ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 8, Issue 3, 2015

ISSN - 0974-2441

Review Article

CHEMISTRY AND PHARMACOLOGY OF SYRINGIN, A NOVEL BIOGLYCOSIDE: A REVIEW

MAHADEVA RAO US*, THANT ZIN, MUHAMMAD ABDURRAZAK, BASHIR ADO AHMAD

Faculty of Medicine and Health Science, Universiti Sultan Zainal Abidin, Malaysia. *Email: raousm@gmail.com

Received: 21 February 2015, Revised and Accepted: 23 March 2015

ABSTRACT

Syringin**,** a phenylpropanoid glycoside belongs to eleutheroside derivative. This bioactive compound was identified in several plants including *Musa paradisiaca*, *Jasminum mesnyi*, *Edgeworthia chrysantha*, *Acanthopanax senticosus*, etc. According to Nair *et al*., syringin is synthesized from the precursor phenylalanine by a series of reactions. Zhao has described a rapid extraction method based on the ultrasound-assisted extraction of syringin from the bark of *Ilex rotunda* thumb using response surface methodology. Based on the findings made by Jizhong *et al*., the bioactive compound syringin was separated from the n-butanol extract of the stems and barks of *E. chrysantha* Lindl by high-speed counter-current chromatography. According to Choi *et al.*, the enrichment and purification of syringin from *A. senticosus* was performed based on the adsorption and desorption properties of commercial macroporous resins. The pharmacological properties of syringin includes scavenging the free radicals, protection against neuronal cell damage, inhibition of apoptosis, anti-diabetic effect, anti-inflammatory potential, anti-nociceptive action, anti-allergic effect, etc.

Keywords: Phenylpropanoid glycoside, Eleutheroside, Apoptosis, Nociceptive.

INTRODUCTION

Eleutherosides

Eleutherosides are a diverse group of chemical compounds that were isolated from the roots of the herb *Eleutherococcus senticosus* which is commercially offered mostly as extracts. Eleutheroside A is a saponin and sterol glycoside while other Eleutherosides, such as Eleutheroside B (syringin), are phenylpropanoid glycosides. There are no definite effects associated with these constituents, and they rather serve as marker compounds for the thin layer chromatography identification of *E. senticosus* herbal preparations and dietary supplements [1]. Syringin is a natural chemical compound first isolated from the bark of lilac (*Syringa vulgaris*) by Meillet in 1841. It has since been found to be distributed widely throughout many types of plants. Chemically, it is a glucoside of sinapyl alcohol-phenylpropanoid glucoside compound [2- 4].

Sources of syringin

The bioactive compound was determined in several plants. *Jasminum mesnyi* also known as Primrose Jasmine or Japanese Jasmine is an evergreen shrub, in which leaves are opposite and trifoliate attached to the base of branchlets, with yellow colored flowers were found to contain syringin [5]. Syringin was isolated from the bark of *Edgeworthia chrysantha* Lindl [6], a plant used to make paper in Korea and Japan while the flowers and the roots are used as the crude drugs in China [7]. Radix *Acanthopanax senticosus* (RAS) consists of the dried roots and rhizomes of *A. senticosus* (Araliaceae) [8]. RAS has been used extensively in China, Russia, Korea, and Japan as an adaptogen [9, 10]. According to previous research results, syringin is one of the major components attributed to the pharmacological effects of RAS [11]. Another plant from which syringin was extracted is *Ilex rotunda* thumb [12]. It was also determined in Saussurea Involucrata [13]. Using high-performance liquid chromatography (HPLC), the component composition of the bark of *S. vulgaris* has been studied and a procedure has been developed for the quantitative determination of syringin in raw material from this plant [14]. Syringin was also isolated from *Tinospora cordifolia.* The task force on conservation and sustainable use of medicinal plants identified the species as one of the most commercially exploited plants in pharmaceuticals. The estimated annual demand of this species used in the preparation of crude herbal drugs in the Indian system of medicines is 10,000 tons [15]. Syringin was also isolated and characterized from *Musa paradisiaca* tepal extract (MPTE) [16]. An active principle was isolated from the stem bark of *Fraxinus rhynchophylla* and identified as syringin [17]. Syringin was purified from the rhizome and root parts of *Eleutherococcus senticosus* (Araliaceae) [18]. It was also isolated from *Linum olympicum* (The genus Linum belongs to the family Linaceae and comprises about 200 species mainly distributed in the Mediterranean region) and its structure elucidated by ^{1}H-NMR analysis [19]. The accumulation of syringin was reported in different above-ground parts of *Cirsium setosum*. The best time to collect plants rich in biologically active components is when they are in full flower. Leaves and stems gathered during this period contained the highest amount of syringin and could be suitable raw materials for its extraction [20].

According to Joanna *et al*., the occurrence of syringin in eight out of ten investigated plant species of the subtribe centaureinae (Asteraceae) was reported. The compound was isolated from aerial parts of the plants by silica gel column chromatography of methanol extracts. Contents of syringin varied from 0.001 to 0.1% of the dried plant material. *Centaurea bella* Trautv., appeared to be the best of this compound (0.1% dry wt). Chemical study of methanolic extracts from aerial parts of ten plant species belonging to the substribe centaureinae led to the isolation of syringin from all but two extracts (Table 1). Syringin was absent from *Centaurea cyanus* and *Serratula wolffii,* and occurred as a minor constituent (0.001-0.006% of the dried plant material) in

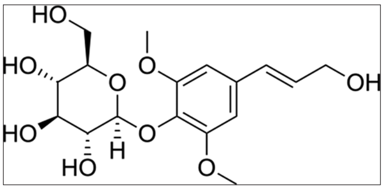
Table 1: Occurence of syringin in some species of the substribe centaureinae

Taxon	Contents* of syringin (% dry wt)	Literature
Acroptilon repens (L.) DC	0.03	[22]
Centaurea bella Trautv.	0.1	[23]
Centaurea crocodylium	0.001	[24]
Centzurea cyanus L	Not detectable	
Chartolepsis pterocaulea (Trautv.) Czer	0.003	[25]
Grossheimia macrocephala Takht	0.001	[26]
Lauzea rhapontica subsp. *Bicknelli* (Briq) J. Holub	0.001	[27]
Psephellus dealbatis (Willd) Boiss	0.002	[25]
Psephellus declinatus (MB) C. Koch	0.006	[25]
Serratus wolffii Andrae	Not detectable	

*Estimated on the basis of isolated amounts of syringin from dried plant materials

Acroptilon repens, Centaurea crocodylum, Grossheimia macrocephala, Leuzea rhapontica, subsp.bicknellii, *Psephellus dealbatus, Psephellus declinatus.* From *Chartolepis pterocaula* and especially from *C. bella* it was isolated in higher amounts (0.03 and 0.1%, respectively) [21].

Chemistry of syringin



Name: Syringin
IUPAC name: 4-[(1E)-3-Hydroxyprop-1-ene-1-yl]-2,6-dimethoxyphenyl β-D- glucopyranoside
Other names: Eleutheroside B; Ilaxanthin, Lilacin, Ligustrina, magnolenin, methoxy coniferin, sinaphyl alcohol 4-oglucoside
Molecular formula: $C_{17}H_{24}O_9$
Molar mass: 372.37g/mol
Appearance: White crystalline solid
Melting point: 192°C
Solubility in water: Slightly soluble

Synthesis of syringin

According to Nair *et al*., syringin is synthesized by the precursor phenylalanine to tyrosine by the action of hydroxylase, then to p-coumaric acid by lyase and to caffeic acid in a reaction catalyzed by monooxygenase; this in turn is converted to ferulic acid and sinapic acid by transferase. The acid further gets coverted by ligase into sinapyl CoA, then to sinapaldehyde by reductase, penultimately to sinapyl alcohol coupled by dehydrogenase and ultimately to syringin by the action of glucosyltransferase [28].

According to Chu *et al*., to promote the efficient production of syringin, a plant-derived bioactive monolignol glucoside, synergistic effects of enzymatic and metabolic engineering were combined. Recombinant UGT72E3/E2 chimeras, generated by exchanging parts of the C-terminal domain including the putative secondary plant glycosyltransferase motif of UGT72E3 and UGT72E2, were expressed in leaves of transgenic arabidopsis plants; syringin production was measured *in vivo* and by enzymatic assays *in vitro*. In both tests, UGT72E3/2 displayed substrate specificity for sinapyl alcohol like the parental enzyme UGT72E3, and the syringin production was significantly increased compared to UGT72E3. In particular, in the *in vitro* assay, which was performed in the presence of a high concentration of sinapyl alcohol, the production of syringin by UGT72E3/2 was 4-fold higher than by UGT72E3. Furthermore, to enhance metabolic flow through the phenylpropanoid pathway and maintain a high basal concentration of sinapyl alcohol in the leaves, UGT72E3/2 was combined with the sinapyl alcohol synthesis pathway gene F5H encoding ferulate 5-hydroxylase and the lignin biosynthesis transcriptional activator MYB58. The resulting UGT72E3/2+F5H+MYB58 OE plants, which simultaneously overexpress these three genes, accumulated a 56-fold higher level of syringin in their leaves than wild-type plants [29].

Ultrasound-assisted extraction (UAE) of syringin

Zhao has described, a rapid extraction method based on UAE of syringin from the bark of *I. rotunda* thumb using a response surface methodology (RSM). The syringin was analyzed and quantified by HPLC coupled with ultraviolet (UV) detection. The extraction solvent, extraction temperature, and extraction time, the three main factors for UAE, were optimized with Box-Behnken design to obtain the highest extraction efficiency. The optimal conditions were the use of a sonication frequency of 40 kHz, 65% methanol as the solvent, an extraction time of 30 minutes and an extraction temperature of 40°C. Using these optimal conditions, the experimental values agreed closely with the predicted values. The analysis of variance indicated a high goodness of model fit and the success of the RSM method for optimizing syringin extraction from the bark of *I. rotunda* [30] (Table 2). The analysis was performed with a HPLC instrument (Agilent 1100, USA) equipped with a quaternary solvent delivery system, a column oven and UV detector. Separation was achieved on a Hypersil ODS2 column (4.6 mm × 250 mm, 5 μm) from Dalian Elite Analytical Instruments Co., Ltd. (Dalian, China). The column temperature was set at 25°C and detection wavelength was set at 265 nm. The mobile phase was 10% CH_3CN with a flow rate of 1.0 mL/minutes. The isocratic elution was employed with 20 μL of injection sample.

Separation and identification of syringin

Based on the findings made by Jizhong *et al.*, the bioactive compound syringin along with Edgeworoside C were separated from the *n*-butanol extract of the stems and barks of *E. chrysantha* Lindl (*E. papyrifera*) by high-speed counter-current chromatography (HSCCC) while it was difficult to purify each compound by silica gel column chromatography. Syringin was isolated from this plant for the first time. The two-phase solvent system used was composed of ethyl acetate-ethanol-water at an optimized volume ratio of 15:1:15 (v/v/v). Preparative HSCCC yielded, from 110 mg of the partially purified extract, 28 mg of syringin, and 45 mg edgeworoside C each at over 96% purity by HPLC analysis. Their structures were identified by electron impact ionization (EI) MS, 1H NMR, and 13C.

The partially purified extract of *E. chrysantha* Lindl and each peak fraction from HSCCC were analyzed by HPLC. The analyses were performed with a Shim-Pack CLC-ODS C18 column (250 mm × 6 mm i.d.). The mobile phase composed of methanol-water (50:50, v/v) was eluted at a flow rate of 0.5 ml/minutes, and the effluent monitored by a Shimadzu SPD10Avp UV detector at 254 nm. Identification of HSCCC peak fractions was carried out by EI MS, 1H NMR, and 13C NMR spectra. NMR spectra were recorded on a Bruker Avance 400MHz spectrometer with TMS (tetramethylsilane) as internal standard. EI-MS was obtained on a HP5989B mass spectrometer [6].

Enrichment and purification of syringin from *A. senticosus*

According to Choi *et al.*, in order to screen a suitable resin for the preparative simultaneous separation and purification of syringin, Eleutheroside E, and isofraxidin from *A. senticosus*, the adsorption and desorption properties of 17 widely used commercial macroporous resins were evaluated. According to Choi's results, HPD100C, which adsorbs by the molecular tiers model, was the best macroporous resin, offering higher adsorption and desorption capacities and higher adsorption speed for syringin, Eleutheroside E and isofraxidin than other resins. Dynamic adsorption and desorption tests were carried out to optimize the process parameters. The optimal conditions were as follows: For adsorption, processing volume: 24 BV, flow rate: 2 BV/h; for desorption, ethanol-water solution: 60:40 (v/v), eluent volume: 4 BV, flow rate: 3 BV/h. Under the above conditions, the contents of syringin, Eleutheroside E and isofraxidin increased 174-fold, 20-fold, and 5-fold and their recoveries were 80.93%, 93.97%, and 93.79%, respectively [31].

Pharmacological properties

Antioxidant property

Sun Ju Kim demonstrated the ability of extracts and active components isolated from nine medicinal, *Poncirus trifoliata, Astragalus membranaceus, Magnolia obovata, Salvia miltiorrhiza, Angelica dahurica, Cornus officinalis,*

Table 2: Optimum conditions and the predicted and experimental yield at the optimum conditions

Status	Methanol (%)	Extraction time (minutes)	Temperature (°C)	Yield of syringin
Optimum condition	65.35	30.74	40.39	9.16 (predicted)
Modified conditions	65	30	40	9.20 (actual)

Cnidium officinale, Pueraria lobata, and *Ostericum koreanum*, to neutralize peroxyl radicals was determined using the total oxyradical scavenging capacity (TOSC) assay. Peroxyl radicals were generated from thermal homolysis of 2,2'-azobis(2-methylpropionamidine) dihydrochloride, which oxidize α-keto-γ-methiolbutyric acid to yield ethylene, and the TOSC of the substances tested is quantified from their ability to inhibit ethylene formation. Extracts from *S. miltiorrhiza*, *M. obovata,* and *P. lobata* were determined to be potent peroxyl radical scavenging agents with a specific TOSC (sTOSC) being at least threefold greater than that of glutathione. Major constituents of the three plants, among which, syringin was examined for the antioxidant potential toward peroxyl radical. Syringin demonstrated the peroxyl radical scavenging capacity comparable to that of glutathione. The implication of peroxyl radical in lipid peroxidation and other cellular damage suggests a possible protective role for the extract and the isolated component in oxidative stress caused by this reactive oxygen species [32]. Kim *et al*. and Yang *et al*. showed that the compounds isolated from *F. rhynchophylla,* among which is syringin, exhibit a radical scavenging effect on 1,1-diphenyl-2-picrylhydrazyl (DPPH) [33], and an inhibitory effect against nitric oxide (NO) synthesis, respectively [34].

Protection against neuronal cell damage

According to Eunju *et al*., the medicinal herb *Jinpi*, derived from the dried stem barks of *F. rhynchophylla* belonging to Oleaceae is widely used as a variety of Korean folk remedies for anti-inflammatory, febricide, antidiarrhea, and antileukorrhea diseases. In the course of screening antidementia agents from natural products, *F. rhynchophylla* showed significant inhibitory activity toward Aβ (25-35)-induced neuronal cell death. An active principle was isolated and identified as syringin. When the neuroblastoma cells were exposed to 50 μM Aβ (25-35), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction rate (survival rate) decreased to 60.21±2.16% over control while syringin treated ones recovered cell viability up to 79.12±1.39% at 20 μM. In addition, 20 μM syringin almost completely removed Aβ (25-35)-induced reactive oxygen species. The neuroprotective effect of syringin seemed to be originated from the reduction of apoptosis since the decrease in caspase-3 activity and expression, reduction in cleaved poly-(ADP-ribose) polymerase (PARP), and DNA fragmentation were observed. These results suggest that *F. rhynchophylla* and syringin are expected to be useful for preventing Aβ (25-35)-induced neuronal cell damage [17] (Figs. 1 and 2).

Syringin inhibits apoptosis

Apoptosis is associated with a series of biochemical changes, including caspase-3 activation, cleavage of the DNA repair enzyme (PARP), and fragmentation of internucleosomal DNA [35]. Caspase-3, a class of the cysteine protease family, has been suggested as playing an important role in Aβ-induced apoptosis [36-38]. To elucidate whether the Aβ-induced neuronal cell death was related to the apoptosis, activity and expression of caspase-3 and cleaved PARP were confirmed. Caspase-3 activity in the 50 μM Aβ (25-35)-treated cells were increased about 1.13±0.02 folds over the control group while those of the 5 and 20 μM syringin-treated cells were suppressed by about 0.98±0.02 and 0.90±0.01 folds, respectively (Fig. 3). In addition, syringin inhibited the cleavage of PARP, indicating that it inhibited the caspase-3 activity via reduction of activated caspase-3 expression (Fig. 4). When neuroblastoma cells treated with 50 μM Aβ (25-35) were incubated with or without syringin, the level of DNA fragmentation caused by Aβ was significantly reduced in syringin-treated cells (Fig. 5). These data indicated that syringin can recover or protect the neurotoxicity of Aβ through inhibition of apoptosis [17].

Antidiabetic effect

Based on Shanmuga Sundaram Chinna Krishnan *et al*., syringin was isolated and characterized, from MPTE and evaluated its anti-diabetic efficacy in streptozotocin-induced diabetic rats. Syringin was isolated from MPTE and characterized using spectral studies. Diabetic rats were administered 50 mg/kg per day syringin orally for 30 days. After the experimental period rats were sacrificed and blood was collected for important biochemical parameters such as blood glucose, insulin, hemoglobin, HbA1c, total protein, urea, uric acid, and creatinine. Serum aminotransferases and alkaline phosphatases were assayed. The data revealed the presence of syringin in MPTE. Elevated blood glucose and HbA1c levels, the reduced plasma insulin and hemoglobin levels in diabetic rats were significantly reversed to near normal after oral administration of syringin. Plasma protein, blood urea, serum creatinine, and uric acid levels were also normalized after treatment. The altered activities of serum transaminases and alkaline phosphatases were normalized upon syringin treatment indicating its nontoxic nature. The ability of syringin to enhance glucose utilization and lower plasma glucose level in rats suffering from insulin deficiency suggest that this chemical may be useful in the treatment of human diabetes [16,39].

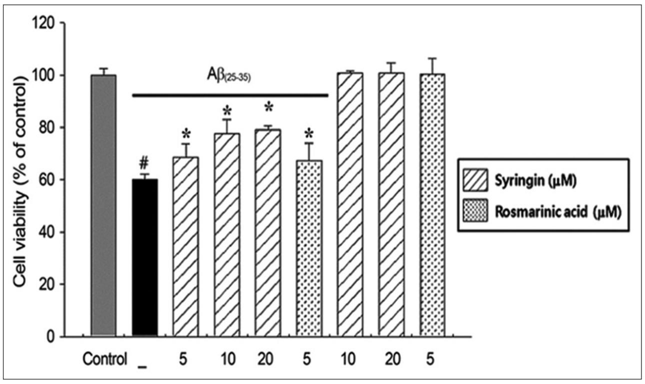


Fig. 1: Neuroblastoma cell-protecting effect of syringin on Aβ (25-35)-induced cell death, cell treated with various concentration of syringin. Rosmarinic acid was used as a positive control. The symbols # and * indicate significant differences (p<0.05). #Compared to control; *compared to Aβ (25-35)

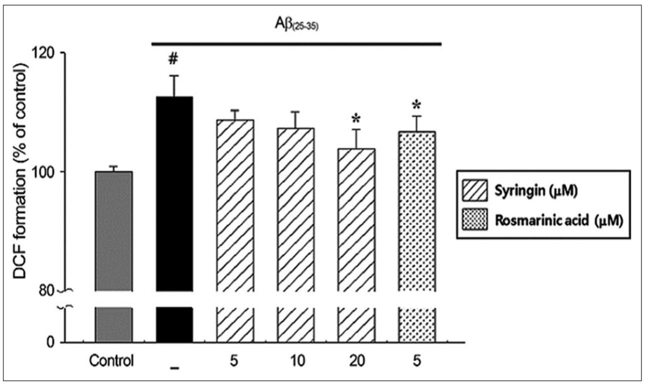


Fig. 2: Inhibitory effect of syringin on Aβ (25-35)-induced reactive oxygen species generation. Neuroblastoma cells were treated with Aβ (25-35) and samples, then H2DCFDA (0.05 mg/mL) solution was added. After 10 minutes of incubation at 37°C, DCF fluorescence was quantified using a microplate fluorescence reader with 485 nm excitation and 510 nm emission filters. Challenge of H2DCFDA and measurement of fluorescence intensity was performed in the dark. Rosmarinic acid was used as a positive control. The symbols # and * indicate significant differences (p<0.05). #Compared to control; *compared to Aβ (25-35)

In another study by Liu *et al*., designed to screen the effect of syringin, an active principle purified from the rhizome and root parts of *E. senticosus* (Araliaceae) on the plasma glucose, and investigate the possible mechanisms. Plasma glucose decreased in a dose-dependent manner 60 minutes after intravenous injection of syringin into fasting Wistar rats. In parallel to the decrease of plasma glucose, increases of plasma insulin level, as well as the plasma, C-peptide was also observed in rats receiving the same treatment. Both the plasma glucose lowering action and the raised plasma levels of insulin and C-peptide induced by syringin were also inhibited by 4-diphenylacetoxy-N-methylpiperdine methiodide, the antagonist of the muscarinic M3 receptors, but not affected by the ganglionic nicotinic antagonist, pentolinium or hexamethonium. Moreover, disruption of synaptic available acetylcholine (ACh) using an inhibitor of choline uptake, hemicholinium-3, or vesicular ACh transport, vesamicol, abolished these actions of syringin. Furthermore, physostigmine at a concentration sufficient to inhibit acetylcholinesterase enhanced the actions of syringin. Mediation of ACh release from the nerve terminals to enhance insulin secretion by syringin can thus be considered. The results suggest that syringin has an ability to raise the release of ACh from nerve terminals, which in turn to stimulate muscarinic M3 receptors in pancreatic cells and augment the insulin release to result in plasma glucose lowering action [18].

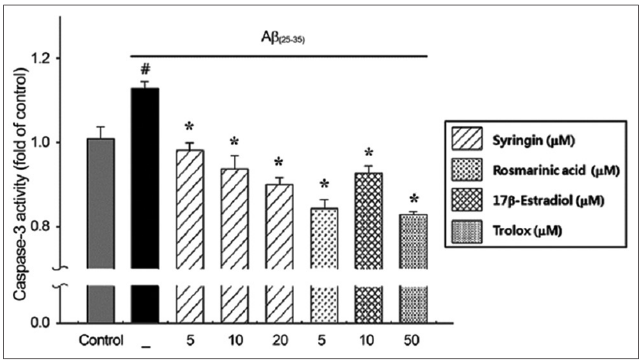


Fig. 3: Reduction of Aβ (25-35)-induced caspase-3 activity in syringin-treated cells. Neuroblastoma cells were seeded at a density of 5×10^5 in 12-well plates and incubated. Then, cells on dishes were washed with phosphate-buffered saline and collected by centrifugation. The washed cell pellet was resuspended in lysis buffer and incubated on ice. After 10 minutes, cell lysates were centrifuged, the supernatant was analyzed for its protein content. To assess the extent of caspase-3 substrate cleavage, the supernatant was transferred to 96-well plates and then treated with DTT solution and DEVD-AFC, which is a substrate for caspase-3 at 37°C. After 1 hr, DEVD-AFC cleavage activity was measured with excitation at 400 nm and emission at 505 nm using microplate fluorescence reader. Rosmarinic acid, 17β-estradiol, trolox were used as positive controls. The symbols # and * indicate significant differences (p<0.05). #Compared to control; *compared to Aβ (25-35)

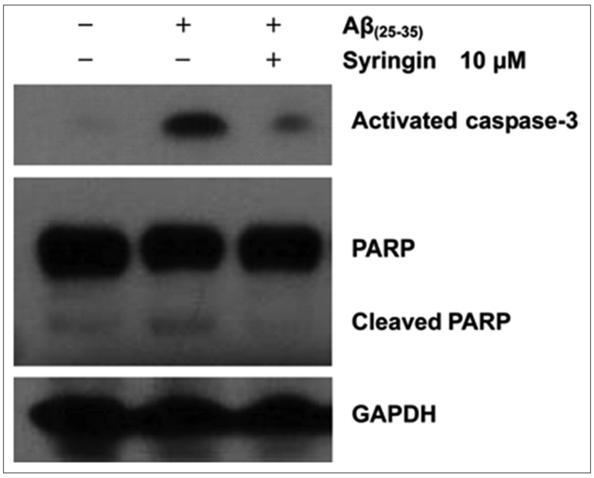


Fig. 4: Reduction of Aβ (25-35)-induced caspase-3 protein manifestation in syringin-treated cells. Neuroblastoma cells were treated with syringin in the presence or absence of Aβ (25-35). Caspase-3 manifestation was measured by Western blot with anti-caspase-3 and anti-poly-(ADP-ribose) polymerase antibody

Anti-ulcer property of syringin

A. senticosus (Rupr. et Maxim) is a plant found in China. Several kinds of chemical compounds have been reported, among which, phenolic compounds such as syringin and Eleutheroside E, were considered to be the most active components. Considerable pharmacological experiments both *in vitro* and *in vivo* have persuasively demonstrated that AS possessed antiulcer activity [40].

Syringin acts as anti-inflammatory and anti-nociceptive agent

Syringin, isolated by activity guided fractionation of the ethyl acetate (EtOAc) extracts of the stem bark of *Magnolia sieboldii*, and sinapyl alcohol, the hydrolysate of syringin, were evaluated for anti-inflammatory, and antinociceptive activities. Sinapyl alcohol (20, 30 mg/kg/day, p o.) inhibited increased vascular permeability by acetic acid in mice and reduced acute paw edema by carrageenan in rats more so than syringin. When analgesic activity was measured using the acetic acid-induced writhing test and the hot plate test, sinapyl alcohol was much more potent than syringin in a mouse model. In addition, sinapyl alcohol more potently inhibited lipopolysaccharide (LPS)-induced NO, prostaglandin E2, and tumor necrosis factor (TNF)-alpha production by macrophages than syringin. Consistent with these observations, the expression levels of inducible NO synthase and cyclooxygenase (COX)-2 was reduced by sinapyl alcohol in a concentration-dependent manner. These results suggest that the anti-inflammatory and antinociceptive effects of syringin after oral administration may be attributed to its *in vivo* transformation to sinapyl alcohol [31].

Carduus schimperi Sch. Bip. ex A. Rich (Asteraceae) is a perennial herb, and its roots are used in some localities in Ethiopia for orofacial inflammation in the form of warm aqueous macerate. In the present study, the *in vivo* anti-inflammatory and antinociceptive effects of the aqueous root extracts of *C. schimperi* were investigated. The anti-inflammatory effect was evaluated using carrageenan-induced mouse pedal (paw) edema model, while the formalin test in mice was employed to study the antinociceptive activity. Administration of 400 mg/kg p.o. of the aqueous extract of the roots of *C. schimperi* produced significant anti-inflammatory effects against carrageenan-induced acute inflammation and formalin-induced nociceptive pain stimulus in mice. Bioassay guided fractionation of the total extract indicated that the water fraction was by far the most potent in both

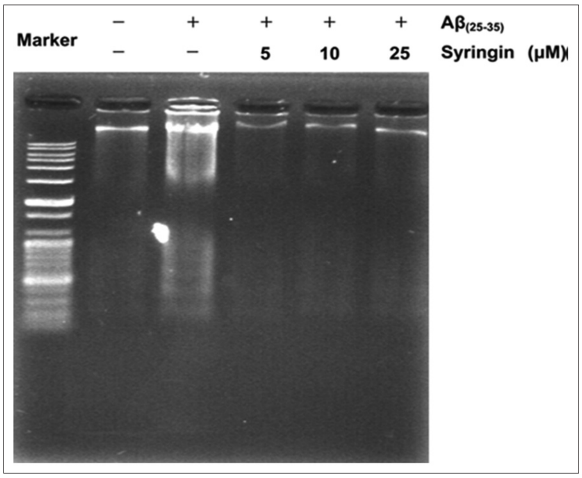


Fig. 5: Effect of syringin on Aβ (25-35)-induced DNA fragmentation. Neuroblastoma cells were seeded at a density of 1×10^6 in 6-well plates and treated with Aβ (25-35) and various concentrations of syringin. After 24 hrs, DNA was extracted with phenol-chloroform (1:1 v/v%) and analyzed by electrophoresis on a 1.2% agarose gel

models. Syringin, which was isolated for the first time from the active fraction of *C. schimperi* showed significant anti-inflammatory and anti-nociceptive activities when tested at a dose of 100 mg/kg, p.o. These findings indicated that *C. schimperi* possesses genuine anti-inflammatory and antinociceptive properties, lending pharmacological support to folkloric or anecdotal use of the plant in the treatment and/or management of painful inflammatory conditions. Syringin appears to be one of the active ingredients of the plant [41].

Anti allergic effect of syringin (Immunomodulatory effect)

Syringin was found to possess immunomodulatory activity by which it inhibited the *in vitro* immunohemolysis of antibody-coated sheep erythrocytes by guinea-pig serum through suppression of C3-convertase of the classical complement. In this study, we examined its *in vitro* and *in vivo* activity on TNF-α and NO production, CD4 + T cell, and CD8+ cytotoxic T-cell (CTLL-2) proliferation, and croton oil-, arachidonic acid-, and fluorescein-isothiocynate (FITC)-induced mouse ear edema model. Syringin significantly inhibited both TNF-α production from LPS-stimulated RAW264.7 cells and CD8+ T-cell (CTLL-2) proliferation in a dose-dependent manner, whereas neither NO production nor CD4+ T-cell proliferation were blocked even by high concentrations of syringin. In the *in vivo* experiments, syringin also significantly suppressed FITC-induced ear edema in mice, but not the ear edema induced by croton or arachidonic acid. These results suggest that syringin may be implicated as an immunomodulator having an anti-allergic effect rather than an anti-inflammatory effect. The anti-allergic effect of syringin seems to be due, in part, to inhibition of TNF-α production, and cytotoxic T-cell proliferation [42].

CONCLUSION

This review presents some sources and detailed pharmacological information of syringin. The review of pharmacological studies suggests that the traditional uses of the compound in ulcer, diabetes, hypertension, anti-allergic, antioxidants, etc., are scientifically valid. However, clinical studies in humans are still not available that may provide evidence of efficacy of the compound syringin.

REFERENCES

1. Yu S, Ovodov G, Frolova M, Yu M, Nefedova G, Elyakov B. The glycosides of *Eleutherococcus senticosus* II. The structure of eleutherosides A, B1, C, and D. Chem Nat Compd 1967;3(1):53-4.
2. Meilet A. Lilacin in justus liebigs annalin der chemie. Eur J Organ Chem 1841;40(3):319-20.
3. Yin L, Yang YH, Wang MY, Zhang X, Duan JA. Effects of syringin from *phellodendron chinensis* on monosodium urate crystal-induced inflammation and intracellular adhesion molecule-1 (ICAM-1) expression. Afr J Pharm Pharmacol 2012;6(21):1515-9.
4. Porter N, editor. Webster's Revised Unabridged Dictionary. C. & G. Merriam Co.; 1913.
5. Jain A, Sharma R, Kumar A, Sharma S. *Jasminum* species: An overview. Int J Inst Pharm Life Sci 2011;1(1):251-66.
6. Yan J, Tong S, Chu J, Sheng L, Chen G. Preparative isolation and purification of syringin and edgeworoside C from *Edgeworthia chrysantha* Lindl by high-speed counter-current chromatography. J Chromatogr A 2004;1043(2):329-32.
7. Hashimoto T, Tori M, Asakawa Y. Piscicidal sterol acylglucosides from edgeworthia. Phytochemistry 1991;30(9):2927.
8. WHO. WHO Monographs on Selected Medicinal Plants. Geneva, Switzerland: World Health Organization; 2004.
9. Brekhman II, Dardymov IV. New substances of plant origin which increase non-specific resistance. Annu Rev Pharmacol 1969;9:419-30.
10. Davydov M, Krikorian AD. *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (*Araliaceae*) as an adaptogen: A closer look. J Ethnopharmacol 2000;72(3):345-93.
11. Yang F, Yang L, Wang W, Liu Y, Zhao C, Zu Y. Enrichment and purification of syringin, eleutheroside E and isofraxidin from *Acanthopanax senticosus* by macroporous resin. Int J Mol Sci 2012;13(7):8970-86.
12. Wang JX, Zhang YY, Jia XN, Yang YZ. HPLC determination of syringin in *Ilex rotunda* Thunb. Chin J Pharm Anal 2008;28(5):788-9.
13. Zhai KF, XingJG, YangWJ, Huang HY. HPLC determination of syringin, chlorogenic acid and rutin in *Saussurea* involucrate Kar.et Kir. Chin J Pharm Anal 2008;28(5):762-5.
14. Kurkin VA, Grinenko NA, Zapesochnaya GG, Dubichev AG, Vorontsov ED. TLC and HPLC analysis of *syringin* in *Syringa vulgaris*. Chem Natural Compd 1992;28(1):36-9.
15. Singh BG, Warrier RR. *Tinospora cordifolia*. Indian Forester 2004;130:1806.
16. Krishnan SS, Subramanian IP, Subramanian SP. Isolation, characterization of syringin, phenylpropanoid glycoside from *Musa paradisiaca* tepal extract and evaluation of its antidiabetic effect in streptozotocin-induced diabetic rats. Biomed Prev Nutr 2014;4(2):105- 11.
17. Yang EJ, Kim SI, Ku HY, Lee DS, Lee JW, Kim YS, *et al.* Syringin from stem bark of *Fraxinus rhynchophylla* protects Abeta(25-35)-induced toxicity in neuronal cells. Arch Pharm Res 2010;33(4):531-8.
18. Liu KY, Wu YC, Liu IM, Yu WC, Cheng JT. Release of acetylcholine by syringin, an active principle of *Eleutherococcus senticosus*, to raise insulin secretion in Wistar rats. Neurosci Lett 2008;434(2):195-9.
19. Konuklug B, Bahadir O. Phenylpropanoid glycosides from *Linum olympicum* (Linaceae). Turk J Chem 2004;28:741-4.
20. Syrchina AI, Vereshchagin AL, Kostyro YA, Gorshkov AG, Semenov AA. Contents of some flavonoid compounds and syringin in different parts of *Cirsium setosum* (Willd.) Bess. Rastitel'nye Resursy 2000;36(2):73-9.
21. Cis J, Nowak G, Horszkiewicz-Hassan M, Kisiel W. Syringin in some species of the substribe centaureinae of the asteraceae. Acta Soc Botanicorum Pol 2003;72(2):105-7.
22. Fischer HB, List EJ, Koh RC, Imberger J, Brooks NH. Mixing Inland and Coastal Waters. Vol. 25. New York: Academic Press; 1979. p. 114- 25.
23. Nowak G. Chromatography of twenty six sesquiterpene lactones from *Centaurea bella.* Chromatographia 1993;35:325-8.
24. Horoszkiewcz-Hassan M, Nowak G. Germ kranolidy W *Centaurea crocodylium* L. Herb Prolonicer 2001;47:122-4.
25. Nowak G, Drozoz B, Holub M, Lagodzinska A. Sequisterpene lactonesxxxiii. guaianolidos in the subgenus psephellus (Cass) selimalli genus centaurea L. Acta Soc Bot Pol 1986;55:629-37.
26. Daniewski W. Wawrzun A. Bloszyk E, Drozdz B, Holub M. Sesquiterpenic lactones from grossheimia macrocephala. Structure of grosheiminlo. Collect Czechoslov Chem Commun 1982;47:3160-3.
27. Cis J, Nowak G, Grabarczyk H. Preliminary identification of unknown and well known guaianosides of the genus Leuzea DC. 2nd International Symposium on chromatography of natura products in Kazimirerz. Dolny Book of Abstracts; 2000. p. 61.
28. Nair RB, Bastress KL, Ruegger MO, Denault JW, Chapple C. The Arabidopsis thaliana reduced epidermal fluorescence1 gene encodes an aldehyde dehydrogenase involved in ferulic acid and sinapic acid biosynthesis. Plant Cell 2004;16(2):544-54.
29. Chu Y, Kwon T, Nam J. Enzymatic and metabolic engineering for efficient production of syringin, sinapyl alcohol 4-O-glucoside, in Arabidopsis thaliana. Phytochemistry 2014;102:55-63.
30. Zhao LC, He Y, Deng X, Xia XH, Liang J, Yang GL, *et al.* Ultrasound-assisted extraction of syringin from the bark of *Ilex rotunda* thumb using response surface methodology. Int J Mol Sci 2012;13(6):7607-16.
31. Choi J, Shin KM, Park HJ, Jung HJ, Kim HJ, Lee YS, *et al.* Anti-inflammatory and antinociceptive effects of sinapyl alcohol and its glucoside *syringin*. Planta Med 2004;70(11):1027-32.
32. Kim SJ, Kwon do Y, Kim YS, Kim YC. Peroxyl radical scavenging capacity of extracts and isolated components from selected medicinal plants. Arch Pharm Res 2010;33(6):867-73.
33. Kim HC, An RB, Jeong GS, Oh SH, Kim YC. 1,1-Diphenyl-2- picrylhydrazyl radical scavenging compounds of *Fraxini Cortex*. Nat Prod Sci 2005;11:150-4.
34. Kim NY, Pae HO, Ko YS, Yoo JC, Choi BM, Jun CD, *et al*. *In vitro* inducible nitric oxide synthesis inhibitory active constituents from *Fraxinus rhynchophylla*. Planta Med 1999;65:656-8.
35. Hu R, Kim BR, Chen C, Hebbar V, Kong AN. The roles of JNK and apoptotic signaling pathways in PEITC-mediated responses in human HT-29 colon adenocarcinoma cells. Carcinogenesis 2003;24(8):1361-7.
36. Wolf BB, Green DR. Suicidal tendencies: Apoptotic cell death by caspase family proteinases. J Biol Chem 1999;274:20049-52.
37. Allen JW, Eldadah BA, Huang X, Knoblach SM, Faden AI. Multiple caspases are involved in beta-amyloid-induced neuronal apoptosis. J Neurosci Res 2001;65(1):45-53.
38. Morais Cardoso S, Swerdlow RH, Oliveira CR.Induction of cytochrome c-mediated apoptosis by amyloid beta 25-35 requires functional mitochondria. Brain Res 2002;931:117-25.

39. Niu HS, Liu IM, Cheng JT, Lin CL, Hsu FL. Hypoglycemic effect of syringin from *Eleutherococcus senticosus* in streptozotocin-induced diabetic rats. Planta Med 2008;74(2):109-13.
40. Huang L, Zhao H, Huang B, Zheng C, Peng W, Qin L. *Acanthopanax senticosus*: Review of botany, chemistry and pharmacology. Pharmazie 2011;66(2):83-97.
41. Wolde-Mariam M, Veeresham C, Asres K. Anti-inflammatory and antinociceptive activities of extracts and *syringin* isolated from *Carduus schimperi* Sch. Bip.ex A. Rich. Pharmacology 2012;3(2):252-62.
42. Cho JY, Nam KH, Kim AR, Park J, Yoo ES, Baik KU, *et al. In-vitro* and *in-vivo* immunomodulatory effects of *syringin*. J Pharm Pharmacol 2001;53(9):1287-94.