

## THE NATURAL PRODUCT CURMERIC®: FROM RESEARCH TO THE CUBAN BASIC LIST OF MEDICINES AND NATURAL PRODUCTS.

Prof. Valdés- González Tania, PhD

Head, Theragnostic Laboratory University Hospital General Calixto García- CEADEN

Head, National Project MINSAP

Director, Local development Project (FARMABANA-CEADEN)

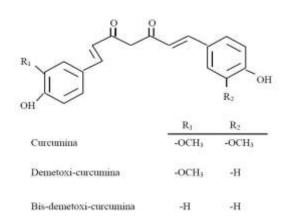
<u>taniavaldes@infomed.sld.cu</u> September 21st , 2024

#### Curcuma longa

Curcuma longa (Turmeric) is one of the most used plants as spice and medicine from ancient times, in India and other Asian countries. It has shown antimicrobial, anti oxidant and anti inflammatory properties.



Curcuminoids (curcumin), are major poliphenols, which are related to the beneficial effects of *Curcuma longa*. It also contains volatile oils such as turmerone, atlantone and zingibereno.

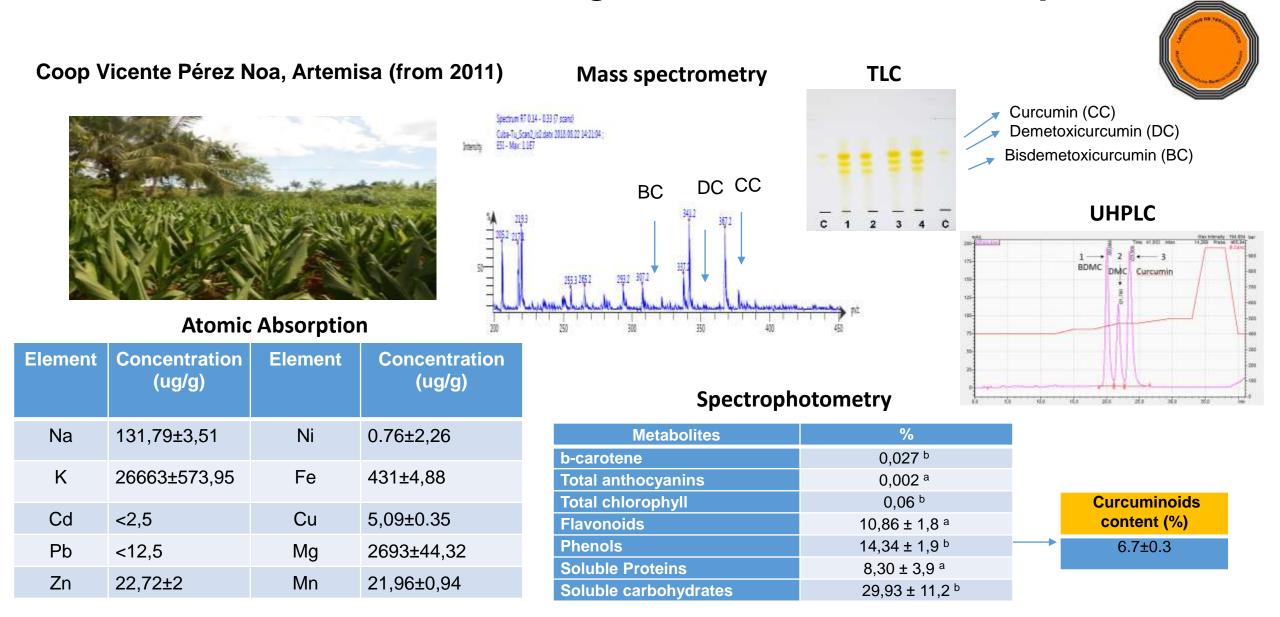


Turmeric has been used for the treatment of artritis, atherosclerosis, respiratory disorders, gastrointestinal (hepatic) and skin diseases.

Currently, several research groups are studying the impact in cancer and neurodegerative diseases.

Classified as GRAS (Generally Regarded as Safe) by the FDA.

#### Characterization of Curcuma longa cultivated in Artemisa province



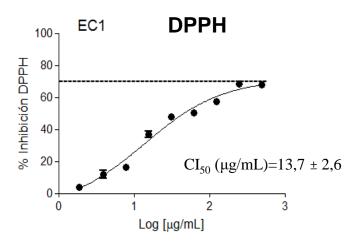
Valdés- González T y cols. Archivos del Hospital Calixto Garcia 2019:1

#### Antioxidant and anti inflammatory activities

(Institute for Marine Sciences, ICIMAR)



#### **Anti-oxidant activity**



#### **FRAP**

Concentración [mg/mL]	(mM equivalentes de ácido ascórbico*)
500	$3599,0 \pm 20,8$
250	$1585,7 \pm 26,5$
125	$350,1 \pm 22,2$
62,5	NE

### Cytotoxic activity- lung cancer cell line

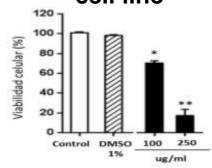


Figure 4 Cynotoxicity of the nutrationists of C livings in NGLHH460 cells. I partiaming of cell violating of the NGLH4460 cells currounce (control), seen with 1% DH600 or exposed to concentrations of 100 and 230 g/ml as sho "gr00.03 and "hyd.0.01 with respect to common cells (Annova and the Dissition a pottletter). The cells were incubated with the products file 48 is

#### **Anti-inflammatory activity (granuloma method)**

* p<0,05, ** p<0,01 y ***	p<0,00
(ANOVA and Dunnett a poste	eriori)

Treatment	Dosis (mg/kg)	Transudative weigth (mg)	Tissue associated to granuloma (mg)	Activity antiinflamatory (%)
Control	CMC (0,5%)	88,85	18,38	
	0,1	89,57	18,97	4,40
Curcura	1	85,51	16,63	4,23
Curcuma	10	66,10 **	17,21**	28,85
longa	50	64,57 **	14,51**	30,79
nutraceutical	100	60,34 **	11,55***	36,15
	200	60,33 ***	12,40***	36,17

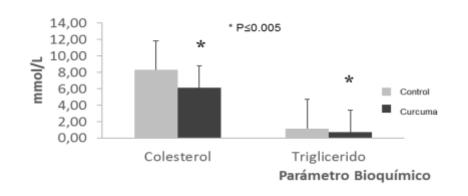
Valdes- Gonzalez el al. Pharmacy and Pharmacology International Journal 2019;7(6):319-328

## Lipid lowering and anti inflammatory properties of *Curcuma longa* nutraceutical in knock out ApoE mice

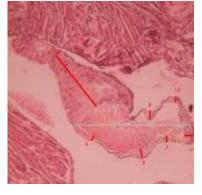


Finlay Institute for Vaccines (IFV)- Centre for Production of Laboratory Animals, CENPALAB

## Effect of *Curcuma longa* nutraceutical on total cholesterol and triglycerides

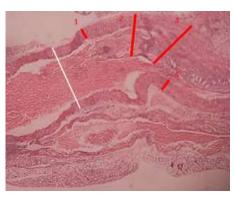


#### **Treated ApoE mice**



H.E.x120

#### **Control ApoE mice**



H.E.x120

#### Relative size vessel wall-atheroma

Group	Vessel Wall	Atheroma	Vessel wallI+Atheroma
Treated	0.059	0.066	0.124
No treated	0.193	0.475	0.700

## Use of Curcuma longa nutraceuticals in chronic diseases patients of the University Hospital General Calixto García



(University Hospital General Calixto Garcia, HUGCG)

**Triglycerides Glycemia Cholesterol** Curcuma longa supplements 90 days 56 50 63 CURCUMA 180 days 80% 73

#### **Natural Product Curmeric®**



Concept: Natural antiviral/ antibacterial molecular complex Chemical barrier + sistemic effect Safe

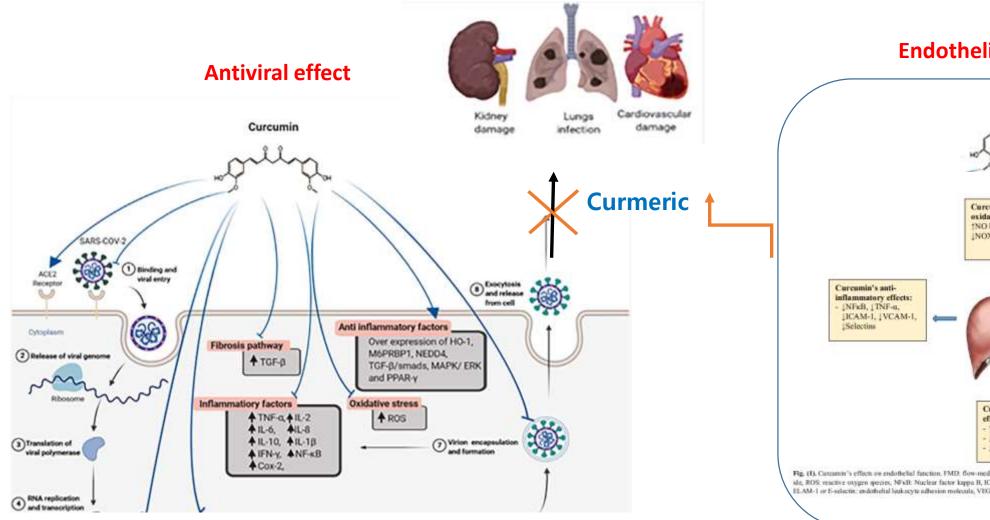
- ✓ Curmeric: Combined natural emulsion (with *Cúrcuma longa* extracts), which contains vitamin E, omega fatty acids, minerales and other oligoelements.
- ✓ Patent request: 020-25 (OCPI) CEADEN
- Current products : Nasal drops
   Mouth wash/ Gargle
   Oral formulation



- ✓ Registered: National Institute for Hygiene, Epidemiology and Microbiology (INHEM).
- ✓ Produced by Medilip, Biocubafarma in collaboration with CEADEN and FARMABANA

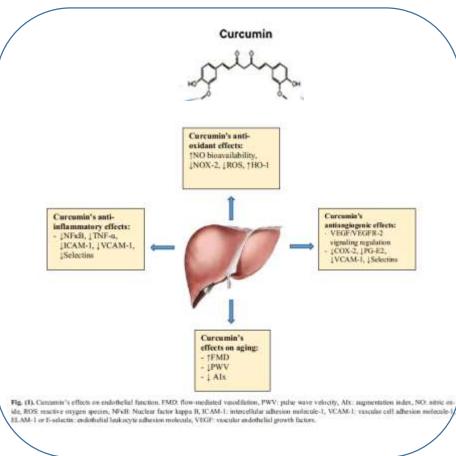
#### Curmeric- combined effects in COVID-19





Fatemeh Zahedipour et al. Potential effects of curcumin in the treatment of COVID-19 infection Phytotherapy Research. 2020;1–10.

#### **Endothelial protection**



Karimiam M et al Curcumin and Endothelial Function Evidence and Protective effects. Current Pharmaceutical Design, 2017, 23, 2462-2473

## Antibacterial effect in strains isolated from samples of patients with severe respiratory infection diseases Microbiology Laboratory, HUGCG



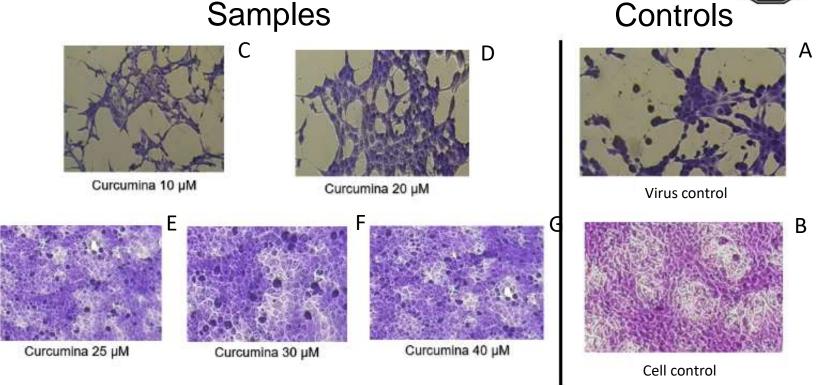
Strain	Sample	Curcuma longa extract	Curmeric nasal drop	Curmeric Oral solution
Proteus spp	Sample 6-18 Traqueobronchial sample Patient UCIM	(+)	(++)	(+++)
Escherichia coli spp	Sample 1-21 Traqueobronchial sample Patient post Neurosurgery	(+)	(++)	(+++)
Staphylococcus aureus spp	Sample 8-27 Secreción traqueobronquial Patient UTI	(+)	(++)	(+++)

#### Curmeric anticoronavirus activity in vitro

(National Centre for Animal Health, CENSA)

At curcumin concentration of 10µM (D) and 20µM (D), detached and rounded cells typical of the effect of this virus, were observed (A).

The antiviral activity was observed from curcumin at 25µM (E, F, G). The cell monolayer was confluente, similar to the cells without inoculation (B).



Antiviral activity of Curmeric against bovine coronavirus Mebus. Staining with crystal violet 5 days post virus inoculation in fetal bovine serum.

**Controls:** Cytopatic effect of bovine coronavirus Mebus in celular line MBDK (A, virus control). Cells MBDK without virus inoculation (B, cell control).

**Samples:** Cells MBDK treated with curcumin at concentrations of 10uM-40uM and inoculated with bovine coronavirus (D-G).

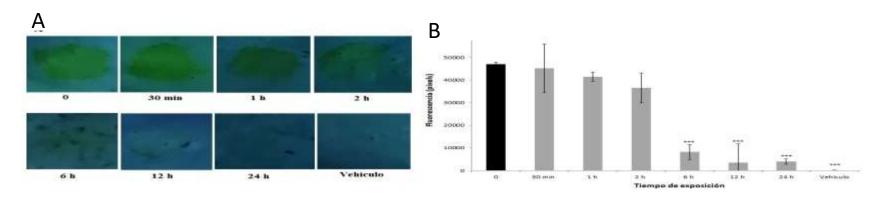
#### **Evaluation of skin absorption of Curmeric in Balb/c mice**





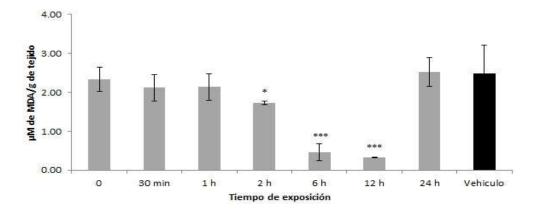
Absorption of Curmeric –nasal drops on the cutaneous tissue of Balb/c mice for 24h





\*\*\* p< 0.001 (Prueba de *Dunnett*).

#### Levels of malondialdehyde (MDA) in homogenates of skin exposed to Curmeric –nasal drops



\* p< 0.05, \*\*\* p< 0.001 (Prueba de *Dunnett*)...

#### Curmeric for protection of health care workers, University Hospital General Calixto Garcia (HUGCG), march 2020



#### Participants in the clinical study

Group Study		Group Control		
Services or Departaments	n	Services o Departaments	n	
Respiratory Sympt. Service	25	Intermediate Care Unit	43	
Allergy Service	43	Intensive Care Unit	65	
Clínical Laboratory	80			
Microbiology Laboratory	8			
Total	91	Total	108	

**COVID-19 cases confirmed by PCR** 

Group Study		Group Control				
Servicios o Departamentos	n	Servicios o Departamentos	n			
Respiratory Symp. Service	0	Intermediate Care Unit	9			
Allergy Service	0	Intensive Care Unit	3			
Clinical Laboratory	0					
Microbiology LAbortory	0	11%				
Total	0	Total	12 *			

Study period: from march 19<sup>th</sup> to April 18<sup>th</sup> 2020, before the application of PrevengHo- Vir at the hospital.

No report of related adverse event.

COVID-19 cases in the control group (\*Fisher exact test p=0,0054 for p<0,05).

Based in these results, it was indicated the use of Curmeric in 16 services and departaments of the del hospital.

Valdes-Gonzalez T Journal of Integrative Medicine Japan 2024

## Curmeric in Primary Health Care for prevention of COVID-19 transmission Safety studies (sept-dec 2020)



	Curmeric			Total	Study/			Inten	sity E	Α		Caus	ality	EA	
Clinical study	Formulatio n	Date	Municip ality	participant s	Control Patients	COVID- 19	EA	Slight	Moder ate	Se ver e	No related	Condit ional	Possib le	Probab le	Related
Safety study in Primary Health Care	Mouth wash/	Sep- Oct 2020	Plaza de la Revoluci ón	186	186/0	0	9	9	0	0	0	9	0	0	0
Preventive effect in	wash/ Gardle	Oct- Nov	Plaza de la Revoluci on	112	66/66	0	1	1	0	0	1	0	0	0	0
Primary Health Care	Guigio	2020	Regla	234	117/117	0	9	9	0	0	8	1	0	0	0
Preventive effect in Primary Health Care		Nov- Dec 2020	Regla	83	42/41	0	2	2	0	0	1	1	0	0	0
Total				615	227/228	0	21	21	0	0	10	11	0	0	0



#### Curmeric for protection of health care workers of stomatological services in Plaza de la Revolucion municipality, Havana (jan-march 2021)

#### Participants in the clinical study

Services or Departmets	CLINIC H Y 21	CLINIC MININT	CLINIC PUENTES GRANDES
Management	9	2	6
Administration	20	7	8
Medical assistance	137	26	41
Total		201	55
COVID-19 cases		0	<b>7</b> * <b>(</b> 12%)





(\* Fisher exact test p=0.0054 for p<0.05).

## Curmeric as complemmentary treatment for COVID-19 patients with mild symptoms and 5th day positive PCR



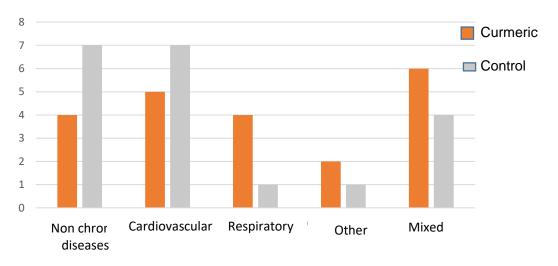
"Dr. Luis Díaz Soto" Hospital (apr-jul 2021)

Participants	Group Treatment	Group Control
38	18	20

#### **Demographic data**

Variab	les	Group Treatment	Group Control
	Age	46,1±1.7	54,2±1.9
Demografics	Female	9	12
	Male	9	8
	Tobbaco	5	0
Tóxic habits	Coffee	9	12
	Alcohol	3	1

#### **Chronic diseases**



#### Classification of COVID-19 pacients in the study <sup>a</sup>

Clasification	Grupo Treatment	Group Control
High risk	76%	66%
Low risk	24%	34%

<sup>&</sup>lt;sup>a</sup> Protocol for COVID-19 MINSAP. Version 1.6, jan 2021











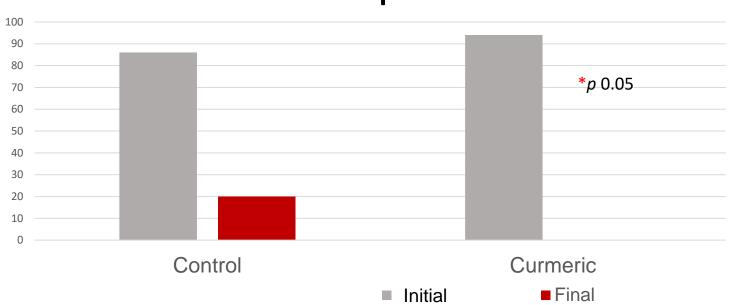


#### Efects of Curmeric on the improvement of disease condition

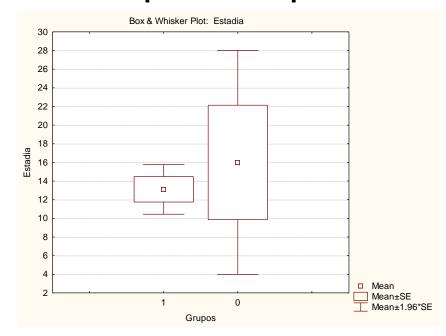


"Dr. Luis Díaz Soto" Hospital (apr-jul 2021)

## Effect of Curmeric in symptom relief in COVID-19 patients



#### Hospitalization period



\* No severe adverse events related with Curmeric

Group Curmeric: 13.1 days
Group Control: 16 days

## SARS-CoV2 inhibition effect "Dr. Luis Díaz Soto" Hospital – CIGB (apr-jul 2021)



#### **SARS-CoV-2 Inhibition % (Curmeric)**

11,95000

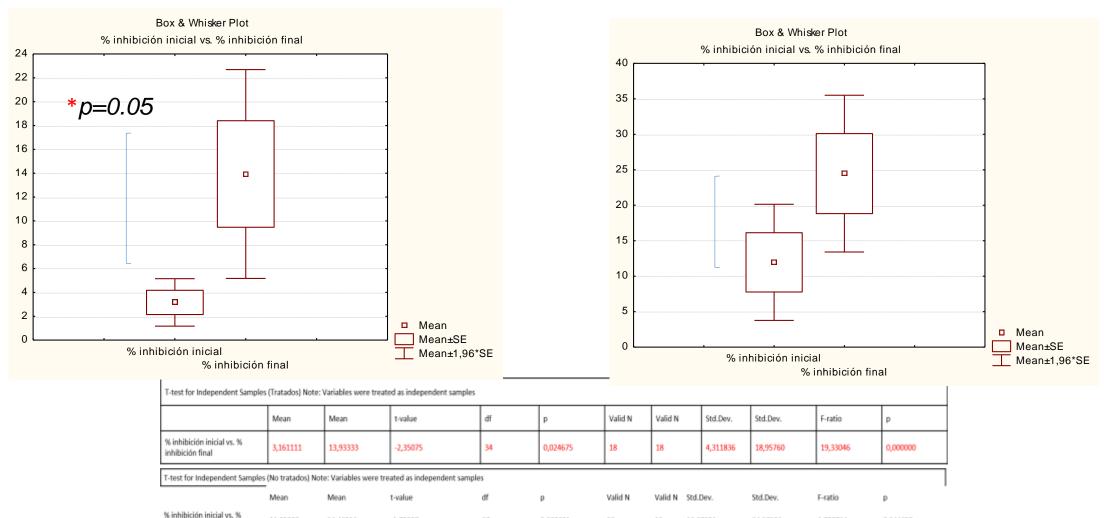
inhibición final

24,46316

-1,79627

37

#### **SARS-CoV-2 Inhibition % (Control)**



0,080621

18,67691

24,57106

1,730764

0,244658

#### Clinical laboratory database

-tests; Grouping: Grupos (BD en uso.sta) Group 1: 1 Group 2: 0											
	Mean	Mean	t-value	df	р	Valid N	Valid N	Std.Dev.	Std.Dev.	F-ratio	р
Glicemia Inicial	4.9800	5.4830	-2.08686	36	0.044044	18	20	0.6795	0.7935	1.364	0.524630
Glicemia final	5.5589	5.0584	1.14243	35	0.261031	18	19	1.5711	1.0573	2.208	0.104677
2 Colesterol inicial	3.7944	3.7745	0.08869	36	0.929823	18	20	0.6853	0.6983	1.038	0.944336
2 Colesterol final	9.9296	4.1895	1.06556	35	0.293918	18	19	23.4882	0.7196	1065.520	0.000000
3 Triglicéridos inicial	1.2642	1.4270	-0.61658	35	0.541502	17	20	0.8030	0.7979	1.013	0.968343
3 Triglicéridos final	1.6194	6.8037	-0.92343	34	0.362288	17	19	1.6625	23.0587	192.371	0.000000
4 Ácido úrico inicial	304.9412	291.7000	0.47201	35	0.639846	17	20	81.8180	87.6567	1.148	0.788138
1 Ácido úrico final	343.0000	324.0526	0.54808	34	0.587221	17	19	86.1996	116.8325	1.837	0.227249
6 Creatinina inicial	93.2222	98.3158	-0.55015	35	0.585708	18	19	22.6367	32.5065	2.062	0.142464
5 Creatinina final	90.3889	85.5556	0.68276	34	0.499383	18	18	19.4517	22.8839	1.384	0.510023
6 TGO inicial	33.3889	40.5000	-0.78810	36	0.435797	18	20	22.4293	31.8012	2.010	0.153699
TGO final	22.2778	27.7368	-0.76736	35	0.448016	18	19	4.2538	29.8754	49.326	0.000000
7 TGP inicial	37.1667	39.1000	-0.24954	36	0.804364	18	20	28.7714	18.3530	2.458	0.061206
	28.8889	31.7222	-0.34413	34	0.732870	18	18	12.4659	32.6313	6.852	0.000250
	42.5000	70.5000	-1.32928	36	0.192120	18	20	35.2675	82.7739	5.509	0.000879
	33.2222	54.8947	-1.69102	35	0.099720	18	19	22.3332	49.8106	4.974	0.001759
9 Proteinas totales nicial	68.2778	76.8250	-3.36957	36	0.001807	18	20	4.7992	9.7411	4.120	0.005014
Proteinas totales final	74.2611	70.4000	0.95581	35	0.345725	18	19	12.3574	12.2096	1.024	0.956771
LO Albúmina inicial	43.3056	47.9700	-1.47490	36	0.148933	18	20	3.3550	13.0178	15.055	0.000001
LO Albúmina final	43.7722	42.9167	0.39581	34	0.694720	18	18	3.9795	8.2623	4.311	0.004348
L2 Fosfatsa alcalina nicial	170.7778	203.5500	-1.32745	36	0.192717	18	20	45.5897	95.2943	4.369	0.003576
.2 Fosfatsa alcalina final	183.9444	193.5789	-0.50669	35	0.615549	18	19	47.6982	65.9506	1.912	0.188211
13 LDH inicial	378.3889	455.6500	-1.49099	36	0.144675	18	20	114.0491	191.2101	2.811	0.036927
	357.4444	408.7895	-1.89125	35	0.066891	18	19	69.5297	93.1734	1.796	0.233862

## Clinical studies with Curmeric in COVID-19 epidemy in Havana Public Cuban Register of Clinical Trials (CENCEC)



Registro primario de la OMS
Primary registry of WHO (ICTR

# ENSAYOS REGISTRADOS Por tipo de intervención Por estado de reclutamiento Por promotor Por fecha de registro Búsqueda avanzada de ensayos PROCESO DE REGISTRO Para registrar un ensayo Formulario del Promotor

Para registrar un ensayo
Formulario del Promotor
Formulario de ensayos del RPCEC
Para actualizar un ensayo registrado
Para reportar los resultados de un ensayo registrado

#### Inicio Búsqueda avanzada de ensayos La búsqueda puede ser realizada por cualquiera de estos campos. Tipo de la intervención Estado de reclutamiento Fa - Todos -- Todos -Países de reclutamiento Buscar por términos Aplicar CEADEN Título abreviado del estudio Curmeric-Nasal-Seguridad - Eficacia-Comunidad-Aislamiento-COVID19 Curmeric-Seguridad - Eficacia - Comunidad-Aislamiento - COVID19 Curmeric-Seguridad -Comunidad-Aislamiento- COVID19 Curmeric-Prevención-COVID-19- Personal de Salud- Hospital Universitario General Calixto García

Equipo de Trabajo del RPCEC | CENCEC - MINSAP rpcec@cencec.sld.cu

Calle 5ta A Edificio CECMED-CENCEC 2do piso e/ 60 y 62 Miramar, Playa CP 11300. La Hal Telef: (537) 216-4126 | (537) 216-4212 | (537) 216-4218. Copyright © 2014-2022 All Rights Reserved.

#### Scale-up production of Curmeric for health interventions



FARMABANA-CEADEN-Medilip (agosto 2021-jul 2022)







**August 4<sup>th</sup> 2021** Indication from the Minister of Health for health intervention in provinces with high COVID-19 transmission.

**August 13th 2021:** 1<sup>st</sup> 300L batch of Curmeric-nasal drops produced in Medilip, Biocubafarma

## Health intervention with Curmeric DPS Ciego de Ávila (Sept- Dic 2022)

#### Ciego de Ávila



Total population: 143 449 inhab

Number of municipalities: 11

Natural product: Curmeric-nasal drops



**HEALTH WORKERS** 

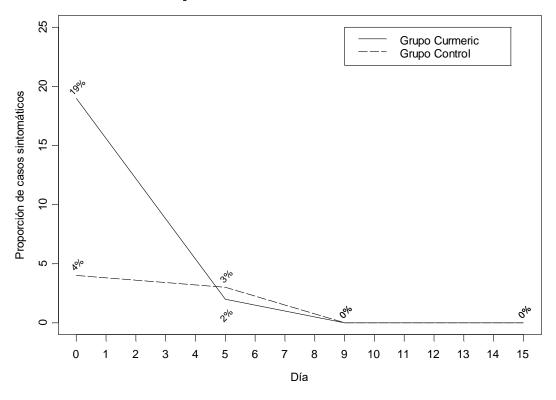
CLOSE CONTACTS OF PATIENTS
WITH RESPIRATORY
SYMPTOMS

TOURISM WORKERS



## Effect of Curmeric in COVID-19 transmission in suspicious patients and their contacts, Ciego de Ávila Sep 2021 (CENCEC)

## Evaluation of respiratory symptoms during 15 days treatment with Curmeric



Reported Adverse Events= 9, all mild



Municipality Ciego de Ávila Control n= 100 (Policlínic Belkys Sotomayor) Curmeric n=100 (Policlínic Norte)

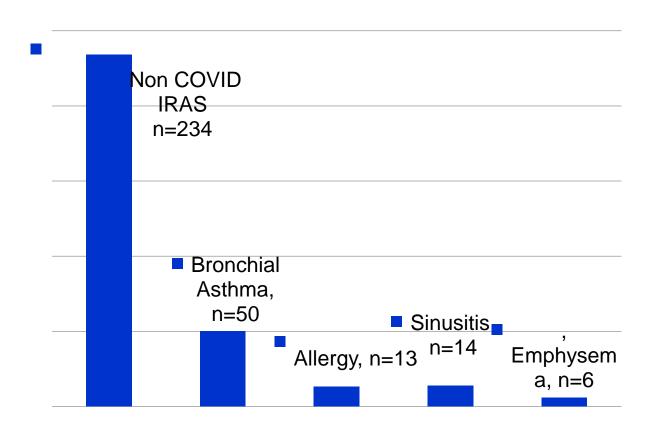
#### Protection of health care workers with Curmeric nasal drops

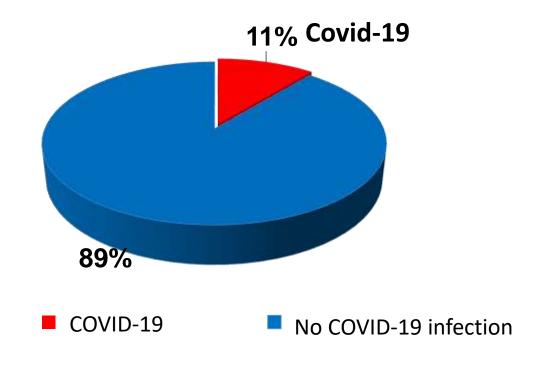


#### **Antonio Luaces Provincial Hospital**

**Effect of Curmeric nasal drops in COVID-19 respiratory diseases** 

**Curmeric in health workers** 

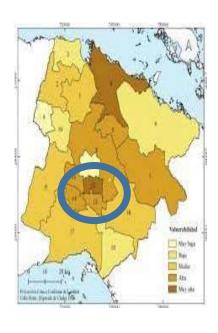




#### Patients with respiratory symptoms treated with con Curmeric

#### Policlinic Belkis Sotomayor Health area (sept 2021-April 2022)

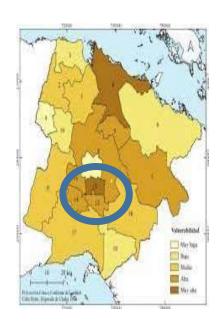
			Confirmed COVID-19				
Mnth	Number of patients	Patientes with comorbidities	#	%	Develppment of severe symptoms		
September	192	38	17	8.8	0		
October	178	46	15	8.4	0		
November	30	10	2	6.6	0		
December	54	9	0	0	0		
January	250	75	41	16.4	0		
February	206	81	21	10.1	0		
March	59	12	9	15.2	0		
April	32	8	3	9.3	0		
TOTAL	1001	279	108	10.7	0		



#### Effect of Curmeric nasal drops in cohabitants of COVID-19 patients

Policlinic Belkis Sotomayor Health área (sept 2021-April 2022)

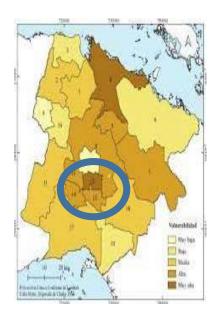
Month	Number of persons	Comorbidities		Developed symptoms		
		M	F		#	%
Sept	721	509	212	102	21	2.9
Oct	286	145	141	57	8	2.8
Nov	94	46	44	40	5	5.3
Dec	29	12	17	10	2	6.8
Jan	735	608	129	158	39	5.3
Feb	480	291	189	116	20	4.1
Mar	449	220	229	99	12	2.7
Apr	103	67	36	50	7	6.7
TOTAL	2877	1898	979	632	114	3.9



#### **Adverse Events**

#### Policlinic Belkis Sotomayor Health área (sept 2021-April 2022)

Total Treated Patient s	No Adverse Events Patients	Adverse Events	No. de persona s	%	Intensity
		Burning Nose	24	82.8	Mild
		Cefalea	3	10.4	Mild
3356	3327	Runny Nose	1	3.4	Mild
		Nausea	1	3.4	Mild
			29 (0.9 %)		All mild



#### Prevention of the COVID-19 transmission in the tourism workers

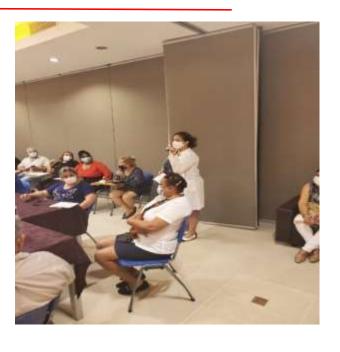
Cayo Largo, Ciego de Avila province (15 Nov. –31Dec 2021)

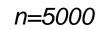












99 tourists diagnosed with COVID-19 in the evaluated period

No tourism worker diagnosed with COVID-19 in the evaluated period.





#### Health intervention in Granma province

nov 2021 - dec 2022







Total population **:** 833600 inhab

Number of municipalities: 13

Natural product: Curmeric-nasal drops

Current and formulation

Curmeric oral formulation



CLOSE CONTACTS OF PATIENTS
WITH RESPIRATORY
SYMPTOMS

**COVID-19 PATIENTS** 

Post COVID-19
PATIENTS



## Symptom relief with Curmeric-nasal drops in patients with respiratory symptoms



#### **Bayamo municipality**

Symptoms	Total of symptoms T=0 days	Total of symptoms T=5 days	% (5 days)	Total of symptoms T=15 days	% (15 days)	Total of symptoms T=15 days	% Symptom relief
Headache	344	275	79.94	69	20.06	344	100
Runny nose	143	89	62.23	54	37.76	143	100
Dry cough	306	176	57.51	128	41.83	304	99.35
Joint pains	197	90	45.68	100	50.76	190	96.44
Loss of taste and smell	40	20	50	12	30.00	32	80.00
Nasal obstruction	87	74	85.07	10	11.49	84	96.55
Sore throat	326	274	84.05	52	15.95	326	100
Muscle pain	388	239	61.59	119	30.67	358	92.26
Fatigue	184	110	59.78	74	40.22	184	100
Fever	141	141	100	0.0	0.0	141	100
Total	2156	1488	69.01	618	28.66	2106	97.68





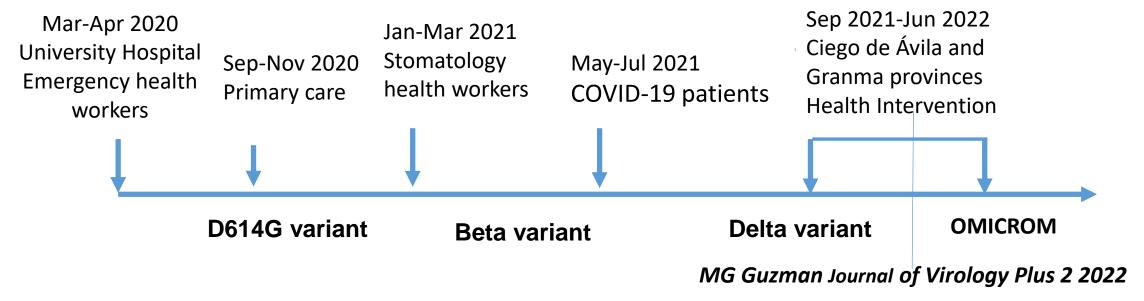
#### **Cauto Cristo municipality**

Symptoms	Number of patients with symptoms T=0 days	Symptoms relief in 7 days	%	Symptoms relief in 15 days	%	Total %
Dry cough	17	14	82,3	3	17,6	99.9
Joint pains	5	3	60	2	40	100
Fatigue	13	9	69,2	4	30,7	99.7
Total	31	22	70,9	9	29,0	99.9

#### General aspects of clinical studies with Curmeric in COVID-19

THE CONTRACTOR CONTRACTOR

- 1. Total number of participants n= 100 028
- 2. The studies were performed transversal to all COVID-19 variants from the very beginning of epidemic.



- 3. Transmission prevention studies were performed in non vaccinated population
- 4. Treatment studies with COVID-19 and post COVID-19 patients were performed in vaccinated population
- 5. The post- COVID studies were extended to December 2022 (less dengue cases in the municipalities where Curmeric was applied)

#### **Conclusions**

- ✓ Curmeric is a safe natural emulsion obtained with high technology, which contains polyphenols (curcuminoids), vitamin E, omega-3, minerals and other trace elements.
- ✓ Curmeric showed antivirus activity (anti-coronavirus), as well as anti-bacterial effects *in vitro*. Moreover it has shown antioxidant, anti inflammatory, hypolipemiant properties.
- ✓ Clinical studies and health intervention performed in 100 028 subjects during the COVID19 pandemic in Cuba, indicated that Curmeric products are safe and that the nasal drops, and gargles could help to decrease the disease transmission. Moreover, together with the oral formulation could improve symptoms in COVID-19 and post-COVID-19 patients, and other non COVID-19 respiratory diseases.
- ✓ The nasal drops have been included in the Cuban Basic List of Drugs and Natural Products in 2023 and are currently commercialized by the national system of pharmacies.
- ✓ A clinical study to evaluate the effect of Curmeric oral formulation in dengue infection started from June 2024.

#### **Collaborators**



FARMABANA MEDILIP CEADEN University Hospital General Calixto García

ICIMAR CENCEC UH (IFAL, FLEX, INSTEC, FacMat) CENSA

Hospital Dr. Luis Díaz Soto (Naval)

CIM

IPK

CIGB

DPS La Habana DPS Ciego de Avila DPS Granma Section of Drugs and Technologies, MINSAP

Department of Natural and Tradicional Medicine, MINSAP

Committee of Science and Innovation, MINSAP

## Local Development Project (FARMABANA-CEADEN) Co-working with BIOCUBAFARMA



Cúrcuma longa as raw material is obtained with agroecological techniques applying Circular Economy.







- Renewable Energy sources (solar dehydration).
- Environment Protection
- Inclusion of women and people with special physical needs.

**Curcuma natural products for the National Basic List of Drugs and Natural Products.** 





- Good Manufaturing Practices
- Quality System
- Clinical and Non-Clinical Research

## ALL INVITED TO THE PANEL CURMERIC IN DENGUE AND OROPOUCHE AT 2PM

#### **MUCHAS GRACIAS!**