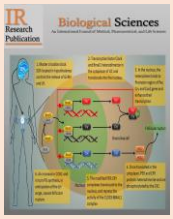
REVIEW ARTICLE

Biological Sciences
(An International Journal of Medical, Pharmaceutical, and Life Sciences)

Journal home: https://irrespub.com/biolsciences/index.php/1/index



Exploring the Therapeutic Potential of Natural Alkaloids Against Covid-19: A Tripartite Investigation of their Efficacy Through In-vivo, In-vitro and In-silico Models

Bazil Ekuh Ewane

Department of Chemistry, Faculty of Sciences, University of Dschang, Cameroon.
Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, 410001, Nigeria.

ARTICLE HISTORY

Received: 29-10-2024
Revised: 16-01-2025
Accepted: 21-01-2025
Online: 16-03-2025

KEYWORDS

Covid-19
Alkaloids
Folkloric medicine
QSAR
SARS-CoV
Vaccines
3CLpro
PL^{pro} inhibitors

ABSTRACT

In recent times, the world has been experiencing the worst outbreak of Coronavirus disease 2019 (covid-19), a highly contagious disease which originated in Wuhan, China, and has had a global socioeconomic and health impact. Evidence from folkloric medicine show that the disease caused by coronavirus SARS-COV-2 has been treated traditionally while recent advances in sciences show that many vaccines have been produced, tested, approved and used to prevent the spread and contamination of covid-19, some alongside vaccine boosters. Therefore, as a matter of urgency, there is need to discover especially from natural sources, safer, efficient and little or no side effect drugs which can inhibit covid protein target as well as viral enzyme replication such as 3CL^{pro} and PL^{pro}. This research focuses on alkaloids with possible anti-covid-19 activity. Some of these compounds have demonstrated high in-vitro, and in-silico antiviral activity against the recent covid-19 pandemic. A total of 21 alkaloids, isolated between 2000 and 2020 were investigated and reviewed as possible multi-target drugs for the treatment of this disease. The discovery of drugs for the treatment of this disease should therefore be prioritized to drugs from natural sources. Lead drug molecules could be designed from in vivo studies, clinical trials as well as QSAR (quantitative structure-activity relationship) analyses to effectively develop novel drug candidates to tackle this covid-19 pandemic.

**Address for correspondence*
Department of Chemistry, Faculty of Sciences, University of Dschang, Cameroon; Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, 410001, Nigeria.
Email: engineerekuh@yahoo.com
ewane.bazil.pg01196@unn.edu.ng
DOI: https://doi.org/10.55006/biolsciences.2025.5106
Published by IR Research Publication;

Introduction

In late 2019 (December), the world has been at the peak of an outbreak of Coronavirus disease 2019 (covid-19) pandemic caused by SARS-CoV-2 (severe acute respiratory syndrome-coronavirus 2) and transmitted by various ways including coughing, sneezing, handshakes and more. The causative agent is a single stranded positive sense RNA genome coronavirus family has brought the globe to a standstill [1]. SARS-CoV has been

reported to produce some functional proteins including a spike protein (S) gene, an envelope protein (E) gene, a membrane protein (M) gene, and a nucleocapsid protein (N) gene [2]. The inhibition of the main protein, protease has been confirmed to affect the replication of the virus, thus it could be a therapeutic target [3]. The discovery of efficient drugs for the treatment of covid-19 could be done either by screening the different already existing antiviral drugs or testing the existing drugs for antiviral activity.

Folkloric medicine has and still plays an inevitable role in the management of viral infections. Varieties of medicinal plants have been studied, and many sources have proven to be a great contributing factor in the discovery and development of novel drug molecules. During several stages in viral replication, many of these molecules have successfully inhibited some of these stages [4]. Herbal medicine with folkloric remedies has been used for different kinds of diseases especially viral ailments and so there is need to search for new bioactive components with antiviral activity coupled with the fact that there is an increasing resistance to antiviral drugs [5, 6]. Viral resistance and latency are a crucial aspect which always leads to recurrent viral infections in immunocompromised patients as it has so far been documented [7-9]. Many medicinal plants and other natural sourced compounds have shown to have antiviral activity and many extracts from plant sources have been screened for this activity while some compounds have also been isolated from these natural sources of novel drug molecules. The discovery of the latest coronavirus disease 2019 (covid-19) in late 2019 which started spreading in a small community in China has resulted in many clinical trials of some active drugs against the covid-19 including derivatives of quinine such as chloroquine and hydroxychloroquine as potent candidate drug on a small study scale but requires a large scale in-vivo trial. In-silico studies have been conducted on some of these isolated antiviral compounds to project if any could be a potential candidate drug for the covid-19 pandemic. Since the beginning of life, human has been vulnerable to attacks of various microorganisms including viruses and this usually results from mild fever to more serious diseases. These reactions have given sleepless nights to scientist who work so hard to develop and discover vaccines in order to prevent the various infections. Many antimicrobial drugs have been developed from terrestrial and aquatic life forms, and they have successfully been used to treat patients with such infections [10]. Some of the microbial vectors have become resistant to some of these antibiotics.

Historical Perspective on Alkaloids in Drug Discovery

Secondary metabolites especially alkaloids have been playing an inevitable role in drug discovery since the creation of human. Plants especially have played a pivotal role in the discovery of leads/drugs and as a result, they could act as the stopping point to find novel antiviral drugs. Many alkaloids have been sourced from plants, fungi/bacteria as well as marine organisms and some examples of isolated and pharmacologically tested alkaloids include; Brucine and strychnine (Figure 1), morphine (Figure 2), caffeine (Figure 3), cocaine (Figure 4), and quinine (and its derivatives), which have been used to moderate the effect of many diseases.

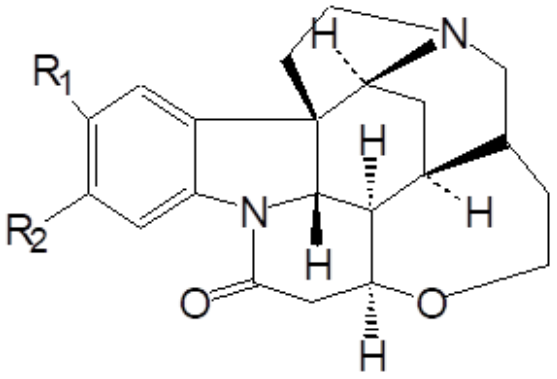


Figure 1. Brucine (R_1=R_2=OCH_3) and strychnine (R_1=R_2=H) structures.

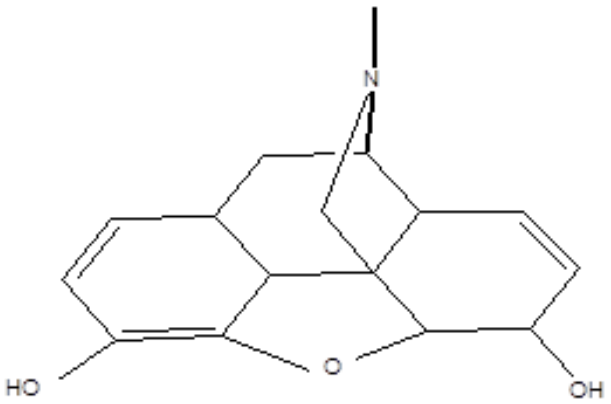


Figure 2. Morphine structure.

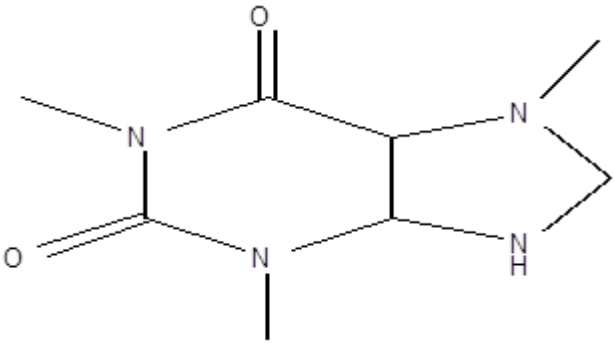


Figure 3. Caffeine structure.

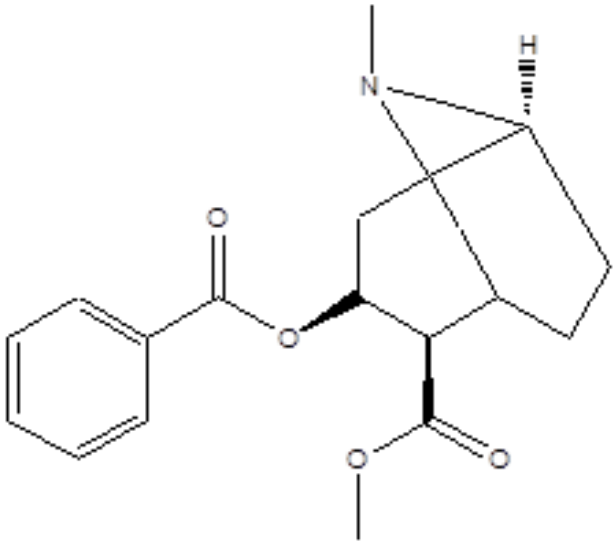


Figure 4. Cocaine structure.

Quinine (Figure 5) for example was isolated from Cinchona tree bark in 1818 by two French Pharmacists Pelletier and Caventou. This drug has been used in treating malaria since its discovery and its derivatives, chloroquine and hydrochloroquine (Figure 6) have been used as an antiviral drug especially SARS-2.

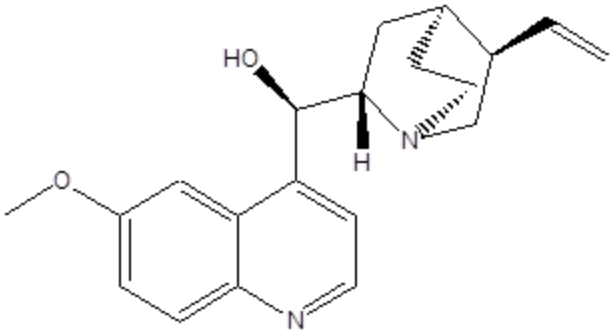


Figure 5. Quinine structure.

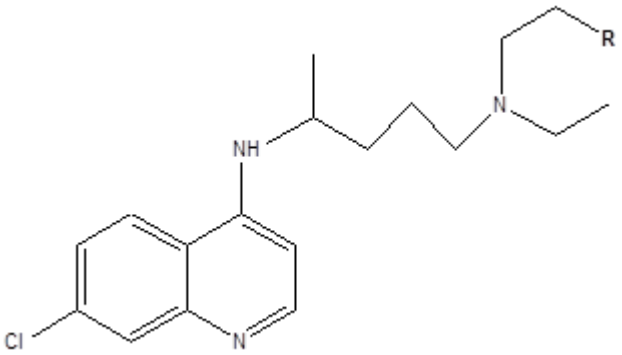


Figure 6. Chloroquine (R=H) and hydrochloroquine (R=OH)

Alkaloids as Potential Anti Covid-19 Agents

The SARS-CoV-2 spike protein directly binds with the host cell ACE-2 receptor facilitating virus entry and replication. It is known that viruses, without an independent enzyme system, can mutate easily exhibiting some changes in virulence, antigens, and resistance hence, SARS-CoV-2 mainly targets viral spike proteins, 3-chymotrypsin-like protease (3CLpro), 3 CL hydrolase, papain-like protease (PL^{pro}), RNA-dependent RNA polymerase, envelop proteins, 2′-O-ribose methyltransferase, and non-structural protein-3 (Nsp3) and nucleocapsid protein [11, 12]. Alkaloids are N-containing secondary metabolites, and they are alkaline in nature due to the presence of one or more N atoms in their structures hence, their high therapeutic effect even in little doses. They are bioactive with antiviral pharmacological activity, and they originate from amino acids. Sources of secondary metabolites include bacteria, fungi, plants and marine organisms and over 10,000 alkaloids being isolated from these sources. However, the number of studies carried out on their antiviral and immunomodulatory properties.

Lycorine

Lycorine (Figure 7) exert antiviral effects on both RNA and DNA-containing viruses. It possesses high antiretroviral activity accompanied by low therapeutic indices [13]. This bioactive compound has been tested against flavi viruses as well as to a lesser degree, bunya viruses. Lycorine serves as an anti-SARS-CoV (severe acute respiratory syndrome-associated Coronavirus). It also shows a labelled activity against coxsackie, poliomyelitis, and herpes type 1 viruses [14].

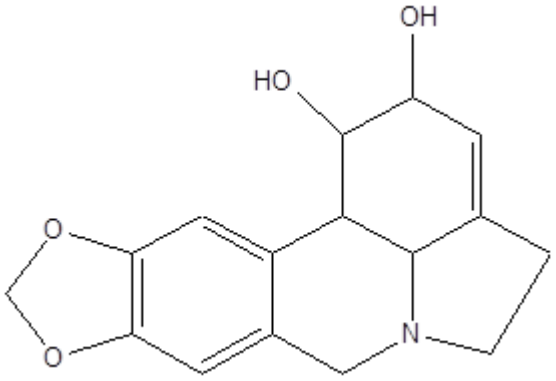


Figure 7. Lycorine structure.

10-Hydroxysambarensine and Cryptoquidoline

The binding affinities of two potent natural alkaloids 10-hydroxysambarensine (Figure 8) and cryptoquidoline (Figure 9) against the 3-chymotrypsin-like protease (3CLpro), were found to be potent of inhibiting both SARS-CoV-2 and SARS-CoV and as a result, they could be subjected to advance experimental research against SARS-CoV-2

3CLpro for the prevention and treatment of covid-19 [15].

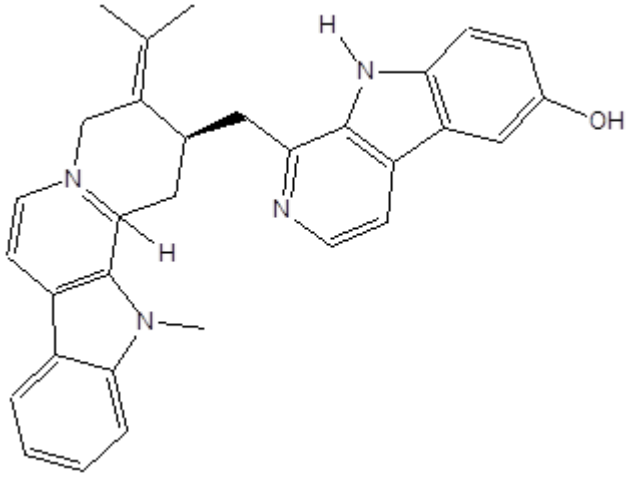


Figure 8. 10-hydroxysambarensine structure.

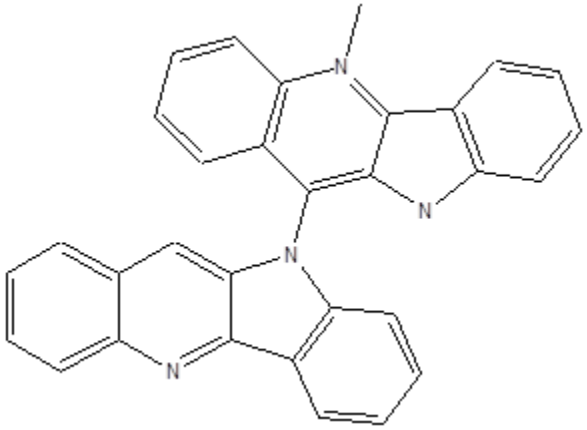


Figure 9. Cryptoquidoline structure.

Indigo and sinigrin

Isatis indigotica belonging to Brassicaceae family of plants is a medicinal plant and it has been used in folkloric medicine. Some of the isolated and tested compounds against SARS-CoV 3CLpro effects from this medicinal plant includes basically three alkaloids namely indirubin, indican, indigo, and a glucosinolate sinigrin and β-sitosterol (phytosterol). Indigo (Figure 10), Sinigrin (Figure 11), β-sitosterol (Figure 12) inhibited cleavage activity of the 3CLpro in cell-free and cell-based assay [19].

Sanguinarine, tabersonine and palmatine

A benzophenanthridine alkaloid (Sanguinarine (Figure 13), monoterpenoid indole alkaloid (tabersonine (Figure 14) and an isoquinoline alkaloid (palmatine (Figure 15) have shown a promising ADMET (absorption, distribution, metabolism, excretion and toxicity) properties as well a suitable binding affinity to 3CLpro. They have also shown good inhibitory effects on inflammatory

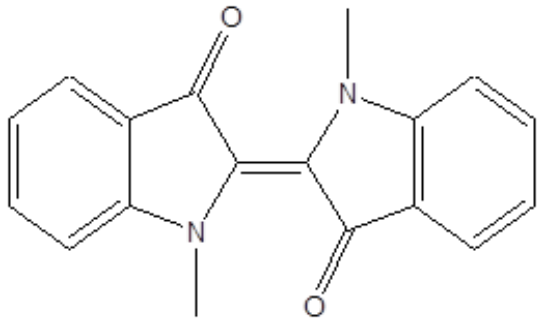


Figure 10. Indigo structure.

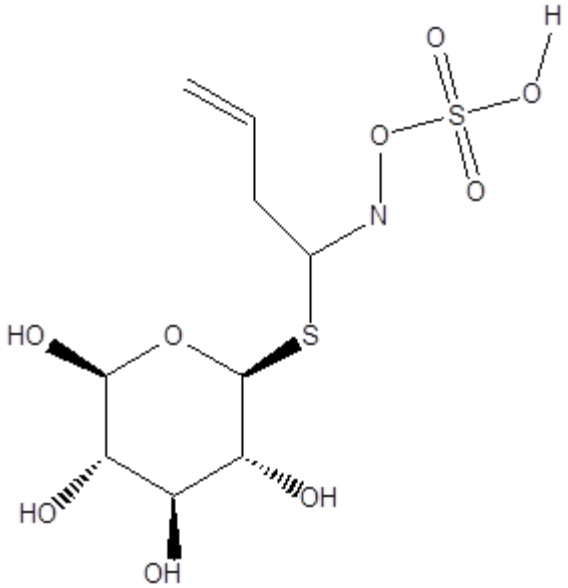


Figure 11. Sinigrin structure.

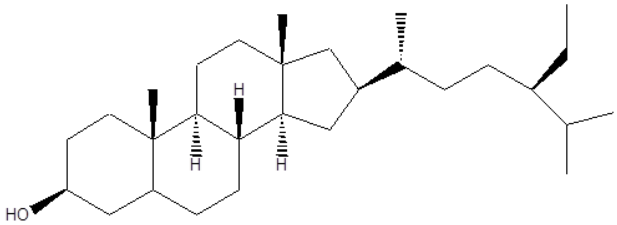


Figure 12. β-sitosterol structure.

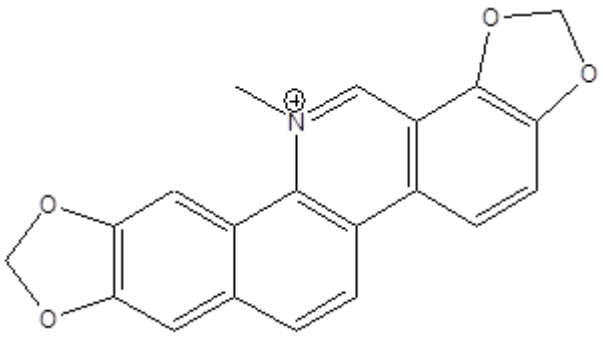


Figure 13. Sanguinarine structure.

signaling pathway of COX-2 (cyclooxygenase -2) although Sanguinarine shows some AMES toxicity [16].

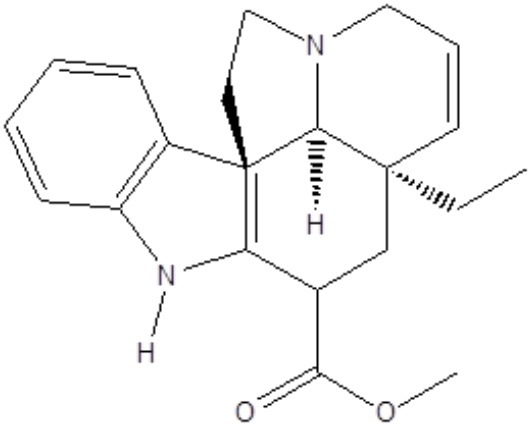


Figure 14. Tabersonine structure.

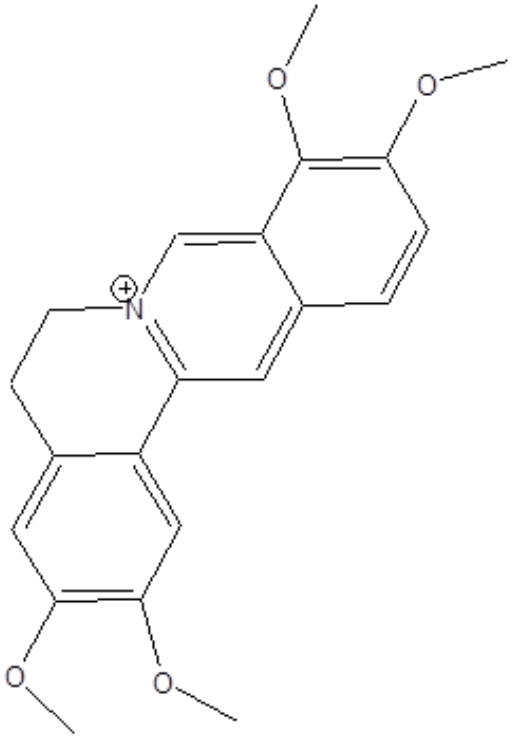


Figure 15. Palmitate structure.

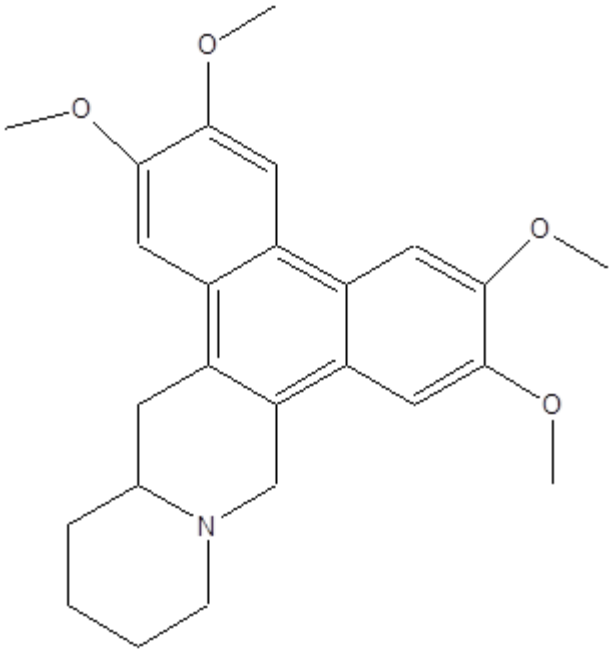


Figure 16. 7-methoxycryptopleurine structure.

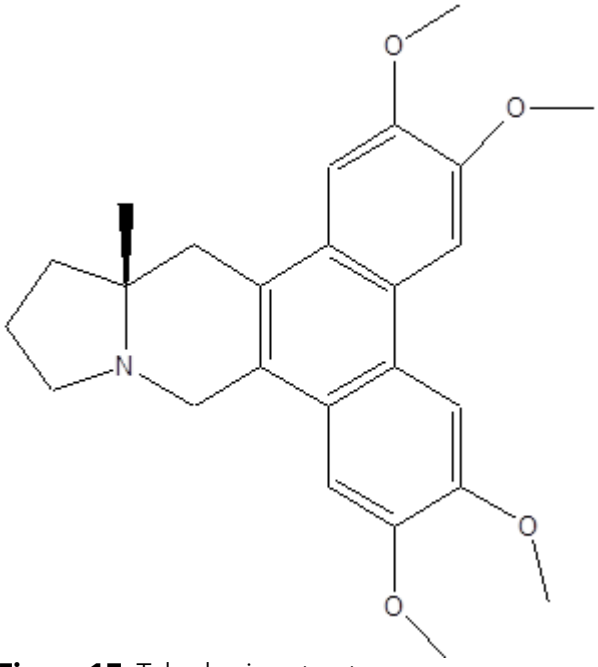


Figure 17. Tylophorine structure.

Tylophorine and 7-methoxycryptopleurine

In a research carried out by Joshi et al. (2020) in Vero 76 cells via the inhibition of S and N proteins and 3CLpro proved that 7-methoxycryptopleurine (Figure 16) (<0.005 μM), a phenanthroindolizidine alkaloid as well as tylophorine (19) (0.018 μM), phenanthroindolizidine alkaloid showed suitable anti-SARS-CoV activities [16].

(-)-asperlicin C and oriciacridone F

Joshi et al. also showed that oriciacridone F (Figure 18), which had a high binding affinity to RdRp (−9.6 kcal/mol) and (-)-asperlicin C (Figure 19) had high binding affinity to 3CLpro (−9.7 kcal/ mol) and ACE2 (−9.5 kcal/mol) with a high binding affinity to RdRp (−9.6 kcal/mol) [16].

Prospects of using Computational Chemistry to Determine the Antiviral Activity of some Alkaloids

Zhang et al. (2020b) recently reported the crystal structure of the SARS-CoV-2 main protease (Mpro also called 3CLpro), which is essential for viral replication. The availability of the crystal structure allows compounds, which have shown activity against SARS-CoV proteases, and other similar compounds to be screened through computational

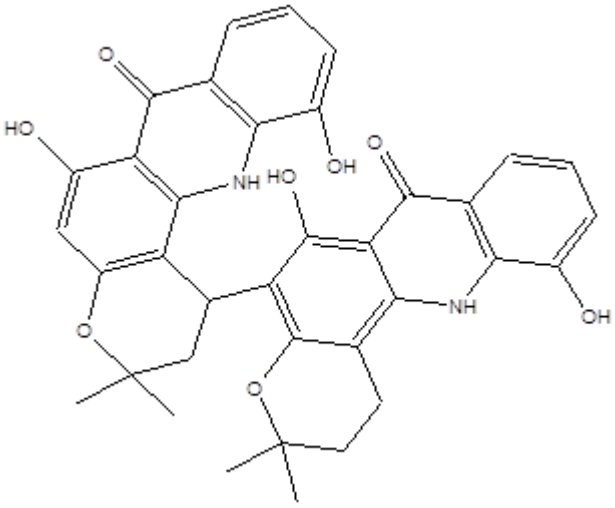


Figure 18. Oriciacridone F structure.

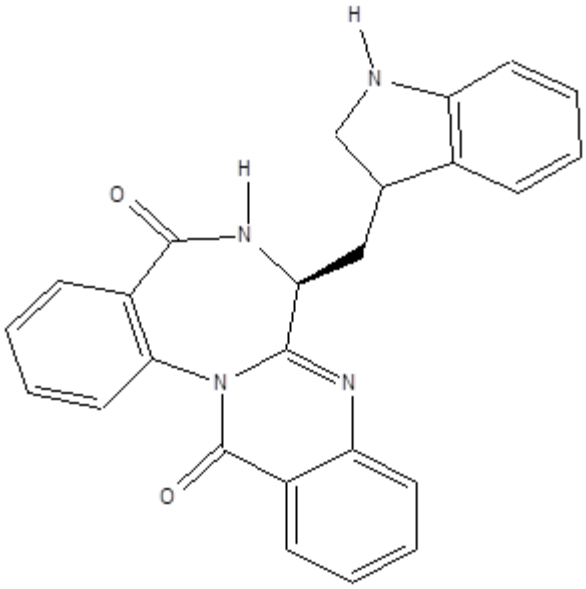


Figure 19. Asperlicin C structure.

studies to identify possible lead molecules active against covid-19 [17]. Based on a molecular docking study reported by Khaerunnisa et al. (2020), quercetin, luteolin- 7-O-glucoside, naringeni, desmetho-xycurcumin, curcumin, apigenin-7-O-glucoside, oleuropein, catechin, and epicatechin-gallate could potentially inhibit SARS-CoV-2 3CLPro and therefore act as anti-covid-19 agents. However, in vitro studies are required to assess these results further [18]. According to another report, the host receptor for SARS-CoV-2, ACE2 (angiotensin-converting enzyme 2), is the same as the host receptor of SARS-CoV; therefore, the inhibitors of SARS-CoV ACE2 might be able to inhibit the same receptor in SARS-CoV-2 [19]. Based on the molecular docking study performed by Chen and Du (2020), baicalin, scutellarin, hesperetin, nicotianamine and glycyrrhizin have been identified as potential ACE2 inhibitors and could be used as possible anti covid-19 drug candidate [20]. Molecular docking can be a useful tool to describe binding affinities and molecular interactions and is a rapid technique in which to identify potentially active compounds during drug discovery. However, in vitro or in vivo antiviral tests are crucial in order to support molecular docking data, which describes a compound with potent activity. Studies have shown that a positive correlation between docking scores and pharmacological activity are relatively low and docking is not very effective in ranking active compounds [21]. All Molecular docking experiments were performed using AutoDock 4.0 software, based on the Lamarckian genetic algorithm, which combines energy evaluation through grids of affinity potential to find the suitable binding position for a ligand on a given protein [21, 22].

The biological active alkaloids; deoxytryptoquivaline (Figure 20), deoxynortryptoquivaline (Figure 21) and norquinadoline A (Figure 22) are secondary metabolites which are isolated from the mangrove-derived fungus Cladosporium sp. PJX-41 and showed anti-influenza A (H1N1) activity [33]. These three alkaloids have also been predicted to bind strongly with three proteins studied. A recent study involving fungal secondary metabolites mainly quinazoline and quinoline alkaloids shows that norquinadoline A and deoxynortryptoquivaline virtually screened against SARS-CoV-2 are possible inhibitors of protease [32, 33]. They had a docking score of 0.72 and 0.58 respectively with no cytoxicity indicated [32].

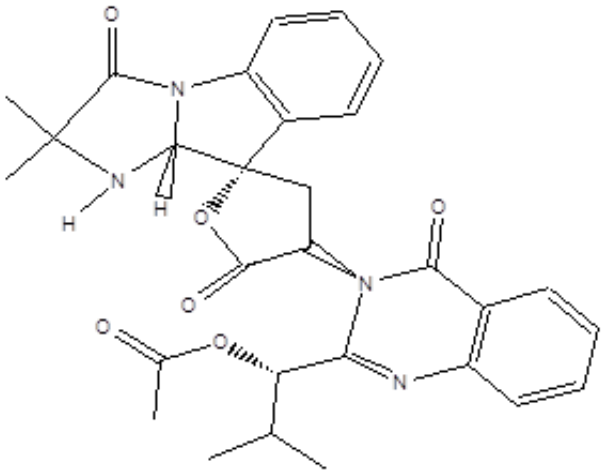


Figure 20. Deoxytryptoquivaline structure.

According to other research sources, some of the marine and plant-derived alkaloids including; berberine, tetrandrine, cepharanthine, lycorine, ergotamine, crambescidin 786, palmatine, noscapine, and quinine with prominent antiSARS-CoV-2 effects along with antipyretic, anti-inflammatory, antitussive and lung injury, immunomodulatory, and protective effects against

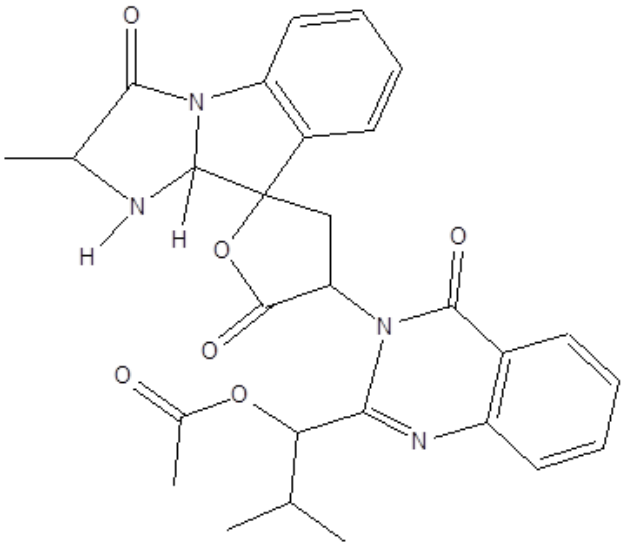


Figure 21. Deoxynortryptoquivaline structure.

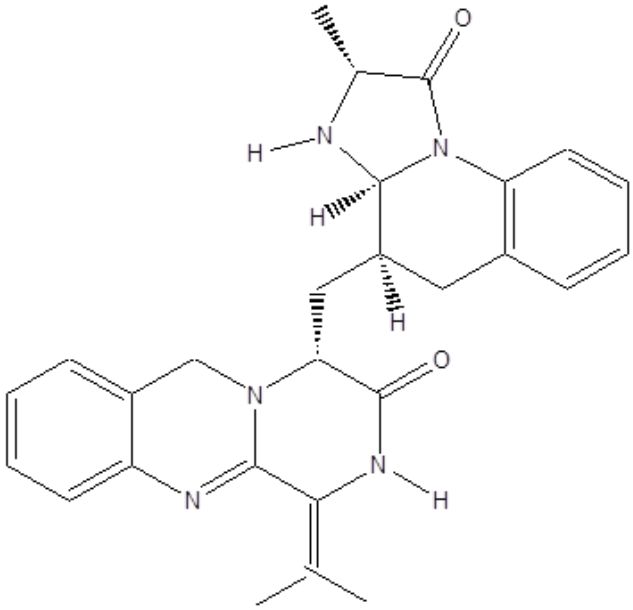


Figure 22. Norquinadoline structure.

neurotoxicity, cardiotoxicity, nephrotoxicity, and hepatotoxicity could be promising candidates for covid-19 treatment [25, 26, 32, 33].

Limitations

The study of anti-covid-19 drug discovery from natural sources would require a lot of in-vivo research which has not been looked up here and as such more clinical research to standardize, analyze, validate and confirm the use of naturally sourced drug leads in the treatment of covid-19.

Conclusion

Even at the discovery of vaccines to prevent covid-19 pandemic, there is still an inevitable need to do more search and research that will lead to the discovery of anti-covid-19 drug candidates. Due to the high therapeutic effect of drugs from natural sources especially from alkaloids, there is always need to standardize naturally sourced drugs which may be used as prophylaxis as well as immune boosters against covid-19. The study of toxicity, pharmacokinetic and pharmacodynamics could be of valuable importance in order to identity drug targets. New drug molecules could also be designed from SAR analyses as well as in-vivo studies and clinical trials to effectively develop new and promising drug candidates from alkaloids against covid-19 pandemic.

Contribution of authors

Not Applicable

Acknowledgments

Not Applicable

Conflict of Interest

None declared

Funding

No source of funding is associated with this research.

Data Availability

No reported data was used to support this research.

References

1. N. Lo, M. Zhou, X. Dong et al., "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study," 6e Lancet, vol. 395, no. 10223, pp. 507–513, 2020.
2. N. Zhu, D. Zhang, W. Wang et al., "A novel coronavirus from patients with pneumonia in China, 2019," New England Journal of Medicine, vol. 382, no. 8, pp. 727–733, 2020.
3. N. Yamamoto, R. Yang, Y. Yoshinaka et al., "HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus," Biochemical and Biophysical Research Communications, vol. 318, no. 3, pp. 719–725, 2004.
4. Chattopadhyay D, Naik TN. Antivirals of ethnomedicinal origin:structureactivity

Table 1. Some alkaloids, their mechanism of action and effective concentration (EC50).

Name of alkaloid	Mechanism of action	EC50	Type of study	References
Lycorine	Mpro inhibitor	15 nM 0.15 μM 0.47 μM	In-vitro	[1]
7-Methoxycryptopleurine	Blocking the S and N proteins, $3CL^{pro}$ inhibitor (in-silico study)	58 nM	In-vitro	[23]
Quinine	Mpro and S proteins inhibitor (in-silico study)	10.7 μM	In-vitro	[25, 26]
Tylophorine	Blocking the S and N proteins, $3CL^{pro}$ inhibitor	20 nM	In-vitro	[27]
(-)-asperlicin C	3CLpro inhibitory, Blocking ACE2	-	Molecular docking	[16]
10-Hydroxyusambarensine	$3CL^{pro}$ inhibitor	-	Molecular docking	[28]
Caffeine	Blocking ACE2	-	Molecular docking	[29]
Cryptoquindoline	Mpro and RdRp inhibitor	-	Molecular docking	[28]
Indican	Mpro inhibitor	-	Molecular docking	[30]
Indirubin	Mpro inhibitor	-	Molecular docking	[31]
Indigo	Mpro inhibitor	-	Molecular docking	[30]
Norquinadoline A	Blocking ACE2 and PL^{pro} inhibitor	-	Molecular docking	[31, 32]
Oriciacridone F	$3CL^{pro}$ inhibitory, Blocking ACE2	-	Molecular docking	[16]
Palmatine	$3CL^{pro}$ inhibitor	-	Molecular docking	[16]
Sanguinarine	$3CL^{pro}$ inhibitor	-	Molecular docking	[16]
Tabersonine	$3CL^{pro}$ inhibitor	-	Molecular docking	[16]

relantionship and scope. Mini Rev Med Chem 2007; 7: 275–301.
5. Vanden DA, Vlietinck AJ, Van Hoof DL. Plant products as Potential antiviral agents. Bull Inst Pasteur 1986; 84:101-147.
6. De Clercq E. Antiviral agents: characteristic activity spectrum depending on the molecular target with which they interact. Adv Virus Res 1993; 42: 1-55.
7. Field A. K, Biron K. K. The end of innocence. Revisited: Resistance of herpes viruses to antiviral drugs. Clin Microbiol Rev 1994; 7:1-13.
8. Severson J. L, Tyring S. K. Relation between herpes simplex viruses and human immunodeficiency virus infections. Arch Dermatol 1999; 135:1393-1397.
9. Khan M. T, Ather A., Thompson K.D., Gambari, R. Extracts and molecules from medicinal plants against herpes simplex viruses. Antiviral Res 2005; 67:107-119.
10. Oku N, Gustafson KR, Cartner LK, Wilson JA, Shigematsu N, Hess S, et al. 2004. Neamphamide A, a new HIV-inhibitory depsipeptide from the Papua New Guinea marine sponge Neamphius huxleyi. J. Nat. Prod. 67, 1407–1411.
11. Khan SA, Zia K, Ashraf S, Uddin R, Ul-Haq Z. Identification of chymotrypsin-like protease inhibitors of SARS-CoV-2 via integrated computational approach. J Biomol Struct Dyn 2020;1-10
12. Sarma P, Shekhar N, Prajapat M, Avti P, Kaur H, Kumar S, et al. Insilico homology assisted identification of inhibitor of RNA binding against 2019-nCoV N-protein (N terminal domain). J Biomol Struct Dyn 2020:1-9.
13. L. Szla´ vik, A. Gyuris, J. Mina´ rovits, P. Forgo, J. Molna´ r, and J. Hohmann. (2004). Planta Med. 70, 871.
14. S. Y. 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, and X. Tan. (2005). Antiviral Res. 67, 18.
15. H. S¸. G¨ulaçtı Topçu, A. T. G¨ulbahar Ozge,

and M. A. Vecdi. 2020.¨ "Natural alkaloids as potential anti-coronaviruse compounds," Bezmialem Science, vol. 8, pp. 131–139.
16. T. Joshi, H. Pundir, P. Sharma, S. Mathpal, and S. Chandra. (2020). "Predictive modeling by deep learning, virtual screening and molecular dynamics study of natural compounds against SARS-CoV-2 main protease," Journal of Biomolecular Structure and Dynamics, pp. 1–19.
17. Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., et al. (2020b). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved a-ketoamide inhibitors. Science 368 (6489), 409–412.
18. Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartati, S., and Soetjipto, S. (2020). Potential Inhibitor of COVID-19 Main Protease (Mpro) From Several Medicinal Plant Compounds by Molecular Docking Study. Preprints J. 1–14.
19. Chen, H., and Du, Q. (2020). Potential natural compounds for preventing 2019-nCoV infection. Preprints 1–17.
20. Vilar, S., and Costanzi, S. (2012). "Predicting the biological activities through QSAR analysis and docking-based scoring," in Membrane Protein Structure and Dynamics. Methods in Molecular Biology. Ed. J. Walker (Totowa: Humana Press), 271–284.
21. G. M. Morris, D. S. Goodsell, R. S. Halliday. "Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function," Journal of Computational Chemistry, vol. 19, no. 14, pp. 1639–1662, 1998.
22. G. M. Morris, R. Huey, W. Lindstrom. "AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility," Journal of Computational Chemistry, vol. 30, no. 16, pp. 2785–2791, 2009.
23. C.-W. Yang, Y.-Z. Lee, I.-J. Kang.Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. Antiviral Research, vol. 88, no. 2, pp. 160–168, 2010.
24. M. Gendrot, J. Andreani, M. Boxberger. Antimalarial drugs inhibit the replication of SARS- CoV-2: An in vitro evaluation. Travel Medicine and Infectious Disease, vol. 37, Article ID 101873, 2020.
25. D. Roza, R. Selly, R. Munsirwan, and G. Fadhilah. Molecular docking of quinine derivative as inhibitor in Sars-Cov-2. Journal of Physics: Conference Series, vol. 1819, no. 1, Article ID 012053, 2021.
26. J. Peng, T. Lin, W. Wang et al., (2013). "Antiviral alkaloids produced by the mangrove-derived fungus Cladosporium sp. PJX-41," Journal of Natural Products, vol. 76, no. 6, pp. 1133–1140.
27. G. A. Gyebi, O. B. Ogunro, A. P. Adegunloye, O. M. Ogunyemi, and S. O. Afolabi. Potential inhibitors of coronavirus 3-chymotrypsin-like protease (3CLpro): an in silico screening of alkaloids and terpenoids from African medicinal plants. Journal of Biomolecular Structure and Dynamics, pp. 1–19, 2020.
28. S. Mohammadi, M. Heidarizadeh, M. Entesari. In silico investigation on the inhibiting role of nicotine/caffeine by blocking the S protein of SARS-CoV-2 versus ACE2 receptor. Microorganisms, vol. 8, no. 10, p. 1600, 2020.
29. R. R. Narkhede, A. V. Pise, R. S. Cheke, and S. D. Shinde. Recognition of natural products as potential inhibitors of COVID-19 main protease (Mpro): in-silico evidences. Natural Products and Bioprospecting, vol. 10, no. 5, pp. 297–306, 2020.
30. E. M. Ismail, S. W. Shantier, M. S. Mohammed, H. H. Musa, W. Osman, and R. A. Mothana. Quinoline and quinazoline alkaloids against COVID-19: an in silico multitarget approach. Journal of Chemistry, vol. 2021, Article ID 3613268, pp. 11, 2021.
31. M. T. J. Quimque, K. I. R. Notarte, R. A. T. Fernandez. Virtual screening-driven drug discovery of SARS-CoV2 enzyme inhibitors targeting viral attachment, replication, post- translational modification and host immunity evasion infection mechanisms," Journal of Biomolecular Structure and Dynamics, pp. 1–18, 2020.
32. N. Kumar, D. Sood, P. J. van der Spek, H. S. Sharma, and R. Chandra, "Molecular binding mechanism and pharmacology comparative analysis of noscapine for repurposing against SARS-CoV-2 protease," Journal of Proteome Research, vol. 19, no. 11, pp. 4678–4689, 2020.
33. A. El-Demerdash, A. M. Metwaly, A. Hassan

et al., "Comprehensive virtual screening of the antiviral potentialities of marine polycyclic guanidine alkaloids against SARS-CoV-2 (COVID-19)," Biomolecules, vol. 11, no. 3, p. 460, 2021.