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DNA intercalators alkaloids as Potential candidates to fight COVID-19 disease: Systematic review

Houria BECHLEM[1] *, Feryal BENAYACHE [2], Djamila BENOUCHENNE [1], Amira LABED [1]

1 Pharmaceutical sciences research center, Constantine, Algeria.
2 Research Unit Development of Natural Resources, Bioactive Molecules and Physiochemical and Biological Analysis, Department of Chemistry, Constantine 1 University, Constantine, Algeria
* Corresponding Author. E-mail: houria.bechlem@umc.edu.dz (H.B.); Tel. 00213793812722

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ABSTRACT: The main objective of the current systematic review was to report the antiviral and anti-inflammatory effects of bioactive molecules class known as alkaloids against SARS-COV-2 disease. These bioactive compounds were characterized by their potential replication inhibitory ability by DNA intercalating effect, and might be powerful agents against infections caused by several viruses, therefore it can be a viable strategy for COVID-19 management.
PubMed, ScienceDirect, Google Scholar and SpringerLink, databases have been chosen to look for keywords like DNA intercalators, alkaloids, antiviral activity, anti-inflammatory effect, coronavirus, SARS-CoV-2. Two reviewers have evaluated the quality of 60 articles extracted from the four databases till 15th of May 2021, using inclusions and exclusions criteria, 25 papers were accepted and treated in this systematic review, performed based on PRISMA protocol. Results disclosed that alkaloids have key roles in viral replication inhibition, quinine and emetine showed a noticeable therapeutic effect against SARS-COV-2 virus, however emetine revealed modifications in the electrocardiogram (ECG), unlike sanguinarine and berberine that showed low human toxicity. Tetrandrine, fangchinoline and cepharantine could be classified as remedies in case of Coronavirus ailment. Chelidonine, coptisine, skimmianine, protropine, palmatine, cinchonine, harmine and dictamine represented important agents for clinical researches or as precursors for antiviral drug's formulation.
KEYWORDS: SARS-CoV-2; DNA intercalators; Alkaloids; Coronavirus; Antiviral activity.

1. INTRODUCTION

Viruses are quite and diverse biological entities which expose a remarkable threat to human and animal health [1]. Multiple viruses, including influenza A virus (FLUAV), Ebola virus (EBOV), Zika virus (ZIKV), Rift Valley fever virus (RVFV) and Middle East respiratory syndrome coronavirus (MERS-CoV), induce severe illnesses, with few or no available therapies to limit disease morbidity and mortality [2]. Recently, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) the main cause of the COVID-19 ailment propagation. The world health organization stated this pathology as a global pandemic on March 11, 2020 [3]. It spread first in Wuhan, China, December 2019 [4], the hypothesis of virus transmission proposed that the virus was attained from animals and dispersed through direct contact [5]. The COVID-19 disease clinical symptoms are like the viral pneumonia infection as fever, tiredness, cough, shortness of breath, and other complications [6, 7].

Nowadays, the development of efficacious therapies against this pandemic in a short time become a challenge for researchers and scientists, therefore numerous drugs of other illnesses are repurposed to be used for the SARS-CoV-2 treatment infected patients, as well as called for regeneration of viral replication inhibitors were lanced [8]. Based on the use of anti-inflammatory and anti-viral drugs for creating new protocols may be an alternative therapeutic approach, plant metabolites are a source of countless medicinal compounds such as flavonoids, Terpenes, essential oils and alkaloids [9].

Alkaloids were found to have key functions for the viral replication inhibition [10]. This class of basic heterocyclic nitrogenous compounds has a wide range of pharmacological activities and biological effects for the plant and for the human health, including antiarrhythmic (quinidine), antiasthma (ephedrine), antimalarial (quinine), cholinomimetic (galantamine), antibacterial activity (chelerythrine), anticancer (homoharringtonine), vasodilatory (vincamine) and analgesic (morphine) [11, 12, 13]. Some alkaloids presented DNA intercalating properties, which makes them able to inhibit the transcription, and replication, of genetic material and stabilizing the cell structure [14], by a special mode of DNA binding, where the aromatic part of these molecules is introduced between a bases pair, leading to DNA structural changes and

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resulting in its functional interruption [15]. Therefore, these plant's bioactive molecules can stop the replication process and the development of coronavirus inside the host cells [16, 17]. The objectives of the present review were to examine the anti-SARS-CoV-2 potential of several alkaloids' products (sanguinarine, berberine, emetine, quinine, cinchonine, harmine, chelidonine, coptisine, tetrandrine, fangchinoline, cepharanthine, skimmianine, dictamine, protopine and palmatine) extracted from different medicinal plants, to validate their antiviral effects as well as to use them as precursors to discover and find a new drug from natural resources.

2. METHODS

2.1. Search strategy

Google Scholar, PubMed, ScienceDirect and Springer Link databases were consulted to seek for keywords as: COVID-19, DNA intercalators, alkaloids, antiviral activity and anti-inflammatory effect for papers published until 15.5.2021. Two reviewers extracted the data of interest independently, in order to eliminate duplicate papers. Same for the titles and abstracts that have been separately reviewed by the two reviewers.

2.2. Included studies

Studies reported the class of alkaloids, characterized by DNA intercalating properties, stated antiviral and/or anti-inflammatory effects on sever acute respiratory syndrome of coronavirus 2 (SARS-CoV-2) inhibition were included.

2.3. Excluded studies

In silico studies papers and articles reported only abstracts where the full texts are not accessible were excluded from this systematic review. Furthermore, papers about SARS and MERS subjects only without showing any relationship with 2019-nCoV were removed.

2.4. Data extraction

The data presented in the table (**Table 1**) were obtained from scanned and skimmed articles achieved by two different reviewers. This systematic review was represented based on PRISMA protocol [18] as shown in (**Fig. 1**).

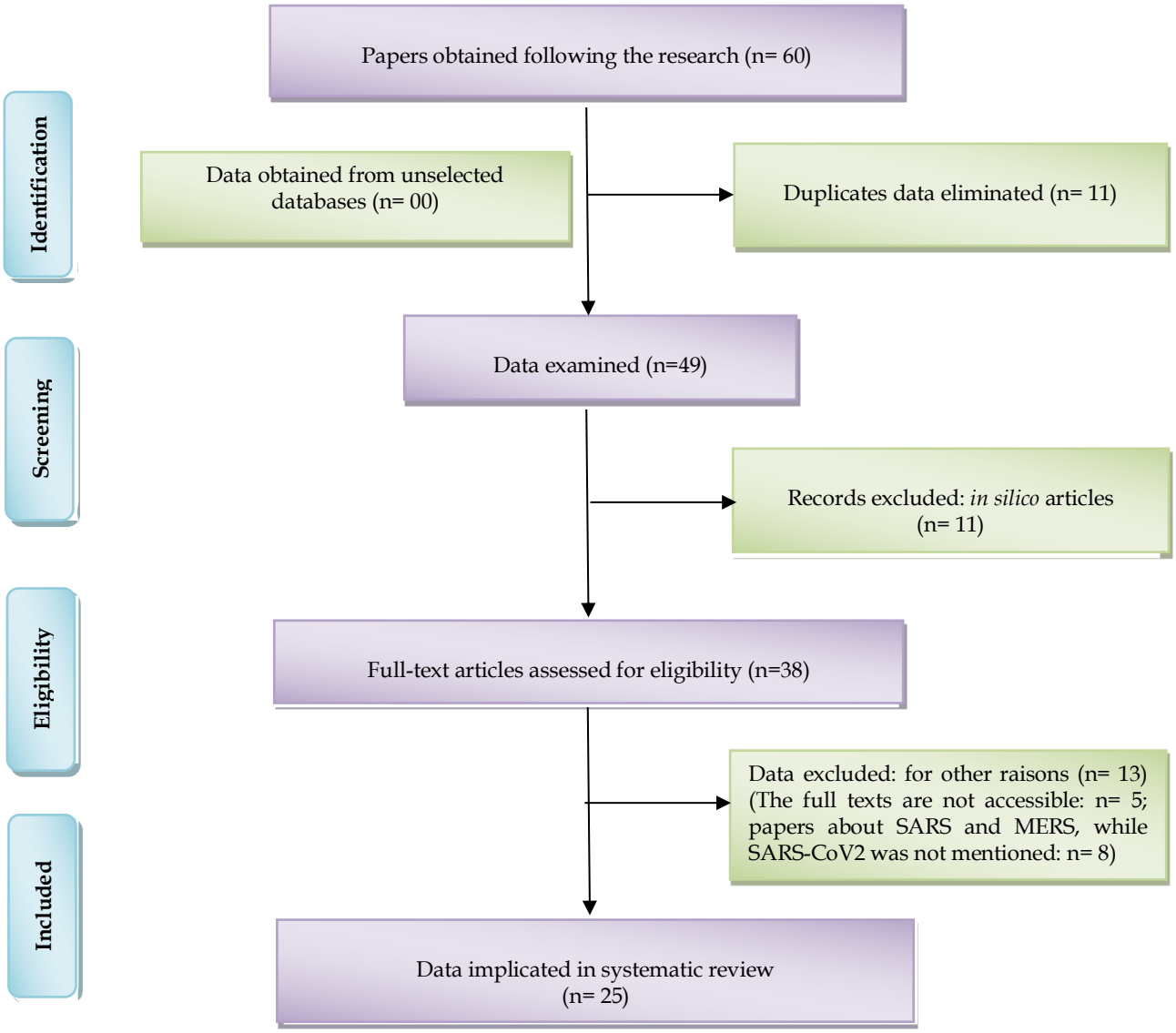


Fig. 1. Flowchart of the article's selection [18]

3. RESULTS

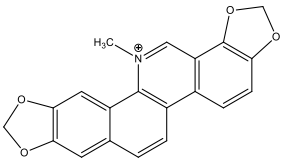
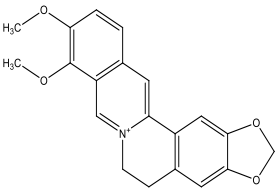
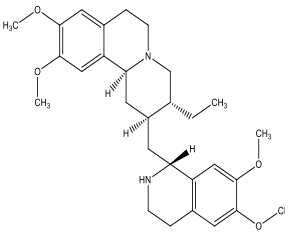
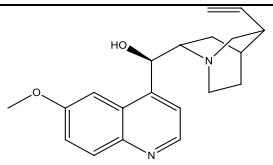
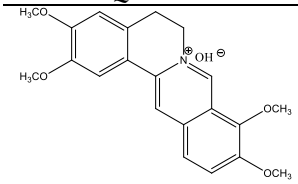
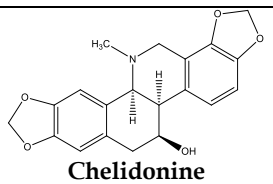
3.1. Study selection

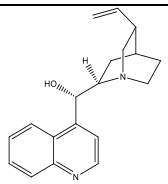
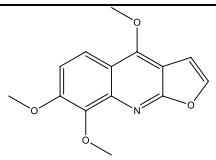
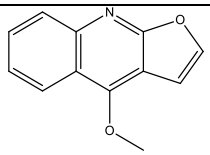
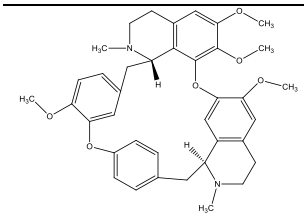
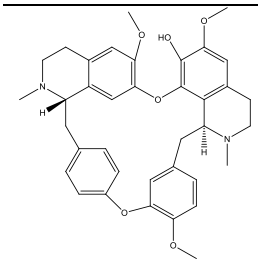
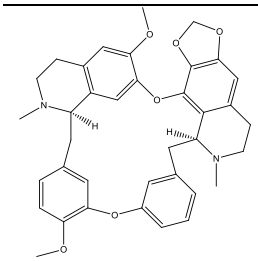
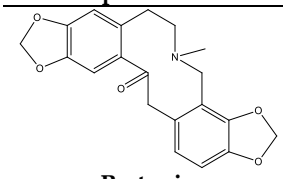
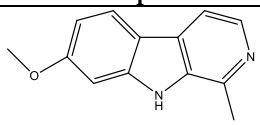
For this systematic review 60 potentially appropriate papers were collected from preliminary databases researches, 22 were omitted, 11 are duplicated, and the rest were *in silico* studies. 13 articles concerning SARS and MERS only and not 2019-nCoV, or with full text not accessible were also excluded, so articles selected at the end of the analysis were 25.

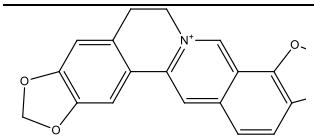
3.2 Study characteristics

Besides to inclusion criteria, only English language articles were evaluated. Zotero library (Version 5.0.96.2) was a tool elected to organize all articles references and to remove repeated papers. The majority of selected articles were issued till 15.05.2021, while the most of them were published in 2020.

Table 1. Antiviral activity of selected DNA-intercalating alkaloids.

Alkaloids	Vegetal drugs	Antiviral activity	Mechanism of action / targets	Ref.
 **Sanguinarine**	- *Argemone mexicana* - *Chelidonium majus* - *Macleaya cordata*	- HSV - IV	- DNA intercalating activity.	[19, 20, 21, 22, 23, 24, 25]
 **Berberine**	- *Berberis vulgaris* - *Berberis lycium* - *Berberis aquifolium* - *Berberis integerrima* - *Berberis aristata* - *Chelidonium majus* - *Coptidis rhizoma* - *Coptis chinensis* - *Hydrastis canadensis* - *Xanthoriza simplicissima*	- CHIKV - HSV - HCV - IV - SARS-CoV - SARS-CoV-1 - SARS-CoV-2	- DNA intercalating activity. - Blocking hampers Influenza virus replication. - Blocking of hepatitis C virus entry in host cell.	[19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32]
 **Emetine**	- *Cephaëlisa cuminata* - *Cephaëlis* - *Carapichea* - *Ipecacuanha* L. - *Ipecac* root - *Lycoris radiata*	- SARS-CoV - MERS-CoV - SARS-CoV2 - HCoV-OC43 - HCoV-NL63 - HSV - MuV - ZIKV - HIV - HCMV - IBV	- DNA intercalating activity. - Inhibit the Zika virus NS5RNA polymerase activity. - Inhibit Protein synthesis by binding to ribosomal E site. - Destroy the SARS-CoV-2 mRNA link to eIF4E.	[14, 20, 21, 22, 23, 24, 25, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43]
 **Quinine**	- *Cinchona officinalis*	- HSV - IV - SARS-CoV-1 - SARS-CoV-2	- DNA intercalating activity.	[20, 21, 25]
 **Palmatine**	- *Coptidis rhizoma* - *Coptis chinensis* - *Berberis* genus	- ZIKV - SARS-CoV - HSV - CHIKV - HCV	- DNA intercalating activity	[20, 21, 22, 23, 24, 39]
 **Chelidonine**	- *Chelidonium majus* L	- HSV - HIV - SARS-CoV-2	- DNA intercalating activity	[20, 22, 23, 24]

 **Cinchonine**	- *Cinchona* bark	- SARS-CoV-2 - SARS-CoV-1	- DNA intercalating activity	[21, 23, 25]
 **Skimmianine**	- Rutaceae	- SARS-CoV-2 - SARS-CoV-1	- DNA intercalating activity	[23, 25]
 **Dictamine**	- *Dictamnus dasycarpus* - *Zanthoxylum wutaiense*	- SARS-CoV-2 - SARS-CoV-1	- DNA intercalating activity	[23, 25, 44]
 **Tetrandrine**	- *Stephania tetrandra S. Moor*	- HCoV-229E - HCoV-OC43	- DNA intercalating activity - Pauses the expression of viral S and N protein	[20, 21]
 **Fangchinoline**	- *Stephania tetrandra*	- HCoV-229E - HCoV- OC43	- DNA intercalating activity - Blocs the expression of S and N protein of the virus	[20]
 **Cepharanthine**	- *Stephania tetrandra* - *Stephania cepharantha*	- HCoV-229E HCoV-OC43	- DNA intercalating activity - Stops the translation of viral S and N protein	[20, 21]
 **Protopine**	- *Argemone mexicana*	- SARS-CoV-2	- DNA intercalating activity	[19]
 **Harmine**	- *Peganum harmala*	- HCoV-OC43 - HCoV-NL63 - MERS-CoV - MHV-A59	- DNA intercalating activity	[21, 39]

 **Coptisine**	- *Coptis chinensis*	- SARS-CoV - SARS-CoV-1 - HSV - CHIKV - HCV	- DNA intercalating activity	[23]

HSV: Herpes Simplex virus ; **HCV:** Hepatitis C virus ; **IV:** Influenza virus ; **CHIKV**: Chikungunya virus ; **HCoV-OC43**: Human coronavirus OC43 ; **HCoV-NL63**: Human coronavirus NL63 ; **MERS-CoV**: Middle East respiratory syndrome coronavirus; **MHV-A59**: coronavirus mouse hepatitis virus A-59 ; **HCoV-229E**: Human coronavirus 229E ; **HIV**: Human Immuno-deficiency virus ; **CHIKV**: Chikungunya virus ; **HCMV**: Human cyto-megalovirus ; **MuV**: Mumps virus ; **IBV**: Avian infectious bronchitis virus ; **SARS-CoV-1**: Sever acute respiratory syndrome coronavirus 1; **SARS-CoV-2:** Sever acute respiratory syndrome coronavirus 2.

4.DISCUSSION

Alkaloids are antiviral agents, classified into diverse categories, based on their aromatic ring structure and their biosynthetic precursors. They comprise pyrrolidines, tropanes, purines, isoquinoline, imidazoles, indoles, quinolizidines, piperidines and pyrrolizidines. In the **Table 1**, the antiviral activity of isoquinoline and quinoline intercalators alkaloids that have a rationale for a putative inhibitory effect against coronavirus was summarized.

a- Isoquinoline

Sanguinarine is an isoquinoline alkaloids extracted from *Argemone mexicana*, *Chelidonium majus*, and *Macleaya cordata* [44]. It penetrates membranes by binding to negative charge proteins, this planar molecule with a cationic nature has a high affinity with thiol (SH) groups, which explain the inhibition of membrane and cytosolic enzymes, such as Na^+ / K^+ ATPase [19]. In 2020, Gürü et al. [20] proved the antiviral activity of sanguinarine against Human Immunodeficiency virus protease and Herpes Simplex virus. This toxic alkaloid has the ability to intercalate in a DNA fragment, in order to inhibit transcription and replication, of genetic material, for that it was suggested as an anti-SARS-CoV-2 [19].

Berberine is one of the famous Chinese herbal alkaloids presented numerous pharmacological properties as antiviral, antimicrobials, anti-diarrheal, anti-depressant, anti-hypertensive, anti-oxidant, hepatoprotective, and antitumor [29]. Clinical studies realized on berberine 's antiviral effect have proved a significant anti-herpes virus development, including hepatitis C virus, dengue virus (DENV), Zika virus (ZIKV), influenza and respiratory syncytial viruses [29]. Berberine presented activity against SARS-CoV-1 with an inhibition concentration at 50 % (IC_{50}=2µg/mL) [28], HSV types 1 and 2 [28]. It inhibits the replication by DNA intercalating properties [29]. Berberine 's antiviral activity was evaluated by Pizzorno et al. in Vero E6 cells model of SARS-CoV-2 infection, and disclosed an inhibition concentration (EC_{50}) value of 10.6 µM [26]. Gu et Zhu (2021) proposed that berberine could be a powerful drug against COVID-19 inflammation. In another study bereberine showed a strong ability in increasing the viability and reducing the production of inflammatory cytokines caused by SARS-COV-2 spike protein while entering host cells [45]. At a concentration of 20 µg/ml, Patel et al. [31] reported that berberine/NIT-X (immunotherapeutic-berberine nanomedicine) play a crucial role in the reduction of cytokine storm threat and pneumonia in COVID-19 disease by diminishing the pro inflammatory cytokines and chemokines production, including CCL-2, IL-2, IL-1α and IL-8.

It has been reported that **emetine** presented a strong apt against HCoV-NL43, SARS-CoV, and MHV-A59, as well as, it was stated that at a concentration of 0.5 M, emetine might powerfully bloc the replication of SARS-CoV-2 virus [34]. A study achieved in 2021, by Bolarin and his colleagues to evaluate the antiviral potential of numerous bioactive molecules in Vero E6 cells against coronaviruses, the findings disclosed that emetine could stop the SARS-COV-2 replication with an inhibition concentration of 0.46 µM, as well as, MERS-CoV (EC_{50} of 0.16 µM) and HCoV-OC43 (EC_{50} of 0.34 µM) [33]. Also, Emetine presented an important antiviral potential against several RNA and DNA viruses as, Ebola virus, human cytomegalovirus, Zika virus, HIV-1, echovirus 1, bovine herpesvirus 1, herpes simplex virus-2, metapneumovirus, rabies virus and Rift Valley fever virus, in a study realized by Bleasel et al. in 2020, they reported also that emetine showed an inhibition concentration of EC_{50} of 0.054 µM against severe acute respiratory syndrome (SARS), while it revealed an EC_{50} of 0.014 µM against Middle East respiratory syndrome (MERS) coronaviruses. From these results emetine might be suggested to be an effective treatment for coronavirus disease [36].

The isoquinoline alkaloids, including **tetrandrine**, **fangchinoline** and **cepharanthine** extracted from *Stephania tetrandra* exhibited a potential inhibitory effect against HCoV- OC43 infection in MRC-5 human lung cells. The findings demonstrated that tetrandrine could reduce HCoV- OC43 with IC_{50} of 0.33 µM, cepharanthine presented IC_{50} of 0.83 µM, while fangchinoline exerted an IC_{50} of 1.01 µM, furthermore, the

mentioned alkaloids proved a significant inhibitory action of the viral spike (S) and nucleocapsid (N) protein expression [21]. Also, Majnooni et al. confirmed that Cepharanthine could stop the MAPKs chain reactions and its mediators (TLR4), and inflammatory cytokines (IL-1β, IL-6, and TNF-α), as a result it showed a strong effect during lung injury [22].

Chelidonine and **palmatine** alkaloids were described as intercalating agents, that can be proposed as interesting drug precursors to fight SARS-CoV-2 [21]. Palmatine was reported also as an effective suppressor for West Nile and Zika virus replication, as well as Chelidonine exhibited an antiviral effect against Herpes Simplex, Human Immunodeficiency and the influenza viruses [20]. Das et al. declared that **Coptisine** and palmatine extracted from traditional Chinese medicinal plants (*Coptis chinensis*) were effective agents to battle SARS-CoV-1 [16]. **Protopine** isolated from *A. mexicana* could inhibit the viral replication of SARS-CoV-2 RNA polymerase.

b- Quinoline

Cinchonine, **skimmianine, dictamine**, and **quinine** can act as DNA intercalators, resulting virus replication inhibition [16, 14, 19]. They exhibited a strong impact on SARS-CoV-1 pathologies [16, 19]. Dictamine which was extracted from *Zanthoxylum wutaiense* roots, was stated to present a mild anti-tubercular action (H37Rv strain) with a minimal inhibitory concentration of 30 µg/ml [37]. Quinine is used as an antiviral agent against Herpes Simplex, Dengue, and influenza viruses [13]. A study has shown that quinine can prevent SARS-CoV-2 virus infection by interacting with the Lys 353 residue in the peptidase region of the ACE2 receptor [13]. **Harmine** is a quinoline alkaloid of *Peganum harmala* inhibited viral replication, where it exposed a powerful capacity against HCoV-OC43 (EC_{50} = 1.90 µM) and MERS-CoV (EC_{50} =4.93 µM), whereas it revealed an inhibitory concentration of 13.46 and 13.77 µM against HCoV-NL63 and MHV-A59 [32].

Alkaloids presented a main function in the inhibition of viral reproduction, via arresting viral DNA polymerase action [14]. In a study realized by Shen et al, berberine was considered as an activator of AMPK (adenosine-monophosphate activated protein kinase) same as metformin, showed less death danger when administered to hospitalized COVID-19 diabetic patients [39]. On the other hand, isoquinolines: tetrandrine, fangchinoline and cepharanthine were proposed as drug agents to fight against SARS-CoV-2, as a result of their effect on SARS-CoV-OC43 spike protein and nucleocapsid protein [14]. The intercalating alkaloids sanguinarine, chelidonine, coptisine, skimmianin, palmatine, cinchonine, harmine and dictamine represented major agents for the development of antiviral remedies, or preliminary clinical research. Same as quinine and emetine that revealed an important therapeutic potential to battle COVID-19 [13, 14].

In the literature, it was reported that side effects like asphyxia, paralysis or death were observed following the consumption of some alkaloids, duo to their diverse chemical structures and action mechanisms, for that, several studies have been launched to synthesize potential alkaloids derivatives drugs, with low toxicity and more effective against large range of microorganisms [40]. Besides, other study stated that changes in the electrocardiogram (ECG), prolongation of the QT interval (ventricular depolarization and repolarization time), elevation of the ST segment (the flat, isoelectric section of the ECG between the end of the S wave -the J point- and the beginning of the T wave) and T wave inversion were associated with the emetine administration [29].

In 2020, chloroquine and hydroxychloroquine derivatives of quinine, also received a great deal of attention as a possible treatment of COVID-19. But there have been great concerns over the safety of these alkaloids. For example, during the investigation for a suitable treatment of coronavirus disease, in glucose-6-phosphate dehydrogenase deficiency patients, the use of chloroquine or hydroxychloroquine caused a hemolysis in three African American males [41], the increase of cardiotoxicity was another significant problem associated with the administration of these molecules at the appropriate concentration in COVID-19 patients, also the use of an overdoses resulted in cardiovascular collapse leading to death [16].

5. CONCLUSİON

Alkaloids could afford a varied possibility as healing medications against COVID-19 pathology. DNA-intercalating agents inhibit the viral replication inside the host cells. The alkaloids particularly quinolines and isoquinolines revealed lung damage therapeutic apt via obstructing the MAPKs way and inflammatory cytokines (IL-1β, IL-6, and TNF-α) production. The alkaloids sanguinarine, berberine, emetine, quinine, palmatine, chelidonine, harmine, cepharanthine, tetrandrine, cinchonine skimmianine, dictamine, protropine, fangchinoline and coptisine represented important agents for the synthetic antiviral drugs formulation. Furthermore, the low toxicity of some alkaloids gave numerous supplementary rewards in their fast and wide usage. Several molecules disclosed an effective antiviral ability against at least two coronaviruses' types, presented an interesting inhibition concentration value. To conclude, these bioactive products can be proposed as an important and effective remedies against COVID-19 disease.

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Author contributions: Concept – H. B.; Design – H. B.; Supervision – H. B.; D. B.; Resources – H. B.; F. B. Materials – H. B.; D. B.; Data Collection and/or Processing – H. B., A. L.; F. B.; Analysis and/or Interpretation – H. B., F. B., D. B.; Literature Search – H. B., F. B.; Writing – H. B.; D. B.; F. B.; Critical Reviews – D. B., F. B., A. L.
Conflict of interest statement: The authors stated that there was no conflict of interest.

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