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Anti-viral compounds from *Jatropha curcas* seed extract with anti-HIV-1 and anti-SARS-CoV-2 action

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Many studies have dealt with the medicinal properties of Jatropha curcas; however, there are limited studies on the scope of its antiviral potential. This is a fact associated with the current challenges posed by HIV-AIDS and COVID-19, which has reinforced the need to expand the knowledge about its antiviral resource. Based on the search for natural products with anti-HIV-1 and anti-SARS-CoV-2 activities, this work analyzed the extract of *J. curcas* seed, the structure of the plant whose antiviral references were not found in the literature, and the compounds that can potentiate it as a candidate for herbal medicine. GC-MS analysis was used to screen for the active substances of the *J. curcas* seeds, and the literature was searched to find those with anti-HIV-1 and anti-SARS-CoV-2 indication. The results showed they have 27 compounds, of which glycerol 1-palmitate, stigmasterol and gamma-sitosterol were shown to have antiviral action in the literature. Regarding glycerol 1-palmitate, no detailed description of its antiviral action was found. Stigmasterol and gamma-sitosterol act as anti-HIV-1 and anti-SARS-CoV-2, respectively, inhibiting the reverse transcriptase of HIV-1, the proteases 3CLpro, PLpro and the spike proteins of SARS-CoV-2. However, despite the fact that the extract of *J. curcas* seeds consist of antiviral compounds that fight against the etiological agents of HIV-AIDS and COVID-19, it is concluded that there is a need to deepen this evidence, by in vitro and in vivo assays.

Key words: Compounds, antivirals, *Jatropha curcas*, HIV, SARS-CoV-2.

INTRODUCTION

Jatropha curcas is a plant with a diverse spectrum of pharmacological properties. It contains mixtures of different chemical compounds that act individually or collectively to improve human health (Prasad et al., 2012). It is used for medicinal purposes because it has antifungal, antibacterial, antitumor, antiviral, anti-inflammatory (Silva Filho et al., 2009) and antioxidant effects (Rocha, 2013; Ribeiro et al., 2020).

However, despite all the potentialities of the plant reported earlier, this work focuses on the antiviral property of *J. curcas* because first, public health is faced with numerous challenges imposed by viral diseases, such as HIV -AIDS, COVID-19, new variants of SARS-CoV-2 and also existing drugs are no longer effective

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against HIV; second, Ferrão and Janeque (2019), in their work, found that the compounds present in the seeds of this plant species have multiple functions.

Furthermore, regarding studies that report that *J. curcas* can be used to treat HIV-AIDS, it is important to note that the experimental work carried out by Matsuse et al. (1999) and Dahake et al. (2013) showed promising results. The first group of authors that used the extracts from the stem bark of this plant observed that cytopathic effects induced by HIV were inhibited with low cytotoxicity, and the second group that analyzed the effect of the leaf extracts on HIV concluded that it is an excellent candidate for herbal medicine. However, there is no evidence on the use of this plant in the treatment of COVID-19.

Ferrão and Janeque (2019), in their work, used gas chromatography-mass spectrometry (GC-MS) to identify compounds present in the extracts of *J. curcas* seeds used for treating people in the municipal village of Massinga, Mozambique. Thus, based on the work of Ferrão and Janeque (2019) and the literary matrix that deals with substances with antiviral effect, the present work aims to trace compounds with anti-HIV and anti-SARS-CoV-2 potential in this plant structure.

MATERIALS AND METHODS

The data obtained from the work of Ferrão and Janeque (2019) were used for the present study. The method adopted by these authors was GC-MS. Also, bibliographic consultations were carried out.

This research analyzed and discussed the results of Ferrão and Janeque (2019) obtained from the GC-MS analysis of *J. curcas* seed extracts. Ferrão and Janeque (2019) collected the material from Massinga district, Inhambane province, based on the procedure of Bessa et al. (2013), to reduce the degree of humidity. This process prevents microbial activity and hydrolysis. Therefore, the materials were left in the oven at a temperature of 40°C for 24 h. The *J. curcas* seeds underwent the process of Soxhlet extraction and maceration.

GC-MS analysis

GC-MS analysis was carried out at the Research and Extension Laboratory of the Department of Chemistry, Eduardo Mondlane University, Mozambique, as part of the work of Ferrão and Janeque (2019).

Sample preparation

According to Ferrão and Janeque (2019), about 80 mg of the plant was extracted in a 15 mL polypropylene tube, mixed with 1 mL of ethanol (99.9%) using a vortex mixer at 2200 rpm for 5 min. Then, the mixture was centrifuged for 1 min and the supernatant was transferred to another polypropylene tube. The procedure was repeated two more times (to complete 3 extractions) and the supernatants were collected into the same polypropylene tube. Also, the extract was subsequently evaporated to dryness on a rotary evaporator at 65 to 67°C. It was recovered with 1 mL of methanol, filtered and injected into GC-MS.

GC-MS

J. curcas seed extract (2 µL) was injected into a capillary column (HP 5MS IU: 30 m × 250 µm × 0.25 µm, -60 - 325°C) by splitless mode. Helium (99.9%) was used as a 1 mL-1 mobile phase. The analysis was performed in electron impact mode with ionization energy of 70 eV. The injection temperature was maintained at 250°C. The initial column temperature was 50°C (3 min), then it was raised to 280°C (3 min) at a rate of 10°C/min and finally to 300°C (10 min) at a rate of 20°C/min. The total analysis time was 40 min. Peak identification was performed by comparing the spectra of each eluted component with the spectra present in the NIST library database.

Articles reviewed

Articles, communications and papers available or not on online platforms (Google Scholar, Elsevier, Research Gate, Science Direct and Scielo) were consulted as the following. The works of Ferrão and Janeque (2019), Verma et al. (2015), Kaur et al. (2011), Abdelgadir and Van Staden (2013), Vincent et al. (2020), Fadilah et al. (2020), Sharmila et al. (2016), Kamiyama et al. (2013), Venkata et al. (2012), Hadi et al. (2016), Chinsembu (2019), Kaur et al. (2020), Bapia et al. (2021), Siwe-Noundou et al. (2019), Terefe et al. (2022), Silva Filho et al. (2009), Matsuse et al. (1999), Dahake et al. (2013), Padmashree et al. (2018b), Godara et al. (2019), and Beckstrom-Sternberg and Duke (1996).

The articles reviewed comprised two stages: the first concerned the articles that deals with the antiviral activity of *J. curcas*, and the second focused on the material that reports the compounds found in the extracts of this plant with anti-HIV-1 and SARS-Cov-2 indication, in order to explain their forms of action.

RESULTS AND DISCUSSION

The extract recovered with 1 mL of methanol, filtered and injected into GC-MS showed the presence of n-Propyl acetate, ethanethioic acid, S-(dihydro-2,5-dioxo-3-furanyl) ester, thymine, 4H-Pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl, d-Glycero-d-ido-heptose, 5 hydroxymethylfurfural, ethanol, 2-(2-butoxyethoxy)-,acetate, l-Pyrrolid-2-one, N-carboxyhydrazide, methyl 6-oxoheptanoate, 2,4,7,9-tetramethyl-5-decyn-4,7-diol, hexadecanoic acid, methyl ester, melezitose, n-Hexadecanoic acid, 9,12-Octadecadienoic acid (Z,Z)-, methyl ester, 6-octadecenoic acid, methyl ester, (Z)-, 9,12-Octadecadienoic acid (Z,Z)-, cis-Vaccenic acid, oleic acid, octadecanoic acid, hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester, glycerol 1-palmitate, 9,12-octadecadienoic acid (Z,Z)-, 2-hydroxy-1-(hydroxymethyl) ethyl ester, 9-octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl) ethyl ester; squalene, campesterol, stigmasterol, and gamma-sitosterol.

Table 1 show the retention times and areas of these compounds and the respective biological activities reported in the consulted bibliography.

Table 1. Compounds found in *Jatropha curcas* seed extract by GM-CS.

Order	Compounds	Retention time	Holding area	Biological action	References
1	n-Propyl acetate	3.688	5790494.07	Larvicide	Jeyasankar and Chinnamani (2017)
2	Ethanethioic acid, S-(dihydro-2,5-dioxo-3-furanyl) ester	4.406	455574.54	Not reported	-
3	Thymine	9.455	6866372.8	Anti-cancer	Darweesh and Ahmed (2016)
4	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl	10.5	1427368.41	Antioxidant, anti-inflammatory; pro-apoptotic, anti-proliferative; antifungal	Shukla et al. (2018)
5	d-Glycero-d-ido-heptose	10.897	281379.27	anti-inflammatory	Haider et al. (2016) and Zimila et al. (2020)
6	5-Hydroxymethylfurfural	11.773	8331923.17	Antioxidant, anti-inflammatory;, anti-hypoxic, antimicrobial, anti-apoptotic	Gao et al. (2015)
7	Ethanol, 2- (2-butoxyethoxy)-, acetate	13.655	1187014.42	Not reported	-
8	l-Pyrrolid-2-one, N-carboxyhydrazide	13.853	687896.81	Not reported	-
9	Methyl 6-oxoheptanoate	14.048	321445.54	Anti-cancer	Idan et al. (2015) and Al-Garaawi et al. (2019);
10	2,4,7,9-Tetramethyl-5-decyn-4,7-diol	14.34	620292.26	Not reported	-
11	Hexadecanoic acid, methyl ester	20.107	3433719.91	Antifungal, antioxidant, hypocholesterolemic, antiandrogenic, hemolytic, anti-5α reductase, antimicrobial.	Sudha et al. (2013); Darweesh and Ahmed (2016)
12	Melezitose	20.251	388346.99	Anti-bacterial	Zimila et al. (2020)
13	n-Hexadecanoic acid	20.458	10892987.53	Anti-androgenic, hemolytic, antioxidant, hypocholesterolemic, anti-5α reductaze, anti-inflammatory, antibacterial, nematocide	Jebastella and Appavoo (2015)
14	9,12-Octadecadienoic acid (Z,Z)-, methyl ester	21.757	1752547.29	Analgesic, anti-inflammatory and ulcerogenic; hepatoprotective, antihistaminic, antieczemic, hypocholesterolemic.	Hadi et al. (2016); Arora et al. (2017)
15	6-Octadecenoic acid, methyl ester, (Z)-	21.803	2364928.1	Analgesic, anti-inflammatory and antipyretic	Jaddoa et al. (2016)
16	9,12-Octadecadienoic acid (Z,Z)-	22.129	16011563.31	Anti-inflammatory, hypocholesterolemic, anti-cancer, anti-arthritis, hepatoprotective, anti-androgenic, antihistamine, anti-eczemic, anti-coronary	Krishnamoorthy and Subramaniam (2014)
17	Cis-Vaccenic acid	22.171	15721057.68	Anti-inflammatory; antibacterial and hypolepidemic in rats	Hussein et al. (2016); Semwal et al. (2018)

Table 1. Cont'd

17	Cis-Vaccenic acid	22.171	15721057.68	Anti-inflammatory; antibacterial and hypolepidemic in rats	Hussein et al. (2016); Semwal et al. (2018)
18	Oleic Acid	22.268	1495912.71	Dermatitigenic, hypercholesterolemic, anti-inflammatory; antibacterial and antifungal	Gideon (2015); Agoramoorthy e al. (2007)
19	Octadecanoic acid	22.344	6141608.22	Anti-inflammatory, anti-oxidant; anti-fungal, anti-bacterial, anti-microbial, anti-tumor; hypocholesterolemic, suppository, propectic;	Alamery and Algaraawi (2020); Arora et al. (2017); Padmashree et al. (2018)
20	Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester	25.266	3103202.91	Hemolytic, Antioxidant, Pesticide	Ashwathanarayana and Naika (2018); Tyagi and Agarwal (2017)
21	Glycerol 1-palmitate	25.347	374245.95	Cytotoxic and antiviral; pro-inflammatory	Sharmila et al. (2016); Jahan et al. (2020)
22	9,12-Octadecadienoic acid (Z,Z)-, 2-hydroxy-1-(hydroxymethyl) ethyl ester	26.713	8202030.7	Hypocholesterolemic, anti-arthritis, hepatoprotective, anti-androgenic, hypocholesterolemic, anti-5α reductase, antihistamine, anti-coronary, anti-eczemic, anti-acne	Ashwathanarayana and Naika (2018)
23	9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl) ethyl ester	26.776	1768007.66	Anti-imicrobial, anti-cancer, diuretic and anti-inflammatory	Hussein et al. (2016)
24	Squalene	27.993	3648385.81	Anti-Bacterial, Antioxidant, Cancer-preventive, Immunostimulating, Lipoxygenase-Inhibitor; anti-tumor, anti-cancer, blood hypocholesterol;	Verma et al. (2015); Shefeek and Jaiganesh (2020)
25	Campesterol	32.32	2772945.33	Antioxidant, hypocholesterolemic, anti-cancer	Godara et al. (2019)
26	Stigmasterol	32.705	15721057.68	Anti-hepatotoxic, anti-inflammatory, anti-osteoarthritis, antioxidant, antiviral, reduces blood LDL, antitumor, antivirus and anti-HIV reverse transcriptase; cytotoxic	Verma et al. (2015); Abdelgadir and Van Staden (2013)
27	Gamma-sitosterol	33.47	1495912.71	Antifungal, antibacterial, hypocholesterolemic antiviral, antidiabetic, anti-inflammatory, antioxidant, anti-cancer; anti-SARS-CoV-2	Verma et al. (2015); Vincent et al. (2020) and Fadilah et al. (2020)

Source: Authors (2022).

As can be seen in Table 1, among the compounds detected from the GC-MS analysis, glycerol 1-palmitate, stigmasterol and gamma-sitosterol have antiviral action. However, it is important to note that there are no works that show glycerol 1-palmitate has anti-HIV and/or anti-SARS-CoV2 action, hence, it is not the subject of discussion in this research. There are studies that show stigmasterol and gamma-sitosterol have these

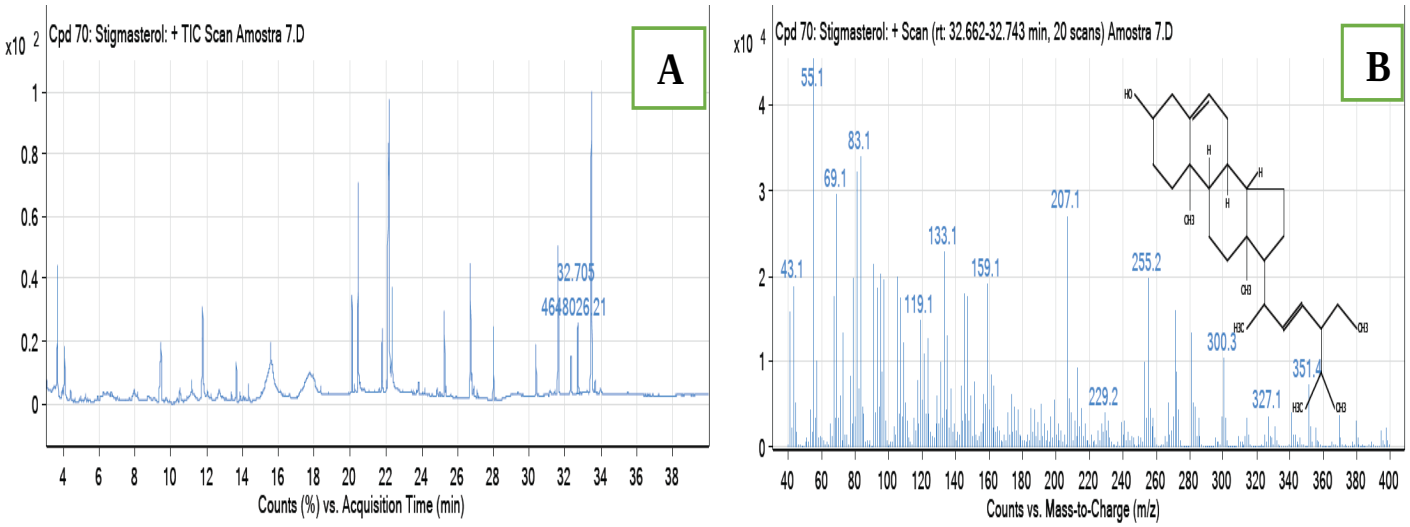

Figure 1. GC-MS chromatogram of *Jatropha curcas* seed extract showing peak area, retention time and structure of stigmasterol.
Source: Ferrão and Janeque (2019).

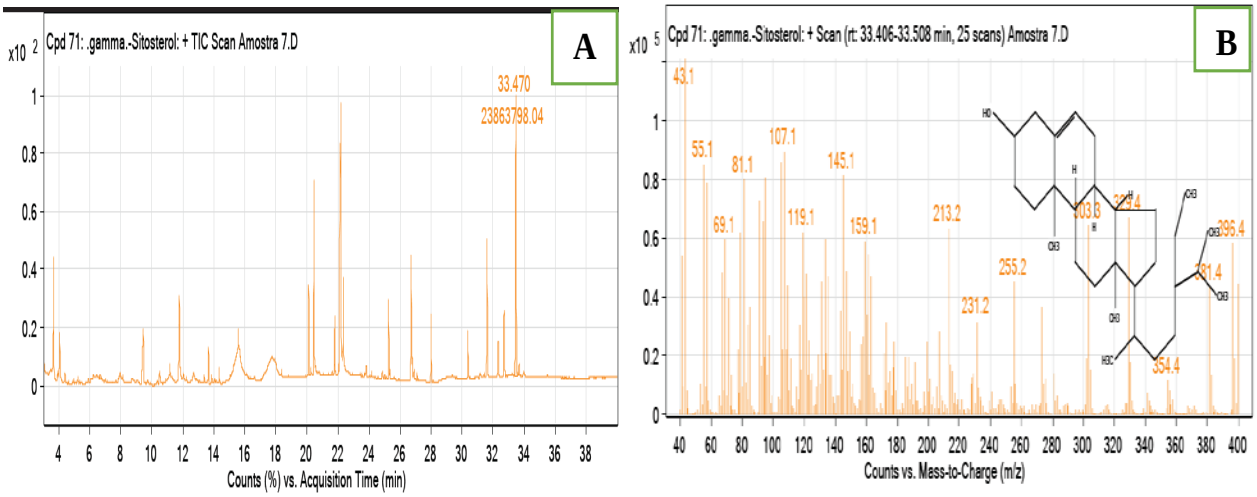

Figure 2. GC-MS Chromatogram of *Jatropha curcas* seed extract showing peak area, retention time and structure of Gamma-sitosterol.
Source: Ferrão and Janeque (2019)

actions, as shown in the following.

Verma et al. (2015), Kamiyama et al. (2013), Venkata et al. (2012), and Hadi et al. (2016) report anti-HIV activity of stigmasterol. Vincent et al. (2020) and Fadilah et al. (2020) verified from their molecular modeling studies, in which computational method was used for the rational planning of bioactive compounds (Sant'Anna, 2009) that there is a possibility that gamma-sitosterol acts as an anti-SARS-CoV-2.

Figures 1 and 2 present the chromatograms resulting from the GC-MS analysis of stigmasterol and gamma-sitosterol. Figures 1 and 2 show the retention times and peak areas corresponding to stigmasterol and gamma-sitosterol. The retention time and peak area of the first compound was 32.705 min and 4648026.21, respectively, and the second was 33.47 min and 23863798.04. In the research on antiviral compounds, attention is paid to those that interfere both in the mechanism of infection and in the process of viral multiplication, preventing its continuity (Kaur et al., 2020).

In this regard, Chinsembu (2019) and Kaur et al. (2020) explain how interference occurs in the HIV viral cycle, while Vincent et al. (2020) do the same for SARS-CoV-2.

Stigmasterol and HIV-1

Verma et al. (2015), Padmashree et al. (2018b), Godara et al. (2019), and Beckstrom-Sternberg and Duke (1996) linked stigmasterol to antiviral activity. Terefe et al. (2022) evaluated the anti-HIV action of some compounds and found the following results for stigmasterol: IC50 (µg/mL) 0.14 ± 0.04, EmaxAV (%) 76.77 ± 23.24 and SI 86.5. In another line of investigation, Kamiyama et al. (2013) found that the test compound does not affect the transduction efficiency of the HIV-1 vector during the infection phase within the viral cycle.

Regarding the group of substances with anti-HIV-1 reverse transcriptase properties in some plant species, Chinsembu (2019) mentioned stigmasterol. In describing these substances, this author stated that they have a structure that is similar in form to nucleoside analogues, and appear to be close homologs that share structural and functional similarities with non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Sluis-Cremer (2018), cited by Chinsembu (2019), defines NNRTI as "small molecules that bind to the HIV-1 reverse transcriptase site distinct from the enzyme DNA polymerase active site and block the reverse transcription of HIV-1 through an allosteric mechanism of action". Therefore, if stigmasterol shows structural and functional similarities with non-nucleoside reverse transcriptase inhibitors, it can be assumed that it has the same mechanism of action.

Still on natural reverse transcriptase inhibitors, Chinsembu (2019) highlights the pleiotropic effect and its pharmacological benefits. Supporting his point of view, this author states that, during infection, pleiotropic inhibitors help to fight opportunistic diseases due to the diverse spectrum of action they can present. In the case of stigmasterol, several actions that may be beneficial during infection and disease have been reported, namely: anti-hepatotoxic, anti-inflammatory, anti-osteoarthritis, antioxidant, hypocholesterolemic and antitumor.

In another aspect, Kaur et al. (2020), when discussing the mechanism of action of anti-HIV phytochemicals, refer to the role of antioxidants in inhibiting HIV-1 transcription. Arguing, these authors advance that many reactive oxygen species are produced due to reduced levels of antioxidant enzymes, which, in addition to causing DNA damage, can stimulate the nuclear factor kappa B (NF-κB factor) that helps in the transcription of HIV, thus promoting its replication. In the same context, Bapia et al. (2021), when studying the isolation of stigmasterol from Kra Don (*Careya arborea* Roxb.) and the bioactivity of its crude extracts against free radicals and human immunodeficiency virus, referred to several authors who reinforced the perspective presented by Kaur et al. (2020). Among them are Eldeen et al. (2011), Kapewangolo et al. (2013), Valle et al. (2013) and Allard et al. (1998). In this order of ideas, it can be understood that as an antioxidant, stigmasterol has the ability to act by reducing reactive oxygen species and contributing to the reduction of conditions for viral replication. However, it is assumed that this hypothesis must be proven in experimental work.

In an experimental work, Siwe-Noundou et al. (2019) tested all compounds isolated from the crude methanolic extract of *Alchornea cordifolia* as anti-HIV integrase (anti-HIV IN) and found activity against HIV-1 IN, including for stigma sterol (IC50=20, 5 µg/ml).

Gamma-sitosterol and SARS-CoV-2

Shortly after Covid-19 was considered a pandemic by the World Health Organization (WHO), in 2020, studies around SARS-CoV-2 gained interest. According to Vincent et al. (2020), in the structure of this virus, the S proteins (spike) responsible for the viral invasion of the host cell stand out. This is as a result of the affinity they have with the receptor of the target cell (the angiotensin 2 converting enzyme ACE2), and the proteases Mpro (3C-Like also called 3CLpro) responsible for replication, viral transcription and protein cleavage. This inhibits the processes for which it is responsible and PLpro (enzyme of protein cleavage and suppression of the innate immune response of the host).

Based on the knowledge we have about the structure of SARS-CoV-2, research is being carried out in search of compounds that inhibit the replication or maturation processes of this virus, or those that act by blocking its binding to the receptors of target human cells. Subsequently, Gamma-sitosterol, a compound with antiviral properties (Venkata et al., 2012; Verma et al., 2015) ended up being studied by Vincent et al. (2020) and Fadilah et al. (2020).

Vincent et al. (2020), through molecular docking, evaluated the ability of *Kabasura kudineer* phytochemicals to bind to one of the main proteases of this virus (3CLpro), inhibiting the processes it is responsible for. In this study, these authors found that gamma-sitosterol is part of the group of compounds that showed affinities for 3CLpro with binding energy of -81.94 kcal/mol, which comprises the interaction of van der Waal and hydrogen. This finding shows that gamma-sitosterol can act as an inhibitor of 3CLpro and, because of this, *J. curcas* seed extracts can be candidates for *in vitro* assays.

In turn, using the molecular docking method, Fadilah et al. (2020) evaluated the phytochemicals of *Psidium guajava*, having also observed that gamma-sitosterol has affinities to the proteases 3 CLpro, PLpro, Spike proteins

(S or surface binding proteins) and ACE2 (angiotensin-converting enzyme 2, cell receptor hostess). These data reinforce the evidence found by Vincent et al. (2020).

From the aforementioned, it can be inferred that, by competitively binding the S protein of the virus or ACE2, gamma-sitosterol prevents the interaction between them, blocking the fusion and consequently the viral entry. In another aspect, by binding the proteases Mpro (3CLpro) and PLpro, this compound interferes with the functions of these enzymes during viral replication, inhibiting the process. In fact, in this regard, Khan et al. (2021) explain the mechanism of action of different substances on the coronavirus, stating that a drug candidate may be useful if it inhibits viral entry, replication, or even provokes an immune response to produce Type I IFN against SARS-CoV-2.

Toxicity

Khan et al. (2021) advance that safety aspects should always be taken into account, despite the perception that herbal medicines are completely safe and free from any side effects.

The imperative to consider the safety aspects in relation to these drugs, despite having the perception mentioned earlier, is reinforced by Sharmila et al. (2016), Abdelgadir and Van Staden (2013), and Alamery and Algaraawi (2020) who indicated glycerol 1-palmitate, stigmasterol and gamma-sitosterol as cytotoxic compounds. In addition to these compounds, the plant under analysis has others such as Phorbol Ester and Curcin, considered the most toxic phytochemicals found in its seeds (Devappa et al., 2010a cited by Abdelgadir and Van Staden, 2013). These facts make this part of the plant potentially toxic, thus requiring a toxicity assessment.

Conclusion

GC-MS analysis of *J. curcas* seed extracts showed the presence of three compounds with antiviral reference in the literature, namely, glycerol-1-palmitate, stigmasterol and gamma-sitosterol. Stigmasterol and gamma-sitosterol were associated with anti-HIV-1 and anti-SARS-COV-2 activity, respectively. Glycerol-1-palmitate was not discussed in this study, due to insufficient information on its mode of action. As an anti-HIV-1, stigmasterol can act on the enzymes HIV-1TR and HIV-1 IN. Gamma-sitosterol is associated with the inhibition of the main proteases of SARS-VOC-2. The results of the present research provide horizons for the next level of research, *in vitro* assays, as they support the hypothesis that the seed exhibits antiviral properties against HIV-AIDS and COVID-19. The presence of cytotoxic in *J. curcas* seed extracts suggests that, in case the extracts are proven to be effective in *in vitro* studies, their toxicity should also be evaluated**.**

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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