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Dark chocolate (70% cocoa) reduces craving in smokers with severe cardiovascular comorbidities without interference in anthropometric measures

Chocolate amargo (70% cacau) reduz fissura em tabagistas com comorbidades cardiovasculares graves sem interferir nas medidas antropométricas

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ABSTRACT

Objective: Analyze craving in smokers with cardiovascular comorbidities submitted to a nutritional approach. **Methods:** Two groups were randomized and submitted to clinical intervention (n = 32): Group 1 (G1, n = 15): ingested 40 g of chocolate containing 70% cocoa/day and behavioral intervention for smoking cessation for one month; Group 2 (G2, n = 17): control group, only behavioral intervention. Questionnaire of Smoking Urges-Brief (QSU-Brief) - Brazil version measured total craving and its factors. Anthropometric measurements verified the nutritional interference of the procedure and the serum assessment verified the interference of inflammatory processes related to smoking. The study was registered on the Brazilian Registry of Clinical Trials (ReBEC): RBR-83jr3. **Results:** After one month, compared to the initial evaluation, the G1 reduced the craving evaluated by the QSU-Brief and its Factors 1 and 2. Total QSU-Brief: 44.27 ± 15.82 x 27.00 ± 18.03 (p = 0.008); Factor 1: 21.90 ± 7.70 x 12.90 ± 8.87 (p = 0.006); Factor 2: 11.90 ± 6.30 x 7.00 ± 6.63 (0.007). G2 showed a reduction in total QSU-Brief and Factor 1, but not in Factor 2. QSU-Brief total 28.17 ± 17.24 x 19.52 ± 9.50 (p = 0.049); Factor 1: 14.47 ± 8.74 x 9.23 ± 6.11 (p = 0.046). Serum levels of cortisol, leptin, serotonin, C-Reactive Protein (CRP) and insulin did not show differences (p > 0.05). No anthropometric differences were found. **Conclusion:** The results demonstrate that daily consumption of chocolate for one month (70%) reduced craving in smokers at the beginning of treatment. Chocolate potentiated the well-known effect of behavioral counseling on Factor 1 (pleasurable drug effects) and also interfered with factor 2 (unpleasant withdrawal effects).

KEYWORDS

Smoking, food, chocolate, craving, comorbidity.

RESUMO

Objetivo: Analisar o *craving* em fumantes com comorbidades cardiovasculares submetidos a uma abordagem nutricional. **Métodos:** Intervenção clínica (n = 32) com dois grupos randomizados: Grupo 1 (G1, n = 15): recebendo 40 g de chocolate contendo 70% de cacau/dia e intervenção comportamental para cessação do tabagismo por um mês; Grupo 2 (G2, n = 17): grupo controle, recebendo apenas intervenção comportamental pelo mesmo período. O *Questionnaire of Smoking Urges-Brief* (QSU-Brief) – versão Brasil foi utilizado para avaliar o *craving*. As medidas antropométricas verificaram a interferência nutricional do procedimento e a avaliação sérica, a interferência de processos inflamatórios relacionados ao tabagismo. O estudo foi registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC), RBR-83jr3. **Resultados:** Um mês depois, comparado à avaliação inicial, o G1 reduziu o *craving* total e seus fatores (1 e 2). QSU-Brief total: 44,27 ± 15,82 x 27,00 ± 18,03 (p = 0,008); Fator 1: 21,90 ± 7,70 x 12,90 ± 8,87 (p = 0,006); Fator 2: 11,90 ± 6,30 x 7,00 ± 6,63 (0,007). G2: redução no QSU-Brief total e Fator 1, mas não no Fator 2. QSU-Brief total 28,17 ± 17,24 x 19,52 ± 9,50 (p = 0,049); Fator 1: 14,47 ± 8,74 x 9,23 ± 6,11 (p = 0,046). Níveis séricos de cortisol, leptina, serotonina, proteína C-reativa (PCR) e insulina não apresentaram diferenças (p > 0,05). Não foram encontradas diferenças antropométricas significativas. **Conclusão:** Os resultados demonstram que o consumo diário de chocolate por um mês (70%) reduziu o *craving* em fumantes no início do tratamento. O chocolate potencializou o conhecido efeito do aconselhamento comportamental sobre o Fator 1 (efeitos prazerosos da droga) e também interferiu no fator 2 (efeitos desagradáveis da abstinência).

PALAVRAS-CHAVE

Fumante, alimento, chocolate, fissura, comorbidade.

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INTRODUCTION

Smoking is a clinical condition that may result in nicotine dependence. This is classified by the World Health Organization, as belonging to mental and behavioural disorders resulting from the use of psychoactive substances. Smoking is recognized as a risk factor for cardiovascular disease increasing cardiovascular mortality[1]. Worldwide, when the population is older than 15 years old it's found that 942 million men and 175 million of women are smokers. Smokers are exposed to more than 7.000 toxic chemicals. From these, at least 70 are known carcinogens. Recent studies suggested that smoking is associated to increased risks of kidney failure, intestinal ischemia, and systemic arterial hypertension (SAH)[2].

Nicotine, the main psychoactive component of tobacco, can stimulate the release of corticosterone. Increased serum levels of corticosterone are found as proportional to the increase of smoking, both active and passive. Increased response to stress, can contribute to a change in levels of serotonin (5-hydroxytryptamine or 5-HT), which receptors are associated with mood disorders and depression, common symptoms perceived in the early stages of smoking cessation[3-6].

Within this context, literature suggest that chocolate has properties that can modulate stress. Sunni and Latif demonstrated that the consumption of 40 g of dark and milk chocolate for two weeks reduced the perceived stress in women[3]. The regular consumption of chocolate can reduce the body's response to stressful situations and promote less response from the adrenal gland[7]. In addition, the polyphenols present in cocoa have an anti-inflammatory effect, reducing the pro-inflammatory cytokines such as TNF-alpha (tumour necrosis factor alpha), leptin, C reactive protein (CRP) and improve insulin sensitivity. These actions could contribute to an improvement in the metabolic parameters of individuals with sustained inflammation caused by smoking[8].

Literature suggests that the consumption of chocolate is related to a reduction in mortality from cardiovascular diseases (CVD)[9,10]. Less is known about the chocolate diet in the process of smoking cessation. Studies suggested that chocolate decreases the degradation of anandamide. As the endocannabinoid system has been associated with chemical dependence[11] it is reasonable to suppose that manipulation of diet that could interfere with its functioning would change treatment prognosis. The present study was designed to test if the introduction of a sample of chocolate containing 70% cocoa would reduce craving and mental stress. Achieving abstinence is an arduous and complex process that involves several neurobiological and environmental factors. Recent evidence of the involvement of the endocannabinoid system on different biological systems make the search of nutritional approaches that can affect it important. In order to establish if there were also effects on the inflammatory processes related to nicotine and because volunteers of the study were compromised by comorbidities the interference of chocolate on levels of cortisol, leptin, serotonin, CRP and insulin was measured.

METHODS

Design and location of the study

This is a clinical intervention study, conducted with a non-probabilistic sample, in which smokers were followed up at the Unit of Integral Assistance to Smoking (UIA-S), from the *Núcleo Interdisciplinar de Estudos e Pesquisa em Nefrologia* (NIEPEN) at the city of Juiz de Fora – MG, Brazil, from April 2017 to April 2019. This group is directed to the treatment for smoking cessation of patients with SAH, diabetes mellitus (DM) and chronic kidney disease with high cardiovascular risk, according to the normative of the National Cancer Institute (NCI), in its cognitive behavioral and medication approach. It was considered as a brief smoking cessation, the cessation during the 4 weeks after the end of the sessions of the behavioral approach. The inclusion criteria adopted were: users of more than 20 cigarettes/day, with SAH, DM, and high cardiovascular risk. The non-inclusion criteria were: users of psychoactive substances, patients with psychiatric diseases or cognitive deficits, cancer, Acquired Immunodeficiency Syndrome (AIDS), those who were in nutritional follow-up, and those who didn't fill the inclusion criteria. The proposal was approved by the Research Ethics Committee of the UFJF (CAAE: 57832916.1.0000.5147/1942.851).

Clinical trial

The clinical trial was performed over four weeks, being a weekly meeting. During this period, structured sessions were also held for smoking cessation, where NCI provided booklets were discussed and the habits necessary for the success of smoking cessation were reinforced. The participants were recruited monthly to the UAI-T treatment group, and the recruitment of volunteers for the research occurred one week before the start of treatment and the clinical trial, at the awareness meeting. In this meeting, smokers were informed of the research objectives and gave their consent for participation.

The intervention consisted in the formation of two distinct groups, randomized, all receiving the intervention recommended by NCI, being, Group 1 (G1): patients receiving 40 g of chocolate containing 70% cocoa per day. The chocolate was obtained from a commercial source and had

approximately 140 kcal/portion. Group 2 (G2), control group, receiving only NCI intervention for four weeks.

This clinical trial was registered and published on the Brazilian Clinical Trials Registry (ReBEC) platform, with the number: RBR-83jr3x.

Procedures

After the four-week period of the clinical trial, chocolate was interrupted but behavioral approach was maintained and volunteers continued the follow-up at UAI-T, with fortnight meetings, until they completed twelve weeks of treatment. In the twelfth week, those who remained on treatment for smoking cessation were reevaluated for the same initial parameters, both, anthropometric, clinical and biochemical, which will be described below. The twelfth week is equivalent to the continuation of the treatment for smoking cessation proposed by NCI and represents the end of the period of brief smoking cessation.

Craving was evaluated weekly during the clinical trial, in the beginning and after four weeks, through the Questionnaire of Smoking Urges-Brief (QSU-Brief), Brazil version[12]. The QSU-Brief has 10 affirmative questions and is evaluated for two factors. Factor 1 (positive reinforcement) measures the intention to smoke due to the pleasure associated with this behavior and Factor 2 (negative reinforcement) is associated to the increased desire to smoke due to cigarette withdrawal. Factor 1 consists of the following questions: 1) I want to smoke a cigarette now; 3) If it was possible, I would probably smoke now; 7) Smoking a cigarette would be nice at that moment; 10) I will smoke as soon as possible. The Factor 2, consists of the following statements: 4) I would control things better, at this moment, if I could smoke; 8) I would do just anything for a cigarette now; 9) Smoking would make me less depressed. The classification for the Factor 1 is: from 0 to 6 points, minimum craving; from 7 to 15, light; 16 to 23, moderate; and 24 or more points, intense craving. For Factor 2: from 0 to 2 points, minimum craving; from 3 to 4, light; 5 to 9, moderate; and 10 or more points, intense craving. The total score is obtained by summing the numbers marked by the participant in each question, which ranges from a scale between 1 and 7, being 1 (strongly disagree) and 7 (strongly agree).

The Fagerstrom Test for Nicotine Dependence (FTND), applied in the first week of intervention, consists of six questions that aim to identify smokers' behavior. There is a corresponding value for each question in the questionnaire. The values when added result in a score that indicates the degree of dependence: low (0 to 4 points), moderate (5 points), or high (5 to 10 points)[13].

Anthropometric nutritional assessment was performed at the initial meeting, at the fourth and at the twelfth week of follow-up. Weight and height data were collected to calculate the Body Mass Index (BMI). To measure body weight, the Welmy® was used, adjusted for each measurement, with a capacity of 150 kg. At the time of measuring body weight, participants were barefoot and wearing light clothing. To measure height, the Alturaexata® portable anthropometer was used.

The BMI was calculated using the following formula: BMI = Weight (kg) / Height^2 (m). The criteria were used for the classification of adults: low weight (BMI < 18.5 kg/m^2); eutrophic (18.5 to 24.9 kg/m^2); overweight (25 to 29.9 kg/m^2) and obese (≥30 kg/m^2)[14]. For the elderly was adopted Lipschitz classification: underweight (BMI < 22 kg/m^2), eutrophic (22-27 kg/m^2), overweight (>27 kg/m^2)[15].

The measurement of the abdominal circumference (AC) was performed with the use of flexible and inelastic tape in the abdomen at the height of the umbilicus. The interpretation of the results followed the cutoff points ≥ 90 cm and ≥ 80 cm, for men and women respectively, which indicates the accumulation of abdominal fat, is related to a higher risk of developing chronic diseases such as cardiovascular diseases (CVD) and diabetes mellitus (DM)[15].

Biochemical analysis

Blood samples were collected at Côrtes Villela Clinical Analysis Laboratory, in Juiz de Fora – MG, at the beginning of treatment with individuals still smoking, after the intervention at the fourth week and at the twelfth week. The collect was performed in the morning after 8 hours of fasting of the volunteers. The blood samples were centrifuged and stored at -80 ºC, in the Instrumental Analysis Laboratory of the Nutrition Department at UFJF, until the analyzes were performed. The analyzes were performed at the Côrtes Villela Clinical Analysis Laboratory by Enzyme-Linked Immunosorbent Assay (ELISA), using specific standardized analysis kits.

Statistical analysis

The quantitative variables that presented a symmetrical distribution were described using mean ± standard deviation and those that presented an asymmetric distribution were described using the median (interquartile range). To evaluate the normality of the data, the Kolmogorov-Smirnov test was used. To compare the differences between the means and medians, the T-Student and T Paired tests were used. The data were processed and analyzed using the IBM SPSS 23.0 and, for effect of interpretation, the limit type I error was up to 5% ($p < 0.05$).

RESULTS

Participated of this study 32 volunteers, all smokers initially, aiming to achieve smoking cessation. Regarding the degree of nicotine dependence, measured by FTND, the volunteers in Group 1 (70% chocolate), presented a mean of 5.73 ± 2.37 points and Group 2 (control): 4.75 ± 1.77 points, and there was no significant difference among the groups (p = 0.518). The FTND means to indicate a moderate to high dependence on these individuals. The mean age of male volunteers was 59.26 ± 5.06 years, while of the female was 60.84 ± 7.07 years (p = 0.440), which brings the participants closer to the elderly population in Brazil (over 60 years). Table 1 presents sociodemographic data where it is possible to observe that most women smoked less than 20 cigarettes per day.

In the present study, the data of QSU-Brief and its Factors 1 and 2 of the volunteers who started brief smoking cessation, were evaluated in the initial period, at the fourth week and at the twelfth week. There were no statistical differences in QSU-Brief and its Factors 1 and 2 among the groups at the beginning of intervention (Table 2; p > 0.05).

Table 1. Sociodemographic characteristics and clinical history of the research volunteers (n = 48)

	Male n = 15 (31.25%)	Female n = 33 (68.75%)	p
Schooling			
Elementary school	10 (31.2%)	22 (68.8%)	0.595
High school	5 (35.7%)	9 (64.3%)	
University	0 (0%)	2 (100.0%)	
Work situation			
Work	4 (21.1%)	15 (78.9%)	0.217
Pensioner	11 (37.9%)	18 (62.1%)	
Sedentary			
Yes	2 (14.3%)	12 (85.7%)	0.104
No	13 (38.2%)	21 (61.8%)	
Obesity			
Yes	3 (17.6%)	14 (82.4%)	0.132
No	12 (38.7%)	19 (61.3%)	
Systemic arterial hypertension			
Yes	12 (31.6%)	26 (68.4%)	0.924
No	3 (30.0%)	7 (70.0%)	
Diabetes mellitus			
Yes	8 (44.4%)	10 (55.6%)	0.127
No	7 (23.3%)	23 (76.7%)	
Alcohol			
Yes	4 (26.7%)	11 (73.3%)	0.644
No	11 (33.3%)	22 (66.7%)	
Addiction time			
Less than 30 years	1 (20.0%)	4 (80.0%)	0.566
More than 30 years	14 (32.6%)	29 (67.4%)	
Number of cigarettes/day			
Less than 20 cigarettes/day	9 (23.7%)	29 (76.3%)	**0.027**
More than 20 cigarettes/day	6 (60.0%)	4 (40.0%)	
Previous attempts to quit smoking			
Yes	12 (30.0%)	28 (70.0%)	0.676
No	3 (37.5%)	5 (62.5%)	
Previous treatments for smoking cessation			
Yes	6 (31.6%)	13 (68.4%)	0.968
No	9 (31.0%)	20 (69.0%)	

Chi Square/Fisher Exact.

Table 2. Mean and standard deviation of the sum of the QSU-Brief and its Factors 1 and 2, at the beginning and at the fourth week in each follow-up group

	Group 1 – Chocolate	p	Group 2 – Control	p
Total QSU-Brief Week 0	44.27 ± 15.82	**0.008**	28.17 ± 17.24	**0.049**
Total QSU-Brief Week 4	27.00 ± 18.03		19.52 ± 9.50	
Factor 1 – Week 0	21.90 ± 7.70	**0.006**	14.47 ± 8.74	**0.046**
Factor 1 – Week 4	12.90 ± 8.87		9.23 ± 6.11	
Factor 2 – Week 0	11.90 ± 6.30	**0.007**	6.70 ± 5.03	**0.463**
Factor 2 – Week 4	7.00 ± 6.63		5.82 ± 3.81	

T-Paired – Test

Comparing the differences in QSU-Brief and its factors in each intervention group, at the beginning and at the fourth week of follow-up, in the chocolate group, G1, it is noted that, the QSU-Brief and its Factors 1 and 2, reduced at the end of the intervention, showing a significant effect of the consumption of dark chocolate together with behavioral counseling in the decrease of craving for cigarettes. Behavioral counselling alone also reduced QSU after 4 weeks as shown in the results for G2. However, the reduction was in Factor 1 alone as shown in Table 1, thus showing the effect of behavioral intervention on smoking for pleasure. Although also significant at a p level of 0.05 the difference was less significant when chocolate was not provided.

Table 3 presents the anthropometric data of the volunteers at the beginning and after the four-week intervention period. In the analysis stratified by BMI (<25 kg/m^2 or >25 kg/m^2), indicating excess weight above > 25 kg/m^2 and for AC (<90 cm and >90 cm), indicating cardiovascular risk for AC above 90 cm, no significant differences were found (p = 0.059). Thus, there was no effect of the group on the anthropometric values described for BMI and AC. Also, there were no statistical differences in anthropometric parameters among the groups at the twelfth week (p > 0.05).

The analyses of serum levels of cortisol, leptin, serotonin, CRP and insulin, didn't show significant differences among volunteers according to the group of intervention (Table 4). This Table presents the comparison of the parameters analyzed at the beginning and after the four-week intervention.

Table 3. Mean and standard deviation of the anthropometric parameters of body weight, body mass index (BMI) and abdominal circumference (AC) of the volunteers at the beginning and at the fourth week of intervention

	Group 1 – Chocolate	Group 2 – Control	p
Body weight (kg) – week 0	75.92 ± 17.22	64.40 ± 12.99	0.090
Body weight (kg) – week 4	73.02 ± 18.04	64.38 ± 13.12	0.116
Body mass index (kg/m^2) – week 0	30.36 ± 6.56	25.03 ± 3.24	**0.025**
Body mass index (kg/m^2) – week 4	29.81 ± 7.11	25.03 ± 3.40	0.052
Abdominal circumference (cm) – week 0	99.57 ± 15.56	86.58 ± 10.45	**0.030**
Abdominal circumference (cm) – week 4	99.36 ± 17.00	86.17 ± 10.78	0.053

T Student Test.

Table 4. Mean and standard deviation of serum levels of serotonin, cortisol, leptin, insulin and CRP of the participants at the beginning and at the fourth week of follow-up according to the intervention group

	G1 – Chocolate 70%	G2 – Group Control	p
Serotonin (ng/mL) – week 0	193.43 ± 182.54	140.08 ± 115.14	0.226
Serotonin (ng/mL) – week 4	196.97 ± 137.95	157.98 ± 130.88	0.583
Cortisol (mcg/dL) – week 0	10.51 ± 4.41	10.93 ± 3.01	0.188
Cortisol (mcg/dL) – week 4	10.74 ± 4.14	11.23 ± 2.37	0.860
Leptin (ng/mL) – week 0	8.17 ± 7.67	8.13 ± 7.30	1.000
Leptin (ng/mL) – week 4	10.54 ± 7.33	6.25 ± 5.11	0.242
Insulin (mUI/L) – week 0	24.25 ± 18.61	8.58 ± 5.58	0.127
Insulin (mUI/L) – week 4	38.03 ± 19.96	10.14 ± 6.21	0.129
CRP (mg/dL) – week 0	0.47 ± 0.39	0.47 ± 0.14	0.132
CRP (mg/dL) – week 4	0.83 ± 0.44	0.72 ± 0.29	0.942

CRP – C-Reactive Protein. T-Student Test.

DISCUSSION

This study suggested a significant reduction in craving in volunteers who consumed chocolate 70% cocoa, daily for four weeks. This evidence is important for the population studied, as they are individuals with numerous cardiovascular risk factors, in which the reduction of craving by cigarettes, could contribute to increasing abstinence rates. The reduction of Factors 1 and 2 obtained are relevant in the process of treatment of nicotine addiction. In addition, therapies involving nicotine replacement in this population are questionable because of the cardiovascular risks of nicotine itself. QSU has been analyzed by dividing its punctuation into factors[16]. Factor 1, refers to the use of nicotine as a habitual behavior, where the individual uses the cigarette due to the pleasure associated with this behavior. In contrast, Factor 2 refers to the search for cigarettes to relieve withdrawal symptoms, being a strong predictor of relapse.

The literature points that the consumption of chocolate and its components positively influence cognitive function and mood, however, it remains unknown whether the effects of chocolate on mood are due to its oro-sensorial characteristics or to the pharmacological actions of its constituents[17]. However, a recent meta-analysis indicates that eating cocoa-rich products, such as dark chocolate, may provide short-term benefits for mood and affective symptoms[18].

The pioneering study of Di Tomaso *et al.* demonstrated that a group of pharmacological constituents present in chocolate targets the endogenous cannabinoid system in the brain. The authors consider that chocolate, being rich in fat, may contain lipids that are chemically and pharmacologically related to anandamide, and also inhibits its degradation. This could be an explanation mechanism for the pronounced effects obtained in this research with chocolate[19].

In the study of Pase *et al.* randomized, double-blind, placebo-controlled, 72 healthy and middle-aged individuals received a drink containing dark chocolate, with respectively 500mg, 250 mg or 0 mg of polyphenols (placebo), once daily for 30 days. The authors found positive effects on mood, but not on cognitive function. The authors suggest the need for more research about the effects of chocolate polyphenols on improving symptoms of other disorders such as depression and anxiety[20]. Decroix *et al.*[21], suggested that the consumption of cocoa polyphenols is capable of increasing the cerebral oxygenation of individuals who practice physical activity, generating a greater sense of well-being. These possible effects of polyphenols, could in the studied population, be contributing to the control of the intense craving inherent to this phase of treatment considered a great predictor of relapse.

Although the ingestion of foods with high amounts of fat and sugar activates the mesolimbic reward system, and also oral and gustatory brain regions, contributing to an increase in food consumption[22]. Stice *et al.* evaluated the effect of an equicaloric chocolate milkshake with a high fat or sugar content on the activation of these regions. The authors found that the increase in sugar caused greater activity in the gustatory regions and the increase in fat didn't affect this activation. The results suggest that sugar recruits, more effective, rewarding and gustatory regions. In the present study, the use of dark chocolate, containing 70% cocoa, could attenuate the reward effects caused by sugar[23].

Serotonin levels may be influenced by the degree of inflammation in the body, the use of drugs that inhibit its reuptake in the synaptic cleft, stress, as well as its availability in food. Among these aspects, we highlight this large variation in serum levels found in the sample, the condition of sustained inflammation due to the long period of smoking, associated with metabolic changes resulting from chronic non-transmissible diseases, in which the individuals are carriers. However, no differences were detected.

No differences in serum levels of leptin, cortisol, insulin and CRP were observed among the volunteers. The main result was the reduction of negative reinforcement by cigarettes (Factor 2), however this reduction didn't occur via changes in serum levels of cortisol, leptin, serotonin and CRP, which modulate inflammatory and reward responses in the body.

The main limitation of this study is the relatively small sample size. However, the present study showed the effectiveness of a non-drug and low-cost measure that can be adjuvant in the smoking cessation process, especially in the case of this population that have difficulty adhering to treatment and have limitation toward nicotine replacement therapies.

CONCLUSION

The present study showed that through nutritional intervention, it's possible to reduce craving and assist in strengthening smokers to achieve smoking cessation. It's noteworthy to mention the viability of execution and the reproducibility of the intervention proposed in this study in the treatment of other smokers, especially those with less severity and fewer cardiovascular complications.

Reducing the craving and strengthening the abstinence process is relevant because they are patients with difficulties in stopping smoking. This study suggested that complementary approaches (chocolate 70% cocoa), can help in the process of smoking cessation in a sample where quitting

smoking is mandatory as related to a well-documented reduction in morbidity and mortality.

AUTHOR CONTRIBUTIONS

Arthur da Silva Gomes, Nathércia Percegoni, Aline S. de Aguiar e Vilma A. S. Fonseca – Equally contributed to the conception and design of the research.
Arthur da Silva Gomes, Marcela Melquíades Melo, Thayzis de Paula Silva, Arise Garcia de Siqueira Galil, Shiela Luquetti and André Netto – Contributed to the acquisition, analysis, and interpretation of the data.
All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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