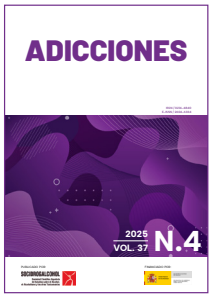
SOCIDROGALCOHOL
Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y las otras Toxicomanías

ADICCIONES
2025 ■ VOL. 37 ■ N. 4 ■ PAGES 311–322
www.adicciones.es



ORIGINAL

Soy isoflavones for the treatment of cocaine use disorder: An open-label pilot study

Isoflavonas de soja para el tratamiento del trastorno por consumo de cocaína: Un estudio piloto abierto

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Abstract

Soybeans contain different isoflavones (mainly daidzein) which work as reversible inhibitors of aldehyde-dehydrogenase-2 enzyme (ALDH2). This activity has been related in animal experiments with a reduction of cocaine use. Our aim was to carry out an open-label pilot study to evaluate the possible efficacy of soy isoflavones as natural inhibitor of ALDH2 in cocaine use disorder. Nine subjects with severe cocaine use disorder participated in a single-center, open, non-controlled trial during 12 weeks of treatment and 4 of follow-up. The Substance Use Report (SUR) showed that three subjects (33.3%) reported a cocaine consumption of less than 20% (80% non-use days) from 10 to 12 weeks of the treatment period, from two (22.2%) at baseline, although non-significant. A finding that could not be confirmed by the detection of urine metabolites of cocaine. Seven participants (77.8%) completed the study at 16 weeks and one (1.11%) at 12 weeks. Urine concentrations of isoflavones, demonstrated that eight participants (88.9%) followed the treatment along the study. The Severity Dependence Scale (SDS) score showed a significant decrease between baseline to 12 weeks, baseline to 16 weeks and 12 to 16 weeks; the Brief Substance Craving Scale (BSCS) and Cocaine Selective Severity Assessment (CSSA) decreased their values but not significantly. Significant improvements in different areas of the SF-36 scale were observed: body pain scores decreased from baseline to 16 weeks statistically significant; social function improved its scores from baseline to 12 weeks and from baseline to 16 weeks significantly; the rest of areas increased their scores but not significantly. These findings show lower ratios of cocaine use days, and high retention and adherence to treatment although the acquisition of complete abstinence was not observed. Soy isoflavones could be considered a potential treatment in future research, to be confirmed by placebo-controlled studies with adequate sample size.
Keywords: cocaine, aldehyde-dehydrogenase-2 enzyme, daidzin, daidzein, soy isoflavone extract, clinical trial

Resumen

La soja y sus habas contienen diferentes isoflavonas (principalmente daidzeína) que actúan como inhibidores reversibles de la enzima aldehído-deshidrogenasa-2 (ALDH2). Esta actividad se ha relacionado en experimentos con animales con una reducción del consumo de cocaína. Nuestro objetivo fue llevar a cabo un estudio clínico piloto abierto para evaluar la posible eficacia de las isoflavonas de soja, como inhibidor natural de ALDH2, en el trastorno por consumo de cocaína. Nueve sujetos con trastorno grave por consumo de cocaína participaron en un ensayo unicéntrico, abierto y no controlado durante 12 semanas de tratamiento y 4 de seguimiento. El Substance Use Report (SUR) mostró que tres sujetos (33,3%) informaron un consumo de cocaína inferior al 20% (80% de días sin consumo) entre las semanas 10 y 12 del periodo de tratamiento, frente a dos (22,2%) al inicio, aunque sin significación estadística. Un hallazgo que no pudo ser confirmado mediante la detección de metabolitos urinarios de cocaína. Siete participantes (77,8%) completaron el estudio en la semana 16 y uno (11,1%) en la semana 12. Las concentraciones urinarias de isoflavonas demostraron que ocho participantes (88,9%) siguieron el tratamiento a lo largo del estudio. La puntuación de la Severity Dependence Scale (SDS) mostró una disminución significativa entre el inicio y las 12 semanas, entre el inicio y las 16 semanas y entre las semanas 12 y 16; la Brief Substance Craving Scale (BSCS) y la Cocaine Selective Severity Assessment (CSSA) disminuyeron sus valores pero no significativamente. Se observaron mejoras significativas en diferentes áreas de la escala Health Survey SF-36 (SF-36): las puntuaciones de dolor corporal disminuyeron desde el inicio hasta 16 semanas de forma estadísticamente significativa; la función social mejoró sus puntuaciones desde el inicio hasta 12 semanas y desde el inicio hasta 16 semanas de manera significativa; el resto de las áreas aumentaron sus puntuaciones pero sin significación. Estos hallazgos muestran menores proporciones de días de consumo de cocaína, y elevada retención y adherencia al tratamiento, aunque no se observó la adquisición de abstinencia completa. Las isoflavonas de soja podrían considerarse un tratamiento potencial en futuras investigaciones, lo cual deberá confirmarse en estudios controlados con placebo y tamaño muestral adecuado.
Palabras clave: cocaína, enzima aldehído-deshidrogenasa-2, daidzina, daidzeína, extracto de isoflavonas de soja, estudio clínico

■ *Received: May 2025; Accepted: September 2025.*

■ ISSN: 0214-4840 / E-ISSN: 2604-6334

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The 2024 World Drug Report, published by the United Nations Office on Drug and Crime (UNODC, 2024), states that in 2022 approximately 23 million individuals (range: 18.5-29.6 million; 0.45%-0.57% of the total population), had used cocaine almost once in the previous year. According to the 2024 European Drug Report from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (EMCDDA, 2024), cocaine has become the second most frequently consumed illicit drug in Europe. The report also warns about the increasing potential health risks.

Cocaine acts by inhibiting the monoamine transporters of the presynaptic neuronal membrane. Through this inhibition it blocks the reuptake of monoamines resulting an increase of dopamine and the other monoamine concentrations (norepinephrine and serotonin) in the synaptic cleft (Camí et al., 2003; Fernàndez-Castillo et al., 2021). Euphoria, feeling of pleasure, and other positive reinforcing effects of cocaine are related not only with changes in dopamine transporter at the presynaptic level but also with changes in dopamine homo and heteroreceptor complexes at the post-synaptic level and with the maladaptive development of drug memory, in both anti-reward and reward ventral striato-pallidal GABA pathways (Borroto-Escuela et al., 2019; Milton & Everitt, 2012). Continued, chronic administration of cocaine induces changes in several neurotransmitter systems affecting the function of several areas and circuits such as the mesocorticolimbic system (nucleus accumbens, ventral tegmental and prefrontal cortex) (Fernàndez-Castillo et al., 2021). Produces a reduction in the number of dopamine receptors in the central nervous system and, as a result, a decreased sensitivity of the reward system (Ashok et al., 2017). However, recent works demonstrate that other changes at the dopamine receptor structure and function must be considered, for instance, cocaine induced pathological A2AR-D2R, D2R-Sigma1R and A2AR-D2R-Sigma1R complexes which may form a long-term memory with a strong and permanent D2R brake, leading to cocaine addiction (Borroto-Escuela et al., 2017; Borroto-Escuela et al., 2018; Koob & Volkow , 2010). At the clinical level such molecular changes result in an increase in repetitive and compulsive consumption (binge use) (Koob & Volkow, 2010) and loss of behavioral control. Neuroanatomical abnormalities have been described in cocaine users such as a reduction in the grey matter volumes in the prefrontal cortex and consequent dysfunction of this region (Ciccarone & Shoptaw, 2022; Hirsiger et al., 2019; Volkow et al., 2011)

There are as yet no specific drugs or psychotherapy for the treatment of cocaine substance use (Farrel et al., 2019; Kampman, 2019). Data about the therapeutic use of certain drugs, including anticonvulsants (Alvarez et al., 2010; Minozzi et al., 2015), psychostimulants (Castells et al., 2016; Pérez-Mañá et al., 2011) , antidepressants (Pani et al., 2011; Torrens et al., 2011) and antipsychotics (Álvarez et al., 2013; Bentzley et al., 2021; Indave et al., 2016), have been published although lacking sufficient efficacy and evidence. Current lines of research are focused on the production mechanisms of different monoamines (Kohut et al., 2017), and, to date, disulfiram, which interacts with dopamine production, has shown the most promising clinical outcomes (Gaval-Cruz et al., 2009; Kampangkaew et al., 2019; Pani et al., 2010; Schroeder et al., 2010; Weinshenker, 2010;). Findings are, however, still controversial as some studies have reported beneficial results while others have not (Carroll et al., 2016). On the other hand, considering the high rates of concomitant consumption of alcohol and cocaine (60% or more) in the population (Araos et al., 2017) there is a crucial limitation in the use of disulfiram. This compound is contraindicated if alcohol is simultaneous consumed because it is an irreversible inhibitor of aldehyde dehydrogenase-1 (ALDH1) and could induce an adverse reaction.

Several studies have suggested that selective inhibitors of the aldehyde-dehydrogenase-2 enzyme (ALDH2) could be effective in the treatment of cocaine use disorder (Koppaka et al., 2012; Weinshenker, 2010; Yao et al., 2010). Inhibition of ALDH2 blocks the conversion of the substrate 3,4-Dihydroxyphenylacetaldehyde (DOPAL) to 3,4-Dihydroxyphenylacetic acid (DOPAC) increasing its levels and consequently forming with dopamine the product of condensation tetrahydropapaveroline (THP) in the ventral tegmental area. THP decreases dopamine biosynthesis through the inhibition of the tyrosine hydroxylase (TH) and, as a result, the ability to produce positive reinforcement is reduced. Natural selective reversible inhibitors of ALDH2 have been described in soy extract isoflavones (Lowe et al., 2008). The most prominent of which are genistin, glycitin, and especially daidzin. The active metabolites of daidzin, genistin, and glycitin are daidzein, genistein, and glycitein, respectively. In addition, at the intestinal level, bacteria transform daidzein into another active metabolite, equol. Various studies have confirmed the selective action of isoflavones on ALDH2, but not on ALDH1, in contrast to disulfiram. As a consequence, if alcohol is consumed the related adverse effects will not appear (Amigdala Neurosciences, 2025; Martínez-Riera et al., 2019; Penetar et al., 2011). For centuries traditional Chinese medicine has employed isoflavones for the treatment of the alcohol use disorder (Lu et al., 2009; Overstreet et al., 2003), and studies in animals (Arolfo et al., 2009) and humans have demonstrated a reduction in alcohol intake (Lukas et al., 2013; Penetar et al., 2015). There are, however, no data in humans measuring the possible effects of isoflavones or other synthetic inhibitors of ALDH2 on cocaine use. In animal models, the administration of different isoflavones has resulted in specific results, such as the reduction of relapses

conditioned by environmental stimuli and a decrease in repeated consumption (Martin et al., 2021; Yao et al., 2010).

Traditional abstinence-only approaches to substance use disorder treatment often fail to engage many individuals who are not ready or willing to stop using substances entirely (Paquette, 2022). Recognizing that addiction is a chronic condition rather than a binary state, incorporating non-abstinence strategies can increase treatment engagement, retention, and effectiveness by aligning with patients' goals and focusing on alternative endpoints, such as reduced use and improved quality of life, rather than strict abstinence. (Compton & Volkow, 2024; Volkow, 2020)

The objective of this study is to assess the effects of soy isoflavones in patients with cocaine use disorder.

Material and method

Ethics Approval

The study protocol was approved by the local Human Research Ethics Committee (CEIC-Parc de Salut Mar, ref. 2014/5580) and conducted in accordance with the Declaration of Helsinki (Fortaleza, 2013) and local legislation (Biomedical Research Law, 2008).

Study Design

An open-label, single-center, clinical trial was carried out during 12 weeks of treatment and 4 weeks follow-up. All the participants were informed about the study and signed a written consent before taking part. Subjects participated in a financial incentive program to facilitate retention and adherence. All the participants received the same treatment and dose of soy isoflavone extracts (two capsules/12h, see section Soy Isoflavone Extract). The principal study variable was to assess cocaine use days from 10 to 12 weeks of the treatment period. This was measured by the percentage of cocaine use days self-reported by the subjects and confirmed by the detection of urine cocaine metabolites (benzoylecgonine and ecgonine methyl ester). The secondary variables included the mean percentage of negative urine samples for the cocaine metabolites from all the scheduled urine samples from 5 to 12 weeks of the treatment period, retention to treatment, adherence to treatment, reduction in craving and severity of cocaine substance use, and quality of life (see Clinical Evaluation Instruments).

Soy Isoflavone Extract

A commercially available soy extract product (Super-Absorbable Soy Isoflavones®, hard gelatine capsules, Life-Extension, US) was used. Preparation was previously selected after pharmacokinetic (Rodríguez-Morató et al., 2015) and safety studies (Martínez-Riera et al., 2019). Each capsule, according to the manufacturer, was composed of 54mg of total isoflavones (22mg daidzin-daidzein, 28mg genistin-genistein, and 4mg glycitin-glycitein). The dose administered (four capsules/day, two in the morning and two at night), was adjusted to give a total daidzein/daidzein content of approximately 88mg. It was selected so as to be double that recommended as herbal medicine for asthma therapy (Smith et al., 2015), and similar or double doses for menopausal symptoms (according to the technical sheet of the product and others on the market) (Carmignani et al., 2010; Khaodhiar et al., 2008; Rebcack et al., 2004; RxList, 2022; Yang et al., 2012) and knowing the safety of these doses from previous studies (Martínez-Riera et al., 2019).

Subjects

Participants, eight men and one woman, from the Outpatient Treatment Center of Substance Use, Institut de Neuropsiquiatria i Addiccions, Parc de Salut Mar from Barcelona, Spain, with a cocaine use disorder were recruited according to DSM-5 (American Psychiatric Association, 2013) guidelines. They met the following inclusion criteria: (i) aged ≥ 18 years and< 60 years; (ii) seeking treatment for cocaine use disorder; (iii) having at least one positive urine sample in the two weeks prior to commencement of the study sessions; and (iv) women with reproductive potential taking contraceptives. Exclusion criteria were: (i) presenting an active substance use disorder (DSM 5) other than cocaine in the previous year except tobacco, cannabis and alcohol without severe symptoms of physical withdrawal; (ii) having been in treatment with a substitutive opioid (methadone, buprenorphine) in the previous 2 months; (iii) presenting a neurologic or severe psychiatric illness that could interfere with the development of the study; (iv) any serious medical conditions that could interfere with the safety of the subjects or the development of the study; (v) HIV, hepatitis, active syphilis, tuberculosis; (vi) being under a compulsory treatment; (vii) personal history of endometrial or breast cancer or other hormone-dependent cancer; (viii) hypersensitivity to soy derivatives; (ix) under treatment with soy derivatives for another reason; (x) to have been/or be under treatment with drugs that could have adverse symptoms interacting with isofla-vones or could interfere with the study results; and (xi) to be pregnant o lactating.

Clinical Assessment

Sociodemographic data, and previous history of medical and psychiatric illnesses were collected.

Cocaine Use Days

To assess the cocaine use days the Substance Use Report/Inventory (SUR) (Weiss et al., 1995) was used. This is a self-reported questionnaire with a daily calendar that measures recent use of drugs, dose, and route of administration. Less than 20% self-reported cocaine use days was considered a promising result.

Urine samples were collected three times a week to quantify concentrations of urine metabolites of cocaine.

Cocaine non-use values were benzoylecgonine<150ng/ml and ecgonine methyl ester<15ng/ml. Less than 20% positive urine samples were considered a promising result.

Retention and Adherence to Treatment

Retention was measured by the number of subjects who finished the study. Adherence to treatment was assessed by the determination in urine of daidzein, genistein, and the endogenous metabolite equol through liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS) using a validated method (Rodríguez-Morató et al., 2015). Samples were collected three times a week.

Clinical Evaluation Instruments

Psychiatric diagnosis was performed with the Spanish Version of the Psychiatric Research Interview for Substance and Mental Disorders IV (PRISM-IV) (Torrens et al., 2004). This is a semi-structured interview designed to evaluate current and life-long disorders of DSM-IV-TR (American Psychiatric Association, 2000).

In addition, the following instruments in their validated Spanish versions were administered:

- Clinical Global Impression (CGI) (Guy, 1976), a hetero-applied scale composed of two sub-scales CGI-S (measures disorder severity) and CGI-I (measures disorder improvement during the consultations). Each is composed of a unique item scored with a Likert-type scale response format. A CGI-S score of 0 represents non-evaluated, and then ranges from 1 "healthy subject" to 7 "extremely ill subject"; a CGI-I score of 0 represents non-evaluated, and then ranges from 1"significant improvement" to 7 "most severe deterioration".
- Addiction Severity Index Lite (ASI-lite) (Cacciola et al., 2007), a semi-structured interview which is the shortened version of the Addiction Severity Index (ASI). It evaluates addiction severity in several areas: medical, psychological, family/social, legal, employment, use of drugs, and use of alcohol. Lifetime information and data within the previous 30 days are obtained. The scores for each area are from 0 to 1, the higher is the score, the greater the severity of use disorder.
- Severity Dependence Scale (SDS) (González-Saiz et al., 2008), a self-applied instrument that measures addiction severity with five items rated with a Likert-type scale from 0 to 3. The global score is the sum of the scores in every item. The higher the punctuation, the greater the severity of use disorder.
- Cocaine Selective Severity Assessment (CSSA) (Kampman et al., 1998, Pérez de los Cobos et al., 2014), a hetero-applied scale that specifically measures severity of cocaine substance use. It is composed of eighteen items about symptoms that usually appear when cocaine consumption suddenly ceases (e.g., craving, depressive symptoms, changes in appetite, sleep disorders, lethargy, and bradycardia). Each item is graded with a Likert-type scale from 0 to 7. The global punctuation is the sum of the scores in every item. The higher the punctuation, the greater the severity of use disorder.
- Brief Substance Craving Scale (BSCS) (Somoza et al., 1995), a self-applied scale that measures the intensity and frequency of the craving for cocaine and other substances in the previous twenty-four hours. There are sixteen items scored with a Likert-type scale from 0 to 4. The global score is the sum of the scores in every item. The higher the punctuation, the greater the severity of use disorder.
- SF-36 Health Survey (SF-36) (Alonso et al., 1995), a self-applied scale that assess quality of life related to health. It measures eight dimensions (physical function, physical role, body pain, general health, vitality, social function, emotional role, and mental health) with a rating from 0 to 100. The higher the score, the better the level of health.
- Revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) (Sullivan et al., 1989), a hetero-applied scale that measures the severity of alcohol abstinence syndrome. It has ten items punctuated with a Likert-type scale from 0 to 7 with the exception of one item "orientation and clouding of sensorium", which is scored from 0 to 4. The global punctuation is the sum of the scores in every item. The higher the score, the greater the severity of abstinence.
- HIV Risk-Taking Behaviour Scale (HRBS) (Darke et al., 1991), a hetero-applied scale that evaluates the use of intravenous drugs and sexual risk behaviours. There are eleven items scored with a Likert-type scale from 0 to 5. The higher the score the greater the degree of risk-taking.
- Hamilton Rating Scale for Depression (HAM-D) (Bobes et al., 2003), a hetero-applied scale measuring the patient's subjective level of depression with twenty one symptoms. The global score is the sum of the scores for each item. The higher the punctuation, the greater the severity of depression.
- Columbia Suicide Severity Rating Scale (C-SSRS) (Al-Halabí et al., 2016), a semi-structured scale for the assessment of the intensity of suicide risk. It measures four constructs: severity of ideation, intensity of ideation, behaviour, and lethality.

Procedure

During the screening session, the participants underwent a general physical examination, a 12-lead electrocardiogram, a complete blood and urine analysis (including drugs of abuse), and a pregnancy test in the case of women. In

addition, the following scales were administered: PRISM, SUR, SDS, CSSA, BSCS, CIWA-Ar, HAM-D, and C-SSRS.

The subjects underwent 12 weeks of treatment and 4 weeks of follow-up. Urine samples were collected three times a week during the study. Blood samples at weeks 6, 12, and 16, pregnancy test at baseline, 6, and 12 weeks, and a 12-lead ECG at 12 weeks were carried out. CGI, SUR, SDS, CSSA, BSCS and the assessment of possible adverse effects, were collected at baseline, 2, 4, 6, 8, 10, 12, and 16 weeks. The ASI-Lite scale was performed at baseline and 12 weeks. SF-36 and HRBS were evaluated at baseline, 12, and 16 weeks. C-SSRS and HAM-D scales were administered at baseline, 4, 8, 12, and 16 weeks.

Statistical Analysis

A description of all the variables of interest was carried out using descriptive statistics (percentages, frequencies, and measures of central tendency and dispersion). An intent-to-treat population (ITT) analysis was performed to examine the outcomes. Inferential statistics was carried out to assess the cocaine use days self-reported less or more than 20% from 10 to 12 weeks with the chi-squared test, and to check absolute score changes for the Clinical Evaluation Instruments during the study weeks for ASI-lite from baseline to 12 weeks by the paired sample T-test. A One factor repeated measures ANOVA (factor time) was used for CGI, SDS, CSSA, BSCS, SF-36 Health Survey, HRBS, HAM-D and C-SSRS including baseline, 12 weeks and 16 weeks results. When significant, a Tukey post-hoc multiple comparison analysis was performed to compare baseline-12 weeks, baseline-16 weeks, and 12-16 weeks All the statistical tests were performed using SPSS Statistics 23.0 (SPSS, Chicago, IL, United States). A value of $p<0.05$ was considered statistically significant for chi-squared test, paired sample T-test and for One factor repeated measures ANOVA. Sample size was calculated to evaluate a clinical efficacy equal to or greater than 20% using the Gehan method for phase II clinical trials (9-11 subjects was recommended) (Machin et al., 2009).

Results

Sociodemographic Characteristics

Nine subjects were recruited (eight men and one woman) with a mean age of 48±9.27 years. Mean weight was 84.1±16.19 kg and body mass index 27.3±4.4. Six (66.7%) subjects were married, four (44.4%) had primary school studies, five (55.6%) high school diplomas or higher, and four (44.4%) were employed at the moment of conducting the study (Table 1).

Clinical Characteristics

All the participants suffered severe cocaine use disorder according to DSM-5 criteria. Mean age of onset of the disorder was 30.44±9.28 years. Of the nine participants, six (66.7%) had a previous history of substance use disorder treatment. Four (44.4%) subjects had a prior history of alcohol use disorder before the previous year and one (11.1%) in the previous year. One participant (11.1%) had a prior history of cannabis use disorder before the previous year and one (11.1%) in the previous year. One subject (11.1%) had prior history of opioid use disorder but not in the previous year. Seven of them (77.8%) had familiar history of substance use disorders (Table 1).

The results of the PRISM interview showed that four (44.4%) were diagnosed with an affective disorder in remission.

Table 1
Sociodemographic and Clinical Characteristics of the Sample (N = 9)

Characteristic	Mean (SD) or n (%)
Sociodemographic Characteristics	
Gender (men/women)	8 (88.9%) / 1 (11.1%)
Age, M (SD), years	48 (9.27)
Weight, M (SD), kg	84.1 (16.19)
Body mass index, M (SD), kg/m²	27.3 (4.4)
Marital status (married)	6 (66.7%)
Education — Primary education	4 (44.4%)
Education — High school diploma or higher	5 (55.6%)
Employment status (employed)	4 (44.4%)
Clinical Characteristics	
Cocaine use disorder (DSM-5, severe)	9 (100%)
Age of onset, M (SD), years	30.44 (9.28)
Previous treatment for substance use disorder	6 (66.7%)
Alcohol use disorder — Prior to the previous year	4 (44.4%)
Alcohol use disorder — In the previous year	1 (11.1%)
Cannabis use disorder — Prior to the previous year	1 (11.1%)
Cannabis use disorder — In the previous year	1 (11.1%)
Opioid use disorder — Prior to the previous year	1 (11.1%)
Family history of substance use disorders	7 (77.8%)

Note. M = mean; SD = standard deviation. Percentages are calculated over N = 9.

Cocaine Use Days, Retention and Adherence to treatment

Cocaine Use Days

With respect to self-reported cocaine use, from 10 to 12 weeks three subjects (33.3%) reported a cocaine consumption of less than 20% (80% non-use days), and two (22.2%) from baseline, findings, however, that were non-significant. None of the participants showed less than 20% positive urine analysis from 10 to 12 weeks. The mean percentage of negative urine samples for the cocaine metabolites from all the scheduled urine samples from 5 to 12 weeks of the treatment period was 15.8%.

Retention and Adherence to Treatment

A total of seven (77.8%) subjects completed the 16 weeks of the study. One (11.1%) completed 12 weeks, and another (11.1%) dropped out during the 4 weeks of the study. According to the urine quantitative analysis of the isoflavones, eight (88.9%) participants followed the treatment during the study, and only one (11.1%) did not (isoflavone concentrations in urine were below detection limit).

Other Outcomes

Clinical Global Impression (CGI)

No differences were found throughout the study for each participant regarding score changes in the CGI scale, both in the severity assessment subscale (CGI-S) and in the improvement assessment one (CGI-I) (Table 2).

Addiction Severity Index Lite (ASI-lite)

No differences were observed during the study weeks in the scores of the 7 areas evaluated by the ASI-Lite scale.

Severity Dependence Scale (SDS)

The SDS score showed a significant decrease between baseline to 12 weeks, baseline to 16 weeks and 12 to 16 weeks (Table 2).

Cocaine Selective Severity Assessment (CSSA)

Values in the CSSA decreased but were not significant (Table 2).

Brief Substance Craving Scale (BSCS)

Values in the BSCS scale decreased but were not significant (Table 2).

SF-36 Health Survey (SF-36)

In the case of the SF-36 questionnaire, increases in the scores were observed in some areas. The areas physical function, physical role, general health, vitality, emotional role and mental health increased their scores but not significantly. Body pain scores decreased from baseline to 12 weeks but not significantly, from baseline to 16 weeks the decrease was statistically significant but increased the scores from 12 to

Table 2
Absolute Scores for the Clinical Evaluation Instruments (n = 9)

Scale	Baseline, M (SD)	12 weeks, M (SD)	16 weeks, M (SD)	ANOVA-1F p value	Group differences*
CGI					
CGI-S	2.78 (1.64)	2.89 (1.45)	3.33 (1.50)	0.429	NS
CGI-I	3.78 (0.67)	3.67 (2)	3.33 (1.41)	0.415	NS
SDS	12.11 (3.92)	8.11 (4.99)	6.33 (3.74)	< 0.001	a, B, c
CSSA	26.56 (1.93)	25.56 (25.42)	24.78 (17.23)	0.902	NS
BSCS	9.00 (3.50)	7.11 (4.70)	6.56 (3.64)	0.128	NS
SF-36					
Physical Function	92.78 (8.33)	93.33 (7.91)	96.11 (6.01)	0.132	NS
Physical Role	71.52 (36.39)	72.92 (27.60)	82.64 (22.05)	0.132	NS
Body Pain	80 (19.87)	67.78 (31.77)	70.11 (26.79)	0.001	NS, b, C
General Health	54.44 (20.47)	60.78 (21.02)	69.33 (18.75)	0.220	NS
Vitality	41.66 (18.22)	52.77 (21.45)	57.64 (21.60)	0.266	NS
Social Function	63.89 (15.86)	66.67 (26.52)	70.83 (25)	0.001	A, b, NS
Emotional Role	60.18 (39.48)	60.18 (32.21)	63.89 (31.73)	0.584	NS
Mental Health	47.78 (20.93)	56.11 (22.88)	61.11 (19.65)	0.16	NS
HRBS	3 (5.24)	1.67 (2.45)	1.78 (2.95)	0.696	NS
HAM-D	3.44 (3.61)	5.78 (5.93)	3.11 (3.51)	0.24	NS
C-SSRS	0	1.22 (3.67)	1.22 (3.67)	0.29	NS

Note. M = mean; SD = standard deviation.
Note. CGI = Clinical Global Impression; CGI-S (measures disorder severity) and CGI-I (measures disorder improvement during the consultations); SDS = Severity Dependence Scale; CSSA = Cocaine Selective Severity Assessment; BSCS = Brief Substance Craving Scale; SF-36 = SF-36 Health Survey; HRBS = HIV Risk-Taking Behaviour Scale; C-SSRS = Columbia Suicide Severity Rating Scale.
Note. ANOVA-1F = Repeated measures one factor analysis of variance (time). NS = not-significant differences.
Note. Tukey post-hoc test statistical significant differences ($p < .05$) between conditions are indicated as "a" (baseline–12 weeks), "b" (baseline–16 weeks), "c" (12 weeks–16 weeks). Tukey post-hoc test statistical significant differences ($p < .01$) are indicated as "A" (baseline–12 weeks), "B" (baseline–16 weeks), "C" (12 weeks–16 weeks).

16 weeks significantly. The social function area improved its scores from baseline to 12 weeks and from baseline to 16 weeks significantly, and between 12 to 16 the increased was not statistically significant (Table 2).

Other Psychiatric Sales

During the screening session and throughout the study, none of the participants presented significant changes in the scores for the HRBS, HAM-D, and C-SSRS. During the screening session participants presented values of CIWA-Ar according with the inclusion criteria.

No serious adverse side effects were observed throughout the study.

Discussion

Our findings do not allow a conclusive statement about the possible efficacy of soy isoflavones as a treatment of cocaine use disorder, because the main outcome of self-reported reduction in cocaine use is not significant and not confirmed by urine probes as objective measures and other outcomes are not significant. Nevertheless, our results show that soy isoflavone treatment could produce a reduction of self-reported cocaine use days, although the increase in the number of patients who reported a consumption of cocaine less than 20% was not significant and it was not possible, however, to confirm this decrease by the detection of urine metabolites of cocaine. The intervention improved retention, resulted in adequate adherence, reduced severity of cocaine use, and augmented participants' quality of life.

The percentage of positive urine analyses for cocaine metabolites we observed is similar to other authors regarding the treatment of cocaine use disorder. A recent study in cocaine and opioid co-dependent patients reported a significant reduction of cocaine positive urine during 12 weeks of treatment with disulfiram versus placebo from 79% at study week 1–2 to 63% at study week 11–12 (Kampangkaew et al., 2019). The percentage of positives at cessation of the study was not, however, less than 20% (a value that is considered a positive outcome in our study), as we reported from weeks 10 to 12. Nevertheless, it should be highlighted that, according to the self-registration of daily consumption, in our study three subjects (33.3%) reported a consumption of less than 20% between weeks 10 and 12, and two from baseline, although the difference was not significant. Considering that the participants were patients presenting a serious disorder such an outcome could be an indicator of the reduction of frequency of cocaine use. A possible reason for this not being corroborated by urine analysis could be due to the fact it was performed three times a week. Taking into account the elimination half-life of cocaine metabolites (6-8 hours for benzoylecgonine and 3-8 hours for ecgonine methyl ester) (Farré et al., 1997), some self-reported non-use days could have resulted positive. In addition, missing urine analyses were considered positive.

Considering that all the participants were affected by a serious cocaine use disorder, the retention rates to soy isoflavone treatment were very positive. Seven subjects (77.8%) completed the study at 16 weeks and one (11.1%) dropped out at 12 weeks. A higher figure than that found in the literature which usually cites treatment retention rates for cocaine use disorder at 50% (Stotts et al., 2007). Analysis of urine concentrations of daidzein, genistein, and equol also provided positive results regarding good adherence to soy isoflavone treatment. Eight (88.9%) of the participants followed correct intake. The good tolerance of soy isoflavones throughout the study weeks supports high rates of adherence to treatment.

We observed relevant outcomes indicating that soy isoflavone treatment reduces the severity and craving of cocaine use, as previously indicated in animal studies (Martín et al., 2021; Yao et al., 2010). A significant reduction of the SDS scale scores throughout the study weeks, and a decrease of the scores of the BSCS and CSSA scales, although without achieving significant changes, were found. Previous reports with antipsychotic treatment for cocaine use disorder did not describe a reduction in cocaine use severity with the ASI-lite and CGI scales (Álvarez et al., 2013) as we found in our study. They did not, however, employ other specific scales such as the SDS, CSSA, and BSCS.

Promising data showing an improvement in specific areas of the SF-36 questionnaire (body pain, social function) were observed. Moreover, increases in other areas, even though not statistically significant, reinforce the possible use of soy isoflavone treatment for cocaine use disorder.

Several studies with animals, have suggested that isoflavones have antidepressant-like effects through the regulation of the transcription of BDNF in the brain (Lu et al., 2019; Tantipongpiradet et al., 2019). Other studies in animals suggest that BDNF has an important role for the cocaine use disorder, attenuating relapse for cocaine seeking for a long time (Li & Wolf, 2015; McGinty, 2022). These could be another hypothesis to explain the possible effects of the isoflavones for the cocaine use disorder.

Limitations

Some positive outcomes were found in this trial; nevertheless, there are a few limitations. The most important is the fact that it is an open-label pilot study, and the sample was small, wich limits statistical power and generalizability. The lack of previous studies in humans led us to carry out this pilot study to evaluate possible hypotheses about the use of soy isoflavones for cocaine use disorder. In order to enable a conclusive evaluation of the efficacy of soy isoflavones and considering that in this trial only three

parameters showed significant improvements, a greater sample has to be investigated and compared to a control condition. Although according to the elimination half-life of cocaine metabolites, urine analyses were conducted only three times per week, could be a possibility some missing use days. The isoflavone doses were in accordance with those usually recommended for menopausal climacteric symptoms. We are unaware whether higher ones could provide better results. Neither do we know the possible effect of the isoflavones (daidzein and genistein) when taken separately as we used a compound containing them in a fixed combination. Altough patients were advised to avoid soy products, there was no formal control for soy-based nutrition, otherwise, at the baseline, seven (77.8%) of them referred never taking and two (22.2%) not to taking soy derivatives usually. Also, it was an exclusion criterion to be under treatment with soy derivatives for another reason. As only one woman participated in the study, possible differences between genders could not be assessed.

Conclusions

Our preliminary results suggest the possible action of soy isoflavone treatment in reducing cocaine use days. According to our results, three subjects (33.3%) reported a cocaine consumption less than 20% during the period from 10 to 12 weeks of treatment. This is even though complete abstinence was not observed by urine analysis. Data also suggest that soy isoflavone treatment could improve treatment retention, reduce the severity of cocaine use disorder, and improve patients' quality of life. Soy isoflavones were well tolerated and good adherence was observed. Based on these results, placebo-controlled studies with adequate sample size are needed to evaluate whether soy isoflavones can be effective in treating cocaine use disorder. Finally, based on our results and emerging perspectives in the treatment of substance use disorders, future research should consider non-abstinence-based strategies as a therapeutic goal. These should focus on improving treatment retention, reducing the severity of cocaine use disorder, and enhancing patients' quality of life. This study represents a pioneering step in the exploration of alternative treatments for cocaine use disorder. Given the current lack of effective therapeutic options for this condition, it is particularly relevant to further investigate the potential effects of isoflavones in this context.

Ethics statement

The study protocol was approved by the local Human Research Ethics Committee (CEIC-Parc de Salut Mar, ref. 2014/5580) and conducted in accordance with the Declaration of Helsinki (Fortaleza, 2013) and local laws (Biomedical Research Law, 2008). Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper if applicable.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

Conception and design of the work, M.T., R.M.-R, F.F., and M.F.; validation and investigation, M.T., R.M.-R., F.F., L.G., R.T., J.M., N.P., M.F.; analysis and interpretation of the data, M.T., R.M.-R., F.F., J.M., N.P., R.T., M.F.; draft preparation, R.M.-R., M.T., M.F.; critical review, all authors. All the authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

Supported in part by grants from Ministerio de Sanidad (Investigación Clínica Independiente, grant number: EC-10-166); Instituto de Salud Carlos III (ISCIII, Fondo de Investigación en Salud (FIS)-Fondo Europeo de Desarrollo Regional (FEDER): grants ISCIII-RTA RD16/0017/0003 and RD16/0017/0010, and ISCIII-RICORS-RIAPAd RD21/0009/0004 and RD21/0009/0001, AGAUR Gencat Suport Grups de Recerca (2017 SGR 316 and 2017 SGR 530). L. Galindo was a Rio Hortega fellowship, (CM14/00111).

We would like to acknowledge the initial contributions to the study design made by José Carlos Bouso and Jose Luis Pérez de Heredia.

References

Al-Halabí, S., Sáiz, P. A., Burón, P., Garrido, M., Benabarre, A., Jiménez, E., Cervilla, J., Navarrete, M. I., Díaz-Mesa, E. M., García-Álvarez, L., Muñiz, J., Posner, K., Oquendo, M. A., García-Portilla, M. P. & Bobes, J. (2016). Validación de la versión en español de la Columbia-Suicide Severity Rating Scale (Escala Columbia para evaluar el riesgo de suicidio). *Revista de Psiquiatría y Salud Mental*, *9*(3), 134–142. https://doi.org/10.1016/j.rpsm.2016.02.002

Alonso, J., Prieto, L. & Antó, J. M. (1995). La versión española del SF-36 Health Survey (Cuestionario de Salud SF-36): Un instrumento para la medida de los resultados clínicos. *Medicina Clínica*, *104*(20), 771–776.

Alvarez, Y., Farré, M., Fonseca, F. & Torrens, M. (2010). Anticonvulsant drugs in cocaine dependence: A syste-

matic review and meta-analysis. *Journal of Substance Abuse Treatment*, *38*(1), 66–73. https://doi.org/10.1016/j.jsat.2009.07.001

Álvarez, Y., Pérez-Mañá, C., Torrens, M. & Farré, M. (2013). Antipsychotic drugs in cocaine dependence: A systematic review and meta-analysis. *Journal of Substance Abuse Treatment*, *45*(1), 1–10. https://doi.org/10.1016/j.jsat.2012.12.013

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). American Psychiatric Publishing.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Publishing.

Amygdala Neurosciences. (n.d.). *Amygdala Neurosciences*. https://amygns.com/

Araos, P., Vergara-Moragues, E., González-Saiz, F., Pedraz, M., García-Marchena, N., Romero-Sanchiz, P., Ruiz, J. J., Campos-Cloute, R., Serrano, A., Pavón, F. J., Torrens, M. & Rodriguez de Fonseca, F. (2017). Differences in the rates of drug polyconsumption and psychiatric comorbidity among patients with cocaine use disorders according to the mental health service. *Journal of Psychoactive Drugs*, *49*(4), 306–315. https://doi.org/10.1080/02791072.2017.1342151

Arolfo, M. P., Overstreet, D. H., Yao, L., Fan, P., Lawrence, A. J., Tao, G., Keung, W. M., Vallee, B. L., Olive, M. F., Gass, J. T., Rubin, E., Anni, H., Hodge, C. W., Besheer, J., Zablocki, J., Leung, K., Blackburn, B. K., Lange, L. G. & Diamond, I. (2009). Suppression of heavy drinking and alcohol seeking by a selective ALDH-2 inhibitor. *Alcoholism: Clinical and Experimental Research*, *33*(11), 1935–1944. https://doi.org/10.1111/j.1530-0277.2009.01031.x

Ashok, A. H., Mizuno, Y., Volkow, N. D. & Howes, O. D. (2017). Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine. *JAMA Psychiatry*, *74*(5), 511–519. https://doi.org/10.1001/jamapsychiatry.2017.0135

Bentzley, B. S., Han, S. S., Neuner, S., Humphreys, K., Kampman, K. M. & Halpern, C. H. (2021). Comparison of treatments for cocaine use disorder among adults. *JAMA Network Open*, *4*(5), e218049. https://doi.org/10.1001/jamanetworkopen.2021.8049

Bobes, J., Bulbena, A., Luque, A., Dal-Ré, R., Ballesteros, J., Ibarra, N. & Grupo de Validación en Español de Escalas Psicométricas. (2003). A comparative psychometric study of the Spanish versions with 6, 17, and 21 items of the Hamilton Depression Rating Scale. *Medicina Clínica*, *120*(18), 693–700.

Borroto-Escuela, D. O., Narváez, M., Romero-Fernández, W., Pinton, L., Wydra, K., Filip, M., Beggiato, S., Tanganelli, S., Ferraro, L. & Fuxe, K. (2019). Acute cocaine enhances dopamine D2R recognition and signaling and counteracts D2R internalization in Sigma1R-D2R heteroreceptor complexes. *Molecular Neurobiology*, *56*(10), 7045–7055. https://doi.org/10.1007/s12035-019-1580-8

Borroto-Escuela, D. O., Narváez, M., Wydra, K., Pintsuk, J., Pinton, L., Jimenez-Beristain, A., Di Palma, M., Jastrzębska, J., Filip, M. & Fuxe, K. (2017). Cocaine self-administration specifically increases A2AR-D2R and D2R-Sigma1R heteroreceptor complexes in the rat nucleus accumbens shell: Relevance for cocaine use disorder. *Pharmacology, Biochemistry and Behavior*, *155*, 24–31. https://doi.org/10.1016/j.pbb.2017.03.003.

Borroto-Escuela, D. O., Wydra, K., Filip, M. & Fuxe, K. (2018). A2AR-D2R heteroreceptor complexes in cocaine reward and addiction. *Trends in Pharmacological Sciences*, *39*(12), 1008–1020. https://doi.org/10.1016/j.tips.2018.10.007

Cacciola, J. S., Alterman, A. I., McLellan, A. T., Lin, Y.-T. & Lynch, K. G. (2007). Initial evidence for the reliability and validity of a "Lite" version of the Addiction Severity Index. *Drug and Alcohol Dependence*, *87*(2–3), 297–302. https://doi.org/10.1016/j.drugalcdep.2006.09.002

Camí, J. & Farré, M. (2003). Drug addiction. *The New England Journal of Medicine*, *349*(10), 975–986. https://doi.org/10.1056/NEJMra023160

Carmignani, L. O., Pedro, A. O., Costa-Paiva, L. H. & Pinto-Neto, A. M. (2010). The effect of dietary soy supplementation compared to estrogen and placebo on menopausal symptoms: A randomized controlled trial. *Maturitas*, *67*(3), 262–269. https://doi.org/10.1016/j.maturitas.2010.07.007

Carroll, K. M., Nich, C., Petry, N. M., Eagan, D. A., Shi, J. M. & Ball, S. A. (2016). A randomized factorial trial of disulfiram and contingency management to enhance cognitive behavioral therapy for cocaine dependence. *Drug and Alcohol Dependence*, *160*, 135–142. https://doi.org/10.1016/j.drugalcdep.2015.12.036

Castells, X., Cunill, R., Pérez-Mañá, C., Vidal, X. & Capellà, D. (2016). Psychostimulant drugs for cocaine dependence. *Cochrane Database of Systematic Reviews*, *2016*(9), CD007380. https://doi.org/10.1002/14651858.CD007380.pub4

Ciccarone, D. & Shoptaw, S. (2022). Understanding stimulant use and use disorders in a new era. *Medical Clinics of North America*, *106*(1), 81–97. https://doi.org/10.1016/j.mcna.2021.08.010

Compton, W. M. & Volkow, N. D. (2024). Reductions in substance use as outcome targets for treatment development. *American Journal of Psychiatry*, *181*(11), 947–948. https://doi.org/10.1176/appi.ajp.20240841

Darke, S., Hall, W., Heather, N., Ward, J. & Wodak, A. (1991). The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. *AIDS*, *5*(2), 181–185.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). (2024). *European Drug Report 2024: Trends and developments*. https://www.emcdda.europa.eu/publications/european-drug-report/2024_en

Farré, M., de la Torre, R., González, M. L., Terán, M. T., Roset, P. N., Menoyo, E. & Camí, J. (1997). Cocaine and alcohol interactions in humans: Neuroendocrine effects and cocaethylene metabolism. *The Journal of Pharmacology and Experimental Therapeutics*, *283*(1), 164–176.

Farrell, M., Martin, N. K., Stockings, E., Bórquez, A., Cepeda, J. A., Degenhardt, L., Ali, R., Tran, L. T., Rehm, J., Torrens, M., Shoptaw, S. & McKetin, R. (2019). Responding to global stimulant use: Challenges and opportunities. *The Lancet*, *394*(10209), 1652–1667. https://doi.org/10.1016/S0140-6736(19)32230-5

Fernàndez-Castillo, N., Cabana-Domínguez, J., Corominas, R. & Cormand, B. (2021). Molecular genetics of cocaine use disorders in humans. *Molecular Psychiatry*, *27*(1), 624–639. https://doi.org/10.1038/s41380-021-01256-1

Gaval-Cruz, M. & Weinshenker, D. (2009). Mechanisms of disulfiram-induced cocaine abstinence: Antabuse and cocaine relapse. *Molecular Interventions*, *9*(4), 175–187. https://doi.org/10.1124/mi.9.4.6

González-Saiz, F., de las Cuevas, C., Barrio, G. & Domingo-Salvany, A. (2008). Spanish version of the Severity of Dependence Scale (SDS). *Medicina Clínica*, *131*(20), 797–798.

Guy, W. (1976). *ECDEU Assessment Manual for Psychopharmacology*. U.S. Department of Health, Education, and Welfare, Rockville, MD.

Hirsiger, S., Hänggi, J., Germann, J., Vonmoos, M., Preller, K. H., Engeli, E. J. E., Kirschner, M., Reinhard, C., Hulka, L. M., Baumgartner, M. R., Chakravarty, M. M., Seifritz, E., Herdener, M. & Quednow, B. B. (2019). Longitudinal changes in cocaine intake and cognition are linked to cortical thickness adaptations in cocaine users. *NeuroImage: Clinical*, *21*, 101652. https://doi.org/10.1016/j.nicl.2019.101652

Indave, B. I., Minozzi, S., Pani, P. P. & Amato, L. (2016). Antipsychotic medications for cocaine dependence. *Cochrane Database of Systematic Reviews*, *2016*(6), CD006306. https://doi.org/10.1002/14651858.CD006306.pub3

Kampangkaew, J. P., Spellicy, C. J., Nielsen, E. M., Harding, M. J., Ye, A., Hamon, S. C., Kosten, T. R. & Nielsen, D. A. (2019). Pharmacogenetic role of dopamine transporter (SLC6A3) variation on response to disulfiram treatment for cocaine addiction. *The American Journal of Addictions*, *28*(4), 311–317. https://doi.org/10.1111/ajad.12891

Kampman, K. M., Volpicelli, J. R., McGinnis, D. E., Alterman, A. I., Weinrieb, R. M., D'Angelo, L. & Epperson, L. E. (1998). Reliability and validity of the Cocaine Selective Severity Assessment. *Addictive Behaviors*, *23*(4), 449–461.

Kampman, K. M. (2019). The treatment of cocaine use disorder. *Science Advances*, *5*(10), eaax1532. https://doi.org/10.1126/sciadv.aax1532

Khaodhiar, L., Ricciotti, H. A., Li, L., Pan, W., Schickel, M., Zhou, J. & Blackburn, G. L. (2008). Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. *Menopause*, *15*(1), 125–132.

Kohut, S. J. & Bergman, J. (2017). Medication strategies for the management of cocaine use disorder.. *The Neuroscience of Cocaine* (pp. 627–637). Elsevier. https://doi.org/10.1016/B978-0-12-803750-8.00063-4

Koob, G. F. & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, *35*(1), 217–238. https://doi.org/10.1038/npp.2009.110

Koppaka, V., Thompson, D. C., Chen, Y., Ellermann, M., Nicolaou, K. C., Juvonen, R. O., Petersen, D., Deitrich, R. A., Hurley, T. D. & Vasiliou, V. (2012). Aldehyde dehydrogenase inhibitors: A comprehensive review of the pharmacology, mechanism of action, substrate specificity, and clinical application. *Pharmacological Reviews*, *64*(3), 520–539. https://doi.org/10.1124/pr.111.005538

Li, X. & Wolf, M. E. (2015). Multiple faces of BDNF in cocaine addiction. *Behavioural Brain Research*, *279*, 240–254. https://doi.org/10.1016/j.bbr.2014.11.018

Lowe, E. D., Gao, G. Y., Johnson, L. N. & Keung, W. M. (2008). Structure of daidzin, a naturally occurring anti-alcohol-addiction agent, in complex with human mitochondrial aldehyde dehydrogenase. *Journal of Medicinal Chemistry*, *51*(15), 4482–4487. https://doi.org/10.1021/jm800488j

Lu, L., Liu, Y., Zhu, W., Shi, J., Liu, Y, Ling, W. & Kosten, T. R. (2009). Traditional medicine in the treatment of drug addiction. *The American Journal of Drug and Alcohol Abuse*, *35*(1), 1–11. https://doi.org/10.1080/00952990802455469

Lu, Y., Zhu, S., He, Y., Peng, C., Wang, Z. & Tang, Q. (2019). Phytochemical profile and antidepressant effect of Ormosia henryi Prain leaf ethanol extract. *International Journal of Molecular Sciences*, *20*(14), 3396. https://doi.org/10.3390/ijms20143396

Lukas, S. E., Penetar, D., Su, Z, Geaghan, T., Maywalt, M., Tracy, M., Rodolico, J., Palmer, C., Ma, Z. & Lee, D. Y. W. (2013). A standardized kudzu extract (NPI-031) reduces alcohol consumption in nontreatment-seeking male heavy drinkers. *Psychopharmacology*, *226*(1), 65–73. https://doi.org/10.1007/s00213-012-2884-9

Machin, D., Campbell, M. J., Tan, S. B. & Tan, S. H. (2009). *Sample size tables for clinical studies: Chapter 16, Phase II trials*. Wiley-Blackwell. pp. 207–236.

Martin, M., Gutiérrez-Martos, M., Cabrera, R., Langohr, K., Maldonado, R., Farré, M. & de la Torre, R.

(2021). Daidzein modulates cocaine-reinforcing effects and cue-induced cocaine reinstatement in CD-1 male mice. *Psychopharmacology*, *238*(7), 1923–1936. https://doi.org/10.1007/s00213-021-05820-z

Martínez-Riera, R., Pérez-Mañá, C., Papaseit, E., Fonseca, F., de la Torre, R., Pizarro, N. & Torrens, M., Farré, M. (2019). Soy isoflavone extract does not increase the intoxicating effects of acute alcohol ingestion in human volunteers. *Frontiers in Pharmacology*, *10*, 131. https://doi.org/10.3389/fphar.2019.00131

McGinty, J. F. (2022). BDNF as a therapeutic candidate for cocaine use disorders. *Addiction Neuroscience*, *2*, 100006. https://doi.org/10.1016/j.addicn.2022.100006

Milton, A. L. & Everitt, B. J. (2012). The persistence of maladaptive memory: Addiction, drug memories and anti-relapse treatments. *Neuroscience & Biobehavioral Reviews*, *36*(4), 1119–1139. https://doi.org/10.1016/j.neubiorev.2012.01.002

Minozzi, S., Cinquini, M., Amato, L., Davoli, M., Farrell, M. F., Pani, P. P. & Vecchi, S. (2015). Anticonvulsants for cocaine dependence. *Cochrane Database of Systematic Reviews*, *2015*(10), CD006754. https://doi.org/10.1002/14651858.CD006754.pub4

Overstreet, D. H., Keung, W. M., Rezvani, A. H., Massi, M. & Lee, D. Y. W. (2003). Herbal remedies for alcoholism: Promises and possible pitfalls. *Alcoholism: Clinical and Experimental Research*, *27*(2), 177–185. https://doi.org/10.1097/01.ALC.0000051022.26489.CF

Pani, P. P., Trogu, E., Vacca, R., Amato, L., Vecchi, S. & Davoli, M. (2010). Disulfiram for the treatment of cocaine dependence. *Cochrane Database of Systematic Reviews*, *2010*(1), CD007024. https://doi.org/10.1002/14651858.CD007024.pub2

Pani, P. P., Trogu, E., Vecchi, S. & Amato, L. (2011). Antidepressants for cocaine dependence and problematic cocaine use. *Cochrane Database of Systematic Reviews*, *2011*(12), CD002950. https://doi.org/10.1002/14651858.CD002950.pub3

Paquette, C. E., Daughters, S. B. & Witkiewitz, K. (2022). Expanding the continuum of substance use disorder treatment: Nonabstinence approaches. *Clinical Psychology Review*, *91*, 102110. https://doi.org/10.1016/j.cpr.2021.102110

Penetar, D. M., MacLean, R. R., McNeil, J. F. & Lukas, S. E. (2011). Kudzu extract treatment does not increase the intoxicating effects of acute alcohol in human volunteers. *Alcoholism: Clinical and Experimental Research*, *35*(4), 726–734. https://doi.org/10.1111/j.1530-0277.2010.01390.x

Penetar, D. M., Toto, L. H., Lee, D. Y. W. & Lukas, S. E. (2015). A single dose of kudzu extract reduces alcohol consumption in a binge drinking paradigm. *Drug and Alcohol Dependence*, *153*, 194–200. https://doi.org/10.1016/j.drugalcdep.2015.05.025

Pérez de los Cobos, J., Trujols, J., Siñol, N., Vasconcelos e Rego, L., Iraurgi, I. & Batlle, F. (2014). Psychometric properties of the Spanish version of the Cocaine Selective Severity Assessment to evaluate cocaine withdrawal in treatment-seeking individuals. *Journal of Substance Abuse Treatment*, *47*(3), 189–196. https://doi.org/10.1016/j.jsat.2014.05.004

Pérez-Mañá, C., Castells, X., Vidal, X., Casas, M. & Capellà, D. (2011). Efficacy of indirect dopamine agonists for psychostimulant dependence: A systematic review and meta-analysis of randomized controlled trials. *Journal of Substance Abuse Treatment*, *40*(2), 109–122. https://doi.org/10.1016/j.jsat.2010.08.012

Reback, C. J., Larkins, S. & Shoptaw, S. (2004). Changes in the meaning of sexual risk behaviors among gay and bisexual male methamphetamine abusers before and after drug treatment. *AIDS and Behavior*, *8*(1), 87–98. https://doi.org/10.1023/B:AIBE.0000017528.39338.75

Rodríguez-Morató, J., Farré, M., Pérez-Mañá, C., Papaseit, E., Martínez-Riera, R., de la Torre, R. & Pizarro, N. (2015). Pharmacokinetic comparison of soy isoflavone extracts in human plasma. *Journal of Agricultural and Food Chemistry*, *63*(31), 6946–6953. https://doi.org/10.1021/acs.jafc.5b02891

RxList. (n.d.). *Soy: Uses and effectiveness*. RxList. https://www.rxlist.com/soy/supplements.htm#UsesAndEffectiveness

Schroeder, J. P., Cooper, D. A., Schank, J. R., Lyle, M. A., Gaval-Cruz, M., Ogbonmwan, Y. E., Pozdeyev, N., Freeman, K. G., Iuvone, P. M., Edwards, G. L., Holmes, P. V. & Weinshenker, D. (2010). Disulfiram attenuates drug-primed reinstatement of cocaine seeking via inhibition of dopamine β-hydroxylase. *Neuropsychopharmacology*, *35*(12), 2440–2449. https://doi.org/10.1038/npp.2010.127

Smith, L. J., Kalhan, R., Wise, R. A., Sugar, E. A., Lima, J. J., Irvin, C. G., Dozor, A. J. & Holbrook, J. T. (2015). Effect of a soy isoflavone supplement on lung function and clinical outcomes in patients with poorly controlled asthma. *JAMA*, *313*(20), 2033–2043. https://doi.org/10.1001/jama.2015.5024

Somoza, E., Dyrenforth, S., Goldsmith, J., Mezinskis, J. & Cohen, M. (1995). In search of a universal drug craving.. *Annual Meeting of the American Psychiatric Association*.

Stotts, A. L., Mooney, M. E., Sayre, S. L., Novy, M., Schmitz, J. M. & Grabowski, J. (2007). Illusory predictors: Generalizability of findings in cocaine treatment retention research. *Addictive Behaviors*, *32*(12), 2819–2836. https://doi.org/10.1016/j.addbeh.2007.04.020

Sullivan, J. T., Sykora, K., Schneiderman, J., Naranjo, C. A. & Sellers, E. M. (1989). Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). *The British Journal of Addiction*, *84*(11), 1353–1357.

Tantipongpiradet, A., Monthakantirat, O., Vipatpakpaiboon, O., Khampukdee, C., Umehara, K., Noguchi, H., Fujiwara, H., Matsumoto, K., Sekeroglu, N., Kijjoa, A. & Chulikhit, Y. (2019). Effects of puerarin on the ovariectomy-induced depressive-like behavior in ICR mice and its possible mechanism of action. *Molecules*, *24*(24), 4569. https://doi.org/10.3390/molecules24244569

Torrens, M., Martínez-Sanvisens, D., Martínez-Riera, R., Bulbena, A., Szerman, N. & Ruiz, P. (2011). Dual diagnosis. *Addictive Disorders & Their Treatment*, *10*(2), 50–59. https://doi.org/10.1097/ADT.0b013e318215f322

Torrens, M., Serrano, D., Astals, M., Pérez-Domínguez, G. & Martín-Santos, R. (2004). Diagnosing comorbid psychiatric disorders in substance abusers: Validity of the Spanish versions of the Psychiatric Research Interview for Substance and Mental Disorders and the Structured Clinical Interview for DSM-IV. *The American Journal of Psychiatry*, *161*(7), 1231–1237. https://doi.org/10.1176/appi.ajp.161.7.1231

United Nations Office on Drugs and Crime (UNODC). (2024). *World Drug Report 2024*. United Nations.

Volkow, N. D., Wang, G.-J., Fowler, J. S., Tomasi, D. & Telang, F. (2011). Addiction: Beyond dopamine reward circuitry. *Proceedings of the National Academy of Sciences*, *108*(37), 15037–15042. https://doi.org/10.1073/pnas.1010654108

Volkow, N. D. (2020). Personalizing the treatment of substance use disorders. *American Journal of Psychiatry*, *177*(2), 113–116. https://doi.org/10.1176/appi.ajp.2019.19121284

Weinshenker, D. (2010). Cocaine sobers up. *Nature Medicine*, *16*(9), 969–970. https://doi.org/10.1038/nm0910-969

Weiss, R. D., Hufford, C., Najavits, L. M. & Shaw, S. R. (1995). *Weekly Substance Use Inventory*. Unpublished measure, Harvard Medical School, Boston.

Yang, T. S., Wang, S. Y., Yang, Y. C., Su, C. H., Lee, F. K., Chen, S. C., Tseng, C. Y., Jou, H. J., Huang, J. P. & Huang, K. E. (2012). Effects of standardized phytoestrogen on Taiwanese menopausal women. *Taiwanese Journal of Obstetrics and Gynecology*, *51*(2), 229–235. https://doi.org/10.1016/j.tjog.2012.04.011

Yao, L., Fan, P., Arolfo, M., Jiang, Z., Olive, M. F., Zablocki, J., Sun, H., Chu, N., Lee, J., Kim, H., Leung, K., Shryock, J., Blackburn, B. & Diamond, I. (2010). Inhibition of aldehyde dehydrogenase-2 suppresses cocaine seeking by generating THP, a cocaine use–dependent inhibitor of dopamine synthesis. *Nature Medicine*, *16*(9), 1024–1028. https://doi.org/10.1038/nm.2200

Data availability statement

The datasets for this manuscript are not publicly available. Requests to access the datasets should be directed to Magi.Farre@uab.cat.