GAS Journal of Clinical Medicine and Medical Research (GASJCMMR)

OPEN ACCESS

Volume 2, Issue 1, 2025 Journal Homepage: https://gaspublishers.com/gasjcmmr/ ISSN: 3049-1568
Email: gaspublishers@gmail.com

Antimalarial Drugs Artesunate, Artemether and Artemisin-Based Combination Therapies (ACTS) Have Promising Anti-Sars-Cov-2 (Covid-19) Effects. A Mini Review

Pradhan B[1], Barik H.[2]

[1,2,] GAS Journal of Clinical Medicine & Medical Research

Received: 01.01.2025 | **Accepted:** 05.01.2025 | **Published:** 06.01.2025

***Corresponding Author:** Pradhan B[1], Barik H.[2]

DOI: 10.5281/zenodo.14910098

Abstract **Original Research Article**

There is accumulating emerging evidences on the extended therapeutic potential of antimalarial drugs, particularly artemisinin derivatives have anti-SARS-CoV-2(COVID-19) effects. The artemisinin derivative Artesunate and Artemether have most promising agents exhibiting improved pharmacokinetic properties and have pleotropic effects. Artemisinin-based combination therapy (ACT) at recommended doses clinically used in malaria, showed in-vitro inhibition of SARS-CoV-2 replication and ACTs containing Artemether/Artesunate in combination with Lumefantrine/Mefloquine/Amodiaquine would be attractive candidates for treatment of COVID-19 considering their excellent safety profiles in humans and available at a relatively low cost.

Keywords: SARS-CoV-2, COVID-19, ACT, Artesunate, Artemether, Lumefantrine, Amodiaquine

INTRODUCTION:

To date, there is no safe effective therapy for treatment of the COVID-19 (SARS-CoV-2) and treatment remains largely supportive, resulting increased mortality and morbidity across the planet. FDA approved drugs already licensed for other diseases can be used to treat COVID-19 infection to avoid costly clinical trials, and to discover new drugs and obtaining regulatory approval take years. Such FDA approved drugs reduce concerns regarding adverse effects in patients as they have gone through rigorous safety and risk testing for human use. Such drugs even only partially effective, the total viral load in the host cells would reduce and prevent the critical threshold of becoming severe illness, could be applied as "off-label" to decrease the progression of disease hence morbidity and mortality and spreading of disease. Accumulating evidences on the extended therapeutic potential of artemisinin derivatives are emerging. The artemisinin derivative Artesunate and artemether have anti-SARS-CoV-2 effects in-vitro and exhibit improved pharmacokinetic properties with excellent safety profiles in humans, also have favorable pleotropic effects. The widely available low cost ACTs containing Artemether/Artesunate in combination with Lumefantrine/Lumefantrine/Amodiaquine showed significant in-vitro inhibition of SARS-CoV-2 replication can be use for treatment of COVID-19.[1]

IN-VITRO ACTIVITY OF ANTI-MALARIAL DRUGS AND ACTs AGAINST SARS-CoV-2:

(i) **Lumefantrine in-vitro activity against SARS-CoV-2 in Vero E6 cells study**: the EC_{50} was 23.17±3.22µM (12.26µg/ml) and CC_{50} was >100µM and SI of 4.40±0.61. Lumefantrine has low hepatic clearance and negligible renal excretion leads to prolonged half-life of 6 days or > 119 hours in healthy volunteers, thus has cumulative plasma and lung concentration after multiple

administration of ACT combination Artemether 80mg + Lumefantrine 480mg, (twice daily x3 days) and can achieve the EC_{50} in both plasma and the lungs tissue could exceeds Lumefantrine EC_{50} of 23.17µM. Lumefantrine with an EC_{50} of 23.17±3.22µM is not prominent; however, Lumefantrine showed therapeutic promise due to high plasma and lung concentrations after multiple dosing causes drug accumulation. To cure malaria Lumefantrine concentration of 175-280ng/ml should be kept for 7 days to minimize risk of malaria re-infection and Lumefantrine concentration on day 7 ranges from 170ng/ml to 500ng/ml.[2] Lumefantrine concentration ≥ 200ng/ml associate with >98% cure rate in parasitemia of <135000/µL. For higher density of parasitemia the 7th day drug concentration should be > 256ng/ml. Concentration of Lumefantrine is decreased in young children, pregnancy, smoker, unsupervised intake, with Etonavir & Rifampicin intake. Lumefantrine recommended doses for malaria are: 90mg/kg (48-114mg) for Infants, 65mg/kg (30-111mg) for child with >1-4 years age, 72mg/kg (48-110mg) for 5-11 years age and 58mg/kg (19-108mg) for >12 years age.[3]

(ii) **Artemether in-vitro activity against SARS-CoV-2 in Vero E6 cells study**: The EC_{50} was 73.80±26.91µM and CC_{50} was >200µM and SI of 3.13±1.4.The Cmax of Artemether was found to be low (0.28 µM); however, the partner Lumefantrine Cmax is much higher.

(iii) **Artesunate and DHA in-vitro activity against SARS-CoV-2 in Vero E6 cells study :** showed EC_{50} values of 12.98±5.30 µM and 13.31±1.24µM respectively, which could be clinically achievable in plasma after intravenous bolus administration of Artesunate.[4]

(iv) **Artemether 80mg + Lumefantrine 480mg** in antimalarial doses leads to Cmax of DHA and Lumefantrine around 126ng/ml and 6.98µg/ml (1µM&33µM) respectively and inhibit SARS-CoV-2 by 27.1%. Lumefantrine EC_{50} was 24.7 ± 3.6, CC_{90} = 59.8 ± 26.8 and CC_{50} = 87.7 ± 11.9 & SI of 4. A single oral dose of Lumefantrine (480 mg) led to Cmax of 1.1 µM.The EC_{50} of DHA was 20.1 ± 4.5, EC_{90}=41.9 ± 18.0, CC_{50}=58.9 ± 7.4 and SI of 3.

(v) **Mefloquine: -** Mefloquine showed anti-SARS-CoV-2 activity with EC_{50} of 1.8 µM and EC_{90} of 8.1µM, CC_{50}=14.4±2.1 and SI of 8. Antimalarial drugs concentrated 10 to 160 folds more in lungs than in blood and Mefloquine concentrated >10 folds in the lungs than plasma, thus 100% inhibition of SARS-CoV-2 could occur in the lungs Mefloquine administered at anti-malaria dose of 1250 mg led to a blood concentration of 1648ng/ml (around 4 µM) in healthy males.

(vi) **Mefloquine +Artesunate** at 550mg+250mg (equivalent blood concentration 8.3 and 5µM) lead to 72.1±18.3% inhibition of SARS-CoV-2 in-vitro. Lumefantrine, Piperaquine and DHA showed anti-SARS-CoV-2 activity with EC_{50} of 24.7, 33.4 and 20.1µM respectively. However, ACTs (Artemether + Lumefantrine, Artesunate + Amodiaquine, DHA+ Piperaquine, and Artesunate + Pyronaridine, evaluated plasma concentrations at recommended doses used in uncomplicated malaria treatment, showed in-vitro inhibition of SARS-CoV-2 replication by 30%.[5] A fixed-dose of Artemether+Lumefantrine (80mg+280mg, in the ratio of 1:6) led to plasma Cmax of DHA and Lumefantrine around 126ng/ml and 6.98mg/ml (in experiment estimated at 1 and 33 µM).[6] The terminal half-life of Artemether + DHA was < 1h and < 0.1h respectively and Lumefantrine terminal half-life had 3-5 days in malaria patients. The plasma AUC of Lumefantrine on the 7th day could be >280-500ng/ml. Lumefantrine oral absorption is increased by 16 folds and Artemether by 2 folds with high fat meals. Viral nucleoproteins of SARS-C0V-2 is completely inhibited by Artesunate, DHA and Lumefantrine at 25µM, 25µM and 100µM respectively in-vitro and all acts at post-entry stages. **Artesunate** following single IV dose of 120mg (312.5µmol/L)

produce Cmax of 42µM which is greater than EC_{50} of Artesunate 13.31±1.24µM against SARS-CoV-2. Artesunate could inhibit SARS-CoV-2 in a dose dependent manner. As the Cmax of IV bolus Artesunate is 20 fold higher than IM route used in the same dose, IV bolus Artesunate is preferable .[7] Artesunate having antiviral properties with multiple pleotropic effects is a perfect potential agent for the treatment of symptomatic COVID-19 infection and its related hyper inflammation states.[8] Empirical IV bolus (within 2-10 minute) Artesunate 4mg/kg administered twice daily for five days among rapid antigen test(RAT) and RT-PCR negative hospitalized moderate to severe clinically proven COVID-19 patients was safe and effectively decreasing morbidity and mortality without any adverse effect.[9]

(vii) **Pyronaridine:-** EC_{50} was 0.72 ± 0.6, EC_{90}= 0.75±0.4, CC_{50}=15.9±1.6, and SI of 22.[5] Pyronaridine inhibit SARS-CoV-2 replication with a half maximal inhibitory concentration (IC_{50}) of 1.084µM and a half maximum cytotoxic concentration (CC_{50}) was 37.09µM and SI of 34.22 at 24 hr post infection (hpi) in Vero E6 cell. The corresponding value for Artesunate IC_{50} was 51.06µM and CC_{50} of >100µM & SI of 1.885.**In Calu-3 cells study:**-(human airway epithelial cell origin representing susceptible cells in COVID-19 infection), Artesunate IC_{50} against SARS-CoV-2 was 1.76 µM at 24 hr (hpi) & CC_{50} was > 100µM and SI of >57.82 and Pyronaridin**e** at 24 hr IC_{50} was 6.413µM, CC_{50} was 43.08µM & SI of 6.718 and at 48hr hpi IC_{50} was 8.577µM & CC_{50} was >100µM & SI of >11.66. Both Artesunate and pyronaridine reduce viral replication in a concentration dependent manner and function at post entry stages. Antiviral effect occurs by Artesunate and its metabolite DHA contribute equally. Pyronaridine + Artesunate are currently under a phase-II trial in R Korea for COVID-19 treatment.[10]

In vitro Antiviral Effects of Selected Anti-malarial drugs against SARS-Cov-2:- S Krishna et.al. Reported that Artesunate IC_{50} in Vero E6 cell was 53 µM and **in Calu-3 cell** it was 1.8 µM. Lumefantrine IC_{50} in Vero E6 cell was 33 µM and Mefloquine had between 1-2.5 µM and 2.0-1.3 respectively. Hydroxychloroquine (HCQ) IC_{50} in Vero cell was 1.1 µM, but in Calu-3 Cell it was 103 µM and it was ineffective in human clinical trials. Pyronaridine IC_{50} **in Vero cell** it was > 0.5-1.0 µM and Piperaquine + DHA had between 4.0- 5.0 and 2.0-2.5 µM.[11] Artesunate EC_{50} in-vitro Vero cell had between 7µg/ml and 12µg/ml and was highest potency among all artemisinin derivatives against SARS-CoV-2 and complete inhibition was observed at concentration of 15µg/ml. Artemether has no significant effect at concentration up to 179µg/ml and CC_{50} was 1220µg/ml and SI of <7. **In human hepatoma cell (Huh7.5**) Artesunate EC_{50} was 11µg/ml and close complete viral inhibition occurred at 22µg/ml & CC_{50} was 93µg/ml and SI of 8. Artemether EC_{50} was 135µg/ml and close complete inhibition of virus occurs at 179µg/ml and SI was 2 and CC_{50} was 303µg/ml. Following Artemether administration Cmax value were between 311-776ng/ml which is close to 3 orders of magnitude below EC_{50} value for SARS-CoV-2. Artesunate EC_{50} was 13µM vs 18µM in this study. The EC_{50} of Artemether was 8 fold higher and >8 fold higher in Vero cell than Cao et al[4] study. Artesunate had higher potency against the virus tested in Vero E6 cell and Huh1 cell. Artesunate only showed EC_{50} value in the range of clinically achievable plasma and tissue concentration when used in the dose of 2-4 mg/kg body weight by IV bolus and reported peak plasma concentrations (Cmax) were between 19.4 & 29.7µg/ml in patients and Cmax/EC_{50} value were between 2.5 & 4.2 in animal study. Artesunate tissue concentrations were several folds higher than plasma concentration.[1] Artemether efficacy estimated at EC_{50} of 1.23 µM (Nair MS et al) [13] and was cytotoxic at concentrations slightly above that level, while Cao ET al.[4] reported an IC_{50} of 73.8 µM but with less toxicity. Hot water extract of Artemisia Annua IC_{50} was <12 µM (Artemisinin 12.3-18.5 µM=1.7-2.6 µg/ml), Amodiaquine IC_{50} was 5.8 µM and Lumefantrine had IC_{50} of >70 µM in this study versus in Cao R et al,[4] it was 23.2 µM. Artesunate & DHA EC_{50} was more than 100µM and for Artesunate

it was 53µM in Vero Cell & a CC_{50} of higher than 100 µM (> 100 µM) and an SI of > 1.885.The inhibitory effects of Artesunate in Calu-3 cell IC_{50} was 1.76 µM (1.8µM), CC_{50}>100 µM, and SI > 56.82 (Bae JY et al)[10], were notably better than those of in Vero cells and Artesunate EC_{50} was 18.2µM in study of MS Nair et al.[13] A recent report showed that artemisinin-related compounds have some anti-SARS-CoV-2 activity, with DHA, Artesunate, and Arteannuin B having IC_{50} values <30 µM (Cao et al., 2020),[4] and DHA having IC_{50} values of 1–10 µM (Bae et al., 2020).[10] Artesunate have IC_{50} values against SARS-CoV-2 of 7–12µg/ml (0.7–1.2 µM by Gilmore et al [12] and 2.6 µM (Bae et al.[10] There were also anti-SARS-CoV-2 activity of other non-artemisinin antimalarial drugs including Lumefantrine reported IC_{50} was 23.2µM.[7] Artesunate proved to be most potent against SARS-CoV-2 with ranges of different EC_{50} in different physiologically relevant cell culture models, such as Vero E6, human hepatoma Huh7.5 cell and human lung carcinoma cell line A549-hACE2. Artesunate EC_{50} of 7-12 µg/ml and Artemether EC_{50} of 53-98µg/ml, Artemisinin annua extract EC_{50} of (83-260µg/ml, and Artemisinin of 151 to 208µg/ml, the SI were mostly below 10(ranges 2-54) suggesting small therapeutic window. The typically used doses of Artesunate 2 to 2.4 mg/kg IV bolus administration reported peak plasma concentrations (Cmax) were between 19.4 and 29.7µg/ml in patients, thus Cmax of Artesunate exceeding EC_{50} can be achievable clinically. In animal studies following administration of a single dose of Artesunate, tissue concentrations including lung, kidney, intestine, and spleen concentrations were several-fold higher than plasma concentrations. In contrast, following administration of artemether, Cmax values were between 6 and 190ng/ml which is two to several orders of magnitude below determined EC50 values. Artesunate targeted SARS-CoV-2 at post-entry level. Clinical studies are required to further evaluate the utility of these compounds as anti-COVID-19 treatment.[13] Amodiaquine and Mefloquine, are two quinoline ACT partners, are active in-vitro at micromolar concentrations against SARS-CoV-1 and SARS-CoV-2 at EC_{50} of 2.5 and µM 10 µM, respectively. About 0.07% of the administered oral dose (8.6 mg/ kg) of Amodiaquine was found in rat lung.[14] A fixed-dose of Artesunate-Amodiaquine (200mg/540mg) led to plasma Cmax of DHA and desethylamodiaquine around 802 and 879ng/ml (experimental fixed-dose estimated at 5 and 4 µM).[15] A fixed-dose of Artesunate-Mefloquine(250 mg/550 mg) led to plasma Cmax of DHA and Mefloquine around 698ng/ml and 1392ng/ml (experimental fixed-dose estimated at 5 and 8.3 µM).[16] Artesunate showed the highest potency against SARS-CoV-2 among the pure compounds tested in VeroE6, Huh7.5, and A549-hACE2 cells, with EC_{50} of 13-18µM followed by artemether and Artemisinin. SI of the tested compounds were relatively low (mostly < 10), suggesting a relatively small therapeutic window. Artesunate in doses of 2 to 2.4 mg/kg bolus intravenous administration reported peak plasma concentrations (Cmax) were between 19.4 and 29.7µg/ml in patients. Following administration of artemether, Cmax values between 311-776ng/ml were reported, which are three to several orders of magnitude below determined EC_{50} values of 53-98µg/ml.[1] The Cmax of Artesunate following single 120mg IV bolus injection produces a Cmax of 42µM which is greater than EC_{50} of 13.31±1.24µM of DHA. After 120mg IV Artesunate Cmax of was 11343ng/ml and for DHA it was 2646ng/ml.[17]

Table. In-vitro anti-SARS-COV-2 potential of antimalarial drugs and ACT:

Authors/ Investigators	**Antimalarial drugs**	**50% effective concentrations = EC_{50} (µM)**	**Median cytotoxic concentration = CC_{50} (µM)**	**CC_{90} (µM)**	**CC_{50}/EC_{50} = SI (selectivity index)**	**Culture Cell types**	**SARS-CoV-2 Inhibition %**
Y Zhou et al. Ref.1	Lumefantrine	>70				Vero E6	

	Artesunate	7–12µg/ml (18µM)	41-93µg/ml		< 8	Vero E6,	
		11µg/ml	93µg/ml		8	Huh7.5	100% at 22µg/ml
		12				A549-hACE2	
	Artemether	53–98µg/ml	127-360µg/ml		< 8	VeroE6	100% at ≥ 153µg/ml
		53				A549-hACE2	
		64				Huh7.5	
	Mefloquine	10				Vero E6	
	Amodiaquine	2.5-5.8				Vero E6	
R Cao, et al. Ref.2	Lumefantrine	23.17±3.22	>100		4.40±0.61	VeroE6	
	Artemether	73.80±26.91	>200		3.31±1.4	VeroE6	
	Artesunate	12.98±5.30				VeroE6	
	DHA(Dihydroartemisinin)	13.31±1.2				Vero E6	
M Gandrot, et al. Ref.5	Lumefantrine	24.7±3.6	87.7±11.9	59.8 ± 26.8	4	Vero E6	27.1-30%
	DHA	20.1±4.5	58.9±7.4	41.9±18	3		
	Mefloquine	1.8±1.0	14.4±2.1	8.1±3.7	8		
	Pyronaridine	0.72±0.6	15.9±1.6	0.75±0.4			
	Piperaquine	33.4					
	Mefloquine + Artesunate						72.1±18.3%
Bae JY, et al Ref.8	Artesunate	51.06	>100		1.885	Vero E6	
		1.76	>100		>56.82	Calu-3	
	DHA	1-10					
	Pyronaridine	1.084	37.09		34.22	Vero E6	
		6.413	43.8		6.718	Calu-3	
S Krishna et al Ref.9	Hydroxychloroquine (HCQ)	1.1				Vero E6	
		103				Calu-3	

	Artesunate	53				Vero E6	
		1.3				Calu-3	
	Lumefantrine	33				Vero E6	
	Mefloquine	1-2.5 & 2.0-1.3				Vero E6	
Gilmore et al Ref.10	Artesunate	0.7-1.2µM (7-12µg/ml)				Vero E6	100% at 15µg/ml
		11 µg/ml	93 µg/ml		8	Huh7.5	100% at 22µg/ml
	Artemether		1220 µg/ml		<7	Huh7.5	179µg/ml, No effect
		135 µg/ml	303 µg/ml		2	Huh1-5	100% at 179µg/ml
	Artesunate	18 µg/ml	93µg/ml		8	Huh7.5	100% at 22µg/ml
MS Nair et al Ref.11	Artesunate	18.2µM				Vero E6	
	DHA	1-10				Vero E6	
	Artemether	1.23				Vero E6	

N.B: *Artesunate and DHA, the FDA approved malaria drug, showed the highest potency against SARS-CoV-2 among the artemisinin derivatives tested in VeroE6, Huh7.5, and A549-hACE2 with* EC_{50} *of 13-18µM followed by artemether.* ***Vero E6 cells*** *(kidney epithelial cells from African green monkey),* ***Calu-3 cell*** *(human airway epithelial cell origin representing susceptible cells),* ***Huh7.5*** *(Human hepatoma cell),*

PLEOTROPIC EFFECTS OF ARTEMISININ DERIVATIVES:

Artemisinin derivatives show a wide range of pleotropic effects, such as antioxidant, anti-inflammatory, antimicrobial, antitumor, immunomodulatory, and neuroprotective effects. Artemether is also characterized by potent anticancer, anti-allergic, anti-inflammatory, antiviral, and anti-parasitic activities and decrease oxidative stress. Artemether exhibits potent anti-inflammatory and antioxidant activities. Artemether has neuroprotection effects towards Aβ-induced neurotoxicity and AMPK/GSK3β phosphorylation activity and increased expression of the activated Nrf2 signaling pathway in Alzheimer's disease (AD). By induction of phosphorylation of the AMPK/GSK3β pathway which activated Nrf2, increasing the level of antioxidant protein HO-1. These activities probably produced the antioxidant and anti-inflammatory effects. The neuroprotective effect was expressed by a significant reduction of the intracellular ROS levels, reduction of caspase-3 activities, and correction of the mitochondrial membrane potential. Artemether treatment reduced the production of ROS, corrected mitochondrial membrane potential, and conferred neuroprotection by inhibiting aponecrosis of the neurons.[18] Artemisinin and its derivatives exert potent immunosuppressive effect. In-vivo, administration of Artemether attenuated CD4 T-cell-mediated DTH reaction, and suppressed antigen-specific T-cell response in immunized mice. In primary T cells, Artemether profoundly inhibited anti-CD3-induced phosphorylation of Raf1 and activation of Ras. The immunosuppressive effect of Artemether was directly on T cells both in-vitro and in-vivo. Artemether exhibit more potent anti-proliferation activity dose-dependently than its parent compound artemisinin. Dihydroartemisinin (DHA) a metabolite

of Artemether is a semi-synthetic derivative blocked Ikβ degradation and inhibited the nuclear factor kappa-β (NF-kβ). Immunosuppressive effect of artemisinin and its derivatives suggested as potential new and effective treatment of T-cell-mediated autoimmune diseases.[19] Acute lung injury (ALI) is characterized by extreme inflammation, the release of pro-inflammatory cytokines, excessive neutrophil infiltration and lung endothelial/epithelial cell injury, resulting in edema and gas exchange deterioration. Macrophages, the principal immune cells in the lungs, produce inflammatory molecules and carry out vital functions in the molecular mechanisms of ALI, such as boosting neutrophil infiltration and triggering inflammatory reactions. Neutrophils trigger the release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6. Oxidants, which are associated with the activation of nuclear factor kappa-β (NF-κβ), enhancer of activated B cells eventually contributing to ALI. Oxidative stress is increased in lipopolysaccharide (LPS) -induced ALI. The transcription factor, nuclear factor-erythroid 2 related factor 2 (Nrf2), plays a critical role in protection against ALI by inducing the expression of antioxidant and detoxifying enzymes and proteins. Nrf2 attenuates ALI and inflammation by suppressing Toll-like receptor (TLR) 4 and Akt signaling. Dihydroartemisinin (DHA), is the major active metabolite of Artemisinins and Artesunate is more stable and ten times more effective than Artesunate. DHA exerts anticancer, anti-organizational fibrosis and anti-neuronal cell death effects. DHA attenuated LPS-induced pulmonary pathological damage, suppresses the LPS-induced infiltration of inflammatory cells, the elevation of myeloperoxidase activity, oxidative stress and the production of pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α(TNF-α) and interleukin-6(IL-6). Furthermore, DHA reduced the LPS-induced inflammatory response by suppressing the degradation of I-κB and the nuclear translocation of nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB)/p65 in-vivo and in-vitro. DHA activated the nuclear factor-erythroid related factors-2 (Nrf2) pathway, which was suppressed by LPS. DHA exerts therapeutic effects against LPS-induced ALI by inhibiting the Nrf2-mediated NF-κB activation in macrophages. These studies demonstrate that Artesunate and its metabolite DHA exhibits anti-inflammatory activities and may be a therapeutic candidate for the treatment of ALI caused by COVID-19.[20, 21]

CONCLUSION:

There is no safe effective therapy for COVID-19 infection available till date. The commonly used selected FDA approved antimalarial drugs have in-vitro anti-SARS-CoV-2 effects. The Artemisinin-based Combination Therapy (ACT) commonly available cheaper drugs also have anti-SARS-CoV-2 activities. ACTs, such as Artemether+Lumefantrine, Artesunate+Mefloquine, Artesunate+Amodiaquine, at recommended doses clinically used in malaria are appear to be effective in COVID-19 infection can be used in mild to moderately severe cases to decrease the progression of disease severity, hence decrease the morbidity and mortality and spread of infection. Empirical high dose IV bolus Artesunate $\geq$ 4mg/kg (administrated in 2-10 minute) twice daily for five days among hospitalized moderate to severe clinically proven COVID-19 patients appears be safe and very effective therapy in severe to very severe COVID-19 infection. In addition artemisinin derivatives have many pleotropic effects such as anti-inflammatory, immunosuppressive, immunomodulatory, anticytokine, antioxidant, and organs protective effects etc.,if administered at an early stage of disease can prevent progression of disease and its complications. In our personal experience(unreported), treatment of hundreds of clinically proven mild to moderate severe COVID-19 cases with Artemther+Lumefantrine in malarial doses appears to be very effective and safe.Howevere, to determine the effectiveness and recommendation of selected ACTs for COVID-19 infection requires large randomized double blind placebo controlled, clinical trials among mild to moderately severe COVID-19 infection.

Conflict of interest: Nil.

REFERENCES

1. Yuyong Zhou, Kerry Gilmore, Santsecharay Ramirez,Eva Settels,Kerla A,Gammeltofe,Long V,Ulrik Fahnee,Shan Feng, Anna Offersgaard,Jakob Trimpert,Jens Bukh,Klaus Osterricder,Judith M Gottwein, Pater H Seeberder. In vitro efficacy of artemisinin-based treatment against SARS-CoV-2.Science Reports/(2021)11:14571/https://doi.org/10.1038/s41598-021-93361-y. Natureportfolio.www.nature.com.
2. Myaing M Nyunt, Vy K Nguyen,Richard Kajubi. Artesunate, Lumefantrine pharmacokinetics and clinical response are minimally altered in pregnant Ugandan women treated for uncomplicated pf. Malaria. Antimicrobial Agent and Chemotherapy.March 2016,V-60,No.3.1274-1282.
3. Worldwide Anti-malarial resistance network (www ARN) Lumefantrine PK/PD study group-BMC medicine (2015)13.227.doi.10.1186/s 12916-015-0456-7.
4. R Cao, H Hu, Y Li, X Wang, M Xu, J Liu, H Zhang, Y Yan, L Zhao, W Li, T Zhang, D Xiao, X Guo, Y Li, J Yang, Z Hu, M Wang,Wu Zhong. Anti-SARS-CoV-2 Potential of Artemisinins In Vitro. https:// dx. doi.org/ 10.1021/acsinfecdis.0c00522. PMID-32786284. ACS Infect. Dis.
5. Gandro Mathieu ,Isabelle Duflot,M Boxberger Delandre,P Jardot et al.Anti-malarial Artemisinin-based combination therapy(ACT) and COVID-19 in Africa: In-vitro inhibition of SARS-CoV-2 replication by Mefloquine Artesunate .Inf J Dis.99(2020):437-440.
6. Ali S, Najmi MH, Tarning J, et al. Pharmacokinetics of artemether and dihydroartemisinin in healthy Pakistani male volunteers treated with artemether-Lumefantrine. Malar J 2010; 9:275. Ashley EA, Stepniewska K, Lindegardh N, et al. Pharmacokinetic study of artemether-lumefantrine given once daily for the treatment of uncomplicated multidrug-resistant falciparum malaria. Trop Med Int Health 2007; 12:201–8, doi: http://dx.doi.org/10.1111/j.1365-3156.2006.01785.x.
7. Kenneth F Ilett,Kevin T Belly,Shane M Powel,Tren Quang Binh,Le Thi Anhthe et al.The pharmacokinenetic properties of IM and Rectal DHA in Uncomplicated plasmodium falciparum malaria.Br J Cli Phrmacol.2002 Jan :53(1):23-30.Doi.10.1046/j.O306-5251-2001.o1519.x.PMID-11849191.
8. Dr (Prof.) Butungeshwar Pradhan et al. Artesunate: an Artemisinin Derivative having Antiviral Properties with Multiple Pleotropic Effects is a Perfect Potential Agent for the Treatment of Symptomatic COVID-19 Infection and Related Hyper inflammation States. JMSCR Volume 08 Issue 10 October 2020.p-215-224.
9. Pradhan B et al. Efficacy Outcomes on morbidity and mortality of Intravenous Bolus Artesunate Therapy among Rapid Antigen Test and RT-PCR Negative Hospitalized Moderate to Severe Clinically Proven COVID-19 Patients: A Breakthrough large case series JMSCR Volume 09 Issue 08 August 2021.p-121-136.
10. Bae Joon-Yong, Gee Eun Lee,Heedo Park, Juyoung Cho,Yung-Eui Kim, Joo-Yeen Lee, et al. Pyronidine and artesunate potential antiviral drugs against COVID-19 and Influenza .bioRxiv Preprint doi.https://doi.org/10.1101/2020-07.28.225102.
11. S Krishna,Y Augustin,J Wang, C Xu, Henry M Staines,H Platteeuw et al. Repurposing Antimalarials to tackle the COVID-19 pandemic. Trends in Parasitology, Jan 2021, vol.37.No.1,p-9-11.
12. Gilmore Kerry, Yuyang Zhou,Sante Seharay Ramirez Long V Pham, Utric Fabnoe et al. Artemisinin-based treatment against SARS-CoV-2.bioRxiv preprint doi.https:// doi.org/ 10.1101/2020.10-05.326637.oct 5,2020,acc-by NO40 International license.
13. MS Nair, Y.Huang, D.A. Fidock, S.J. Polyak, J. Wagoner, M.J. Towler, P. J. Weathers. Artemisia annua L. extracts inhibit the in vitro replication of SARS-

CoV-2 and two of its variants.Journal of Ethnopharmacology, 274 (2021) 114016. www.elsevier.com/locate/jethpharm.
14. Fan HH, Wang LQ, Liu WL, et al. repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus (2019-nCoV) related coronavirus model. Chin Med J 2020 ;(133):1051–6, doi:http://dx.doi.org/10.1097/CM9.0000000000000797.
15. Winstanley PA, Edwards G, Curtis CG, et al. Tissue distribution and excretion of amodiaquine in the rat. J Pharm Pharmacol 1988; 40:343–9.
16. Navaratnam V, Ramanathan S, Wahab MSA, et al. Tolerability and phramacokinetics of non-fixed and fixed combinations of artesunate and amodiaquine in Malaysian healthy normal volunteers. Eur J Clin Pharmacol 2009;65:809–21, doi:http://dx.doi.org/10.1007/s00228-009-0656-1.
17. Qisui LI,Lowis R Catilena ,Kevin J Leary,George A,Saviolakis R,Scott Miller ,Victor Melendez,,Peter J Weina. Pharmacokinetic profiles of Artesunate after single intraveinous dose at 0.5.,1,2,4 and 8mg/kg in healthy volunteers; A phase I study.Am J Trop Med Hyg.81(4);2009;pp-615-621.doi.10.4269/ajtmh.2009.09.0150.
18. J-X Wang, W Tang, L-P Shi, J Wan, R Zhou, J Ni, Y-F Fu, Y-F Yang, Y Li, J-P Zuo. Investigation of the immunosuppressive activity of artemether on T-cell activation and proliferation. British Journal of Pharmacology (2007) 150, 652–661. doi:10.1038/sj.bjp.0707137; published online 29 January 2007.
19. Valea I, Tinto H, Traore/Coulibaly M, et al. Pharmacokinetics of co-formulated mefloquine and artesunate in pregnant and non-pregnant women with uncomplicated Plasmodium falciparum infection in Burkina Faso. J Antimicrob Chemother 2014;69:2499–507, doi:http://dx.doi.org/10. 1093/jac/dku154.
20. Shuai Li, Xia Zhao, Philip Lazarovici, Wenhua Zheng. Artemether Activation of AMPK/GSK3β (ser9)/Nrf2 Signaling Confers Neuroprotection towards β-Amyloid-Induced Neurotoxicity in 3xTg Alzheimer's Mouse Model. Hindawi Oxidative Medicine and Cellular Longevity. Volume 2019, Article ID 1862437. https://doi.org/10.1155/2019/1862437.
21. Xiao Ting Huang, Wei Liu, Yong Zhou, C Xia Hao, Yan Zhou, Chen Yu Zhang, Chen Chen Sun, Z Qiang Luo and S Yuan Tang. Dihydroartemisinin attenuates lipopolysaccharide-induced acute lung injury in mice by suppressing NF-κB signaling in an Nrf2-dependent manner. International JournaL of Molecular Medicine 44: 2213-2222, 2019. DOI: 10.3892/ijmm.2019.4387.