

HEALTH tone

RHEA
Pharmaceutical Sciences



Our Credentials



Rhea Pharmaceutical Sciences is a Singapore-based biopharmaceutical company with combined experiences in natural supplements and chemical molecule design, synthesis, microbiology and virology research.

Our company's product portfolio is mainly focused on the anti-infective market. Our group's research has been focused on successfully developing different supplements and molecules for viral, bacterial and fungal infections.



Introducing HealthTone

A Natural Food Supplement with Antiviral, Antibacterial and Immunomodulatory Properties

- Throughout years of research, we have successfully developed essential oil based compositions which show beneficial properties and efficacy against bacteria and viruses. In addition, the compounds also shows immunomodulatory properties and are proven non-toxic since they are derived from all-natural materials.
- The beneficial properties of the compounds is tested for human use. The results of the studies describing the beneficial properties are summarized in the table:

Summary of beneficial properties for Human Use		
Beneficial Properties	Test Methodology	Results
Antifungal	MIC / Inhibition zone	Effective
Antibacterial	MIC / Inhibition zone	Effective
Anti-inflammatory	In Vitro	Suppressing IL-1 β , TNF α , IL6, IL10
Immunomodulatory	In Vitro	Modulating IL-2
Non-specific antiviral	In Vitro	Activating IFN- γ
Antitumorigenic	In Vivo (Rat Model)	Significant (-) in tumor size
Anticarcinogenic	In Vivo (Rat Model)	Significant (-) in tumor size
Antioxidant	In Vitro	Potent Antioxidant



Antiviral
Antioxidant
Immunity Booster

100%
Natural

Repairs and protects cells
from oxidative stress
and free radicals

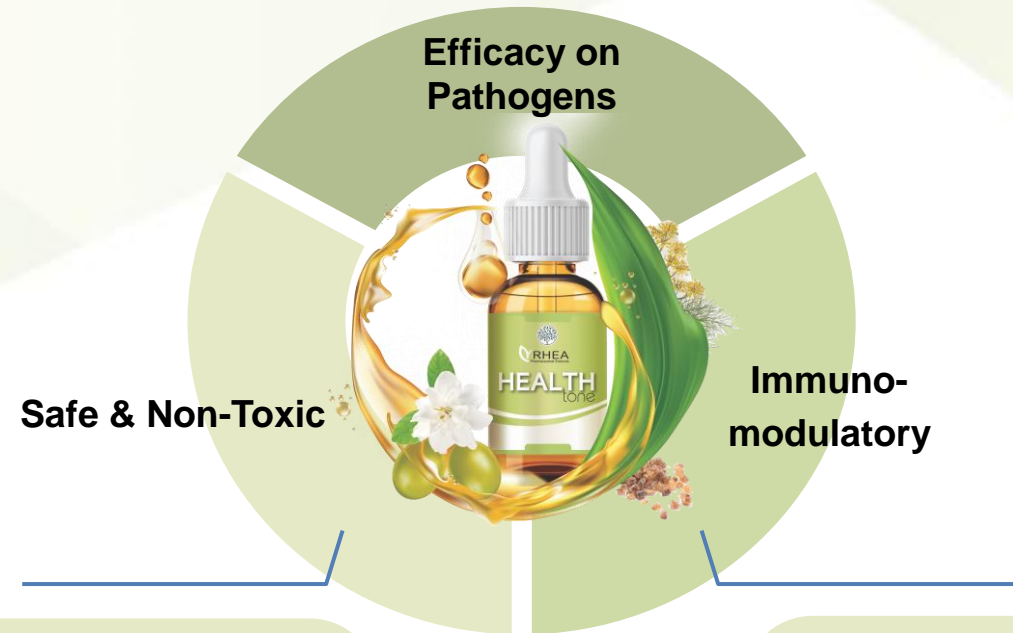
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We believe our supplement is the early viable solution for the fight against COVID-19 in the following ways :



Could be made available to the general public in a relatively short-amount of time (compared to new antiviral therapies)

- It enhances healthy people's immune system
- It assists natural recovery of infected and sick patients through improving immune functions



Immunity
Booster

100% Natural



Antiviral

Antioxidant

HealthTone consists of:

- Gardenia Jasminoides
- Commiphora myrrha
- Boswellia serrate
- Foeniculum vulgare
- Daucus carota



HEALTH tone

Immunity
Booster



Antiviral

Antioxidant

100% Natural



Detailed Product Description & Usage Recommendation



Registration and Recognition by legal Bodies

REGISTRATION CERTIFICATE under EURASIA ECONOMIC UNION

Certificate no. : AM.01.48.01.003.E.000024.03.19
Certified as of : March 12th, 2019
Union Members : Armenia, Belarus, Kazakhstan, Kyrgyztan, Russia

Recognition from Ministry of Health – ARMENIA

Highlighted excerpt from the letter :

“Taking into account the discussion and conclusion of the meeting conducted by the specialized consultants, leading scientists, and key opinion leaders from the Ministry of Health, Health Tone (produced by RHEA Pharmaceutical) can be considered an adjuvant therapy for patients infected by SARS-CoV-2 (COVID-19)”.

STATE REGISTRATION CERTIFICATE – INDONESIA

Certificate no. : POM TI204633151
Certified as of : April 2nd, 2020



RHEA PHARMACEUTICAL, LLC Dear Mrs. EVGENIA MELKONYAN

Dear Mrs. Melkonyan, I want to share with you the following information about the biologically active supplement (Health Tone) that was designed by Professor Yusef Babikyan and produced by RHEA Pharmaceutical.

Taking into account the discussion and conclusion of the meeting conducted by the specialized consultants, leading scientists, and key opinion leaders from the Ministry of Health, Health Tone (produced by RHEA Pharmaceutical) can be considered an adjuvant therapy for patients infected by SARS-CoV-2 (COVID- 19).

Respectfully Yours, 23.04.2020

LUSINE KOCHARYAN



Study of Antibacterial Activity against Bacteria, Yeast Strains & pathogenic Microorganisms

- Screening of Health Tone for antibacterial activity was done by the disk diffusion method. Results are depicted in the table below :

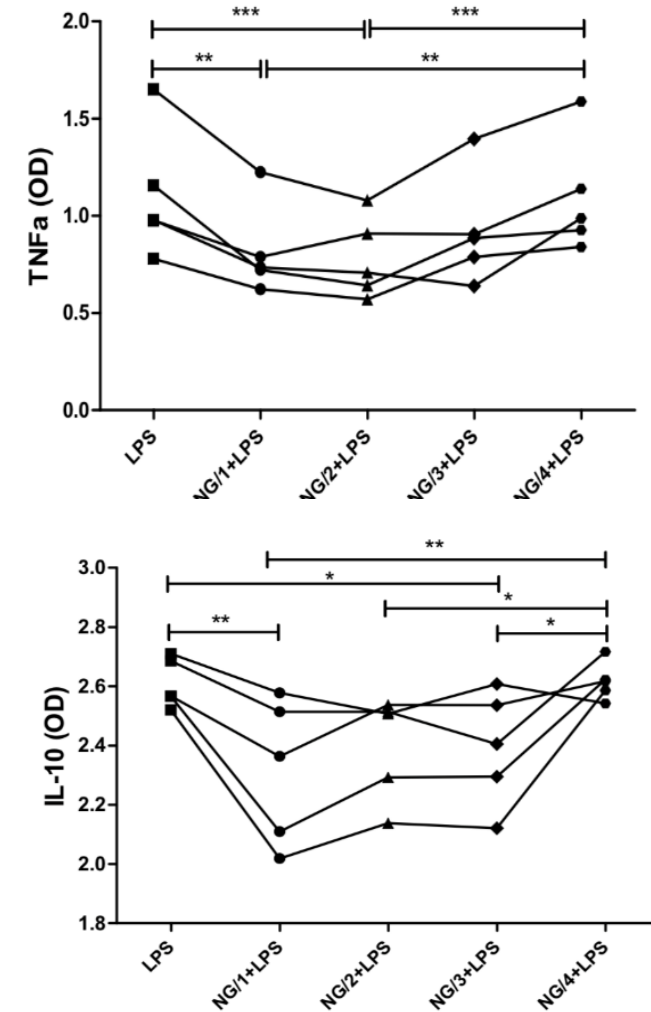
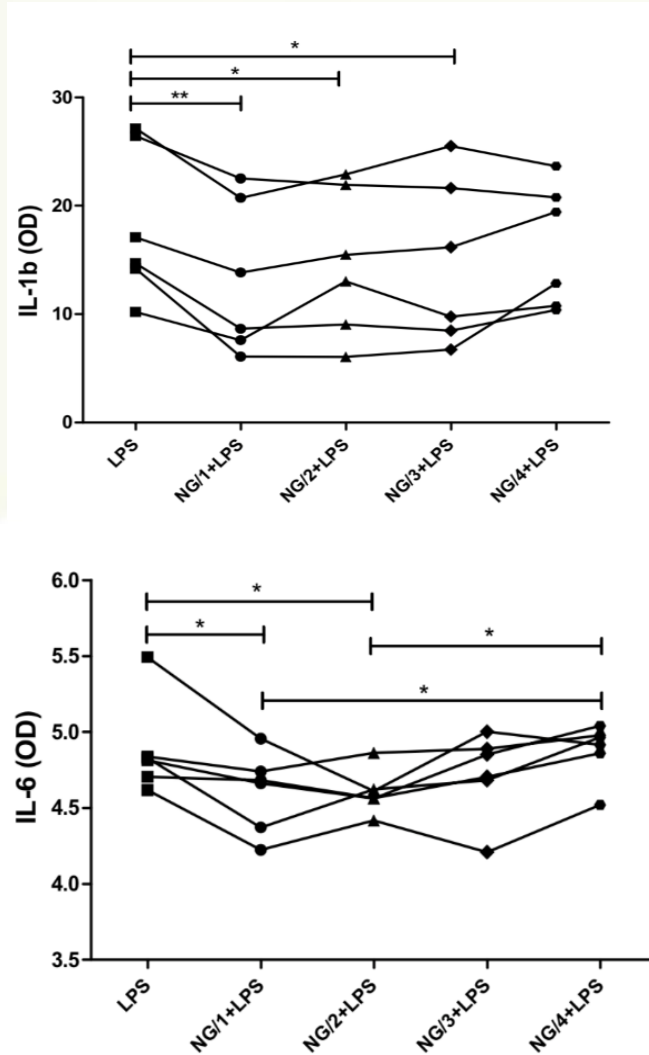
Bacterial & yeast strains	Health Tone Formulation 10 μ l	Tetracycline 30 μ g	Fluconazole 40 μ g
Staphylococcus aureus ATCC-6538	10.5 \pm 1.7	32.1 \pm 0.8*	ND
Staphylococcus epidermidis ATCC-12228	8.3 \pm 0.7	12.3 \pm 5.8	ND
Escherichia coli ATCC-8739	7.1 \pm 0.05	19.1 \pm 1.5*	ND
Salmonella enterica serovar Typhimurium ATCC-14028	7.1 \pm 0.07	20.5 \pm 1.0*	ND
Pseudomonas aeruginosa ATCC-9027	12.6 \pm 0.4*	8.7 \pm 1.5	ND
Micrococcus luteus ATCC-10240	10.3 \pm 0.9	28.9 \pm 1.0*	ND
Candida albicans ATCC-10231	7.1 \pm 0.3	ND	27.4 \pm 0.9*
Candida albicans NCTC-885-653	7.0 \pm 0.03	ND	25.5 \pm 1.4*

- Microdilution susceptibility assay was performed for the determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). Results are depicted in the table below :

Bacterial & yeast strains	Health Tone Formulation (mg/ml)	Tetracycline (μ g/ml)	Fluconazole (μ g/ml)
Staphylococcus aureus ATCC-6538	2.5	0.006	ND
Staphylococcus epidermidis ATCC-12228	2.5	6.25	ND
Escherichia coli ATCC-8739	2.5	24.8	ND
Salmonella enterica serovar Typhimurium ATCC-14028	2.5	23.5	ND
Pseudomonas aeruginosa ATCC-9027	2.5	13.3	ND
Micrococcus luteus ATCC-10240	2.5	29.4	ND
Candida albicans ATCC-10231	1.25	ND	250
Candida albicans NCTC-885-653	0.625	ND	500

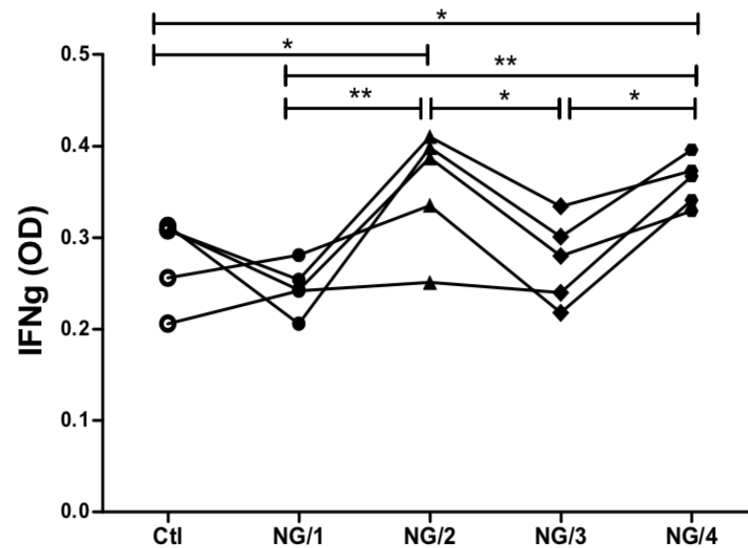
*) Represents statistically significant difference ($p \leq 0.05$) in the size of inhibition zones formed under the paper disc between Health Tone and the control

The potent anti-inflammatory activity of Health Tone Oil becomes evident by suppressing levels of cytokines such as IL-1 β , TNF- α , IL-6, IL-10 in in-vitro assays (results are depicted in the charts below) :



Study of potent Anti-Viral Activity

The potent anti-viral activity of Health Tone Oil is expressed by activation of $\text{INF-}\gamma$. Results are depicted in the charts below :

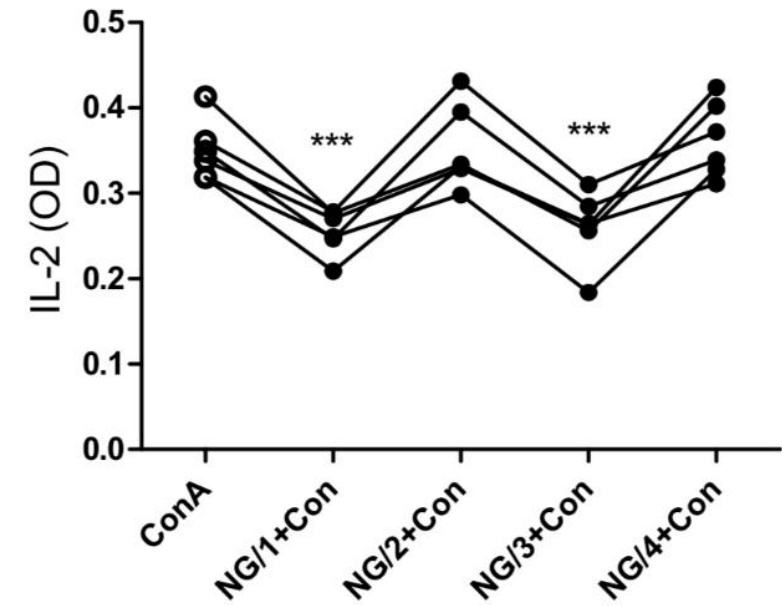
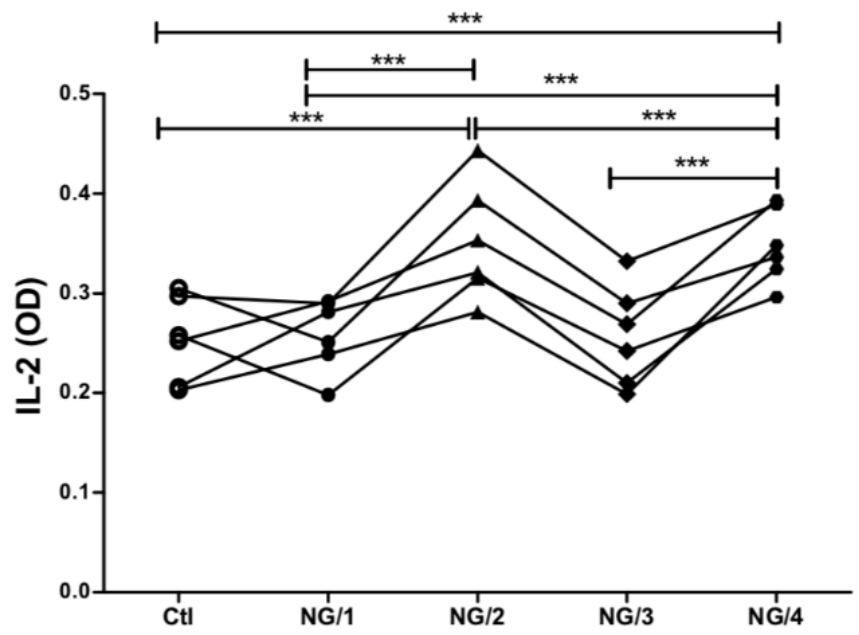


Dose-dependent alteration of interferon gamma production in untreated and E.coli lipopolysaccharide-treated human peripheral blood lymphocytes culture



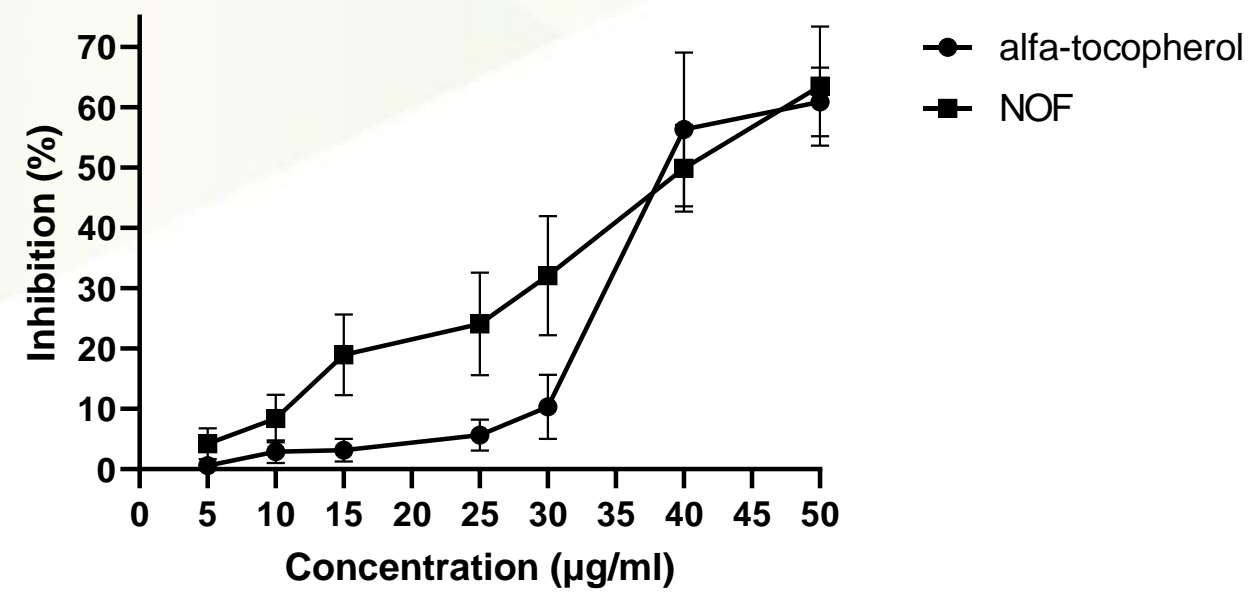
Study of Immune Modulating Properties

The potent anti-inflammatory activity of Health Tone Oil becomes evident by suppressing levels of cytokines such as IL-2 in in-vitro assays (results are depicted in the charts below) :



Study of potent Anti-Oxidant Activity

We observed that the natural oil Health Tone formulation was able to promote the scavenging of free radicals, displaying a high dose-response representing a significant antioxidant activity



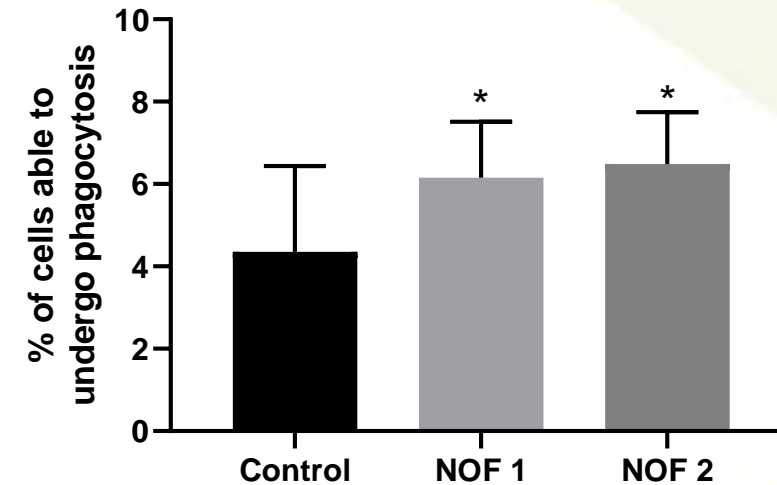
In vitro antioxidant activity of the NOF was evaluated by DPPH radical scavenging. The oil interacted with DPPH by transfer of electrons or hydrogens, neutralizing its free radical character. The oil was able to promote the scavenging of the DPPH radical, displaying a high dose-response ($r^2 = 0.96$), with inhibition varying from 5 to 65 %, at concentrations from 5 to 50 µg/ml.

Study of Immune Modulating Properties :

Modulation of polymorphonuclear neutrophils respiratory burst & inducing human neutrophil phagocytosis

In this study we demonstrated that Health Tone does not affect human PMN spontaneous oxidative burst but dramatically decreases fMLP- and PMA-induced, oxidative burst of cells (as depicted in the figure & the table below).

Human polymorphonuclear neutrophils	Spontaneous	fMLP	PMA	E. coli
Whole blood control	11.2±2.5	57.1±13.9	98±0.8	99.6±0.1
Whole blood + 6*10 ⁻³ µg/µl NOF	11.6±3.9	31±9.5•	57.4±2•	56.5±3.2•
Whole blood + 6*10 ⁻⁴ µg/µl NOF	14.5±5.2	37±13.6•	46.6±12.1•	51.7±13.2•



Accordingly, Health Tone could serve as a potential antioxidant capable restoring impaired intracellular production of ROS in PMN and down-modulation of overwhelming inflammatory response of PMN to chemotaxis- and phagocytosis-mediated respiratory burst induction.

Inactivation of infectious bronchitis Virus H120 with Health Tone Oil

1. Reagent and Material

- HT Oil
- Saline solution 0.85%
- Allantoic fluid of IB H120 Virus

2. Methods

a. Trial will be conducted in 5 group treatments of oil Group

b. Inactivation

- Mix the diluted oil solution using vortex for \pm 30 seconds.
- Gently transferred the oil solution to Erlenmeyer flask antigen contained.
- Incubate the specimen in a 37°C shaker incubator for 16-18 hours.

c. Inoculation

- Prepare 10 days embryonated eggs for 5 groups of treatment, positive control and negative control group.
- 5 treatment groups : inoculated with 0.2 ml mixture.
- IBV negative control : without inoculation.
- IBV positive control : inoculated with 0.2 ml IBV H120 virus.
- Incubation the eggs for 6 days at 36.5°C incubator with daily observation. Eggs with dead embryos within 24 hours post-inoculation will be discarded as non-specific.
- At the end of observation all of the eggs will be chilled in a refrigerator and harvested.

Group	NG oil (ml)	Saline (ml)	IBV H120 (ml)
I	2.5	2.5	5
II	1.25	3.75	5
III	0.625	4.375	5
IV	0.3125	4.688	5
V	0.156	4.844	5

Control group	Inoculation
Positive	0.2 ml IBV H120
Negative	without inoculation

INACTIVATION OF INFECTIOUS BRONCHITIS VIRUS H120 WITH HEALTH TONE OIL

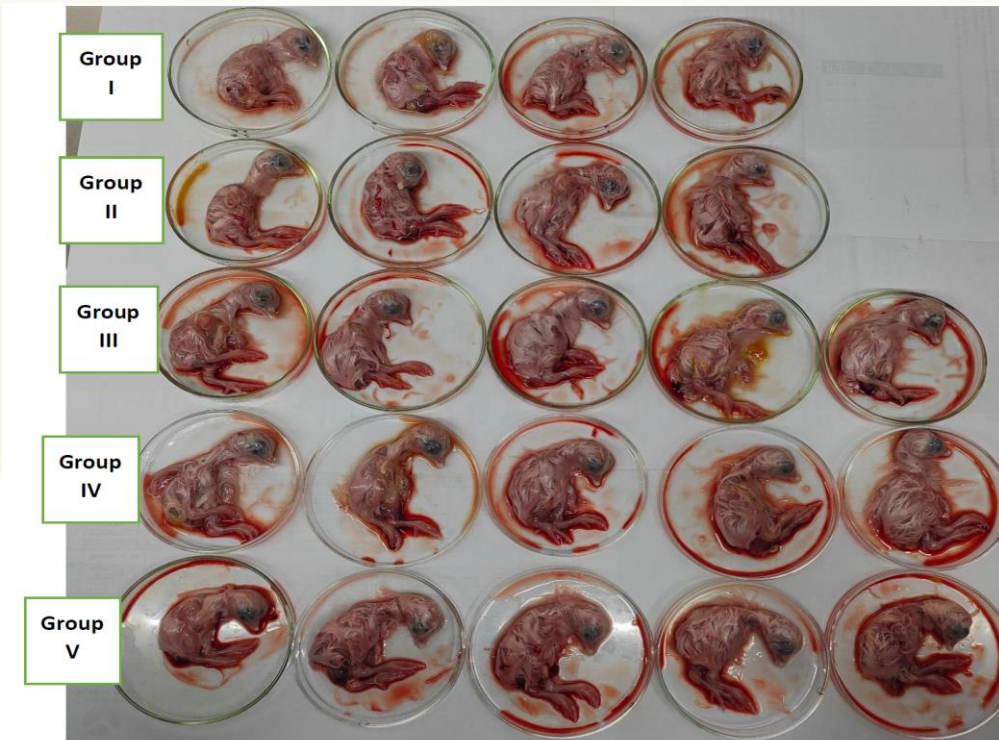


Figure 1. Embryos' feature of treatment groups, similar with IBV negative control



Figure 2. Comparison of IBV negative and positive control embryos

IBV negative control : embryos were normal

IBV positive control : embryos were dead and stunted

Key Results from Human Clinical Study

Erebuny Hospital data Yerevan , Armenia (April – June 2020)

Trial on Erebuny Hospital Yerevan, Armenia (April – June 2020)			
Department	Number of Health Care Professional (HCP)	Infected HCP before HealthTone application	Infected HCP after HealthTone application
Reception	49	3 (6.1%)	1 (2%)
ICU	41	24 (58.5%)	3 (7.3%)
Hemodialysis	24	5 (20%)	1 (2.2%)
ENT	45	2 (4.4%)	1 (2.2%)
GYN / OBS	31	9 (29%)	3 (9.6%)
Policlinic	51	14 (24.4)	3 (9.6%)
Others	13	0	0
Total	240	57 (23.7%)	9 (3.7%)

- The data depicted above was based on the product trial conducted for 1 month starting from late April 2020 to early June 2020.
- Based on the trial, the number infected HCP drops significantly after Health Tone Oil application.
- Findings described above implied HealthTone efficacy in supporting the prevention from COVID-19.

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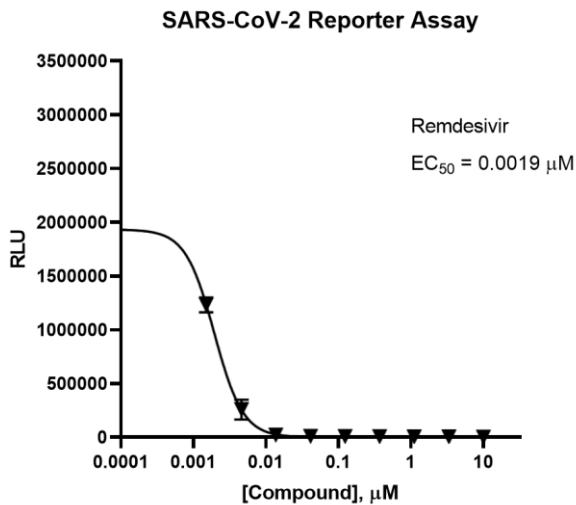
Update on cell-based anti-SARS-CoV-2 activity for Rhea's essential Oil tested at the University of Texas Medical Branch (UTMB)



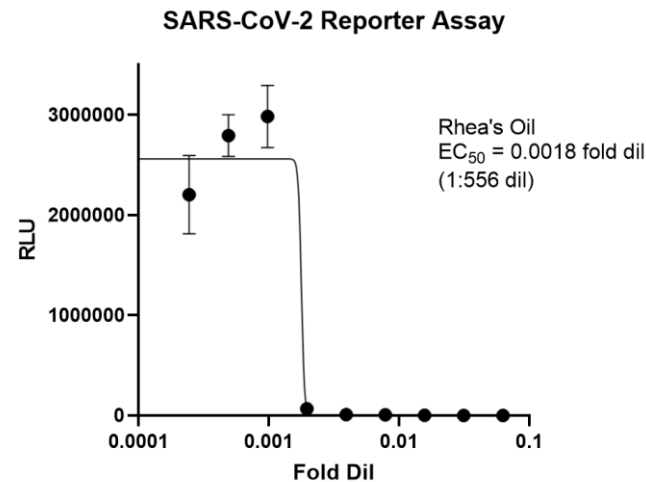
Cell-based anti-SARS-CoV-2 Activity

Experimental Drug Development Centre (EDDC) and University of Texas Medical Branch (UTMB)

Test Result from UTMB, June 2020

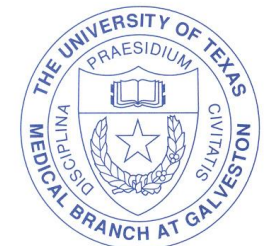


Positive Control



Essential Oil in HealthTone

- Test methodology: Comparing Remdesivir's antiviral properties with Health Tone's essential oil components using a cell based SARS-CoV-2 reporter assay
- The left chart indicates Remdesivir's potent inhibitory effects on viral replication in A549 cells infected with SARS-CoV-2.
- The right chart indicates the effects of the essential oil components in HealthTone showing similar potent inhibitory properties at certain dilutions



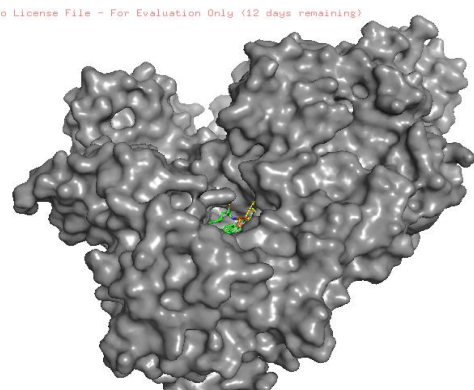
*A549 are adenocarcinoma derived human alveolar basal epithelial cells

Prediction of Small Molecules Targeting the Severe Acute Respiratory Syndrome Coronavirus-2 RNA-dependent RNA Polymerase (Example: Remdesivir)

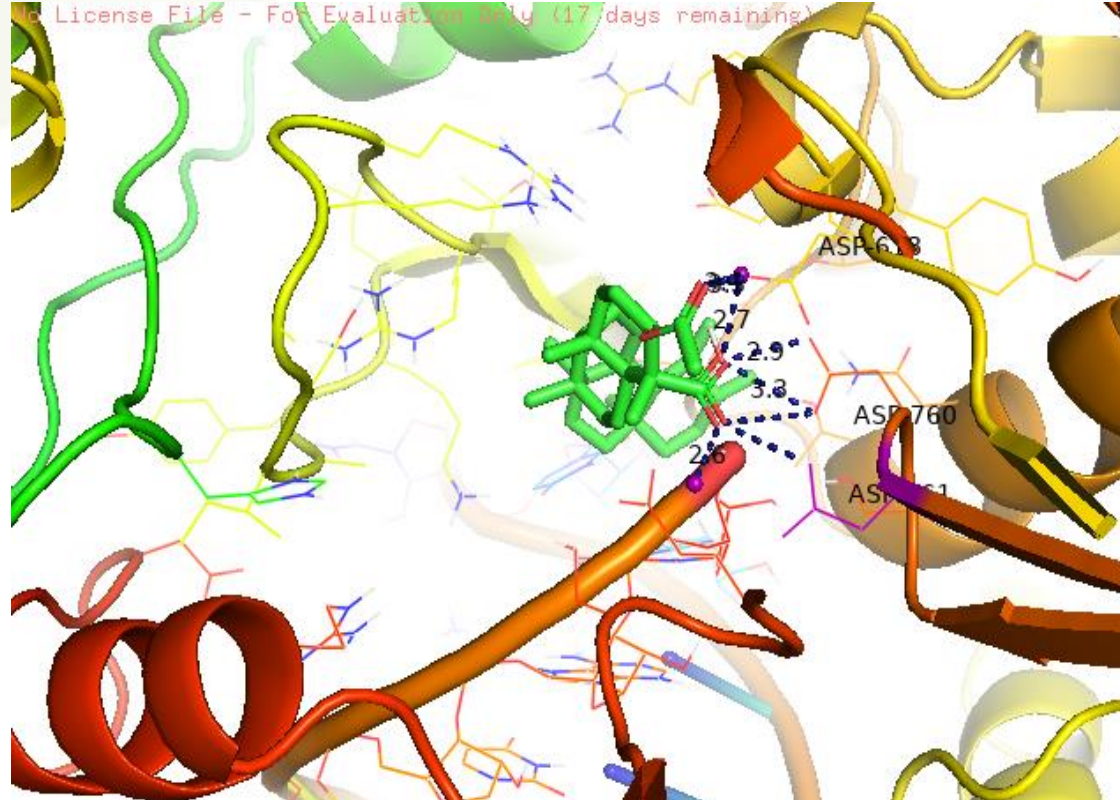
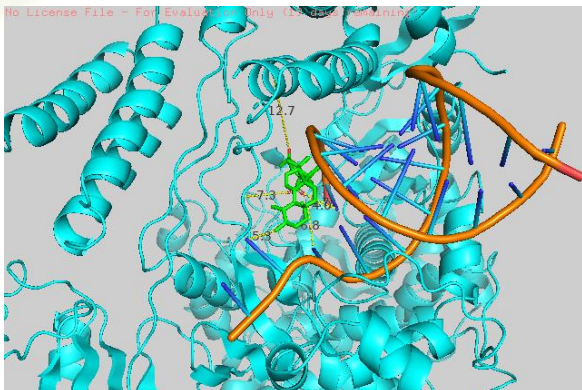
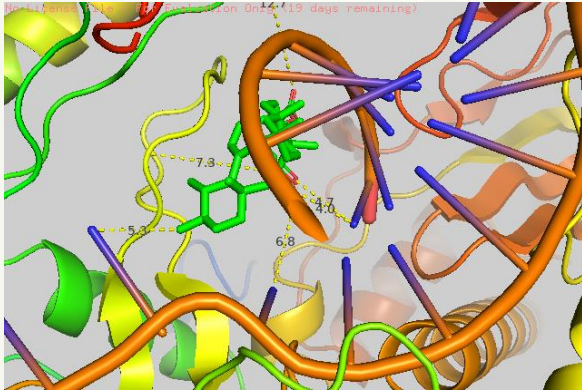


Nonstructural protein 12/7/8 (nsp12/7/8, RNA-dependent RNA polymerase, RdRp): Nsp12 is the polymerase which is bound to its essential cofactors, nsp7 and nsp8. It is important in replication and transcription of the viral genome. The structure of RdRp in complex with RNA and the triphosphate form of Remdesivir (RTP) was downloaded from the PDB database with code 7BV2. Thus we defined two sites for small molecule docking: the RTP binding site (RTP site), and the RNA binding site (RNA site) and prepared the target structure. For small molecule docking, four structures were provided: the complex form of nsp12/7/8, and the single chain of nsp12, nsp7, and nsp8.

Molecular structure of RdRp. The cartoon with the RTP and RNA binding site is shown (top). Remdesivir in the binding cavities is shown in the surface model with carbon, nitrogen, oxygen, in green, blue, red colors, respectively. Molecular interactions of Remdesivir and bond distances with the amino acid residues at the binding sites are shown (bottom).



Prediction of Small Molecules Targeting the Severe Acute Respiratory Syndrome Coronavirus-2 RNA-dependent RNA Polymerase (Example: Components of Health Tone Oil)



Molecular docking of 3-Acetyl-beta-boswellic acid onto the predicted GTP site and its molecular interactions with the RdRp amino acid residues. Molecular interactions of 3-Acetyl-beta-boswellic acid and bond distances with the amino acid residues at the GTP binding sites are shown. The 3-Acetyl-beta-boswellic acid in the stick model with carbon, nitrogen, oxygen, in green, blue and red colors, respectively.

Prediction of Health Tone Small Molecules Targeting the Severe Acute Respiratory Syndrome Coronavirus-2 RNA-dependent RNA Polymerase

Ligand name	Essential oil source	Docking Score (kcal/mol)	RF Score Value (pKd)	H-bond Residues
Remdesivir	Synthetic	-8.20	7.43	Lys545, Arg553, Asn691, Asp760, Arg836, Asp845, Ser759, Lys500
3-Acetyl-beta-boswellic acid	Boswellia serrata	-9.70	7.90	Asp618, Asn691, Lys545, Asp760, Asp761, Arg553, Arg836, Asp623, Thr687, Lys551
11-Oxo-beta-boswellic acid	Boswellia serrata	-10.10	7.07	Arg553, Asp760, Lys500, Asp623, Lys545, Thr687, Ser759, Asp761
alfa-pinene	Boswellia serrata	-6.10	4.44	No H-bonds detected
alfa-thuiene	Boswellia serrata	-6.20	4.45	No H-bonds detected
furanodiene	Commiphora myrrha	-8.30	6.68	No H-bonds detected
curzerenone	Commiphora myrrha	-7.70	6.54	Lys545, Arg836
furanoedesma-1,3-diene	Commiphora myrrha	-8.40	6.65	Lys593, Asn691, Ser759

Prediction of HT Small Molecules Targeting the Severe Acute Respiratory Syndrome Coronavirus-2 RNA-dependent RNA Polymerase

Ligand name	Essential Oil Source	Docking Score (kcal/mol)	RF Score Value (pKd)	H-bond Residues
Remdesivir	Synthetic	-8.20	7.43	Lys545, Arg553, Asn691, Asp760, Arg836, Asp845, Ser759, Lys500
Anethole	Foeniculum vulgare	-6.50	4.42	No H-bonds detected
3-hydroxy-p-anisaldehyde	Foeniculum vulgare	-9.00	7.19	Lys593, Arg858
Gardenin B	Gardenia Jasminoides	-7.80	5.71	Arg836, Lys545, Asp845, Asn497
Gardoside	Gardenia Jasminoides	-7.80	5.18	Lys545, Arg553, Asn691, Asp623, Arg624, Asp836, Ser759, Thr687, His439
Geniposide	Gardenia Jasminoides	-7.90	5.34	Lys545, Arg836, Asn691, Asp623, Asp845, Asp760, Ser759, Thr680, Thr687, Asn497
beta-selinene	Daucus carota	-7.00	6.32	No H-bonds detected
Bergamotene	Daucus carota	-7.50	5.85	No H-bonds detected
Apigenin	Daucus carota	-9.30	6.40	Asn691, Lys593, Ser759, Asp895, Arg858

Included under BPOM's list of accompaniment for clinical trial of herbal products with immuno-modulatory properties

PENDAMPINGAN PENELITIAN PRODUK HERBAL UNTUK PENANGGULANGAN COVID-19



No	Produk	Instansi Terkait	Site Uji
1	Cordycep (POM TR 162397831) dan Deteflu (POM TR 152388391)	LIPI, PDPOTJI, dan UGM dengan industri PT. Kalbe Farma	RS Darurat Wisma Atlet Kemayoran
2	Penelitian ekstrak daun jambu biji	BRIN, IPB dan industri PT. SOHO.	RS UI dan RS. Persahabatan Jakarta
3	Penelitian Health Tone Oil (Obat Tradisional Impor dari Armenia)	PT. RHEA Pharmaceutical	Rumah Sakit Hasan Sadikin dan RSD Wisma Atlet
4	Melaleuca Alternifolia Concentrate (MAC Oil)	PT. Neumedik Indonesia	RS Persahabatan dan RSD Wisma Atlet
5	Ekstrak etanol Ketepeng Cina (Cassia alata) dan Ekstrak Benalu (Dendrophthoe petandra (L) Miq)	LIPI	-
6	Virgin Coconut Oil (VCO)	SetJend Pertahanan Nasional Tim peneliti RS POLRI	RS Polri Sukanto, RS Brimob, RS Wisma Atlet, dan RS Pertamina
7	Minyak Atsiri Daun Eucalyptus	Kementerian Pertanian	RS Unhas
8	Penelitian Galobe, untuk produk: Golarend, Pangiar, Laorend, Bintang Laut Mera	STIKMAH Halmahera Utara	RS Kandau Manado, RSUD Chasan Boeoirie Ternate



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 **RHEA**
Pharmaceutical Sciences

Thank You!

