

Contribution to the Evaluation of the Anti-inflammatory, Analgesic and Antipyretic Activities of Covid-Organics

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Abstract Covid-Organics is an improved traditional medicine made from a plant called *Artemisia annua* Linn. It is developed by the Malagasy Institute for Applied Research with the aim is to treat coronavirus disease or Covid-19. The present study aims to justify the use of Covid-Organics by evaluating the anti-inflammatory, analgesic and antipyretic activities. Acute inflammation was induced by using the carrageenan and formaldehyde models. The results obtained show that Covid-Organics at the doses used significantly reduces ($p < 0.05$; $p < 0.01$; $p < 0.001$) the edema induced by carrageenan and formaldehyde. Chronic inflammation was evaluated using the model of formaldehyde induced arthritis in rat. Results obtained show that Covid-Organics and diclofenac (standard drug) significantly reduce ($p < 0.001$) the evolution of edema throughout the period of the experiment compared to the control group. The analgesic effect was evaluated by using the method of acetic acid and formaldehyde induced pain. Covid-Organics significantly reduced ($p < 0.001$) the number of abdominal writhing induced by acetic acid, as well as the number of formaldehyde-induced paw licking and biting ($p < 0.01$ and $p < 0.001$). The antipyretic effect was induced using brewer's yeast induced pyrexia. The results obtained showed that Covid-Organics (0.6 and 1.2 mL/100g) increased significantly ($p < 0.05$; $p < 0.01$ and $p < 0.001$) pyrexia induced by brewer's yeast compared the control group. In conclusion, Covid-Organics (0.6 and 1.2 mL/100g) has anti-inflammatory, analgesic and antipyretic effects. These observations justify the use of Covid-Organics against the symptoms of coronavirus disease.

Keywords: anti-inflammatory, analgesic, antipyretic, Covid-Organics

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1. Introduction

Population health has always been a major public concern involving national and international systems, research and information organizations. Indeed, following the coronavirus disease-2019 pandemic, also called Covid-19, the world is plunged into a health and socio-economic crisis, putting pressure on each country affected by this pandemic. This infectious disease is caused by a virus called severe acute respiratory syndrome coronavirus 2 which uses angiotensin 2 cell receptors (ACE2) to enter the host cell and then cause inflammation of the respiratory cells, mainly type II pneumocytes, leading to symptoms such as fever, chest pain, cough, headache, sore throat, etc... [1]. The fever, inflammation and pain that accompany not only this infectious disease but also many

other communicable and non-communicable diseases, constitute a major public health problem. This disease is one of the so-called emerging diseases, it nowadays has a significant impact on the economy and global public health. In this regard, Worldwide, out of a population of 7.874.965.730, there are 6.344.729 deaths and 552.498.044 confirmed cases [2]. Faced with this slaughter, many countries have embarked on the search for remedies to protect their population. Which research continues to this day. This is how several vaccines have been developed. However, apart from the manufacture of these vaccines and the use of therapeutic combinations for the management of this pandemic, man has used medicinal plants in the response against it. In China, for example, studies have shown the use of many recipes based on medicinal plants against this pandemic [3]. Thus, many recipes based on medicinal plants have been developed, including Covid-Organics, developed by the

Malagasy Institute for Applied Research. This herbal tea or traditional recipe is made from *Artemisia annua* Linn, a plant generally used in traditional Chinese medicine to treat malaria and fever but; According to the literature, this plant is rich in secondary metabolite and also has other pharmacological activities, namely: antiviral, anti-inflammatory, anti-parasitic, anti-viral, anti-inflammatory, anti-fungal and anti-bacterial, anti-cancer, immunoregulation, anti-osteoporotic [4]. The present study aims to justify the use of *Covid-Organics* in the treatment of COVID-19 by evaluating its effects on inflammation, pain and fever which are among the symptoms that accompany this disease.

2. Material and Methods

2.1. Vegetable Material

The *Covid-Organics* (Figure 1) preparation was used. This preparation developed by the Malagasy Institute for Applied Research.



Figure 1. Illustration of Covid-organic 33cl

2.2. Animal Material

Males and females albinos rats weighing between 150-200 g and albinos mice males and females weighing between 25-30 g were used. These animals were provided by the laboratory of Faculty of Science and Techniques (Université Marien NGOUABI). They were fed with a standard food with a free access to water. They were acclimatized during one week before experimentation and were maintained under standard conditions (12 hours light and 12 hours dark) and at the temperature of 24 ± 1 °C. The rules of ethics published by the International Association for the Study of Pain [5] have been considered

2.3. Carrageenan Induced Inflammation

Method described by Elion Itou et al. (2014) [6] was used. Carrageenan is a polysaccharide which, when injected into an animal, causes acute inflammation 30 minutes later during which the volume of the paw increases over time [7]. The animals were divided into groups of 5 rats each. Different doses of *Covid-Organics*

(0.6 and 1.2 mL/100g, diclofenac (standard drug, 5 mg/kg) and distilled water (control group, 0.5 ml/100 g) were administered orally to groups, 1 h prior to the local injection of carrageenan (0.2 ml, 1%) into the plantar aponeurosis of the right paw. Edema was measured by using pletysmometer (LE 7500 DIGITAL BIOSEB) at 1/2, 1, 2, 3, 4, 5, 6 and 24th.

2.4. Formaldehyde Induced Paw Inflammation

Inflammation was induced by administration of 2.5% formaldehyde [8]. The animals were divided into groups of 5 rats each. Different doses of *Covid-Organics* (0.6 and 1.2 mL/100g, diclofenac (standard drug, 5 mg/kg) and distilled water (control group, 0.5 ml/100 g) were administered orally to groups, 1 h prior to the local injection of formaldehyde (0.2 ml, 2.5%) into the plantar aponeurosis of the right paw. Edema was measured by using pletysmometer (LE 7500 DIGITAL BIOSEB) at 1, 2, 3, 4 hours.

2.5. Formaldehyde-induced Arthritis Test

Osteoarthritis was induced by administration of formaldehyde solution (2.5 %). The animals were divided into groups of 5 rats each. Different doses of *Covid-Organics* (0.6 and 1.2 mL/100g, diclofenac (standard drug, 5 mg/kg) and distilled water (control group, 0.5 ml/100 g) were administered orally to groups, 1 h prior to the local injection of formaldehyde (0.2 ml, 2.5%) into the plantar aponeurosis of the right paw. Animals were treated during 9 days with only one administration of the products tests. The second administration of formaldehyde was made the third day of treatment [9] in the same paw. Edema was measured by using pletysmometer (LE 7500 DIGITAL BIOSEB).

2.6. Acetic Acid-induced Abdominal Writhing in Mice

The administration of 0.6 % acetic acid intraperitoneally to the mice causes a pain syndrome. The pain syndrome is characterized by stretching movements of the hind legs and torsion of the dorso-abdominal muscles. An analgesic would act by decreasing the number of abdominal writhing compared to the control group. The animals were divided into groups of 5 rats each. Different doses of *Covid-Organics* (0.6 and 1.2 mL/100g), paracetamol (standard drug, 100 mg/kg) and distilled water (control group, 0.5 ml/100 g), 1 hour before intraperitoneally administration of the acetic acid solution to the animals [6]. 5 minutes after the injection of acetic acid, the number of abdominal writhes developed by the animals was recorded during 20 min [7].

2.7. Formaldehyde-induced Paw Licking

The formaldehyde-induced paw licking was studied in rat using the method reported by Elion Itou et al, (2017) [7]. Sub plantar administration of formaldehyde 2.5 % induces neurogenic pain and inflammatory pain. The

animals were divided into groups of 6 mice each. The different doses of *Covid-Organics* (0.6 and 1.2 mL/100g), tramadol (standard group, 10 mg/kg) distilled water (control group, 0.5 mL/100g) were administered orally to groups, 1 h prior to the local injection of formaldehyde subcutaneous plantar of the right paw. Immediately, animals were placed in various cages to observe the noxious effects. The frequency that the animal licks or bites its paw was monitored over 0 to 10 min for neurogenic pain response and 10 to 30 min for inflammatory pain response.

2.8. Brewer's Yeast Pyrexia Test

The subcutaneous administration of the 20 % brewer's yeast induces 24 hours after hyperthermia. An antipyretic would act by decreasing this hyperthermia. For selected the animals, the normal rectal temperature of each rat was measured using a digital thermometer. Fever was induced in all animals by subcutaneous administration of 20 % solution of brewer's yeast (*Saccharomyces cerevisiae*) 10 mL/kg [10]. 24 hours later, the rectal temperature of the animals was measured again. All animals that did not show an increase in rectal temperature of 0.5 °C were excluded from the experiment [11]. The animals selected were divided into groups of 5 rats each and treated orally with the different doses of *Covid-Organics* (0.6 and 1.2 mL/100g), paracetamol (standard drug, 100 mg/kg) and distilled water (control group, 0.5 mL/100 g). Rectal temperature was measured at 1, 2, 3, 4 and 5 hours after administration of the products.

2.9. Statistical Analysis

All values were expressed as mean $\pm$ standard error of mean (SEM). Analysis of variance followed by Student-Fischer t test "t" was performed. The significance level was set at $p < 0.05$

3. Results

3.1. Effect of *Covid-Organics* on Carrageenan Edema

Table 1 shows the effect of *Covid-Organics* on the edema evolution. Thirty minutes (30 minutes) after Subplantar injection of the carrageenan produced an inflammatory edema which increased gradually with a maximum between at the 4th hour after injection. At 4th, the inflammatory edema are 1.90 ± 0.05 ; 0.47 ± 0.07 ; 0.79 ± 0.01 and 0.70 ± 0.01 respectively for the control group, diclofenac, *Covid-Organics* (0.6 and mL/100g). This figure also shows 1th after administration of carrageenan, *Covid-Organics* at the doses used did not significantly ($p > 0.05$) reduce the evolution of edema compared to the control group. However, 2th after administration of carrageenan, the diclofenac used as reference molecule and *Covid-Organics* at the doses used (0.6 and 1.2 mL /100g) significantly ($p < 0.05$; $p < 0.01$ and $p < 0.001$) decrease the evolution of the inflammatory edema compared to control group. At 4th, the percentage of inflammatory edema is 75.26; 58.42; and 63.15% respectively for diclofenac and *Covid-Organics* at the respective doses of 0.6 and 1.2 mL/100 g.

3.2. Effect of *Covid-Organics* on Formaldehyde Edema

The effect of *Covid-Organics* on formaldehyde-induced edema is given in Table 2. *Covid-Organics* (0.6 and 1.2 mL /100g) and diclofenac (standard drug, 5 mg/kg) significantly decrease ($p < 0.001$) the evolution of the animal's paw inflammatory edema from the first hour (1st) until the fourth hour (4th) of the experiment. At 4th, the volumes of the paw inflammatory edema are 1.26 ± 0.02 ; 0.43 ± 0.03 (65.85 % inhibition); 0.85 ± 0.03 (32.53 % inhibition) and 0.70 ± 0.02 (44.44 % inhibition) respectively for control group, diclofenac and for *Covid-Organics* (0.6 and 1.2 mL/100g).

Table 1. Effect of *Covid-Organics* in edema evolution induced by carrageenan in rat

Treatment	Doses	Volume of edema (ml)							Inhibition (%)		
		½ H	1H	2H	3H	4H	5H	6H	2H	4H	6H
Control group	5 mL/kg	1.02±0.24	1.60±0.24	1.65±0.07	1.77±0.05	1.90±0.05	1.67±0.09	1.62±0.04	/	/	/
Diclofenac	5 mg/kg	0.59±0.01ns	0.59±0.01*	0.63±0.01***	0.52±0.01***	0.47±0.07***	0.45±0.01***	0.44±0.01***	61.81	75.26	72.82
Covid organics	0.6 mL/100g	0.73±0.03ns	1.16±0.03ns	0.92±0.01***	0.85±0.04***	0.79±0.01***	0.70±0.02***	0.64±0.01***	44.24	58,42	60.49
	1.2 mL/100g	0.54±0.01ns	1.15±0.01**	0.86±0.02***	0.85±0.05***	0.70±0.01***	0.55±0.01***	0.54±0.02***	47.87	63,15	66.66

Each value represents the mean $\pm$ ESM. of edema volume. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ Significant different (Student t-test) versus control group.

Table 2. Effect of *Covid-Organics* in edema evolution induced by formaldehyde in rat

Treatment	Doses	Volume de l'œdème (ml)				Inhibition (%)	
		1H	2H	3H	4H	2H	4H
Control group	5 mL/kg	1.15 ± 0.01	1.18 ± 0.04	1.25 ± 0.04	1.26 ± 0.020	/	/
Diclofenac	5 mg/kg	$0.68 \pm 0.02^{***}$	$0.75 \pm 0.01^{***}$	$0.46 \pm 0.01^{***}$	$0.43 \pm 0.03^{***}$	36.44	65.85
<i>Covid organics</i>	0.6 mL/100g	$0.87 \pm 0.01^{***}$	$1.05 \pm 0.08^{***}$	$0.88 \pm 0.00^{***}$	$0.85 \pm 0.03^{***}$	11.01	32.53
	1.2 mL/100g	$0.89 \pm 0.01^{***}$	$0.99 \pm 0.01^{***}$	$0.89 \pm 0.00^{***}$	$0.70 \pm 0.02^{***}$	16.10	44.44

Each value represents the mean $\pm$ ESM Of edema volume. *** $p < 0.001$ Significant different (Student t-test) versus control group.

3.3. Effect of Covid-Organics on Formaldehyde Induced Osteoarthritis

The effect of *Covid-Organics* (0.6 and 1.2 mL/100g) and diclofenac on osteoarthritis is given in Table 3. These results show that *Covid-Organics* and diclofenac decrease significantly ($p < 0.001$) the evolution of the osteoarthritis throughout the period of the experiment compared to the control group (Table 3). The inhibition of osteoarthritis evolution are 54.92; 68.84; 44.73; 65.71 and 64.64 % for diclofenac respectively on D1, D3, D5, D7 and D9 (Table 3). They are 40.14; 40.44; 24.34; 40.00 and 36.36 % for *Covid-Organics* (0.6 mL/100 g) respectively on D1, D3, D5, D7 and D9. For *Covid-Organics* (1.2 mL/100) they are 47.18; 61.02; 32.89; 52.14 and 40.44 respectively on D1, D3, D5, D7 and D9.

3.4. Effect of Covid-organics on Abdominal Writhing

The results of the effect of *Covid-Organics* on abdominal writhing are given in Table 4. This table shows that diclofenac and *Covid-Organics* at the doses used significantly ($p < 0.001$) reduce the number of abdominal cramps compared to the control group. The number of abdominal writhing produced by the mice of each

groups is 65.00 ± 2.78 ; 33.6 ± 0.88 ; 49.56 ± 2.21 ; 43.32 ± 1.10 respectively for control group, paracetamol and *Covid-Organics* (0.6 and 1.2 mL/100g). In addition, the percentages of pain inhibition are 48.30% for the mice treated with paracetamol, 23.75 and 33.35% for the mice treated with *Covid-Organics* at the respective doses of 0.6 and 1.2 mL/100 g (Table 4).

3.5. Effect of Covid-Organics on formaldehyde-induced pain

Subplantar administration of formaldehyde induces neurogenic and inflammatory pain response (Table 5). *Covid-Organics* (0.6 and 1.2 mL/100 g) and tramadol (10 mg/kg) significantly decrease ($p < 0.001$) compared to the control group the frequency of licking and biting the paw on the two phases. The paw licking and biting frequency is 15.40 ± 1.14 ; 5.50 ± 0.28 ; 11.90 ± 0.64 and 9.25 ± 0.47 respectively for distilled water (control group), tramadol (standard drug) and *Covid-Organics* (0.6 and 1.2 mL / 100g) for neurogenic pain response (Table 2). In inflammatory pain response, the frequency is 35.25 ± 0.25 ; 5.25 ± 0.47 ; 18.25 ± 1.11 ; 18 ± 0.64 . The percentage inhibition of tramadol and *Covid-Organics* (0.6 and 1.2 mL/100 g) are respectively of 64.28; 22.72 and 39.93% for neurogenic pain response. howether it is of 85.10; 48.22 and 48.93% for inflammatory pain response (Table 5).

Table 3. Effect of aqueous extract of *Covid organics* on osteoarthritis induced by formaldehyde

Treatment	Doses	Volume of edema					Inhibition %				
		D1	D3	D5	D7	D9	D1	D3	D5	D7	D9
Control group	5 mL/kg	1.42 $\pm$ 0.13	1.36 $\pm$ 0.10	1.52 $\pm$ 0.02	1.40 $\pm$ 0.16	0.99 $\pm$ 0.08	/	/	/	/	/
Diclofenac	5 mg/kg	0.64 $\pm$ 0.03***	0.43 $\pm$ 0.02***	0.84 $\pm$ 0.81***	0.48 $\pm$ 0.03***	0.35 $\pm$ 0.01***	54.92	68.38	44.73	65.71	64.64
<i>Covid organics</i>	0.6 mL/100g	0.85 $\pm$ 0.01***	0.81 $\pm$ 0.02***	1.15 $\pm$ 0.01***	0.84 $\pm$ 0.09***	0.63 $\pm$ 0.06***	40.14	40.44	24.34	40.00	36.36
	1.2 mL/100g	0.75 $\pm$ 0.01***	0.53 $\pm$ 0.02***	1.02 $\pm$ 0.02***	0.67 $\pm$ 0.01***	0.59 $\pm$ 0.03***	47.18	61.02	32.89	52.14	40.40

Each value represents the mean $\pm$ ESM of edema volume. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ Significant different (Student t-test) versus control group.

Table 4. Effect of aqueous extract of *Covid organics* on abdominal writhes induced by 0.6 % acetic acid solution in mice

Traitement	Doses	Number of abdominal writhes	Inhibition (%)
Control group	0,5 mL/100 g	65.00 $\pm$ 2.78	/
Paracetamol	100 mg/kg	33.6 $\pm$ 0.88***	48.30
<i>Covid-Organics</i>	0.6 mL/100 g	49.56 $\pm$ 2.21***	23.75
	1.2 mL/100 g	43.32 $\pm$ 1.10***	33.35

Each value represents the mean $\pm$ ESM. *** $p < 0.001$ Significant different (Student t-test) versus control group.

Table 5. Effect of *Covid-Organics* on neurogenic and inflammatory pain response induced by formaldehyde in rat

Treatment	Doses	Neurogenic pain response (0-10 min)		Inflammatory pain response (10-30 min)	
		Frequency of legs licking and of biting	Inhibition %	Frequency of legs licking and of biting	Inhibition %
Control group	0.5 mL/100g	15.40 $\pm$ 1.14	/	35.25 $\pm$ 0.25	/
Tramadol	10 mg/kg	5.50 $\pm$ 0.28***	64.28	5.25 $\pm$ 0.47***	85.10
<i>Covid-Organics</i>	0.6ml/100g	11.90 $\pm$ 0.64**	22.72	18.25 $\pm$ 1.11***	48.22
	1.2 ml/100g	9.25 $\pm$ 0.47***	39.93	18 $\pm$ 0.64***	48.93

*** $p < 0.001$; (Student t-test). Each value represents the mean $\pm$ ESM; versus control group.

Table 6. Effect of *Covid organics* on pyrexia induced by the Brewer's yeast (*Saccharomyces cerevisiae*) in rat

Treatment	Doses	T ⁰ normal	Temperature(T°) after pyrexia induced					
			0h (24 th after)	1h	2h	3h	4h	5h
Control group	(0.5 mL/100g)	35.30±0.38	37.42±0.24	37.56±0.24	37.48±0.15	37.26±0.20	37.08±0.19	36.82±0.10
Paracétamol	(100 mg/kg)	35.24±0.28	37.06±0.26	36.12±0.23**	35.96±0.30**	35.56±0.29**	35.22±0.24***	35.06±0.24***
<i>Covid-Organics</i>	(0.6 mL/100g)	34.62±0.27	36.18±0.30	36.72±0.40ns	35.90±0.23**	35.76±0.27**	35.58±0.19**	35.56±0.20**
	(1.2 mL/100g)	35.28±0.30	36.78±0.14	36.44±0.22*	35.84±0.21***	35.54±0.33**	35.48±0.31**	35.42±0.30 **

Each value represents the mean ± ESM of temperature. *p<0.05, **p < 0.01 and ***p < 0.001 significant different (Student t-test) versus control group. ns= no significant value p>0.05.

3.6. Effect of *Covid-Organics* on Pyrexia

The results of the effect of *Covid-Organics* (0.6 and 1.2 mL/100g) on brewer's yeast-induced hyperthermia are shown in Table 6. They show that paracetamol (100 mg/kg) and *Covid-Organics* (0.6 and 1.2 mL/100g) decrease significantly (p<0.05; p<0.01 and p< 0.001) the hyperthermia induced by ordinary yeast throughout the period of the experiment compared to the control group. However, *Covid-Organics* (0.6mL/100g) did not decrease the hyperthermia (p>0.05) induced by ordinary yeast at the first hour compared to the control group. At the second hour, the decrease in hyperthermia is 4.21% for paracetamol and *Covid-Organics* 0.6 mL/100g; 4.37% for *Covid-Organics* 1.2 mL / 100 g. At the fifth hour (5th), they are 4.78; 3.42 and 3.80% respectively for paracetamol and *Covid-Organics* (0.6 mL/100g and 1.2 mL/100g).

4. Discussion

This work aimed to justify the use of *Covid-Organics* in the treatment against the coronavirus called SARS-CoV-2. The choice of this product is justified by the fact that *Covid-Organics* is cited among the recipes used against the coronavirus disease pandemic. Coronavirus disease is a disease caused by inflammation of respiratory cells by SARS-CoV-2. It is with this in mind that we have chosen to evaluate the anti-inflammatory properties of *Covid-Organics*. To do this, three methods were used to assess the anti-inflammatory activity of *Covid-Organics*, namely: inflammation induced by carrageenan and formaldehyde for the study of acute inflammation as well as osteoarthritis induced by formaldehyde in the study of chronic inflammation. On the other hand, since inflammation is usually accompanied by pain followed by fever, we also evaluated the analgesic activity of *Covid-Organics* using the acetic acid-induced pain test as well as the test of pain induced by formaldehyde in order to highlight respectively peripheral type and central type pain. In addition, the ordinary yeast test was used to assess the antipyretic activity of *Covid-Organics*.

The subplantar administration of carrageenan induces 30 min after an acute inflammation which is manifested by the appearance of an inflammatory edema. Indeed, carrageenan is a polysaccharide which injected into animals induces local inflammation characterized by an increase in vascular permeability. It is an excellent representative model of acute inflammation [6]. Its action is biphasic, the first phase begins 30 to 1 hour after administration and involves the release of

amino-vasoactive mediators (histamine, serotonin), the second phase (beyond 1 hour) is mediated by prostaglandins. The transition between the two (02) phases is ensured by kinins [12]. By this method, *Covid-Organics* showed a very interesting anti-inflammatory effect and almost identical to that of diclofenac used as standard drug. Indeed, *Covid-Organics* at the doses used significantly reduce the evolution of inflammatory edema from the first phase to the last phase of inflammation induced by carrageenan. The same effects have been observed on inflammation induced by formaldehyde, the mechanism of action of which also involves the release of vasoactive mediators. These results suggest that *Covid-Organics* would interact with the mechanisms involved in the release of mediators involved in the inflammatory process such as tissue necrosis factors (TNF-α), interleukin IL-1β, IL-6, IL-8 or the release of prostaglandins. These results are in agreement with those of certain authors who have demonstrated the anti-inflammatory effect in certain species of plants belonging to the Asteraceae family (*Artemisia* Leaf); Rubiaceae (*Heinsa crinita*) and Dilleniaceae (*Tetracera alnifolia*) [13]. Acute Inflammation onset can be complicated by the persistence of the pathogen or an exaggeration of cellular functions, hence the need to study chronic inflammation. Indeed, formaldehyde-induced osteoarthritis represents one of the excellent models of chronic inflammation for studying the proliferative phase of inflammation [14]. The *Covid-Organics* significantly opposes the onset of osteoarthritis compared to the control group. This effect could be explained by the fact that *Covid-Organics* would interact with the mechanisms of installation of osteoarthritis. Inflammation is manifested by various symptoms such as edema (tumefaction or tumor), pain, heat or fever. Nevertheless, pain is closely related to it. This is why the evaluation of the analgesic effect is necessary.

Intraperitoneal administration of acetic acid in mice causes peripheral pain that manifests as abdominal writhing. Acetic acid stimulates the release of endogenous mediators such as histamine, serotonin, bradykinin, prostaglandins, cytokines which are responsible for the stimulation of nociceptor neurons in the peritoneal cavity [15,16]. *Covid-Organics* (0.6 and 1.2 mL/100g) significantly reduced (p<0.001) the number of abdominal writhing compared to the control group. The fact that *Covid-Organics* opposes this type of (peripheral) pain suggests that the effect of *Covid-Organics* could be through interference with one of the mechanisms of induction of abdominal writhing by acid. In addition, *Covid-Organics* also seems to have a central effect because it inhibits pain induced by formaldehyde. Indeed,

the subplantar administration of formaldehyde to rats causes neurogenic and inflammatory pain response which is manifested by licking or biting of the paws. Neurogenic pain response is the result of direct stimulation of C and Aδ fibers which translates central type pain regulated by the release of substance P [17] while inflammatory pain response is regulated by the release of substance P, histamine, serotonin, bradykinins and prostaglandins which translate peripheral type pain. *Covid-Organics* (0.6 and 1.2 mL/100g) significantly reduced the frequency of paw licking or biting during both phases compared to the control group. These results suggest that *Covid-Organics* could contain substances that interfere with the mechanisms of pain induction by formaldehyde. These results corroborate those of certain authors who have demonstrated the analgesic activity of the stem bark of *Anogeissus latifolia* Roxb [18].

The hyperthermia induced by the injection of yeast is the result of the release of cytokines (TNFα, IL1β, and IL6) which, having reached the blood vessels, stimulate the biosynthesis of prostaglandins (PGE2) at the level of the hypothalamic thermoregulatory center [19,20]. *Covid-Organics* significantly reduced ($p < 0.05$; $p < 0.01$ and $p < 0.001$) yeast-induced hyperthermia two hours after the onset of fever. These results suggest that *Covid-Organics* could interfere with the mechanisms of hyperthermia by reducing the synthesis of prostaglandins as would paracetamol used as the standard drug. Our results are in agreement with those of certain authors who demonstrated that *Artemisia annua* Linn possessed antipyretic properties [21,22].

The anti-inflammatory, analgesic and antipyretic effects observed could be by the presence of flavonoids, terpenoids and alkaloids [23,24] already highlighted from the plant *Artemisia annua* Linn, main plant of the *Covid-Organics* preparation.

5. Conclusion

This work aimed to justify the use of *Covid-Organics* in the treatment of coronavirus disease. To do this, we evaluated the anti-inflammatory, analgesic and antipyretic activities of *Organics Organics*. It appears from this study that *Covid-Organics* at doses of 0.6 and 1.2 mL / 100g has anti-inflammatory, analgesic and antipyretic properties which could be justified by the presence of secondary metabolites present in the plant *Artemisia annua* Linn contained. These results could justify the use of *Covid-Organics* against coronavirus symptoms.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

- [1] Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W et al., "A pneumonia outbreak associated with a new coronavirus of probable bat origin", *Nature*. 579(7798). 270-3. Mar 2020.
- [2] Hannah, Ritchie., Edouard, Mathieu., Lucas, Rodés-Guirao., Cameron, Appel., Charlie, Giattino., Esteban, Ortiz-Ospina., Joe, Hasell., Bobbie Macdonald., Diana Beltekian., Saloni Dattani., et Max Roser., "Coronavirus Pandemic (COVID-19)" [archive], sur *Our World in Data*, 2020-2021 (consulté le 8 juillet 2022)
- [3] Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartari, S., Soetjipto, S., "Potential inhibitor of COVID-19 Main protease (M^{pro}) From Several Medicinal Plant Compounds by Molecular Docking Study", Preprints, Mars. 2020.
- [4] Feng, Xinch., Shijie, Cao., Feng, Qiu., Boli, Zhang., "Traditional application and modern pharmacological research of *Artemisia annua* L". *Pharmacol Ther.* 2020 Dec; 216: 107650.
- [5] Zimmermann, M., "Ethical guidelines for investigations of experimental pain in conscious animals", *Pain*, 16(2). 109-10. Jun. 1983.
- [6] Romaric, De Garde, Elion Itou., Rokia, Sanogo., Arnaud, Wilfrid, Etou Ossibi., Freddy, Gelase, Nsonde Ntandou., Radard, Ondélé., Bonaventure, Max, Pénemé., Nadège Okiémy Andissa., Drissa, Diallo., Jean, Maurille ,Ouamba., Ange ,Antoine, Abena., "Anti-Inflammatory and Analgesic Effects of Aqueous Extract of Stem Bark of *Ceiba pentandra* Gaertn"; *Pharmacology & Pharmacy*, 5. 1113-1118. Nov 2014.
- [7] Elion, Itou, R.D.G., Etou, O.A.W., Epa, C, Nsonde N.G.F., Bokia, C.B., Ouamba, J.M., Abena A.A., "Anti-inflammatory and analgesic effects of leaves of *Chromolaena odorata* L. (King and Robinson)", *African Journal of Pharmacy and Pharmacology*, 11(17). 217-223. May 2017.
- [8] Sudo, Roberto, T ., Miguel, L, Neto., Carlos E.S, Monteiro., Rachel, V., Amaral, Ângela, C, Resende., Pergentino, J.C, Souza., Gisele, Zapata-Sudo., and Roberto, S, Moura., "Antinociceptive effects of hydroalcoholic extract from Euterpeoleraea Mart.(Açaí) in a rodent model of acute and neuropathic pain"; *BMC Complementary and Alternative Medicine*, 15: 208. Jul. 2015.
- [9] Sarahi, Mendoza., Miriam, Noa., Maikel, Valle., Nilda, Mendoza., Rosa, Ma., "Effects of D-002 on Formaldehyde-Induced Osteoarthritis in Rats", *IOSR Journal Of Pharmacy*, 3(7). 09-12. Aug. 2013.
- [10] Abdur, R., Rehan, K., Haroon, K., Barkat U., Samreen, P., "Antipyretic and antinociceptive potential of extract/fractions of *Potentilla evestita* and its isolated compound, acacetin", *BMC Complementary Altern Med*, 14: 448. Nov. 2014.
- [11] Muhammad, N., Muhammad, S., Haroon, K., "Antipyretic, analgesic and anti-inflammatory activity of *Viola betonicifolia* whole plant", *BMC Complementary Altern Med*, 12:59. May 2012.
- [12] Perianayagam JB, Sharma SA, Pillai KK et al., "Anti-inflammatory activity of *Trichodesma indicum* root extracts in experimental animals", *J. of Ethnopharmacol*, 104. 410-414. Apr 2006.
- [13] Chanyong, Y., Youngchul, J., Woojoo C., Beodeul, Y., Junghyun, R., Chiyeon L., Jung-Hoon, K., Hyungwoo, K., Su-in, C., "Anti-inflammatory Effect of *Artemisia* Leaf Extract in Mice with Contact Dermatitis in Vitro and in Vivo", *Mediators Inflamm*. Aug 2016.
- [14] Mahadi, M.d Hasan ., Nizam, Uddin., M.d, Rakib, Hasan ., A. F.M, Mahmudul, Islam., M.d, Monir, Hossain ., Akib, Bin, Rahman., M.d, Sazzad, Hossain., Ishtiaque, Ahmed, Chowdhury., M.d, Sohel, Rana., "Analgesic and anti-inflammatory activities of leaf extract of *Mallotus repandus* (Willd.)", *Biomed Res Int*. Dec 2014.
- [15] Marieb, E. and Hoehn, K., "Anatomie et physiologie humaines", *Editions du Renouveau Pédagogique Inc*, 2010, 563.
- [16] Carolina, Babosa, Brito da Matta., Éverton, Tenório de Souza., Aline, Cavalcanti de Queiroz., Daysianne, Pereira de Lira., Morgana, Vital de Araújo., Luiz Henrique Agra, Cavalcante-Silva., George, Emmanuel C, de Miranda., João, Xavier de Araújo-Júnior., José Maria, Barbosa-Filho., Bárbara, Viviana, de Oliveira Santos., and Magna, Suzana, Alexandre-Moreira., "Antinociceptive and Anti-Inflammatory Activity from Algae of the Genus *Caulerpa*", *Mar Drugs*, 9(3). 307-318. Mars. 2011.
- [17] Beaulieu, P. et Lambert, C., "Précis de pharmacologie: Du fondamental à la Clinique", *Les presses de l'université de Montréal*, 2010, 877.
- [18] Vikas, Chandra ,Sharma1., Atul, Kaushik., Yadu, Nandan, Dey., Bhavana, Srivastava., Manish Wanjari., and Bhagat, Jaiswal., "Analgesic, anti-inflammatoire and antipyretic activities of ethanolic extract of stem bark of *Anogeissus latifolia* Roxb". *International Journal of Phytomedicine and Phytotherapy*, 6(22). April. 2020.

- [19] Ribeiro, R.V., Matos, da Silva R., Corsino, da Silva JL., Tabajara, de Oliveira, MD., "Antiinflammatory, antinociceptive and antipyretic effects of hydroethanolic extract from *Macrosiphonia velame* (A. St.-Hil.)", *Pharmaceut Sci*, 46 (3). 515-523. Jul.2010.
- [20] Sajeli, Begum ., Bhagawati, Saxena., Madhur Goyal., Rakesh Ranjan., Vijaya, B, Joshi., C.h.V, Rao., Sairam, Krishnamurthy., Mahendra, Sahai., "Study of anti-inflammatory, analgesic and antipyretic activities of seeds of *Hyoscyamus niger* and isolation of a new coumarinolignan", *Fitoterapia*, 81(3). 178-184. Aug. 2009.
- [21] Huang C., Wang Y., Li X, Ren L., Zhao J., Hu Y., et al., "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet*, 395.497–506. January. 2020.
- [22] Lubbe, A., Seibert, I., Klimkait, T., Kooy, FD., "Ethnopharmacology in overdrive: the remarkable anti-HIV activity of *Artemisia annua*", *Journal of Ethnopharmacology*, 141(3). 854-859. June.2012.
- [23] Cafferata, L.F., Gatti, W.O., Mijailosky, S., "Secondary gaseous metabolites analyses of wild *Artemisia annua* L", *Mol Med Chem* 21: 48-52. Apr. 1 2010
- [24] Ferreira, J.F., Luthria., D.L, Sasaki, T., Heyerick, A., "Flavonoids from *Artemisia annua* L. as antioxidants and their potential synergism with artemisinin against malaria and cancer". *Molecules*, 15(5). 3135-3170. Apr. 2010.



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