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ORIGINAL ARTICLE

Preventive effects of Pycnogenol® on cardiovascular risk factors (including endothelial function) and microcirculation in subjects recovering from coronavirus disease 2019 (COVID-19)

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ABSTRACT

BACKGROUND: The aim of this open supplement study was to evaluate the effects of Pycnogenol® in comparison with controls on symptoms of post-COVID-19 syndrome and in improving endothelial function, microcirculation, inflammatory markers and oxidative stress over 3 months in symptomatic subjects recovering from COVID-19.

METHODS: Sixty subjects recovering from symptomatic COVID-19 were included. One group of 30 followed a standard recovery management while 30 comparable subjects received a supplement of 150 mg Pycnogenol® daily (in 3 doses of 50 mg) in addition to standard management.

RESULTS: Two groups of selected subjects were comparable at baseline. The groups progressively improved both with the SM (standard management) and with the SM in combination with the supplement. Patients, supplemented with Pycnogenol® showed significantly better improvement compared to the control group patients. No side effects from the supplementation were observed; tolerability was optimal. The progressive evolution over time was visible in all target measurements. Physiological tests: endothelial function, low in all subjects at inclusion was assessed by flow mediated dilation (FMD) and finger reactive hyperemia in the microcirculation (laser Doppler measurements) after the release of an occluding suprasystolic cuff. It was significantly improved in the Pycnogenol® group after one month and after 3 months ($P<0.05$ *vs.* controls). The rate of ankle swelling (RAS) by strain gauge decreased significantly in the supplemented group ($P<0.05$) in comparison with controls showing an improvement of the capillary filtration rate. At inclusion, the kidney cortical flow velocity indicated a decrease in perfusion (lower systolic and diastolic flow velocity) in all patients. Kidney cortical flow velocity increased significantly with the supplement ($P<0.05$) in comparison with controls with improvement in systolic velocity and in diastolic component. High sensitivity CRP (hs-CRP) and Il-6 plasma levels decreased progressively over 3 months with a significant more pronounced decrease in the supplement group ($P<0.05$). The number of patients with normal plasma IL-6 levels at the end of the study was higher ($P<0.05$) with the supplement. ESR followed the same pattern with a progressive and a more significant decrease in the supplemented subjects ($P<0.02$). Oxidative stress decreased significantly in the supplemented group ($P<0.05$) compared with the control group. Systolic blood pressure was significantly lower in the supplemented group ($P<0.05$) at the end of the study. Finally, the scores of Quality-of-life, mood and fatigue questionnaire and the Karnofsky Scale Performance Index significantly improved in the supplement group ($P<0.05$) compared to controls after 1 and 3 months. All other blood parameters (including platelets and clotting factors) were within normal values at the end of the study.

CONCLUSIONS: In conclusion, Pycnogenol® may offer a significant option for managing some of the signs and symptoms associated with post-COVID-19 syndrome. This pilot evaluation offers some potential rationale for the use of Pycnogenol® in this condition that will have significant importance in the coming years.

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KEY WORDS: Pycnogenols; Heart disease risk factors; COVID-19.

During the ongoing worldwide pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of patients recovering from coronavirus disease 2019 (COVID-19) is constantly growing.[1] COVID-19 can result in a multi-organ disease with a broad spectrum of symptoms, ranging from pulmonary problems, thrombotic complications and cardiovascular dysfunctions, renal dysfunction, gastrointestinal symptoms, neurological problems, and many more.[2] This pleiotropic clinical picture has been attributed to endothelial dysfunction, coagulopathy, microcirculatory and inflammatory problems.[3-8] But, even after recovery from the acute COVID-19, there are many reports of persistent symptoms.[1, 9-12] A great responsibility now is to find and establish solutions for this growing worldwide problem of the post-COVID-19 condition.

After a SARS-CoV-2 infection, significant pulmonary symptoms may persist, particularly in subjects who have been admitted to the hospital and have been managed for at least 1 week on hospital wards.[1]

Subjects admitted to intensive care units tend to have more important residual, morphologic, particularly respiratory damage because of the combination of disease, systemic complications, treatments and intubation.

But also COVID-19 patients with non-severe symptoms suffer from long-lasting effects such as fatigue, recurrent headaches, attention disorders, anxiety or depression and many more.[9]

Permanent lung damage and scarring may also be seen after significant lung and respiratory involvement during viral infections.[13] Post COVID-19 fibrosis is estimated to be prevalent in 1/3 of SARS-CoV-2 infected hospitalized patients.[13] The prolonged effects of the viral infection and their consequences render most patients symptomatic, weak, with sleep difficulties and unable to lead a normal life or work for a long period of time, often for more than six months.[1, 14]

Pycnogenol®, an antioxidant and anti-inflammatory extract from a natural source (the bark of the French Maritime Pine) has been used for years to control post inflammatory symptoms and recently, the initial pulmonary fibrosis after COVID-19.[15, 16] Based on its various beneficial effects, Pycnogenol® supplementation has been suggested to support the recovery of patients suffering from the vast health problems, persisting after a SARS-CoV-2 infection.[17] Besides its anti-inflammatory effects and its ability to reduce platelet hyperactivity, Pycnogenol® also showed in several studies to improve endothelial function as well as microcirculation, which are negatively affected in COVID-19 and post-COVID-19 syndrome patients.[17]

The aim of this open supplement, controlled study was to evaluate the effects of Pycnogenol® in comparison with controls on symptoms of post-COVID-19 syndrome and in improving endothelial function and microcirculation; inflammatory markers and plasma reactive oxygen metabolites were investigated in this 3-month registry study in symptomatic subjects recovering from COVID-19.

Materials and methods

Subjects recovering from COVID-19 between 35-70 years old, with no significant medical history before COVID-19 and willing to participate were included in the registry. No drug treatment was used except for symptomatic and occasional pain treatments, as well as appropriate vitamins and diet.

Subjects were included at least 2 months after viral infection. Diagnosis of COVID-19 was performed by detection of SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR), using nasopharynx samples.

Exclusion Criteria were any acute or systemic disease, intake of drugs or other supplementation. In the 90-day registry, the 60 subjects recovering from diagnosed COVID-19 received either a standard management (SM) or Pycnogenol® in combination with SM. One group of 30 subjects followed a standard recovery management while 30 comparable subjects were supplemented with 150 mg of Pycnogenol® daily (in 3 doses of 50 mg) in addition to standard management. Follow-up was for 3 months.

The study parameters of all patients were assessed at baseline, 2 weeks, 1 month and 3 months at the end of the registry study.

The supplement study was open and comparative.

Study endpoints

All study parameters were assessed before 10 am, in a room at constant temperature (20 C°), after 20 minutes of acclimatization.

The following study endpoints were considered:

• 1. Endothelial function and microcirculation.

• a. Flow-mediated dilatation: flow-mediated dilatation (FMD) of the brachial artery is an established noninvasive technique to assess endothelial function. The technique was performed like it was described previously[18, 19] by measuring brachial artery dilatation after a period of suprasystolic occlusion; artery size was measured before and 1 minute after brachial cuff release using high-resolution ultrasound.[20]

• b. Reactive hyperemia: reactive hyperemia is a noninvasive assessment of peripheral microvascular function and for assessment of endothelial function.[19] A laser Doppler flowmeter (LDF) noninvasively measures skin flux (a defined LDF unit) in minutes following arterial occlusion. Flux was measured after occlusion, during the same procedure described to evaluate the brachial artery (during the same test and within the same time frame). Finger flux was measured at rest, before occlusion as the average of a one-minute continuous recording. The distal, pulpar laser-Doppler finger flux increase was measured after occlusion as previously described.[19, 21, 22] This flux increase is considered a microcirculatory measure of reactive hyperemia and it is decreased or abolished in patients with severe vascular disease or diabetic microangiopathy. It was measured as skin flux increase after occlusion (% laser Doppler flux increase).

• c. Rate of ankle swelling (RAS): this test quantifies capillary filtration at the ankle. RAS was measured using a strain gauge plethysmograph (SPG16, Hokanson, USA), with the gauge placed at the minimum ankle circumference while the patient is resting supine for 30 minutes. The patient is then asked to move to a standing position. RAS is measured by considering the volume in the supine position and after standing (at 10 and 20 minutes) in mL/min per 100 cm^3 of tissue.[22]

• d. Kidney cortical flow was measured as flow velocity of the arteries (in cm/sec) with a high resolution color Duplex (Preirus, Hitachi, Japan).[23, 24]

• 2. Inflammatory markers and oxidative stress.

• a. Blood high-sensitivity C-reactive protein (hs-CRP).[25] The standards for hs-CRP level, applied in this study were: lower than 1.0 mg/L (low risk of cardiovascular disease, CVD); hs-CRP between 1.0 mg/L and 3.0 mg/L (moderate risk of CVD); hs-CRP level of more than 3.0 mg/L (high risk of CVD).

• b. Interleukin-6 plasma levels in pg/mL: Elevated IL-6 levels may indicate an ongoing inflammatory response and could be consistent with a systemic infection, localized infection, or chronic inflammatory disease. IL-6 is considered a nonspecific marker associated with an inflammatory response; it is not diagnostic of any specific disease or disease process (including COVID-19). Elevated IL-6 levels must be interpreted in the clinical context of the patient. Normal IL-6 levels do not exclude the possibility of an ongoing inflammation.[26, 27]

• c. Interleukin-6 (IL-6): proportion of patients with normal IL-6 (value ≤1.8 pg/mL).

• d. Erythrocyte sedimentation rate (ESR) in mm/hr: the plasma ESR has been used as a laboratory test to assess acute phase response to inflammation for a long time. ESR is slightly slower and less sensitive than hs-CRP measurement, however provides further accurate and valuable information on the inflammation status of the patient.[28] The norms, applied in this study were as follows: men >50 years, normal ESR value is less than 20; men <50 years, normal ESR value is less than 15; women > 50 years, ESR value is less than 30; women <50 years, normal ESR value is less than 20.

• e. Oxidative stress is assessed by measuring plasma free radicals in a drop of blood taken from the fingertip and expressed in Carr Units.[29]

• 3. Quality-of-life (QOL), mood and fatigue were evaluated by a QOL questionnaire with a score ranging from 0 to 35.[10]

• 4. The Karnofsky Performance Scale Index ranges from 0% to 100%. At inclusion, the scale of included patients was between 60 and 80% (Table I),[30-32] indicating a significant impact of post-COVID-19 condition.

TABLE I.—*The Karnofsky Performance Scale Index.*

Karnofsky Performance Status Scale definitions rating (%); criteria	
100	Normal no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease. Able to carry on normal activity and to work; no special care needed.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs. Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly. Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.
0	Dead

• 5. Blood pressure (systolic SBP and diastolic DBP) and heart rate (HR).

The primary assessment during the study was endothelial function and microcirculation parameters at each visit. Secondary clinical outcomes – all altered at inclusion – included inflammatory markers such as hs-CRP and IL-6, oxidative stress, blood pressure/heart rate, and quality of life, mood and fatigue with a final assessment based on the Karnofsky Performance Scale Index.

Supplement studies

This study was conducted as a supplement registry study, as described before.[33] The role of Pycnogenol® in controlling inflammation, oxidative stress and fibrosis has been documented in several recent studies.[17, 34]

This highly standardized supplement is produced by Horphag Research.

Statistical analysis

A number of at least 20 subjects for each group (SM and SM+supplementation) was considered necessary to evaluate differences in target parameters over 12 weeks. All results and data were considered as non-parametric; the Mann-Whitney U-test and the ANOVA were used for the main symptoms/complaints and for the tests. A predictive analysis was performed at the end of the study based on the observed data and results.[35-37]

Results

Sixty subjects recovering from symptomatic COVID-19 were included into the study. Two groups were formed. One group of 30 patients followed the standard management (SM, control group) while 30 comparable subjects received Pycnogenol® in addition to SM. The two groups were comparable at inclusion. There were no dropouts.

No side effects of supplementation were observed; tolerability was optimal.

At the end of the study all subjects were positive for antibodies against SARS-CoV-2.

The results of the assessed parameters of the study are shown in Table II.

The parameters progressively improved in both groups, both with SM and with SM in combination with supplementation for all measured parameters.

At the time of inclusion, vascular screening showed no significant vascular problems (plaques, intima-media thickening, aneurysms) in all included subjects. This is important to note as vascular atherosclerotic lesions may alter endothelial function.

Endothelial function and microcirculation flow mediated dilation (FMD) was low in all subjects at inclusion. It improved significantly in both groups. After 1 month, FMD was significantly higher in the Pycnogenol® group (12.6±0.9%) in comparison with controls (8.0±0.9%) ($P<0.05$ *vs.* controls) and after 3 months it was even higher (18.8±2.8%) in the Pycnogenol® group in comparison with controls (8.8±1.4%) ($P<0.05$ *vs.* controls).

This improvement was also observed in reactive hyperemia measured by skin flux increase (laser Doppler measurements) after release of the occlusive suprasystolic pressure cuff. The difference with controls was already statistically significant after 2 weeks (16.0±1.0% *vs.* 11.0±0.9%) and continued to increase after 1

TABLE II.—*Summary including all assessed parameters.*

		Visit 1 baseline	Visit 2 2 weeks	Visit 3 1 month	Visit 4 3 months
Number	PY	30 (14 F)	30	30	30
	CON	30 (13F)	30	30	30
1. Endothelial function and microcirculation					
a. FMD [%]	PY	6.5±1.2	6.6±1.0	12.6±0.9*	18.8±2.8*
	CON	7.2±1.0	7.3±2.1	8.0±0.9	8.8±1.4
b. Reactive hyperemia: Finger skin flux after occlusion [% increase]	PY	11.2±2.0	16.0±1.0*	18.0±0.8*	24.2±2.3*
	CON	10.4±2.0	11.0±0.9	13.0±1.0	15.0±1.2
c. RAS rate of ankle swelling	PY	2.22±0.01		1.23±0.08*	1.22±0.02*
[mL/min per 100 cm^3 of tissue]	CON	2.26±0.02		2.02±0.04	2.03±0.01
d. Kidney systolic cortical					
Flow velocity [cm/sec]	PY	20.2±2.0	21.0±1.5	23.0±1.4*	23.2±2.2*
	CON	19.8±1.6	19.7±0.7	19.6±0.8	20.2±1.0
Diastolic component	PY	6.1±1	8.0±0.9	11.0±0.4*	14.0±0.9*
	CON	6.4±0.9	7.0±0.9	8.0±0.8	9.2±0.7
2. Inflammatory markers and oxidative stress					
a. Plasma hs-CRP [mg/L]	PY	3.3±0.5	3.0±0.6	1.2±0.6*	1.2±0.3*
	CON	3.2±0.4	3.2±0.4	2.7±0.5	2.4±0.2
b. IL-6 [pg/mL]	PY	3.0±0.7		1.6±0.5*	1.2±0.3*
	CON	2.8±0.4		2.3±0.3	2.2±0.8
c. Number of patients with normal IL-6 ≤1.8 pg/mL	PY	2/30		25/30*	26/30*
	CON	3/30		11/30	16/30
d. ESR [mm/hr]	PY	26.6±2.2	18.0±1.1	13.0±1.0*	11.0±3.0*
	CON	27.3±3.0	26.0±0.9	23.0±1.1	19.4±2.2
e. Oxidative stress	PY	411±16	365±11*	358±9*	362±8*
	CON	418±13	399±22	384±19	387±22
3. Quality-of-life, mood and fatigue Score [0-35]	PY	22.3±2.0		32.0±2.3*	33.2±2.0*
	CON	23.4±1.2		27.3±1.7	26.7±1.5
4. Karnofsky Scale Index [0-100%]	PY	67.3±2.3		90±2.2	92±3.3*
	CON	66.3±3.5		85±2.6	83.2±2.2
5. SBP [mmHg]	PY	138±3.1	135±3.0	133±3.0	131±2.2*
	CON	139±2.5	138±2.5	137±2.2	137±2.0
DBP [mmHg]	PY	92±3.0	91±2.2	88±2.0	89±2.3
	CON	93±2.0	92±2.4	92±3.1	91±2.0
Heart rate [beats per minute]	PY	76±3.0	74±3.0	73±2.0	71±2.2
	CON	75±3.2	74±2.2	75±3.1	75±2.2

*P<0.05 *vs.* controls.
PY: Pycnogenol®; CON: controls.

month (18.0±0.8% *vs.* 13.0±1.0%) and 3 months (24.2±2.3% *vs.* 15.0±1.2%). This confirms not only the improvement of the endothelial function but also of the microcirculation.

The average rate of ankle swelling (RAS) measured in mL/min per 100 cm^3 of tissue, decreased significantly in the supplemented group (P<0.05) in comparison with the controls. The difference with controls was statistically significant after 1 month (1.23±0.08 *vs.* 2.02±0.04) and after 3 months (1.22±0.02 *vs.* 2.03±0.01). This showed a significant improvement of the capillary filtration rate, an important parameter of microcirculation.

Kidney cortical flow velocity at inclusion was low in all patients, indicating a significant decrease in perfusion (lower systolic peak flow and lower diastolic flow velocity components). It increased significantly with the supplement in comparison with controls with a significant improvement of the systolic velocity from 20.2±2.0 to 23.2±2.2 cm/s for the supplement group *versus* 19.8±1.6 to 20.2±1.0 cm/sec in the control group. The diastolic component, which is the ratio of diastolic to systolic flow velocity expressed as a percentage, significantly increased by more than two-fold in the Pycnogenol® group (from 6.1±1 to 14±0.9%) compared with controls, where it increased from 6.4±0.9 to 9.2±0.7%.

Regarding inflammatory markers, plasma lev-

els of hs-CRP and IL-6, which were elevated at baseline, gradually decreased over the 3 months. After 3 months, both hs-CRP and IL-6 levels were significantly lower in the Pycnogenol® group compared to controls (P<0.05). The difference was significant after 1 month for hs-CRP where it decreased from 3.3±0.5 to 1.2±0.5mg/L and after 3 months where it remained at 1.2±0.3 mg/L compared to controls where it decreased from 3.2±0.4 to 2.4±0.2 mg/L. Plasma IL-6 levels also decreased drastically in the Pycnogenol® group from 3.0±0.7 to 1.6±0.5 pg/mL after one month and to 1.2±0.3 pg/mL after 3 months. The difference with the control group is statistically significant at 1 and 3 months. In the control group, plasma IL-6 levels decreased from 2.8±0.4 to 2.3±0.3 pg/mL after 1 month and to 2.2±0.8 pg/mL after 3 months.

The proportion of patients with IL-6 levels in the normal range (*i.e.* ≤1.8 pg/mL) was also higher (P<0.05) with the supplement after 1 and 3 months compared with controls (25/30 and 26/30 vs 11/30 and 16/30).

After 3 months, ESR followed the same pattern with a more progressive and a more significant (P<0.02) decrease in the supplemented subjects (from 26.6±2.2 to 11.0±3.0 mm/hr) compared to the control patients (from 27.3±3.0 to 19.4±2.2 mm/hr).

Plasma oxidative stress was assessed by measurement of plasma free radicals (PFR). The level of PFR expressed in Carr units decreased significantly (P<0.05) in the supplemented group (from 411±16 to 362±8 Carr units) compared with the control group (from 418±13 to 387±22 Carr units), which showed a lower and slower rate of improvement over time.

Finally, the scores of Quality-of-life, mood and fatigue questionnaire and the Karnofsky scale performance index were significantly improved (P<0.05) in the supplement group (from 22.3±2.0 to 33.2±2.0 for QOL score and from 67.3±2.3 to 92±3.3 for Karnofsky scale) compared to controls (from 23.4±1.2 to 26.7±1.5 for QOL score and from 66.3±3.5 to 83.2±2.2 for Karnofsky Scale) after 1 and 3 months.

All other blood parameters (including platelets and clotting factors) were within normal values at the end of the study.

Physiological tests: blood pressure and heart rate were monitored. Systolic blood pressure (SBP) was significantly lower (P<0.05) in the supplemented group at the end of the study (from 138±3.1 to 131±2.2 mmHg with the supplement vs from 139±2.5 to 137±2.0 mmHg in the control group).

Discussion

The immediate and long-term consequences of COVID-19 are numerous, including neurological symptoms such as loss of smell and taste, headache, anxiety and depression, muscular disorders like weakness and fatigue, forms of vasculitis, renal dysfunction, coagulopathies and even pulmonary fibrosis and are matter of ongoing research.[1, 9-13]

The clinical situation of post-COVID-19 patients include the usual symptoms of convalescence.

A more severe situation is named "long-COVID" condition with clinically severe symptoms and signs, abnormalities in blood tests, an altered Karnofsky Performance Scale Index, all lasting several months.[38, 39] In these cases, the clinical picture compromises a normal lifestyle and standard activity level. The prevalence of prolonged convalescence of at least 3 months after COVID-19 with one or more persisting COVID-19 symptoms was investigated and strongly varied between 32% and 96%.[12, 40-42]

The management of the clinical situation is not clearly established yet and there are no real guidelines. Relieve of convalescence symptoms may be a significant problem to address in a short period of time.[43] Specific evaluation methods are still needed and are in development.[44, 45]

Most physicians try to work a therapeutic plan that is primarily related to individual subjects and symptom control.[44, 46, 47]

A high level of inflammation may be present in the recovering patients for a long period of time.

Pycnogenol® is a "soft", safe, natural anti-inflammatory and antioxidative extract studied in several preventive and clinical conditions.[34] This natural agent, with high levels of safety and highly standardized composition is used to con-

trol inflammation.[48] Naturally-derived products — when possible — may offer a safe solution to avoid the constant use of drugs with adverse effects, such as NSAIDs or corticosteroids.

In many previous clinical studies, Pycnogenol® supplementation showed beneficial effects for patients with conditions that are also described and possibly persisting after a SARS-CoV2 infection, such as endothelial dysfunction, microcirculatory problems and coagulopathy.[17]

Pycnogenol® contributes to these beneficial effects by its proven anti-inflammatory effects on the endothelium. Pycnogenol® consists mainly of procyanidins and small molecules such as catechin, ferulic acid, caffeic acid, and taxifolin. The procyanidins in Pycnogenol® are metabolized by gut bacteria into smaller molecules[34, 49, 50] including metabolite M1 (δ-(3,4-dihydroxy-phenyl)- γ-valerolactone). These compounds could be detected in the plasma of volunteers, supplemented with Pycnogenol®.[50] The metabolite M1 was found to be selectively incorporated by blood cells and endothelial cells, where it is highly enriched by facilitated uptake, showing anti-inflammatory effects within the cells.[51] As COVID-19 was described as an "endothelial disease",[4, 6, 52, 53] Pycnogenol® may support recovery from a SARS-CoV2 infection by its anti-inflammatory properties, which are directly exerted in the endothelium.[17]

In addition, some of the flavonoids, found in plasma after Pycnogenol® intake were shown to be potential inhibitors of angiotensin-converting enzyme 2 (ACE2), the receptor protein necessary for SARS-CoV-2 infection.[54]

The present study shows that patients, recovering from COVID-19 and supplemented with Pycnogenol® have improved endothelial and microcirculatory function and lower levels of inflammation in the blood compared to the control group.

Based on these various beneficial effects on health, Pycnogenol® may be used as a valuable tool for physicians in a condition that has no clear or significant solution at the moment.

A new post-COVID-19 lung study including the evaluation of the evolution into fibrosis of post-COVID-19 lung with and without the supplementation of Pycnogenol® is in press and could offer a solution for the many patients affected by a post-COVID-19 lung condition following pneumonia and its complications.[15]

Conclusions

In conclusion, Pycnogenol® may offer a significant solution for managing some of the signs and symptoms associated with post-COVID-19 syndrome.

Studies are still in progress, but this pilot evaluation offers some interesting and potential rationale for the use of Pycnogenol® in this condition that will have significant importance in the coming years.

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