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Pycnogenol supplementation as an adjunct treatment for antidepressant-induced sexual dysfunction

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Introduction: Major depressive disorder is a serious mental disorder in which treatment with antidepressant medication is associated with incidence of adverse events, such as constipation, diarrhea, dry mouth, headache, insomnia, and sexual dysfunction (SDys). Escitalopram (ESC), an effective and safe selective serotonin reuptake inhibitor with good tolerability, was used in this study. In this study, we investigated the prospective effect of Pycnogenol (PYC), an antioxidant, anti-inflammatory, and vasodilator agent, on ESC-induced SDys. *Methods:* This was a randomized, parallel, open-label study. Seventy-two outpatients of both genders with depression were randomized into two groups as follows: 37 patients from the ESC + PYC group took 50 mg of PYC per day for 4 months in ESC co-treatment, and 35 subjects from the ESC group took ESC only. Five patients dropped out and were excluded from the analysis. The participants were examined every month (visits 1–4). *Results:* ESC use led to improvement of depressive symptoms and severity scored by standardized psychiatric tests. PYC co-treatment resulted in attenuation of SDys beginning at 1 month of treatment and continuing for two consecutive months. Furthermore, an increase in heart rate in the PYC group was registered. *Conclusions:* We propose that PYC-mediated SDys attenuation is based on its ability to improve endothelial functions by its antioxidant, anti-inflammatory, vasodilatory, and anticoagulant action. We assume that the action of PYC on heart rate is in accordance with the aforementioned vasodilatory action of PYC and consequent baroreflex-mediated heart rate response. PYC co-treatment reduced ESC-induced SDys and elevated heart rate.

Keywords: Pycnogenol, depression, sexual dysfunction, escitalopram, heart rate

Introduction

Major depressive disorder (MDD) is a mental disorder that is manifested by mood changes, irritability, and sadness that are accompanied by several psychophysiological alterations, such as sleep disturbances, perturbations in appetite and sexual desire, constipation, crying, and suicidal

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thoughts (5). The pharmacotherapy of MDD consists of the use of antidepressants, which operate on the central neurotransmitter system and modulate its action (19). Antidepressant treatment is associated with an incidence of adverse events, which are the most frequently reported causes of treatment discontinuation and non-compliance (3, 23). Refinement of side effects has become an urgent topic, because in 2014, 7.2% of adults in the European Union (EU) took antidepressants at some time, and 58% of them took them regularly (27).

In 2008, the most frequently prescribed class of antidepressants in Europe was the selective serotonin reuptake inhibitors (SSRIs) (4). SSRIs possess strong serotoninergic side effects, including diarrhea, insomnia, nervousness, and sexual dysfunction (SDys) (6). SDys is manifested by a decrease in libido, male impotence, delayed ejaculation, and anorgasmia (14). Corona et al. (9) reported that the incidence of SDys in men taking SSRIs is 71%; however, Park (36) did not validate this finding. A direct connection between taking SRRI antidepressants and SDys is made obvious by the fact that SSRIs are the first choice in treatment of premature ejaculation with expected results and ejaculation delay (17).

Escitalopram (ESC), an SSRI, was shown to have superior efficacy and tolerability compared to other SSRIs (e.g., citalopram, fluoxetine, paroxetine, and sertraline); nevertheless, ESC possesses the aforementioned side effects including SDys (8, 22).

A growing number of scientists perform clinical studies to investigate complementary supplementation of natural compounds and extracts in the conventional treatment of MDD to improve response in patients (18).

Pycnogenol (PYC) is a *Pinus pinaster* (synonym: *Pinus maritima*) bark extract and a powerful antioxidant (44). It consists of phenolic compounds (catechin and epicatechin) and condensed tannins (procyanidines and proanthocyanidines) (44). In humans, daily administration of PYC decreased glucose levels, improved vasodilatation, reduced oxidative stress, reduced inflammatory response, inhibited enzymatic activity of cyclooxygenase (COX)-1 and COX-2, inhibited activation of nuclear factor NF-κB, and increased plasma levels of total antioxidant status (10, 15, 33).

The discovery of the prospective effect of PYC on erectile dysfunction (ED) (12) encouraged us to hypothesize that adjunctive supplementation of PYC in ESC-treated subjects reduces antidepressant-induced SDys. The aim of this study was to assess the effect of PYC on ESC-induced SDys.

Materials and Methods

Trial design

This was a randomized, parallel, open-label study performed in the middle Slovakia region. Patients were randomly assigned into two groups, as follows: (1) the ESC + PYC group, receiving both ESC and PYC and (2) the ESC group, receiving ESC without any additional supplementation. The duration of the study was 12 weeks. Participants were examined every month in four visits (V1–4, with an average frequency of 28 ± 2 days) to assess severity of depression, symptom severity and improvement, sexual function, blood pressure, and heart rate.

Participation

Participants were regular outpatients with MDD at the Outpatient Psychiatric Clinic, Bojnice, Slovakia. Before beginning the study, all participants took ESC in monotherapy for at least 4 weeks (31 ± 3.4 days), in doses ranging from 10 to 20 mg/day (17.2 ± 2.1 mg/day).

The inclusion criteria were the following: depressive episode or recurrent depressive disorder diagnosed by a specialist–psychiatrist according to the *Diagnostic and Statistical Manual of Mental Disorders*-5 criteria for MDD, responders to ESC therapy, and age of 18–65 years.

The exclusion criteria included intellectual disability, co-medication, psychotherapy, psychiatric comorbidity, somatic morbidity with effects on sexual functions (cardiovascular diseases, diabetes mellitus, endocrinopathies, and thyroid gland diseases), and psychotic depression.

Seventy-two patients of both genders were recruited and randomly assigned into one of the two treatment conditions (allocation ratio 1:1). Three patients from the ESC + PYC group and two patients from the ESC group prematurely terminated the study because of a depression relapse.

Randomization and blinding

This was an open study, and no placebo control was engaged. Since this study was performed between 2013and 2017, the following randomization was chosen. After receiving a written consent, the practitioner allocated a number to every patient in the order in which the patient entered the study. Participants with odd numbers were assigned to the ESC + PYC group, and participants with even numbers were assigned to the ESC group.

Sample size

Thirty-four Caucasian participants were assigned to the ESC + PYC group (11 men; aged 42 ± 10.3 years), and 33 patients were assigned to the ESC group (9 men; aged 44.4 ± 12.5 years). Both groups matched in terms of education level, occupational status, and age (Table I). All participants were recruited from the Outpatient Psychiatric Clinic, Bojnice, through information provided by face-to-face conversation with a psychiatrist, with specialization in sexology, and the study was conducted between 2013 and 2017.

Table I. Demographic characteristics of the experimental groups

	ESC + PYC		**ESC**	
Variables	**Frequency (*n*)**	**Percentage (%)**	**Frequency (*n*)**	**Percentage (%)**
Gender				
Male	11	32.35	9	27.27
Female	23	67.65	24	72.73
Education level				
High school	29	85.30	28	84.85
Degree/diploma	5	14.70	5	15.15
Occupational level				
Employed	25	73.53	23	69.70
Disabled	9	26.47	10	30.30

ESC: escitalopram; PYC: Pycnogenol

Interventions

The ESC group received 10–20 mg/day of ESC, and the ESC + PYC group received 10–20 mg/day of ESC and an additional supplementation with PYC at a dose of 50 mg/day. The PYC used in this study was a commercially available 95% *P. maritima* extract (approved by the Ministry of Health of the Slovak Republic No. OHVBPKV/7792/2014/Ht). The dose of 50 mg/day of PYC was indicated by the summary of product characteristics as recommended by The State Institute for Drug Control of the Slovak Republic and the Categorisation Committee for Drugs, Ministry of Health.

Visit 1 was performed before the PYC supplementation had been started. The values measured during V1 were considered to be baseline characteristics. All participants were examined every month for 3 months with an average frequency of 28 ± 2 days.

Data collection and measurement

The severity of depressive episodes was evaluated by the Montgomery–Åsberg Depression Rating Scale (MADRS), which was administrated at each visit. MADRS was developed in 1979 to differentiate between responders and non-responders to the antidepressant treatment, and it is widely used in depression research (29, 32).

Symptom improvement and severity were evaluated with the Clinical Global Impression – Improvement (assessed at V2–V4) and the Clinical Global Impression – Severity (assessed at each visit) Scales, respectively, because of their sensitivity to clinical change.

Sexual function was determined by the Arizona Sexual Experiences Scale (ASEX). The ASEX questionnaire consists of five questions exploring five conditions of sexual functioning (desire, arousal, penile erection in men, vaginal lubrication in women, orgasm, and orgasm satisfaction). At each visit, all participants were asked to complete the ASEX questionnaire.

Patient's blood pressure was measured using the oscillometric method by an electrical manometer (OMRON M6 AC, HEM-7322-E, OMRON Corporation, Kyoto, Japan) certified every 2 years for accurate functioning. Heart rate (beats per minute) was measured on the arteria radialis using the palpation method. Measurements of blood pressure and heart rate were performed according to recommendations of Perry et al. (37). All patients were free from caffeine, nicotine, and physical exercise at least 30 min before examination. Heart rate was counted for 30 s. This number was multiplied by 2 to calculate the rate for 1 min. If the rate was abnormal, counting lasted for 1 min.

Research ethics

All participants gave a written informed consent to participate in the study. This study was approved by the local ethics committee of Trencin (4/2011), and has been conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964).

Statistical analysis

The statistical analysis was performed using IBM SPSS version 24 (USA). The data of Gaussian/non-Gaussian distribution were assessed using the Shapiro–Wilk test. Due to the non-parametric distribution of the data, the following tests were used: the Wilcoxon test for comparison in each group (ESC and ESC + PYC) and the Mann–Whitney *U* test for between-group (ESC vs. ESC + PYC) comparison. Data were expressed as mean ± standard deviation. The probability $p < 0.05$ was considered significant.

Results

The process of this study is depicted on the Consolidated Standards of Reporting Trials flow diagram (Fig. 1).

Table II shows values for evaluated tests and heart rate. Briefly, both groups responded to ESC treatment. ESC treatment significantly reduced the MADRS scores ($p \leq 0.05$, Wilcoxon signed-rank test), and PYC supplementation did not evoke any difference. Symptom severity and improvement showed amelioration ($p \leq 0.05$, Wilcoxon signed-rank test) but was not dependent on PYC supplementation. The ESC + PYC group exhibited significant reduction of total ASEX score after 1 month of PYC co-treatment, and this amelioration persisted up to the last visit (V1 vs. V2, V3, V4; $p \leq 0.05$, Wilcoxon signed-rank test).

Our findings indicate higher heart rate in the ESC + PYC group compared to the ESC group ($p \leq 0.05$, Mann–Whitney *U* test). The systolic and diastolic blood pressures were found without significant changes (Table II).

At the first visit, members of the ESC + PYC group showed significantly worse ASEX 1 score (*$p \leq 0.05$, Mann–Whitney *U* test; Fig. 2). Although this situation reversed at V2, the amelioration continued over the examination period. No significant gender-related difference was found in the ASEX score. The status of the ASEX 1 score in the ESC group did not change.

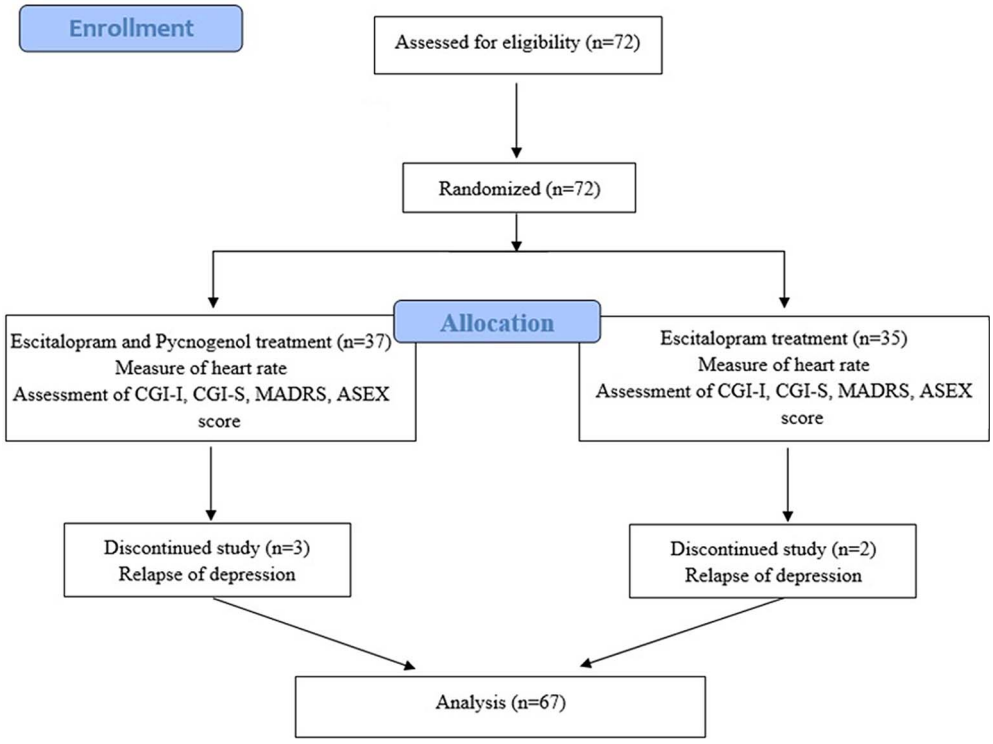

Fig. 1. Consolidated Standards of Reporting Trials flow diagram of the study procedure. ASEX scale: Arizona Sexual Experiences Scale; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; MADRS: Montgomery–Åsberg Depression Rating Scale

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Table II. Median (interquartile change) MADRS score, CGI-I and CSI-S scale, total ASEX score, heart rate, and systolic and diastolic blood pressure values of experimental groups in corresponding visits

	ESC + PYC				ESC			
	V1	**V2**	**V3**	**V4**	**V1**	**V2**	**V3**	**V4**
MADRS	17.5 (14, 23.75)[a]	15 (12.5, 22.25)[b]	14 (11, 20)[c]	13 (7, 15)[d]	20 (13, 17)[a]	18 (11, 24)[b]	13 (10, 20)[c]	12 (9.75, 16)[d]
CGI-I		2.5 (2, 3)[a]	2 (2, 3)[b]	2 (1, 3)[c]		3 (2, 3)[a]	2 (2, 3)[b]	2 (1.75, 2)[bc]
CGI-S	3 (3, 3)[a]	2.5 (2, 3)[b]	2 (2, 3)[c]	2 (1, 3)[d]	3 (2, 4)[a]	3 (2,3)[b]	2 (2, 3)[c]	2 (1.75, 2)[d]
Total ASEX score	15 (12.25, 16)	12.5 (11.25, 15)**	12 (11, 15)**	12 (11, 15)**	13 (11, 15)	13 (10, 14)	13 (10, 14)	13 (10, 14)
Heart rate	74 (68, 80)	77 (72, 80)[#]	78 (70, 80)[#]	76 (70, 80)[#]	70 (68, 76)	72 (68, 76)	70 (68, 75)	72 (67, 77)
Systolic blood pressure	120 (115, 130)	125 (116.25, 130)	120 (115, 130)	120 (115, 130)	120 (115, 130)	120 (115, 130)	125 (120, 130)	120 (117.5, 130)
Diastolic blood pressure	82.5 (76.25, 90)	80 (80, 85)	80 (75, 85)	80 (78.75, 85)	75 (70, 85)	80 (70, 80)	75 (75, 80)	80 (70, 80)

Data are expressed as median and interquartile range. ASEX scale: Arizona Sexual Experiences Scale; CGI-I: Clinical Global Impression – Improvement; CGI-S: Clinical Global Impression – Severity; MADRS: Montgomery–Åsberg Depression Rating Scale. Superscript letters (a–d) indicate statistically significant intragroup differences between individual visits ($p \leq 0.05$, Wilcoxon signed-rank test).

**Statistically significant intragroup difference vs. V1 ($p \leq 0.01$, Wilcoxon signed-rank test).

[#]Statistically significant intergroup difference between groups in corresponding visit ($p \leq 0.05$, Mann–Whitney *U* test)

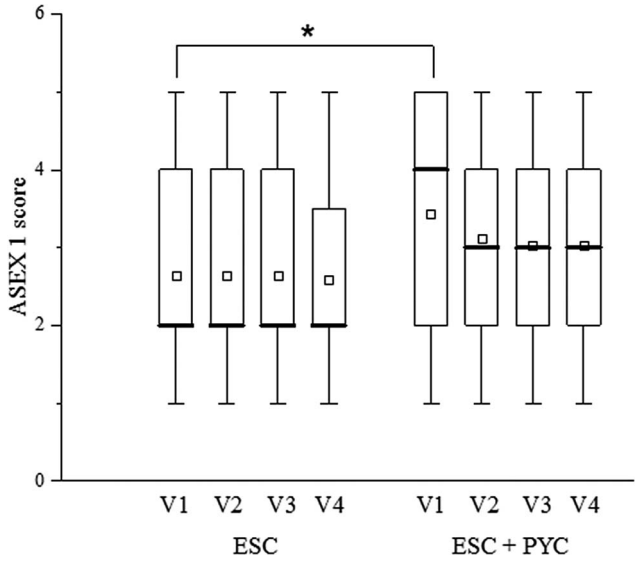

Fig. 2. Arizona Sexual Experiences Scale 1 (ASEX 1) score box plot of the ESC + PYC group and ESC group during indicated visit. ESC + PYC vs. ESC $*p < 0.05$, Mann–Whitney *U* test. The box contains 50% of the data [25–75 percentile, interquartile range (IQR)]; the line in the box is the median; the square inside each box represents mean values; whiskers represent the range within 1.5 IQR. There were no outliers. ESC: escitalopram; PYC: Pycnogenol

During the study, no participant declared any adverse effects related to PYC ingestion.

Discussion

Polyphenols are composed of four classes: phenolic acids, flavonoids, stilbenes, and lignans. Polyphenols are most abundant in fruits, vegetables, chocolate, wine, tea, and coffee. Beneficial health-related effects of polyphenols have been reported elsewhere (35). Risk assessment for polyphenols is complicated. This complication arises from their bioavailability after ingestion *in vivo* and production of several active metabolites from a single polyphenol (30). Another complication in safety assessment represents dose recommendation. In general, herbal extracts can possess adverse effects, mainly when used in high doses, and can be illustrated by a study that showed that high doses of green tea extract (27% catechins and 7% caffeine) led to moderate toxicities in cancer patients. This was reported to be caffeine-related (39).

Although PYC is generally regarded to be safe, there are some adverse effects reported following PYC treatment. Mülek et al. (31) observed only one side effect. One patient with severe osteoarthritis reported flatulence after ingestion of 100 mg PYC twice a day for 3 weeks (31). In patients with increased cardiovascular disease risk, adverse effects such as headache, sleepiness, gastrointestinal discomfort, frequent urination, and insomnia were reported following 12 weeks of daily intake of 200 mg PYC (11). However, in patients with chronic venous insufficiency, no side effects during 8 weeks of daily ingestion of 150 mg PYC were reported (7). No such adverse effects or any other PYC ingestion-related health issues were reported during this study.

PYC has rapid bioavailability of its bio-effective compounds after oral ingestion in humans (38). Grimm et al. (16) focused on detection and quantification of constituents and metabolites of PYC in plasma of healthy volunteers after ingestion. After a single dose of 300 mg catechin, ferulic acid, caffeic acid, δ-(3,4-dihydroxy-phenyl)-γ-valerolactone, taxifolin, and 10 unknown compounds were detected (30). PYC is able to directly interact with

the erythrocyte membrane, its metabolites or components were found in erythrocytes, and they also permeate synovial fluid (31, 41). However, according to the results of Jankyova et al. (21), administration of separated fractions of PYC is not as effective as PYC complex mixture, suggesting a synergic action of its individual components.

The effect of PYC has reportedly affected human circulation. A 2-week oral administration of PYC (180 mg/day) resulted in an increase in endothelium-dependent vasodilatation measured via forearm blood flow response in healthy young men (33). Improved flow-mediated dilatation following PYC administration (200 mg, 8 weeks) was also shown in patients with arterial disease (13). Hosseini et al. (20) detected a significant decrease in systolic blood pressure following 8 weeks of PYC intake in mildly hypertensive patients; however, they found no change in heart rate. These discoveries demonstrate a PYC-mediated improvement of endothelial functions under physiological as well as pathophysiological conditions. In this study, we found that 12 weeks of treatment with PYC induce an increase in heart rate.

We suggest that the heart rate changes in the manner of increase in ESC + PYC group could be explained from several aspects. First, we suggest vasodilatory, antioxidant, and anti-inflammatory effect of PYC on neurocardiac complex regulation and integrity (13, 15, 38). Consequently, we could hypothesize that the neurocardiac control of the heart rate mediated through baroreflex resulting in tachycardia – increased heart rate – might represent an important mechanism in patients treated by ESC and PYC. Although there are several studies regarding the vasodilatory effect of PYC (13, 28, 33), alternation in heart rate has not been reported.

We theorize a crucial role of endothelial function in PYC-mediated amelioration of sexual function (21, 33). Endothelial function improvement by PYC could be mediated by vasodilation via enhanced endothelial nitric oxide synthase (eNOS) expression as well as reduction of platelet aggregation as reported in smokers and decreased levels of serum tromboxane B2 (2, 21, 33, 34).

The main purpose of this study was the evaluation of the action of PYC on ESC-induced SDys. In our results, we found that PYC attenuates SDys in men and women. It has already been shown that 3 months of oral treatment with PYC (40 mg, three times a day) in patients diagnosed with ED improved erectile function compared with the state before treatment (12). PYC action on SDys in men was repeatedly studied in preparations containing PYC in combination with other compounds (24, 25). Stanislavov and Nikolova (42) reported a synergic effect of L-arginine and PYC in men with SDys. L-arginine is a substrate for eNOS and is believed to improve endothelial function (40). A 1-month treatment with PYC in a patented dietary supplement (80 mg PYC, 3 g L-arginine per tablet) was shown to improve sexual function scored with the International Index of Erectile Function (IIEF) in patients with mild-to-moderate SDys (43). This treatment also resulted in an increase in the amount of eNOS in the lysate of spermatozoa, increased testosterone levels in the plasma, decreased systolic and diastolic blood pressures, and decreased cholesterol (43). A different composition of the same dietary supplement (20 mg PYC, 700 mg L-arginine per tablet) administered 4 times a day for 6 months significantly improved IIEF score and increased total plasma levels of testosterone in patients with ED (42). The amelioration of sexual function was prominent as soon as 3 months after the start of treatment (26). Yagi et al. (45) suggest another food supplement containing PYC (16 weeks, 6 tablets a day, 1 tablet consisting of 10 mg PYC, 115 mg L-arginine, and 92 mg aspartic acid) as a possible treatment for SDys (45). Treatment on using this supplement (6 tablets, 8 weeks) improved IIEF score in terms of hardness of erection and intercourse satisfaction (45). This was associated with a significant decrease in diastolic blood pressure; salivary testosterone concentration remained unchanged (1).

This study found a beneficial effect of PYC treatment on antidepressant-induced SDys in both genders. It seems that PYC supplementation could be useful in reducing the antidepressant-mediated adverse effect on sexual function.

Limitations of the study

The limitation of this study represents applying single-blind study, where participants are unaware of the group assignments and detailed information, whereas the investigator has full knowledge about the study. We did not choose double-blinding, because manufacturing placebo pills (of equal physical appearance as the commercially available 95% *P. maritima* extract pills) would cost additional financial resources.

Abbreviations

ASEX scale : Arizona Sexual Experiences Scale
CGI-I : Clinical Global Impression – Improvement
CGI-S : Clinical Global Impression – Severity
COX : cyclooxygenase
DSM-5 : Diagnostic and Statistical Manual of Mental Disorders-5
ED : erectile dysfunction
SDys : sexual dysfunction
eNOS : endothelial nitric oxide synthase
ESC : escitalopram
IIEF : International Index of Erectile Function
IL : interleukin
IQR : interquartile range
LDL : low-density lipoprotein
MADRS : Montgomery–Åsberg Depression Rating Scale
MDD : major depressive disorder
NF-κB : nuclear factor-κB
PYC : Pycnogenol
SSRI : selective serotonin reuptake inhibitor
TNF-α : tumour necrosis factor α
TX : thromboxane

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Conflict of interest

The authors declare no conflict of interest.

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