Research Article

Pomegranate Juice Consumption by Patients Under Medication for Addiction Treatment as Regulator of Craving and Blood Redox Status: The Study Protocol of a Randomized Control Trial (The NUTRIDOPE Study)

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ABSTRACT

Background: Buprenorphine and methadone are considered the "gold standard" medication for addiction treatment (MAT) for patients with opioid use disorders (OUDs). However, they may cause side effects promoting craving. Pomegranate is a natural substance that contains antioxidant polyphenolic compounds, which have been associated with craving reduction.

Aim: The NUTRIDOPE (NUTRItion - driven Detoxification of OPioid addicted patieEnts) study aims to investigate the role of pomegranate juice consumption by opioid patients under buprenorphine and methadone on craving, as the primary outcome, and biopsychosocial parameters.

Methodology: NUTRIDOPE study is a randomized control trial with repeated measures: - that has been registered in ClinicalTrials.gov (Identifier: NCT05861544). The participants, who will be patients with OUDs attending rehab programs in the Greek Organization Against Drugs (OKANA), will be randomly divided into the experimental and the control groups and both groups will be further stratified into two subgroups, i.e., methadone and buprenorphine, according to the maintenance treatment program they attend. Pomegranate juice will be administered to the participants of the experimental group, whereas their counterparts in the control group will not consume any similar beverage. The administration regimen will be 250 ml, seven days/week, and four months.

Anticipated Results and Conclusion: NUTRIDOPE is a hypothesis-driven, evidence-based, multifactorial project that proposes a nutrition-based solution towards craving reduction for opioid patients under MAT, potentially assisting towards their successful rehab and societal reintegration.

Key Words: Pomegranate juice, Craving, Buprenorphine, Methadone, Oxidative stress, Inflammation

Introduction

Opioid use disorders (OUDs), comprise impaired function of nervous system compromising the organismal and behavioral health of patients under opioid dependence [1]. Addiction to opioids constitutes a globally great problem that affects the patients and also the healthcare system, hence the society itself [2]. Indeed, the economic burden of OUDs and fatal opioid overdose has been recently estimated in the United States at $1.02 trillion and the patients with OUDs were rated at 40.5 million worldwide in 2017, whereas 3.6 million were lost in 2016 due to OUDs [2,3]. The most common therapeutic approaches against OUDs are based on medication-assisted treatment (MAT). It appears that approximately only 25% of patients facing OUDs participate in MAT programs [4]. methadone maintenance treatment (MMT), buprenorphine maintenance treatment (BMT) and naltrexone with parallel psychosocial support are the main interventions used to help patients face the manifold health consequences of opioid use via reducing craving which is an essential feature of OUDs [5,6]. Craving

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refers to the desire or urges to re-experience a previously used psychoactive substance after a period of detoxification affecting parameters in physical, emotional, cognitive, and behavioral context [7-9]. Buprenorphine and methadone are considered effective and the "gold standard" approach for the treatment of OUDs, although diverse dropout rates have been observed [10, 11].

Methadone triggers similar, to the known opioids, effects as a full synthetic agonist of M-opioid receptors (MORs), whereas it partially acts also to K-opioid receptors (KORs) and D-opioid receptors (DORs) inducing euphoria, analgesia. Therefore, it plays a key role in the reward system and leads to confinement of drug-seeking behaviors and decrease of craving [9, 10]. Buprenorphine is a semi-synthetic and partial agonist with high affinity for MORs, and an antagonist of KORs and DORs [11]. Because of the "ceiling effect" observed, the euphoria feeling, and the respiratory depression are limited, whereas it also reduces craving [15, 16].

Buprenorphine and methadone, are considered effective in lowering the risk of overdose death, in inhibiting transmission of communicable diseases, as well as in reinforcing immune system [17]. However, given their opioid nature, they may cause serious side effects that negatively affect the therapeutic process by inducing responses, potentially leading patients towards craving and not rehabilitation [17]. Research evidence indicates that they act detrimentally on the cognitive level of the patients, they deteriorate constipation, and they cause serious sleep disturbances [18-20]. Buprenorphine and methadone have also been associated with impairment of blood antioxidant defense probably through enhancement of the levels of reactive oxygen species (ROS), whereas they have been related to inflammation and boost of craving and drug-seeking behavior [21-23].

Unfortunately, buprenorphine and methadone exert under circumstances toxic actions, whereas the possibility of craving is far from being disappeared. Therefore, several studies have proposed the use of alternative, non-opioid, and nutrition-based interventions to back-up MAT and reduce craving. To that end, the use of natural products, such as honey and plant extracts derived from the plants *Nigella sativa* and *Phoenix dactilyfera* has been advocated [24-26]. The putative beneficial effects of administered plant extracts in parallel to MAT is mainly attributed to the potent antioxidant and anti-mutagenic action of plant substances due to their high polyphenolic content [27-30]. Indeed, polyphenols modulate central reward pathways *In vitro*, whereas other antioxidants compounds (i.e., *Nigella sativa* and quercetin) block opioid induced tolerance and withdrawal symptoms [31-34]. Furthermore, the administration of fruits rich in polyphenols, such as pomegranate, in diverse forms is also supported by the literature due to their potential contribution to face addiction and disease prevention [35]. Pomegranate is a rich source of polyphenols with a high level of flavonoids, tannins and anthocyanins contributing to the enhancement of the poor antioxidant defense of the organism and to the decrease of inflammatory process, which are common molecular side effects of patients with OUDs [36, 37]. Ellagic acid, a polyphenol with antioxidant properties present in pomegranate seems to alleviate morphine dependence and tolerance [38]. Nevertheless, to our knowledge, there is not available evidence regarding the potential beneficial action of pomegranate on craving or other health aspects of patients with OUDs.

Based on the above, it becomes evident that a nutrition-based intervention could act synergistically in terms of reducing craving in patients under MAT. Thus, the main objective of the NUTRIDOPE study, as a hypothesis-driven, evidence-based, multifactorial project, is to investigate the putative role of pomegranate juice consumption on patients under MAT on craving reduction, which is the primary outcome. Furthermore, biochemical parameters involving blood redox status, inflammation and hormone levels, as well as psychosocial and physiological parameters, namely quality of life, sleep, fatigue, constipation, fecal quality, and mood will be evaluated.

Materials and Methodology

■ Study design and description

The NUTRIDOPE study is a randomized controlled trial with repeated measures, whose rationale is depicted in Figure 1 and Figure 2 illustrates its experimental design. According to it, the participants will be randomly divided into the experimental and control groups. Regarding the randomization process, the volunteers using the unique code they obtain during entering the MAT programs of the Organization Against Drugs (OKANA, Greece), will be randomly

divided in the study groups, matched-up based on their demographic characteristics. The randomization will be performed by an independent individual, who will not participate in the data collection and evaluation procedures. This individual will have access to interim results and decide to terminate the trial in case there is a need for that or check for any adverse effects before addresses to the appropriate expert. The volunteers will be informed about the group they have been allocated through a message in an opaque envelope. The participants of both groups will be further stratified into two subgroups, i.e., MMT and BMT, according to the maintenance treatment program they attend. Pomegranate juice, which is the examined nutritional intervention, will be administered to the participants of the experimental group, whereas their counterparts in the control group will not consume any similar beverage. Therefore, this is a double-blinded and not a triple-blinded design, since the researchers and analysts but not the participants will be blinded. The juice will be administered to the patients at the following dosage: 250 ml/day, seven days/week, for four months. According to the literature, administration of pomegranate juice at a similar dosage exerts beneficial effects on overweight patients with dyslipidemia, on patients with type 2 diabetes, and on patients at moderate risk for coronary heart disease [39-41]. Moreover, no adverse effects have been referred to, however parameters of the participants such as blood pressure, heart rate and concentrations of liver transaminases will be regularly measured. Specific validated self-reported instruments for the assessment of the effects of pomegranate juice on craving, quality of life (QoL), mood, fatigue level, bowel function, constipation and cognitive function will be completed by the participants at four time points, namely, before the start of the experiment (i.e., day 1), in the middle (i.e., day 60), at the end of the experiment (i.e., day 120) and six months following the end of the experiment (i.e., follow-up measurements). Furthermore, whole blood samples will be collected at the same timepoints where several established redox biomarkers, inflammation markers and hormones will be measured.

Supply of the pomegranate juice

The pomegranate juice that will be used in the experiment is a 100% natural product without conservatives. It will kindly be donated from the company Rodi Hellas SA, Pella, Greece. The product is in line with the quality assurance certificates ISO 22000:2005, Global Gap, Grasp and Kosher.

Participants

Patients under MAT that are active members of the OKANA therapeutic units will be recruited for this investigation. The inclusion and exclusion criteria are shown in Table 1. The patients will be informed about the objectives of the study, the risks, and difficulties as well as the expected benefits they will gain after the fulfillment of this investigation. Each patient will sign a written consensus form before the experimental procedure starts. This form will be collected by the aforementioned independent individual. The highest adherence rate is

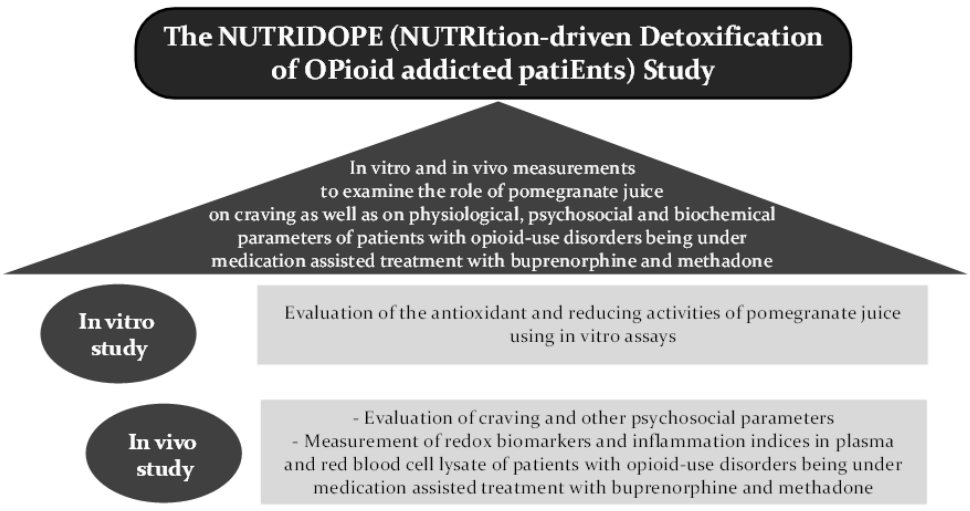

Figure 1: The rationale of the NUTRIDOPE study.

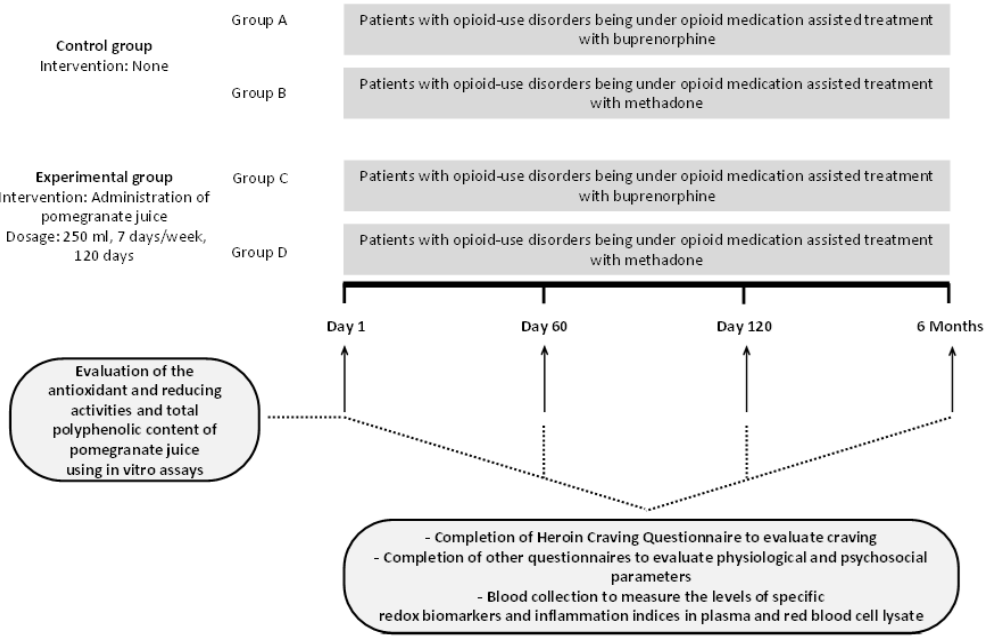

Figure 2: The experimental design of the NUTRIDOPE study.

Table 1: The inclusion and exclusion criteria of the study.

Inclusion criteria	Exclusion criteria
Over 20 years of age	Serious medical problems, such as infection by human immunodeficiency virus or hepatitis B virus
Long-term heroin or other opioid drug use	Current use of anti-inflammatory medication
Suffering from physical and mental dependence due to chronic opioid use	Relapse to other addictive substances (i.e., opioids, methamphetamine, benzodiazepines, cannabis, tetrahydrocannabinol, amphetamine) - To rule out the use of such substances, all participants underwent weekly urine tests during the four-month period of the experiment

anticipated to be achieved through informing the volunteers regarding the putative beneficial role of the nutritional intervention on several parameters of their life. Furthermore, the patients will be allowed to follow their regular program in OKANA (i.e., accept psychiatric care and psychosocial support). All personal data and information obtained will be unequivocally confidential and the investigators only will strictly have access on them. Moreover, the data obtained will be kept in password protected computers that will stay within OKANA and will never be transferred outside the premises of this Institution.

Medication for Addiction Treatment (MAT)

The patients under MAT receive daily methadone hydrochloride solution (10 mg/ml) and uprenorphine / buprenorphine-naloxone pills (2 mg - 8 mg), according to the existing dose guidelines (National Organization for Medicines).

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Demographic data

Before the start of the experimental procedures, demographic data will be collected by all participants. Information such as the sex, the age, the educational level, the nationality, the marital status, the professional status, the area of residence, the number of years attending a rehab program in OKANA, the age of onset, the duration of substance use before entering the MAT program and the chronic diseases they putatively suffer from will be obtained.

Outcomes

The primary outcome of the NUTRIDOPE study is craving, a psychosocial parameter that

is of utmost important towards the trajectory of the patients to rehabilitation. Craving will be assessed through a validated and reliable self-reported questionnaire. Secondary outcomes comprise blood redox status, through measuring specific redox biomarkers in blood, and QoL evaluated through another validated and reliable self-reported questionnaire. Further outcomes include physiological, psychosocial, and biochemical parameters that are analyzed in the following paragraphs. These outcomes are of high clinical relevance since they are fundamental factors for the maintenance of mental and organismal equilibrium of the patients. In case any protocol modification is needed, this will be communicated to relevant parties.

■ Description of the instruments

The main characteristics (outcome measured, title and description of the instruments) of the questionnaires that will be used in the study are shown in Table 2 and a detailed description can be found below. All instruments have been used after obtaining the appropriate permission by the researchers that introduced them.

■ Heroin Craving Questionnaire (HCQ)

The HCQ will be used for the assessment of pomegranate juice effects on craving consisted of 45 questions divided in 5 dimensions, namely desire to use heroin, intentions and planning to use heroin, anticipation of positive outcome, relief from withdrawal or dysphoria, and lack of control overuse. The score is calculated with a 7-point Likert scale ranging from 1 (i.e., strongly disagree) to 7 (i.e., strongly agree). Internal consistency reliability was accepted with Cronbach's alpha equal to 0.90 [42].

■ Nottingham Health Profile (NHP)

The NHP questionnaire will be used for the assessment of the pomegranate juice effects on the QoL of the patients. The questionnaire consists of two parts; the first part assesses parameters such as activity, pain, emotional reaction, sleep, social isolation, and mobility, whereas the second part evaluates the effects of health or disease on

Table 2: The questionnaires administered to the participants of the NUTRIDOPE study (days 1, 60, 120, and six Months after the end of the experiments as a follow-up measurement).

Outcome	Questionnaire	Description	Example
Heroine craving	Heroin Craving Questionnaire	5 Dimensions: Desire to use heroin; Intentions and planning to use heroin; Anticipation of positive outcome; Relief from withdrawal or dysphoria; Lack of control overuse 45 Items	For each question, please click between 1 (strongly disagree) to 7 (strongly agree) E.g., I intend to use heroin as soon as possible
Quality of life	Nottingham Health Profile	First part: Assessment of activity, pain, emotional reaction, sleep, social isolation, mobility Second part: Evaluation of the effects of health or disease on the presence of the patients at the working environment and inside their household, social life, home life, sex life, interests, and vacations.	Please provide yes-or-no answers E.g., I experience unstable sleep; I am getting tired very easily
Sleep quality and quantity	Pittsburgh Sleep Quality Index	7 Components: Subjective sleep quality; Sleep latency; Sleep duration; Habitual sleep efficiency; Sleep disturbances; Use of sleep medication; Daytime dysfunction 19 Items Lower obtained scores indicate better sleep quality	Please complete the following items based on the past month: E.g., Did you have bad dreams? (never during the last month, less than once/week, once or twice/week, more than 3 times/week)
Fatigue	Fatigue Severity Scale	9 Items Higher obtained scores indicate worse experienced fatigue	For each question, please click between 1 (strongly disagree) to 7 (strongly agree) E.g., Fatigue is one out of three symptoms that make difficult my everyday routine
Effect of constipation on quality of life	Patient Assessment of Constipation - Quality of Life	4 Dimensions: Physical discomfort; Psychosocial discomfort; Treatment satisfaction; Worries discomfort 28 Items	Please click 1 (zero) to 5 (constantly) E.g., How many times have you felt uncomfortable due to constipation when you meet other people?
Faecal Evaluation	Bristol Stool Form Scale	Assessment of the type (types 1 to 7) of stools	Please click the box that represents your situation E.g., Your stools are of type 6 (pulpy)
	Faecal Colour Assessment	Assessment of the colour (scale from 1 to 6) of faeces	Please click the box that represents the colour of your faeces 1 for green to 6 for cherry red
Mood states	Profile of Mood States (POMS-short version)	6 Dimensions: Tension; Depression; Anger; Vigour; Fatigue; Confusion 37 Items	For each question, please click between 0 (not at all) to 7 (very much) E.g., I am currently feeling desperate

the activities of daily living. The patients will complete the NHP questionnaire using yes-or-no answers. The questionnaire is highly valid and reliable in its version in the Greek language (i.e., test-retest reliability coefficients and Spearman's R-value range between 0.77 and 0.86) [43].

■ Pittsburgh Sleep Quality Index (PSQI)

PSQI is a 19-item self-reported questionnaire, which subjectively assesses sleep quality and quantity, sleep habits related to quality and occurrence of sleep disturbances in adults consisting of 7 components. Each component score is marked on a 0–3 scale, and the PSQI is calculated as the sum of the 7 components ranging between 0 and 21. The Cronbach's alpha for global PSQI score was equal to 0.76 [44].

■ Fatigue Severity Scale (FSS)

FSS is a 9-item, self-administered questionnaire which assesses the magnitude of fatigue that the patients have experienced throughout the past weeks. Each item is scored on a 7-point Likert scale ranging from 1 (i.e., completely disagree) to 7 (i.e., completely agree). The Cronbach's alpha for all FSS was 0.953 [45].

■ Patient Assessment of Constipation - Quality of Life (PAC-QOL)

The PAC-QOL questionnaire consists of 28 self-reported items that assess the effects of constipation on the patient QOL in the last 2 weeks. The responses are scored on a Likert scale ranging from 0 to 5. Higher score indicates increase of severity of the negative effects of the intervention in question on QOL [20].

■ Bristol Stool Form Scale (BSFS)

The BSFS is a pictorial representation of each stool type ranging from the hardest (i.e., type 1) to the softest (i.e., type 7) related to specific bowel symptoms, such as constipation, diarrhea [46].

■ Faecal colour assessment

This is a tool for the evaluation of the colour of faeces using a 1-6 scale. There is a 6-colour scale for the faecal assessment comprising the colours green, brown, white, yellow, black and red indicating specific bowel symptoms and diaseases, as bilirubin deficiency, liver or gallbladder abnormalities, bleeding from gastrointestinal system [47].

■ Profile of Mood States (POMS-short version)

The POMS questionnaire consists of 37 self-administered items and assesses current mood states in 6 dimensions, namely tension, depression, anger, vigour, fatigue, and confusion. Each item is scored on a 5-point Likert scale from 0 (i.e., not at all) to 4 (very much). The instrument has been validated in Greek and the Cronbach's is ranged between 0.72 and 0.93 [48].

■ Blood collection and handling

Plasma and erythrocytes will be collected following a procedure that has been previously described [49]. In brief, whole blood samples from a forearm vein of seated individuals will be collected in vacutainers with ethylene diamine tetra acetic acid (EDTA) as an anticoagulant agent. The samples will be centrifuged, and the plasma will be collected and stored at -80°C until analyses. Then, distilled water will be added to the packed erythrocytes (1:1 v:v) and following a centrifugation, the Red Blood Cell Lysate (RBCL) will be collected and stored also at -80°C.

■ *In vitro* experiments - Evaluation of the antioxidant and anti-mutagenic activities of pomegranate juice *in vitro*

The capacity of pomegranate juice to reduce the DPPH (2,2-Diphenyl-1-Picrylhydrazyl), ABTS (2,2′-Azino-bis(3-Ethylbenzothiazoline-6-Sulfonic acid), hydroxyl and superoxide radicals, as well as Fe^{+3} to Fe^{2+} using the reducing power assay will provide evidence regarding the antioxidant/reductive properties of the administered juice. Furthermore, the antimutagenic activity of the juice will be evaluated through measuring its ability to protect plasmid DNA from the oxidative action of peroxyl radicals (ROO). Finally, the total polyphenolic content of the pomegranate juice will be measured through the Folin-Ciocalteau assay [29, 44, 50].

■ *In vivo* experiments - Measurement of biomarkers in blood

Redox biomarkers: Several well-established redox biomarkers will be measured for the assessment of the effects of pomegranate juice consumption on blood redox status of the patients. In particular, the following three categories of redox biomarkers will be examined:

Biomarkers of antioxidant profile comprising the antioxidant enzymes catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase, and the reduced form of Glutathione (GSH) as a crucial antioxidant

molecule, which will be measured in RBCL, as well as total antioxidant capacity that will be assessed in plasma spectrophotometrically[49, 50].

Biomarkers indicating the oxidative modification of biomolecules, namely protein carbonyls as a biomarker of protein oxidation and thiobarbituric acid reactive substances as a biomarker of lipid peroxidation that will be assessed in plasma spectrophotometrically [49, 50].

Biomarkers evaluating the reductive capacity of plasma through measuring its ability to reduce the hydroxyl (OH•) and superoxide (O2-•) radicals, as well as Fe^{+3} to Fe^{2+} using the reducing power assay. All three assays are spectrophotometric [50].

■ Biomarkers of inflammation

Pro-inflammatory cytokines namely Interferon Gamma (IFN-γ), Interferon Alpha-2 (IFN-a2), Interleukin-1 Betta (IL-1β), Interleukin-1 Alpha (IL-1a), interleukin-8 (IL-8), Monocyte Chemoattractant Protein-1 (MCP-1) and Tumor Necrosis Factor Alpha (TNF-a) will be measured in plasma through immunofluorescence.

■ Hormones

Melatonin and cortisol levels will be measured in plasma using Enzyme-Linked Immunosorbent Assay (ELISA).

■ Ethical considerations

The NUTRIDOPE study in terms of ethics and methodology has been approved by the Review Board of the OKANA (ref. number 44482-2/12/2020) and the implemented procedures are in accordance with the Declaration of Helsinki, as revised in 2013. The trial has also been registered in ClinicalTrials.gov (Identifier: NCT05861544).

■ Statistical analyses and power calculation

A preliminary statistical power analysis was performed using the online available sample size calculator ClinCalc.com. The primary outcome for this analysis will be the reduction of craving. The relevant literature has demonstrated that MAT induce a 30% reduction of craving in patients with OUDs [51, 52]. We anticipate that pomegranate juice will lead to a further 10% craving reduction. On that basis, the statistical power analysis showed that at least 16 participants for each group (i.e., control and experimental) are needed to obtain statistically meaningful results. The input variables for the analysis were as follows: alpha error =0.05; power=0.90; enrollment ratio=2 (for additional safety data). However, due to potential dropouts, the final number of the participants with a dropout rate equal to 10% is: n = 18 for the control group and n=35 for the experimental group.

The results from the demographic data of the participants will be expressed as mean ± standard deviation. If the results obtained from the Kolmogorov-Smirnov test indicate that our data follows normality, parametric tests will be used for their evaluation. The effects of pomegranate juice consumption on the measured parameters in all four time points will be analyzed using 3-way ANOVA with repeated measures. The results from the psychosocial parameters obtained through the questionnaires will be correlated with the results from the biochemical parameters (i.e.., redox status, inflammation, hormones) through Spearman's rank correlation (R-value). Furthermore, to study the topological behavior of the data set and uncover hidden patterns, unsupervised learning methods will be utilized. Nonlinear visualization and clustering techniques able to handle mixed data, will allow us to examine groups of samples with similar characteristics [53]. The outcome will be validated through various internal clustering metrics along with visual investigation of 2-dimensional scatter plots. In the presence of a hierarchical clustering structure, additional machine learning methods will be used (tree-based methods) to provide the importance metrics that significantly discriminate groups of samples. Statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS, version 21.0 Chicago, IL) and the R Project for statistical computing (version 4.1.3, The R Foundation, Vienna, Austria). The source code for the machine learning and statistical analysis processes developed in R will be available under an open-source license .

Discussion

The NUTRIDOPE study comprises a nutritional approach that intends to introduce pomegranate juice consumption as an auxiliary treatment alongside with MAT that will further reduce craving of patients under MAT towards their trajectory to successful rehabilitation. Concerning psychosocial parameters, it appears to be beneficial against impaired cognitive function in opioid-dependent *in vitro* and *in vivo* models [54-56]. Moreover, pomegranate seems to be effective on depression and anxiety of OUDs patients [57] as well as on the

improvement of impaired behavioral aspects ameliorating aggressiveness through the inactivation of ROS, whose enhanced levels have been associated with aggressive behavior [58]. Finally, pomegranate contributes to pain management, memory function [53, 50] and quality of life in menopausal women [59-61].

The rich polyphenolic content of pomegranate is the main contributor for its notable and diverse biological properties in regulating antioxidant defense and inflammation, and a protective factor against muscle damaging exercise-induced oxidative stress, probably via urolithins, which are metabolites of ellagitannins [62, 63]. It also exerts beneficial effects, on several cancer types, namely prostate, lung and breast, colon and skin cancer [64] as well seems to improve blood pressure and hypertension [65].

At the molecular level, the antioxidant activity of pomegranate is linked to nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which seems to be activated with a concurrent downregulation of cyclooxygenase 2 and a decrease of prostaglandin 2 production [63]. Furthermore, punicic acid appears to be involved in preventing the action of tumor necrosis factor-a, which is activated by NADPH-oxidase, targeting to the p38-MAP kinase pathway and myeloperoxidase release that is a mediator for ROS generation and inflammation [66]. NF-κB, since it controls transcription of DNA, cytokine production and cell survival, plays a key-role in addiction and seems to be a target of the DeltaFosB transcription factor that is affected by punicalagin [67]. This factor facilitates the development and maintenance of dependence on addictive stimuli by its interaction with the Jun family of proteins and the formation of the protein-1 (AP-1) activator [68]. AP-1 may lead to genetic, molecular, and structural changes in the reward system of the brain, especially in Nucleus Accumbens (NAc) and dorsal striatum area [69]. In addition, DeltaFosB has been linked to drug-related behaviors through affecting the overexpression of dopamine receptor-1 in the NAc inducing reward sensitization [70, 71] leading to organic and behavioral changes [68]. Recent evidence in morphine-administered mice has pointed out the positive effects of anthocyanins present in pomegranate by reducing MORs and cyclic AMP [56]. This molecular pathway is crucial in opioid dependence and withdrawal [72].

The NUTRIDOPE study has been designed to offer solutions regarding decrease of craving and, as a result, the successful rehabilitation and reintegration of patients under MAT into the societal network. According to our hypothesis, pomegranate juice is expected to help patients towards this direction by improving several psychosocial, clinical and biochemical parameters measured herein. It must be stressed that patients with OUDs are victims of discrimination and negative bias through stigma that derives mainly from the fact that they are considered law violators, whilst the moral blame against them also exists [73]. Consequently, they have low self-esteem and decreased well-being, thus they usually postpone seeking for healthcare help as they are discouraged by society [74]. Interestingly, the stigma provoked by drug use exerts higher impact on diverse life parameters of the patients than the discrimination because of race, financial status, and sex [75]. It can be deduced, hence, that MAT patients must fight against health disparities along with the known disadvantages of opioids on their mental and physical health status.

Conclusion

According to the expected outcomes of the NUTRIDOPE study, consumption of pomegranate juice is anticipated to decrease craving and to improve most of biopsychosocial parameters to patients under MAT. It is expected that the proposed practice will enhance the opportunities of these patients to leave behind drug seeking behavior and succeed rehabilitation.

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