Yellow Medicine of Nature- The future Chartbuster Protoberberine Antivirals

Narasimhan S
Department of Biotechnology, Manipal Academy of Higher Education, Manipal, Karnataka 576104

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ABSTRACT
Emerging viral diseases are one of the principal threats towards the plants, animals and humans. Viruses are fast evolving, resulting in reduced effectiveness of existing drugs and vaccines. At this juncture, the importance of traditional medicine, as well as medicinal plant active principles, occupies central attention of researchers across the world. Protoberberine alkaloids, an essential group of isoquinoline family of alkaloids, exhibit properties were affecting the life cycle of DNA and RNA viruses. However, from this protoberberine group, only berberine alkaloid has been studied in detail for its mechanism of action. Berberine is useful both in the case of enveloped and non-enveloped viruses. Berberine inhibits viral life cycle by modulating NF-κB signalling, targeting viral glycoproteins and downregulation of MEK-ERK signalling. Apart from this, berberine also inhibits ACE. All protoberberine alkaloids share a characteristic protoberberine skeleton. The protoberberine containing botanicals also exhibited antiviral properties. Therefore protoberberine alkaloids and protoberberine containing botanicals are interesting to experiment in detail for their antiviral properties and mechanism of action in emerging viral diseases of plants, animals and humans.

INTRODUCTION
Viruses use bacteria, animals and plants for their reproduction as well as survival. This creates a disease condition in host organisms. Medicinal plants are used against viral infections in several parts of the world based on ethnobotanical and traditional systems of medicine. Antiviral herbs are full spectrum. Therefore it is unlikely that viruses will develop resistance. They act by multiple mechanisms that interfere with the viral life cycle (Qing et al., 2017). Plants constitute a significant portion of the annual global medicine market. Across the world, researchers are aiming at natural products as a promising source for novel drug molecules. Currently, the interest in natural products is increasing due to mutation in viruses leading them to resistant. It is a fact that several viruses do not have a preventive vaccine. Therefore there is an added importance towards natural products and herbal medicines as effective antiviral agents.

Protoberberines are one of the essential group of isoquinoline alkaloids (Warowicka et al., 2019). Isoquinolines are one of the diverse and most abundant groups of natural products with various pharmaceutical properties (Qing et al., 2017). Protoberberine alkaloids were isolated from the members of the species belonging to the angiosperm plant families such as Ranunculaceae, Papaveraceae, Berberidaceae, Menispermaceae and Rutaceae. The isoquinoline group is considered as a good group because of its diverse functions such as antibacterial, antiviral, antimalarial and proapoptotic activities (Orhan et al., 2007). The primary mechanism
of the activity of isoquinolines, such as berberine is because of its nucleic acid binding ability (Warowicka et al., 2020). Isoquinolines are yellow or yellowish and therefore, can be addressed as “Yellow medicine” (Dipasquale, 2010). The current review discusses the mechanism of action of antiviral protoberberine alkaloids. The article also lists out another potential relatively new protoberberine alkaloids as well as their natural sources.

Protoberberines
Protoberberines constitute a significant group of isoquinoline alkaloids. Several protoberberine alkaloids have been isolated from various plants. All protoberberines possess a protoberberine skeleton (Figure 1). These tetracyclic alkaloids can be derived from benzylisoquinolines. The process involves coupling with the N-methyl group forming the berberine bridge (Gunatilaka, 1998). Among the protoberberines, berberine is a well-known and well-studied alkaloid. Other important alkaloids belonging to protoberberines family are palmatine, jatrorrhizine and coptisine. Protoberberine alkaloids are effective against (+) Sense, single-stranded RNA, (-) Sense single-stranded RNA as well as double-stranded DNA containing viruses (Table 1).

Berberine
Berberine is an important isoquinoline alkaloid present in many members of the family Menispermaceae. It also the most studied isoquinoline alkaloid for its chemistry as well as biological activities. Berberine is also a potent antiviral compound (Warowicka et al., 2020). According to (Wu et al., 2011), berberine significantly reduced the mortality rate in virus-induced pneumonia models of mice from 90% to 55%. Another important finding of this study is that berberine reduced viral titer in the lungs. The in vivo and in vitro models confirmed the potential use of berberine against influenza through lung histology score, TNF alpha and MCP-1 activity (Wu et al., 2011). Berberine reduces viral infection by modulating the NF-kB pathway (Song et al., 2014). This study was conducted on HSV and confirmed that berberine worked against the virus infection during the initial stages of infection.

Berberine also exhibited antiviral property on other viruses such as HCV by explicitly targeting the HCV E2 glycoprotein (Hung et al., 2019). Berberine isoquinoline alkaloid was effective in inhibiting the replication cycle of enteroviruses. Experiments found that berberine targets virus replication through the downregulation of autophagy and MEK-ERK signalling mechanism (Wang et al., 2017). Similar action of berberine was also found in Chikungunya virus (Varghese et al., 2016). This study was conducted on different compounds, and berberine was found to be the only alkaloid which inhibits the Chikungunya virus in a dose-dependent manner. MAPK is crucial for successful survival and reproduction of virions and therefore, essential for infection. Several viruses, including coronavirus as well as HIV, exhibit activation of MAPK signalling (Gong et al., 2011). Further, it has been proved that berberine affects the function of reverse transcriptase (Qing et al., 2017). Based on these pieces of evidence, it can be concluded that berberine is a potent antiviral natural product.

Jatrorrhizine
Jatrorrhizine is another protoberberine alkaloid which exhibits several inhibitory properties (Qing et al., 2017). Jatrorrhizine exhibited properties such as reverse transcriptase inhibition and thereby reducing the proliferation of HIV (Ng et al., 1997). There are no further reports available regarding the antiviral activity and its mechanism of jatrorrhizine. A recent molecular docking study conducted in 2174 natural products, indicated that jatrorrhizine exhibited docking with Semliki forest virus protease (Byler et al., 2016). Molecular docking studies also proved that Jatrorrhizine is capable of interacting at the binding site of HCV non-structural protein 5B (Mirza et al., 2015).

Palmatine
Palmatine is a well-known protoberberine alkaloid found in several medicinal plants and exhibits antiviral properties. A study conducted in analysing its effect on West Nile virus, dengue virus and yellow fever virus, it was found that palmatine is a potent compound in inhibiting the virus life cycle in host cells. The critical effect of palmatine is due to its ability to inhibit WNV NS2B-NS3 protease (Jia et al., 2010).
Table 1: Protoberberine alkaloids with proved antiviral activity

| Name of the alkaloid | Antiviral activity | Virus type | Viral genome | References |
|----------------------|-------------------|------------|--------------|------------|
| Berberine            | Influenza virus   | Enveloped  | (-) Ss RNA   | (Wu et al., 2011) |
|                      | Herpes simplex virus | Enveloped  | ds DNA       | (Song et al., 2014) |
|                      | Hepatitis C virus | Enveloped  | (+) Ss RNA   | (Hung et al., 2019) |
|                      | Enterovirus       | Non-enveloped | (+) SsRNA   | (Wang et al., 2017) |
| Jatrorrhizine        | Semliki forest virus | Enveloped  | (+) SsRNA    | (Byler et al., 2016) |
|                      | Hepatitis C virus | Enveloped  | (+) SsRNA    | (Mirza et al., 2015) |
|                      | West Nile virus   | Enveloped  | (+) SsRNA    | Jia et al. (2010)  |

Table 2: Few Botanical sources of protoberberine alkaloids yet to be screened for antiviral properties.

| Plant Family and species | Protoberberines | References |
|--------------------------|-----------------|------------|
| Annonaceae               |                 |            |
| Schefferomitra subaequalis | Aequaline and schefferine | (Gellert and Rudzats, 1972) |
| Berberidaceae            |                 |            |
| Berberis aristata       | Palmatine, Karachine | (Blasko et al., 1982) |
| Menispermaceae           |                 |            |
| Anamirta Cocculus       | Columbamine, (—)–8-oxotetrahydropalmatine, oxypalmatine | (Gunatilaka, 1998) |
| Papaveraceae             |                 |            |
| Chelidonium majus        | Berberine, coptisine, chelidonine, chelerythrine, sanguinarine, and protopine | (Warowicka et al., 2019) |
| Ranunculaceae            |                 |            |
| Thalictrum sp            | Thalifendine, thalifendlerine, thalidastine, coptisine, berberine, jatrorrhizine | Shamma and Dudock (1968) |

Protoberberine alkaloids are structurally related compounds. Many of the medicinal plants containing these alkaloids are exhibiting antiviral properties. For example, extracts prepared from the dried stem of Tinospora cordifolia, a protoberberine containing botanical exhibits useful properties in reducing HSV-1 infection (Purthvish and Gopinatha, 2018). Such plant-based medicines will be economical, more effective and less toxic (Maddi et al., 2018). However, extensive study of their antiviral property along with their mechanism has been only investigated regarding berberine. The closely related unexplored protoberberine metabolites may exhibit enhanced activity and can be more potent as well. Still, they remain entirely unexplored (Table 2).

Minor protoberberine alkaloids

There exist few studies on minor protoberberine alkaloids regarding their antiviral properties. Columbamine has also been evaluated for their ability to inhibit the HIV life cycle by affecting reverse transcriptase (Ng et al., 1997). Studies conducted by (Orhan et al., 2007) experimented the use of isoquinoline alkaloids from plants such as Fumaria and Corydalis. This study revealed that the use of protoberberines such as (D)-canadine, dehydrocavidine, dehydrocorydaline, (D)-ophiocarpine, (D)-corydalidzine, (D)-sinactine, (D)-style pine, corydalmine, palmatine and ophiocarpine-N-oxide. Therefore they may be future antivirals and may exhibit promising results.

Prospects

Among the pharmacological properties of protoberberine, inhibition of ACE attracts special attention. ACE inhibition is the reason for the hypotensive effect in experimental rats (Kang et al., 2002). ACE inhibitors occupy a central attraction in search of drugs for Covid-19 treatment because ACE is the receptor for SARS Covid-19 (Balmeh et al., 2020). The extracts of Coscinium fenestratum exhibited significant properties of ACE inhibition (Khan et al., 177).
Based on these pieces of evidence, it is highly recommended and the need of the hour to evaluate antiviral properties and mechanism of inhibition of protoberberine alkaloids.

Abbreviations
ACE: Angiotensin-Converting Enzyme; ERK: Extracellular signal Regulated Kinase; Ds= Double-stranded; HCV: Hepatitis C Virus, HSV: Herpes Simplex Virus, MAPK: Mitogen-Activated Protein Kinase; MEK: Mitogen-activated Protein/Extracellular Signal-regulated Kinase Kinase; MCP-1: Monocyte Chemoattractant Protein 1; NF-κB = Nuclear Factor-κB; Ss= Sense single-stranded; TNF: Tumor Necrosis Factor

CONCLUSIONS

Medicinal plants belonging to the lower angiosperm families contains many alkaloids, especially the protoberberine group. Even though the antiviral property of berberine is well established, but other related members of the group is yet to be studied. In the recent era of emerging diseases and vaccine resistance or vaccine non-availability, these compounds may serve as magic drugs for inhibiting the viral resistance. Mechanism of action of berberine and palmatine is known, but other protoberberine alkaloids in the same group are yet to be studied. As protoberberine differ slightly in their structures, how this structure difference reflects in the mechanism of action is interesting and may emerge as chartbuster antivirals. Further, it is interesting to study the mechanism of action and how they interact with the reproductive cycle of the virus and viral binding.

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Conflict of interest

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