In a new study in *Cell Discovery*, Chen-Yu Zhang's group at Nanjing University and two other groups from Wuhan Institute of Virology and the Second Hospital of Nanjing present a novel finding that absorbed miRNA MIR2911 in honeysuckle decoction (HD) can directly target SARS-CoV-2 genes and inhibit viral replication. Drinking of HD accelerates the negative conversion of COVID-19 patients.

The search for clinically effective therapy for Covid-19 has not been successful to date. Many broad spectrum anti-viral agents have failed the test. In previous studies, Zhang's group has demonstrated that a plant microRNA, MIR2911, which is enriched in HD, could directly target influenza A viruses (IAV) including H1N1, H5N1 and H7N9. Drinking of HD can prevent IAV infection and reduce H5N1-induced mice death. They have also revealed that absorbed exogenous miRNAs (including MIR2911 in HD) can be packaged into exosomes, released to circulation, and then delivered into recipient cells as functional secreted miRNAs.

In the current study, they report that MIR2911 in HD can also suppress SARS-CoV-2 infection. The SARS-CoV-2 genome has up to 28 binding sites of MIR2911 which were confirmed by the classic luciferase assay. Cellular-exosomal-MIR2911 at 13.2 pM concentration (cellular exosomes were collected from culture medium of HEK293T cells transfected with synthetic MIR2911 or control ncRNA) inhibited 93% virus replication, indicating that exosomal MIR2911 directly and sufficiently inhibits SARS-CoV-2 replication. The MIR2911 concentration in HD was about 52.5 pM (10.5 pmol/200 ml/30 g dried honeysuckle). Serum levels of MIR2911 in healthy volunteers two hours after drinking 200 ml HD were about 0.67 pM. The antiviral function of exosomes with/without MIR2911 collected from the same donor before and after drinking HD were assessed. Exosomes containing MIR2911 (MIR2911 levels: nondetectable before drinking; 57.9 fM after drinking) significantly inhibited virus replication.

A clinical study further confirmed the anti-viral effect of MIR2911 from HD. Patients who already received routine antiviral therapy were divided into two groups, one group received additionally MIR2911 in HD (10.5 pmol/200 ml/30 g dried honeysuckle/day, MIR2911+), the other group receive normal traditional Chinese medicine (TCM) mixture (sequenced to be free of MIR2911-). The time taken to become SARS-CoV-2 PCR-negative (TTN) significantly favored patients treated with HD-MIR2911 (median 4.0 vs 12.0 days, HR 0.11, 95% CI 0.025-0.46, P=0.0028), indicating that MIR2911 in HD accelerates the negative conversion of infected patients.

1. This study demonstrated that absorbed plant MIR2911 in honeysuckle decoction inhibits SARS-CoV-2 replication and accelerates the negative conversion of infected patients.
2. It provides a practicable and reliable therapeutic strategy to treat SARS-CoV-2
3. This is the first time that exosomes with/without MIR2911 collected from the same donor before and after drinking HD ware used to assess absorbed dietary miRNA function, further supporting that absorbed dietary miRNA plays the important role of cross-kingdom regulation in human consumer.

4. The data that MIR2911 (~60 fM) in exosomes significantly inhibits virus replication not only confirms the extra-high antiviral activity of MIR2911 (compared to that of remdesivir: 3.7 ?M and Chloroquine: 10 ?M) but also provides a novel and the most similar condition in vivo to assess the efficacy of potential drugs in vitro.

"We wished we could provide really useful information to help stop the pandemic in the darkest hour," Chen-Yu Zhang said. "The focus of this study is to demonstrate that absorbed plant MIR2911 in honeysuckle decoction inhibits SARS-CoV-2 replication sufficiently. On the other hand, in the study titled "Decreased HD-MIR2911 absorption in human subjects with the SIDT1 polymorphism fails to inhibit SARS-CoV-2 replication," we have shown that synthetic MIR2911, cellular-exosomal MIR2911 and serum-exosomal MIR2911 directly inhibited SARS-CoV-2 S-protein expression and SARS-CoV-2 replication. More importantly, decreased HD-MIR2911 absorption resulted in non-inhibitory effect on replication, indicating that MIR2911 in HD is necessary to suppress SARS-CoV-2. Therefore, we propose medical doctors and scientists from all over the world to carry out HD-MIR2911 clinical trails in order to help treating SARS-CoV-2 infection." Zhang added.

More information: Zhou et al. Absorbed plant MIR2911 in honeysuckle decoction inhibits SARS-CoV-2 replication and accelerates the negative conversion of infected patients, Publishing in Cell Discovery in press. DOI: 10.1038/s41421-020-00197-3

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