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Research Article

# The Potential Protective Effects of Yellow Star on Comorbidity Risk Factors and Disorders Associated with Severe COVID-19 Outcomes

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## Abstract

This study aimed to evaluate the effects of Yellow Star on some disorders and risk factors of comorbidity associated with COVID-19. These effects were evaluated in male and female rats by daily gavage (5 mL/Kg of body weight) for 7 and 14 days. The effects on the composition of the intestinal microbiota were evaluated in the feces, and the effects on coagulation, oxidative stress, lipid profile, and atherogenicity were assessed in plasma. Administration of Yellow Star inhibited the growth of *Bacteroidetes* and stimulated the growth of *Bifidobacterium, Lactobacillus*, and *Lactococcus* in both sexes. Yellow Star ($p < 0.05$) inhibits coagulation in rats regardless of sex. We noted an increase in the antioxidant status and a decrease in pro-oxidant status in both sexes. At the same time, a decrease in plasma levels of MDA was noted. Finally, the administration of the Yellow Star resulted in a decrease in the plasma levels of triglycerides, total cholesterol, VLDL, total lipids, and the TC / HDL-c ratio; and an increase in HDL-c. At the end of this work, it seems justified to recommend the consumption of Yellow Star in the prevention and management of certain disorders accentuated by a SARS-CoV-2 infection.

**Keywords:** Yellow Star, COVID-19, dysbiosis, coagulation, oxidative stress, and dyslipidemias.

## 1 INTRODUCTION

The COVID-19 pandemic is a global health and economic emergency due to the associated high mortality as well as the adverse effects on the global economy. It is caused by SARS-CoV-2 (Coronavirineae), a 30 kb double-stranded retrovirus. Like all intracellular viruses, its entry into cells requires binding to a specific cellular receptor, the ACE-2 (Angiotensin Converting Enzyme-2) receptor in this case [1]. ACE-2 controls the intestinal absorption of tryptophan, and regulates the expression of antimicrobial peptide mRNA [2]. These different peptides can influence the composition of the intestinal microbiota [3], leading to the survival of pathogenic bacteria and intestinal dysbiosis. This dysbiosis is characterized by a decrease in beneficial bacteria (*Firmicutes* and *Bifidobacterium*) and an increase in harmful bacteria, in particular *Bacteroidetes* [4]. Among these *Bacteroidetes*, we have the *Prevotella*, which express SARS-CoV-2 (ACE-2) receptors on their surface. The entry of SARS-CoV-2 would lead to a malfunction of these receptors making them pathogenic. This pathogenicity is notably associated with an increased production of lipopolysaccharides, which in addition to dysbiosis causes inflammation and therefore the reduction of beneficial bacteria. This often results in a general weakening of the immune system. The commensal bacteria mentioned above are involved in the stimulation of both innate and acquired immunity. However, these beneficial bacteria are also involved in the transmission of anti-inflammatory signals, which in the context of a cytokine storm often seen in SARS-CoV-2 infection, could independently amplify inflammation and increase the risk of developing respiratory syndrome [5]. Studies have shown that lung cells strongly express ACE-2 receptors favoring the entry of SARS-CoV-2 [6]. The pro-inflammatory cytokines produced as a result of the attack on these cells are thought to activate vascular endothelial cells in lung tissue, increasing the risk of endothelial damage which can lead to the formation of microcloths, and therefore possibly to thrombosis [7,8]. This would partly explain the high frequency of respiratory

disorders and pneumonia in patients with COVID-19. Symptoms associated with respiratory disorders are accentuated with hypercoagulation and coagulopathy has been observed in several severe cases of COVID-19 [9]. Notwithstanding that inflammation exacerbates the production of reactive oxygen species, which can generate oxidative stress [10].

Studies carried out on experimental animal models have confirmed a positive correlation between SARS, the level of reactive oxygen species, and the dysfunction of endogenous defenses during infection with SARS-CoV [11]. The inflammation and stress associated with COVID-19 may mediated by dyslipidemia, amplifying cardiovascular risk, a major cause of death in people infected with SARS-CoV-2 [12]. Because of these various disorders associated with COVID-19, looking for compounds capable of limiting their appearance seems an emergency to improve prevention or management by reducing in particular the risk of a contaminated subject developing an infection. Viable forms of SARS-CoV-2 have already been detected in feces [13,14], as well as its RNAs in wastewater [15,16], which may be linked to the fecal-oral transmission. This transmission is favored by the presence of cellular receptors for SARS-CoV-2 on the surface of these enterocytes [17] and intestinal dysbiosis, which can lead to an increase in intestinal permeability [18]. Studies show that exposure of a virus to polar substances such as detergents promotes hydrolysis of the viral envelope; similarly, exposure of viral DNA polymerase to zinc may reduce the rate of replication [19].

Our recent paper on Yellow Star opens up potential new avenues of research in the control of SARS-CoV-2 virus transmission via feces [20]. Yellow Star is a yellow soup supplemented with garlic and zinc. Yellow soup is consumed in Cameroon with a tuber called taro; it is an organic soap obtained by a reaction between palm oil and sodium bicarbonate, with as other ingredients many spices with antiviral, antibacterial, and antioxidant activities. The purpose of this study was to evaluate the effects of the Yellow Star on a few disorders associated with mortality caused by COVID-19: dysbiosis, coagulation, oxidative stress, and dyslipidemia.

## 2 METHODS

### 2.1 Chemicals

All the chemicals used were of analytical grade and were purchased from Sigma Co., Louis, MO, USA.

### 2.2 Yellow Star preparation

Yellow Star has been prepared by blending the following ingredients, the amounts of which are given in Table I.

**Table I: Composition of Yellow Star**

| Ingredients | Quantities |
|---|---|
| Palm oil (L) | 0.5 |
| Water/Beef stock (3/1; v/v) (L) | 2 |
| Limes stone (g) | 30 |
| *Capsicum annum* (g) | 2 |
| *Dichrostachys glomerata* (g) | 5 |
| *Tetrapleura tetraptera* (g) | 4 |
| *Monodora myristica* (g) | 3.1 |
| *Piper guineense* (g) | 3.4 |
| *Cucumeropsis mannii* (g) | 6 |
| *Allium sativum* (g) | 2 |
| *Scorodoploeus zenkeri* (g) | 3.3 |
| *Xylopia parviflora* (g) | 2.4 |
| *Afrostyrax lepidophyllus bark* (g) | 18 |

The Yellow Star was transported to the laboratory in an isothermal bag, so as not to break the cold chain; upon arrival at the laboratory, it was placed in the refrigerator at a temperature of 4±1°C for further experiments.

### 2.3 Microbiological quality of the Yellow Star

Under aseptic conditions, the yellow sauce sample was processed following the method ISO 6887-1 (2017). Briefly, 10 mL of sample was added to 90 mL of sterile physiological water (0.85% NaCl) and homogenized. Successively, serial 10-fold dilutions in tubes containing 9 mL of sterile physiological water were performed. For the enumeration of the total aerobic mesophilic flora, the pour plate method was used (ISO 4833-2, 2013). 1 mL of the different dilutions was inoculated into Petri dishes followed by the addition of cooled sterile nutrient agar. After solidification at room temperature, the plates were incubated under aerobic conditions at 37°C for 48h. The detection of *Salmonella* spp. and *Shigella* spp. was carried out in three steps following the method ISO 6579-1 (2017). The sample was pre-enriched in sterile peptone water for 16 h at 37°C, then enriched in selenite cystine broth for 24 h at 37°C before being streaked onto Salmonella and Shigella agar. After incubation at 37°C for 24 h, colorless colonies with black were considered Salmonella while colorless colonies were considered Shigella. Regarding the enumeration of *Escherichia coli*, 0.1 mL of the different dilutions was spread on sterile Eosin Methylene Blue agar followed by incubation at 44°C for 24 h. Colonies with a metallic green sheen were considered as *E. coli* (ISO 16654, 2001). To quantify the total anaerobic sulfite-reducing bacteria, 1 mL of the dilutions was introduced into Petri plates and 15 mL of cooled sterile Perfringens Agar Base was added. After homogenization and solidification, a layer of cooled sterile Perfringens Agar Base was carefully added. The plates were then incubated at 37°C for 48 h under anaerobic conditions (ISO 15213-1, 2023).

### 2.4 Experimental animals

Adult male and female Wistar albino rats weighing 180-230 g were obtained from the animal house of the Department of Biochemistry, University of Yaoundé I, Cameroon. The experimental procedures were approved by the Institutional Animal Care and Use Committee at the Faculty of Science, Yaounde University. The animals were acclimatized in the experimental animal room for 7 days with a 12-hour light and 12-hour dark cycle before the start of experimentation. Animals were housed individually at a constant temperature of 25 ˚C. Standard feed and water were provided ad libitum to all experimental animals.

### 2.5 Animal experimentation

The effects of Yellow Star on coagulation and dyslipidemia were evaluated in rats. For this purpose, 32 rats (16 males and 16 females) weighing between 180 and 230 g were used, divided into 4 groups of 8 rats (4 per sex) each as follows:

- Group 1 (Control 1): Rats fed a normal diet and given water (5 mL/Kg of body weight) by gavage for 7 days;

- Group 2 (Control 2): Rats fed a normal diet and given water (5 mL/Kg of body weight) by gavage for 14 days;

- Group 3 (Test 1): Rats fed a normal diet and given Yellow Star (5 mL/Kg of body weight) by gavage for 7 days;

- Group 4 (Test 2): Rats fed a normal diet and given of Yellow Star (5 mL/Kg of body weight) by gavage for 14 days.

At the end of 7 days for the Control and Test 1 group; and at the end of 14 days for Test 2, the rats were sacrificed by light ether anesthesia, the caecal and fœtal contents collected and were immediately frozen at - 25 ˚C. Blood was collected in citrated and heparinized tubes for the preparation of plasma

### 2.6 Bacteria enumeration of the feces

On the 7th and 14th days of experimentation, animals' feces were carefully collected into sterile boxes, weighed, and stored at 4°C for microbiological analyses. That analysis consisted of the enumeration of *Bifidobacteria*, *Lactobacillus spp*., *Lactococcus spp*., and *Bacteroides*.

In the experimental procedure, the feces samples were crushed and homogenized; 1 g was taken and mixed with 9 mL of sterile triptone-salt-water. The suspension was homogenized, allowed to stand on the bench for 30 min, and was serially diluted (10-6 to 10-12). Then, 1 mL of the different dilutions was introduced into Petri plates followed by addition of sterile cooled MRS agar, M17 agar, modified MRS agar (MRS + Sodium propionate, Neomycin, Paromomycin, LiCl + L-cysteine HCL at 0.05%), and the media of Ho et al. (2007) [21] for the enumeration of *Lactobacillus* spp., *Lactococcus* spp., *Bifidobacteria* and *Bacteroides*, respectively. After solidification, a second layer of these respective sterile and cooled culture media was carefully added and the plates were incubated under anaerobic conditions at 37°C for 24-48 h.

Colonies forming units appearing on the different Petri plates after incubation were counted and the results were expressed as Log colonies forming unit per gram of feces.

### 2.7 Coagulation status Evaluation

The coagulation status was evaluated by the Prothrombine Time test using the commercial kit (FORTRESS diagnostics). The methodology followed the manufacturer's instructions and the test was carried out using the self-analyzer (MICROLAB).

### 2.8 Evaluation of the markers of lipid profile

Triglycerides, total cholesterol, and HDL-c were determined using commercial kits (FORTRESS diagnostics) from the autoanalyzer (MICROLAB), then LDL-c and the ratios LDL-c/HDL-c, Cholesterol/HDL-c were obtained from the device.

### 2.9 Evaluation of the markers of oxidative stress

The prooxidant system was evaluated by the determination MDA lipid peroxidation marker was estimated by the method of Yagi (1976) [22]. The antioxidant system was evaluated by determination of FRAP (Ferric Reducing Antioxidant Power) by the method of Benzie and Strain (1996) [23].

### 2.10 Statistical analysis

All data were expressed as mean ± standard deviation. Significant differences among the groups were determined by the test of Kruskal-Wallis followed by the Bonferonni post hoc test using the Statistical Package for Social Sciences (SPSS) analysis program. Results were considered statistically significant at $p < 0.05$.

## 3 RESULTS

### 3.1 Pathogenic bacteria in Yellow Star

The loads of certain pathogenic bacteria in Yellow Star are shown in Table II. No *E. coli, Salmonella sp,* and *Shigella sp* were found in Yellow Star.

**Table II: Content of some pathogenic bacteria of Yellow Star**

| Genus/Specie | Microbial load |
|---|---|
| *E. coli* | Absent |
| *Salmonella sp* | Absent |
| *Shigella sp* | Absent |

### 3.2 Effects of Yellow Star on gut microbiota

The effects of the Yellow Star on some major groups of beneficial microorganisms present in the intestinal microbiota of mice are shown in Table III. In general, Yellow Star inhibited the growth of *Bacteroidetes* and stimulated the growth of *Bifidobacterium, Lactobacillus,* and *Lactococcus* irrespective of sex and time of experimentation; moreover, the effects were more pronounced in males and during the second week of experimentation.

During the first week, the concentration of *Bacteroidetes, Bifidobacterium, Lactobacillus,* and *Lactococcus* in females receiving Yellow Star were 8.875 logCFU/g, 11.769 logCFU/g, 12.210 logCFU/g, and 11.991 logCFU/g respectively; compared to 9.947 logCFU/g, 10.943 logCFU/g, 12.064 logCFU/g, and 11.823 logCFU/g in the control. In the males that received Yellow Star, the concentrations of *Bacteroidetes, Bifidobacterium, Lactobacillus* and *Lactococcus* were respectively 8.512 logCFU/g, 12.322 logCFU/g, 13.173 logCFU/g, and 13.204 logCFU/g; compared to 9.998 logCFU/g, 11.025 logCFU/g, 12.696 logCFU/g, and 12.246 logCFU/g in the control.

At the end of the second week, the *Bacteroidetes, Bifidobacterium, Lactobacillus,* and *Lactococcus* loads in the females that received Yellow Star were 6.813 logCFU/g, 11.898 logCFU/g, 12.628 logCFU/g, and 12.531 logCFU/g, respectively; versus 8.068 logCFU/g, 11.086 logCFU/g, 12.531 logCFU/g, and 11.915 logCFU/g in the control. In the males that received Yellow Star, the loads of *Bacteroidetes, Bifidobacterium, Lactobacillus* and *Lactococcus* were 8.459 logCFU/g, 12.324 logCFU/g, 13.740 logCFU/g, and 13.516 logCFU/g, respectively; compared to 9.959 logCFU/g, 10.996 logCFU/g, 12.858 logCFU/g, and 12.412 logCFU/g in the control.

**Table III: Effects of Yellow Star on gut microbiota during experimentation**

| Experimentation Times | Groups | *Bacteroidetes* (CFU/g) | *Bifidobacterium* (CFU/g) | *Lactobacillus* (CFU/g) | *Lactococcus* (CFU/g) |
|---|---|---|---|---|---|
| 1 week | Control 1 (female) | 9.997±1.2$^{a}$ | 10.943±2.2 $^{a}$ | 12.064±1.9 $^{a}$ | 11.823±1.2 $^{a}$ |
| | Control 1 (male) | 9.998±0.9 $^{a*}$ | 11.025±0.2 $^{a*}$ | 12.696±1.3 $^{a*}$ | 12.246±1.7 $^{a*}$ |
| | Test 1 (female) | 8.875±0.8 $^{b}$ | 11.769±2.3 $^{b}$ | 12.210±0.8 $^{b}$ | 11.991±0.9 $^{b}$ |
| | Test 1 (male) | 8.512±1.5 $^{b*}$ | 12.322±0.8 $^{b*}$ | 13.173±2.5 $^{b*}$ | 13.204±1.3 $^{b*}$ |
| 2 weeks | Control 2 (female) | 8.068±0.4$^{a\#}$ | 11.086±1.8 $^{a\#}$ | 12.531±1.1 $^{a\#}$ | 11.915±1.1 $^{a\#}$ |
| | Control 2 (male) | 9.959±1.6 $^{a*\#}$ | 10.996±1.7 $^{a*\#}$ | 12.858±2.2 $^{a*\#}$ | 12.412±0.6 $^{a*\#}$ |
| | Test 2 (female) | 6.813±0.4 $^{b\#}$ | 11.898±1.6 $^{b\#}$ | 12.628 ±1.4$^{b\#}$ | 12.531±1.4 $^{b\#}$ |
| | Test 2 (male) | 8.459±1.1 $^{b*\#}$ | 12.324±2.3 $^{b\#*}$ | 13.740±2.5 $^{b*\#}$ | 13.516±1.7 $^{b*\#}$ |

*Different letters: significant difference compared to the control at the same time of experimentation and in the same sex. *: significant difference compared to females for the same treatment. #: significant difference compared to the first week of experimentation for the same sex and the same treatment.*

### 3.3 Effects of Yellow Star on coagulation

The results of the Yellow Star anticoagulant activity test are shown in Table IV. It was noted an inhibition of coagulation after administration of Yellow Star whatever the sex and the duration of experimentation. While in the controls, prothrombine times were in the normal range between 13 and 16 s, in the test groups, prothrombine times between 16.2 and 20.8 s were noted.

Activity was greater in females with prothrombine times of 17.3 and 20.8 s after 1 and 2 weeks respectively, compared to 16.2 and 18.6 s in males.

**Table IV:** Effect of Yellow Star on Prothrombin Time during experimentation

| Experimentation duration | Groups | Female | Male |
|---|---|---|---|
| 1 week | Control 1 | $14.2\pm1.2^{a}$ | $13.6\pm0.9^{a}$ |
| | Test 1 | $17.3\pm2.2^{b}$ | $16.2\pm1.4^{b}$ |
| 2 weeks | Control 2 | $14.8\pm1^{a}$ | $14.1\pm0.8a^{b}$ |
| | Test 2 | $20.8\pm2.1^{b\#}$ | $18.6\pm1.7^{b*\#}$ |

*Different letters: significant difference compared to the control at the same time of experimentation and in the same sex. *: significant difference compared to females for the same treatment. #: significant difference compared to the control at the first week of experimentation for the same sex and the same treatment.*

### 3.4 Effects of Yellow Star on oxidative stress

The effects of the Yellow Star on oxidative stress are shown in Table V. Yellow Star caused a decrease in plasma MDA in both males and females; and an increase in FRAP only in males. No significant differences were noted based on the duration of the experiment.

Concerning MDA content, the values obtained in females receiving Yellow Star were 1.98 µM and 2.08 µM in the first and second weeks compared to 2.38 µM and 2.42 µM in the control. In males treated with Yellow Star, MDA levels were 2.07 µM and 2.08 µM in the first and second week, respectively, compared with 2.37 µM and 2.39 µM in the control.

For FRAP, the values obtained in males treated with Yellow Star were 153.73% and 166.90% respectively in the first and second week compared to 106.68% and 120.22% in the control.

**Table V:** Effects of Yellow Star on oxidative stress

| Experimentation duration | Groups | MDA **(µM)** | | FRAP (%) | |
|---|---|---|---|---|---|
| | | Female | Male | Female | Male |
| 1 week | Control 1 | $2.38\pm0.009^{a}$ | $2.37\pm0.028^{a}$ | $176.35\pm11.82^{a}$ | $106.68\pm06.73^{a*}$ |
| | Test 1 | $1.98\pm0.120^{b}$ | $2.07\pm0.278^{b}$ | $162.72\pm15.81^{a}$ | $153.73\pm16.54^{b}$ |
| 2 weeks | Control 2 | $2.42\pm0.019^{a}$ | $2.39\pm0.033^{a}$ | $188.05\pm15.32^{a}$ | $120.22\pm12.31^{a*}$ |
| | Test 2 | $2.08\pm0.077^{b}$ | $2.08\pm0.018^{b}$ | $178.53\pm06.54^{a}$ | $166.90\pm18.45^{b}$ |

*MDA: Malondialdehyde; FRAP: Ferric Reducing Antioxidant Power. Different letters: significant difference compared to the control at the same time of experimentation and in the same sex. *: significant difference compared to females for the same treatment. #: significant difference compared to the control at the first week of experimentation for the same sex and the same treatment.*

### 3.5 Effects of Yellow Star on lipid profile

The effects of the Yellow Star on the lipid profile are shown in Table VI. The Yellow Star showed beneficial effects on markers of lipid profile by increasing HDL-c and decreasing triglycerides, total cholesterol, VLDL, total lipids, and TC/HDL-c ratio. The effects were most pronounced in the first week and varied by gender depending on the marker studied. No significant effect was noted in females for total cholesterol throughout the experiment; and for total lipids and TC/HDL-c ratio during the second week. Similarly, in males, no significant differences were noted for VLDL during the first week and TC/HDL-c during the second week.

In the first week, the triglyceride, HDL-c, VLDL, total lipid and TC/HDL-c values for Yellow Star-treated females were 70.95 mg/dL, 43.15 mg/dL, 14.13 mg/dL, 193.75 mg/dL and 1.615, respectively; compared with 111.65 mg/dL, 23.35 mg/dL, 21.83 mg/dL, 236.45 mg/dL and 2.36 in the control. The triglyceride, total cholesterol, HDL-c, total lipid and TC/HDL-c values for Yellow Star-treated males were 82.24 mg/dL, 65.10 mg/dL, 43.30 mg/dL, 204.35 mg/dL and 1.655, respectively; compared with 108.95 mg/dL, 74.10 mg/dL, 32.35 mg/dL, 257.15 mg/dL and 2.22 for control males.

At the end of the second week, the triglyceride, HDL-c, and VLDL values in females treated with Yellow Star were 99.30 mg/dL, 64.80 mg/dL, and 18.86 mg/dL, respectively; compared with 131.05 mg/dL, 50.22 mg/dL and 26.21 mg/dL in the control. In males treated with Yellow Star, the values for triglycerides, total cholesterol, HDL-c, VLDL, total lipids and TC/HDL-c were 84.00 mg/dL, 70.80 mg/dL, 74.80 mg/dL, 16.80 mg/dL and 225.60 mg/dL, respectively; compared with 118.13 mg/dL, 72.22 mg/dL, 66.10 mg/dL, 23.63 mg/dL and 274.57 mg/dL in control males.

**Table VI:** Effects of Yellow Star on lipid profile

| Groups | TG (mg/dL) | TC (mg/dL) | HDL-c (mg/dL) | VLDL (mg/dL) | Total Lipid (mg/dL) | TC/HDL-c |
|---|---|---|---|---|---|---|
| Control 1 (female) | 111.65$^{a}$ ±11.45 | 62.90$^{a}$ ±1.10 | 23.35$^{a}$ ±1.55 | 21.83$^{a}$ ±4.79 | 236.45$^{a}$ ±14.25 | 2.36$^{a}$ ±0.22 |
| Control 1 (male) | 108.95$^{a}$ ±9.35 | 74.10$^{a*}$ ±0.60 | 32.35$^{a*}$ ±0.65 | 21.79$^{a}$ ±1.87 | 257.15$^{a*}$ ±8.15 | 2.22$^{a}$ ±0.35 |
| Test 1 (female) | 70.65$^{b}$ ±4.35 | 61.55$^{a}$ ±2.25 | 43.15$^{b}$ ±2.15 | 14.13$^{b}$ ±0.87 | 193.75$^{b}$ ±10.15 | 1.615$^{b}$ ±0.17 |
| Test 1 (male) | 82.24$^{b}$ ±6.26 | 65.10$^{b}$ ±0.70 | 44.30$^{b}$ ±1.20 | 18.33$^{a}$ 0.63 | 204.35$^{b*}$ ±12.95 | 1.655$^{b}$ ±0.21 |
| Control 2 (female) | 131.05$^{a\#}$ ±14.25 | 68.30$^{a}$ ±3.12 | 50.22$^{a\#}$ ±3.70 | 26.21$^{a}$ ±1.13 | 247.05$^{a}$ ±16.70 | 1.15$^{a\#}$ ±0.27 |
| Control 2 (male) | 118.13$^{a}$ ±16.46 | 78.22$^{a}$ ±5.80 | 66.10$^{a*\#}$ ±6.88 | 23.63$^{a}$ 1.63 | 274.57$^{a*\#}$ ±20.86 | 1.18$^{a\#}$ ±0.11 |
| Test 2 (female) | 99.30$^{b\#}$ ±4.50 | 65.10$^{a}$ ±1.10 | 64.80$^{b\#}$ ±2.00 | 18.86$^{b}$ ±0.10 | 229.50$^{a\#}$ ±9.70 | 1.005$^{a\#}$ ±0.28 |
| Test 2 (male) | 84.00$^{b*}$ ±2.00 | 70.80$^{b}$ ±4.50 | 74.80$^{b*\#}$ ±4.07 | 16.80$^{b}$ ±2.33 | 225.60$^{b\#}$ ±18.60 | 0.95$^{a\#}$ ±0.10 |

*TG : Triglycerides ; TC : Total Cholesterol. Different letters: significant difference compared to control at the same time of experimentation and in the same sex. *: significant difference compared to females for the same treatment. #: significant difference compared to the control at the first week of experimentation for the same sex and the same treatment.*

## 4 DISCUSSION

With the advent of COVID-19, the world faces one of the most serious health and socio-economic crises of modern times. Due to a relatively short period since the discovery of SARS-CoV-2, several co-morbidity factors have been associated with this infection. These include dysbiosis, coagulation, oxidative stress, and dyslipidemia. Thus justifying the validity of the present work, the effect of the Yellow Star, in the modulation of some comorbid factors associated with COVID-19, was not aimed at. It has been established that SARS-CoV-2 affects the gut microbiota [24]. Likewise, there is a strong correlation between changes in the composition of the gut microbiota, diet, obesity, and respiratory infections [25].

It is therefore logical that the first part of this work aimed to investigate the probable effect of regular consumption of Yellow Stars on the composition of the intestinal microbiota, notwithstanding the search for the possible presence of commensal bacteria in Yellow Star. The results showed that the Yellow Star contains acceptable levels of aerobic bacterial flora, it was free of pathogens studied, in this case, *E. coli, Shigella sp,* and *Salmonella sp*. Analysis of the fecal microbial load is an interesting indicator of the quality of a probiotic. A case-control study conducted in China in patients with COVID-19 showed dysbiosis with a decrease in *Bifidobacterium* and *Lactobacillus* [26]. Analysis of the bacterial load of the feces shows that the administration of Yellow Star significantly modified the content of certain bacteria. Indeed, a reduction in the load of *Bacteroidetes* has been observed. At the same time, the increased load of *Bifidobacterium, Lactobacillus,* and *Lactococcus* was recorded, with a more pronounced effect in male rats. Also, the importance of these results increased with the duration of the experiment (Table III). The quality of the composition of the gut microbiota following treatment and the increase in the content of certain strains with the duration of exposure suggests that the Yellow Star would have a commendable effect on the composition of the microbiota.

Given its ability to promote overexpression of the proteins involved in the growth of SARS-CoV-2 and hence to amplify the severity of the pathology, *Prevotella,* one of the strains of the *Bacteroidetes* genus, constitutes an aggravating factor of this infection [27]. Furthermore, significant amounts of *Prevotella* have been found in clinical samples from patients infected with SARS-CoV-2 [28] The ability of the yellow soup to reduce the load of *Bacteroidetes* would limit *Prevotella* multiplication, and reduce the risk for a SARS-CoV-2 infected subject to develop complications. The genus *Bifidobacterium*, for its part, has shown interesting properties, by significantly reducing the rate of replication of the Coronavirus. Indeed, studies have shown that in a situation of SARS-CoV-2 infection, an increase in the autophagy of said bacteria is observed, an immune defense mechanism capable of increasing the stress of the endoplasmic reticulum mediated by the release of IL-17 [29]. On the other hand, it should be mentioned that the genera *Bifidobacterium* and *Lactobacillus*, due to their ability to ferment carbohydrates, produce acidic residues that lower the pH of the medium, a condition which favors the inactivation of viral enzymes. Studies are showing that at low acidic pH, the multiplication of SARS-CoV-2 was significantly reduced [30]. That said, in addition to its power to stimulate the growth of the genera *Bifidobacterium* and *Lactobacillus*, the regular consumption of Yellow Star would limit viral replication and multiplication, reducing the load of *Bacteroidetes*. An effect that could be amplified by the zinc content of *Cucumeropsis mannii* [31], several studies have shown a correlation between zinc intake and the inhibition of the activity of RNA polymerase [32]. Without forgetting the presence of *Allium sativus*, a plant rich in allicin, and whose beneficial effects on the growth of Lactobacillus [33] and the harmful effects on that of *Prevotella* [34] do not more than demonstrate. *Prevotella* infection independent of SARS-CoV-2

is associated with an exacerbated inflammatory reaction that can lead to the activation of the coagulation process and the release of thrombin, hence the expression of thrombo-inflammation [35,36]. In addition, the presence of ACE-2 receptors on endothelial cells may worsen an inflammatory condition in the intestinal epithelium and adjacent tissues. The cells infiltrated by the virus are more prone to undergo an inflammatory reaction, or even to be destroyed by apoptosis. Not to mention that most of the contaminated subjects who have a seizure following infection with SARS-CoV-2 present an inflammatory dysfunction marked by a storm of cytokines and the deterioration of the peripheral tissues that result from it. That said, the combination of these factors a priori increases the risk of microvascular thrombotic events [37]. Cardiovascular disease is one of the leading causes of death in patients with COVID-19 [38]. Hence the interest in evaluating the effects of Yellow Star on one of the markers of coagulation. The dosage of Prothrombin Time is one of the tests recommended by ISTH in patients with COVID-19, to monitor the level of expression of disseminated intravascular coagulation factors [39], and immediately reduce the risk of vascular accidents. Administration of the Yellow Star to both male and female rats resulted in inhibition of coagulation, illustrated by the achievement of significantly higher PT values compared to values in the control groups (Table IV). The prothrombin level is used to determine the blood clotting time at 37 ° C. It measures the effectiveness of several factors involved in coagulation (factors VII, V, X, and prothrombin). This rate is expressed as a percentage (or in seconds) relative to a control blood. These anti-thrombotic effects could be attributed to the presence of capsaine, an identified secondary metabolite of *Capsicum annum*. In addition to anticoagulant properties, this bioactive compound is believed to have vasodilator effects through modulation of the NO synthetase pathway [40]. The effect of an increase in the lumen of the arteries and a reduction in the plasma content of coagulation factors on the risk of thrombosis is no longer to be demonstrated.

Often, in a situation of SARS-CoV-2 infection, hypoventilation and hypoxemia are observed in patients, thus contributing to the increase in the production of reactive oxygen species and therefore to oxidative stress, which disorder is accentuated by the significant release of pro-inflammatory cytokines [41,42,43]. The antioxidant effects of the Yellow Star were evaluated by assaying two markers: the level of FRAP (a marker of antioxidant status) and the level of MDA (a marker of prooxidant status). Administration of Yellow Star resulted in decreased plasma MDA levels in male and female rats, but increased plasma FRAP only in males (Table V). These results could be justified by the presence in the different ingredients of Yellow Star of many bioactive compounds such as capsaine which, in addition to possessing anti-inflammatory properties, through the inhibition of pro-cytokine production pathways. -inflammatory, would reduce the content of reactive oxygen species. On the other hand, it should be noted that the various constituent spices of this dish are rich in phenolic compounds and particular flavonoids. Secondary metabolites through their hydroxyl group can easily transfer electrons to pro-oxidant molecules, a responsible reaction capable of justifying the reducing power of these compounds and the low content of oxidative stress markers recorded by Liguori *et al.* (2019) [44]. Several studies have demonstrated the merits of preventing or treating oxidative stress through an exogenous supply of antioxidant molecules such as polyphenols capable of boosting the body's antioxidant system. But also, a supply of trace elements such as certain vitamins and minerals. The scientific literature has recognized, zinc a mineral present in *Cucumeropsis mannii* as a cofactor of SOD, an endogenous antioxidant enzyme involved in the neutralization of the superoxide anion [45].

Several studies have shown that oxidative stress, inflammation, and dysbiosis are all factors capable of independently aggravating disorders of the lipid profile. In addition, in an infection situation, a higher expression of ACE-2 receptors specific to SARS-CoV-2 was observed on the surface of adipocytes in comparison to lung cells, showing that adipose tissue is strongly affected by COVID-19 and that obesity plays a major role in the pathogenesis of this infection [46]. Based on this observation, we set out to evaluate the effects of yellow soup on dyslipidemia. Administration of yellow soup resulted in a reduction in plasma triglycerides, total cholesterol, VLDL, total lipids, and TC / HDL-c ratio in rats concomitantly with an increase in HDL-c (Table VI). These effects may be due to the beneficial effects of yellow soup on the gut microbiota as demonstrated above. Indeed, many studies have established a positive correlation between dysbiosis and lipid profile disorders [47,48]. The Yellow Star being a product of saponification, that is to say, a detergent, could as such alter the viral proteins thus preventing the recognition or the binding of the viral proteins on the ACE-2 receptors expressed by certain somatic cells such as adipocytes, thus limiting the lipid profile disturbances observed. On the other hand, the reduction in the contents of total lipids, triglycerides, and total cholesterol would have accentuated the observed effects. Certain compounds present in Yellow Star are capable of inhibiting cell entry and viral replication. This is because lipids can act as cell receptors or cofactors for viral entry at the cell surface or in endosomes, they also play an important role in the formation and functioning of the viral replication complex, as well as in the production of energy required for viral replication [49,50]. Lipid rafts play an important role during the early multiplication phase of many viruses, including SARS-CoV [51]. Cholesterol is a key element in the cell membrane synthesis of viruses, and cholesterol-lowering substances could be a weapon in the management of COVID-19 [52]. The increase in HDL-c and the decrease in HDL-c would reflect a protective effect against atherosclerosis and its cardiovascular complications.

## 5 CONCLUSION

The Yellow Star is a blend of plants rich in bioactive compounds that give it beneficial effects on the intestinal microbiota, coagulation disorders, oxidative stress, and lipid profile. These different effects would explain the functionality of this food in the management of disorders associated with mortality in patients with COVID-19. This work is a motivation in the research of the effects of Yellow Star on the pathogenesis of the COVID-19 virus.

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## Competing interests

The authors have declared that no competing interests exist.

## Authors' contributions

Julius Oben: Conceptualization (lead), Resources. Guy Takuissu: Implementation and Writing - Original draft (lead). Guy Takuissu, Inelle Makamwe, Imelda Djuikoo, Gildas Kamdem, Remy Orang: Methodology (equal). Sylvain Sado and Hippolyte Mouafo: Writing - Review & editing (equal). Janvier Youovop and Abraham Nkoue: Software and Formal analysis (equal). Julius Oben and Sylvain Sado: Validation

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