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Il contributo di **ADAMAS Biotech** alla **ricerca nutraceutica**
e nella lotta contro la
sindrome da COVID-19

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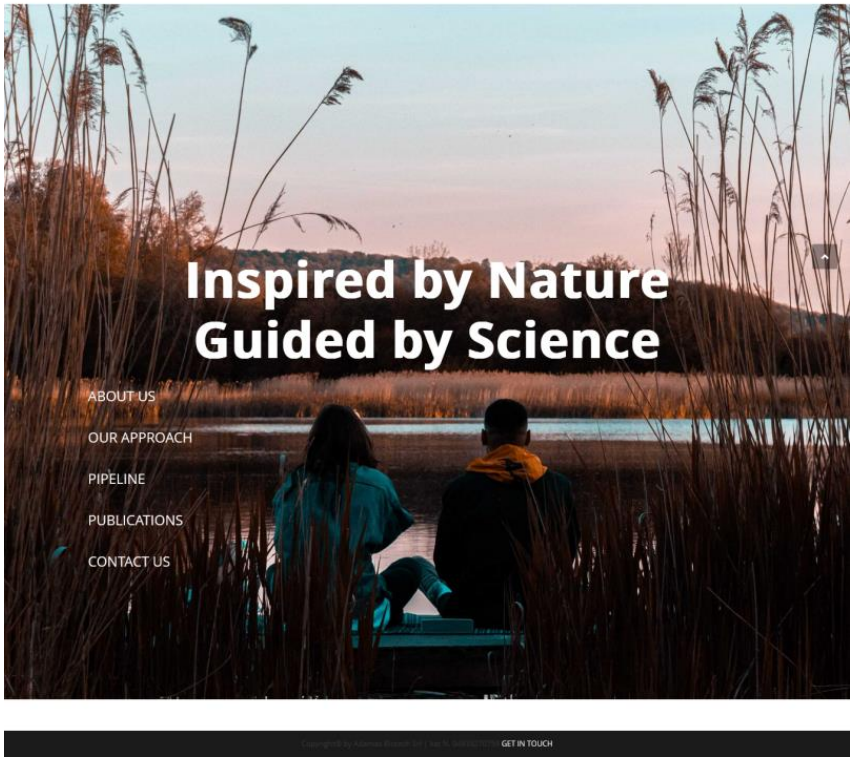
CONGRESSO INBB
Roma, 17 Novembre 2022



Soluzioni per la **salute** basate sulle **proprietà benefiche scientificamente dimostrate** di **prodotti naturali**

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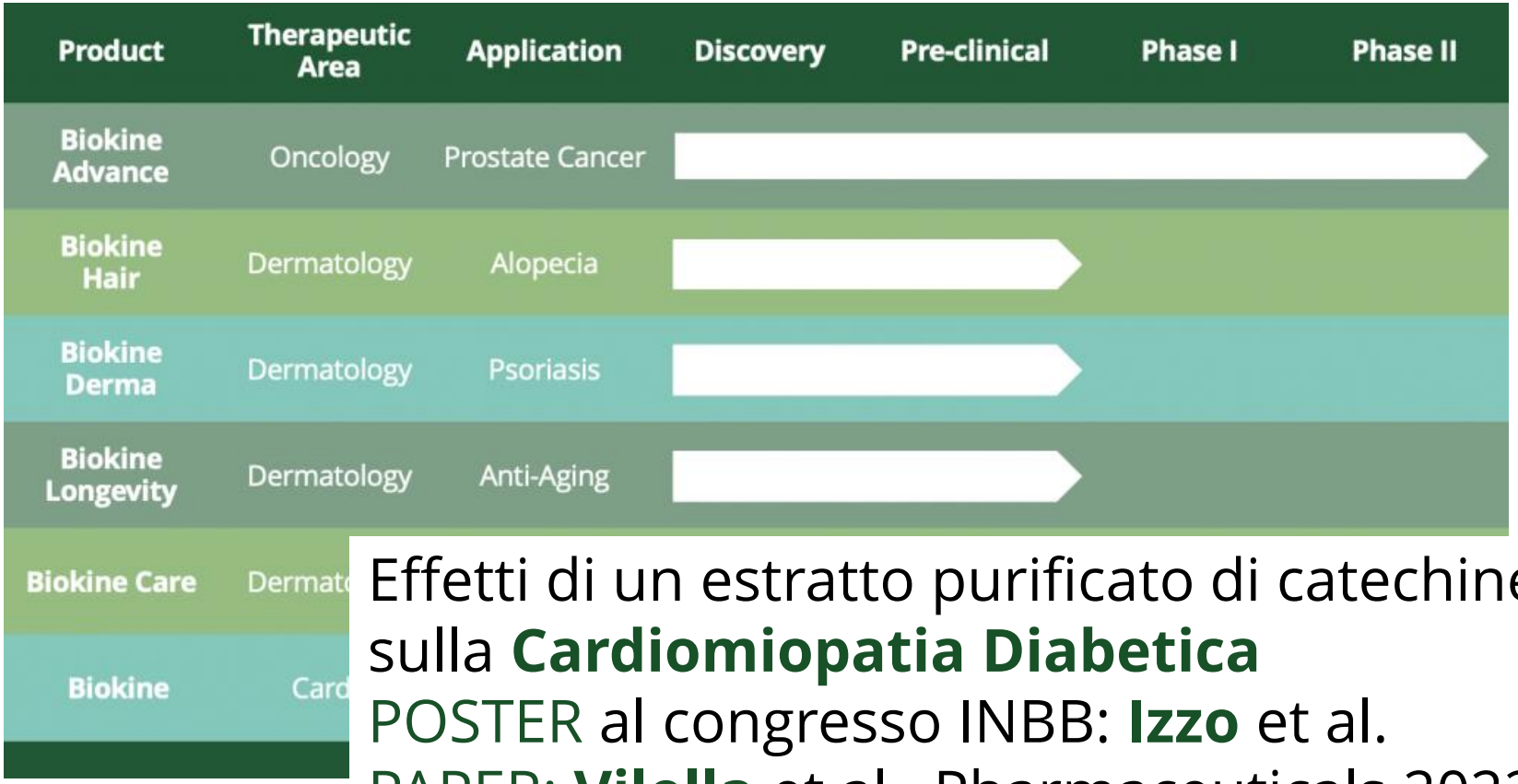
Pipeline: **ambiti di ricerca ed applicazioni**



Effetti di un estratto purificato di catechine sulla **Cardiomiopatia Diabetica**
POSTER al congresso INBB: **Izzo** et al.
PAPER: **Vilella** et al., Pharmaceuticals 2022, Volume 15, Issue 11, 1337

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Ambito: lotta contro la sindrome **COVID-19**

COVID

MDPI

Article

Efficacy of a Polyphenolic, Standardized Green Tea Extract for the Treatment of COVID-19 Syndrome: A Proof-of-Principle Study

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INTRODUCTION

In the autumn of 2020 Italy was among the first countries to be hit hard by the **COVID-19 pandemic**, and one of the first country to adopt the **lockdown protocol** at national level. All activities were paralyzed. In the building where I live there are 10 apartments. Three of these were quarantined, and **four of my neighbors died**, rapidly.

I could not stand and watch.

My research group already had considerable experience in **studying the beneficial properties of purified green tea extracts rich in catechins (GTC) *in vivo***.

The **anti-inflammatory** and **anti-viral properties** of green tea catechins were already known, and **much data were available** in the scientific literature.

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In ADAMAS, a particularly pure formulation of GTC was ready available both as **capsules** and **pure extract**, ready to be dissolved in solution.

Hence the idea of proposing **a compassionate study on a limited number of subjects, to be treated at home**, as a collaborative joint study of ADAMAS and INBB. In case of success, this would have eased the pressure on hospital wards, already overloaded with patients.

I proposed this idea to a hospital doctor (S.C.), on the front line of the local hospital, and to a family doctor (L.G.) as well.

To this aim, we recruited **10 patients for a pilot, compassionate study** performed under strict lockdown rules at the end of 2020.

We tested the effect of the **combined administration** of **capsules, by mouth**, plus **inhalation, by respiratory route**.

Green tea is a good source of catechins (polyphenolic compounds).

Catechins are a family of structurally related polyphenols compounds such as: EGCG, EGC, ECG, EG, EC and others.

In a green tea infusion, the most abundant catechin is epigallocatechin-3-gallate (**EGCG**, about 60%), followed by epigallocatechin (**EGC**, about 20%), epicatechin-3-gallate (**ECG**, about 14%) and epicatechin (**EC**, about 6%).

High quality, purified green tea catechins (**GTC**) exhibit powerful **antioxidant, antiviral and anti-inflammatory properties**.

Their **mechanism of action** has been extensively studied, and much information are available in the literature. **EGCG** is the most active compound. For instance, EGCG binds to 67-kDa laminin receptor (LamR: OMIM, 150370), which use cell rafts as a platform.

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Patients infected with SARS-COV-2 who develop pneumonia often die of a severe acute respiratory syndrome induced by a cytokine-mediated inflammatory response (“**cytokine storm**”).

Several studies have identified **IL-6** levels as **prognostic for severe disease** in COVID-19 positive patients at presentation.

GTC have demonstrated **strong positive effects** on the innate immune system **in animal models of acute respiratory distress syndrome**.

In vitro, GTC or EGCG **reduce cytokine production** from activated immune cells such as macrophages and neutrophils.

In addition to anti-inflammatory properties, the **antiviral action** of catechins is well known since the 1990s.

Recently, Ohgitani et al., 2020 demonstrated 3 logs of **inhibition of infectivity of SARS-COV-2** when the inoculant is exposed to 500 µM **EGCG**.

A review of *in silico* molecular docking studies showed that green tea catechins, in particular EGCG, GCG, and CG, are **among the molecules with the highest binding affinity to the active site of the SARS-COV-2 3CLpro protease** and, therefore, possess the theoretical ability to inhibit its activity.

The authors urged **clinical trials based on these molecules** (Peterson, L et Al. 2020; Mhatre, S et Al, 2021).

Notably, catechins, are **safe for human use**. In the past, our **clinical trials** with GTC only showed mild side effects.

For these reasons we investigated a standardized GTC own by ADAMAS **(ThE)** in the real clinical setting.

The batch of **ThE** that we used was composed of **85–95% total catechins** and **65–70% total EGCG**, virtually free **of caffeine (< 0.5%)**.

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THE COMPASSIONATE TRIAL

We recruited 10 COVID-19 patients, **symptomatic, and with positive nasopharyngeal swab tests** for the SARS-COV-2 virus.

We treated them **for 15 days at home** while they were awaiting hospitalization. Four of them were receiving standard of care therapy.

The study was performed by **family doctors** in accordance with the rules in force during the lockdown in the Emilia-Romagna region of Italy.

Our trial has to be considered a pilot, compassionate, proof-of-principle study.

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First of all, we tested the safety and tolerability of **inhalation + capsule administration** in two healthy volunteers, both negative for COVID-19, but affected by symptoms of influenza. The treatment was well tolerated and **the flu symptoms disappeared rapidly**.

Later, the study doctor Dr. SC was badly exposed to the virus when her personal protective equipment failed while treating a violently-ill COVID-19 patient in the ward. She used the treatment as described below: she had no adverse effects, and **never got sick**.

One first volunteer with COVID-19 symptoms and positive swab test was treated at home by the Dr. SC early in the pandemic. No side effects occurred, and **the patients recovered very soon**. No need for hospitalization.

Then we recruited 9 more patients in the fall surge, all symptomatic and with positive nasopharyngeal swabs for COVID-19, while they were awaiting hospitalization. The **vaccine was not available**, hospitals were crowded, and triage kept those with mild or moderate symptoms **at home**; they were visited and treated there by an **hospital doctor**, Dr. SC and a **family doctor**, Dr. LG.

Dose and Method of Administration

1. **Nebulization**: 5 mL of a 0.3% ThE solution, made fresh daily in phosphate saline buffer at pH 5.8, with a breathing mask, twice a day, for up to 15 days (total catechins: 27 mg/day; EGCG: 19 mg/day);

2. **Oral administration**: 3 cps/day for up to 15 days. Each capsule contained 300 mg of ThE (813 mg total catechins/day and 576 mg EGCG/day).

The combined **total daily dose** was **595 mg of EGCG**: considered safe, because it was "below 800 mg EGCG", as suggested by the European Food Safety Agency (EFSA).

(*Considering the average content of catechins found in brewed green tea, this total daily dose corresponded to about 850 mL of a tea infusion**).

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For **nebulization** at home (twice a day), we used simple breathing mask, which are cheap and freely sold in Italy in pharmacies, parapharmacies and health shops.

These are just examples:

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Inclusion criteria: Symptomatic, over 18y, with a positive nasopharyngeal swab for COVID-19. Symptoms: fever > 38°C, loss of taste, smell, and respiratory or gastrointestinal symptoms. **Exclusion criteria**: none. Patients: n = 10.

Primary objective: Patient recovery. Secondary objectives: reduction of markers of inflammation and time until negative SARS-COV-2 swab.

According to the lockdown rules, patients had to be symptomatic to receive a nasopharyngeal swab test for SARS-COV-2. Following the positive result, they were visited and treated by their family doctors at home (Dr. LG and Dr. SC) within a few days (median 5 days) of their symptoms worsening.

First blood sample: On recruitment day (T0);

Second blood sample: when patients' symptoms were gone, at a median of 9 days later, range of 7–15 (T1).

Blood samples were sent to different laboratories in the territory for **standard analyses**.

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Symptoms, etc, at the time of doctor's first visit

Table 1. Patients of the trial at the time of the doctor's first visit, with demographics, co-morbidities, and other medications including duration and dosage.

Patient number	1	2	3	4	5	6	7	8	9	10
Symptoms:										
Difficulty breathing	yes	yes		yes					yes	
Cough	yes	yes		yes	yes	yes	yes	yes	yes	yes
Tiredness 30 d after	yes	yes								
No sense of smell						yes		yes		
No sense of taste						yes		yes		
Signs:										
Fever (Temperature)	>38 °C	>38 °C		>38 °C	>38 °C	>38 °C	>38 °C	>38 °C	>38 °C	>38 °C
Pneumonia CT score	10–15%	10–15%		10–15%					40%	
Hospitalized	no	no	no	no	no	no	no	no	yes	no
Patient demographics:										
Age	74	73	50	53	47	27	55	28	66	38
Gender	M	F	M	M	F	F	F	F	F	F
Comorbidities	yes	yes							yes	
Other treatments:										
Steroids	yes 10 days	yes 10 days								
Azithromycin 500 mg	Yes 10 days	yes 10 days		yes 4 days					yes 4 days	
Low Mol Weight Heparin	yes 10 days	yes 10 days		yes 10 days					yes 10 days	
Hydroxychloroquine 400 mg once, plus 200 mg later									yes 5 days	
Methylprednisolone 32 mg, one shot				yes 2 days						

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Laboratory and SWAB result: result of first nasopharyngeal swab test (before treatment) and second test (during ThE treatment): positive/negative; (*) PT 7 was positive at second test but with a very low load of virus nucleic acid. T0–2nd swab: elapsed time (days) from T0 to second swab, i.e., (**) time to first negative swab during ThE treatment for 7/10 patients; **T0–T1: elapsed time from start of ThE therapy to full recovery of patients (days).** Statistical analysis by paired T-test (2-tails) shows **statistical significance** ($p < 0.05$) for **Eosin, AAT and CRP**. Seven patients showed **a decrease of IL-6 and ESR** following treatment. **Abbreviations**: PT, patient; white, white blood cell count; Hb, hemoglobin; Neutro, neutrophils; Lymph, lymphocytes; Mono, mononuclear cells; Eosin, eosinophils; ESR, erythrocyte sedimentation rate; AAT, α-1 antitrypsin; CRP, C-reactive protein; IL-6, interleukin-6 cytokine; ND = no data.

Table 2. Laboratory data at recruitment (T0, first blood withdrawal, beginning of ThE treatment) and at second blood withdrawal (T1, full recovery of patients).

Patient Number	Blood Withdr.	White	Hb	PLT	Neutro	Lymph	Mono	Eosin	ESR	AAT	CRP	IL-6	Swab Result	Time T0–2nd Swab	Time T0–T1
		$\times 10^3/\mu L$	g/dL	$\times 10^3/\mu L$	%	%	%	%	mm	mg/dL	mg/L	pg/L			
1	T0	7.36	13.5	242	82.4	10.6	6.9	0	55	165	5.65	26.03	pos		
	T1	6.77	13.3	179	86.1	9.4	4.1	0.2	18	139	0.41	1.5	NEG	6	9
2	T0	6.06	13.7	295	62.4	27.1	9.2	0.8	71	235	27.9	55.5	pos		
	T1	9.27	14.3	325	83.7	11.5	4	0.3	20	158	0.76	5.21	NEG	6	9
3	T0	4.99	15.3	315	71.6	22.4	5.6	0	29	114	0.4	6	pos		
	T1	5.03	14.3	254	51.4	38.4	7.8	1.4	16	97	0.61	24.19	POS	6	9
4	T0	8.33	14.9	269	73.8	19.6	4.7	1.7	38	170	23	69.09	pos		
	T1	8.65	15.5	460	59.6	28.4	7.6	3.7	55	155	6.33	9.9	NEG	10	7
5	T0	4.7	10.9	275	49.4	35.5	12.6	2.3	74	166	15	8.25	pos		

Table 2. *Cont.*

Patient Number	Blood Withdr.	White	Hb	PLT	Neutro	Lymph	Mono	Eosin	ESR	AAT	CRP	IL-6	Swab Result	Time T0–2nd Swab	Time T0–T1
		×10³/ µL	g/dL	×10³/ µL	%	%	%	%	mm	mg/dL	mg/L	pg/L			
	T1	9.3	10.4	396	54.7	33.9	8.6	2.6	38	114	0.61	2.87	NEG	13	15
6	T0	6.63	13.8	197	41.8	48	9.4	0.3	22	207	3.72	7.82	pos		
	T1	5.91	13.4	261	59.9	33.2	4.5	1.8	19	230	6.54	4.34	NEG	10	12
7	T0	7.27	13.1	205	58.8	32.3	8	0.8	6	120	3.72	184.95	pos		
	T1	8.13	13.6	265	63.3	29.4	6.2	0.7	10	116	0.42	3	POS	(*) 4 (*)	7
8	T0	7.12	12.3	277	61.5	25.6	9.6	2.7	6	127	1	12.75	pos		
	T1	7.41	11.7	258	61.9	23.9	10.5	3.2	2	81	0.39	12.75	NEG	6	9
9	T0	4.16	14.2	142	59.2	35.3	5	0	78	254	18	124.42	pos		
	T1	7.63	12.5	ND	66.1	23.3	7.6	2.5	ND	ND	13.3	14.76	NEG	10	8
10	T0	5.13	13.4	192	61.2	30.6	7.6	0.4	34	151	0.53	17.37	pos		
	T1	6.26	13	210	65.3	28.1	5.9	0.5	21	136	0.29	194.05	POS	6	7
	Normal range	4–10	13.5–18.0	150–400	40–75	15–45	3–12	1–8	2–25	90–200	< 5.00	0–10			
Mean T0		6.174	13.51	240.9	62.21	28.7	7.86	0.9	41.3	170.9	9.89	51.22		8.7 (**)	9.2
Mean T1		7.414	13.28	299.667	65.2	25.95	6.68	1.69	22.11	136.22	2.97	7.26		6–13 (days)	7–15 (days)
SD T0		1.377	1.256	54.836	11.705	10.226	2.448	1.68	23.56	137.89	2.99	9.59			
SD T1		1.53	1.5	89.202	11.326	9.353	2.125	0.9	41.3	170.9	9.89	51.22			
	T-test for paired data, bilateral, 2 tails							<0.05		<0.05	<0.05				

PS: Patients 3, 7 and 10 tested swab-negative approximately 7-10 days after the end of the study

RESULTS

All 10 patients recovered fully within treatment time with a **median of 9 days** (range: 7–15 days).

Seven out of 10 patients had a **negative SARS-COV-2 swab at a median of 9 days from starting ThE therapy** (range: 6–13 days).

Only PT 3, 7 and 10 had a positive second swab at days 6, 5 and 6, respectively, but **all three were free of symptoms and fully recovered a few days later, exiting quarantine at the end of ThE therapy**. They finally tested swab-negative approximately 7-10 days later. Anyhow, they did not infect anyone afterwards, including cohabiting persons.

PT 1, 2, 5 and 8 were nested in **familial clusters**. Family members of the clusters who refused to sign the informed consent form did not receive the ThE treatment, only standard of care therapy (*n* = 4). **All of them took longer until their first negative swab (< 1 month) and recovery (from 2 to 6 months).**

These subjects may be considered as **internal controls for the study**.

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IL-6 level was the most informative in the blood tests. Seven of 10 patients had an IL-6 greater than 10 pg/mL, and three of 10 had greater than 100 pg/mL. The four oldest (PT 1, 2, 7, and 9) had high IL-6 values: 26, 55, 185 and 124 pg/mL, respectively. These **high values would normally indicate that these patients were developing SARS**.

A statistical analysis performed on the **patients with age > 52 years** (*n* = 5; PT 1, 2, 4, 7, and 9), who were **at high risk** as demonstrated by high IL-6 values, showed that **IL-6 significantly decreased after treatment (t-test, *p* <0.03).**

Therefore, **their rapid recovery was surprising**.

Statistical analyses (paired T-test, two tails) showed **a significant decrease of eosinophils, AAT, and CRP** in the patients following treatment.

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DISCUSSION

We discussed the results on a peer-to-peer basis at the time of publication on COVID Journal. In the end, the conclusion was that the standard of care treatments administered to 4 patients **cannot explain the result obtained with ThE in this study**.

Rapid recovery: Mancuso et Al. 2020 followed 4,480 patients with a positive swab and date data in Reggio Emilia province, Italy, from 26 February to 22 March (the province of Reggio Emilia is next to the province of Parma). Only symptomatic patients were tested. In their study, the **median time to a first negative swab was 31 days** from the first positive swab (IQR 24–41), estimated using the Kaplan-Meier method. **At 10 days after the first swab, only 0.7% of these patients had a first negative swab, versus 70% in our study** (see Table 2).

A statistical comparison between Mancuso's data and ours showed the **one-tailed probability by the Fisher-Yates test that this would happen by chance after 10 days was $p < 0.0023$, and $p < 0.005$ at 20 days**.

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The **anti-inflammatory effects** of GTC have been studied and demonstrated repeatedly, as discussed above. The concentration of EGCG in the nebulizer solution used for the trial was 5 mM, **ten times** 500 µM (Ohgitani et al. 2020), and the exposure time was **much longer**. A direct **anti-viral action in the lungs** has been suggested. **Direct inactivation of fresh virus** in the lung may be part of the effectiveness of this therapy.

Other mechanisms may be present. Besides important factors like purity and dosage, we may speculate that **delivery to the lungs** may be important for efficacy, and avoidance of the "**cytokine storm**".

Further clinical studies, with more patients, will be necessary to properly address this issue.

We recently searched the scientific literature, but **did not find any evidence showing that drinking green tea by itself prevents infection with SARS-COV-2 or is curative for COVID-19 syndrome (*).**

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This is the **first report documenting the efficacy of a highly purified green tea catechin extract (ThE) against COVID-19 syndrome in a real clinical setting.**

The major limitation of our study was the small number of patients; nevertheless, **the most important results reached statistical significance**. The very high rate of positive response that we observed may open new perspectives in the fight against COVID-19 syndrome.

Early treatment with GTC at first appearance of symptoms could be a **complementary therapy made at home** that can complement official therapies, including vaccination, and therefore decrease the pressure on hospital wards.

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A direct implementation for the market of our study:

the **Dtech biogel spray** against SARS-COV2 and COVID-19 syndrome

A collaboration with D-Tech and Cube-Labs

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Article

Efficacy of a Polyphenolic, Standardized Green Tea Extract for the Treatment of COVID-19 Syndrome: A Proof-of-Principle Study

COVID **2021**, *1*(1), 2-12;
https://doi.org/10.3390/covid1010002

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THANK YOU FOR YOUR ATTENTION

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Citation: Bettuzzi, S.; Gabba, L.; Cataldo, S. Efficacy of a Polyphenolic, Standardized Green Tea Extract for the Treatment of COVID-19 Syndrome: A Proof-of-Principle Study. *COVID* **2021**, *1*, 2–12. https://doi.org/10.3390/covid1010002

free of symptoms. Inflammation markers α-1 anti-trypsin, C-reactive protein and eosinophils had significantly decreased. The IL-6 and erythrocyte sedimentation rate decreased in 7 out of 10 patients. To the best of our knowledge, this is the first report of the efficacy of green tea catechin against COVID-19 syndrome. These results may open new perspectives in the fight against the disease.

Keywords: antioxidant; antiviral; catechin; COVID-19; cytokine storm; EGCG; green tea; IL-6; inflammation; polyphenols; SARS-COV-2; theaphenon E

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