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Review

Review on pharmacological activities of liriodenine

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This review describes the pharmacological properties of liriodenine. This alkaloid has been isolated from plant species of many genera and exhibits a wide range of pharmacological activities that have been reported. This present paper enumerates an overview of pharmacological aspects that are useful to researchers for further exploration in order to develop the potential of this alkaloid.

Key words: Liriodenine, alkaloid, pharmacological activities, *Liriodendron tulipifera* L.

INTRODUCTION

Liriodenine (8*H*-benzo[γ]-1,3-benzodioxo[6,5,4-en]-quinolin-8-one) is an oxoaporphine alkaloid (Figure 1). This alkaloid was isolated for the first time from *Liriodendron tulipifera* L., and was subsequently isolated from plant species of many genera (Warthen et al., 1969), mainly found in the families of Magnoliaceae, Annonaceae, Rutaceae, Monimiaceae, and Menispermaceae (Bentley, 2001; Hsieh et al., 2005; Lan et al., 2003; Lin et al., 1994; Nissanka et al., 2001; Woo et al., 1997; Wu et al., 1990). This has a wide range of pharmacological activities, such as activity against Gram-positive bacteria (Camacho et al., 2000; Chang et al., 2004; Li et al., 2009; Mohamed et al., 2010; Rahman et al., 2005; Waechter et al., 1999), antifungal (Hufford et al., 1980; Khan et al., 2002), antitumoral (Chen et al., 2009, 2012; Liu et al., 2009), antiarrhythmic activity (Chang et al., 1996, 2001; Chung et al., 2004), antiviral activities (Mohamed et al., 2010) and antiplatelet actions (Chen et al., 1997; Pyo et al., 2003). The objective of this work was to compile information about liriodenine, which may help researcher to understand the efficacy and potency of this alkaloid.

PHARMACOLOGICAL ACTIVITIES

Antimicrobial and antifungal properties

Liriodenine, was identified as a potentially useful antimicrobial antibiotic against *Staphylococcus aureus, Mycobacterium smegmatis, Candida albicans* and *Aspergillus niger* (Hufford et al., 1975, 1980). Mice were injected with a lethal dose of *C. albicans* NIH B311 and were administered varying doses of liriodenine. Reductions in the number of colony-forming units (CFU) measured per milligram of kidney tissue were observed in drug-treated animals compared to vehicle-treated control mice (Clark et al., 1987). The IC_{50}/minimum inhibitory concentration values of liriodenine against *C. albicans*, *Cryptococcus neoformans*, *S. aureus*, and Methicillin-resistant *S. aureus* (MRS) were 3.5/6.25, 2.0/12.5, 2.0/3.13, and 2.0/3.13 µg/ml, respectively (Zhang et al., 2002).It has recently been reported that liriodenine has great potential as an environmental benign wood preservative (Wu et al., 2012). Thus, it is effective against the white-rot fungi *Lenzites betulina* and *Trametes*

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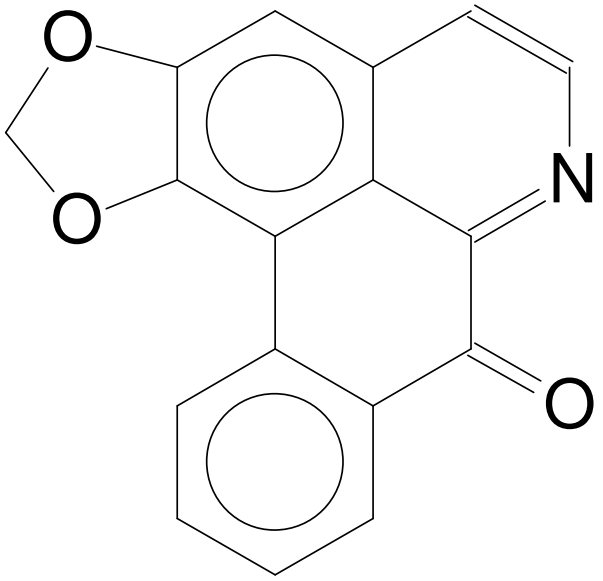

Figure 1. Structure of liriodenine.

versicolor and the brown-rot fungi *Laetiporus sulphureus, Gloeophyllum trabeum,* and *Fomitopsis pinicola*, suggesting effectively inhibiting the growth of wood-rotting fungi.

Antitumor activity

Owing to planar aromatic structure, the antitumor activities of liriodenine can be primarily attributed to intercalate between the neighboring base pairs of the DNA double helix (Woo et al., 1997). The importances of the oxo function induce cytotoxicity as well as inhibitory effects on precursor incorporation into DNA (Tzeng et al., 1990). Moreover, liriodenine also catalytically inhibits topoisomerase II to block DNA synthesis inducing cell cycle G1 arrest and increases tumor suppressor p53 and inducible nitric oxide synthase expression (Chang et al., 2004; Hsieh et al., 2005; Wu et al., 1990). Meanwhile, liriodenine has been shown to raise induced oxide nitric synthase (iNOS) expression and oxide nitric (NO) production, followed by increasing p53 production, and then up-regulating the p21 and p27 expressions (Chen et al., 2012). These events decreased the expressions of cyclin D1 and cyclin-dependent kinase, followed by reducing the pRb phosphorylation (ppRb), and finally triggering the G1/S arrest of cell cycle on human SW480 colon cancer cells (Chen et al., 2012). Furthermore, liriodenine has been demonstrated to block cell cycle progression at the G2/M phase by reduction of G1 cyclin D1, accumulation of G2 cyclin B1 and the decrease of enzymatic activity of the cyclin B1/cyclin-dependent kinase 1 complex in human A549 lung cancer cells (Chang et al., 2004). Liriodenine, isolated from the roots of *Cyathostemma argenteum*, has been reported to exhibit moderate cytotoxic activity against breast cancer cell lines (Khamis et al., 2004). The anti-cell activity of liriodenine from *Liriodendron tulipifera* has been shown to have effects on human melanoma A375.S2 cells (Chiu et al., 2012). Cell growth inhibition activity of liriodenine demonstrated a potent cytotoxicity against KB, A-549, HCT-8, P-388 and L-1210 cells with IC_{50} values of 3.6, 2.6, 2.5, 2.1, and 8.5 μM, respectively (Guo et al., 2005).

Cardiovascular effects

Liriodenine at the dose of 10^{-6} g/kg diminished the left ventricular end-systolic elastance E_{es} and effective arterial elastance E_a (Chang et al., 2001). The *in vivo* biological studies indicated that through inhibition of the Na^+ and I_{to} channels, liriodenine suppresses antiarrhythmic activity induced by myocardial ischaemia reperfusion (Chang et al., 1996). An increased concentration of NO limits myocardial ischemia-reperfusion injury. Liriodenine has been shown to reduce the extent of cardiovascular injuries under ischemia-reperfusion conditions by preserving the eNOS and the NO production (Chang et al., 2004). The transient coronary artery occlusion often leads to malignant ventricular arrhythmias during the ischaemic and reperfusion periods (Ferrier et al., 1985). Therefore, liriodenine may provide a satisfactory therapeutic potential in the treatment of cardiac arrhythmias.

Antiplatelet actions

Liriodenine inhibited the contractile responses of guinea-pig trachea and acted as a M3 receptor antagonist in paced left as well as in spontaneously heartbeat right atria of guinea-pigs (Lin et al., 1994). Moreover, liriodenine abolished adenosine diphosphate (ADP)-induced aggregation activity in human whole blood (Moharam et al., 2010) and on washed rabbit platelets (Chen et al., 1997).

Medicinal inorganic chemistry properties

Since the success of *cis*-platin and related platinum complexes as anticancer agents, developing other active transition metal anticancer complexes with better efficiency and new mechanisms of action has attracted many bioinorganic chemists' interest and has became one of the focused research fields of bioinorganic chemistry (Liu et al., 2009). Based on the planar character and N-7/O-8 electron donor sites, liriodenine has the coordination capacity by forming chelates with several metal ions such as metal ions to form metal-based function bifunctional compounds with potential synergistic effects on antitumor activity.

Liriodenine (L) reacted with Mn(II), Fe(II), Co(II) and Zn(II) to afford four metal complexes: $[MnCl_2(L)_2]$, $[FeCl_2(L)_2]$, $[Co(L)_2(H2O)_2$ $Co(L)_2(CH3CH2OH)_2](ClO4)_4$, and $[Zn_2(L)_2(m2\text{-}Cl)_2Cl_2]$, all complexes bind more intensively to the DNA helix than does liriodenine and effectively inhibit topoisomerase I even at a low concentration (≤10 µM) (Liu et al., 2009). Furthermore, Pt(II) and Ru(II) were chosen for the synthesis of metal complexes with liriodenine as ligand. The antitumoral activities against a series of human tumor cell lines *in vitro* showed that these complexes exhibit higher antitumor activities than liriodenine or cisplatin does (Chen et al., 2009). These results demonstrated that the metal complexes of planar liriodenine reinforce the DNA-binding ability. Beside two-metal ion, liriodenine was used as a bioactive ligand to react with gold(III) compounds. The *in vitro* cytotoxicity towards five human tumor cell lines showed that antiproliferative properties of the complex are compared with free liriodenine, with IC_{50} values falling in the 2 to 16 µM range. The complex induced an S-phase arrest and significantly inhibits topoisomerase I *in vitro* at low concentration (≥ 25 µM or lower) (Chen et al., 2012). Liriodenine metal complexes may offer a new effective strategy to achieve higher cytotoxic activities.

Central nervous system activities

Liriodenine is reported as a sedative of the central nervous system (Rios et al., 1989). Furthermore, liriodenine has been shown to regulate dopamine biosynthesis by partially reducing tyrosine hydroxylase (TH) activity and TH gene expression and has protective effects against L-DOPA-induced cytotoxicity in PC12 cells (Jin et al., 2007). It is suggested that the isoquinoline ring planarity play a key role in the inhibition of dopamine.

CONCLUSION

This review provides the multiple biology effects of liriodenine which made it a valuable potential of molecule. The pharmacological aspects of liriodenine have been studied extensively; however, this alkaloid has not yet been developed as a drug. Ongoing and detailed research is required for the identification, cataloging and documentation of this alkaloid, which may provide scientific and encourage development of this alkaloid for pharmaceutical uses or therapeutic uses.

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