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Anticholinergic, antimicrobial, and anticancer perspectives of atropine: a mini-review

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ABSTRACT

Atropine metabolite as a tropane alkaloid is mainly applied as anticholinergic medication. Other therapeutic activities such as anticancer and antimicrobial effects have been found for this metabolite. Several side effects such as blurred vision, dryness of the mouth, dry eyes, confusion, photophobia, dizziness, tachycardia, fatigue, flushing, palpitations, urinary hesitance or retention, headache, constipation, nausea, and vomiting have been identified for this bioactive compound. Therefore, the reduction of these side effects is critical to obtain effective therapeutic activities of atropine in physiological conditions. Application of micro and nanoformulations and combination therapy may be desirable strategies. This mini-review has attempted to discuss both advantages and disadvantages of these novel strategies based on recent advances.

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Introduction

The medicinal applications of bioactive compounds related to plants, bacteria, fungi, and lichens in effective micro and nanoformulations can provide promising therapeutic effects in combination with synthetic drugs [1-6]. Atropine ($C_{17}H_{23}NO_3$) is a tropane alkaloid related to a class of secondary metabolites that have a tropane ring in their chemical structure (Figure 1). These types of alkaloids can be isolated from many plant species of the family Solanaceae such as *Atropa belladonna*. There are various true and proto alkaloids derived from amino acids, wherein atropine is derived from L-ornithine [7]. As a natural alkaloid, atropine has anticholinergic properties that are used to reduce heart rate and treat cancer, nervous agents, and poisoning. Atropine acts as a competitive antagonist for muscarinic acetylcholine receptors (mAChRs) and inhibits the parasympathetic nervous system by blocking these receptors [8, 9]. Atropine has several medicinal applications including the reduction of salivary and bronchial secretions, prevention of vomiting, the treatment of anterior and posterior segment ocular disorders in the topical formulation [10], modulation of the secretion and motility of the gut by atropine-functionalized gold nanoparticles [11], antibacterial activity in the formulation of choline-binding protein F (CbpF) complexed with atropine and ipratropium [12], antiviral activity [13], the treatment of clozapine-induced sialorrhea [14], anticancer activity by suppressing of epithelial–mesenchymal transition (EMT) in breast cancer cells [15], and anticholinergic activity as antimuscarinic and antinicotinic agents [16]. In this mini-review, anticholinergic (the treatment of mushroom poisoning or overdose of cholinergic drugs), antimicrobial, and anticancer activities of atropine in new formulations have been discussed considering their progress and limitations.

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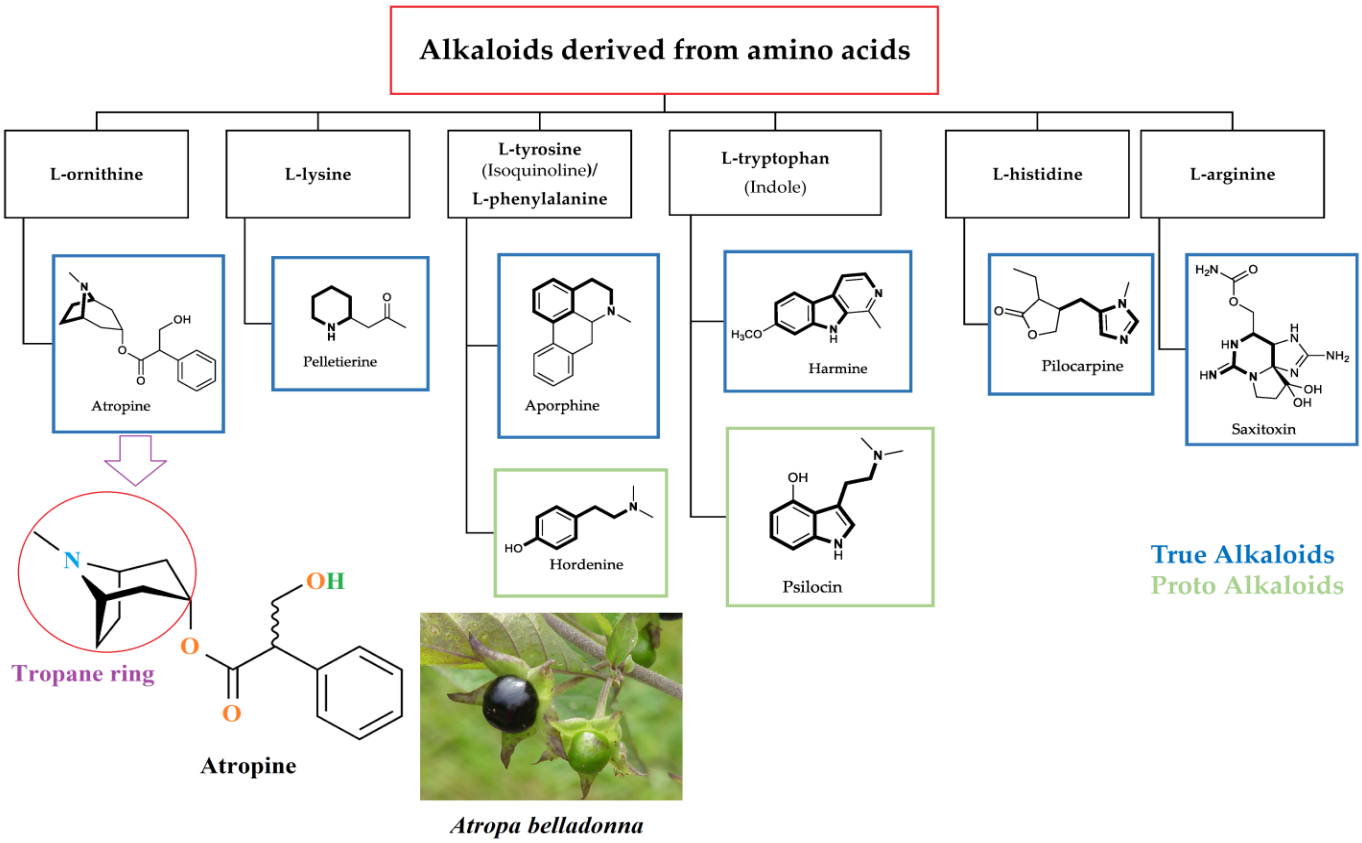

Fig. 1. Atropine with related plant source (*Atropa belladonna*) as true alkaloids derived from amino acid of L-ornithine (adapted and modified from [7]).

Anticancer

Atropine can hinder EMT and decrease stemness in drug-resistant breast tumor cells by blocking two major signaling molecules contributing to EMT regulation including E-cad (E-cadherin) and ZEB-2 (zinc finger E-box binding homeobox). A molecular docking study enclosed that binding energies between atropine with E-cad and Zeb-2 were 6.75 and 4.78 kcal/mol, respectively. in this regard, the hydrogen bond was the major bond of the interaction of atropine with these receptors [15]. The mAChRs are expressed in neurons and various tumors, including breast cancer of animal and human origin [17]. Activation of mAChRs causes cell proliferation, migration, invasion, and metastasis and is considered a valuable target for metronomic chemotherapy. The results show that atropine significantly reduces the survival of cancer cell lines at concentrations of 10 µM compared to normal cell lines. These results indicate that atropine is a genotoxic compound that decreases cell viability in breast cancer cell lines such as MDA-MB-231 and T47D. Cancerous tumors, especially breast cancer, and epithelial-mesenchymal transition (EMT), are mediated by increased AChR expression [18]. EMT epithelial-mesenchymal transition is a reversible physiological process. EMT is involved in cancer progression through morphological suppression of epithelial markers such as E-cadherin, claudins, occludins, and mesenchymal markers such as vimentin, fibronectin, and N-cadherin [19]. On the other hand, tumors may acquire the stemness characteristics of cancer cells and promote the maintenance, differentiation, and survival of cancer cells, which depends on the organization of stemness-supportive microenvironments [20]. For example, the secretion of inflammatory cytokines creates an inflammatory microenvironment that may trigger EMT and then lead to the generation of cancer stem cells [19, 20]. Our in silico docking analysis shows that atropine has a virtual binding, with stable binding energy, to two E-cad and ZEB-2 molecules. These molecules are the main signaling molecules involved in the regulation of EMT. For both of them, the results of gene and protein expression levels show that atropine is an effective molecule in reducing the

epithelial-mesenchymal transition of EMT. Colony formation was induced by TGF-B or carboplatin in both mesenchymal-like cell lines MDA-MB-231 and T47D-like epithelial cells. In general, it can be concluded that atropine as a potential EMT suppressor and mAChRs factor blocking agent and competitive antagonist can be prescribed with other chemotherapy drugs to reduce stemness in drug-resistant breast tumor cells [21]. Atropine is a parasympatholytic alkaloid used as an antidote to acetylcholinesterase inhibitors. Cabello et al. 2003 developed an experimental model of breast cancer in which epithelial cells in the rat mammary gland were transformed into malignant cells by exposure to pesticides. They aimed to investigate the effects of parathion, malathion, and atropine in inducing the progression of malignant transformation of a human breast epithelial cell line, MCF7. The results showed that parathion and malathion increased PCNA and increased the expression of mutant p53 protein in MCF7 cells compared to the control group, and atropine inhibited this action. Their results showed that organophosphorus pesticides can cause more changes in this malignant breast cell line and create another step in the progress of the transformation process, and on the other hand, atropine prevents the effect of these substances [22]. The existence of autoantibodies in cancer has been raised in recent years. Carbachol is a miotic drug (these drugs lead to the pupil to contract) with parasympathomimetic action. Carbachol causes cholinergic effects by binding to acetylcholine receptors. Lombardi et al. 2013 showed that the action of carbachol decreases in the presence of atropine. Carbachol may increase VEGF-A production and neovascularization induced by breast tumor cells through the activation of muscarinic receptors. These effects may accelerate breast tumor progression, an effect that is reversed by the muscarinic antagonist atropine [9]. In 2022, Larabee et al reviewed the role of atropine in colon cancer. As we know, the level of miR-222 in colon cancer is three times the normal state, and acetylcholine (ACh) treatment strongly induces the expression of miR-222. Their results showed that atropine affects the expression of miR-222 by blocking the acetylcholine factor (ACh) and preventing the proliferation of colon cancer cells [23]. AKR1B1 and AKR1B10 are active aldo-keto reductases in colon cancer. Ejaz et al. (2023) showed that the inhibitory potential of atropine is greater for AKR1B1 than for AKR1B10. The results of molecular docking analysis along with root mean square deviation (RMSD) and root mean square fluctuations (RMSF) showed that atropine is an inhibitor of AKR1B1. As a result, atropine can be used as an original compound for the synthesis and treatment of colon cancer associated with a sudden expression of AKR1B1 [24].

Antimicrobial activity

The growth of some bacteria can be inhibited by the treatment of atropine. For instance, the growth of *Bacillus ceruse* ATCC 33018 was severely decreased as an inhibition zone diameter (IZD) of 3.0 ± 0.6 mm and minimum inhibitory concentration (MIC) value of 1000 ppm upon the effect of atropine. The antibacterial activity of atropine against *B. ceruse* was lower compared to gallic acid with an IZD value of 9.0 ± 0.6 mm [25]. Choline-binding surface proteins (CBPs) are a family of surface proteins related to the morphology and virulence of *Streptococcus pneumoniae*. In this regard, atropine as esters of bicyclic amines (EBAs) can act as choline analogs and significantly compete with teichoic acids in binding to CBPs. Atropine by this function reduced cell viability and bacterial growth, and changed cell morphology. Atropine demonstrated a higher binding affinity compared to choline against several CBPs such as CbpE, LytC, LytA, and LytB [26]. In a comparative study, antibacterial, antiviral, and antifungal activities of several bioactive compounds such as atropine (tropane-type), gallic acid, trigonelline (pyridine-type), allantoin (imidazolidine-type), and colchicine (tropolone-type) were evaluated against Gram-negative and Gram-positive bacteria, fungi, RNA of human parainfluenza virus type-3 (HPIV-3), and DNA of herpes simplex virus type -1 (HSV-1). In this sense, gallic acid and atropine had a strong antiviral effect in the cytopathogenic effect (CPE) inhibitory concentrations of 0.8-0.05 µg/mL against both viruses of HPIV-3 and HSV-1[27]. Improving innate immunity and hindering viral replication can be caused by optimized formulation of atropine. Atropine as the antimuscarinic metabolite exhibited antiviral activity against HSV-1 by reducing the formation of new virions at a concentration of 200 µg/mL. As the main antiherpesvirus action, atropine blocked the glycosylation of viral proteins of HSV-1[28].

Plasmodium vivax as a protozoal parasite can be a human pathogen. In a comparative investigation, anti-plasmodial activity of methanolic extracts from the leaves and seeds of several medicinal plant species including *Dodonaea viscosa*, *Datura stramonium*, *Calotropis procera*, *Eucalyptus oblique*, and *Parthenium hysterophorus* were evaluated against *P. vivax*. This study showed that in contrast to the leaf extracts of other medicinal plants, atropine isolated from *E. oblique* extract had significant anti-plasmodial activity (68.02%) against *P. vivax* at a concentration of 0.1 mg/mL [29].

Anticholinergic activity

As mentioned in the above sections, atropine shows competitive antagonists of acetylcholine muscarinic receptors and modulates the central nervous system (CNS) [30]. As an anticholinergic agent, atropine can block the action of acetylcholine (the neurotransmitter at synapses in the peripheral and central nervous system. Atropine in combination with Ca^{2+}-channel blocker magnesium sulfate led to reverse nerve agent induced bronchoconstriction and prominent airway relaxation [31]. In addition, during flexible bronchoscopy, atropine can reduce airway secretions without striking a decrease in oxygen desaturation, cough, and patient discomfort [32].

Conclusions

The major therapeutic effect of atropine is anticholinergic activity, which is along with side effects. This metabolite has competitive antagonists of mAChRs and modulates the CNS. Atropine by acting antagonist towards mAChRs and inhibiting the parasympathetic nervous system can hinder these receptors, which are expressed in neurons and various tumors, including breast cancer of animal and human origin. For antibacterial activity, atropine can act as a choline analog and significantly compete with teichoic acids in binding to CBPs. As the main antiviral mechanism against HSV-1, atropine blocked the glycosylation of viral proteins. In addition, the anti-plasmodial activity of atropine metabolite against *P. vivax* was indicated at the suitable concentration. Combination therapy can be an effective strategy for decreasing the dose of atropine or its side effects.

Study Highlights

- The major therapeutic effect of atropine is anticholinergic activity.
- Atropine has competitive antagonists of mAChRs and modulates the CNS.
- Atropine by acting antagonist towards mAChRs and inhibiting the parasympathetic nervous system can hinder these receptors.
- As the main antiviral mechanism against HSV-1, atropine blocked the glycosylation of viral proteins.
- Combination therapy can be an effective strategy for decreasing the dose of atropine or its side effects.

Abbreviations

CbpF: Choline-binding protein F
CBPs: Choline-binding surface proteins
CNS: Central nervous system
CPE: Cytopathogenic effect
EBAs: Esters of bicyclic amines
E-cad: E-cadherin
EMT: Epithelial–mesenchymal transition
HPIV-3: Human parainfluenza virus type-3
HSV-1: Herpes simplex virus type 1
IZD: Inhibition zone diameter
mAChRs: Muscarinic acetylcholine receptors
MIC: Minimum inhibitory concentration
ZEB-2: Zinc finger E-box binding homeobox

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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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