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Review Article

Phytochemical and pharmacological overview on Liriopes radix

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Abstract

Liriopogons (Liriope and Opiopogon) species are used as the main medicinal ingredient in traditional medicine in several Asian countries. The roots or tubers of Liriope plants (Liriopes radix; LR) have traditionally been used for hundreds of years to treat cough, insomnia, constipation, asthma, and inflammation. The present review discusses extensively the available knowledge on its phytochemical and pharmacological activities in vitro and in vivo. The review does not include other parts of these plants. Literature evidence has been analyzed to identify responsible phytochemicals and their wide range of pharmacological activities. Further studies are needed for the isolation of purified compounds in order to understand their mechanisms of action and for clinical application.

Keywords: *Diabetes, Liriope platyphylla, Neuroprotective, Phytochemistry, Steroidal glycosides*

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INTRODUCTION

The uses of bioactive natural products derived in traditional oriental medicine are attractive sources for developing novel therapeutics because of their safety, affordability, long-term use, and ability to target multiple pathways. The present review aims to summarize and discuss the available information about the advances in the phytochemistry, toxicology, and pharmacological properties of *Liriopes Radix* (LR) in order to facilitate future research and support the utilization of it as a novel drug. LR is the swelling part of the roots from *Liriope platyphylla* Wang et Tang, *Ophiopogon japonicus* Ker-Gawl., *O. stolonifer* Levl. et Vant., *Mondo japonicum* (L. f.) Farwell, and *Liriope spicata* (Thunb.) Lour. Botanically, liriopogons may be either *Liriope* or *Ophiopogon* belonging to the Liliaceae family, and are abundantly distributed in subtropical and temperate regions globally. LR has been used as a therapeutic drug for the treatment of cough, expectoration, nutrition, sthenia, diuresis, suppression of thirst, blood glucose regulation, and xerostomia. It has been demonstrated to have multiple pharmacological activities for the treatment of cough, inflammation, airway inflammation, obesity, and diabetes [1].

PHYTOCHEMISTRY

Quality evaluation of traditional medicinal products is very important for guaranteeing safety, efficacy, and stability. Almost all traditional medicines contain multiple known or unknown constituents that vary greatly in content, chemical, and physical properties. Many studies have revealed steroidal saponins and their glycosides, phenolic compounds, secondary metabolites from *L. platyphylla* and *L. spicata*, whereas steroidal glycosides and

homoisoflavones from *O. japonicus* are considered as active constituents in LR. The saponins and steroidal glycosides were tabulated in Table 1. (-)-liriopein A, and B, (3R)-3-(20,40-dihydroxybenzyl)-5,7-dihydroxy-6-methyl-chroman-4-one, (3R)-3-(20,40-dihydroxybenzyl)-5,7-dihydroxychroman-4-one, (3R)-3-(40-hydroxybenzyl)-3,5-dihydroxy-7-methoxy-6-methylchroman-4-one, (3R)-3-(40-hydroxybenzyl)-5,7-dihydroxy-6-methyl-chroman-4-one, (3R)-3-(40-hydroxybenzyl)-5,7-dihydroxylchroman-4-one, 3-(40-hydroxybenzylidene)-5,7-dihydroxychroman-4-one, stigmasteryl-β-D-glucoside, β-sitosteryl-β-D-glucoside, (+)-platyphyllarins A and B, isoliquiritigenin, (S)-N-cis-feruloyltyramine, (S)-N-cis-p-coumaroyloctopamine, (S)-N-trans-feruloyltyramine, (S)-N-trans-p-coumaroyloctopamine, 3-(4-hydroxy-3-methoxyphenyl)-N-[2-(4-hydroxyphenyl)-2-methoxyethyl]acrylamide, N-transferuloyl tyramine, (-)-syringaresinol, hexadecanoic acid-2',3'-dihydroxypropyl ester, indole-3-carboxylic acid, 4-hydroxybenzaldehyde, 4-hydroxybenzoicacid methyl ester, vanillin, and ethyltributanoate were isolated [2]. Moreover, methylophiopogonanone A and B [3], β-sitosterol, tran-p-hydroxycinnamic acid, 2-(4′-hydroxybenzoyl)-5,6-methylenedioxy-benzofuran, 2-(4′-hydroxybenzyl)-5,6-methylenedioxy-benzofuran, 5-hydroxymethyl-2-furaldehyde, allylpyrocatechol, 2,6-dimethoxy-4-nitrophenol, syringic acid, and vanillic acid [4] were also reported from LR.

Table 1: Steroidal glycosides and saponins from *Liriopes radix*

Steroidal glycosides and saponins	Reference
Daucosterol	[4]
Diosgenin 3-*O*-[2′-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)]-β-D-xylopyranosyl-(1→3)-β-D-glucopyranoside	[5]
Lirioprolioside A (=25(*S*)-ruscogenin 1-*O*-[α-L-rhamnopyranosyl(1→2)][β-D-xylopyranosyl(1→3)]-β-D-fucopyranoside-3-*O*-α-L-rhamnopyranoside)	[6]
Lirioprolioside B (=25(*S*)-ruscogenin 1-*O*-[3-*O*-acetyl-α-L-rhamnopyranosyl(1→2)]-β-D-fucopyranoside)	[6]
Lirioprolioside C (= 25(*S*)-ruscogenin 1-*O*-[2-*O*-acetyl-α-L-rhamnopyranosyl(l→2)]-β-D-fucopyranoside)	[6]
Lirioprolioside D (= ruscogenin 1-*O*-[2-*O*-acetyl-α-L-rhamnopyranosyl(1→2)]-β-D-fucopyranoside)	[6]
Neoruscogenin 1-*O*-2-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)]-β-D-fucopyranoside	[5]
Neoruscogenin 1-*O*-3-*O*-acetyl-α-L-rhamnopyranosyl-(1→2)]-β-D-fucopyranoside	[5]
Neoruscogenin 1-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-fucopyranoside	[5]
Neoruscogenin	[5]
Ophiofurospiside A (=26-*O*-β-D-glucopyranosyl-(22*S*, 25*R*)-furospirost-5-ene-3β, 17α, 26-triol-3-*O*-[α-l-rhamnopyranosyl-(1→2)]-[β-D-xylopyranosyl-(1→4)]-glucopyranoside)	[5]
Ophiogenin	[5]
Ophiogenin 3-*O*-α-L-rhamnopyanosyl-(1→2)-β-D-glucopyranoside	[5]
Ophiopogonin A (= ruscogenin 1-*O*-[3-*O*-acetyl-α-L-rhamnopyranosyl(1→2)]-β-D-fucopyranoside)	[6]
Ophiopogonin B	[5]
Ophiopogonin D	[5]
Ophiopogonin D′	[5]
Ophiopogonin E (= pennogenin 3-*O*-β-D-xylopyranosyl (1→4)-β-D-glucopyranoside)	[5]
Pennogenin 3-*O*-α-L-hamnopyranosyl-(1→2)-β-D-xylopyranosyl-(1→4)-β-D-glucopyranoside	[5]
Prazerigenin A	[5]
Prazerigenin A 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside	[5]
Prazerigenin A 3-*O*-β-D-glucopyranoside	[5]

Prosapogenin I (= 25(*S*)-ruscogenin 1-*O*-β-D-fucopyranoside)	[7]
Prosapogenin II (= 25(*S*)-ruscogenin 1-*O*-β-D-xylopyranosyl (1$\rightarrow$3)-β-D-fucopyranoside)	[7]
Prosapogenin III (=25(*S*)-ruscogenin 1-*O*-β-D-glucopyranosyl (1$\rightarrow$2)-β-D-fucopyranoside)	[7]
Ruscogenin	[5]
Ruscogenin 1-*O*-sulfate	[5]
25(*R*,*S*)-ruscogenin	[5]
25(*S*)-ruscogenin	[6]
25(*S*)-ruscogenin 3-O-methylether	[7]
25(*S*)-ruscogenin 3-*O*-α-L-rhamnopyranoside	[5]
Ruscogenin 1-*O*-β-D-fucopyranoside	[5]
25(*R*,*S*)-ruscogenin 1-*O*-β-D-fucopyranoside	[5]
25(*S*)-ruscogenin 1-*O*-β-D-fucopyranosido-3-*O*-α-L-rhamnopyranoside (= glycoside B)	[5,6,8]
25(*S*)-ruscogenin 1-*O*-β-D-xylopyranosido-3-*O*-α-L-rhamnopyranoside	[8]
25(*R*)-spirost-5,8(14)-diene-3β-ol-3-*O*-α-L-rhamnopyranosyl-(1$\rightarrow$2)-[β-D-xylopyranosyl-(1$\rightarrow$4)]-β-D-glucopyranoside	[5]
25(*R*,*S*)-ruscogenin 1-*O*-[β-D-glucopyranosyl-(1$\rightarrow$2)] [β-D-xylopyranosyl-(1$\rightarrow$3)]-β-D-fucopyranoside	[5, 8]
25(*S*)-ruscogenin 1-*O*-[2-*O*-acetyl]-α-L-rhamnopyranosyl(1$\rightarrow$2)][β-D-xylopyranosyl(1$\rightarrow$3)]-β-D-fucopyranoside	[8]
Ruscogenin 1-*O*-α-L-rhamnopyranosyl-(1$\rightarrow$2)-4-*O*-sulfate-α-L-arabinopyranoside	[5]
Ruscogenin 1-*O*-α-L-rhamnopyranosyl-(1$\rightarrow$2)-4-*O*-sulfate-α-L-fucopyranosido-3-*O*-β-D-glucopyranoside	[5]
Ruscogenin 1-*O*-α-L-rhamnopyranosyl-(1$\rightarrow$2)-4-*O*-sulfo-α-L-arabinopyranoside-3-*O*-β-D-glucopyranoside	[5]
25(*R*,*S*)-ruscogenin 1-*O*-α-L-rhamnopyranosyl-(1$\rightarrow$2)-β-D-fucopyranoside	[5]
25(*S*)-ruscogenin 1-*O*-α-L-rhamnopyranosyl(1$\rightarrow$2)-β-D-xylopyranoside	[5]
25(*S*)-ruscogenin 1-*O*-[α-L-rhamnopyranosyl(1$\rightarrow$2)[β-D-xylopyranosyl(1$\rightarrow$3)]-β-D-fucopyranoside	[6]
25(*R*,*S*)-ruscogenin 1-*O*-[3-*O*-acetyl-α-L-rhamnopyranosyl-(1$\rightarrow$2)]-β-D-fucopyranoside	[5,8]
25(*S*)-ruscogenin 1-*O*-[3-*O*-acetyl-α-L-rhamnopyranosyl-(1$\rightarrow$2)] [β-D-xylopyranosyl-(1$\rightarrow$3)]-β-D-fucopyranoide	[5,8]
25(*S*)-ruscogenin 1-*O*-[α-L-rhamnopyranosyl-(1$\rightarrow$2)]-β-D-xylopyranosyl-(1$\rightarrow$3)]-β-D-fucopyranoside	[5,6]
25(*S*)-ruscogenin 1-*O*-2,3-*O*-diacetyl-α-L-rhamnopyranosyl-(1$\rightarrow$2)-[β-D-xylopyranosyl-(1$\rightarrow$3)]-β-D-fucopyranoside	[5]
Spicatoside A (= 25(*S*)-ruscogenin 1-*O*-β-D-glucopyranosyl (1$\rightarrow$2)-[β-D-xylopyranosyl (1$\rightarrow$3)]-β-D-fucopyranoside)	[7,9]
Spicatoside B (= 26-*O*-β-D-glucopyranosyl 25(*S*)-22-*O*-methyl-furost-5-en-1β, 3β, 26-triol 1-*O*-β-D-glucopyranosyl (1$\rightarrow$2)-[β-D-xylopyranosyl (1$\rightarrow$3)]-β-D-fucopyranoside)	[7]
Spicatoside D (= 26-*O*-β-D-glucopyranosyl-25(*S*)-furost-5(6)-ene-1β-3β-22α-26-tetraol-1-*O*-β-D-glucopyranosyl(1$\rightarrow$2)-[β-D-xylopyranosyl-(1$\rightarrow$3)]-β-D-fucopyranoside	[9]
Yamogenin 1-*O*-[α-L-rhamnopyanosyl-(1$\rightarrow$2)]-[β-D-xylopyranosyl-(1$\rightarrow$3)]-β-D-glucopyranoside	[5,8]
Yamogenin 3-*O*-[α-L-rhamnopyranosyl(1$\rightarrow$2)][β-D-xylopyranosyl(1$\rightarrow$3)]-β-D-glucopyranoside	[8]

PHARMACOLOGICAL ACTIVITIES

Toxicity

In ICR mice, the heart and lung tissues showed significantly decreased weights in the 25.0 mg/kg body weight/day of *L. platyphylla* treatment. No significant increase of alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate amino-transferase (AST), and serum creatinine (CA) were reported. However, a significant enhancement of the blood urea nitrogen (BUN) was detected in the 100 mg/kg dosage. Therefore, these results suggest that *L. platyphylla* does not induce any specific toxicity in liver and kidney tissues of mice [10].

Free radical scavenging and antimicrobial activities

The electron donating ability of the *L. platyphylla* was reported as 79 %. The relative inhibitory abilities against lipid peroxidase were also reported [11]. *O. japonicus* had a higher DPPH radical scavenging activity [3]. *L. platyphylla* extracts showed no antimicrobial effect against *Staphylococcus aureus* and *Eschaerichia coli* [11]. The tyrosinase inhibitory activity showed 82.02 % in LR treatment [12]. The ethanolic and aqueous extracts of *L. platyphylla* stimulate the immune response against *Flexibacter maritimus* in olive flounder, *Paralichthys olivaceus* [13].

Anti-inflammatory activity

Macrophages play a central role in various inflammatory responses through the release of inflammatory mediators, such as nitric oxide (NO), generated by activating inducible NO synthase (iNOS), cyclooxygenase-2 (Cox-2), and proinflammatory cytokines, such as interleukin-1β (IL-1β) and IL-6 [14]. *L. platyphylla* tuber water extract significantly decreased the levels of NO, IL-6, IL-10, IL-12p40, interferon-inducible protein-10, keratinocyte-derived chemokine, monocyte chemotactic protein-1, vascular endothelial growth factor, granulocyte macrophage-colony stimulating factor, platelet derived growth factor, prostaglandin E_2 (PGE_2), intracellular calcium (Ca^{2+}), nuclear factor-κB (NF-κB), and cAMP response element-binding protein (CREB) in lipopolysaccharide (LPS)-induced RAW264.7 cells [15].

Treatment with prosapogenin III of spicatoside A potently inhibited phosphorylation of MAPKs in LPS-stimulated RAW264.7 macrophages. It also resulted in the suppression of the nuclear translocation of NF-κB, NO production through suppression of iNOS, Cox-2, IL-1β, and IL-6 [14].

The *L. platyphylla* exerted no significant cytotoxicity in the microglial BV2 cells. PGE_2, NO levels, Cox-2, and iNOS were significantly decreased in the LPS and LR-treated group [16]. Fermented *L. platyphylla* extract decreased the generation of intracellular reactive oxygen species (ROS) and NO production dose dependently, and increased antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in LPS-stimulated RAW 264.7 macrophage cells.

The expressions of NF-κB, iNOS, Cox-2, and pro-inflammatory cytokines were inhibited by the LR [17]. The steroidal saponins from the roots of *O. japonicus* and *L. spicata* showed excellent anti-inflammatory activities against neutrophil respiratory burst stimulated with phorbol myristate acetate (PMA) [5].

Anti-allergic activity

L. platyphylla showed a dose-dependent decrease in histamine release at the concentrations of 1 to 1 000 mg/mL [18]. The ethyl acetate fraction (1 μg/mL) showed the greatest inhibition of histamine release induced by compound 48/80. The cAMP levels in RPMCs treated with LR were significantly greater than in cells treated with compound 48/80 alone. LR also alleviates immediate (type 1) hypersensitivity reactions through the increase of cAMP levels in the mast cells [19]. 2-(4′-hydroxybenzyl)-5,6-methylenedioxy-benzofuran and 2-(4′-hydroxybenzoyl)-5,6-methylenedioxy-benzofuran isolated from LR exhibited significant inhibitory activity against neutrophil respiratory burst stimulated by PMA with IC_{50} values of 4.15 ± 0.07 and 5.96 ± 0.37 μM, respectively [4].

Anti-asthma activities

Inhaled treatment of LR extract can attenuate airway hyper responsiveness (AHR) in an ovalbumin-induced asthmatic mouse model. Moreover, LR decreases inflammatory cytokine levels, such as cotaxin, IL-5, IL-13, RANTES, and TNF-α in the bronchoalveolar lavage (BAL) fluid of asthmatic mice [20]. *L. platyphylla* reduces eosinophil and total lung leukocytes numbers by reduction of IL-5, IL-13, IL-4, and IgE levels in the BALF and serum.

LR decreased eosinophic CCR3 expression and CD11b expression in lung cells against ovalbumin (OVA)-induced airway inflammation and murine asthma model [21]. Aqueous extract of LR, ophiopogonin D, and spicatoside A affect basal or PMA-induced airway mucin production

and secretion from NCI-H292 airway epithelial cells [22].

Effect on atopic dermatitis

A strong luciferase signal detected in the abdominal region of IL-4/Luc/CNS-1 Tg mice with phthalic anhydride (PA) was significantly reduced in treatment with aqueous extract of *L. platyphylla* (AEtLP). Common allergenic responses, including increases in ear thickness, lymph node weight, IgE concentration, and infiltrated mast cells were also decreased in IL-4/Luc/CNS-1 Tg [23] and NC/Nga mice [24]. The weight of the lymph node and thymus in immune organs were gradually decreased, while the weight of the spleen was slightly increased [24].

Effect on Sjogren syndrome

LR polysaccharides treated for 6 weeks after 2 weeks of acclimatization in male Wister rats significantly increased the amount of salivary secretion, and the relative weight of the spleen, thymus, and submandibular glands revealed that LR exert a protective effect against tissue damage in rats with Sjogren syndrome [25].

Laxative effects

AEtLP increased the amounts of stool and urine excretion in rats. It also induced an increase in villus length, crypt layer, and muscle thickness in the constipation model. Furthermore, a dramatic reduction of key factors level of the muscarinic acetylcholine receptors (mAChRs) signaling pathway. AEtLP improves constipation induced by loperamide through an increase in crypt layer and stimulation of lipid droplet secretions [26].

Anti-osteoclastogenesis activity

Water extract of LR significantly inhibited the receptor activator of NF-κB ligand (RANKL)-induced osteoclast differentiation in bone marrow macrophages. Expressions of c-Fos, NFATc1, tartrate resistant-acid phosphatase (TRAP), cathepsin K, and phosphorylation of p38 induced by RANKL was inhibited by LR [27]. The ethanolic extract of LR, dihydrobenzofuroisocoumarins, and homoisoflavonoids showed potential oestrogenic and anti-platelet activities [2]. Spicatoside A and 25(s)-ruscogenin were downregulated the MMP-13 expression in IL-1β-treated SW1353 cells. Spicatoside A reduced the glycosaminoglycan (GAG) release from IL-1α-treated rabbit joint cartilage culture [28].

Anti-diabetic, anti-lipidemic, and insulin sensitizer activities

Water extract and crude polysaccharides from the LR did not show any appreciable effect on fasting blood glucose (FBG) in normal mice, but caused a marked decrease of FBG and a significant improvement on glucose tolerance and insulin resistance in streptozotocin (STZ)-induced type 2 diabetic BABL/c mice [29]. The glycogen content and glucokinase (GK) activity in the liver was significantly increased, yet the glucose-6-phosphatase (G6Pase) activity was decreased [30]. The polysaccharides from *L. spicata* have possesses remarkable hypoglycemic activities in type 2 BABL/c diabetic mice [31]. The LR polysaccharides also caused a remarkable decrease of FBG and significant improvement of insulin resistance and serum lipid metabolism in diabetic KKAy mice [32]. It lowers total cholesterol, triglyceride, and LDL levels, while elevated the relatively HDL/TC in serum of BABL/c diabetic mice [29]. They significantly ameliorated the hepatocyte hypertrophy and decreased the lipid accumulation in KKAy mice liver [32]. Also effectively inhibited hepatic gluconeogenesis and increased hepatic glycolysis and hepatic glycogen content and increased expression of IRα, IRS-1, PI3K, and PPARγ in KKAy mice [32] and BABL/c mice [30].

The lipid components in serum, liver, and feces were lower in LR extracts (aqueous extract was better than MeOH extract) treated male Sprague-Dawley rats fed with a high cholesterol diet [33]. LR polysaccharides treatment to high-fat diets fed with STZ-induced diabetic rats reduced hyperglycemia, inhibited damages to liver and pancreas tissues and glycogen content, GK and glycogen synthetase (GS) activities, and suppressed the elevation of G6Pase and glycogen phosphorylase (GP) activities. In addition, it inhibits glycogen synthase kinase-3β (GSK-3β) expression and increases IR, IRS-1, PI3K, protein kinase B (Akt), and glucose transport protein (GLUT)-4 expressions in the liver [34]. AEtLP dramatically decreased the abdominal fat mass and slightly decreased the glucose concentration [35], although no significant differences in body weight, glucose tolerance, and glucose concentration [36] in Otsuka Long-Evans Tokushima Fatty (OLETF) rats. AEtLP to ICR mice displayed a significant reduction of the glucose and increased insulin concentrations [37]. Significant alterations on serum adiponectin and lipid concentration [35,36] with GLUT-3, GLUT-1, JNK, and p38 pathway [35] and SOD expressions [37] were also reported. The insulin level was dramatically elevated upon co-treatment with high glucose

and AEtLP in INS-1 cells may be tightly correlated with calcium regulation [38,39]. The LR also increased the insulin-stimulated glucose uptake in 3T3-L1 adipocytes and glucose transporters contents through IRS-1-PI3K-Akt signaling mechanism [40]. LP9M80-H isolated from *L. platyphylla* induced a significant decrease in abdominal fat masses, glucose, lipids, and adiponectin levels, whereas an increase in the insulin concentration in the OLETF rats [41]. The expression of the level of GLUT-3 corresponded to the p38 protein and GLUT-1 was significantly increased [42]. It also induces insulin secretion in the HIT-T15 cells [43].

Anti-hepatitis activity

Hepatitis B virus (HBV) is a causative agent that often leads to acute and chronic infections. LPRP-Et-97543 from LR was reported for potential anti-viral effects in HepG2.2.15 cells against HBV by significantly reduced Core, S, and PreS, but not X promotor activities. The nuclear expression of p65/p50 NF-κB member proteins and cytoplasmic IκBα were attenuated and reduced the binding activity of NF-κB protein to CS1 element of HBV surface gene [44].

Cardiovascular activity

Vascular endothelial cells (EC) cover the inner surface of blood vessels and serve as a crucial barrier between tissues and circulation. An imbalance in the repair and injury of EC results in endothelial dysfunction, which is associated with many vascular complications. The ethanol extracts of LR results no significant improvement of systolic blood pressure or aortic wall thickness. The increased expression levels of angiotensin converting enzyme (ACE), ACE2, endothelial NO synthase (eNOS), and SOD activity while the level of malondialdehyde (MDA) and NOx were recovered to the normal level of Wistar Kyoto rats. Furthermore, LR improves vascular dysfunction in the aorta of the hypertensive rats through up regulation of the antioxidant state and down regulation of aldosterone and K ion concentration [45]. DT-13, a saponin from LR, on human umbilical vein endothelial cells (HUVEC) through down regulation of cleaved caspase-3 and cleaved poly (ADP ribose) polymerase (PARP) expression by potentially increased mitochondrial membrane potential and Akt signaling [46].

Neuritogenic activity

Nerve growth factor (NGF), a member of neurotrophic factors, is produced physiologically in the brain. LR butanol fraction conditioned media of C6 and primary astrocyte treated to PC12 cells induces the neurite outgrowth, expression and secretion of NGF [47]. *O. japonicus* also showed neurotrophic effects for the NGF induction [48]. The effects of LR extracts on expression and secretion of NGF, the mRNA and protein expression were reported in the B35 and C6 cells. The culture supernatant from B35 and C6 cells with LR extract for 24 h were treated into PC12 cells and the differentiation level were significantly increased [49]. Moreover, B35 cells conditioned medium treated to PC12 cells showed significantly higher the levels of tropomyosin receptor kinase A (TrkA), ERK phosphorylation, and extracellular calcium levels with a significant decrease in the intracellular calcium levels [50]. LR extracts induced NGF-secretion and NGF mRNA expression with high cell viability *in vitro* and significantly increased the NGF mRNA and hippocampus TrkA and inhibited the $p75^{NTR}$ signaling pathways in C57BL/6 mice [51]. Spicatoside A on PC12 cells induced neurite outgrowth similar to NGF and activated ERK and PI3K/Akt via TrkA, which is responsible for the induction of the neuritic process [52]. Saponins from *O. japonicus* also reported as potent inducers of neuritogenesis and ERK signaling pathway on PC12 cells [53].

Neuroprotective activity

LR administrated mice for 3 days had restored memory up to 33, 32, 45, and 158 % (fractions T, A, C, and M, respectively) against the memory defect due to scopolamine in the passive avoidance test. Induction of depolarization of nerve cells by AMPA (40 μM) was 0.44 mV, while pretreatment of LR (fraction T) markedly reduced the level of depolarization to 0.24 mV in the grease-gap assay. LR (fraction T) induced a 45 % increase in the time to induce death due to the brain metabolism disorder by $NaNO_2$-induced cessation of respiration. ERK I/II and insulin receptor were markedly activated by LR (fractions T, A, C, and M) [1]. Water extract of LR had no toxicity on PC12 cells and showed a non-significant decrease in Bax, and a significant increase in Bcl-2 against 4-hydroxynonenal (4-HNE) [54]. Ethanol extract of LR attenuated the H_2O_2-induced increases of intracellular oxidative stress and mitochondrial dysfunction. It also blocked the PARP and caspase-3 cleavage by modulating p38 activation in SH-SY5Y cells [55]. The 70 % ethanol extract of LR treatments significantly increased the latency time with increased brain-derived neurotrophic factor (BDNF) immunopositive cells and increased NGF [56]. Spicatoside A also enhanced memory consolidation in a dose-dependent manner by increasing hippocampal mature BDNF levels [57].

Anti-cholinesterase activity

Alzheimer's disease (AD) is characterized by extraneuronal deposits of β-amyloid (Aβ) peptide, involved in learning and memory functions. Administration of LR (fractions T, A, C, and M) inhibited cholinesterase activity by 56, 64, 56, and 44 %, respectively [1]. Aβ-42 peptides level was significantly decreased in the brain, while the level of NGF in serum was higher of AEtRLP7-treated Tg2576 mice [58] and NSE/hAPPsw Tg mice [59]. The TrkA and $P75^{NTR}$ proteins were suppressed along with production of Aβ-42, γ-secretase, APH-1, and nicastrin (NCT), whereas the expression of PS-2 and Pen-2 was maintained or increased in NSE/hAPPsw Tg mice [59].

Anti-aging activity

Total saponin of *L. platyphylla* improves the memory in D-galactose-induced aging on mice. They also promote body weight gain and increase the thymus and spleen indexes of the aging mice. It also decreases the levels of MDA and lipofuscin, inhibits monoamine oxidase (MAO), and increases SOD and GPx activities [60].

Anti-cancer activity

The *n*-BuOH fraction of LR and spicatoside A treatments showed growth inhibitory activity on A549, SK-OC-3, SK-Mel-2, XF-498, and HCT-15 carcinoma cells [61]. DT-13 decreased the migratory response by hypoxia also inhibited hypoxia induced expression of αVβ3 integrin, tissue factor (TF), and early growth response gene-1 (Egr-1) and decreased excretion of MMP-9 of MDA-MB-435 cells. DT-13 also inhibits the up regulation of TF mRNA and protein levels and its pro-coagulant activity under hypoxia [62]. Furthermore, DT-13 inhibited the phosphorylation of p38 in MDA-MB-435 cells [63]. DT-13 suppressed the increased level of hypoxia-induced factor 1α (HIF-1α), p-ERK1/2, and p-Akt induced by hypoxia also inhibits angiogenesis induced by vascular endothelial growth factor (VEGF) [64]. DT-13 inhibited MDA-MB-435 cell proliferation, migration, and adhesion significantly, and reduced VEGF and CCR5 mRNAs, and decreased CCR5 protein expression by downregulating HIF-1α [65]. Treatment with LPRP-9 significantly inhibited proliferation of cancer cell lines MCF-7 and Huh-7 and downregulated the phosphorylation of Akt. It also activates the MAPK pathways. (-)-Liriopein B is capable of inhibiting Akt phosphorylation at low concentration [66]. The nontoxic doses are able to inhibit AKT activation in both luminal-like MCF-7 and basal-like MDA-MB231 breast cancer cells. Suppression of EGF-induced EGFR and ERK1/2 activation might contribute in part to retardation of cancer progression. Furthermore, it increases sensitivity of MDA-MB-231 cells to gefitinib. It also has a potent inhibitory effect on multiple kinases, including PI3K, Sr, EGFR, Tie2, lck, lyn, RTK5, FGFR1, Abl, and Flt [67].

CONCLUSION

Liriopes radix from traditional herbal medicine provides a foundation for popular remedies in common use. In this review, we summarized the existing uses of the phytochemical and pharmacological activities of LR. We can conclude that LR are a potential source of natural compounds mainly steroidal saponins and their glycosides, phenolic compounds, homoisoflavones, and secondary metabolites. LR also exerts various pharmacological activities that include anti-inflammatory, anti-microbial, anti-allergic, anti-asthma, anti-atopic dermatitis, anti-osteoclastogenesis, anti-diabetic, anti-lipidemic, anti-hepatitis, anti-cancer, laxative, and neuroprotective. The isolation of purified compounds will be needed to deeper research in order to understand their mechanisms of action as a novel drug for various human diseases.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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