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Therapeutic aspects of berberine and its derivatives: recent advances and challenges

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ABSTRACT

There is an urgent need for the discovery of biocompatible therapeutic drugs that can be administered for long periods without severe side effects. Berberine is an alkaloid metabolite, found in some plant species, commonly applied in animal and clinical productions. This metabolite can be found in the family Ranunculaceae and Berberidaceae. Antibacterial, antiviral, antifungal, and anticancer activities have been identified for this natural hydrophobic cation and its derivatives. As the major limitation for clinical application, the weak pharmacokinetics and quick removal of berberine from the body can result from the poor absorption rate of berberine. Therefore, high doses of this bioactive metabolite are required to obtain acceptable therapeutic activities. However, high concentrations of berberine can lead to some adverse effects. This mini-review has covered the advances and limitations for novel formulations of this metabolite with therapeutic activities considering the recent investigations.

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1. Introduction

Berberine ($C_{20}H_{18}NO_4^+$) is a quaternary ammonium compound (a combination of a negatively charged anion with salts of quaternary ammonium cations) from the protoberberine, a group of alkaloids that can be derived from benzylisoquinoline alkaloids found in the rhizomes, roots, stems, and bark of some plant species of two families of Ranunculaceae and Berberidaceae (Figure 1). Bernerine can be isolated from *Argemone mexicana* [1], *Berberis aristata* [2], *Berberis libanotica* [3], *Berberis vulgaris* [4], *Ceriops decandra* [5], *Coptis chinensis* [6], *Eschscholzia californica* [7], *Glaucium corniculatum* [8], *Hydrastis Canadensis* [9], *Mahonia aquifolium* [10], *Phellodendron amurense* [11], *Poephagus grunniens* [12], *Tinospora cordifolia* [13], and *Xanthorhiza simplicissima* [14]. There are various medicinal perspectives including antibacterial [15], antiviral [16], antifungal [17], anti-parasitic [18], and anticancer [19] activities. One of the main limitations of the clinical application of berberine is the poor pharmacokinetics of this bioactive compound owing to the poor absorption rate and quick removal of this metabolite from the reticuloendothelial system (RES) [20]. In this regard, high concentrations of berberine can result in side effects such as nausea and constipation [21]. This mini-review has discussed the progress and drawbacks of novel formulations of berberine and its derivatives with antibacterial, antiviral, antifungal, antiparasitic, and anticancer activities according to recent studies.

2. Anticancer

Several studies showed berberine can promote cell apoptosis and hinder cell proliferation by interacting with microRNAs, regulating cell cycle and cell autophagy, inhibiting telomerase activity, cell invasion, and metastasis process via blocking epithelial-mesenchymal transition (EMT), down-regulating the expression of metastasis-related proteins, and signaling pathways (Figure 2) [21]. Moreover, regulation of tumor microenvironment, anti-inflammation, and antioxidant properties have been identified for berberine [22]. Nanoformulations of berberine as drug delivery systems can attenuate

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its low bio-stability, limited solubility in plasma, and weak bioavailability [15]. In this way, there are various organic and inorganic nanostructures such as liposomes, synthetic/natural polymeric nanoparticles, and metal/metal oxide nanoparticles (Figure 1) [23]. For example, based on a combinatorial strategy, berberine, and doxorubicin have been co-delivered to breast cancer cells. In two steps, doxorubicin was conjugated to poly (lactic-co-glycolic acid) (PLGA) nanoparticle by carbodiimide reaction, and then the resulting nanocarrier was applied to encapsulation berberine. These nanoformulations demonstrated IC_{50} of 1.02 and 1.94 µM against T47D and MDA-MB-231 breast cancer cell lines. In contrast to T47D cell lines, the reactive oxygen species (ROS) was increased in MDA-MB-231 cells in a dose-dependent way. In addition, *in vivo* studies showed a 14-fold increase in the half-life of formulation concentration in the plasma of Sprague Dawley rats [24].

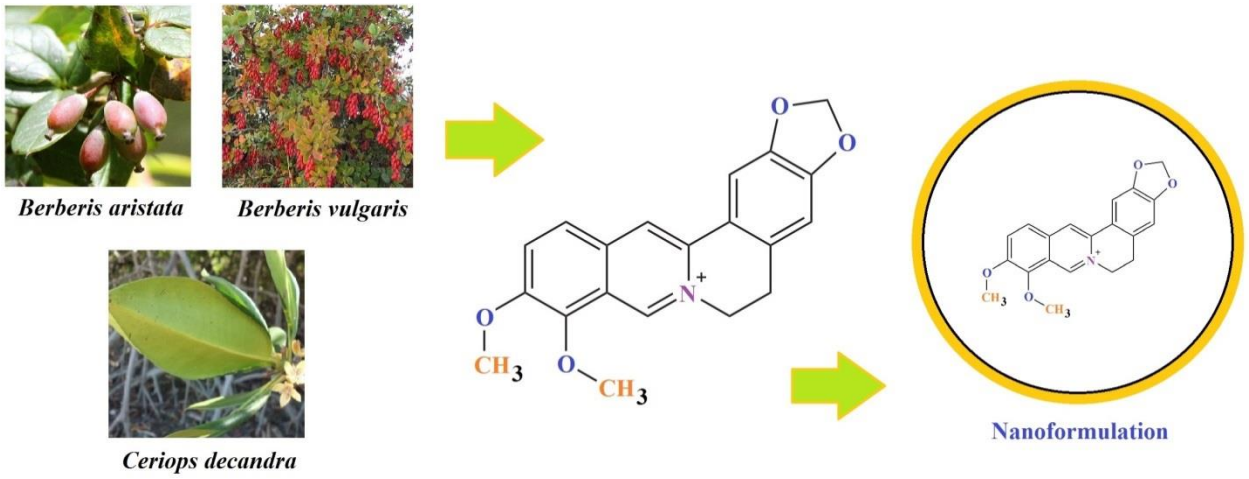

Fig. 1. Isolation of berberine from some plant species and encapsulation in nanoformulations.

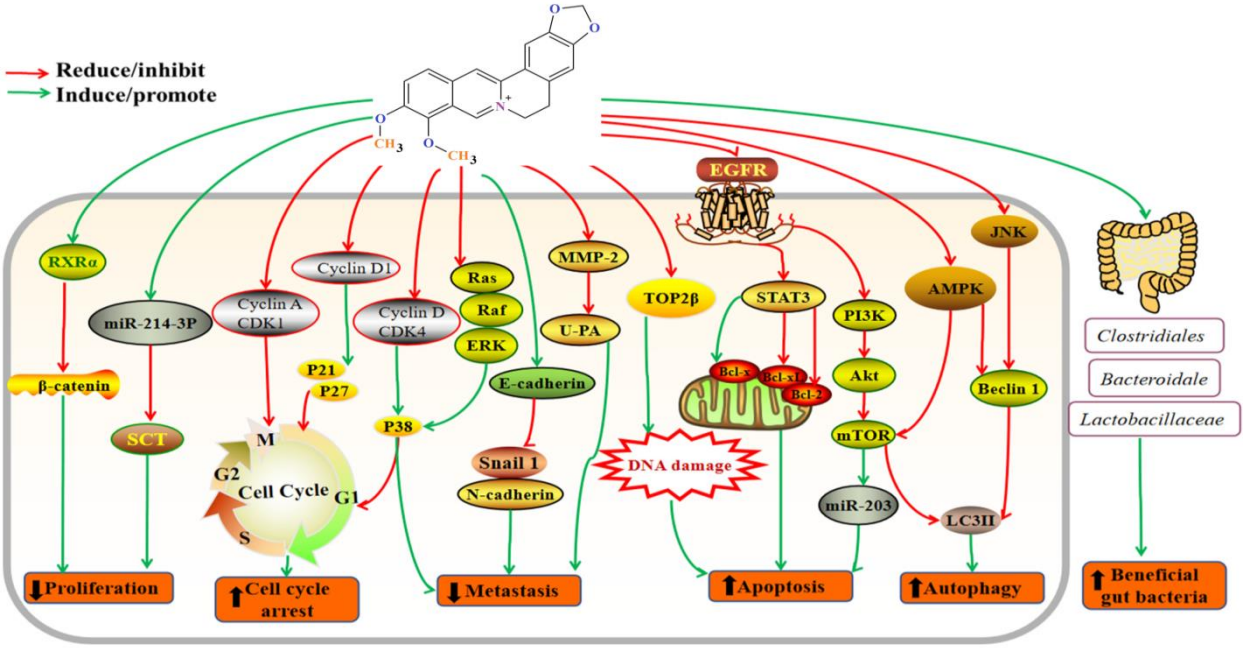

Fig. 2. The main mechanisms for anticancer activity of berberine (adopted and modified from [21]).

3. Antibacterial

The abuse of traditional antibiotics has caused antimicrobial resistance in human pathogenic bacterial strains. Therefore, there is an emergency need to discover effective antimicrobial agents [25, 26]. Berberine can intercalate into DNA and

augment membrane permeability [27]. In addition to the discovery of new effective antimicrobial agents, the development of micro and nano-delivery systems may decrease the frequency and dosage of antibiotics [28]. Self-assembly of molecules generally results from non-covalent interactions including van der Waals, hydrogen, hydrophobic, and Coulomb interactions [29]. One-dimensional and three-dimensional complexes were obtained by natural self-assembling between flavonoid glycosides (baicalin and wogonoside) and berberine through hydrophobic and electrostatic interactions. Two types of nanostructures encompassing nanofibers (berberine and wogonoside) and nanoparticles (berberine and baicalin) caused by the self-assembly process displayed different antibacterial activity against *S. aureus*. A prominent bacteriostatic effect has been indicated for NPs, whereas nanofibers showed a much weaker antibacterial activity compared to berberine [30]. *Streptococcus agalactiae* is a gram-positive coccus related to group B Streptococcus (GBS) infection causing severe invasive infections of meningitis, pneumonia, and septicemia particularly in newborns or the elderly with compromised immune systems [31, 32]. Based on images of the transmission electron microscopy (TEM), berberine at a concentration of 78 μg/mL caused cells unequal division and the fragmentary cell membrane. In addition, damage to the bacterial cell membrane by berberine may result from the synthesis inhibitor of bacterial macromolecules such as DNA and protein [33].

4. Antifungal

Fluconazole is an antifungal drug applied to hindering fungal infections of blastomycosis, candidiasis, cryptococcosis, coccidioidomycosis, dermatophytosis, histoplasmosis, and candidiasis [34]. However, there are adverse side effects of this antifungal medication such as liver problems and seizures [35, 36]. A combination therapy of berberine and fluconazole is used to inactivate *Candida albicans*. Fluconazole at a concentration of >1.9 μg/mL combined with berberine at a similar concentration eliminated *C. albicans* significantly [37]. The significant antifungal mechanisms of berberine against *C. albicans* are the dysfunction of mitochondria and the up-regulation of oxidative stress genes [38].

5. Antiviral

Several investigations have demonstrated that alkaloids specifically, berberine have potential antiviral activity against a variety of types of viruses. Berberine inhibits viral replication by focusing on specific interactions between the virus and its host cellular [39]. Berberine isolated separately from *Berberis vulgaris* and *Hydrastis canadensis* in IC_{50} values of 5.04 μM and 0.01 μM inhibited HSV-2 and H1N1, respectively. For these in vitro studies, the major antiviral mechanisms for berberine were blocking viral attachment/entry, genomic DNA replication, and protein production [40, 41]. Coronavirus disease 2019 (Covid-19) is a global dystrophic disease caused by coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). This phytoactive compound inhibited viral-induced inflammatory responses in the case of Covid-19 disease [25]. These viruses cause acute respiratory distress syndrome (ARDS), acute lung injury (ALI), endothelial dysfunction (ED), and multi-organ failure (MOF) via oxidative changes and inflammation. By inhibiting the release of pro-inflammatory cytokines and inflammatory signaling pathways, berberine decreases the risk of ALI/ARDS in covid-19 patients. In addition, this metabolite reduces ALI/ARDS in patients with severe covid-19 [42].

6. Conclusion

This mini-review has discussed the progress and drawbacks of novel formulations of berberine and its derivatives with antibacterial, antiviral, antifungal, and anticancer activities according to recent investigations. Anticancer activities of berberine can be resulted from promoting cell apoptosis and hindering cell proliferation by interacting with microRNAs, regulating cell cycle and cell autophagy, and hindering telomerase activity, cell invasion, and metastasis process via blocking EMT.

As a significant antibacterial mechanism, berberine as a natural hydrophobic cation can intercalate into DNA and augment membrane permeability. For antifungal mechanisms of berberine against *C. albicans*, the up-regulation of oxidative stress genes

and dysfunction of mitochondria have been reported. Berberine targets various stages of the viral life cycle and can be considered a promising candidate for novel formulations in antiviral drugs. Inhibition of viral attachment/entry, genomic DNA replication, and protein production were the major antiviral mechanisms for berberine. In the case of Covid-19 disease, this metabolite can hinder viral-induced inflammatory responses. Furthermore, combinatorial nanoformulation of berberine and anticancer drug such as doxorubicin by organic or inorganic nanoparticles can lead to a significant synergetic effect.

Study Highlights

- Berberine promotes cell apoptosis and hinders cell proliferation of cancer cells.
- Berberine can intercalate into DNA and augment the membrane permeability of bacteria.
- For antifungal mechanisms of berberine, the up-regulation of oxidative stress genes and dysfunction of mitochondria have been reported.
- Inhibition of viral attachment/entry, genomic DNA replication, and protein production were the major antiviral mechanisms for berberine.
- Nanoformulations of berberine with drugs such as doxorubicin lead to a significant synergetic effect.

Abbreviations

ALI: Acute lung injury
ARDS: Acute respiratory distress syndrome
Covid-19: Coronavirus disease 2019
ED: Endothelial dysfunction
EMT: Epithelial-mesenchymal transition
GBS: Group B Streptococcus
MOF: Multi-organ failure
PLGA: poly (lactic-co-glycolic acid)
RES: Reticuloendothelial system
ROS: Reactive oxygen species
SARS-CoV-2: Severe acute respiratory syndrome
TEM: Transmission electron microscopy

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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, writing the first draft, and revising the manuscript.

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