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Challenges and future directions of potential natural products leads against 2019-nCoV outbreak

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ABSTRACT

Except for Remdesivir® no other drug or vaccine has yet been approved to treat the coronavirus disease (COVID-19) caused by the virus known as, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Remdesivir® an small molecule and nucleic acid analogue, it is used to treat adults and children with laboratory confirmed COVID-19, only administrated in hospital settings. Small molecules and particularly natural products count for almost fifty percent of the commercially available drugs, several of them are marketed antiviral agents and those can be a potential agent to treat COVID-19 infections. This short review rationalized different key natural products with known activity against coronaviruses as potential leads against COVID-19 [1].

Approved small molecules to treat COVID-19

Chloroquine, the first small molecule Food and Drug Administration (FDA) approved to treat COVID-19, later revoked, was inspired and developed from quinine sharing the same quinoline core (Fig. 1). Quinine is the bioactive component, an old antimalarial agent, it was isolated from the bark of *Cinchona officinalis* used for centuries by the Inca empire in South America to treat malaria and other illness [2].

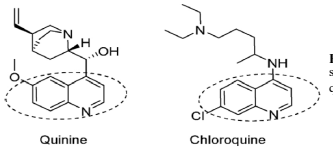

Fig. 1. Quinine and chloroquine chemical structures, dashed ellipse corresponded to the quinoline core.

The chemical structure for Remdesivir® resembles adenosine one (Fig. 2). Imagining under cryo-electron microscopy confirm Remdesivir® latches onto the primer RNA of the virus shutting down the viral reproduction [3].

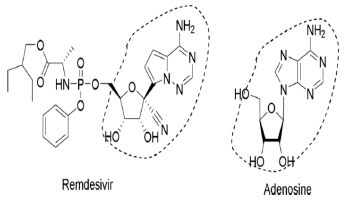

Fig. 2. Chemical structures of Remdesivir® and adenosine.

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ALKALOIDS

Several alkaloids have shown antiviral activity, for example, Kim *et al.* 2019, showed that bis-benzylisoquinoline alkaloids such as, tetrandrine **(1),** fangchinoline **(2),** and cepharanthine **(3)** isolated from *Stephania tetrandra* and other related species of Menispermaceae, (Fig. 3) to have potent activity against human coronavirus OC43 infection [4].

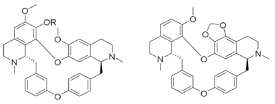


Fig. 3. Chemical structure for selected alkaloids

FLAVONOIDS

In 2005, Lin *et al.* studied phenolic compounds which were evaluated for their inhibitory effects on the SARS- CoV 3CLpro. Aloe-emodin **(9)** and hesperetin **(10)** dose-dependently inhibited cleavage activity of the 3CLpro in *in vitro* cell-free and cell-based assays, the IC50 values of aloe-emodin (9) and hesperetin (10) were 132 μM and 60 μM, respectively [5].

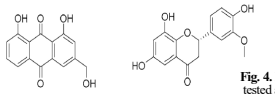


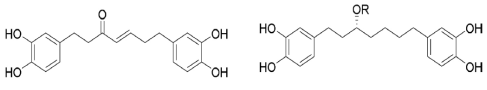
Fig. 4. Phenolic compounds tested against coronaviruses.

TERPENOIDS

Euphorbia neriifolia L. is an herb local to Southeast Asia. From leaves of *E. neriifolia*, 23 compounds were isolated, including 22 triterpenoids and one flavonoid glycoside [6]. The antiviral activity of all the isolated compounds was evaluated. The assay results indicated the highly influence of the antiviral activity with small differences in the structural features of the tested compounds. Among the friedelane derivatives tested, two epimers, 3β- friedelanol and 3α-friedelanol, with difference orientation at C-3 that affected dramatically their antiviral activity while epitaraxerol (25) (Fig. 7), a taraxerane derivative, was the most active derivative [6]. Glycyrrhizin (26), the active component of liquorice roots, has been reported to possess moderate antiviral activity against SARS-CoV in vitro with an EC50 of 300 g/mL [7], however its full mechanism is unclear.

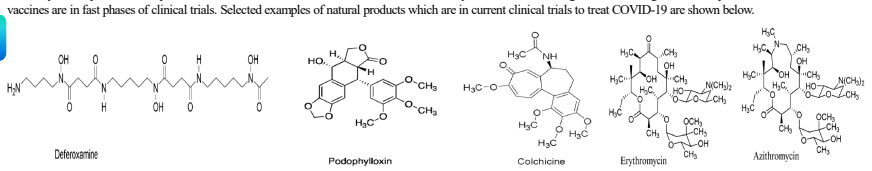
FATTY ACIDS AND POLYKETIDES- DIARYLHEPTANOIDS

Alnus japonica and its constituents exhibit various biological properties, including anti-inflammatory, anticancer, and anti-influenza activities. The ethanol extract of the stem bark of A. japonica exhibited PLpro inhibitory activity. Hirsutenone and rubranoside B exhibited modest activity, with IC50 values of 8.0 and 9.1 μM. These compounds also were tested using recombinant 3CLpro expressed *in vitro*, where rubranoside exhibited stronger 3CLpro inhibition than the other derivatives with IC50 = 36.2 μM.



CURRENT TRENDS AND CLINICAL TRIALS

There are several ongoing clinical trials using repurposed clinical stage or approved drugs such as remdesivir, favipiravir, lopinavir/ritonavir, hydroxychloroquine, and natural or semisynthetic products like quercetin, colchicine, tetrandrine, desferrioxamine B, azithromycin are under investigation for treating COVID-19 patients, as well as several vaccines are in fast phases of clinical trials. Selected examples of natural products which are in current clinical trials to treat COVID-19 are shown below.



CONCLUSIONS

There is an urgent and critical need to identify novel medical countermeasures both for prophylactic and treatment use. Since the production of a vaccine could take 12–18 months, and de novo development of therapies usually requires 10–17 years, repositioning clinically evaluated drugs represents one of the most practicable strategies for the rapid identification and deployment of treatments for emerging infectious diseases such as COVID-19.

ACKNOWLEDGEMENT

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