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Aloe vera (L.) Burm. F. as a Potential Anti-COVID-19 Plant: A Mini-review of Its Antiviral Activity

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Authors' contribution

This work was carried out in collaboration among all authors. Authors PTM, KTNN and DSTT wrote the first draft of the manuscript. Authors BZG, JTK, DTM, CLI, EML and CMM collected information on the plant. Authors AM, GNB and DDT collected information on COVID-19. All authors read and approved the final manuscript.

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ABSTRACT

Aims: A novel β-coronavirus (2019-nCoV) has become a pandemic affecting hundreds of thousands of people worldwide. Since there is no effective treatment, the need of finding alternative methods which can help to curb this pandemic is urgent. This study aims to review the literature on the virucidal and cytotoxic properties of *Aloe vera*, one of the most studied plants considered as a nutraceutical in order to propose it as an alternative solution against COVID-19.
Methodology: The literature review was based mainly on the COVID-19 resources that have been made freely available to the scientific community but also on the usual databases such as Pubmed and Google scholar.

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Results: The literature review shows that the plant has antiviral activity on several types of virus (Haemorrhagic Viral Rhobdavirus Septicaemia, Herpes simplex virus type 1, Herpes simplex virus type 2, Varicella-Zoster virus, human immunodeficiency virus, Influenza virus, poliovirus, Cytomegalovirus, Human papillomavirus) including coronavirus SARS-CoV-1. The plant is consumed orally in several forms and is safe. It is possible that molecules of this plant that have already shown effectiveness on other viruses by some mechanisms such as interaction of virus enzyme, breakdown of the viral envelope etc. could participate in the action of the plant. Also, the presence of minerals such as Zinc, which have shown an effect on SARS-CoV-1, could be involved in the antiviral effect of *Aloe vera*.
Conclusion: Molecular docking of the main molecules of *Aloe vera* with SARS-CoV-2 protease is in progress and clinical trials are necessary to confirm the activity of *Aloe vera* on COVID-19.

Keywords: Aloe vera; COVID-19; antiviral activity; molecular docking; sars-cov-2.

1. INTRODUCTION

Coronavirus disease 2019 (or COVID-19) is an emerging infectious disease caused by a strain of coronavirus called SARS-CoV-2. Comparative genomic studies have shown that SARS-CoV-2 belongs to the Beta coronavirus family and is phylogenetically very similar to SARS-CoV-1, which was responsible for an outbreak of acute pneumonia that occurred in November 2002 in Guangdong Province, China. COVID-19 began in Wuhan in Hubei Province, People's Republic of China, in December 2019, and became a global pandemic, killing hundreds of thousands of people [1-3]. Despite the biosafety and hygiene measures to limit the large-scale spread of this pandemic, there is currently no anti COVID-19 drug approved by the world health authority, the World Health Organization (WHO). Furthermore, the prospect of developing a new drug in the short to medium term is not feasible due to many constraints [4].

Some antivirals already used in the treatment of SARS-CoV and MERS-CoV are recommended. These include lopinavir and ritonavir [5-7]. Chloroquine, a known antimalarial drug used as an immunomodulant in other coronavirus infections, has been proposed but its use is still controversial in the scientific community [8-10]. Therefore, an alternative solution to this major public health problem is urgently needed to save lives, and traditional medicine, which has proved its worth around the world when used against several diseases, remains one of the avenues that can be exploited to counter this pandemic.

The role of traditional medicine in the treatment of COVID-19 has recently been reported in the literature [11]. Indeed, medicinal plants are an important source of molecules with various pharmacological properties including antiviral properties that can be used in the search for the solution against COVID-19. According to the World Health Organization, more than 80% of the population in Africa use Traditional Medicine to solve the primary health problem [12-17]. Nevertheless, it is not unique to Africa or other developing countries where it is recognized as traditional medicine. It is also used in the so-called developed or industrialized countries where it is known as "complementary", "alternative", "unconventional" or "parallel" medicine. It has the advantage of being safe, effective, less expensive and presents less risk, with significantly reduced side effects compared to allopathic drugs [18,19].

Aloe vera (L.) Burm.f. considered as a “miraculous plant” or “wonder plant” is a medicinal plant that has been used for more than 3000 years in various cultures [20]. It is one of more than 400 species in the genus *Aloe* of the family Xanthorrhoeaceae [21]. It is one of the most studied and used medicinal plants worldwide. Its pharmacological properties and phytochemistry are well documented [22-24]. Since the appearance of COVID-19, there has been some information referring to the use of this plant alone or in combination with others against COVID-19 [25].

This study aims to review the literature on the virucidal and cytotoxic properties of *Aloe vera*, one of the most studied plants considered as a nutraceutical. These data would allow this plant to be used as a multifunctional and low toxicity drug candidate for the management of COVID-19.

2. METHODOLOGY

The literature review was based mainly on the COVID-19 resources that have been made freely available to the scientific community [26], but

also on the usual databases such as PubMed and Google scholar. The scientific name of the plant (*Aloe vera*) and COVID-19 were used as keywords for the search. Finally, bibliographical references were made using a bibliographical software "Mendeley".

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Antiviral activity

Antiviral activity of *Aloe vera* and some of its phytochemicals is well documented. Fractions of the gel containing lectins isolated from the plant have been shown to directly inhibit the proliferation of CMC (Cytomegalovirus) in cell cultures [24,27]. Alves et al. [28] report that *A. vera* chrysophanic acid achieves 50% inhibition of viral replication in type 2 and 3 polioviruses at concentrations of 0.21 and 0.02 µg/mL. But, this molecule did not have significant antiviral activity against HSV-1, RRV, CVB4, CVA21 or HRV-2. Aloin has also been reported to have a virostatic effect on HSV (Haemorrhagic Rhadovirus Septicaemia Virus), an RNA-negative enveloped virus [27,28]. The administration of acemannan, one of the major compounds of the plant, intraperitoneally improves both the quality of life and the survival rate of cats with clinical feline leukemia virus symptoms. Another similar study confirmed the antiviral activity of acemannan in cats infected with the Immunodeficiency Virus (HIV) [24,27]. Keivan et al. [29] tested the antiviral activity of a crude hot glycerin extract of *A. vera* gel which was grown in Bushehr (Southwest of Iran) against HSV-2 replication in Vero cell line. This study showed that the extract tested showed antiviral activity against HSV-2, not only before the attachment and the entry of the virus to the Vero cells but also on post attachment stages of virus replication. The IC_{50} before the attachment and the entry of the virus to the cells is 428 µg/mL and the CC_{50} value which is the cytotoxicity of the extract for Vero cells is 3238 µg/mL, while the calculated selectivity index (SI) is 7.56. Also, the IC_{50} of the extract on post attachment stages of replication is 536 µg/mL and the SI value for inhibition of the post attachment stages of HSV-2 replication is 6.04. In another study, the authors demonstrated that the ethanol extract of *A. vera* inhibited autophagy induced by influenza virus in MDCK cells [30]. When studying the antiviral activity of *A. congolensis*, Kahlon et al. [31] indicated that acemannan acts alone and synergistically with azidothymidine (AZT) and acyclovir to block the reproduction of Herpes and the AIDS virus. McGuffin et al. [32] reported that *Aloe* has been used to treat stomach ulcers and AIDS. Recently, *A. vera* ethanol extract (AVE) reportedly has significant anti-influenza virus activity [30]. One of the anthraquinones, named emodin of *Aloe vera*, has been reported to have antiviral activities to some kind of viruses, such as human cytomegalovirus, herpes simplex virus type 1 and poliovirus [33,34].

Table 1 summarizes some phytochemicals from Aloe vera and their effects on viruses.

3.1.2 Phytochemistry and molecules involved in antiviral activity

Many phyto-constituents were identified from different parts of *A. vera*, including nine compounds, namely: Anthraquinones/anthrones (aloe-emodin, aloetic-acid, anthranol, barbaloin, isobarbaloin, emodin, ester of cinnamic acid); chromones (8-C-glusoly-(2'-O-cinnamoly)-7-O-methlyaloediol A, 8-C-glucosyl-(S)-aloesol, 8-C-glucosyl-7-O-methylaloediol A, 8-C-glucosyl-7-0-methylaloediol, 8-C-glucosyl-noreugenin, isoaloeresin D, isorabaichromone, neoalosin A); other organic compounds and lipids (arachidonic acid, Y-linolenic acid); steroids (campesterol, cholesterol, β-sitosterol), triglycerides; triterpenoids; gibberillin; lignins; potassium sorbate; salicylic acid and uric acid [35]. Arunkumar and Muthuselvam [40] reported that qualitatively analyzed tannins, saponins, flavonoids and terpenoids showed positive results, while phlobactanins and steroids showed negative results in *A. vera.* Femenia et al. [41] reported that *A. vera* contains carbohydrates including] pure mannan, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, gluco gluco arabinomannan, pectic substance, xylan and cellulose. The plant contains vitamins A, C, F, B, B2, niacin, choline and folic acid along with traces of vitamin B12 as well as the enzymes such as acid phosphatase, alkaline phosphatase, amylase, lactic dehydrogenase and lipase [35].

Antiviral activity is in general due to anthraquinones. However, several individual compounds involved in antiviral activity were identified in *Aloe vera* including quercetin, catechin hydrate, kaempferol, acemannan, azidothymidine, acyclovir, aloin, emodin [30,31].

Table 1. Summary of antiviral activity of *Aloe vera*

Types of viruses	Genome type	Molecules	Mode of action	References
Haemorrhagic Viral Rhobdavirus Septicaemia (VHS)	RNA	Aloin	Destruction of the phospholipid double layer by incorporation into the viral envelope	[28]
SARS coronovirus (SARS-CoV1)		Aloe-emodin	Aloe-emodin inhibits the cleavage of 3C-like protease, an enzyme that plays an important role in viral replication by acting on the proteolytic process at the replicase level.	[27,29,35,36,37]
Herpes simplex virus type 1 (HSV-1) HSV-2 *Varicella-Zoster virus* (VZV)	DNA		Inhibition of nucleic acid biosynthesis resulting in the termination of protein synthesis	
Influenza virus HIV-1	RNA	Acemannan	Acemannan inhibits glycosylation of viral proteins and inhibits cell fusion and suppression of virus release	[24]
Poliovirus		Chrysophanic acid	This molecule prevents the penetration of the virus into the cell, either the translation of the viral RNA or the initial cleavage of the viral protein.	[27,28]
Cytomegalovirus (CMV)		Lectins	Leptins inhibit CMV proliferation by interfering with protein synthesis.	[38]
Human papillomavirus (HRHPV)	DNA	-	-	[39]

A. vera contains also mineral elements among which Calcium (Ca), magnesium (Mg), Sodium(Na), Potassium (K), Iron (Fe), Copper (Co) and Zinc (Zn). It was shown that Zn^{2+} inhibits coronavirus and arterivirus RNA polymerase activity *in vitro* and Zinc ionophores block the replication of these viruses in cell culture [42].

3.1.3 Oral uses and toxicity

A. vera is widely used in oral route as juice, cream, tablets, tea, capsules, toothpaste, yogurt, jam etc as revealed in Fig. 1. The interest into this plant species is related to its safety both *in vitro* [43] and *in vivo* [44]. Indeed, it was reported that a multiple oral administration of the methanol extract at single dose of 4, 8 and 16 g/kg body weights for 14 days did not produce signs of toxicity [45]. A similar study also showed no toxicity in F344 rats after oral administration of a commercially available *A. vera* decolorized extract beverage up to 13 weeks [46].

However, an adverse effect (hepatotoxicity) was reported by Ha et al. [8] in three individuals after taking *Aloe* preparation for months. This indicates that dietary supplement such as *Aloe* must be used with precaution mainly for prolonged daily use and excessive doses.

3.2 Discussion

Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development. Identification of the antiviral mechanisms from these natural agents has shed light on where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus–host-specific interactions. In this brief report, we summarize the antiviral activities from several natural products and herbal medicines against some notable viral pathogens including coronavirus [47].

To this end, *Aloe vera* is a high-potential anti-COVID-19 plant drug candidate for the management of this disease in the Democratic Republic of the Congo. Indeed, several experimental studies have shown that the *Aloe vera* plant is endowed with formidable virucidal properties with a broad spectrum of action. Its extracts are active against RNA and DNA viruses (Table 1). From the point of view of toxicity, the innocuousness of the extracts of this plant has been proven experimentally both *in vitro* and *in vivo*. For example, *Aloe vera* contains virucidal secondary metabolites such as anthraquinones which, like some antiviral drugs (Lopinavir, ritonavir), may act alone or in synergy with pharmacological targets like SARSCov -2 protease 3CLPro [31,33,34].

Fig. 1. Oral uses of *Aloe vera*

In addition to intrinsic antiviral properties, *Aloe vera* is also endowed with anti-inflammatory and immunomodulatory properties [48]. To this effect, it is not excluded that a phyto-drug based on *Aloe vera* extracts can attenuate in the patient the expression of pro-inflammatory factors and receptors likely to induce acute respiratory distress which is the main cause of mortality associated with COVID-19 while strengthening the immune system. As combination of therapies based on viral protease inhibitors are the best therapeutic option, *Aloe vera* and its major secondary metabolites may play an important role in the management of COVID-19.

These data pave the way for clinical research on anti-COVID-19 herbal medicine. Indeed, in addition to its secondary metabolites endowed with virucidal properties, *Aloe vera* contains zinc (40.8 ppm) [42]. This chemical element, although indispensable as an enzymatic co-factor, a slight increase in its intracellular concentration inhibits the replication of retroviruses including SARS-CoV-1 [47] important in the management of COVID-19.

4. CONCLUSION

The world is going through a major crisis due to COVID-19. This pandemic still has no acceptable remedy. It is therefore important to search for alternative solutions, especially for African countries. *Aloe vera* is a plant widely used for its various activities including antiviral activities. The purpose of this work was to do bibliographic research on the antiviral properties of this plant. The results obtained show that *Aloe vera* possesses not only antiviral properties but also anti-inflammatory and immune-stumulant properties which can be useful in the management of COVID-19. Molecular docking and clinical trials are nonetheless necessary to confirm these positive effects.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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