



# Effects of Omega-3 Fatty Acids on Tobacco Craving in Tobacco Users: A Single-blind, Randomized, Placebo-controlled Study

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## ABSTRACT

**Background:** Tobacco use and its smoke produces oxidative stress in the body, which eventually triggers cell damage by lipid peroxidation. Smokers report lower levels of omega-3 fatty acids (FAs) in their serum as compared to nonsmokers. Omega-3 deficiency impairs neurotransmission, resulting in hypofunctioning of the mesocortical system, which is a reward and dependency system that can raise tobacco cravings, disrupting tobacco quitting efforts. Omega-3 polyunsaturated fatty acid (PUFA) regulates stress, anxiety, and negative emotions that are associated with tobacco urges. Limited research has assessed the supplementation effect of omega-3 PUFA [in the form of alpha-linolenic acid (ALA)] on tobacco craving.

**Aim:** We aimed to explore the effects of omega-3 PUFA (ALA) on the frequency of tobacco use per day, tobacco dependence, and tobacco craving when compared to placebo in regular tobacco users.

**Materials and methods:** Regular tobacco users ( $n = 83$ ) recruited from the Tobacco Cessation Clinic were randomly allocated to two groups. Group 1 was the omega-3 PUFA group, supplemented with 10 mL/day of omega-3 PUFA in the form of ALA (5.1 gm) for 180 days, and the other group received a placebo for the same duration. The outcome was evaluated by means of a case record form (for demographic parameters), self-reports of tobacco use (for frequency of tobacco use per day), as well as psychometric measures (for tobacco dependence and tobacco craving). The evaluations were carried out at baseline and after 180 days of intervention.

**Results and conclusion:** The frequency of tobacco use per day, tobacco dependence, and tobacco craving were found to be significantly decreased ( $p < 0.0001$ ) in the group receiving omega-3 PUFA (ALA) at the end of supplementation. This is a novel approach that ALA supplementation reduces tobacco cravings in regular tobacco users in comparison to a placebo. Thus, omega-3 FAs may be an adjuvant tool in quitting tobacco use by reducing nicotine dependence and tobacco craving. Further studies are necessary with large samples to understand the possible association and explore the probable nonpharmacological approaches for tobacco cessation.

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## INTRODUCTION

Chronic exposure to tobacco smoke, a toxic cocktail of chemicals, leads to progressive pulmonary dysfunction plus carcinogenic lung injury.<sup>1</sup> Over time, exposure to the hazardous components of tobacco smoke produces oxidative stress, which eventually triggers cell damage by lipid peroxidation.<sup>2</sup> Fatty acids (FAs) are carboxylic acids that can be classified as either saturated or unsaturated, with carbon chain lengths ranging from 2 to 36 atoms of carbon.<sup>3</sup> FAs having two or more double bonds are called polyunsaturated fatty acids (PUFAs). One of them is omega-3 FA (the first double bond between the third and fourth carbons when counting from the CH<sub>3</sub> end).<sup>4,5</sup> The three main omega-3 FAs are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).<sup>6</sup>

Smokers report lower levels of DHA and EPA in their serum as compared to

nonsmokers because tobacco smoke inhibits metabolism, bioavailability, plus the absorption of omega-3 FAs.<sup>7-9</sup> Incorporation of Omega-3 FAs into neural membranes increases membrane fluidity, and<sup>10</sup> its deficiency disrupts neurotransmission, leading to hypofunctioning of the mesocortical system, i.e., a reward and dependence system<sup>10,11</sup> which may increase tobacco use urges, interfering with and weakening tobacco cessation.<sup>12</sup> n-3 PUFA deficiency is associated with increased sensitivity to stress.<sup>13</sup>

Epidemiological research has demonstrated an inverse relationship between n-3 PUFA levels and the prevalence of psychological distress, anxiety disorders, and depression.<sup>14-16</sup> On the contrary, a diet high in n-3 PUFAs improves the psychosocial well-being of patients and shows no increase in aggressive behaviors due to stressful situations.<sup>17-19</sup> Omega-3 FA

consumption may elevate brain serotonin levels.<sup>20</sup> Omega-3 FAs are reported to have antistress and regulatory effects on hypothalamic-pituitary-adrenocortical responsiveness by decreasing their activation.<sup>21</sup> Supplementation with PUFAs enhances the capacity for stress coping within the cerebral-limbic system.<sup>22,23</sup>

Essential FAs are crucial for maintaining optimal health; however, they cannot be produced endogenously and must be acquired through dietary intake.<sup>24</sup> The fattiest organ of the body is the brain, which comprises almost 40% PUFA, which is vital for brain development as well as its functioning.<sup>25</sup> Brain pathology plays a role in the development of mood disorders.<sup>26</sup> A three-month supplementation with EPA and DHA led to significant reductions in anger, anxiety scores,<sup>27</sup> impulsive aggressive behavior,<sup>28</sup> symptoms of depression,<sup>29</sup> negative moods,<sup>30</sup> distress symptoms, and basal cortisol secretion.<sup>21</sup>

Prevailing pharmacologic studies with the intervention of first-line treatment [nicotine replacement therapy (NRT), including gums, patches, lozenges] and second-line treatment (such as clonidine, varenicline) have been sparsely done for tobacco cessation. Studies using omega-3 supplementation to treat stress reactions in tobacco users are very rare.<sup>31,32</sup> Tobacco cessation causes psychological stress, which causes the maintenance of cessation.<sup>33</sup> Omega-3 PUFAs help relieve this psychological stress and

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associated symptoms, and thus could help sustain cessation.<sup>34</sup> Smokers have lower levels of EPA and DHA than nonsmokers.<sup>7</sup> Limited research has been conducted thus far on the effects of omega-3 PUFAs on cravings for smokeless tobacco.

Not only tobacco abstinence but also exposure to tobacco cues could heighten tobacco craving by manifesting increased anxiety, stress, negative emotions, increased blood pressure (BP), restlessness, irritability, and a strong desire to use tobacco. Stress can weaken a smoker's ability to resist tobacco urges and compel their use more intensely to get greater satisfaction and reward from tobacco use.<sup>35</sup> The neural networks involved in processing psychological stress and substance cues have a significant overlap, with alterations that occur in corticostriatal limbic circuits that underlie both the emotional and reward processes linked to stress and substance cue-induced craving, as well as a greater likelihood of relapse into addiction.<sup>36</sup>

For this reason, the study was designed to investigate the effects of omega-3 PUFA (ALA) as an edible-grade vegetarian source supplement on tobacco craving in regular tobacco users who refused to take any drug assistance for quitting.

We hypothesized that omega-3 PUFA (ALA) dietary supplementation might have an effect on both daily tobacco consumption and tobacco cravings among regular tobacco users.

## MATERIALS AND METHODS

The sample size has been calculated by the statistician on the basis of a previous study by Rabinovitz (2014).<sup>22</sup> The calculated sample size

was 42 in each group, and after adding 20% dropouts in follow-up losses, the total sample size was 100 (50 in the omega-3 PUFA group and 50 in the placebo group) with a confidence level of 95% and a power level of 80%.

From a pool of 100 screened tobacco users, 90 were included in the study. Four participants refused, leaving 86 to be randomized into two groups through a computer-generated randomization table: 45 in the omega-3 PUFA group and 41 in the placebo group. Among the omega-3 PUFA group, 43 of 45 subjects completed the follow-up, with two discontinuing the intervention, while in the placebo group, 40 completed the follow-up, with one follow-up loss. Thus, a total of 83 subjects completed the follow-ups.

The study participants were recruited from the tobacco cessation clinic at King George's Medical University, meeting inclusion criteria aged between 18 and 60 years, fulfilling ICD-10 criteria for tobacco dependence, of either sex, i.e., both male and female, and being free from significant medical or surgical conditions.

Pregnant or nursing mothers, subjects suffering from any comorbidities, and subjects under conventional treatment for comorbidities were both excluded from the study. Subjects who chose pharmacological treatment (including NRT) for tobacco cessation were excluded. We have also excluded the subjects who have already consumed flaxseed or other commercially available omega-3 PUFA as nutritional supplements in the past 3 months. The study received approval from the Institutional Ethics Committee of King George's Medical University, India, and has been registered at the Clinical Trials Registry-India (identifier CTRI/2022/02/040681). Informed consent was

obtained from all study participants following a comprehensive explanation of the study.

See Table 1 for demographic and basal characteristics at baseline of the total sample and by the two groups (Omega-3 PUFAs and Placebo Group). There were no significant baseline differences in these characteristics.

The study employed a single-blind, randomized, placebo-controlled, parallel-group design. Tobacco users were asked to take the omega-3 rich supplement in place of tobacco when they feel cravings. Subjective craving was reported on two occasions (day 0: baseline and day 180: follow-up). Refer to the flow chart in Figure 1 for an overview. Each PUFA bottle contained 10 mL of food-grade pure flaxseed oil with 5.1 gm of omega-3 PUFA (ALA). The placebo bottles contained mustard oil. Both oils in 10 mL quantities were supplied to the subjects in identical black glass coded bottles. Subjects were advised to consume 1 bottle of oil (10 mL) per day for a period of 180 days (6 months). The PUFA and placebo bottles were well tolerated, with no adverse effects reported. During follow-up interviews, participants from both study groups reported experiencing minimal aftertaste, bitterness, or odor. Compliance was ensured by regular reminders via SMS/WhatsApp and phone calls on a weekly basis to the subjects. We also maintained contact with a family member of each subject to help monitor their compliance. In both groups, adherence to the supplementation protocol was admirable.

Each subject was assessed at two intervals: initially at baseline and then after 180 days of treatment during the follow-up. Demographic measures and tobacco use measures were obtained at baseline itself. Also, at baseline and 180-day follow-up, subjects completed the Fagerström Test for Nicotine Dependence (FTND),<sup>37</sup> the Fagerström Test for Nicotine

**Table 1:** Demographic and basal characteristics at baseline of total sample and by group<sup>†</sup>

	All participants (n = 83)	Omega-3 PUFA group (n = 43)	Placebo group (n = 40)	Statistics
Age (years)	47.19 ± 10.25	47.16 ± 11.04	47.23 ± 9.47	<i>p</i> = 0.9782 <sup>ns</sup>
Gender (male)	75 (90.36%)	40 (93.02%)	35 (87.5%)	<i>p</i> = 0.394 <sup>ns</sup>
Gender (female)	8 (9.64%)	3 (6.98%)	5 (12.5%)	
Marital status				
Married	78 (93.98%)	41 (95.35%)	37 (92.5%)	<i>p</i> = 0.586 <sup>ns</sup>
Single (unmarried)	5 (6.02%)	2 (4.65%)	3 (7.5%)	
Tobacco users				
Smokers	22 (26.51%)	10 (23.26%)	12 (30%)	<i>p</i> = 0.487 <sup>ns</sup>
Smokeless tobacco users	61 (73.49%)	33 (76.74%)	28 (70%)	
Age at the beginning of regular tobacco use (years)	28.37 ± 12.27	27.84 ± 12.64	28.95 ± 11.99	<i>p</i> = 0.5169 <sup>ns</sup>
Duration of tobacco use (years)	19.73 ± 11.71	20.31 ± 13.08	19.59 ± 10.18	<i>p</i> = 0.6416 <sup>ns</sup>
Frequency of tobacco use per day	8.63 ± 6.7	10.19 ± 8.34	6.95 ± 3.72	<i>p</i> = 0.1138 <sup>ns</sup>
FTND and FTND-ST scores	5.88 ± 2.19	6.23 ± 2.21	5.58 ± 2.15	<i>p</i> = 0.0642 <sup>ns</sup>
QSU-brief and QSU-brief (modified) scores	49.61 ± 9.13	49.7 ± 9.9	49.53 ± 8.34	<i>p</i> = 0.4461 <sup>ns</sup>

<sup>ns</sup>*p* > 0.05; <sup>†</sup>data are described as n (%) or mean ± standard deviation

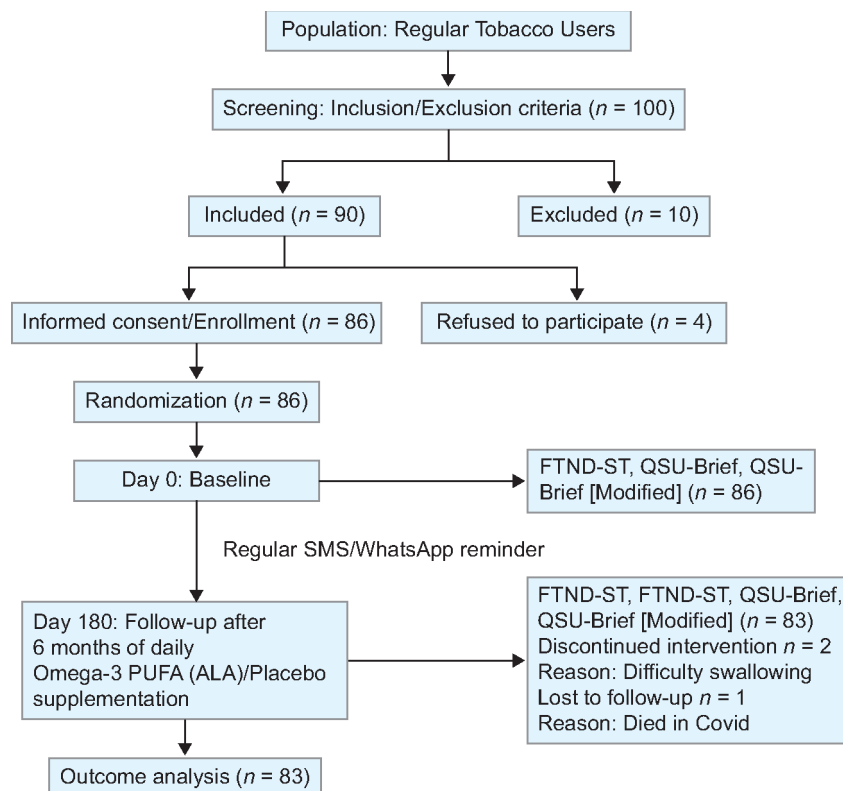


Fig. 1: Flowchart diagram, mapping study subjects and procedures

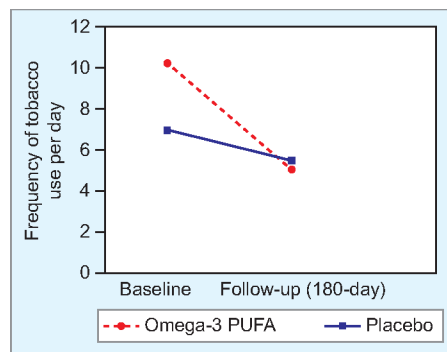


Fig. 2: Frequency of tobacco use daily (mean values) of regular tobacco users at baseline, after 180 days of daily supplementation of omega-3 PUFAs or placebo. The frequency of tobacco intake/day was summed to yield the total frequency per day

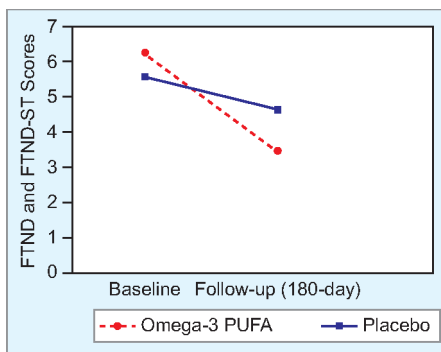


Fig. 3: Nicotine dependence level (mean values) of regular tobacco users at baseline, after 180 days of daily supplementation of omega-3 PUFAs or placebo. Scores assigned to all six items of the questionnaire were summed up to yield a total score

Dependence-Smokeless Tobacco (FTND-ST),<sup>38</sup> the Questionnaire on Smoking Urges-Brief (QSU-Brief),<sup>39,40</sup> and the Questionnaire on Smokeless Tobacco Urges (Modified Questionnaire for Smokeless Tobacco from QSU-Brief).

**Statistical Analysis**

Results are shown as the mean ± standard deviation. Statistical analyses were performed using Microsoft Excel 2021, GraphPad Prism 5, and SPSS 24 (Statistical Package for the Social Sciences 24). The effect of PUFA and placebo treatment within the respective groups was examined by a Wilcoxon matched-pairs

signed rank test and a matched-pairs *t*-test accordingly. The comparison of baseline characteristics involved using the Chi-squared test for qualitative variables and the unpaired *t*-test along with the Mann-Whitney *U* test for quantitative variables. Unpaired *t*-tests and Mann-Whitney *U* tests were also applied for follow-up comparisons of both groups. The statistical significance of the difference is confirmed with *p* < 0.05.

**RESULTS**

All over, there were 83 tobacco users, out of whom 22 were smokers, 61 were using

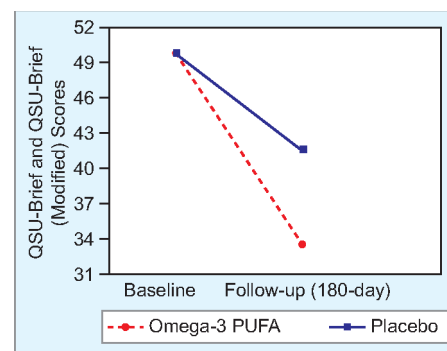


Fig. 4: Tobacco craving level (mean values) of regular tobacco users at baseline, after 180 days of daily supplementation of omega-3 PUFAs or placebo. Scores assigned to all 10 items of the questionnaire were summed up to yield a total score

smokeless forms. In the omega-3 PUFA group, 10 were smokers, and 33 were smokeless tobacco users, while in the placebo group, 12 were smokers and 28 were smokeless tobacco users.

The frequency of tobacco use per day did not have a significant difference (*p* = 0.1138) at baseline among the two groups. The subjects in the omega-3 PUFA group exhibited a significant decrease (*p* < 0.0001) from 10.19 ± 8.34 at baseline to 5.05 ± 4.83 after 180 days of supplementation in the frequency of tobacco use/day. Similarly, the placebo group also showed a significant decrease (*p* = 0.0001) from baseline to 180-day follow-up; however, their mean values had a minor difference, i.e., between baseline (6.95 ± 3.72) and follow-up (5.45 ± 3.85), representing a less significant decrease in frequency of tobacco use per day in the placebo group (Fig. 2). However, there was no significant change (*p* = 0.37) when we compared the follow-up of the omega-3 PUFA group with the placebo group (Table 2).

The difference in nicotine (tobacco) dependence was not statistically significant (*p* = 0.0642) between the omega-3 PUFA group (6.23 ± 2.21) and placebo group (5.58 ± 2.15) at baseline. The omega-3 PUFA group (*p* < 0.0001) and placebo group (*p* < 0.0001) showed a significant decrease in nicotine dependence after 180 days of supplementation, comparing their respective baselines to follow-up (Fig. 3). Moreover, no significant change (*p* = 0.0578) was found when the follow-ups of the omega-3 PUFA group were compared to the placebo group (Table 2).

There was no significant difference in tobacco craving between the omega-3 PUFA and placebo groups at baseline (*p* = 0.4461). The omega-3 (*p* < 0.0001) and placebo groups (*p* < 0.0001) showed a significant decrease in tobacco craving after 180 days of supplementation, comparing their respective baselines to follow-up (Fig. 4). Furthermore,

**Table 2:** Comparison of major findings (baseline-follow-up) within the group<sup>T</sup>

	Omega-3 PUFA baseline (n = 43)	Omega-3 PUFA follow-up (n = 43)	Placebo baseline (n = 40)	Placebo follow-up (n = 40)	p <sup>1</sup> value	p <sup>2</sup> value	p <sup>3</sup> value
Frequency of tobacco use per day	10.19 ± 8.34	5.05 ± 4.83	6.95 ± 3.72	5.45 ± 3.85	p < 0.0001***	p = 0.0001***	p = 0.37 <sup>ns</sup>
FTND and FTND-ST Scores	6.23 ± 2.21	3.44 ± 2.66	5.58 ± 2.15	4.6 ± 2.73	p < 0.0001***	p < 0.0001***	p = 0.0578 <sup>ns</sup>
QSU-brief and QSU-brief (Modified) Scores	49.7 ± 9.9	33.65 ± 10.72	49.53 ± 8.34	41.6 ± 10.77	p < 0.0001***	p < 0.0001***	p = 0.0012**

<sup>ns</sup> p > 0.05; \*\*p ≤ 0.01; \*\*\*p ≤ 0.001; <sup>T</sup>data are described as mean ± standard deviation; p<sup>1</sup>: comparison between the mean baseline and follow-up of omega-3 PUFA group; p<sup>2</sup>: comparison between the mean baseline and follow-up of placebo group; p<sup>3</sup>: comparison between the follow-ups of the two groups

on comparing follow-ups between the two groups, a significant difference (p = 0.0012) was observed in tobacco craving (Table 2).

## DISCUSSION

The role of omega-3 in smoking addiction has been a trending topic of controversial debate for the past two decades. It serves as a nutritional supplement by supplementing with omega-3s, particularly EPA and DHA. It plays an ambiguous role by decreasing both the incidence of smoking and cigarette cravings. Hence, the present study evaluates the effect of omega-3 PUFA's (ALA) daily supplementation for 180 days on tobacco intake frequency/day, nicotine dependence, and tobacco craving. Moreover, we have attempted to explore the research not only on smokers but also on smokeless tobacco users.

Various studies have been conducted to show the beneficial effects of omega-3 FAs (EPA and DHA) on smokers, which we have discussed. Scaglia et al. demonstrated a negative and statistically significant association between the consumption of omega-3 FA-rich fish and smoking, with smokers consuming less of these foods compared to nonsmokers.<sup>7</sup>

The deficiency or lower concentrations of omega-3 FAs affect dopaminergic neurotransmission, leading to hypofunctioning of the mesocortical and mesolimbic pathways responsible for reward sensation.<sup>41-43</sup> Also, this hypofunctioning, in turn, might result in a higher craving reflex and impede smoking-quit efforts. Therefore, re-establishing omega-3 PUFA levels in the body may reduce tobacco consumption.<sup>13</sup> The association between omega-3 FAs and smoking addiction has been demonstrated by the reduced levels of omega-3 FAs observed in smokers.<sup>7-9,44</sup> Not only tobacco addiction but also omega-3 PUFA effects intake of other addictive substances such as alcohol, cocaine, opioids, by replenishing the brain's function, reducing sensitization to dopamine on substance abuse.<sup>45-47</sup> The physiology behind craving is its association with dopaminergic pathways, which leads to

the sensation of craving tobacco in dopamine's absence.<sup>48</sup> Partial agonists at the α4β2 nicotinic acetylcholine receptor (α4β2 nAChR) can promote the release of adequate dopamine to alleviate cravings by inhibiting nicotine binding and its subsequent reinforcing effects.<sup>49,50</sup>

A study performed by Sadeghi-Ardekani et al. reported a greater reduction in nicotine dependence, cigarette craving (QSU scores), and frequency of cigarettes smoked per day among heavy smokers in the omega-3 FA group (fish-oil-derived omega-3 FA) compared to the placebo group for 3 months, and the difference between the two groups increased from baseline to 3-month follow-up.<sup>51</sup> This study supports our study for the effect of a decrease in frequency of tobacco use per day, dependence, and craving among tobacco users. However, significant changes in these characteristics in the placebo group could be due to the placebo effect. Alternatively, in a different experiment, DHA supplementation was administered to a small group of smokers for a few weeks at a low dose, without a control group, and did not result in a decrease in the number of cigarettes smoked during the treatment period.<sup>52</sup>

Furthermore, interventions done among women in the form of a single session of brief intervention or simple advice to quit tobacco were able to show a statistically significant difference in the number of tobacco chews per day and FTND scores.<sup>53</sup> Similarly, we also state a significant change in the frequency of tobacco use per day and its dependence, but with a nutritional intervention and not a behavioral intervention (for quitting tobacco), as reported by the above-mentioned study. Moreover, higher rates of smoking cessation were documented by a significant decrease in measures of nicotine dependence on the FTND scale (from baseline to follow-up) in a group (51%) provided with a combination of nicotine replacement therapy (nicotine gum) and individual counselling as compared to another group (8%) only receiving NRT and simple advice.<sup>54</sup> Corresponding to this, other drugs such as bupropion SR,<sup>55</sup> varenicline,<sup>56</sup> and buprenorphine-naloxone<sup>57</sup> have proven their

efficacy to decrease tobacco craving, tobacco dependence, and tobacco use frequency per day, respectively. On a contrasting note, our research centered on the role of a dietary supplement (omega-3 PUFA) without pharmacological intervention and has sustained a significant change in the results of tobacco dependence, its craving, and its frequency of use per day in the omega-3 PUFA group.

More intriguingly, a Brazilian study<sup>58</sup> reported that supplementation (90 days) of fish oil capsules (omega-3-PUFA) and mineral oil (placebo) was accompanied by a significant reduction (p = 0.03) in the levels of nicotine dependence, according to the FTND test. Our study results agree with these findings, as we have also found a significant reduction in nicotine dependence among tobacco users. Rabinovitz conducted a randomized, placebo-controlled study involving 48 regular cigarette smokers. The study found that intake of 2710 mg of EPA and 2040 mg of DHA per day over 1-month significantly reduced self-reported daily smoking and cravings for tobacco.<sup>22</sup> Similarly, our study elucidates that omega-3 FAs were effective in significantly reducing the levels of tobacco craving, as observed in the study by Rabinovitz.

## CONCLUSION

This study, performed in regular tobacco users with daily supplementation of omega-3 PUFAs for 180 days (10 mL/day), found a significant decrease after the follow-up (180 days) in the frequency of tobacco use per day, its dependence (measured by FTND), as well as decreased craving (measured by QSU-Brief) when compared to baseline. The findings of our study indicate that daily supplementation with omega-3 FAs could play a promising role as an adjuvant tool in reducing nicotine dependence levels as well as tobacco cravings. Despite certain limitations, including a small sample size and the assessment of omega-3 PUFA in serum, this study offers valuable insights. Additionally, the study was open to participants of both sexes, though the number of females recruited was very small. This study helps in providing a noteworthy

direction towards further research on both forms of tobacco (smoking as well as smokeless) and nonpharmacological management for tobacco cessation.

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## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

Anjali Singh, data collection, analysis, interpretation of the results and writing the manuscript; Narsingh Verma, conceptual idea, study framework designing and supervision; Surya Kant, subject enrollment, reviewing and critical feedback; Ajay Kumar Verma, subject enrollment, reviewing and critical feedback; Adarsh Tripathi, verified the analytical methods; Kshitij Bhardwaj, supplied necessary resources and supplements.

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