INTRODUCTION

Tobacco smoking remains a leading cause of preventable mortality and morbidity [1]. Smoking was the leading risk factor for cancers and chronic respiratory disease, and was the second-leading risk factor for attributable mortality, following high-systolic blood pressure [2]. The prevalence of smokers in Indonesia was the highest in Southeast Asia [3] and the third worldwide after China and India [2]. There are many treatments available for a subject who have smoking addiction, but cessation rates in most clinical trials of these therapies still far from expectations [4]. Several recent reports showed that increased reactive oxygen species (ROS) in nucleus accumbens modulate the reinforcing effect of drug abuse [5]. Nicotine induction elevated ROS levels in significant amounts in mesencephalic mouse cells [6] leading to an increased superoxide dismutase (SOD) activity [7]. Quercetin commonly known as antioxidants, acts directly as free radicals scavenger and modulate endogenous antioxidants through Nrf2 activations [8]. Decreased ROS and increased endogenous antioxidants by quercetin may be involved in inhibited reward signaling in the mesolimbic dopaminergic pathway associated with the reinforcing effect of nicotine.

OBJECTIVE

This research aims to evaluate quercetin effects on reducing the risk of nicotine addiction. We evaluated this, in male Balb/C mice, by tested the quercetin administering along with nicotine or cigarette smoke extract (CSE) as an addictive agent then we observed the developed reward effect.

METHODS

The Conditioned Place Preference (CPP) using two compartments was used to evaluate the reward effect [9]. The tests comprised of three different stages namely pre-conditioning, conditioning, and post-conditioning continued with the extinction and the reinstatement stage.

Pre-conditioning test (day 1)

The test performed by placing the mice in a central choice area between the parts of the apparatus then allowed them to access the compartments for 15 min. Each subject’s least preferred compartment was paired with the drug and the most preferred compartment was paired with the drug’s vehicle [9].

Conditioning test (day 2-4)

The conditioning test was carried out for three days, 2 times daily (09.00 am and 03.00 pm) on the selected CPP chamber with a closed partition for 30 min. Mice were received saline 1 ml/kg in the morning and in the afternoon they received treatment (nicotine 0.5 mg/kg, cigarette smoke extract (CSE) 0.5 mg, or along with quercetin 50 mg/kg) depending on the assigned test groups. On the next day, all mice received treatments with a switched schedule between morning and afternoon from the previous day.

Post-conditioning test (day 5) and Extinction test (day 6,8,10,12)

The procedures performed were the same as the procedures performed in the pre-conditioning test.

Reinstatement test (day 13)

Mice were re-injected with nicotine or CSE by giving quercetin 60 minutes in advance, after 10 minutes, mice were put into the drug-paired chamber (15 min) for observation.

RESULTS

Figure 1: Quercetin inhibits the reward effect of nicotine. Conditioned place preference score (post-conditioning – pre-conditioning tests) spent in the non-preferred chamber of the P4 and P5 groups did not increase significantly compared to the P2 and P3 groups. Quercetin administered 60 min before nicotine or CSE in the conditioning phase. Each column represents the mean ± SEM of 5 mice, *p<0.05; **p<0.01. CSE, cigarette smoked extract. P1: normal control, saline 1 ml/kg; P2: nicotine 0.5 mg/kg; P3: CSE contained nicotine 0.5 mg/kg; P4: Quercetin 50 mg/kg + nicotine 0.5 mg/kg; P5: Quercetin 50 mg/kg + CSE contained nicotine 0.5 mg/kg.

Figure 2: Assessment of drug-seeking behavior (craving and relapse to an addictive agent). The duration of the extinction training was insignificant compared to the post-conditioning test. Quercetin administration in the reinstatement test prevented relapse even though it was not significant. Each column represents the mean ± SEM of 5 mice. CSE, cigarette smoked extract.

CONCLUSIONS

Our study demonstrated that quercetin has a potential effect to reduce development of nicotine dependence. Quercetin or a diet containing quercetin may become a prospective supplementation or adjuvant therapy for preventing nicotine addiction.

References