Ivermectin Friend or Foe?

SASOCP
Pharmacists care no matter where

UNIYEIIIT!IT VAN PIUORIA
UNIYEUITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of
Health Sciences
Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

Prof N Schellack
Department of Pharmacology
2021/02/10

Make today matter

Overview of the Presentation

- Introduction and Current Evidence
- Ivermectin – the compound
- Current evidence
- Ivermectin in South Africa
- Conclusion

DAILY MAVERICK HOME | SCORPIO OPINIONISTA ZAPIRO SECTIONS DECLASSIFIED UK DONATE NEWSLETTER LOGIN

DM SHOP

MAVERICK CITIZEN:ANALYSIS

Using ivermectin for Covid-19: what to do when caution and crisis clash?

By Mark Heywood • 15 January 2021

Subscribe 159k

Mark Heywood

In parts of South Africa and internationally a debate is raging about the

IVERMECTIN SHOULDN'T BE USED TO TREAT COVID-19 - INFECTIOUS DISEASES EXPERT

Some health professionals tout Ivermectin as a wonder drug, with therapeutic benefits for COVID-19 patients and even suggested the anti-parasitic drug can be taken as prophylaxis.

The Pharmaceutical Society of SA (PSSA) believes the Gauteng High Court ruling to allow doctors to use ivermectin to treat Covid-19 patients was influenced by social media. File Picture.

Social media pressure blamed for court ruling on the use of Ivermectin to treat Covid-19

Covid-19: Compassionate-use approvals will have no impact on ivermectin's potential registration

health24 Nelisiwe Msomi SHARE

Listen to this article 0:00

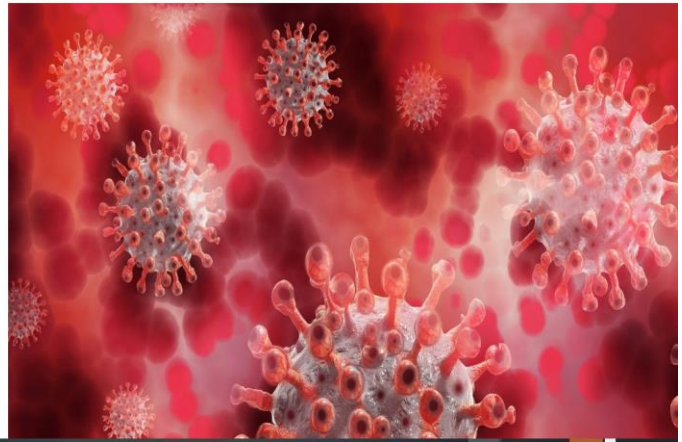
SUBSCRIBERS CAN LISTEN TO THIS ARTICLE

DAILY MAVERICK HOME | SCORPIO OPINIONISTA ZAPIRO SECTIONS DECLASSIFIED UK DONATE NEWSLETTER

GROUNDUP OP-ED

Covid-19: Ivermectin obsession is 'dangerous'

By Nathan Geffen • 29 January 2021



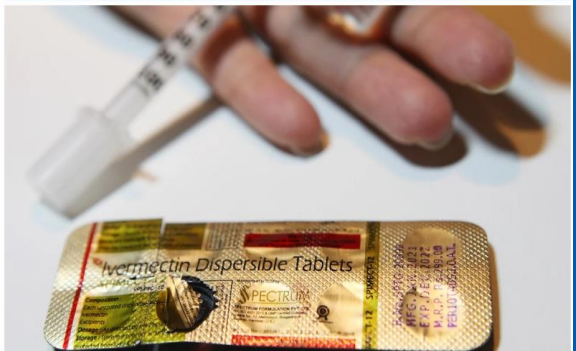
05 Feb

'No meaningful evidence for clinical efficacy in patients with Covid-19' - ivermectin manufacturer

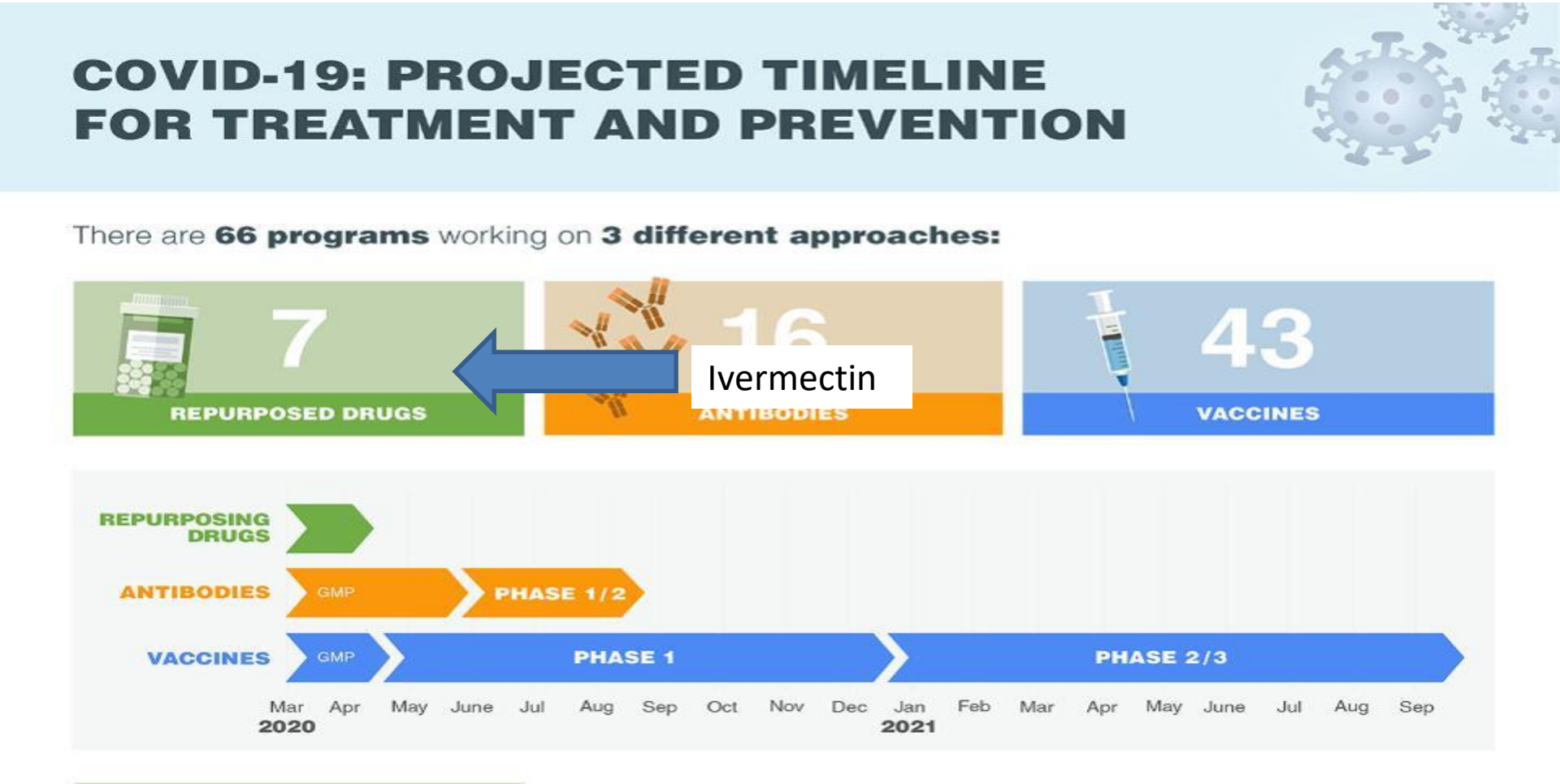
news24 Nicole McCain SHARE

Listen to this article 0:00

SUBSCRIBERS CAN LISTEN TO THIS ARTICLE

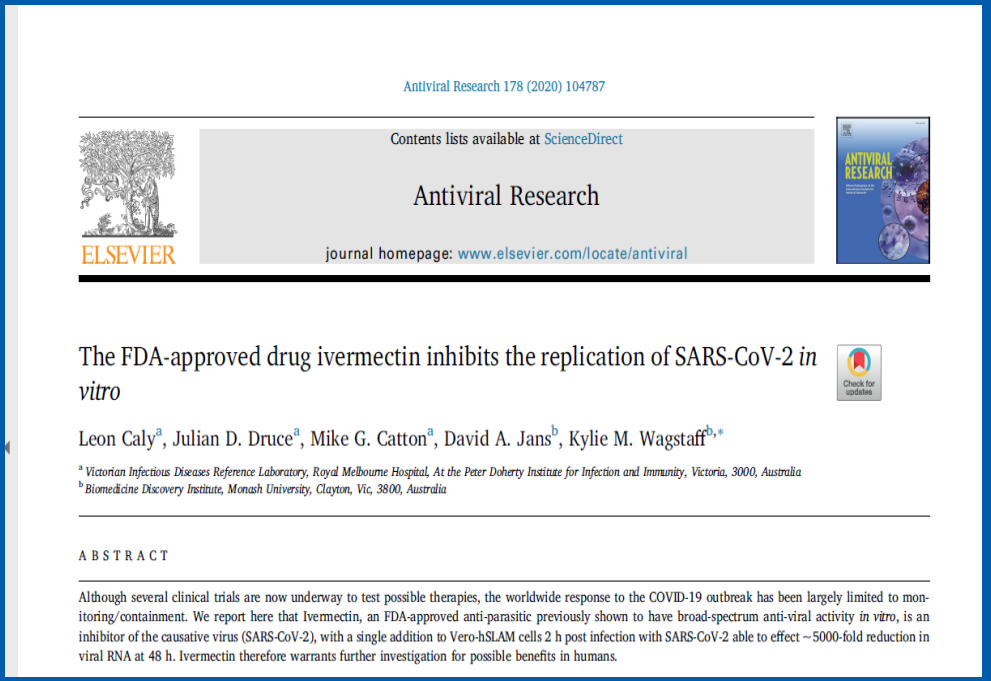


The Great Race!



Current evidence

- Ivermectin is a broad spectrum antiparasitic drug with known antiviral properties.
- On April 3, 2020, Caly et al. published evidence from in vitro experiments showing that ivermectin can inhibit the replication of SARS-CoV-2 at micromolar concentrations.



Antiviral Research 178 (2020) 104787

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*

Leon Caly[a], Julian D. Druce[a], Mike G. Catton[a], David A. Jans[b], Kylie M. Wagstaff[b,*]

[a] Victorian Infectious Diseases Reference Laboratory, Royal Melbourne Hospital, At the Peter Doherty Institute for Infection and Immunity, Victoria, 3000, Australia
[b] Biomedicine Discovery Institute, Monash University, Clayton, Vic, 3800, Australia

ABSTRACT

Although several clinical trials are now underway to test possible therapies, the worldwide response to the COVID-19 outbreak has been largely limited to monitoring/containment. We report here that Ivermectin, an FDA-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity *in vitro*, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. Ivermectin therefore warrants further investigation for possible benefits in humans.

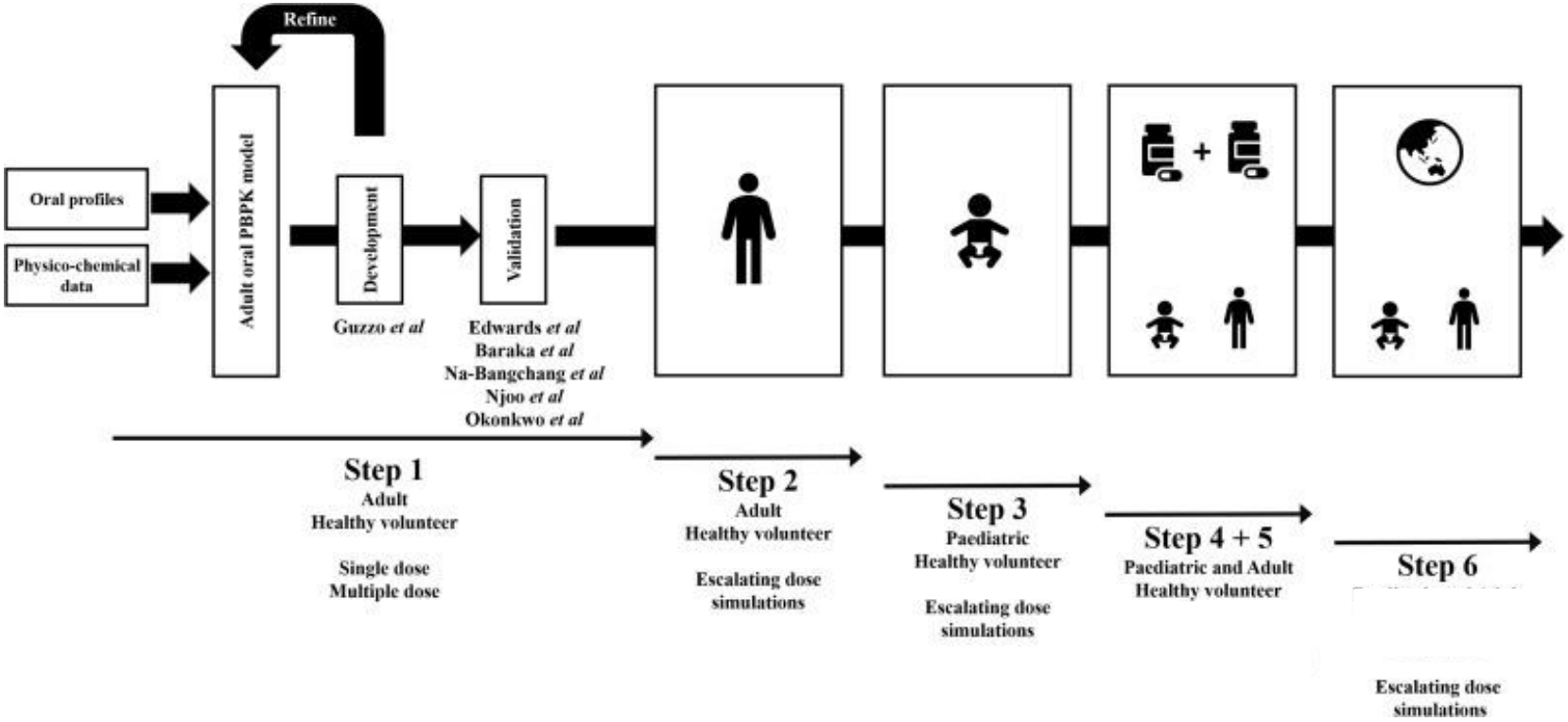
- Vero/hSLAM cells were infected with SARS-CoV-2 isolate Australia/VIC01/ 2020 at an MOI of 0.1 for 2 h, followed by the addition of 5 µM ivermectin.
- At 24 h, there was a 93% reduction in viral RNA present in the supernatant (indicative of released virions) of samples treated with ivermectin compared to the vehicle DMSO.
- Similarly a 99.8% reduction in cell-associated viral RNA (indicative of unreleased and unpackaged virions) was observed with ivermectin treatment.
- By 48 h this effect increased to an ~5000-fold reduction of viral RNA in ivermectin-treated compared to control samples, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 h.
- Consistent with this idea, no further reduction in viral RNA was observed at 72 h.

L. Caly, J.D. Druce, M.G. Catton, D.A. Jans, K.M. Wagstaff, The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro, Antiviral research (2020) 104787.

Current evidence (2)

- This discovery gave hope to the researchers who are screening for drugs that can be repurposed for treating the Coronavirus Disease 2019 (COVID-19).
- This has torn the scientific community into two opposing views, one group calling for avoiding investment and effort in a drug likely to fail clinical trials, and another group calling for rapid scale-up even in the absence of proven safety and efficacy for the potential COVID-19 indication.
- Since April 2020, there has been an abundance of observational trials, case series and ecological analyses suggesting a potential efficacy of ivermectin against COVID-19.
- Yet very few reports of rigorously conducted randomized controlled clinical trials.

Ivermectin – Repurposed?



Sharun *et al. Ann Clin Microbiol Antimicrob (2020) 19:23* https://doi.org/10.1186/s12941-020-00368-w

Ivermectin – Repurposed?

- Ivermectin, is a member of the avermectin family; as these compounds are produced by the soil microorganism, *Streptomyces avermitilis,* they are called avermectins.
- Ivermectin has showed a wide range of activities, ranging from broad-spectrum endo/ecto-parasiticide activity to antiviral, antibacterial, and anticancer activities.
- It was first introduced commercially in 1981 for use in animals. In addition to being used for treating billions of livestock and companion animals worldwide to help maintain food production and animal health, ivermectin is also used for treating several diseases in humans, e.g. a key drug in the elimination programs of onchocercosis.
- Ivermectin is considered a drug of choice for various parasitic diseases. As an anthelmintic drug, its mechanism of action in invertebrates mainly involves the opening of glutamate-gated and Gamma aminobutyric acid (GABA)-gated chloride channels, leading to increased conductance of chloride ions and causing subsequent motor paralysis in parasites

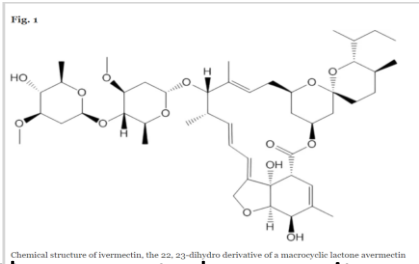
Sharun *et al. Ann Clin Microbiol Antimicrob (2020) 19:23* https://doi.org/10.1186/s12941-020-00368-w

Ivermectin – Drug Properties

Ivermectin is a broad-spectrum highly lipophilic anti-parasite medication.

A small molecule with a group of pentacyclic sixteen-membered lactone (i.e. a macrocyclic lactone disaccharide).

Primarily hepatic metabolism, and/or its metabolites are excreted almost exclusively in the faeces over an estimated 12 days, with less than 1 % of the administered dose excreted in the urine.



Despite this it is moderately well absorbed better absorbed with a high fat meal

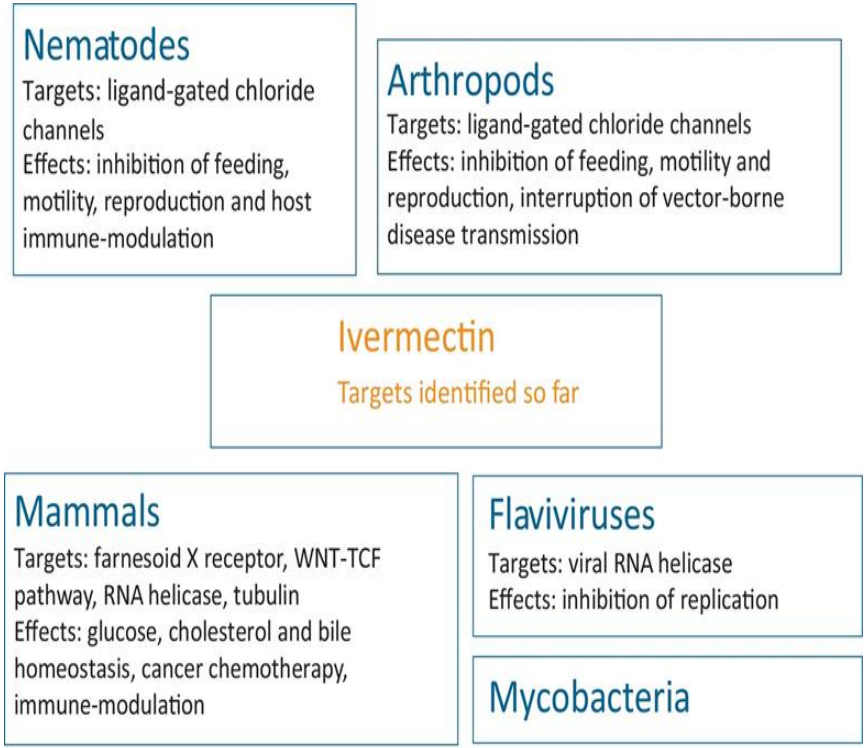
The volume of distribution is 3 to 3.5 L/kg and it does not cross the blood-brain barrier.

For the treatment of intestinal (i.e., nondisseminated) strongyloidiasis due to the nematode parasite Strongyloides stercoralis. Also for the treatment of onchocerciasis (river blindness) due to the nematode parasite Onchocerca volvulus. Can be used to treat scabies caused by Sarcoptes scabiei, and other associated conditions such as Acne Rosacea, Ascaris lumbricoides infection, Cutaneous larva migrans, Demodicidosis, Gnathostomiasis, Mansonella ozzardi infection and others.

Sharun *et al. Ann Clin Microbiol Antimicrob (2020) 19:23* https://doi.org/10.1186/s12941-020-00368-w

Ivermectin – Mechanism of Action

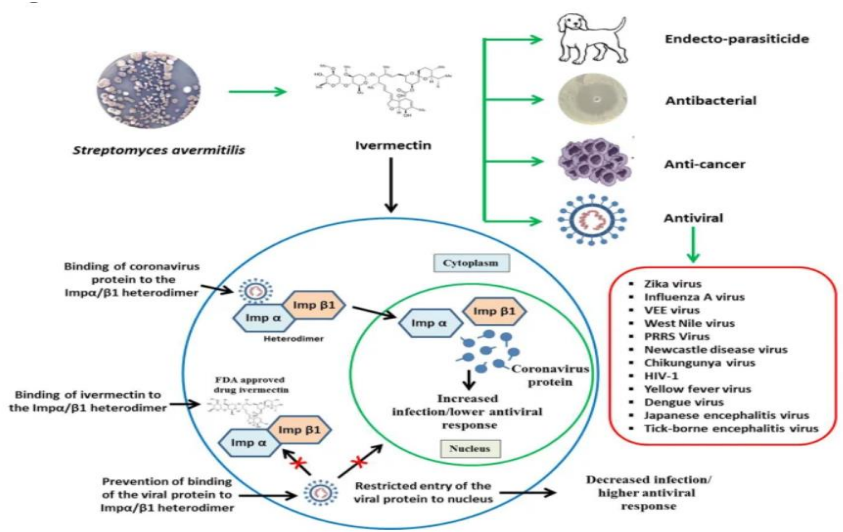
- Agonist for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and can be administered orally, topically or by injection
- Binding GABA-gated chloride and invertebrate-specific glutamate-gated anion channels in peripheral neuromuscular synapses, suppressing nerve impulse conduction
- Its usefulness as an anthelminthic results from differences in the distribution of GABA receptors between mammals and arthropods or nematodes: GABA receptors in mammals are mostly in the central nervous system (CNS) protected by the blood brain barrier, whereas in arthropods and nematodes they are found in the peripheral nervous system at the neuromuscular junction.
- Stimulation of GABA receptors in endo- and ecto-parasites causes flaccid paralysis and inhibits feeding of the parasite



Trends in Parasitology
UNIYERSITEIT YAM PRETORIA

Trends in Parasitology 2017 33463-472DOI: (10.1016/j.pt.2017.02.004)

IVM – RNA Viruses



Potential modes of anti-viral actions of ivermectin

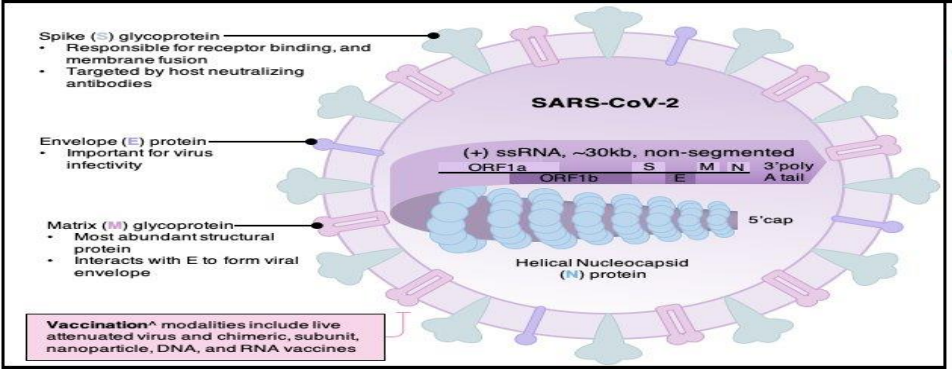
IVM inhibits viral by:

- Blocking viral helicase
- Suppression of viral replication was thought to reflect disruption of viral protein trafficking between the host cell cytoplasm and nucleus by IVM inhibition of importin a/b-mediated transport

Poltronieri P *et al RNA Viruses: RNA Roles in Pathogenesis, Coreplication and viral load – Curr Genomics, 2015; 16(5):327-335*

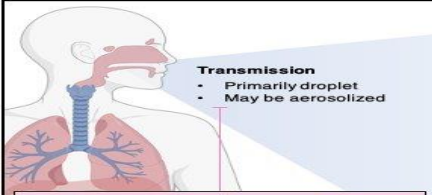
SnapShot: COVID-19

Viral Structure



Vaccination^ modalities include live attenuated virus and chimeric, subunit, nanoparticle, DNA, and RNA vaccines

Clinical Course

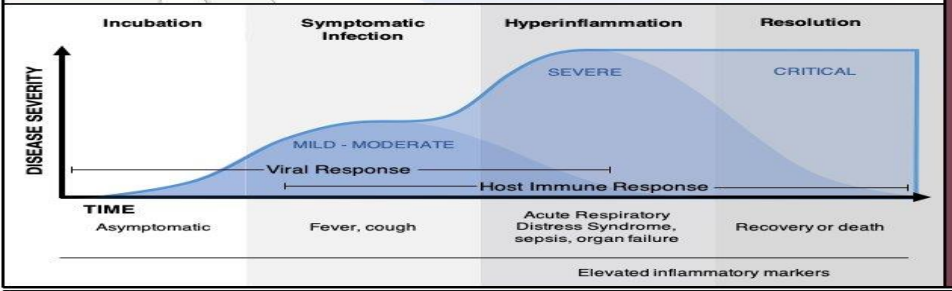


Transmission
- Primarily droplet
- May be aerosolized

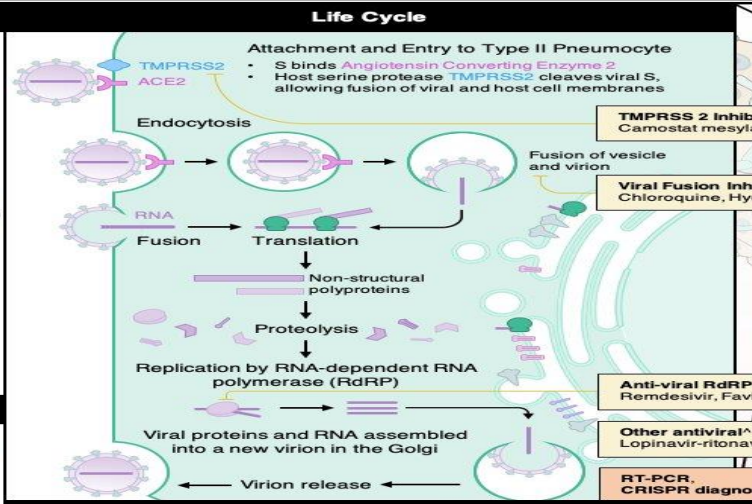
Handwashing, EtOH, H_2O_2, PPE, Distance >2m, Epidemiologic containment

Symptoms

Fever, 87.9% (only 44% at time of diagnosis)	
Dry cough, 67.7%	
Fatigue, 38.1%	
Sputum production, 33.4%	
Dyspnea, 18.6%	
Myalgia/Arthralgia, 14.8%	
Sore throat, 13.9%	
Headache, 13.6%	
Chills, 11.4%	
Nausea/Vomiting, 5%	
Nasal congestion, 4.8%	
Diarrhea, 3.7%	
Anosmia^	



Life Cycle



TMPRSS 2 Inhibitor^
Camostat mesylate

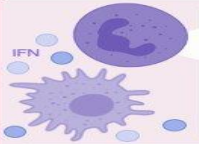
Viral Fusion Inhibitor^
Chloroquine, Hydroxychloroquine

Anti-viral RdRP Inhibitor^
Remdesivir, Favipiravir

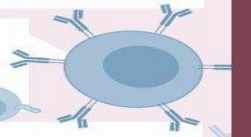
Other antiviral^
Lopinavir-ritonavir

RT-PCR, CRISPR diagnostic^

Immune Response



Innate Immune Response
- Delayed or suppressed Type I Interferon (IFN) response during initial infection
- Viral replication triggers hyperinflammatory conditions and cytokine storm
- Influx of activated neutrophils and inflammatory monocytes/macrophages
- Serum neutrophilia and elevated pro-inflammatory cytokines are associated with severity of disease



Adaptive Immune Response
- T helper cells Th1/Th17 are engaged
- IgM and IgG are usually detectable within two weeks after infection
- Lymphopenia may be related to bone marrow suppression

Laboratory Findings

Mild disease	Lymphopenia (most common finding), leukopenia, ↑CRP
Moderate to severe disease	↑AST, ↑ALT, ↑CK, ↑D-dimer, ↑ferritin, ↑LDH

Anti IL-6R Monoclonal Antibody^
Tocilizumab, sarilumab

Serologic ELISA against IgG and IgM

Convalescent plasma transfer^

KEY
Prevention
Diagnostic
Therapeutic
^Investigational

Oberfeld, B., Achanta, A., Carpenter, K., Chen P., Gilette, N., Langat, P., Said, J., Schiff, A., Zhou, A., Barczak, A., Pillai, S. SnapShot: COVID-19. *Cell*. 2020. DOI: 10.1016/j.cell.2020.04.013

SARS-CoV-2

The protein ACE -2 expresses in high quantities in the respiratory epithelia, allows for viral entry and infection of the lung and alveolar cells

ACE-2 enzyme expression is important for blood pressure regulation and interferon production

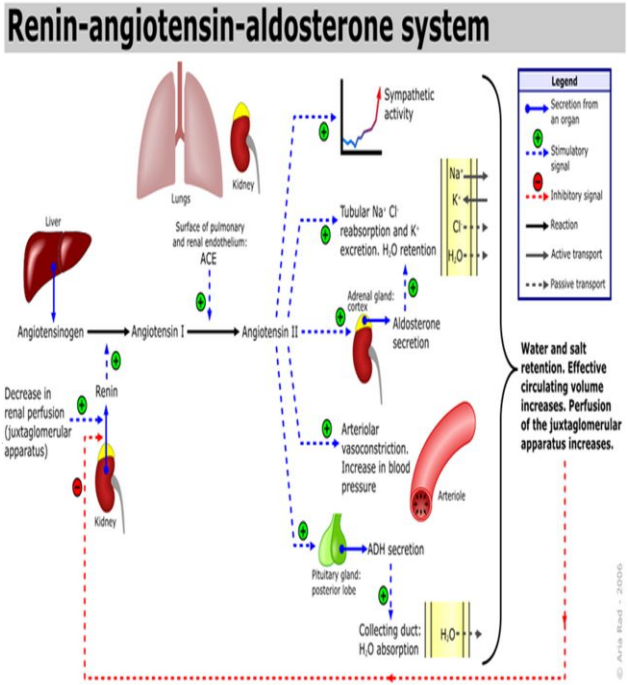
SARS-CoV-2 binding to these receptors impedes these processes

It was known to inhibit the nuclear import of viral and host proteins.

Integrase protein of viruses and the importin (IMP) α/β1 heterodimer was responsible for IN nuclear import which further increases the infection

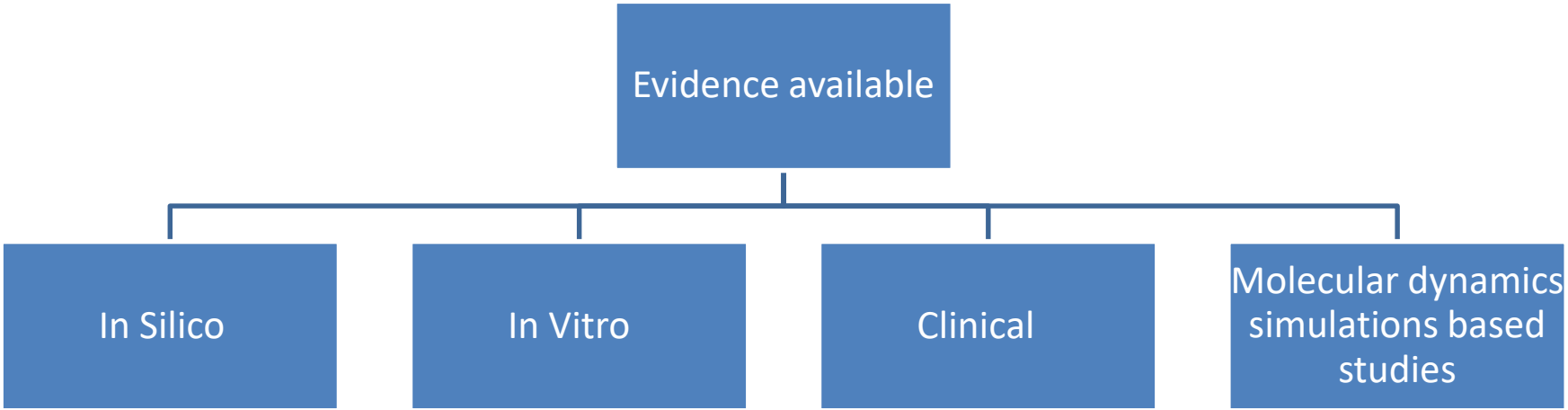
As most of the RNA viruses are dependent upon IMPα/β1 during infection, Ivermectin acts on it and inhibits the import with the increase in antiviral response

CD147 along with ACE-2 has been recognized as a key binding site for SARS-CoV-2 spike protein. Ivermectin shields SARS-CoV-2 spike protein which binds to CD147 and ACE-2.



Kaur et al, Ivermectin as a potential drug for treatment of COVID-19: an in sync review with clinical and computational attributes – Pharmacological reports, 2021

Current Evidence available



In Silico..

In Search for Effective and Safe Drugs against SARS-CoV-2: Part I] Simulated interactions between selected nutraceuticals, ACE2 enzyme and S Protein simple peptide sequences

M. S. A. Abdel-Mottaleb[1] and Yousra Abdel-Mottaleb[2]
[1]Department of Chemistry, Faculty of Science, Ain Shams University (ASU), Abbassia 11566, Cairo, Egypt
[2]Department of Pharmacology, Toxicology and Biochemistry, Faculty of Pharmaceutical Sciences and Pharmaceutical Industries, Future University in Egypt (FUE), New Cairo 11835, Egypt

Corresponding author: m.s.abdelmottaleb@sci.asu.edu.eg
[1]https://orcid.org/0000-0002-4437-7040
[2]https://orcid.org/0000-0002-4327-4920

Abstract:

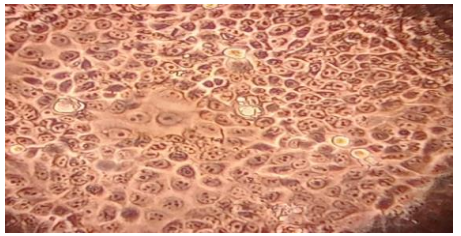
Coronavirus disease (COVID-19) remains a world pandemic with little treatment options. Nature has provided a plethora of compounds that may offer potential protection and/or treatment choices. Earlier studies have shown a pivotal role of Angiotensin converting enzyme 2 (ACE2) in the pathogenesis of COVID-19. In this context, seven natural compounds were selected and their binding to specific peptide sequences of the coronavirus S-protein: ACE2 interface-drug binding adduct were calculated. Further to the natural drugs, we also similarly examined four well-known antiviral drugs. Moreover, the binding-interface of the isolated coronavirus S-protein and the isolated ACE2 receptor were also individually explored. The identified drug molecules positioned itself achieving geometries of minimum energy resulting in limiting viral recognition of host cells or to disturb host-virus interactions. The frontier orbitals (HOMO-LUMO) play crucial role in the binding interactions of the studied molecules. Most of the drugs act as electron sink whereas the S protein behaves as nucleophile. The results reported pave the way for the identification of small-drug molecule of natural origin with potentially tolerable side effects that can offer protection and/or treatment against coronavirus S-protein COVID-19. Experimental validation is of urgent demand.

4- Conclusions

11 ligands (7 natural and 4 synthesized antivirals) were calculated to bind to either the S-protein: ACE2 interface-ligand binding complex or the binding-interface of the isolated S-protein, ACE2, Heme or Heparin. We showed that the identified drugs could be positioned to limit viral recognition of host cells or disturb host-virus. Simplified assumptions of Frontier orbitals interactions are successful in explaining the results. Generally, in presence of ACE2 enzyme, drugs act as Lewis acids (or electron sink molecules) towards the viral S protein that exhibits strong electrophilic property. Hydroxychloroquine, ivermectin and favipiravir are strongest binding drugs to both S protein and ACE2, while raspberry-ketone, menthol, eriodictyol and thymoquinone are potentially bind to S protein. Raspberry-ketone is of comparable binding strength to hydroxychloroquine and ivermectin antiviral drugs, which are currently clinically investigated. Moreover, raspberry ketone seems to block or at least disturb S protein – ACE2 interactions. Other natural drugs did not show affinity to bind to either S protein or ACE2. However, they disturb direct S protein – ACE2 interaction by showing capabilities to receive electrons (electron sink) into its disturbed LUMO from S protein in presence of ACE2. Thymoquinone is the only drug among the tested ones that showed electron acceptor capability towards heme.

Kaur et al, Ivermectin as a potential drug for treatment of COVID-19: an in sync review with clinical and computational attributes – Pharmacological reports, 2021

In vitro



Margo Nell, Chief Research Assistant, Dept. of Pharmacology, University of Pretoria.

Antiviral Research 178 (2020) 104787

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*

Leon Caly[a], Julian D. Druce[a], Mike G. Catton[a], David A. Jans[b], Kylie M. Wagstaff[b,*]

[a] Victorian Infectious Diseases Reference Laboratory, Royal Melbourne Hospital, At the Peter Doherty Institute for Infection and Immunity, Victoria, 3000, Australia
[b] Biomedicine Discovery Institute, Monash University, Clayton, Vic, 3800, Australia

ABSTRACT

Although several clinical trials are now underway to test possible therapies, the worldwide response to the COVID-19 outbreak has been largely limited to monitoring/containment. We report here that Ivermectin, an FDA-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity *in vitro*, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. Ivermectin therefore warrants further investigation for possible benefits in humans.

Caly et al. showed that when 5 μM of ivermectin was added to Vero/hSLAM cells with SARS-CoV-2 isolate Australia/VIC01/2020, viral RNA in the supernatant (indicated virions that were released) was reduced by 93% and RNA of virus associated with cell was reduced by 99.8% (indicated virions that were not released and packaged). Furthermore, it was stated that by 48 h ivermectin brought about 5000 fold reduction of viral RNA and the IC50 was found out to be ~2 μM [2].

Current Studies

Table 1 Clinical trials of ivermectin (from ClinicalTrials.gov and CTRI as of 16-10-2020)

	Trial registration	Phase/status	Intervention/comparator	Study design	Size/location
1	NCT04343092	Phase 1 Completed	Ivermectin	Randomized, parallel Masking: double	100 Iraq
2	NCT04422561	Phase 2/phase 3 Completed	Ivermectin	Randomized, sequential Masking: none	340 Egypt
3	NCT04434144	Completed	Ivermectin + doxycycline Hydroxychloroquine + azithromycin	Prospective, case-only	116 Bangladesh
4	NCT04381884	Phase 2 Completed	Ivermectin plus standard care Control arm will receive standard care	Randomized, parallel Masking: none	45 Argentina
5	NCT04446104	Phase 3 Completed	Hydroxychloroquine sulfate tablets Ivermectin 3 Mg Tab Zinc Povidone-iodine Supplement: vitamin C	Randomized, parallel Masking: none	4257 Singapore
6	NCT04523831	Phase 3 Completed	Ivermectin and doxycycline Standard of care	Randomized, parallel Masking: double	400 Bangladesh
7	NCT04438850	Phase 2 Recruiting	Ivermectin Placebo	Randomized, sequential Masking: quadruple	102 Italy
8	NCT04425707	Not applicable Recruiting	Ivermectin	Randomized, parallel Masking: none	100 Egypt
9	NCT04429711	Not applicable Recruiting	Ivermectin oral product	Randomized, parallel Masking: quadruple	100 Israel
10	NCT04405843	Phase 2| Phase 3 Recruiting	Ivermectin oral product Placebo	Randomized, parallel Masking: quadruple	400 Colombia
11	NCT04445311	Phase 2|Phase 3 Recruiting	Ivermectin	Randomized, parallel Masking: none	100 Egypt
12	NCT04392713	Not applicable Recruiting	Ivermectin 6 MG oral tablet (2 tablets)	Randomized, parallel Masking: none	100 Pakistan
13	NCT04351347	Phase 2|Phase 3 Recruiting	Ivermectin Nitazoxanide with ivermectin Ivermectin wth chloroquine	Randomized, parallel Masking: none	300 Egypt
14	NCT04431466	Phase 2 Recruiting	Ivermectin Standard treatment for COVID-19	Randomized, parallel Masking: triple	64 Brazil
15	NCT04529525	Phase 2|Phase 3 Recruiting	Ivermectin Placebo	Randomized, parallel Masking: quadruple	500 Colombia
16	NCT04384458	Not applicable Recruiting	Hydroxychloroquine Ivermectin	Randomized, parallel Masking: none	400 Brazil
17	NCT04373824	Not applicable Recruiting	Ivermectin	Non-randomized, crossover Masking: None	50 India
18	NCT04403555	Phase 2|Phase 3 Recruiting	Ivermectin Doxycycline Chloroquine	Randomized, parallel Masking: None	200 Egypt
19	NCT04447235	Phase 2 Recruiting	Placebo Ivermectin Losartan	Randomized, parallel Masking: double	176 Brazil
20	NCT04472585	Phase 1|Phase 2 Recruiting	Nigella sativa/black cumin Ivermectin injectable solution Placebo Zinc	Randomized, parallel Masking: quadruple	40 Pakistan
21	NCT04399746	Not applicable Recruiting	Ivermectin Azithromycin Cholecalciferol	Non-randomized, parallel Masking: none	30 Mexico

Table 1 (continued)

	Trial registration	Phase/status	Intervention/comparator	Study design	Size/location
22	NCT04374019	Phase 2 Recruiting	Hydroxychloroquine and azithromycin Ivermectin Camostat mesilate Artemesia annua	Randomized, parallel Masking: none	240 US
23	NCT04391127	Phase 3 Active, not recruiting	Hydroxychloroquine Ivermectin Placebo	Randomized, parallel Masking: double	108 Mexico
24	NCT04390022	Phase 2 Active, not recruiting	Ivermectin Placebo	Randomized, parallel Masking: double	24 Spain
25	NCT04425863	Active, not recruiting	Ivermectin 5 mg/mL	Prospective, cohort	100 Argentina
26	NCT04425850	Active, not recruiting	Iota carrageenan Ivermectin	Prospective, cohort	70 Argentina
27	NCT04407130	Phase 2 Enrolling by invitation	Ivermectin + doxycycline + placebo Ivermectin + placebo Placebo	Randomized, parallel Masking: double	72 Bangladesh
28	NCT04510233	Phase 2 Not yet recruiting	Ivermectin nasal Ivermectin oral Standard care	Randomized, parallel Masking: none	60
29	NCT04360356	Phase 2| Phase 3 Not yet recruiting	Ivermectin plus Nitazoxanide Standard Care	Randomized, parallel Masking: double	100
30	NCT04407507	Phase 2 Not yet recruiting	Ivermectin Placebo	Randomized, parallel Masking: single	66
31	NCT04392427	Phase 3 Not yet recruiting	Nitazoxanide, ribavirin and ivermectin for 7 days	Randomized, sequential Masking: single	100 Egypt
32	NCT04435587	Phase 4 Not yet recruiting	Ivermectin pill Combined ART/hydroxychloroquine	Randomized, parallel Masking: single	80 Thailand
33	NCT04382846	Phase 3 Not yet recruiting	Nitazoxanide Ivermectin Chloroquine Azithromycin	Randomized, parallel Masking: none	80
34	NCT04460547	Not yet recruiting	Convalescent plasma transfusion Hydroxychloroquine DAS181 Ivermectin Interferon beta-1A	Retrospective, cohort	200
35	NCT04482686	Phase 2 Not yet recruiting	Ivermectin Doxycycline Hcl Zinc Vitamin D3 Vitamin C	Randomized, parallel Masking: triple	300 US
36	NCT04551755	Phase 2 Not yet recruiting	Ivermectin and doxycycline Placebo	Randomized, parallel Masking: triple	188
37	NCT04530474	Phase 3 Not yet recruiting	Ivermectin pill Placebo	Randomized, parallel Masking: triple	200 US
38	NCT04527211	Phase 3 Not yet recruiting	Ivermectin	Randomized, parallel Masking: quadruple	550 Argentina
39	CTRI/2020/04/024858	Not yet recruiting	Ivermectin (200–400 mcg/kg on day 1 and 2 in addition to standard treatment) Standard treatment	Non-randomized, active controlled	50 New Delhi, India

Table 1 (continued)

	Trial registration	Phase/status	Intervention/comparator	Study design	Size/location
40	CTRI/2020/04/024948	Phase 2 Not yet recruiting	Ciclesonide (200 mcg twice a day for 7 days) Hydroxychloroquine (400 mg twice a day, Day1 followed by 200 mg twice a day on Days 2–7) Ivermectin (12 mg once a day for 7 days) Standard of care	Randomized, parallel	120 New Delhi, India
41	CTRI/2020/05/025224	Phase 2 Not yet recruiting	Ivermectin (12 mg once a day at night, oral for 2 days with standard of care) Standard of care	Randomized, parallel	50 Madhya Pradesh, India
42	CTRI/2020/06/025960	Not yet recruiting	Ivermectin (12 mg, per orally, once a day for 3 days) Standard of care	Randomized, parallel, active controlled	100 Maharashtra, India
43	CTRI/2020/06/026232	Phase 3 Not yet recruiting	Ivermectin (single oral dose of 200 mcg/kg)	Single arm	50 Andhra Pradesh, India
44	CTRI/2020/08/027225	Not yet recruiting	Ivermectin (12 mg orally on days 1 and 2) Placebo tablets	Randomized, parallel, placebo controlled	90 Bihar, India
45	CTRI/2020/08/027282	Phase 3 Not yet recruiting	Ivermectin 12 mg or 36 mg one dose orally one time a day (two intervention arms) Two multivitamin tablets	Randomized, parallel, multiple arm	180 Uttar Pradesh, India
46	CTRI/2020/09/027944	Phase 3 Not yet recruiting	Cefixime 200 mg (BD, 5 days), Ivermectin 12 mg (OD, day 1), Montelukast 10 mg (OD, 5 days), Ascoril LS 5 ml (TID, 5 days) Cefixime 200 mg, vitamin C, MVBC, antacids	Randomized, parallel group, active controlled	30 Maharashtra, India

https://www.clinicaltrials.gov/

Clinical Studies

Table 2 Clinical efficacy and safety of ivermectin

References	Population	Intervention	Control	Outcome of intervention	Outcome of control	Adverse Event in intervention arm	Adverse Event in control arm
Rajter et al. [20]	280 COVID-19 patients	Ivermectin (at least one oral dose of ivermectin 200 mcg/kg) along with usual clinical care *N* = 173	Usual care *N* = 107	Overall mortality—15.0% Mortality in patients with severe illness—38.8%	Overall mortality—25.2% Mortality in patients with severe illness—80.7%	–	–
Alam et al. [21]	100 RT-PCR confirmed COVID-19 patients with mild to moderate disease	Ivermectin (0.2 mg/kg one dose) and doxycycline (100 mg every day for 10 days) in addition to supportive treatment	–	Symptoms of all the patients improved within 72 h, no side effects were observed, intensive care admission was not required, no deaths were reported, and all of them tested negative	–	–	–
Gorial et al. [22]	87 mild to moderate COVID-19 diagnosed patients	16 patients were given ivermectin (200 mcg/kg on day of admission) in addition to hydroxychloroquine and azithromycin	71 patients were given hydroxychloroquine and azithromycin	Cure rate—100% Mean time to stay in the hospital—7.62 ± 2.75 days	Cure rate—97.2% (69 out of 71 patients) Mean time to stay in the hospital—13.22 ± 5.90 days	–	–
Rahman et al. [23]	400 mild to moderate COVID-19 patients	Ivermectin (18 mg on day 1) and doxycycline (100 mg two times a day for 5 days) *N* = 200	Hydroxychloroquine (800 mg on day 1 and after that 400 mg every day for 10 days) and azithromycin (500 mg on day 1 and after that 250 mg every day for 4 days) *N* = 200	66% viral clearance at day 5 and 83.5% at day 6. 16.5% remained PCR positive after 6th day of taking Ivermectin	77.0% viral clearance at day 11 and 81.5% at day 12 of taking hydroxychloroquine. 18.5% remained PCR positive after day 12	Anorexia (23.5%), diarrhea (12%), skin rash (10%)	Anorexia (31%), diarrhea (7%), Skin rash (1%)
Chowdhury et al. [24]	COVID-19 patients with mild to moderate illness	Ivermectin (200 mcg/kg one dose) and doxycycline (100 mg two times a day for 10 days) *N* = 60	Hydroxychloroquine (400 mg on day 1 and after that 200 mg two times a day for 9 days) and azithromycin (500 mg every day for 5 days) *N* = 56	All patients of reached negative PCR at 8.93 days (mean), symptomatic recovery, at 5.93 days (mean)	96.36% reached a negative PCR at 6.99 days (mean) and were having no symptoms at 9.33 days	Seen in 31.67% patients (comprising lethargy: 23.3%; nausea: 18.3%; and infrequent vertigo: 11.66%)	Seen in 46.43% (comprising mild blurring of vision and headache: 23.21%; enhanced lethargy and dizziness: 39.2%; infrequent palpitation: 17.85%; nausea and vomiting 16.07%)

https://www.clinicaltrials.gov/

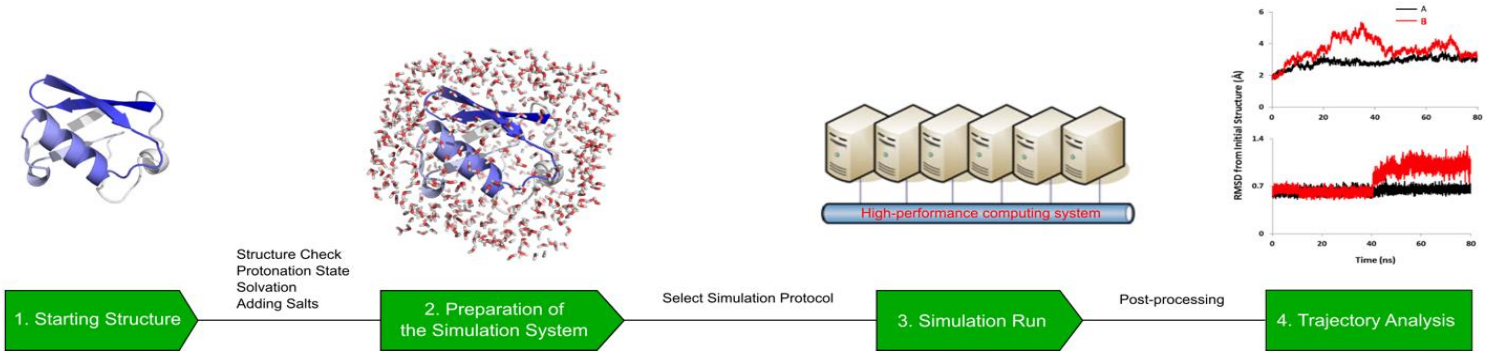
Clinical Studies - Summary

- Some beneficial results have been observed with these studies
- However
  - 12 RCTs were included in the final analysis heterogenous in nature (disease states, populations and controls)
  - most of these studies have been conducted in mild to moderate diseases therefore greater diligence and regulatory review is required for testing of ivermectin in sever conditions
  - Ivermectin targets the invertebrate's glutamate gated chloride channels, and can also cross-target mammalian GABA-gated chloride channels in the CNS
  - In normal conditions, this is prevented by the BBB BUT in individuals having hyperinflammatory states endothelial permeability at BBB may be enhanced leading to drug leakage into the CNS and neurotoxicity
  - ARVs like lopinavir/ritonavir and darunavir inhibit cytochrome P450 3A4 (main metabolic pathway for Ivermectin) if used concurrently can increase systemic exposure to ivermectin. Ritonavir inhibits P-glycoprotein efflux pump in BBB.
  - DOSING – population pharmacokinetic studies (dosed at 200 μg/kg, 60 mg, and 120 mg) after administration of single and repeat fasted dose for total and unbound plasma concentration- time profiles. Indicated that the IC50 value of ivermectin as reported by Caly et al. was much higher than the maximum plasma concentration achieved after administration of the above mentioned three doses when administered fasted. Thus the likelihood of success in a clinical trail at the approved dose of 200 μg/kg is less. A similar study indicated that the excessive dosages used in vitro is not feasible in vitro.
  - TARGET- IVM is HIGHLY protein bound (93 %) making highly unlikely that their will be adequate endothelial uptake
  - TOTAL LUNG CONCENTRATION – animal studies indicate that when 200 μg/kg were injected only 100 ng/g (around 0.1 μM) in the lung tissue of calves – thus at normal conventional dosages one would not achieve therapeutic levels.

Molecular dynamics simulations based studies

- The binding coordinates of ivermectin observed were at the prime regions crucial for the activity of particular SARSCoV proteins. The least structural deviation with the nucleocapsid protein N terminal domain (1.89 Å±0.33) and high interaction ratio points toward the suggestion that ivermectin exhibits relatively high afnity for N protein. The nucleocapsid shuttling has been proposed to be facilitated via human Importin α/β into the nuclear matrix.

- The reported binding of ivermectin to importin α/β and notably low infection in ivermectin treated patients, might also possibly suggest that there is noticeable binding with the nucleocapsid cargo itself.

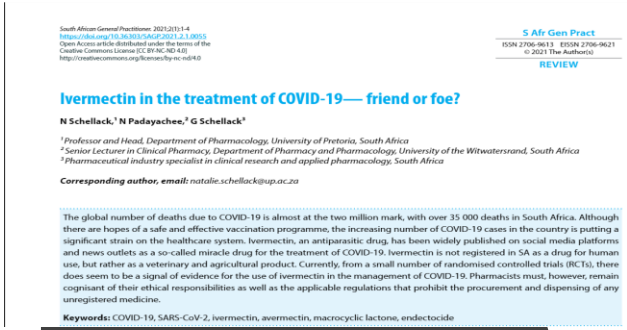


Kaur et al, Ivermectin as a potential drug for treatment of COVID-19: an in sync review with clinical and computational attributes – Pharmacological reports, 2021

What about prophylaxis?

Many studies, only two individual RCTs - included both treatment and prevention groups and has only been reported in pre-print. No detail was provided in the preprint about the baseline characteristics of the trial participants or the time from exposure to receiving ivermectin as prophylaxis.

Challenge with prophylactic dosing - Ivermectin has a plasma half-life of ≈16 to 18hrs with time-length ranging from 4 to 12days. Thus Ivermectin given 1x/month you wouldn't have effective drug in your system after 12 days. This makes a 1x/month dosing scheme pharmacologically irrelevant for the finding



South African General Practitioner. 2021;2(1):1-4
https://doi.org/10.36303/SAGP.2021.2.1.0055
Open Access article distributed under the terms of the Creative Commons License (CC BY-NC-ND 4.0)
http://creativecommons.org/licenses/by-nc-nd/4.0

S Afr Gen Pract
ISSN 2706-9613 EISSN 2706-9621
© 2021 The Author(s)
REVIEW

Ivermectin in the treatment of COVID-19— friend or foe?

N Schellack,[1] N Padayachee,[2] G Schellack[3]

[1] Professor and Head, Department of Pharmacology, University of Pretoria, South Africa
[2] Senior Lecturer in Clinical Pharmacy, Department of Pharmacy and Pharmacology, University of the Witwatersrand, South Africa
[3] Pharmaceutical industry specialist in clinical research and applied pharmacology, South Africa

Corresponding author, email: natalie.schellack@up.ac.za

The global number of deaths due to COVID-19 is almost at the two million mark, with over 35 000 deaths in South Africa. Although there are hopes of a safe and effective vaccination programme, the increasing number of COVID-19 cases in the country is putting a significant strain on the healthcare system. Ivermectin, an antiparasitic drug, has been widely published on social media platforms and news outlets as a so-called miracle drug for the treatment of COVID-19. Ivermectin is not registered in SA as a drug for human use, but rather as a veterinary and agricultural product. Currently, from a small number of randomised controlled trials (RCTs), there does seem to be a signal of evidence for the use of ivermectin in the management of COVID-19. Pharmacists must, however, remain cognisant of their ethical responsibilities as well as the applicable regulations that prohibit the procurement and dispensing of any unregistered medicine.

Keywords: COVID-19, SARS-CoV-2, ivermectin, avermectin, macrocyclic lactone, endectocide

Ivermectin is not currently registered in South Africa, but may be obtained on a named-patient basis with the approval of the local regulatory body, the South African Health Products Regulatory Authority (SAHPRA).[15] Ivermectin has been described as a so-called wonder drug and excitement around repurposing this

In South Africa..

The evidence for the use of ivermectin in COVID-19 has been reviewed by the South African National Department of Health (SA-NDoH), SAHPRA, and the MAC on COVID-19, and the following conclusions were made:[23,26,27]

Until more robust evidence is available, the routine use of ivermectin for either the prevention or treatment of COVID-19 is not justified.

Nonetheless, emerging evidence must be actively sought and carefully reviewed. Reports of clinical trials of ivermectin for the prevention or treatment of COVID-19 must be closely watched, as they become available. As always, reports in peer-reviewed publications will be preferred.

Concluding statements

- Despite nearly 30 years of use in veterinary and human medicine there is much to learn about IVM
- The clinical efficacy and utility of IVM in SARS CoV-2 infected patients are unpredictable at the moment as this is a completely novel virus
- The possible signal of efficacy found with IVM warrants robust larger trials of IVM in SARS CoV-2
- There should be better and more effective communication with the public

Thank You