Antiviral Protection and Therapy of Natural Products

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Abstract

In latest years, researchers have been concerned about the resistance, recurrence, and dormancy of viruses that occurs in the prevention and treatment of viruses. Regarding the current pandemic conditions reported not only to the SARS-CoV-2 virus (2019), but also to the SARS-CoV-1 virus (Severe Acute Respiratory Syndrome Coronavirus from 2013) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus from 2018), it is mentioned that there are scientific publications that demonstrate the benefits of treatments with natural products. Some natural products rich in phytonutrients can be used as an alternative to the prevention and treatment of viral diseases along with some treatments with pharmaceuticals that are very good, but are more aggressive towards the body. Some of the natural products – to be more effective – are used in processed form – as essential oils, as products obtained by distillation under specific conditions, as tinctures or as aqueous or alcoholic extracts – these being tested by in vivo and in vitro experiments. Asia is one of the continent with a tradition in natural herbal treatments, and the origin of these pandemic viruses has further driven researchers to seek and develop new techniques and methods to obtain natural products – concentrated enough to be effective but not no harm to patients. Also, the World Health Organization promotes innovations regarding new potential treatments for new viral diseases and also welcomes traditional, alternative, and complementary medicine – which can have an important role in healthcare. And because some of the viral diseases are found also in animals and humans – the researchers have a very complicated job to find therapies that not only treat and prevent but also are efficient and safe!

Key words: viruses, natural products, viral diseases

1. Introduction

Last years the world experimented some of the most difficult time for treatment and for stopping the spreading of viral diseases, including the SARS-CoV-1 (Severe Acute Respiratory Syndrome Coronavirus from 2013), MERS-CoV (Middle East Respiratory Syndrome Coronavirus from 2018), and SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus from 2019). But, since these viruses are new, there are no approved therapies or protective vaccines that already have long-term studies about the possible side-effects. There are possibilities that some of the coronaviruses cause particularly illness due to the contagious animal-to-human transmission and person-to-person transmission [1]. The latest pandemic coronavirus SARS-CoV-2 started to spread from Hubei Province, Wuhan – China, in December 2019 and the name of the disease was named as Coronavirus Disease 2019 – abbreviated as "COVID-19" (CO – from corona, VI – from virus, and 19 from 2019).

Consequently, aromatic herbs extracts, infusions, tinctures, and oils seem to be an alternative in phyto-medicine, used as a prophylactic or

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preventive therapy approach against even COVID-19 [2]. There are yet lots of countries that encouraging the trust and use of herbs and medicinal plants as natural antiviral prevention, before we will have an approved vaccine [3].

2. Herbs with antiviral activity for coronaviruses

The last decade intensifies the experimental studies regarding the usefulness of plants and herbals as an alternative therapy, especially of Chinese medicine in the treatment of different types of coronavirus infections. A study about statistical evidence in case of Chinese medicine used as a treatment for SARS brought new proves that the traditional Chinese medicine together with Western medicine was useful in the treatment of SARS in 2003.

Chen and Nakamura published in 2004 a short communication where they comparative analyzed the case fatality rates in Hong Kong, Singapore, and Beijing – taking in consideration the Chinese and Western medicine in the treatment of SARS. They suggested that, in case of the three cities taking in consideration for the study, combining the traditional Chinese medicine with Western medicine demonstrated that there is an improve rate of healing and decreased rate of death due to SARS virus [4].

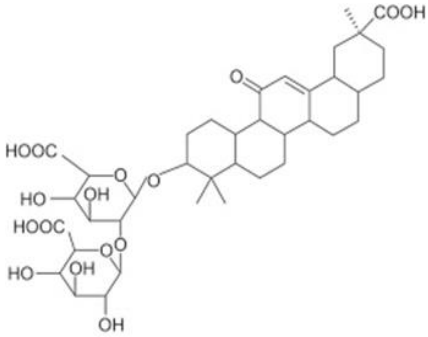
Since 2013, when the coronavirus started to manifest severe acute respiratory syndrome, researchers tried to find quickly new methods to improve the health status, to prevent the infectious disease, and also to find an adjuvant/additional treatment. Thus, there were published different studies regarding various methods of using plants and herbs as a preventive treatment or healing approach for coronavirus, which became more interesting for COVID-19.

Euphorbia neriifolia L. is one of the herbs very rich in triterpenoids, which are secondary metabolites for plants generally belong to Euphorbiaceae family. *E. neriifolia* L. is a spiny herb, found in the South-Asian region, in India, Sri Lanka, and Taiwan countries respectively. Traditional medicine used

the hydro-alcoholic extract of leaves of *E neriifolia* L. as diuretic, bleeding piles and anal fistula, common cold, and also as aphrodisiac treatment. Lately, the researchers tried to use extracts of *E. neriifolia* L. leaves rich in flavonoids, alkaloids, tannins, and also in triterpenoids and triterpenoidal saponins – from which it can be isolated and purified the triterpenoids and use against human coronaviruses (HCoVs) [5].

The collective research leaded by Hoever in 2005, demonstrated that glycyrrhizin (GL) inhibited the SARS-CoV. Modified structure of glycyrrhizin increased the activity against SARS-CoV by introduction of 2-acetamido-β-D-glucopyranosylamine into GL chain resulted in 10-fold increased antivirus activity, while GL amides and conjugated GL with residues of amino acid and a free 30-carboxyl function, presented 70-fold increased activity. Also, this chemical modified structure also increased cytotoxicity and decreased selectivity index, that have to be taken in consideration and also need further experimental studies [6].

Another study against SARS-CoV-2, took in consideration the glycyrrhizic acid – which had been used before in treatment of liver virus diseases (like viral hepatitis). Glycyrrhizic acid is a potent immune-active anti-inflammatory factor and non-hemolytic saponin which modify the cell membrane arrangements of the cholesterol-lipid microdomains – facilitating the entering of coronavirus into the cell. Inside the cell the glycyrrhizic acid can trap a specific highly mobility protein involved which block the signaling function of the high mobility group box 1 (HMGB1) – the most important chromatin protein, secreted by immune cells. So, the glycyrrhizic acid alone or together with (hydroxyl)chloroquine and tenofovir should be taken in consideration in the treatment of COVID-19, also [7].



Glycyrrhiza glabra – is an ancient medicinal plant, belongings to leguminosae family, found

in India, known as liquorice (British English) or licorice (American English) is a very good source of glycyrrhizic acid, glycyrrhizin, isoliquiritin, and isoflavones. The licorice powder and also the aqueous root extract is sweet and has aromatic flavor, and was tested with success as antimicrobial, antiviral, anti-inflammatory, anti-carcinogenic and anti-mutagenic, antitussive and expectorant, and antioxidant, memory enchanting activity, antiulcer, and antidiabetic activity [8].

Phenolic compounds from *Isatis indigotica* as root extract can be used efficiently as inhibitor of 3C-like protease of SARS-CoV. This enzyme mediates the proteolytic activity of replicase specific polypeptides (1a and 1ab) into functional proteins. The most important components of *I. indigotica* from root extract that can be efficiently used against of specific coronaviruses are indigo, indirubin, indicant, sinigrin, β-sitosterol, aloeemodin, hesperetin, and daidzein. From all of this chemical compound of the I. indigotica, the indigo, sinigrin, aloeemodin, and hesperetin in molecular range – demonstrated significant inhibitory effects of inhibitor of 3C-like protease of SARS-CoV [9].

Chinese medicine is known for ancient as a natural efficiently prevention, treatment and recovery option for many ailments. Thus, a Taiwanese group of researchers studied the efficiency of extracts of *Artemisia annua*¸ *Lindera aggregate*, *Lycoris radiata*, and *Pyrrosia lingua* against SARS-CoV strain BJ001. From these, Lycoris radiata extract was more potent as antiviral activity for SARS-coronavirus [10-14].

In 2004, a collective researchers from a Genomic Research Center from Taipei-Taiwan, published a study where they tested about 10,000 natural and synthetic agents against severe acute respiratory syndrome coronavirus (SARS-CoV). From all these compounds tested, about 50 showed efficiency at 10 μM. Some of plant ginsenoides extracts belongs to eucalyptus – *Lonicera japonica* and *Panax ginseng* were also efficient against SARS-CoV in concentration of 100 μM [14].

Another plant known in Chinese Traditional Medicine, *Scutellaria baicalensis*, was used with great results against SARS-CoV-2. In experimental studies the SARS-CoV-2 need to be handle in laboratories with biosafety level 3 or higher, and could be amplified in Vero E6 cells. The extracts of Scutellaria baicalensis is important especially for two flavonoids molecules – baicalein and baicalin – which, at concentration of 100 μM, showed cytotoxic action on Vero E6 cells. Also, baicalin extract in concentration of 75 μM exerts inhibition of replication for VSV (vesicular stomatitis virus) on Vero E6 cells [15].

Different treatment methods could lead to different fatality rate (death) regarding the coronavirus treatment. Thus, we want to bring in attention a very interesting study which was

The herbs extracts manifest antiviral effects and the mechanism of action involve viral replication, effects in host on short-term and also on long-term in both ways: positive effects and negative effects.

3. Antiviral mechanisms and action

In order to infect an organism, the viruses must to enter into the host. So, due to this very important aspect, the researchers have to develop drugs that affect only the virus from inside the living organism, without to harming the host. But drugs with antiviral effect do not kill or inactivate the virus inside the host, but merely interfering into the certain stages of virus life cycle aiming inhibiting the viral reproduction/replication. The virus is outside protected by a protein shell structure, named capsid, and the inside protein shell is found the virus genome containing DNA or RNA. The capsid also can have a lipid shell – named envelope, with specific spike proteins used by the virus to be able to attach to the host. The life cycle of a virus has to follow several stages, such as: attachment of the virus to the host cells; the entry of the virus by endocytosis or fusion; the release of the uncoated genome; viral genome

replication; proteins synthesis and processing; and finally the release of new viruses. Antiviral mechanisms and action of plants or herbs extracts involve agents that interfere with any of the life cycle stages of a virus, aiming the blocking the viral reproduction [16-18].

There are used different phyto-therapeutic products, such as: aqueous or oil extracts, volatile oils, isolated components, different anatomical parts of the plant (root, rhizome, leaves, flowers), and also various extraction products (tincture; decoction; water, oil or alcohol infusions; tea).

4. Conclusions

Phyto-therapy or plants/herbs' extract could be an alternative of prevention and complementary natural treatment of viral diseases.

For the best results it needs to follow in vivo and in vitro experiments, which provide information about the virus life cycle, the viral replication and the specific proteins from the outside membrane with are used to attach the host cells. Also, it is very important to find out which laboratory techniques provide the best and optimum composition for the natural herb/medical plant product, and also how we can expect the highest concentration of phytochemicals with antiviral effect.

Traditional medicine used from ancient different medicinal plants, herbs, and spices to prevent and treat viral disease, and as a supplementation diet with natural powerful phytochemicals – which can enhance the health status of a patient!

References

1. D. Paraskevis, E.G. Kostaki, G. Magiorkinis, G. Panayiotakopoulos, G. Souvinos, S. Tsiodras, *Infect. Genet. Evol.*, 79 (2020) 104212.
2. M.N.Boukhatem, W.N. Setzer, *J. Plants*, 800 (2020) 9.
3. Y. Zhou, Y. Hou, J. Shen, Y. Huang, W. Martin, F. Cheng, Cell. Discov., 6 (2020) 1-18.
4. Z. Chen, T. Nakamura, *Phytother. Res.*, 18 (2004) 592-594.
5. F.R. Chang, C.T. Yen, M. El-Shazly, W.H. Lin, M.H. Yen, K.H.Lin, Y.C. Wu, *Natural Product Communications*, 7(11) (2012) 1415-1417.
6. G. Hoever, L. Baltina, M. Michaelis, R. Kondratenko, L. Baltina, G.A. Tolstikov, H.W. Doerr, J. Cinatl, *J. Med. Chem.*, 48 (2005) 1256-1259.
7. C. Bailly, G. Vergoten, *Pharmacol. Ther.*, 214 (2020) 107618.
8. V. Sharma, A. Katiyar, R.C. Agrawal (Eds.), Chapter 4: *Glycyrrhiza glabra*: Chemistry and Pharmacological Activity, pp. 87-100, in Sweeteners – J.M. Merillon, K.G. Ramawat (Editors), Springer International Publishing, AG
9. C-W. Lin, F-J. Tsai, C-H. Tsai, C-C. Lai, L. Wan, T-Y. Ho, C-C Hsieh, P-D Lee Chao, *Antiviral Res.*, 68 (2005) 36-42.
10. S-h. Li, C. Chen, H-q. Zhang, H-y. Guo, H. Wang, L. Wang, X. Zhang, S-n. Hua, J. Yu, P-g. Xiao, R-s. Li, X. Tan, *Antiviral Res.*, 67 (2005) 18-23.
11. * * * World Health Organization, Regional Office for Africa, WHO supports scientifically proven traditional medicine, 04 May 2020.
12. S. Robertson – Extracts of medicinal plant Artemisia annua interferes with replication of SARS-CoV-2 *in vitro*, News Medical Life Sciences, https://www.news-medical.net/news/20210111/Extract-of-medicinal-plant-Artemisia-annua-interferes-with-replication-of-SARS-CoV-2-in-vitro.aspx
13. M.S. Nair, Y. Huang, D.A. Fidock, S.J. Polyak, J. Wagoner, M.J. Towler, P.J. Weathers – *Artemisia annua* L. extracts inhibit the *in vitro* replication of SARS-CoV-2 and two of its variants, J. Ethnopharmacology, doi.org/10.1101/2021.01.08.425825
14. C-Y. Wu, J-T. Jan, S.H. Ma, C.J. Kuo, H-F. Juan, Y-S. E. Cheng, H-H. Hsu, H-C. Huang, D. Wu, A. Brik, F-S. Liang, R-S. Liu, J-M. Fang, S-T. Chen, P-H. Liang, C-H. Wong, PNAS, 101 (2004) 10012-10017.
15. S. Huang, L. Liu, Y. Zhang, R. Zhang, C. Zhu, L. Fan, G. Pei, B. Zhang, Y. Shi, Signal Transduction and Targeted Therapy, 5 (2020) 266.
16. J. Shang, Y. Wan, C. Luo, G. Ye, Q. Geng, A. Auerbach, F. Li, Proc. Natl. Acad. Sci, 117 (2020), 11727-11734.
17. C. Wang, S. Wang, D. Li, D.Q. Wei, J. Zhao, J. Wang, Gastroenterology, 159 (2020) 1145-1147
18. M. Gur, E. Taka, S.Z. Yilmaz, C. Kilinc, U. Aktas, M. Golcuk, J. Chem. Phys., 153(2020) 75101.