Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

# Modulation in Airway Smooth Muscle Reactivity and Improvement in Lung Function of Cigarette Smokers and Passive Non-smokers Following *Garcinia kola* treatment

Ogechukwu K. Uche* and Masagbor F. Otimize

*Department of Physiology, School of Basic Medical Sciences, University of Benin, PMB 1154, Benin City. 300-001, Nigeria.*

ARTICLE INFO

*Article history:*
Received 14 October 2017
Revised 26 October 2017
Accepted 27 October 2017
Published online 05 November 2017



ABSTRACT

Inhalation of tobacco smoke is a major risk factor for the development of airway hyperreactivity (AHR) in non-cigarette smokers and increase respiratory distress in smokers. *Garcinia kola* has been linked to smooth muscle relaxation and may ameliorate obstruction and resistance to airflow. This study examined the effect of *Garcinia kola* on airflow and reactivity of the airway smooth muscles (ASM) of asymptomatic regular cigarette smokers (CS) and passive non-smokers (PNS) following 10 minutes cigarette smoking and exposure to cigarette smoke. Sixty apparently healthy male undergraduate students comprising cigarette smokers and non-smokers volunteered as subjects. Changes in peak expiratory flow rate (PEFR) in L/min in CS and PNS was measured with Spirometer before and after 10 minutes of smoking and/or exposure to cigarette smoke. Thereafter, half the population of CS and PNS were given *G. kola* (200 mg/kg body weight) and PEFR measured at intervals of 30 minutes for a maximum of 90 minutes. Peak expiratory flow rate significantly decreased ($p < 0.05$) following 10 minutes of smoking and exposure to smoke in both CS and PNS, however, *G. kola* ingestion marginally increased PEFR values significantly at 30, 60 and 90 minutes intervals. Comparatively, increase in PEFR was greater in PNS than in CS ($P < 0.05$) treated with *G. kola* and climaxed at 60 minutes. Conclusively, cigarette smoking and exposure to cigarette smoke compromise lung function with a decrease in peak expiratory flow rate. *G. kola* treatment significantly reversed this trend, cleared the airways, enhanced airflow and improved lung function.

***Keywords***: *Cigarette smoke, Garcinia kola, PEFR, Airway reactivity.*

## Introduction

Smoking is the most common method of consuming tobacco, which is often mixed with additives and then pyrolyzed, and tobacco is the most common substance smoked.[1] During cigarette smoking, nicotine and over 19 known carcinogens (most collectively known as tar, the major chemical constituents that make up the cigarette) and more than 4000 other chemicals[2] are released into the air. The resulting potentially noxious vapours are then inhaled and the active substances are absorbed through the alveoli in the lungs into the bloodstream.[3,4] Cigarette smoking is well known as the most important causative factor for chronic obstructive pulmonary disease (COPD) and bronchogenic carcinoma.[5] Previous studies have also reported the harmful influence of cigarette smoke in the development and/or the exacerbation of asthma[6] and increased morbidity and mortality from asthma in individuals who smoke.[7] Passive smoking is the inhalation of smoke, also called second-hand smoke (SHS) or environmental tobacco smoke (ETS) from tobacco products used by others.[3] More recent studies have confirmed that exposures to ETS are associated with higher prevalence of acute respiratory symptoms and the increase risk of chronic bronchitis and asthma in adults.[8] Epidemiological studies demonstrated an increase in coronary artery disease (CAD) events and mortality with exposure to SHS.[9]

*Corresponding author. E mail: oge.uche@uniben.edu
Tel: +2348037245912

**Citation:** Uche OK and Otimize MF. Modulation in Airway Smooth Muscle Reactivity and Improvement in Lung Function of Cigarette Smokers and Passive Non-smokers Following *Garcinia kola* treatment. Trop J Nat Prod Res. 2017; 1(5):209-212. doi.org/10.26538/tjnpr/v1i5.7



ETS constitutes a major and preventable public health risk as it reportedly causes diseases, disability and death.[10] Thus, the inhalation of tobacco smoke, either via direct smoking or passive exposure, is a major risk factor for the development of airway hyperreactivity (AHR) with increased respiratory symptoms[11] and airway resistance.

*Garcinia kola* Heckel (Family: Guttiferae) also called bitter kola because of its astringent, bitter resinous taste is known to be rich in biflavonoids complex.[12-14] The pharmacological properties and medicinal values of *G. kola* Heckel plant are widely reported and linked with various bioactive compounds including *Garcinia*-biflavonoids GB-1, GB-2 and kolaflavanone with high antioxidant and safety profile.[15] Previous studies have established the hepatoprotective,[16,17] gastroprotective,[18] hypolipidemic, hypoglycaemic[19] and anti-asthmatic[20] effects of *G. kola* on experimental animal models. It has also become increasingly apparent that *G. kola* inhibits smooth muscle activity.[21,22,12] Administration of kolaviron (a *Garcinia kola*-fraction) on isolated rabbit aortic and carotid blood vessels caused vasorelaxation following precontractions with phenylephrine, histamine and 80 mM $K^+$.[23] However, there is a paucity of information on the acute effect of *G. kola* in airflow modulation and airway reactivity of respiratory smooth muscle cells following cigarette smoking and/or exposure to smoke in asymptomatic regular cigarette smokers and passive non-smokers. The present study was designed to evaluate the acute effect of *G. kola* administration on the reactivity of the bronchotracheal smooth muscles and modulation of air flow in apparently healthy regular cigarette smokers and passive non-smokers.

## Materials and Methods

A total of sixty (60) male undergraduate students volunteered for the study. There were no female volunteers as smoking is not an acceptable cultural habit to be associated with women in Nigeria. The volunteers that

smoked where mainly regular smokers who smoked at least half a packet of cigarettes a day. They all filled questionnaires which provided adequate information about personal, familial, medical history, smoking habits of each subject prior to participation, environmental characteristics, sex, age, and anthropometric data and were not on any medication. Volunteers gave informed consent for the study. Lung function was measured with a Spirometer (Samson Right's Students Spirometer, England). After explanation and demonstration of its use, each subject performed at least three acceptable manoeuvers with a nose clip. The best maximal effort test was considered and used for the statistical analysis.

Sixty apparently healthy adult male undergraduate students between the ages of 25-30 years volunteered for this study. The subjects were assigned into groups: Group A were regular cigarette smokers and Group B passive non-smokers. Group A subjects smoked a stick of cigarette each in the laboratory room while subjects in Group B were exposed to the cigarette fumes for a period of 10 minutes during the smoking. This study measured the changes in PEFR in CS and PNS before and immediately after smoking and or exposure to cigarette smoke, respectively. Thereafter, *G. kola* was administered to half of the CS and PNS and their PEFR measured at intervals of 30 minutes, 60 minutes and 90 minutes. Measurements of PEFR was repeated in the sub-groups of CS and PNS that were not given *G. kola*. All measurements of PEFR were done in the sitting down position of the subjects.

### Statistical analysis

Data are presented as Means ± SEM (standard error of means). Comparison of the means was effected using the Student's t-test, ANOVA and Microcal origin 8.0 statistical package. P-Values less than 0.05 ($P < 0.05$) were considered statistically significant for two independent variables (test and control).

## Results and Discussion

*Effect of cigarette smoking and exposure to smoke on PEFR*

Following the smoking of a stick of cigarette by CS and exposure to smoke in PNS for a period of 10 minutes, PEFR in L/min measured before and immediately after a period of 10 minutes of smoking and/or exposure to cigarette smoke showed that there were significant ($P < 0.05$) decreases in PEFR values after a period of 10 minutes of smoking in CS (318.50 ± 7.96; 291.50 ± 8.11) and in PNS (484.50 ± 15.24; 459.50 ± 15.84).

*Effect of G. kola administration on PEFR after smoking and exposure to smoke*

Following the administration of *Garcinia kola* after smoking a stick of cigarette by regular CS and exposure to smoke in PNS for a period of 10 minutes, PEFR values marginally increased significantly ($P < 0.05$) at 30, 60 and 90 minutes intervals (348.00 ± 16.45, 374.00 ± 16.94 and 336.00 ± 14.08 at 30, 60 and 90 minutes, respectively) in smokers administered with *G. kola* in comparison to smokers that did not receive *G. kola* during the same time intervals (271.00 ± 8.09, 305.00 ± 5.00 and 307.00 ± 4.73 at 30, 60 and 90 minutes, respectively) (Figure 2), whereas in PNS, PEFR significantly ($P < 0.05$) increased during measurement at same time intervals (478.00 ± 22.65, 521.00 ± 28.25 and 509.00 ± 22.53 at 30, 60 and 90 minutes, respectively) in contrast to the sub-group of PNS that did not receive *G. kola* (414.00 ± 23.39, 487.00 ± 19.23 and 475.00 ± 19.90 at 30, 60 and 90 minutes, respectively) (Figure 3).

The results of airway reactivity and modulation of pulmonary airflow in cigarette smokers and passive non-smokers following oral administration of *Garcinia kola* after smoking a stick of cigarette and exposure to cigarette smoke comparatively showed that peak expiratory flow rate (PEFR) in L/min was statistically significantly less in the regular cigarette smokers (CS) than in passive non-smokers (PNS) before and after smoking or exposures to cigarette smoke (Figure 1). This observation is in line with previous reports.[24-27] Smoking which is the major process of tobacco consumption has been widely reported to have a deleterious effect on the respiratory airways by decreasing various indices of lung function including: Forced expiratory volume in one second ($FEV_1$), Forced vital capacity (FVC) and PEFR.[28] Furthermore, inhalation of cigarette smoke by PNS which contains many of the same carcinogenic and toxic substances as mainstream smoke inhaled by active smokers have an immediate effect on respiration by inducing airway bronchotracheal

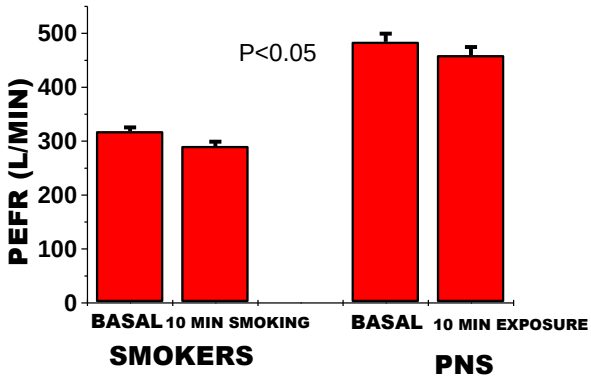


**Figure 1:** The effect of 10-minute cigarette smoking in smokers and exposure to smoke in PNS on PEFR (L/min). PEFR was less in smokers than in PNS and significantly ($p < 0.05$) decreased after cigarette smoking and exposure to smoke in smokers and PNS. Values are means ± SEM. N = 60.

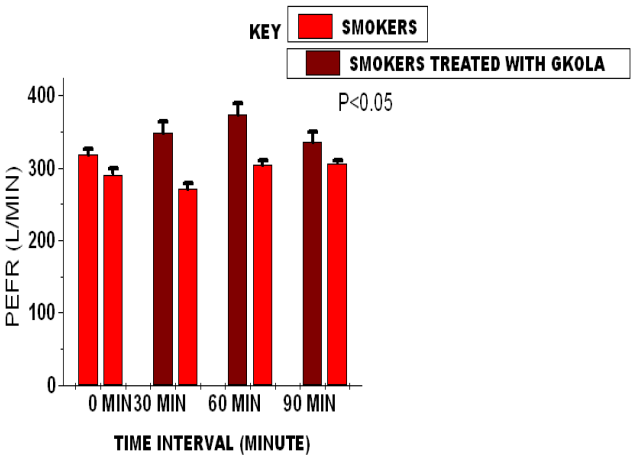


**Figure 2:** The effect *G. kola* (200 mg/kg bw) oral administration in PEFR (L/min) in smokers. PEFR marginally increased significantly ($p<0.05$) and higher than basal PEFR value in smokers treated with *G. kola* in comparison with those that were not given and climaxed after 60 minutes. Values are means ± SEM. N = 40.

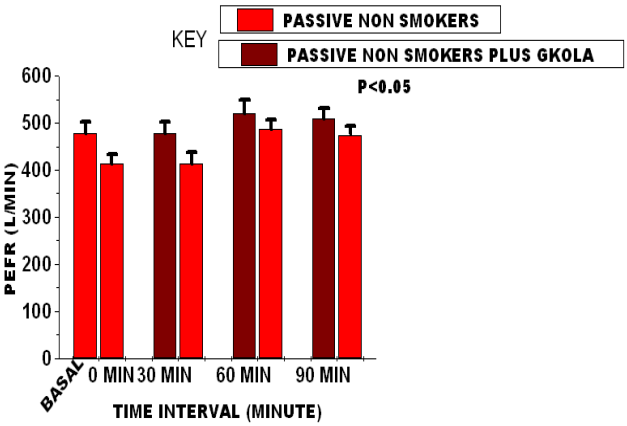


**Figure 3:** The effect of *G. kola* (200 mg/kg bwt) oral administration on PEFR (L/min) in PNS following exposure to cigarette smoke. PEFR significantly ($p < 0.05$) increased in the subjects treated with *G. kola* after exposure to smoke in comparison with those that were not given and climaxed at 60 minutes. Values are mean ± SEM. N = 40.

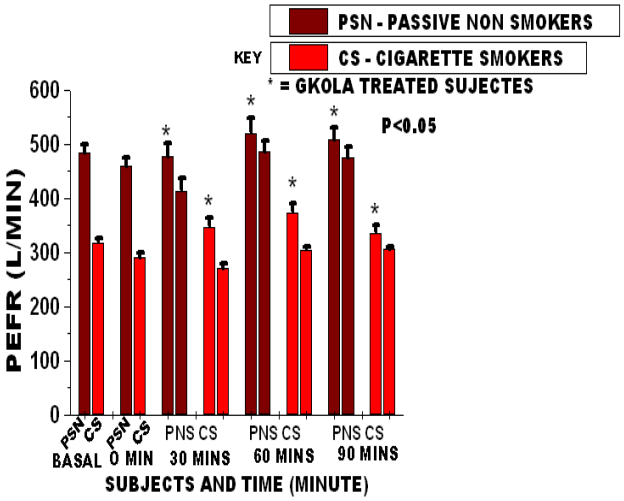


**Figure 4:** Comparative changes in PEFR (L/min) after treatment with *G. kola* following cigarette smoking and exposure to smoke. PEFR was significantly ($p < 0.05$) less in smokers than PNS, but significantly increased in the subjects treated with *G. kola* in both CS and PNS, However, changes in PEFR was more marked in CS than in PNS. Values are means ± SEM. N = 40.

hyperresponsiveness (ABHR) in mucosal epithelial cell lining and increasing airway resistance thereby limiting pulmonary function of ventilation as observed in decreased PEFR (Figure 1). The decrease in PEFR could also be as a result of the inflammatory swelling of the mucus membrane of the respiratory airway activated by inhalation of pernicious cigarette smoke leading to increase in bronchomotor tone and airway resistance. The measured index, PEFR is generally considered as a sensitive indicator for changes in elastic recoil pressure and/or the resistance to airflow in medium and small airways.[29] It is also a useful parameter to monitor airway obstruction, assess its severity and variation and evaluate the effects of treatment.[24] Previous studies have also reported the influence of cigarette smoke in the development and/or the exacerbation of asthma,[7] tracheal hyperresponsiveness to receptors agonists (carbachol and endothelin-1),[13] bronchitis, emphysema and lung cancer,[30,31] chronic obstructive pulmonary disease,[26,32] cerebrovascular disease and risk factor for cardiovascular disorders.[33]

Following oral administration of Gkola however, PEFR progressively increased significantly ($p<0.05$) at time intervals of 30 minutes, 60 minutes and 90 minutes respectively in both CS and PNS in comparison with those that did not receive Gkola. The increase in PEFR was at its maximum 60 minutes after oral administration of Gkola both in CS and PNS. Also in the subjects that were not given Gkola, PEFR dropped steadily within the first 30 and 60 minutes but then increased gradually afterwards during the recovery phase. Several broncho constrictor and dilatory substances are known to influence airways reactivity with consequent modulations in airflow rate in the pathways.[6,9] The pharmacological properties and medicinal values of *Garcinia kola* is linked with various bioactive compounds including *Garcinia* biflavonoids GB-1, GB-2 and *kola* flavanone.[13,14] which have been shown to be effective smooth muscle relaxants,[12,18,22] potent antioxidant,[14-16, 34] anti-inflammatory and antigenotoxic agents believed to result from inhibition of cyclo-oxygenase enzyme, a mechanism associated with chemoprevention against carcinogenic substances.[35] We have recently shown a considerable evidence linking kolaviron, a biflavanoid-complex of *Garcinia kola* seed to vascular smooth muscle relaxation in isolated rabbit aortic arterial rings following precontractions with agonists through receptor operated $Ca^{2+}$ channels (ROCCs) and voltage-operated $Ca^{2+}$ channels (VOCCs).[23] Therefore the increase in PEFR observed in both cigarette smokers and passive non-smokers after *Garcinia kola* administration could be attributed to *G. kola*-induced relaxant effect on bronchotracheal smooth muscles of the respiratory airways and its anti-inflammatory action against mucosal tissue damage and airway hypereactivity resulting in concomitant decrease in airways resistance to airflow and subsequent increase in peak expiratory flow rate. Several bronchoconstrictor and dilatory substances are known to influence airways reactivity with consequent modulations in airflow rate in the pathways. It is in particular the receptors that mediate contraction or relaxation of airway smooth muscles with consequences for control of the bronchial lumen diameter and thus pulmonary ventilation.[6,7,36]

## Conclusion

Cigarette smoking and exposure to smoke have an immediate effect in respiration inducing airway hyperreactivity and bronchotracheal smooth muscle constriction resulting in increased airway resistance and subsequent decrease in lung function and modulation to airflow. Increase in peak expiratory flow rate in cigarette smokers and passive non-smokers following *Garcinia kola* treatment in this study enhances expiratory flow rate by possibly decreasing airway resistance and improving airflow. This may be due to the dilatory effect of *G. kola* on the airway smooth muscles and its anti-inflammatory effect.

## Conflict of interest

The authors declare no conflict of interest.

## Authors' declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

## Acknowledgement

The assistance of Dr. O.I. Ajayi of Physiology Department, University of Benin, Benin in providing the Spirometer for the lung volume measurements is gratefully acknowledged.

## References

1. Wingand JS. Additives, Cigarette Design and Tobacco Product Regulation. WHO (Tobacco free initiative). 2006:1-45.
2. Winstanley M, Woodward S, Walker N. Tobacco in Australia, Facts and Issues, Austr Ann Med. 1995; 16:31-40.
3. Penn A, Chen LC, Snyder CA. Inhalation of steady state Sidestream smoke from one cigarette promotes atherosclerotic plaque Development. Circulation 1994; 90(3):1363-1367.
4. Iyawe VI, Ebomoyi MI, Oboh HA. The effect of a single cigarette puff on air flow in the lungs. J Med Bio Res. 2007; 5(1&2):4-12.
5. Jeneth Berlin Raj T, Loganyaki R, Rajakumar D. Effect of cigarette smoking on forced expiratory lung volumes in asymptomatic smokers. Int J Cur Res Rev. 2013; 05(10):38-42.
6. Cao L, Zhang Y, Cao YX, Edvinsson L, Xu CB. Cigarette smoke upregulates rat coronary artery endothelin receptors *in vivo*. PLoS One. 2012; 7:e33008.
7. Chalmers GWC, Macleod KJ, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroids treatment in mild asthma. Thorax 2002; 57:226-230.
8. Gerbase MW, Schindler C, Zellweger J, Ku¨nzli N, Downs SH,Brandli, Joel Schwartz, Martin Frey, Luc Burdet, Their Rochat, Ursula Ackermann-Liebrich, Philippe Leuenberger Respiratory Effects of Environmental Tobacco Exposure Are Enhanced by Bronchial Hyperreactivity. Am J Resp Crit Care Med. 2006; 174:1125-1131.
9. Stuart JH, Krishnankutty S, Richard ES, Bo-Qing Z, Yi-Ping S, Tony MC, Chatterjee K, Deedwania PC, Cooke JP, Glantz SA, Parmley WW. Effects of L-Arginine on Artherogenesis and Endothelial Dysfunction due to Second hand Smoke. Hypertension 1999; 34:44-50.
10. World Health organization. Framework on Tobacco Control "Parties recognize that scientific evidence has unequivocally established that exposure to tobacco causes death, disease and disability" WHO 2005; 5-6.
11. Cao L, Yaping Z, Yong-Xiao C, Lars E, Cang-Bao XU. Second hand Smoke Exposure Causes Bronchial Hyperreactivity via

Transcriptionally Upregulated Endothelin and 5-hydroxytryptamine 2A Receptors. PLoS ONE. 2012; 7(8):e4417017.
12. Adaramoye OA and Medeiros IA. Endothelium-independent vasodilation induced by kolaviron, a biflavonoid complex from *Garcinia kola* seeds, in rat superior mesenteric arteries. J Smooth Muscle Res. 2009; 45(1):39–53.
13. Adegboye MF, Akinpelu DA and Okoh DI. The bioactive and phytochemical properties of *garcinia kola* (Heckel) seed extract on some pathogens. Afr J Biotech. 2008; 7(21):3934-3938.
14. Iwu MM, Igboko OA, Onwuchekwa U, Okunji CO. Evaluation of the antihepatotoxicity of the biflavonoids of *Garcinia* kola seeds. J Ethnopharmacol 1987; 21:127-142.
15. Olayinka TE, Ore A, Fashiku KA. Kolaviron and L-Ascorbic acid ameliorates Chlorambucil-Induced Hepatic and Renal Toxicity in Rats. Int J Tox App Pharm. 2014; 4(1):23-32.
16. Farombi EO. Mechanisms for the hepatoprotective action of kolaviron studies on hepatic enzymes microsomal lipids and lipid peroxidation in carbon tetrachloride treated rats. Pharmacol Res. 2000; 42:75-80.
17. Adaramoye OA and Adeyemi EO. Hypoglycaemic and hypolipidaemic effects of fractions from kolaviron, a biflavonoid complex from *Garcinia* Kola in streptozotocin-induced diabetes mellitus rats. J Pharm Pharmacol. 2006; 60:121–128.
18. Udia PM, Braide VB, and Owu DU. Antispasmodic and Spasmolytic Effects of Methanolic Extract from Seeds of *Garcinia* Kola on Isolated Rat Small Intestine. Nig J Physiol Sci. 2009; 24(2):111 -116.
19. Ayepola RA, Chegou NN, Brooks NL and Oguntibeju OO;. Kolaviron, a *Garcinia* biflavonoid complex ameliorates hyperglycemia-mediated hepatic injury in rats via suppression of inflammatory responses. BMC Compl and Alt Med. 2013; 13:363-372.
20. Ibulobo MT, Eze GI, Ozolua RI, Baxter-Grillo D, Uwaya DO. Evaluation of the protective and ameliorative properties of *Garcinia* kola on histamine-induced bronchoconstriction in guinea pigs. Pharmacog Res. 2012; 4(4):203-207.
21. Braide VB. Antispasmodic extracts from seeds of *Garcinia* kola. Fitoterapia 1989; 10:123-129.
22. Orie NN and Ekon EU. The bronchodilator effect of *Garcinia kola*. East Afr. Med. J. 1993; 70:143-145.
23. Uche OK, Baseerah EB, Anukam CK. Mechanism of kolaviron-induced relaxation of aortic smooth muscle. J Afr. Ass Physiol Sci. 2014; 2(1):142-148.
24. Tambi M, Rao B N, Glad M I., Praveen K M. Effects of cigarette and cigar smoking on peak expiratory flow rate. J Clin Diag Res. 2013; 7(9):1886-1889.
25. Hussain G, Zafar S, Cha A, Chz A, Ahmad MZ. Comparative Study of Peak Expiratory Flow Rate in Cigarette Smokers and Non-Smokers of Lahore District. Annals of KEM 2007; 13(4):255-259.
26. Karia RM. Comparative study of peak expiratory flow rate and maximum voluntary ventilation between smokers and non-smokers. Nat. J Med Res. 1998; 2(2):191-193.
27. Abdul RA, Ghulam AKN, Ammad AC. Smoking related airflow limitation in asymptomatic healthy adults. Rawal Med J; 2014; 39(4)381-385.
28. Liston J. Breast feeding and the use of recreational drugs-alcohol, caffeine, nicotine and marijuana. Breast-feed Res. 2012; 2:27-30.
29. Josh LN and Hoshia VD. Effect of forced breathing on ventilatory function of lungs. J Postgrad Med. 1998; 44(3):67-69.
30. Wynder EL and Muscat JE. The changing epidemiology of smoking and lung cancer histology. Env Health Persp. 1995; 103(8):143-148.
31. Jeremy PT, Jane W, Charles MW. The respiratory system at a glance, 3rd ed., Wiley-Blackwell. 2006; 11-26 p.
32. Fozia F, Sadia F, Muhammad MN, Munir A, Raheel J, Muhammad S, Muhammad JS, Sana U. Comparison of peak expiratory flow rate and lipid profile in asymptomatic smokers and non-smokers. Ayub Med Coll Abbottabad 2015; 27(1):55-60.
33. Vijayan VK. Chronic obstructive pulmonary disease. Ind J Med Res. 2013; 137(2):251-269.
34. James DB, Adejor EB, Ameh DA, Kadejo AO, Taiye O. Preventive and Therapeutic Effects of *Garcinia* kola Bi-flavonoid Fractions on some Haematological Parameters of P407 Induced Hyperlipidemic Albino Rats. J Nat Remed 2014; 14(1):2320-3358.
35. Liang YC, Huang YT, Tsau SH, Lin-Shiau SY, Chen CF, Lin JK; Suppression of inducible cyclooxygenase and inducible nitric acid synthase by apigenin and related flavonoid in mouse macrophages. Carcinogenesis 1999; 20:1945-1952.
36. Lei C, Yaping Z, Yong-Xiao C, Lars E, and Cange-Bao X;. Second hand smoke exposure causes bronchial hyperreactivity via transcriptionally upregulated endothelin and 5-hydroxytryptamine 2A receptors. PLoS One 2012;7(8): e44170.