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## Repurposing of Adamantanes for the Potential Prevention or Treatment of COVID-19

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# The Sars-Cov-2 Viroporin E and its Interaction with Amantadine an Analysis

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## Abstract

This article discusses the function of the SARS-Cov-2 virus E-channel and its interaction with amantadine.In this analysis it is proposed that amantadine is able to enter the E-channel of the coronavirus, inhibiting the viral content to enter the cell avoiding viral replication. Therefore, amantadine is a drug that can help decrease the symptoms of coronavirus. It is also mentioned how amantadine may be acting with the Spike protein, through a molecular docking study.

## Introduction

At the end of 2019, a new virus called COVID-19 was spreading in an alarming way in Wuhan City in China. This virus belongs to the family Coronoviridae and it is structurally formed by 4 proteins, E and M are part of the viral envelope, N is the one that binds to the viral genome and S (spike) is the one that binds to the human receptor ACE2 [1,2].

### Aspects of channel E

Viroporin E structurally consists of 5 protein chains, formed by 75 amino acids, where 33.33% form an alpha-helix structure (hydrophobic region), 53.33% random-coil, and 13.33% extended chain [3,4]. The E protein is well conserved among the 3 corona virus groups and shows limited homology across the different groups [5,6]. It has been shown that by deleting the E gene, viral replication decreases by 100 to 1000 times that of recombinant wild strains and that this decrease is accompanied by less inflammation in hamster lungs infected with the virus that possesses the E gene deletion [7].

The E protein was mainly located in the Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC) of the cells, where it participates in assembly, budding and intracellular trafficking, in addition to possessing ion channel activity [8,9]. Studies have shown that E is involved in critical aspects of the corona virus life cycle, which could make it a good candidate for the development of vaccines or drugs such as amantadine [1,4].

### Amantadine molecular function

Amantadine has been used as an antiviral therapy against the influenza virus, the proposed mechanism being that it blocks the early stage of replication. When the viral particle enters the cell, an endosomal structure is formed which has a pH of 5, this protein channel is formed by the M2 protein, which carries protons into the virion. Amantadine by its lipophilic nature is able to cross the endosome membrane and interrupt the release of the virion into the cell.

Similarly, amantadine can enter the E-channel of the corona virus by preventing the release of the viral nucleus into the cell [10].

Molecular docking studies have shown that amantadine may interact with the amino acids ALA22 and PHE26 by blocking the protein channel [4] (Figure 1). A mechanism has also been proposed where the entry of SARS-Cov-2 into a cell depends on the binding of the viral spike protein (S) to the cell receptor and the cleavage of the spike protein by host cell proteases such as Cathepsin L (CTSL) and Cathepsin B (CATSB). CTSL/B is a crucial element of the lysosome pathway and both enzymes are found almost exclusively in lysosomes. The interruption of the CTSL offers a potential for COVID-19 therapies. Mechanisms of disruption include: decreased CTSL expression, direct inhibition of CTSL activity, and impairment of CTSL environmental conditions (increased pH in lysosomes). Amantadine could reduce the CTSL, further disrupting the lysosomal pathway and thus interfering with the virus' ability to replicate. Amantadine may lower viral load in SARS-CoV-2 positive patients and, as such, may serve as a potent therapy that decreases virus replication and infectivity, likely leading to improved clinical outcomes [11].

Studies have shown that patients with multiple sclerosis, Parkinson's disease, or cognitive impairment who were SARS-Cov-2

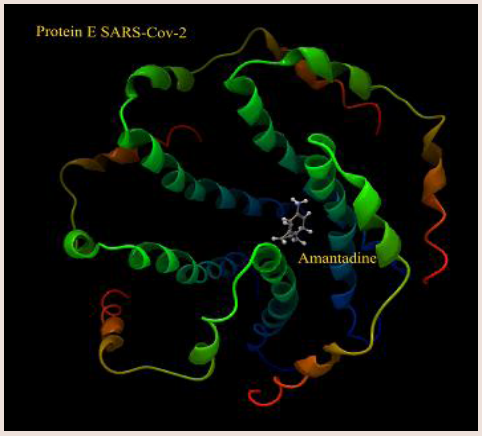


**Figure 1:** SARS-Cov-2 Viroporin E. Amantadine within the E channel of the COVID-19.Molecular docking, PatchDock software, Tel-Aviv University. Coronavirus E Protein, PDB 5X29.

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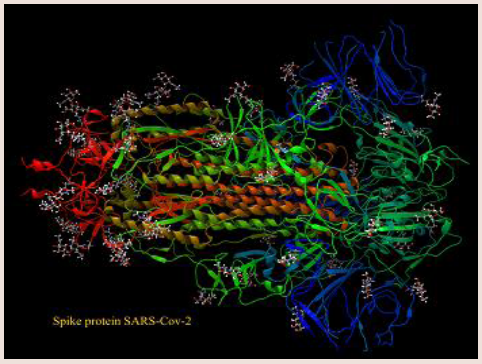


**Figure 2:** SARS-Cov-2 Spike protein. Amantadine interacting with various ASN amino acids. Molecular docking, PatchDock software, Tel-Aviv University. SARS-Cov-2 Spike Glycoprotein, PDB 6X6P.

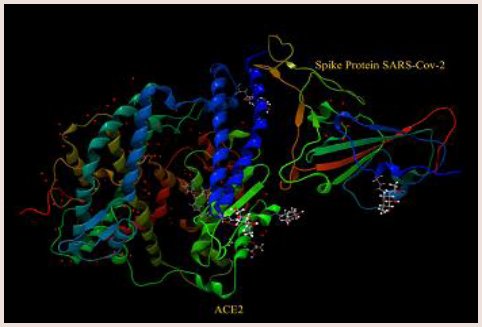


**Figure 3:** SARS-Cov-2 Spike protein. Amantadine interacting with various ASN amino acids. Molecular docking, PatchDock software, Tel-Aviv University. SARS-Cov-2 Spike Glycoprotein, PDB 6X6P.

positive received amantadine or memantine at recommended doses as part of their therapy, results showed that none developed clinical manifestations of the disease from COVID-19 [12,13]. This could be because amantadine could even interact with the Spike protein and not allow it to bind to the ACE2 receptor (Figure 2 and 3).

The lipophilic amantadine, whose chemical formula is C10H17N, is a derivative of the adamantane whose structure consists of 3 cyclohexane rings. It was approved by the FDA in 1976 for the treatment of influenza in adults and studied in vitro as a potential treatment for the SARS epidemic in 2002 [14].

Amantadine is well absorbed orally and well tolerated by the digestive system, has a moderate diuretic effect and is mainly excreted unchanged in the urine by glomerular filtration and tubular secretion. It has a half-life of 10 to 14 h and can generally be given with other drugs such as antihypertensives and antidiabetics [10].

## Conclusion

This pandemic has left at least 500,000 deaths worldwide and it will still take at least a few more months for an effective vaccine to become available, leaving a significant gap in infections and deaths.

This is why it is necessary to search for drugs that can help reduce the effects caused by COVID-19.

Amantadine, because of its characteristics, is emerging as a drug that can mitigate the effects caused by SARS-Cov-2.

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