraperitoneal injection of D-galactosamine (800 mg/kg) and LPS (40 μg/kg). Mice were observed for 1, 8 or 24 h before being sacrificed.	Survival score and serum ALT at 24 h post-induction Serum IL-6 and TNF-α at 1 h post-induction HPE of liver tissue at 8 h post-induction Level of total and phosphorylated STAT3	Geniposidic acid improves the survival rate of D-galactosamine/LPS-induced mice dose-dependently while attenuating the serum ALT level. Level of TNF-α was decreased in geniposidic acid-treated group compared to the induced control, whereas the level of IL-6 was further increased. Geniposidic acid minimised the inflammatory changes of hepatic tissue compared to induced control. Geniposidic acid enhanced the relative level of STAT3/p-STAT3 in induced mice.	Geniposidic acid exerts a hepatoprotective effect by inducing IL-6 expression and activating the STAT3 pathway.
Ko et al. (2017)	Genipin	N/A	Ovalbumin-challenged asthmatic mouse model	Female BALB/c mice were intraperitoneally injected with 20 μg ovalbumin for 14 days and treated with genipin (10 and 20 mg/kg) or control via oral gavage from day 18 to 23. From day 21 to day 23, the mice were challenged with nebulised ovalbumin (1% w/v) from day 21 to 23.	Airway hyperresponsiveness Inflammatory cell counts in BAL fluid Levels of IL-5 and IL-13 in BAL fluid Serum IgE HPE of lung tissue Expression of iNOS, COX-2, and MMP-9 in lung tissue	Genipin attenuates airway hyperresponsiveness, eosinophils count and IL-5, IL-13 and IgE levels in ovalbumin-induced mice compared to control. Asthmatic mice treated with genipin showed minimal airway inflammation with significantly lower mucus production compared to the control. Genipin-treated asthmatic mice had markedly lower expressions of iNOS, COX-2 and MMP-9 in lung tissues compared to control.	Genipin exerts anti-asthmatic action against airway inflammation in an asthmatic mouse model by attenuating the expression of various inflammatory markers.
Koo et al. (2006)	Genipin Geniposide	Compounds purchased from Wako Chemical Co. (Osaka, Japan).	Carrageenan-induced inflammation model	Rat paw oedema:Rats were pre-treated with compounds (genipin: 50 mg/kg; geniposide: 100 mg/kg) or control orally for 1 h before administration of 1% carrageenan via subcutaneous injection at the right hind paw. Air pouch formation: Rats were injected with 20 ml sterile air at the intrascapular region followed by 10 ml injections every 3 days twice. Then, rats were treated with compounds (0.1 mg/pouch) or control orally at 1 h before carrageenan injection into the pouch.	Acute paw oedema volume Exudates formation Nitrite levels in the exudates	Genipin (50 mg/kg) inhibited the increase of paw oedema volume by 49.1% compared to that of geniposide (100 mg/kg)-treated group (31.7%). In carrageenan-induced air pouch formation, genipin and geniposide at similar doses reduced the exudates formation by 51.1 and 45.1%, respectively. Nitrite level was significantly reduced in genipin-treated groups than that of geniposide and was comparable to that of dexamethasone-treated group.	Genipin showed more potent anti-inflammatory activity than geniposide through attenuation of NO production.
Koo et al. (2004)	Genipin	Purchased from Wako, Japan.	Croton oil-induced ear oedema	The right ear of ICR mouse was filled with a solution mixture of croton oil (0.4 μg) and genipin (0.55, 1.1, 2.21 or 4.42 μmol/ear) or control and sacrificed after 5 h.	Inhibition of ear plug weight and thickness	Topical application of genipin reduced the weight and thickness of ear oedema dose-dependently with the highest dose (4.42 μmol/ear) showing 57.1% inhibition compared to the control group.	Genipin has a topical anti-inflammatory activity.

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Ref.	Compound	Source	Experimental model	Study design	Inflammatory parameters	Results	Conclusion
Kumatia et al. (2023)	ML2-2 ML2-3	Isolated from ethanolic leaf extract of *Morinda lucida* (Benth.).	Carrageenan-induced rat paw oedema	The right hind paw of each rat was injected with 1% carrageenan solution followed by a single oral dose of treatment (ML2-2 and ML2-3 at 2 or 10 mg/kg) or control. Rat was observed at 1 h interval for 4 h.	Inhibition of paw oedema volume	Both compounds reduced the oedema volume with ML2-3 (10 mg/kg) showing the highest inhibition at 64.52% compared to control.	The newly isolated unique tetracyclic iridoids showed anti-inflammatory activity.
J. Li et al. (2019)	Genipin	N/A	Hyperoxia-exposed acute lung injury of neonatal rats	SD neonatal rats were divided into four groups: 1. normoxia + DMSO + lentivirus control 2. hyperoxia + DMSO + lentivirus control 3. hyperoxia + genipin (50 mg/kg) + lentivirus control 4. hyperoxia + genipin (50 mg/kg) + lentivirus-GSK-3β Treatments were given intraperitoneally for 2 weeks.	Mononuclear and PMNL cell counts in BAL. HPE of lung tissues. Levels of TNF-α, IL-1β, IL-6 in BAL fluids. Cytosolic and nuclear expressions of NF-κB in lung tissues. mRNA expressions of TNF-α, IL-1β, IL-6, MMP-2 and MMP-9.	Genipin inhibited inflammatory responses in the hyperoxic lungs of neonatal rats by attenuating: the levels of inflammatory markers in BAL. fibrotic changes in lung tissues. the nuclear translocation of the p65 subunit of NF-κB. mRNA expressions of the inflammatory markers.	Genipin regulates GSK-3β to inhibit inflammatory responses via the NF-κB pathway in hyperoxia-exposed neonatal rats with acute lung injury.
Li et al. (2021)	Genipin-1-β-$_{D}$-gentiobioside	Purchased from Shanghai Ronghe Pharmaceutical Technology Development Co., Ltd (Shanghai, China)	High-fat diet and streptozocin-induced diabetic nephropathy (DN) mice	C57BL/6 mice were divided into: 1. Control 2. DN + saline 3. DN + compound (25 mg/kg) 4. DN + compound (50 mg/kg) 5. DN + valsartan (150 mg/kg)	Serum levels of TNF-α, IL-1β, and IL-6. HPE of renal tissues Protein expressions of AMPK/SIRT1/NF-κB pathway in renal tissues.	Treatment with genipin-1-β-$_{D}$-gentiobioside showed: reduction of serum pro-inflammatory cytokines level. attenuation of inflammatory infiltrations and damages in renal tissues. reduced expressions of NLRP3, ASC, p-NF-κB, cleaved caspase-1, GSDMD-N and cleaved IL-1β.	Genipin-1-β-$_{D}$-gentiobioside suppressed renal inflammation in diabetic mice via AMPK/SIRT1/NF-κB pathway.
Murata et al. (2014)	Deacetylasperulosidic acid	Purchased from Chengdu Biopurify Phytochemicals Ltd. (Chengdu, China).	Ehrlich carcinoma-bearing mice	Female BALB/c mice were treated with oral deacetylasperulosidic acid (30 and 100 mg/kg) or *Morinda citrifolia* (Noni) extract (200, 500 and 1000 mg/kg) for 14 days followed by intraperitoneal administration of Ehrlich carcinoma supernatant (derived from ascitic fluid of ICR mice containing Ehrlich carcinoma cells).	Cytokines levels of IL-2, IL-4 and IL-10 in mice splenocytes.	Deacetylasperulosidic acid significantly increased the level of IL-2 in Ehrlich carcinoma mice compared to the untreated mice but not IL-4 and IL-10.	Deacetylasperulosidic acid could exert anti-inflammatory activity in cancer-bearing mice.
Shin et al. (2013)	Monotropein	Methanolic extraction from roots of *Morinda officinalis*	Dextran sulphate sodium (DSS)-induced colitis mice	Mice were given 4% DSS in drinking water together with monotropein (100 or 200 mg/kg/d) or control for 9 successive days.	Colitis severity index MPO activity Expression of iNOS and COX-2 Expression of NF-κB-related proteins	Monotropein protected against DSS-induced colitis by reducing MPO activity and severity index. Monotropein reduced the expression of iNOS and COX-2 in DSS-induced mice. Monotropein inhibited Iκβ-α degradation and attenuated the nuclear translocation of p65 and p50-NF-κB.	Monotropein protects against DSS-induced colon inflammation by inhibiting NF-κB pathway.
Wang et al. (2014)	Monotropein	Isolated from *Morinda officinalis*	Osteoarthritic knee rat model	Kunming rats were subjected to surgical incision of the knee according to Hulth's method (1999) and were treated with monotroprein (25, 50 or 100 mg/kg) via intragastric administration for 6 weeks.	Pro-inflammatory cytokines level in knee synovial fluid HPE of knee joint	The levels of pro-inflammatory cytokines (IL-1β, TNF-α and PGE2) were reduced by monotropein dose-dependently compared to model group. Monotropein (100 mg/kg) showed	Monotropein exhibits protective effects against osteoarthritis by reducing pro-inflammatory cytokines levels.

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Table 5 (*continued*)

Ref.	Compound	Source	Experimental model	Study design	Inflammatory parameters	Results	Conclusion
						osteoarthritic changes by gross and histological observation compared to model group.	
Wang et al. (2019)	Genipin	Purchased from Sigma-Aldrich (Massachusetts, US).	Carbon tetrachloride (CCl_4)-induced acute liver injury mice model	C57BL/6 mice were administered with genipin (2.5 mg/kg) or control via intravenous injection 2 h before injection with a solution mixture of CCl_4: oil (1:1; 2 ml/kg) intraperitoneally. Mice were sacrificed after 12, 24 and 48 h later.	Serum levels of IL-1β, IL-6, CCL20, IL-10, IL-17A, and IL-33 HPE of liver tissue Expression of NF-κB and STAT3 proteins	Genipin inhibited CCl_4-induced production of IL-1β, IL-6, CCL20, and IL-33 and increased that of IL-10. Minimal inflammatory changes in the liver were seen in genipin-treated rats. The expression of NF-κB and STAT3 proteins was reduced in the genipin-treated rats' liver.	Genipin protects against CCl_4-hepatic inflammation by inhibiting NF-κB and STAT3 signalling pathways.
Xiaofeng et al. (2012)	Geniposide	Purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China).	LPS-induced acute lung injury model	Male BALB/c mice were pre-treated with geniposide (20, 40 and 80 mg/kg) or control via intraperitoneal injection and induced with intranasal LPS (10 μg/dose). Mice were sacrificed after 7 h.	Inflammatory cell counts in BAL fluid Levels of TNF-α, IL-6 and IL-10 in BAL fluid Lung MPO activity HPE of lung tissue Expression of NF-κB and MAPK proteins	Geniposide (40 and 80 mg/kg) reduced inflammatory cell counts, and TNF-α and IL-6 in BAL fluid. IL-10 level was increased in geniposide-treated group.Geniposide (40 and 80 mg/kg) inhibited LPS-induced MPO activity in the lungs. Lung inflammation was reduced in all geniposide-treated (20, 40 and 80 mg/kg) LPS-induced mice. Geniposide inhibited nuclear translocation of p65 and phosphorylation of IκB-α, p46-p54 JNK, p42-p44 ERK, and p38 in LPS-induced mice.	Geniposide protects against LPS-induced acute lung injury via NF-κB and MAPK signalling pathways.
Zhang et al. (2017)	Geniposide	Purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China).	Ferrocenecarboxylic acid (FCA)-induced adjuvant arthritis rat model	SD rats were immunised with a single dose of 0.1 ml FCA in the left hind paw and treated with intragastric geniposide (30, 60 and 120 mg/kg) or control from day 17 to 24 post-immunisation.	Arthritis score HPE of MLNL Levels of IL-2, IL-4 and TGF-β1 in MLNL	Geniposide attenuated paw oedema volume and improved arthritis score. Geniposide reduced inflammatory infiltration in MLNL. Geniposide restored the IL-2 level to baseline and increased that of IL-4 and TGF-β1 in MLNL.	Geniposide showed anti-inflammatory effects against adjuvant arthritis in rats.
Zheng et al. (2010)	Geniposide	Purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China).	LPS-induced endotoxaemia mice model	Kunming mice were pre-treated with geniposide (10, 20 and 40 mg/kg) or control followed by single injection of 50 μg/mg of LPS.	Serum LPS level Serum TNF-α and IL-6 levels	Geniposide dose-dependently reduced the level of LPS in mice. Geniposide (40 mg/kg) reduced the serum levels of TNF-α and IL-6 at 2 h post-LPS-induction.	Geniposide attenuates inflammatory cytokines in LPS-induced sepsis mice.

Abbreviations: LPS: lipopolysaccharide; BAL: bronchoalveolar lavage; HPE: histopathological examination; PBS: phosphate buffered saline; ALT: alanine transferase; IgE: immunoglobulin E; SD; Sprague-Dawley; N/A: not available; NF-κB: nuclear factor-kappa B; GSK-3β: glycogen synthase kinase-3 beta; MPO: myeloperoxidase; PMNL: polymorphonuclear leukocytes; MLNL: mesenteric lymph nodes lymphocytes.

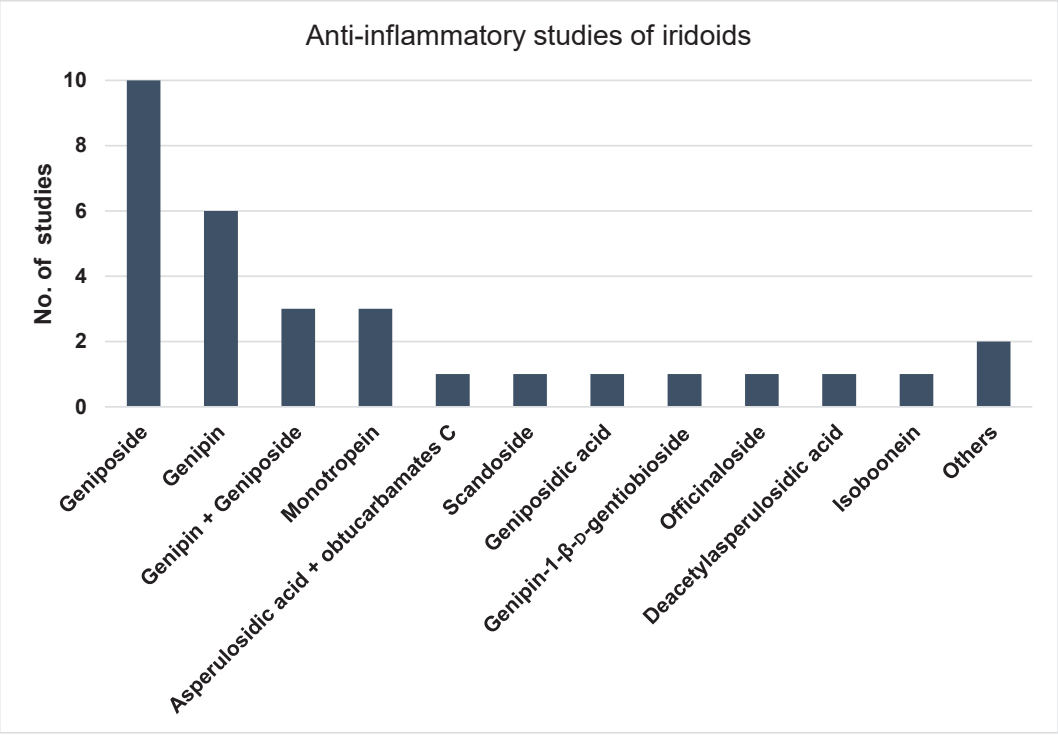


Fig. 5. Number of studies for the selected iridoids.

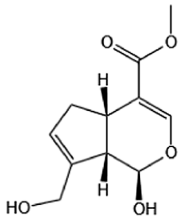
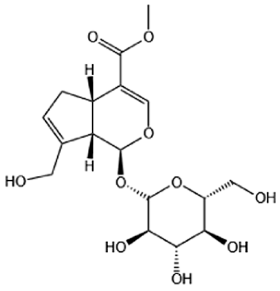
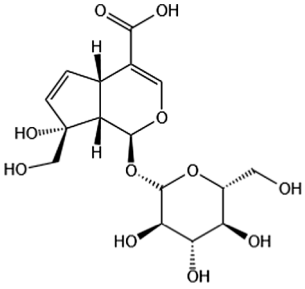
respectively (Yang et al., 2010). The hydrophilic nature of geniposide limits its ability to permeate through the gastrointestinal barrier, resulting in poor oral bioavailability (Wang et al., 2013). A study by Jin et al. (2014) suggested that the bioavailability of geniposide could be affected by the reduced metabolism of the intestinal microbiome in response to multiple antibiotic therapies (Jin et al., 2014). On the other hand, genipin ($C_{11}H_{14}O_5$) is an aglycone iridoid produced by the hydrolysation of geniposide in the liver and intestines by β-glucosidases. Despite limited research on its bioavailability, it is suggested that the biotransformation of geniposide to genipin (the bioactive aglycone form of geniposide) could be the reason for its improved potency and more profound bioactivity in vitro (Habtemariam & Lentini, 2018). Genipin has also been reported to be isolated from *Genipa americana* L. fruit, which is also from the Rubiaceae family (Brauch, 2016). Apart from its medicinal properties, genipin and its derivatives are widely used as a natural blue colourant in food production. This is because genipin has natural cross-linking properties where it can form dark blue pigments through spontaneous reactions with amino acids (Neri-Numa et al., 2017). Monotropein ($C_{16}H_{22}O_{11}$) is an iridoid glycoside most abundant in the roots of *Morinda officinalis* (Rubiaceae). It is strongly hydrophilic in nature due to the presence of polar groups in its chemical structure, which are carboxyl (COOH) and hydroxyl (–OH) groups. Moreover, rapid tissue distribution and elimination were observed following oral administration of monotropein at 10, 20, and 40 mg/kg. Monotropein is also highly distributed in the kidney, which also acts as the excretory organ (Wu et al., 2023). In a separate animal study, the absolute bioavailability of monotropein was 3% after oral administration of a medicinal herbal mixture containing *Morinda officinalis* (Choi et al., 2019). Table 6 summarises the chemical information of geniposide, genipin, and monotropein, including the chemical structures (drawn using KingDraw software version 3.0.2, https://www.kingdraw.cn/en/), chemical formulae, and molecular weights, which were retrieved from PubChem, National Center for Biotechnology Information (NCBI) (https://pubchem.ncbi.nlm.nih.gov/).

4.2. *Effects of selected iridoids against in vitro inflammation*

In the preclinical stages of drug development, a cell culture experiment is an essential prerequisite to investigating the therapeutic potential of the compounds and the possible mechanism of the drug's actions. Several cell culture models have been developed and are well established to mimic the natural inflammatory response across different cell lines. To delve into the molecular mechanisms of a bioactive compound with potential anti-inflammatory activities, specific types of cells capable of producing innate and adaptive immune responses must be selected. The RAW 264.7 cell line is a well-known model of inflammation in the drug discovery field. The cell line is an established monocyte/macrophage-like cell derived from BALB/c mice infected with the Abelson leukaemia virus. RAW 264.7 cells can produce nitric oxide (NO) upon stimulation with lipopolysaccharide (LPS), an endotoxic stimulant derived from the cell wall of a Gram-negative bacteria (Aki et al., 2020). In this review, ten studies were identified for utilising the LPS-induced RAW 264.7 cell culture model to investigate the anti-inflammatory effects of iridoids (Cai et al., 2021; Chang et al., 2019; He et al., 2018; Koo et al., 2004; Li et al., 2020; Lu et al., 2011; Shi et al., 2014; Shin et al., 2013; Tran et al., 2019; Zheng et al., 2010).

Three of the in vitro studies investigated the anti-inflammatory efficacy of geniposide using LPS-induced RAW 264.7 cells. According to Lu et al. (2011), the traditional Chinese herbal decoctions comprised of *Rhizoma coptidis, Radix scutellariae, Cortex phellodendri*, and *Fructus gardenia* exhibited greater anti-inflammatory effects compared to individual iridoids (i.e., geniposide), flavonoids or alkaloids alone. In the study, geniposide produced a considerable anti-inflammatory action against LPS-induced NO production and cytokine levels (Lu et al., 2011). In another investigation, it was proven that geniposide exerts a dose-dependent inhibitory action against LPS-induced NO and PGE2 levels as well as the gene expression of iNOS, COX-2, TNF-α and IL-6. It was also shown that geniposide targeted the NF-κB and MAPK/AP-1 pathways by inhibiting the nuclear translocation of p65 and c-Jun, respectively (Shi et al., 2014). A study by Zheng et al. (2010) compared the efficacy of geniposide against different inflammatory stimulants: LPS,

Table 6
Compound summary of genipin, geniposide and monotropein.

Name	Genipin	Geniposide	Monotropein
Chemical formula	$C_{11}H_{14}O_5$	$C_{11}H_{14}O_5$	$C_{16}H_{22}O_{11}$
Chemical structure			
Molecular weight (g/mol)	226.23	388.4	390.34
PubChem compound ID	442424	107848	73466

lipid A and IL-1β in RAW 264.7 cells. The study concluded that the anti-inflammatory action of geniposide may be due to its main interaction with LPS only (not lipid A or IL-1β), where it inhibits LPS-induced TNF-α, IL-6, and TLR4 expression together with attenuation of p38 MAPK phosphorylation (Zheng et al., 2010). Based on these studies, it can be concluded that geniposide demonstrated significant anti-inflammatory activity against LPS-induced production of inflammatory cytokines and NO in RAW 264.7 macrophages.

To further explore the mechanism of anti-inflammatory action of geniposide, Fu and colleagues utilised two different cellular models of inflammation: 1) LPS-induced primary mouse macrophages and 2) LPS-induced mTLR4 and mMD-2 co-transfected HEK293 cells. In both cell culture models, it was shown that geniposide attenuated LPS-induced TLR4 and inflammatory mediators through inhibition of NF-κB and MAPK pathways (Fu et al., 2012). Porcine intestinal epithelial (IPEC-J2) cells were used as the cellular model for inflammation in a recent study designed to bolster the evidence for the anti-inflammatory activity of geniposide across multiple cell lines. The study established the efficacy of geniposide against LPS-induced inflammatory responses in IPEC-J2 cells by inhibiting the activation of the NF-κB pathway (Shan et al., 2023). Moreover, it has been demonstrated that geniposide exerts anti-inflammatory action in the MH7A cells, which are fibroblast-like synoviocytes derived from rheumatoid arthritis (RA) patients. The author suggested that the anti-inflammatory effect of geniposide in RA could be due to the modulation of miRNA-124a (a microRNA that plays an important role in the attenuation of early RA) as a novel target in the inhibition of the Ras-Erk1/2 pathway (Wang et al., 2018). According to these studies, the use of different cell lines or in vitro models did not affect the in vitro efficacy of geniposide against inflammation.

In this scoping review, three in vitro studies investigated the anti-inflammatory activities of genipin using different cell lines that mimic the inflammatory responses that occur in different types of inflammatory diseases. Koo et al. (2004) demonstrated that treatment of LPS and IFN-γ-stimulated RAW 264.7 cells with 50 to 300 μM genipin reduced the NO level and iNOS expression dose-dependently while inhibiting the degradation of IκB-β of the NF-κB pathway (Koo et al., 2004). In addition, genipin was shown to inhibit neuroinflammation in LPS-induced murine microglial cells (Araki et al., 2014). It has also been found that genipin can suppress the level of the pro-inflammatory cytokine during *H. pylori* infection of the gastric cells (Chang et al., 2017). The evidence showed that genipin has potential anti-inflammatory activity in the nervous system and gastrointestinal tract.

A derivative of free genipin, known as genipin-1-β-$_D$ -gentiobioside, was investigated for its anti-inflammatory potential in hyperglycaemia using the high glucose-induced podocyte model. AMPK (AMP-activated protein kinase) silencing was performed to study the effects of genipin-1-β- $_D$ -gentiobioside on inflammation via the AMPK pathway in a hyperglycaemia-induced injury. The study showed that genipin-1-β-$_D$ -gentiobioside had protective effects against high glucose-induced inflammation in the podocytes by increasing the AMPK and SIRT1 (silencing information regulator-related enzyme 1) expressions (Li et al., 2021). Since both genipin and geniposide have been reported for their efficacy against inflammation with unknown effects on the liver, C. Li et al. (2019) compared their potential hepatotoxic effects in rat liver (BRL-3A) cells. The study demonstrated that both genipin and geniposide at (200 and 300 μg/ml) produced elevated NO, TNF-α, and IL-6 levels. However, genipin and geniposide at a lower dosage (100 μg/ml) had no significant effect on the inflammatory cytokines except for a slight increase in TNF-α level. The selected studies have shown significant therapeutic efficacy of genipin and geniposide against different in vitro models of inflammation, targeting mainly the NF-κB pathway to reduce the production of NO and pro-inflammatory cytokines.

On top of that, two studies examined the anti-inflammatory effects of monotropein against in vitro inflammation. Shin et al. (2013) showed that monotropein inhibited LPS production of NO and PGE2 as well as the expressions of iNOS, COX-2, TNF-α, and IL-1β in RAW 264.7 cells. According to the study, monotropein produced its anti-inflammatory action via the inactivation of IκB-α of the NF-κB pathway (Shin et al., 2013). In a separate study, Wang et al. (2014) stimulated primary rat knee chondrocytes with IL-1β to mimic the osteoarthritic environment and treated the cells with 25, 50, and 100 μg/ml monotropein for 48 h. The study demonstrated significantly lower expressions of inflammatory (COX-2) and apoptotic (MMP-3, MMP-13, caspase-3, and caspase-9) markers in monotropein-treated cells (Wang et al., 2014). Therefore, monotropein demonstrated anti-inflammatory and anti-apoptotic properties in vitro.

4.3. *Effects of selected iridoids against in vivo inflammation*

Animal models of inflammation are useful for evaluating the potential pharmacotherapeutic effects of newly isolated compounds and identifying the lead compounds for future research. Some of the commonly used animal models in inflammation research include carrageenan-induced paw oedema, and LPS-induced inflammation models (Rafiyan et al., 2023). Carrageenan, which is a polysaccharide

extracted from red seaweed, is injected into a rat's paw to induce inflammation, and swelling. The anti-inflammatory activity of the tested compound is then evaluated by measuring the reduction of paw oedema (Tobacman, 2001). Other stimulants, such as LPS, ovalbumin, cotton pellets, titanium dioxide nanoparticles, and complete Freund's adjuvant, have been discussed in a separate review (Rafiyan et al., 2023).

In this article, the selected studies collectively showed the promising anti-inflammatory activities of genipin against a wide variety of diseased animal models. Genipin was demonstrated to exert inhibitory activities against neurodegeneration (Araki et al., 2014), sepsis (Kim et al., 2015), allergic asthma (Ko et al., 2017), acute lung injury (J. Li et al., 2019), and acute liver injury (Wang et al., 2019). Genipin inhibited neuroinflammation in LPS-induced sickness behaviour mice by targeting the inflammatory gene expressions in the mice's brains (Araki et al., 2014). In a study by Kim et al. (2015), septic mice treated with 2.5 mg/kg genipin showed significant improvement in survival rate and decreased levels of inflammatory cytokines compared to untreated control mice (Kim et al., 2015). Genipin was also found to be beneficial against asthmatic disease by reducing airway inflammation in ovalbumin-challenged mice (Ko et al., 2017). Similarly, genipin displayed anti-inflammatory activity in an acute lung damage rat model by modulating GSK-3β via the NF-κB pathway (J. Li et al., 2019). Moreover, genipin-treated mice showed reduced inflammatory changes and cytokine expressions in the hepatic tissue following an acute liver injury. The suppression of the NF-κB and STAT3 signalling pathways may be the mechanism involved in the hepatoprotective activity of genipin in this study (Wang et al., 2019).

Six studies were selected for this review for investigating the anti-inflammatory properties of geniposide using different in vivo models. In two of the studies, the effects of geniposide on adjuvant arthritic rats induced with complete Freund's adjuvant (CFA) (Chen et al., 2015) or ferrocenecarboxylic acid, were examined (Zhang et al., 2017). CFA is a water-in-oil emulsion containing killed mycobacterium - a classical method commonly used to mimic the pathophysiology of joint inflammations (Ismail et al., 2022). Arthritis itself is a large spectrum of diseases related to joint inflammations; categorised into autoimmune (such as rheumatoid arthritis and lupus), degenerative (osteoarthritis), and inflammatory (gout) forms of arthritis. In this review, geniposide-treated adjuvant arthritic rats were found to have significantly improved arthritis scores in both studies and reduced inflammatory changes in the ankle tissues (Chen et al., 2015) and mesenteric lymph node lymphocytes (Zhang et al., 2017). The levels of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) were also reduced in CFA-induced arthritic rats treated with geniposide (60 and 120 mg/kg) while those of the anti-inflammatory cytokine IL-10 was elevated. Geniposide also reduced the phosphorylation of p38, MAPK kinase 3 and 6 (MKK3/6), and MAPK-activated protein kinase 2 (MAPKAP2), suggesting its mechanism of anti-inflammatory action via the MAPK signalling pathway (Chen et al., 2015). Evidence has shown that the MAPK pathway plays a significant role in the pathogenesis of arthritis and may act as the molecular target for inhibition of the inflammatory response, particularly p38 MAPK. Similarly, polyphenols such as epigallocatechin-3-gallate, curcumin, and magnolol were also found to exert their anti-inflammatory properties by targeting MAPK (Behl et al., 2021).

In this review, two in vivo studies independently compared the efficacy of genipin and geniposide against inflammation using different animal models. Koo et al. (2006) compared the anti-inflammatory potential of genipin and geniposide using carrageenan-induced rat paw oedema and an air pouch model. It was found that 50 mg/kg genipin-treated mice showed higher efficacy than that of 100 mg/kg geniposide-treated mice by significantly reducing the oedema volume, exudate formation, and NO production (Koo et al., 2006). In another study, Chang et al. (2017) demonstrated the anti-inflammatory activity of geniposide and genipin in C57BL/6 mice infected with *H. pylori*. The infected mice were shown to have decreased serum cytokines and immunoglobulin levels when treated with 26 mg/kg/day genipin or 62 mg/kg/day geniposide for three days orally. The authors suggested that the mechanism could be related to COX-2 inhibition, as all the treated mice showed reduced COX-2 gene expression in their gastric tissues (Chang et al., 2017). From both studies, it can be concluded that genipin was shown to produce significant anti-inflammatory benefits at half the dosage of geniposide.

Three studies demonstrated the efficacy of monotropein as a potential therapeutic agent against carrageenan-induced paw oedema (Choi et al., 2005), dextran sulphate sodium (DSS)-induced colitis (Shin et al., 2013), and knee osteoarthritis (Wang et al., 2014) in vivo. Choi et al. (2005) discovered the therapeutic efficacy of monotropein (30 mg/kg) in reducing the volume of rat paw oedema by almost 40% as early as 3 h after injection with 1% carrageenan solution, which is comparable to ibuprofen in the study. Moreover, monotropein was found to protect against colon inflammation by attenuating the expression of iNOS and COX-2, responsible for the acute inflammatory response. Monotropein was also found to inhibit the degradation of IκB-α and prevent the nuclear translocation of the p65/p50 subunit of NF-κB, thus inactivating the inflammatory signalling pathway (Shin et al., 2013). In addition, monotropein produced local anti-inflammatory action against inflammatory precursors and mediators in the synovial fluid of an osteoarthritic knee while minimising the local inflammatory infiltrations to prevent the progression of acute knee osteoarthritis to chronic (Wang et al., 2014). These findings suggest that monotropein alleviates inflammation-related conditions by regulating the pro-inflammatory cytokines and mediators involved in the inflammatory signalling pathway and immune responses.

5. Conclusions

The studies selected in this review have highlighted the potential use of iridoids as naturally derived medicines for inflammation-related diseases. Although iridoids have shown promising pharmacological activities, there is still limited research on their pharmacokinetics and toxicological profiles. Moreover, there is a lack of standardisation regarding the plant sources of these iridoids due to several factors, such as geographical location, plant species, harvesting time, and isolation techniques. The availability of several iridoids as synthetic compounds manufactured by commercial pharmaceutical companies has aided the advancement of research progress by minimising the time required for a difficult and lengthy extraction process. Finally, the lack of clinical trials on the efficacy and safety of iridoids as anti-inflammatory agents could hinder the development of these compounds. Therefore, additional research is needed to completely unravel the underlying molecular mechanisms of iridoids and establish their pharmacological safety profile in developing iridoids as a therapeutic alternative agent against inflammation-related diseases.

CRediT authorship contribution statement

Aisyah Jaafar: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Muhammad Amal Zulkipli:** Data analysis and interpretation. **Fazleen Haslinda Mohd Hatta:** Critical inputs and draft revision. **Aisyah Hasyila Jahidin:** Critical inputs and draft revision. **Nurul Alimah Abdul Nasir:** Critical inputs and draft revision. **Mizaton Hazizul Hasan:** Supervision, Project administration, Funding acquisition, Validation, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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