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Therapeutic potentials of reserpine formulations:Recent progress and challenges

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ABSTRACT

Reserpine is an indole alkaloid related to the class of rauwolfia alkaloids used as an alternative drug to manage and treat high blood pressure (hypertension) via acting as an adrenergic uptake inhibitor. Moreover, severe agitation in patients with mental disorders can be treated by this metabolite. Reserpine can slow down the heartbeat and relax the blood vessels. Reserpine can hinder planktonic and biofilm forms of bacteria. Reserpine can block Gram-positive bacterial and mammalian efflux. This alkaloid leads to apoptosis and cell cycle arrest through inhibition of DNA ladder formation, DNA synthesis, an increase in calcium influx, and destabilization of mitochondrial membrane potential. The clinical utility of reserpine is limited due to its neurotoxicity. Low bioavailability and adverse side effects have been reported for this bioactive compound. Therefore, looking for novel strategies for loading and encapsulation of reserpine is needed. This mini-review has tried to present the results of new investigations to finding effective formulations of reserpine in monotherapy and combination therapy.

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Introduction

There are countless primary and secondary metabolites with various therapeutic applications [1-3]. Reserpine ($C_{33}H_{40}N_2O_9$) is an alkaloid medication applied commonly for the treatment of hypertension, generally in combination with a vasodilator and thiazide diuretic [4]. In addition, this bioactive agent can control heart rate, peripheral vascular resistance, and force of cardiac contraction. Reserpine has the ability to deplete catecholamines from peripheral sympathetic nerve endings as an antinoradrenergic mechanism [5]. Reserpine can induce apoptosis and cell cycle arrest at the G2 phase via inhibition of DNA synthesis, DNA ladder formation, and destabilization of mitochondrial membrane potential [6]. This metabolite has been isolated from *Rauvolfia* species including *R. hookeri*, *R. serpentina*, *R. tetraphylla*, *R. micrantha*, and *R. vomitoria* (commonly spelled *Rauwolfia vomitoria*) with a reserpine content of 132.3, 254.8, 450.7, 422.1, and 689.5 µg/g (dry wt.), respectively [7]. There are severe adverse effects from using this indole alkaloid in high doses including bradycardia, chest pain, hypotension, and gastric ulceration [8, 9]. Therefore, the clinical application of this metabolite should be improved by a new formulation design in proper dosage administration. This mini-review has tried to discuss both the therapeutic potential and toxicity of this phytochemical according to recent studies.

Antihypertensive activity

Root extracts of *R. tetraphylla* and *R. serpentine* containing reserpine have potential antihypertensive activity [10]. According to clinical results, a combination therapy of hydrochlorothiazide (a thiazide diuretic) and reserpine leads to reduced hypertension [11, 12]. Reserpine can lower blood pressure and heart rate (12 beats/min) in patients with uncontrolled BP resulting from maximal antihypertensive therapy. In this way, this potent sympatholytic alkaloid, decreased average diastolic and systolic automated office blood pressure (AOBP) by 22.0 and 29.3 mm Hg, respectively [13].

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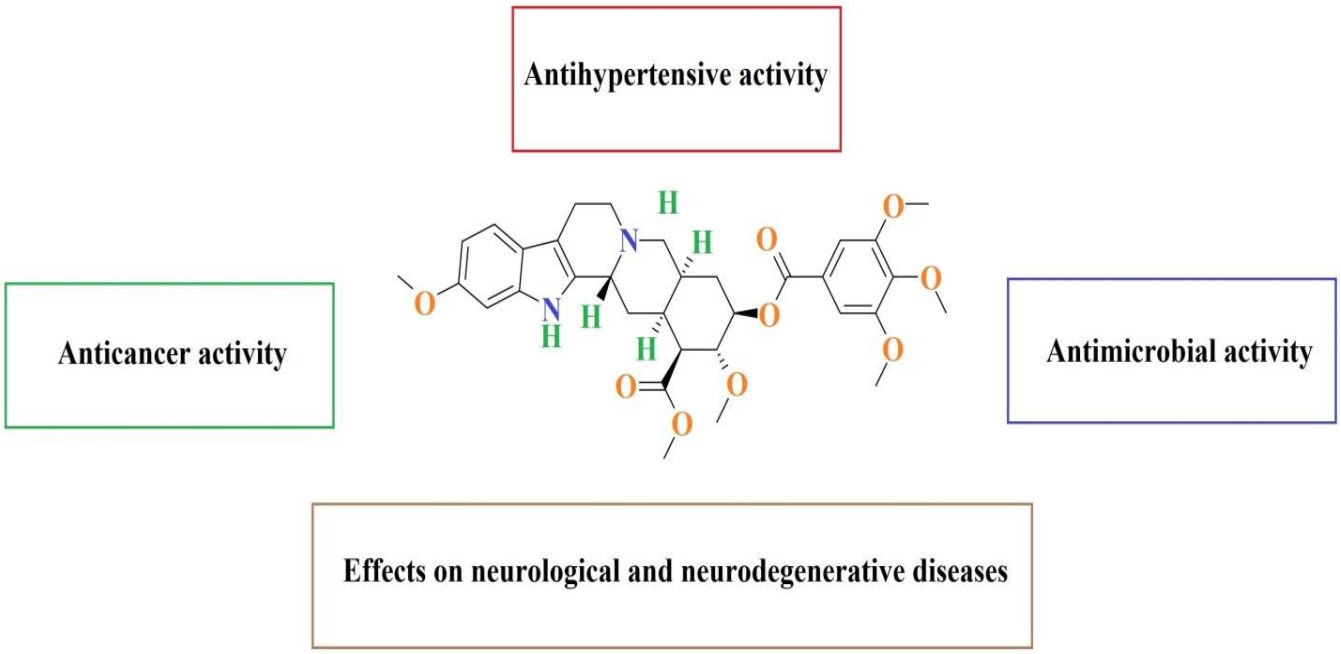

Fig. 1. Chemical structure of reserpine with related pharmacological effects.

Anticancer activity

The root of *R. vomitoria* ethanolic extract decreased cell growth in ovarian cancer cell lines dose-dependently, ovarian tumor growth in mice was also considerably suppressed by 36% or 66% with *R. vomitoria* treatment alone, the effect was comparable to that of carboplatin. Moreover, the result indicated that *R. vomitoria* had relatively low toxicity in normal cells [14]. In the case of prostate cancer cells (hormone-independent type), induction of apoptosis and cell cycle arrest at the G2 phase, by destabilization of mitochondrial membrane potential and DNA ladder formation have been found for reserpine [6]. Methanolic leaves extract of *R. serpentina* exhibited DNA damage, an increase in calcium influx, intracellular reactive oxygen species (ROS), a decrease of membrane potential and mitochondrial mass, and cell cycle arrest in cervical cancer HeLa and human hepatocarcinoma HepG2 cell lines [15]. Induction of apoptosis and hindering cell proliferation, DNA repair, and invasion in oral carcinogenesis by modulation of transforming growth factor-β (TGF-β) signaling were identified for reserpine isolated from *R. serpentine*. In addition, this phytoactive compound stimulated cytochrome C, apoptotic protease activating factor 1 (Apaf-1), Bax, caspase-3 caspase-9, and poly(ADP-ribose)polymerase (PARP) protein expressions [16]. Methanolic extract of *Clerodendrum viscosum* leaves containing reserpine, tannic acid, rutin, and catechin showed significant anticancer effects on breast carcinoma cell lines (MCF-7) by induction of apoptotic peak (sub G1 phase) at a concentration of 50 µg/mL [17].

Antimicrobial activity

Finding multidimensional strategies and discovery of broad sources of antimicrobial agents to combat microbial infections are needed because of emerging antimicrobial resistance. Various genes can contribute to the resistance of pathogenic bacteria. For example, MOX, ACT, and FOX genes have been indicated for clinical isolates of *Klebsiella pneumoniae* stains [18, 19]. Bacteria with multidrug resistance properties apply several mechanisms including overexpression of efflux pump, limiting uptake of a drug, inactivation of an antibiotic by enzymes, and modification of an antibiotic target to neutralize antibiotics [20, 21]. In addition to searching for effective natural antimicrobial materials, some researchers have presented various micro and nano delivery systems to decrease the dosage and frequency of antibiotics [3, 22]. Reserpine can inhibit both Gram-positive bacterial and mammalian efflux [23, 24]. In this regard, reserpine can interact directly with the pneumococcal proteins of specific efflux pumps and lead to the selection of

reserpine-resistant mutant [24]. Reserpine inactivates the NorA pump of *Staphylococcus aureus*, fluoroquinolone resistance, and the antibiotic pumps of other clinical isolates [23]. As the main antiviral mechanism, reserpine hinders the activity of the 3CLpro (3C-like proteinase) enzyme (this enzyme has an important function in the viral life cycle) of severe acute respiratory syndrome (SARS) and interferes with the viral entry to the cell [25, 26].

Effects on neurological and neurodegenerative diseases

Depression is a complex mood disorder, which can further negatively impact health and mental by an abnormality in social behavior, changes in appetite, insomnia, frequent headaches, and fatigue [27]. In contrast to other therapeutic effects, reserpine administration induces anxiety-like behaviors and depression, enhancing pro-inflammatory cytokines and corticosterone in the hippocampus and plasma, respectively. moreover, this metabolite reduced hippocampal pCREB/BDNF expression [28]. The clinical application of reserpine is limited due to its neurotoxicity [23]. However, monoamine oxidase-B (MAO-B) was significantly inhibited by reserpine at a concentration of 40 μM. This enzyme has the main role in the generation of ROS responsible for neurodegeneration in Alzheimer's disease [29].

Conclusions

The clinical utility of reserpine is limited due to its neurotoxicity. Antihypertensive action of reserpine can result from its antinoradrenergic mechanism, an adrenergic uptake inhibition. In this regard, reserpine reduced average heart rate, diastolic, and systolic AOBP. Gram-positive bacterial and mammalian efflux can be blocked by reserpine. Destabilization of mitochondrial membrane potential, DNA ladder formation, an increase in calcium influx, induction of apoptosis, and cell cycle arrest at the G2 phase have been indicated as the significant anticancer mechanisms of reserpine. As the major antiviral mechanism, reserpine hinders the activity of the 3CLpro enzyme of SARS and interferes with the viral entry to the cell. This mini-review showed that combination therapy of reserpine is more effective than monotherapy specifically in hypertension.

Study Highlights

- The clinical utility of reserpine is limited due to its neurotoxicity.
- Antihypertensive action of reserpine can result from its antinoradrenergic mechanism, an adrenergic uptake inhibition.
- Reserpine reduced average heart rate, diastolic, and systolic AOBP.
- Destabilization of mitochondrial membrane potential and DNA ladder formation has been found as the significant anticancer mechanisms of reserpine.
- Gram-positive bacterial and mammalian efflux can be blocked by reserpine.
- Reserpine hinders the activity of the 3CLpro enzyme of SARS and interferes with the viral entry to the cell.

Abbreviations

3CLpro: 3C-like proteinase
AOBP: Automated office blood pressure
Apaf-1: Apoptotic protease activating factor 1
MAO-B: Monoamine oxidase-B
PARP: Poly(ADP-ribose)polymerase
ROS: Reactive oxygen species
SARS: Severe acute respiratory syndrome
TGF-β: Transforming growth factor-β

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

All authors: conceptualization, preparing the first draft, and editing.

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