



Effect of antioxidant activity of *Tinospora cordifolia* on the hemato-biochemical profile in Wistar rats exposed to passive smoking

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ABSTRACT

Passive and active exposure to cigarette smoke is a major leading cause of preventable diseases in humans and animals. Therefore, the main aim of the present study was to investigate the dose-dependent effect of *Tinospora cordifolia* (TC) fresh aqueous leaf extract on hematological and biochemical changes in rats exposed sub-chronically to filtered and non-filtered cigarette smoke. Healthy and adult albino rats of both sexes were exposed to filtered (FC) and non-filtered cigarette (NFC) cigarette smoke for 1 hr/day. The effect of two different doses of TC was studied in these rats. The study was conducted in 2 phases to observe the effect of FC and NFC and the effect of TC after 30 and 60 days. The results clearly confirmed that sub-chronic passive exposure to cigarette smoke had damaging effects on hemato-biochemical profile of rats and that these effects were modulated in groups supplemented with TC leaf extract. The parameters studied were DLC, ESR, AST, ALT, urea, creatinine and blood glucose. It may be concluded that TC extract supplementation attenuated the harmful effects on hematological and biochemical parameters of rats sub-chronically exposed to passive smoke. Thus, the antioxidant property of TC helps to boost the immune system of the body, which is regularly exposed to passive smoking.

Keywords: Filtered cigarette, Non-filtered cigarette, *Tinospora cordifolia*, Hemato-biochemical profile, Albino rat.

INTRODUCTION

Active and passive smoking is a significant cause of morbidity among the global population and is one of the modifiable risk factors for preventable mortality (Lodovici *et al.*, 2004; Nazeem, 2015; Singh and Lal, 2011). Approximately 1 to 1.5 million people die every year in India due to the consequences of smoking (WHO, 2017). India has more than 300 million smokers, and approximately 5500 youth initiate the use of tobacco every day. Numerous chemical substances, some of which are directly harmful and may cause human cancer or mutagenesis, are found in tobacco smoke (IARC, 2004). In addition, carbonyls from

cigarette smoke have been related to leukemia and have been found to irritate the respiratory system of nonsmokers, trigger asthma attacks, and hence are otherwise considered to pollute indoor air (Marchand, 2006; Pang, 2007).

Through secondhand smoke (SHS) exposure, tobacco smoke also negatively affects the health of nonsmokers. Secondhand smoke (SHS) is a combination of the mainstream smoke that smokers exhale and sidestream smoke produced by the burning end of tobacco items. SHS exposure is linked to major health issues such as cancer, lung ailments, and heart disease and is just as dangerous as active smoking. Worldwide, there are more than 1 billion smokers, who may expose everyone else to SHS. Over 600,000 premature deaths occur annually due to SHS exposure worldwide. There is no safe threshold of SHS exposure; even a small amount might have negative health effects (US Department of Health and Human Services, 2016; Reddy *et al.*, 2018).

In cigarettes, tobacco is a commonly used substance that unfavorably affects all the systems in an organism due to the large number of oxidant mediators in its content. Circulating levels of biochemical markers such as creatinine, urea, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) indicates that smoking causes more damage to tissue and impairs the function of some organs (Brzoska *et al.*, 2013). Smoking cigarettes results in a cellular ROS-driven oxidative burst as well. Cellular antioxidant defense mechanisms, which include both enzymatic and nonenzymatic defense systems, regulate the potential negative effects of ROS. The tissue defense system is overwhelmed when there is a severe buildup of free radicals from exogenous sources added to endogenous production, which causes oxidative damage to the tissues (Halliwell, 1994). Smokers have acute antioxidant insufficiency as a result of having to use up all the body's antioxidant reserves to detoxify the alarmingly high amount of these free radicals, making them more susceptible to developing life-threatening disorders (Zondervan *et al.*, 1996). Exogenous antioxidant supplementation has a protective role to play when the body's natural antioxidant defense mechanism is insufficient to eradicate too many free radicals (Rekha *et al.*, 2001). Numerous naturally occurring micronutrients and antioxidants have been demonstrated in experimental studies to be effective preventative measures against oxidative stress caused by cigarette smoking (Anbarasi *et al.*, 2006; Dilsiz *et al.*, 1999; Florek *et al.*, 2009; Hsu *et al.*, 2009). From this perspective, it was intended to assess the protective effect of *Tinospora cordifolia* against oxidative damage caused by filtered and unfiltered cigarette smoke.

Tinospora cordifolia (belongs to the family Menispermaceae; also known as Guduchi or Giloy) is a large deciduous, perennial climbing shrub found throughout India and China with glabrous leaves and fleshy stems (Chi *et al.*, 2016; Singh *et al.*, 2003). The medicinal properties of this plant are due to its several phytoconstituents, for example terpenes, glycosides, alkaloids, steroids and flavonoids (Singh *et al.* 2016; Van Kiem *et al.* 2010). Since ancient times, India has been extensively using both folk medicine and the Ayurvedic medical system. For medicinal purposes, the entire plant is being used. The plant is said to be bitter but harmless, and it can also scavenge free radicals. The plant produces a number of distinct components that are used to make medicines. They fall under various categories, including phenolics, aliphatic chemicals, glycosides, steroids, sesquiterpenoids, diterpenoids, polysaccharides and lactones. The

alkaloids such as tinosporic acid, tinosporin and tinosporol rich in protein, calcium, and phosphorus have been identified in leaves. It's remarkable and notable medicinal properties, such as antidiabetic, antiperiodic, antimalarial, anti-inflammatory, antioxidant, antispasmodic, antiallergic, antistress, antileprotic, antiarthritic, hepatoprotective, blood purification, immunomodulatory and antineoplastic activities, are all well documented.

Despite the fact that *Tinospora cordifolia* is an important medicinal herb, to our knowledge, no study investigating the effect of fresh aqueous extract of guduchi leaves on the passive inhalation of cigarette smoke exposure toxicity has yet been published. Therefore, the present study was conducted to evaluate the effectiveness of the antioxidant and anti-inflammatory properties of aqueous extracts of fresh leaves of *Tinospora cordifolia* in a dose-dependent manner on cigarette smoke-induced hematobiochemical alterations in rats following sub-chronic exposure to passive smoking of both filtered and non-filtered cigarettes.

MATERIALS AND METHODS

Experimental animals

Healthy and adult albino rats of both sexes (100-150 g; n= 6 per group) 4 to 6 weeks old were selected for the present work. After an acclimatization period of ten days, rats were weighed and organized into groups to ensure the same average starting weight in each group. Rats were kept in polypropylene cages and were fed with standard pelleted rat food and water ad libitum. The rats were housed under standard husbandry conditions with a 12 hr light/dark cycle and 60±5% relative humidity. Guidelines of the institutional Animal Ethical Committee were followed throughout the experiment. Rats of both sexes were kept in separate cages.

Cigarettes

In the present study, Cavender's magnum filter cigarettes and Cavender's gold leaf non-filtered cigarettes were used. Of the six experimental groups, the rats in 3 groups were exposed to 6 filtered cigarettes per hour for 30 and 60 days, and the remaining 3 groups were exposed to 5 non-filtered cigarettes/hr for 30 and 60 days. The rats were subjected to whole-body exposure to filtered and non-filtered cigarettes through slow suction in a mini smoke exposure chamber (60 cm x 30 cm x 30 cm) manufactured by Precision Instrument, Varanasi. The rats were exposed to cigarette smoke for periods of 30 and 60 days.

Extraction of aqueous extract of *Tinospora cordifolia* leaves

Tinospora cordifolia fresh leaves were collected and thoroughly cleaned with distilled water and tap water until no contaminants remained. Then, 10 g of leaves was weighed and combined (1:10 w/v) with 100 ml of distilled water in an electric blender. Filter paper was then used to filter the mixture. The resulting filtrate was regarded as the mother solution. Aqueous extracts of different concentrations (200 mg/kg b.w. and 400 mg/kg b.w.) were produced by further diluting the mother extract with the necessary volume of distilled water. Different doses of TC extract were given orally through gavage to the rats in the control and experimental groups.

Study design

Rats were randomly divided into control and experimental groups and subgroups for a 30- and 60-day study, as shown in Table I.

Table 1. Distribution of rats in different groups and subgroups as per the experimental protocol of the study for 30 and 60 days (n=12).

S.No.	Groups	Subgroups	Treatment (For 30- and 60-days)
1	Group I	-	Served as Control
2.	Group II	A	Control with 200 mg/kg <i>Tinospora cordifolia</i> orally (TC Dose 1)
		B	Control with 400 mg/kg TC orally (TC Dose 2)
3.	Group III	C	Exposed to 6 Filtered cigarettes (FC) for 1 hr/day
		D	Exposed to 6 FC followed by the treatment of TC Dose 1 through oral administration
		E	6 FC for 1 hr/day + TC Dose 2 given orally
4.	Group IV	F	Exposed to 5 Non-filtered cigarettes (NFC) for 1 hr/day
		G	Exposed to 5 NFC followed by TC Dose 1 orally
		H	Exposed to 5 NFC for 1 hr/day + Treated with TC Dose 2

Sample collection and Hematological and Biochemical Assessment

Half of the rats in each group and subgroup were sacrificed after 30 days, and the other half were sacrificed after 60 days of the experiment. Fresh blood was collected through cardiac puncture in EDTA vials for hematological analysis. For biochemistry analysis, blood samples were collected in routine biochemical test tubes and allowed to clot, and the serum was removed by centrifugation at $2000 \times g$ for 10 min. All the serum samples were sterile, hemolysis-free and kept at $+4^{\circ}\text{C}$. The parameters analyzed included differential leucocyte count (DLC), viz., lymphocytes, neutrophils, monocytes, eosinophils, basophils, erythrocyte sedimentation rate (ESR), ALT, AST, urea, creatinine and blood glucose. These parameters were obtained at once for each blood sample using an automated hematology analyst. All dosages (for biochemical parameters- alanine aminotransferase-ALT, aspartate aminotransferase-AST) were performed using a Robonik pretest automated biochemistry analyzer. (Spinelli *et al.*, 2014). Blood glucose levels were analyzed using a glucometer.

Data analysis and statistical procedures

All statistical analyses were carried out by using Statistical Package for Social Sciences (SPSS for Windows version 25.0, IBM SPSS). The values are expressed as mean \pm standard error of the mean (SEM). Data were analyzed using ANOVA, and multiple comparisons were performed using the Tukey HSD *post hoc* test. Statistical significance was considered for p values < 0.05 .

RESULTS

The hemato-biochemical parameters of animals, i.e., the differential leucocyte count (DLC), erythrocyte sedimentation rate (ESR), alanine transaminase (ALT), aspartate transaminase (AST), kidney enzymes urea and creatinine and blood glucose levels, were assessed for 30 and 60 days in both the control and experimental groups and are given in Tables 2 and 3 and Figs. 1-11.

Effect of TC leaf extract on hematological parameters in cigarette smoke-exposed rats

After 30 days

In the present study, a rise in the mean concentration of erythrocyte sedimentation rate (ESR) in the blood of rats exposed to filtered cigarette smoke (FC) (2.06 ± 0.4 mm/hr) and non-filtered cigarette (NFC) (2.58 ± 0.36 mm/hr) smoke was found to be significantly higher ($p < 0.05$) in comparison to the control group (0.47 ± 0.12 mm/hr) after 30 days. However, following treatment with TC doses 1 and 2, there was a significant decrease ($p < 0.05$) in ESR levels in both the FC (0.78 ± 0.19 mm/hr and 0.61 ± 0.17 mm/hr) and NFC (1.46 ± 0.29 mm/hr and 1.36 ± 0.28 mm/hr) groups, as shown in Table 2 and Fig. 6. A highly significant increase ($p < 0.001$) was noted in lymphocyte count in rats of both filtered ($7.70 \pm 0.66 \times 10^3/\text{mm}^3$) and non-filtered cigarette smoke ($8.26 \pm 0.33 \times 10^3/\text{mm}^3$) exposed groups in comparison to control group rats ($1.77 \pm 0.74 \times 10^3/\text{mm}^3$). Following oral treatment with TC extract Dose 1, a significant decrease in lymphocyte count was observed in the FC ($4.60 \pm 0.67 \times 10^3/\text{mm}^3$) group, and a highly significant decrease ($p < 0.001$) was noted after TC Dose 2 treatment in the FC group ($2.13 \pm 0.46 \times 10^3/\text{mm}^3$) in comparison to the FC-only exposed group. A highly significant decrease ($p < 0.001$) to that of normal level was obtained in NFC ($4.58 \pm 0.90 \times 10^3/\text{mm}^3$ and $2.64 \pm 0.62 \times 10^3/\text{mm}^3$) exposed groups after TC Dose 1 and Dose 2 administration in comparison to control group rats as shown in Table-2 and Fig.-1. A significant increase in the level of monocytes was observed in NFC-exposed rats ($1.02 \pm 0.31 \times 10^3/\text{mm}^3$) in comparison to the control group ($0.16 \pm 0.06 \times 10^3/\text{mm}^3$). A slight increase in neutrophils, eosinophils and basophils was noted in both the FC and NFC groups after 30 days, as shown in Table 2 and Fig. 2-5. However, the difference was found to be nonsignificant. When treated with TC Dose 1 and Dose 2, the levels of neutrophils, monocytes, eosinophils and basophils were found to be within the normal range in comparison to the control group after 30 days.

After 60 Days

Observations after 60 days showed that there was a significant increase ($p < 0.05$) in ESR levels in rats exposed to FC (2.6 ± 0.26 mm/hr) and NFC (3.38 ± 0.26 mm/hr) in comparison to the control level (0.47 ± 0.12 mm/hr). The same was found to be modified after treatment with Dose 1 in the FC group, while a significant decrease ($p < 0.05$) to that of the control level was obtained in the NFC group treated with TC Dose 1 (1.6 ± 0.57 mm/hr). The effect of Dose 2 on the ESR level was also found to be significant ($p < 0.05$) in rats of both the experimental groups exposed to FC (1.25 ± 0.34 mm/hr) and NFC (1.46 ± 0.51 mm/hr). A highly significant increase ($p < 0.001$) was observed in the lymphocyte count of rats exposed to FC ($8.33 \pm 0.47 \times 10^3/\text{mm}^3$) and NFC ($8.86 \pm 0.30 \times 10^3/\text{mm}^3$) in comparison to the control group ($2.75 \pm 0.43 \times 10^3/\text{mm}^3$). Additionally, a highly significant decrease ($p < 0.001$) in lymphocyte count was also obtained in rats in the FC ($4.24 \pm 0.67 \times 10^3/\text{mm}^3$ and $2.98 \pm 0.79 \times 10^3/\text{mm}^3$) and NFC ($3.77 \pm 0.55 \times 10^3/\text{mm}^3$ and $2.61 \pm 0.60 \times 10^3/\text{mm}^3$)

groups after TC Dose 1 and Dose 2 treatment in comparison to rats exposed to only FC and NFC. Moreover, slightly higher values of neutrophils, eosinophils and basophils were noted in the FC- and NFC-only exposed groups. This difference was nonsignificant. However, a significant increase ($p < 0.05$) in monocytes was noted in the NFC-exposed only group ($1.42 \pm 0.34 \times 10^3/\text{mm}^3$) in comparison to the control group ($0.25 \pm 0.08 \times 10^3/\text{mm}^3$). The values of neutrophils, monocytes, eosinophils and basophils were found to be within the normal range in all the experimental groups after 60 days, as shown in Table 2 and Figs. 2-5.

Effect of TC leaf extract on biochemical parameters in cigarette smoke-exposed rats

After 30 days

The levels of AST and ALT were found to be slightly higher in both the FC- and NFC-only exposed groups than in the control group (Group I) after 30 days. However, this difference was found to be nonsignificant. The effect of TC doses 1 and 2 on AST and ALT was also within the normal range in the experimental groups exposed to FC and NFC after 30 days, as shown in Table 3 and Figs. 7 and 8.

The effect of both filtered and non-filtered cigarette smoke was found to be non-significantly higher on urea levels after 30 days. The effect of TC aqueous fresh leaf extract on urea levels in different doses against FC and NFC was also found to be in the normal range in comparison to control rats (Table-3; Fig.-9). However, a significant ($p < 0.05$) increase in creatinine levels was noted in rats exposed to FC (1.83 ± 0.50 mg/dl) and NFC (2.03 ± 0.45 mg/dl) compared with rats in the control group (0.533 ± 0.14 mg/dl). This change in creatinine level was augmented significantly by TC extract, with a higher effect observed after Dose 1 and 2 administrations to rats in the NFC groups (0.95 ± 0.19 and 0.56 ± 0.11), while a nonsignificant change was observed in the FC groups (Table 3; Fig. 10). Glucose levels were also found to be affected non-significantly in all the experimental groups in comparison to the control group after 30 days (Table 3; Fig. 11).

After 60 Days

After 60 days, the levels of AST, ALT, urea, creatinine and glucose were found to be significantly elevated in both the FC- and NFC-only exposed groups in comparison to the control group. There was a highly significant ($p < 0.001$) increase in AST found in both the FC (164.66 ± 9.78 U/l) and NFC (173.56 ± 9.40 U/l) groups in comparison to the control group (104.93 ± 9.75 U/l). This was modified after treatment with TC Dose 1 in both CS-exposed groups. The difference was highly significant ($p < 0.001$) in the FC group (117.76 ± 9.99 U/l), while a significant decrease ($p < 0.05$) was obtained in the NFC group (132.31 ± 9.09 U/l), as shown in Table 3 and Fig. 8. Similarly, the mean concentration of ALT was also found to be significantly increased ($p < 0.05$) in the FC-only exposed groups (48.88 ± 7.45 U/l) in comparison to control rats (31.18 ± 3.92 U/l). However, a highly significant ($p < 0.001$) elevation in ALT was noted in the NFC-only (61.25 ± 4.80 U/l) exposed group in comparison to the control. The effect of Dose 1 on ALT in the FC group was found to be decreased non-significantly. However, in the NFC group, the effect of Dose 1 on ALT (33.63 ± 5.17 U/l) was observed to be decreased significantly ($p < 0.05$) in comparison to the NFC-only exposed group. The effect of Dose 2 on ALT in the FC group (25.36 ± 5.5 U/l) was found to be decreased

significantly ($p < 0.05$), and a highly significant ($p < 0.001$) decrease was obtained in the NFC group (28.08 ± 4.85 U/l), followed by Dose 2 treatment (Table 3; Fig. 7).

The difference in urea level was found to be highly significantly increased ($p < 0.001$) in both FC (41.68 ± 2.34 mg/dl) and NFC (46.83 ± 1.45 mg/dl) exposed rats in comparison to the control group (20.5 ± 2.74) rats. Co-administration of TC Dose 1 also decreased the urea level significantly in the NFC group (34.63 ± 3.82 mg/dl) compared to that of control rats after 60 days. The effect of TC Dose 2 was found to be significant ($p < 0.05$) in the FC group (27.35 ± 3.35 mg/dl) and highly significant ($p < 0.001$) in the NFC group (26.43 ± 3.01 mg/dl), as shown in Table 3 and Fig. 9. A highly significant increase ($p < 0.001$) in the level of creatinine was observed in the NFC-exposed group (2.55 ± 0.38 mg/dl), and a significant ($p < 0.05$) increase was observed in the FC group (2.16 ± 0.47 mg/dl) in comparison to the control group (0.6 ± 0.14 mg/dl). After TC Dose 1 treatment, a non-significant change was obtained in creatinine in the FC-exposed groups, while a highly significant ($p < 0.001$) decrease was found in NFC-exposed (0.97 ± 0.17 mg/dl) rats. A significant decrease ($p < 0.05$) in the level of creatinine was observed in FC-exposed rats after treatment with Dose 2 of TC (0.78 ± 0.10 mg/dl), whereas a highly significant ($p < 0.001$) decrease in its level was found after treatment with Dose 2 of TC in the NFC group (0.82 ± 0.11 mg/dl) in comparison to the NFC-only exposed group (Table 3; Fig.-10). A significantly low ($p < 0.05$) mean glucose level was observed in the FC- (89.16 ± 8.63 mg/dl) and NFC-only (87.88 ± 15.15 mg/dl) exposed groups. However, a significant increase to normal levels was obtained following treatment with TC Dose 2 (142.16 ± 16.98 mg/dl) in the NFC-exposed group, as shown in Table 3 and Fig. 11.

DISCUSSION

Young rats were selected as an experimental animal in this study because it is relatively easy to examine different characteristics of the nicotine dependence cycle in these animals, whereas it is difficult to do so in humans at the beginning of use. Additionally, nicotine's pharmacokinetics are significantly influenced, and rats show elevated brain and plasma levels of nicotine and its metabolites (Casey and Jones, 2010; Craig *et al.*, 2014). Additionally, human population is more susceptible to the negative effects of inhaling tobacco smoke and mainly to nicotine through passive smoking exposure, especially in the indoor environment (Nazar *et al.*, 2014; Yousuf *et al.*, 2020), and they are more susceptible to the negative effects of smoking tobacco (Tucker *et al.*, 2019).

During the period of experiment, the deteriorating effects were observed immediately after exposure to the cigarette smoke was found to be associated with the action of nicotine and other inhaled toxic compounds from cigarette smoke (Genchi *et al.*, 2020; Wang *et al.*, 2020). Therefore, in the present study, the antioxidant activity of *T. cordifolia* fresh leaf aqueous extract on oxidative damage in the enzymes of the liver and kidney, hemato-biochemical parameters and blood glucose levels of rats passively exposed to filtered and non-filtered cigarette smoke was assessed.

In the present study, the findings revealed that the lymphocyte count was significantly higher in the experimental groups exposed to both types of cigarettes without TC treatment. This can be the result of lymphocytosis caused by inflammation and tissue damage due to smoke-related toxic substances. Nicotine

appears to stimulate hormone synthesis, which in turn elevates leukocyte count. Inflammation and the production of cytokines are caused by irritation of the respiratory mucosa due to smoke, which increases the leukocyte count (Mudassar *et al.*, 2022). Leukocytosis in cigarette smoke-exposed groups is mainly associated with an increased lymphocyte count and 'T' lymphocytes (Silverman *et al.*, 1975). Alterations in T lymphocytes may cause an increased risk of infections and neoplasia in rats exposed to cigarette smoke (Hughes *et al.*, 1985). Additionally, it has been hypothesized that smoking stimulates inflammatory markers in the respiratory bronchial tract, increasing the number of lymphocytes in the blood. Additionally, nicotine causes an increase in blood lymphocyte count (Pedersen *et al.*, 2019). Among other parameters, a slight decrease in neutrophil count was found in cigarette smoke-exposed groups. However, the difference was not statistically significant. Also, a non-significant change was obtained in eosinophil, basophil and monocyte counts (Shenwai and Aundhakar, 2012).

By generating free radicals, including hydrogen peroxide (H₂O₂) and nitric oxide (NO), smoking induces oxidative stress. These free radicals damage the endothelium, increasing whole blood viscosity, producing rouleaux and triggering inflammatory responses. An increase in the erythrocyte sedimentation rate may be indicative of this elevation (Nisa and Zaman, 2003; Sharma *et al.*, 2014). Additionally, smokers had a higher erythrocyte sedimentation rate than nonsmokers. The rise in smoking was observed independent of daily cigarette consumption (Islam *et al.*, 2013; Oke *et al.*, 2012).

Cigarette smoke contains a large number of toxic chemical compounds with potent hepatotoxic potential, including nicotine (Yuen *et al.*, 1995). The reactive oxygen species produced due to cigarette smoke exposure induces degeneration of hepatic cells and microsomal mitochondria because of membrane alterations that allows the passage of intracellular enzymes. Thus, there was a significant increase in liver enzymes (ALT and AST) due to the harmful effect of filtered and non-filtered cigarette smoke passively in the experimental groups (Adekomi *et al.*, 2011; Avti *et al.*, 2010; Ugbor *et al.*, 2013). Despite their non-specificity, ALT and AST are recognized markers of liver diseases (Salunke *et al.*, 2011; Zuo *et al.*, 2014) and are the first enzymes to show their increase in plasma under conditions of hepatocyte damage. Additionally, these effects are mainly due to the presence of phytochemical substances of tobacco, for instance nicotine (Bo *et al.*, 2005; Kerner *et al.*, 2005; Salahshoor *et al.*, 2016), which cause blockage of liver sinusoids, inflammation of hepatocytes, and the formation of oxidants. These oxidants then cause an oxidative stress and the oxidation of thiol groups and proteins (Barreiro *et al.*, 2010; Wieczfinska *et al.*, 2018), which results in the leakage of ALT and AST from the cell content and an increase in plasma levels. Additionally, there is a dosage-response association between serum ALT and AST levels and the number of cigarettes/days smoked (Abdul-Razaq and Ahmed, 2013). Moreover, it was reported that frequent cigarette use enhances AST and ALT levels (Burstyn, 2014; Pekmez *et al.*, 2007; Robinson and Whitehead, 1989).

An elevation in concentrations of urea and creatinine in the plasma of animals in the group exposed to filtered and non-filtered cigarette smoke and not supplemented with TC doses was noted. Cigarette smoke contains nephrotoxic substances, including cadmium (Cd) and lead (Pb) (Desai *et al.*, 2016; Golli *et al.*, 2016), causes an alteration in proximal tubular function and increased levels of creatinine and serum urea.

Moreover, the stable thiol-reactive compounds present in cigarette smoke may activate NADPH oxidase and may cause an increase in the vascular production of reactive oxygen species (ROS), decreasing NO bioactivity and leading to endothelial dysfunction (Jaimes *et al.*, 2004). Due to this, an increased levels of urea and creatinine were obtained. These findings corroborate clinical results, which have proven that smoking stimulates renal damage by increasing intraglomerular and blood pressure, leading to renal dysfunction of endothelial cells in the long term (Orth, 2004). A significant increase in glucose levels was noted in rats exposed to filtered and non-filtered cigarette smoke without TC treatment. The elevated glucose level may return to the effect of smoking on the insulin function sensitivity and cause impairment to glucose tolerance (Fрати *et al.*, 1996).

However, the administration of fresh aqueous leaf extract TC doses to cigarette smoke-exposed experimental groups produced mild to significant effects on almost all blood biochemical profiles in albino rats. It is well reported that *T. cordifolia* is used to treat multiple disorders; it also improves the blood (Aiyer and Kolammal, 1963; Nayampalli *et al.*, 1982; Raghunathan and Mitra, 1982). In certain studies, TC is reported to have antioxidant, anti-inflammatory, and immunomodulating effects, and most of these effects have been demonstrated to be produced by flavonoids, diterpenes, alkaloids and phenolic compounds, which are the active phytoconstituents of TC leaves. In this study, when TC fresh leaf aqueous extract was administered to rats that inhaled cigarette smoke, it was found that a reduction occurred in serum levels of ALT, AST, urea, creatinine and glucose approaching control values.

Thus, it was determined that a damaging effect was observed in liver and kidney functions as well as DLC and ESR in rats after being exposed to cigarette smoke for 30 and 60 days and that this was partly enhanced, by the antioxidant activity of TC aqueous leaf extract.

In this study, it was found that cigarette smoking exerts a negative influence by increasing the levels of lymphocytes, ESR, AST, ALT, urea, and creatinine and decreasing blood glucose levels, indicating increased inflammatory responses in smoke-exposed groups. We have been able to show whether cigarettes with filters were able to have a less harmful effect on hemato-biochemical parameters than non-filtered ones. The results indicated that a filtered-tipped cigarette is equally harmful as a non-filtered cigarette, showing an equivalent toxic effect on blood biomarkers. The only effective way to protect people from the damaging effects of active and passive smoke is to significantly reduce tobacco consumption in society. The study revealed that *Tinospora cordifolia* aqueous extract played a protective role in oxidative stress and inflammation induced by filtered and non-filtered cigarette smoke on DLC, ESR, liver-kidney enzymes and blood glucose levels by reducing the formation of reactive oxygen species and other passive smoke-generated harmful toxic effects in rats. One of the major contributing factors responsible for the anti-inflammatory and antioxidative effects of TC leaves is the combined or individual potential of the phytoconstituents present in leaves of this plant.

ACKNOWLEDGMENTS

The authors would like to thank the Head Department of Zoology and Dean, School of Life Sciences, Dr. Bhimrao Ambedkar University, Agra, Uttar Pradesh, India, for the Animal House facilities.

Credit authorship contribution statement

Khushbu Tarangni Mathur- Methodology, Investigation, Formal analysis, Performed the experiments, Data curation, Writing – original draft. **Geetesh Rawat**- Investigation, Formal analysis. **Geeta Maheshwari**- Conceptualization, Supervision, provided constructive suggestions, Resources.

Conflict of interest

The authors declare that there is not any conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/ or falsification, double publication and/or submission, and redundancy has been completely observed by the authors.

Grant Support Details

The present research did not receive any financial support.

Life Science Reporting

All experiments were performed according to the guidelines of Institutional Ethical Committee (Dr. Bhimrao Ambedkar University, Agra).

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Table 2. Hematological parameters of albino rats in various control and experimental groups after 30 and 60 days of exposure to filtered and non-filtered cigarette smoke along with *Tinospora cordifolia* treatment. The values are expressed as the mean \pm S.Em. ; n = 6/group.

Treatment		Lymphocytes ($\times 10^3/\text{mm}^3$)		Neutrophils ($\times 10^3/\text{mm}^3$)		Monocytes ($\times 10^3/\text{mm}^3$)		Eosinophils ($\times 10^3/\text{mm}^3$)		Basophils ($\times 10^3/\text{mm}^3$)		ESR (mm/hr)	
		30 Days	60 Days	30 Days	60 Days	30 Days	60 Days	30 Days	60 Days	30 Days	60 Days	30 Days	60 Days
Contr ol Group s	I (Control)	1.77 \pm 0.74	2.75 \pm 0.43	0.90 \pm 0.22	0.90 \pm 0.22	0.16 \pm 0.06	0.25 \pm 0.08	0.13 \pm 0.05	0.15 \pm 0.05	0.018 \pm 0.00 4	0.023 \pm 0.00 2	0.47 \pm 0.12	0.47 \pm 0.12
	IIA (Control + 200 mg/kg TC)	2.72 \pm 0.54	3.11 \pm 0.48	0.82 \pm 0.19	0.87 \pm 0.25	0.80 \pm 0.24	0.57 \pm 0.23	0.10 \pm 0.03	0.12 \pm 0.03	0.026 \pm 0.00 3	0.025 \pm 0.00 2	0.98 \pm 0.15	1.45 \pm 0.44
	IIB (Control + 400 mg/kg TC)	2.32 \pm 0.58	2.43 \pm 0.26	0.87 \pm 0.22	0.73 \pm 0.20	0.51 \pm 0.20	0.43 \pm 0.16	0.11 \pm 0.04	0.10 \pm 0.03	0.021 \pm 0.00 4	0.023 \pm 0.00 2	0.85 \pm 0.2	1.05 \pm 0.33
FC Group s ¹	IIIC (FC only)	7.70 \pm 0.66 ^a *	8.33 \pm 0.47 ^{b*}	1.21 \pm 0.28	1.26 \pm 0.18	0.89 \pm 0.23	0.95 \pm 0.36	0.14 \pm 0.01	0.17 \pm 0.04	0.03 \pm 0.002	0.03 \pm 0.004	2.06 \pm 0.4a	2.6 \pm 0. 26b
	IIID (FC + 200 mg/kg TC)	4.60 \pm 0.67 [#]	4.24 \pm 0.67 ^{###}	0.90 \pm 0.21	0.83 \pm 0.20	0.81 \pm 0.26	0.73 \pm 0.20	0.12 \pm 0.03	0.12 \pm 0.05	0.028 \pm 0.00 2	0.025 \pm 0.00 2	0.78 \pm 0.19 [#]	1.91 \pm 0.18b
	IIIE (FC + 400 mg/kg TC)	2.13 \pm 0.46 [#] *	2.98 \pm 0.79 ^{###*}	0.74 \pm 0.16	0.73 \pm 0.30	0.54 \pm 0.22	0.68 \pm 0.23	0.12 \pm 0.02	0.18 \pm 0.09	0.023 \pm 0.00 2	0.027 \pm 0.00 3	0.61 \pm 0.17 [#]	1.25 \pm 0.34 ^{###}
NFC Group s ²	IVF (NFC only)	8.26 \pm 0.33 ^a *	8.86 \pm 0.30 ^{b*}	1.29 \pm 0.23	1.37 \pm 0.23	1.02 \pm 0.31 ^a	1.42 \pm 0.34 ^b	0.17 \pm 0.04	0.20 \pm 0.04	0.028 \pm 0.00 3	0.031 \pm 0.00 3	2.58 \pm 0.36a	3.38 \pm 0.26b
	IVG (NFC + 200 mg/kg TC)	4.58 \pm .90 ^{^*}	3.77 \pm 0.55 ^{^^} *	1.24 \pm 0.20	0.80 \pm 0.22	0.78 \pm 0.21	0.70 \pm 0.24	0.12 \pm 0.03	0.10 \pm 0.03	0.028 \pm 0.00 3	0.026 \pm 0.00 2	1.46 \pm 0.29 [^]	1.6 \pm 0. 57 ^{^^}
	IVH (NFC + 400 mg/kg TC)	2.64 \pm 0.62 [^] *	2.61 \pm 0.60 ^{^^} *	0.56 \pm 0.19	0.67 \pm 0.24	0.72 \pm 0.22	0.65 \pm 0.21	0.08 \pm 0.02	0.09 \pm 0.02	0.023 \pm 0.00 2	0.023 \pm 0.00 2	1.36 \pm 0.28 [^]	1.46 \pm 0.51 ^{^^}

1-Filtered Cigarette; 2- Non-Filtered Cigarette; **a**-Significant difference in comparison to Control after 30 days ($p < 0.05$); **b**- Significant difference in comparison to Control after 60 days ($p < 0.05$); **#**- Significant difference in comparison to Group IIIC after 30 days ($p < 0.05$); **###**- Significant difference in comparison to Group IIIC after 60 days ($p < 0.05$); **^**- Significant difference in comparison to Group IVF after 30 days ($p < 0.05$); **^^**- Significant difference in comparison to Group IVF after 60 days ($p < 0.05$); *****- Highly significant ($p < 0.001$).

Table 3. Biochemical parameters of albino rats in various control and experimental groups after 30 and 60 days of exposure to filtered and non-filtered cigarette smoke along with *Tinospora cordifolia* treatment. The values are expressed as the mean \pm S.Em; n = 6/group.

Treatment		AST (U/l)		ALT (U/l)		Urea (mg/dl)		Creatinine (mg/dl)		Glucose (mg/dl)	
		30 Days	60 Days	30 Days	60 Days	30 Days	60 Days	30 Days	60 Days	30 Days	60 Days
Control Groups	I (Control)	105.43 \pm 11.73	104.93 \pm 9.75	30.18 \pm 3.92	31.18 \pm 3.9 2	24.58 \pm 5.14	20.5 \pm 2.74	0.533 \pm 0.14	0.6 \pm 0.14	167.16 \pm 33.94	176.66 \pm 31.66
	IIA (Control + 200 mg/kg TC)	105.91 \pm 10	100.91 \pm 10.68	27.92 \pm 4.5	28.35 \pm 3.3 5	24.86 \pm 2.92	23.11 \pm 2.85	0.99 \pm 0.19	0.73 \pm 0.13	186.66 \pm 18.73	159.83 \pm 18.63
	IIB (Control + 400 mg/kg TC)	100.21 \pm 9.51	96.05 \pm 11.21	31.43 \pm 5.01	27.96 \pm 2.7 3	20.88 \pm 2.72	19.55 \pm 2.46	0.52 \pm 0.17	0.61 \pm 0.15	173.66 \pm 25.88	158 \pm 19.10
FC Group s ¹	IIIC (FC exposed only)	130.86 \pm 16.25	164.66 \pm 9.78 [*]	32.9 \pm 5.36	48.88 \pm 7.4 5 ^b	34.95 \pm 4.56	41.68 \pm 2.34 ^{b*}	1.83 \pm 0.50 ^a	2.16 \pm 0.47 ^b	109.53 \pm 12.05	89.16 \pm 8.63 ^b
	IIID (FC + 200 mg/kg TC)	107.76 \pm 12.13	117.76 \pm 9.99 ^{##} [*]	32.6 \pm 4.27	36.25 \pm 2.5 5	32.43 \pm 4	36.16 \pm 2.44	1.5 \pm 0.41	1.1 \pm 0.16	117.38 \pm 16.90	123.66 \pm 15.15
	IIIE (FC + 400 mg/kg TC)	109.41 \pm 10.14	116.08 \pm 6.70 ^{##}	22.65 \pm 3.32	25.36 \pm 5.5 ^{##}	25.48 \pm 3.23	27.35 \pm 3.35 ^{##}	0.68 \pm 0.2	0.78 \pm 0.10 ^{##}	156.30 \pm 16.53	128.9 \pm 12.72
NFC Group s ²	IVF (NFC exposed only)	145.23 \pm 11.30	173.56 \pm 9.40 ^{b*}	43.65 \pm 5.07	61.25 \pm 4.8 0 ^{b*}	37.76 \pm 4.08	46.83 \pm 1.45 ^{b*}	2.03 \pm 0.45 ^a	2.55 \pm 0.38 ^{b*}	118.83 \pm 16.42	87.88 \pm 15.15 ^b
	IVG (NFC + 200 mg/kg TC)	110.65 \pm 9.83	132.31 \pm 9.09 ^{^^}	34.65 \pm 4.9	33.63 \pm 5.1 7 ^{^^}	31.9 \pm 4.27	34.63 \pm 3.82 ^{^^}	0.95 \pm 0.19 [^]	0.97 \pm 0.17 ^{^^*}	100.50 \pm 10.28	99 \pm 6.57
	IVH (NFC + 400 mg/kg TC)	107.16 \pm 10.83	110.26 \pm 10.89 [^]	27.83 \pm 4.35	28.08 \pm 4.8 5 ^{^^*}	22.9 \pm 2.93 [^]	26.43 \pm 3.01 ^{^^*}	0.56 \pm 0.11 [^]	0.82 \pm 0.11 ^{^^*}	175.83 \pm 23.82	142.16 \pm 16.98 [^]

1- Filtered Cigarette; 2- Non-Filtered Cigarette; a-Significant difference in comparison to Control after 30 days (p<0.05);

b- Significant difference in comparison to Control after 60 days (p<0.05); #- Significant difference in comparison to Group IIIC

after 30 days (p<0.05); ##- Significant difference in comparison to Group IIIC after 60 days (p<0.05); ^- Significant difference in

comparison to Group IVF after 30 days (p<0.05); ^^- Significant difference in comparison to Group IVF after 60 days (p<0.05);

*- Highly significant (p<0.001).

FIGURES

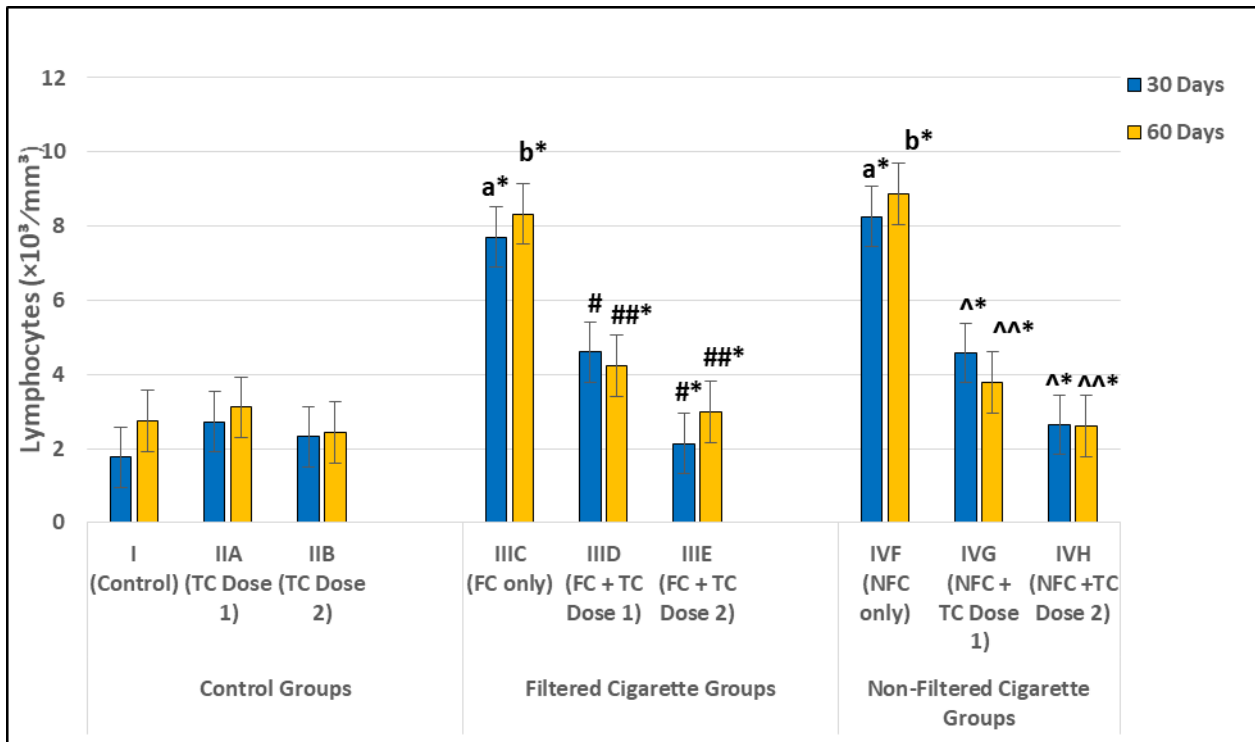


Figure 1. Effect of filtered and non-filtered cigarette smoke on lymphocytes ($\times 10^3/\text{mm}^3$) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; **a**-Significant difference in comparison to the control after 30 days ($p < 0.05$); **b**- Significant difference in comparison to the control after 60 days ($p < 0.05$); **#**- Significant difference in comparison to Group IIIC after 30 days ($p < 0.05$); **##**- Significant difference in comparison to Group IIIC after 60 days ($p < 0.05$); **^**- Significant difference in comparison to Group IVF after 30 days ($p < 0.05$); **^^**- Significant difference in comparison to Group IVF after 60 days ($p < 0.05$); *****- Highly significant ($p < 0.001$). FC- Filtered cigarette; NFC- Non-filtered cigarette; and TC- *Tinospora cordifolia*

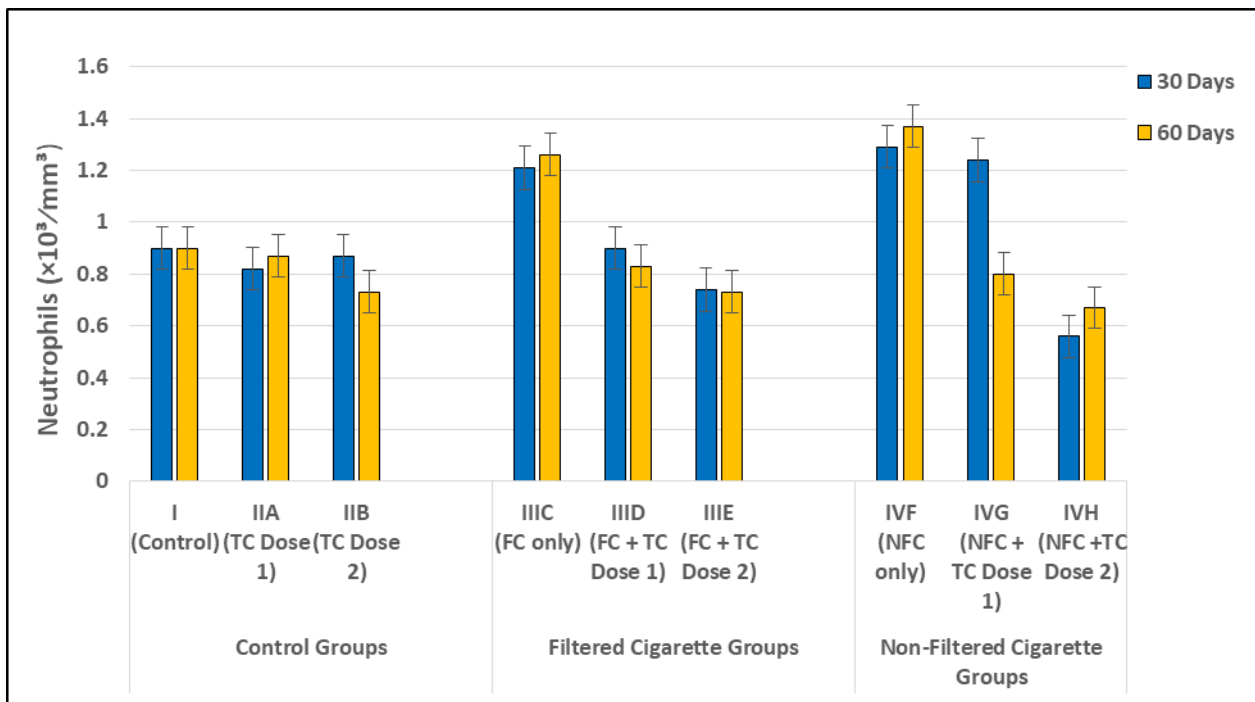


Figure 2. Effect of filtered and non-filtered cigarette smoke on neutrophils ($\times 10^3/\text{mm}^3$) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; FC- filtered cigarette; NFC- non-filtered cigarette and TC- *Tinospora cordifolia*.

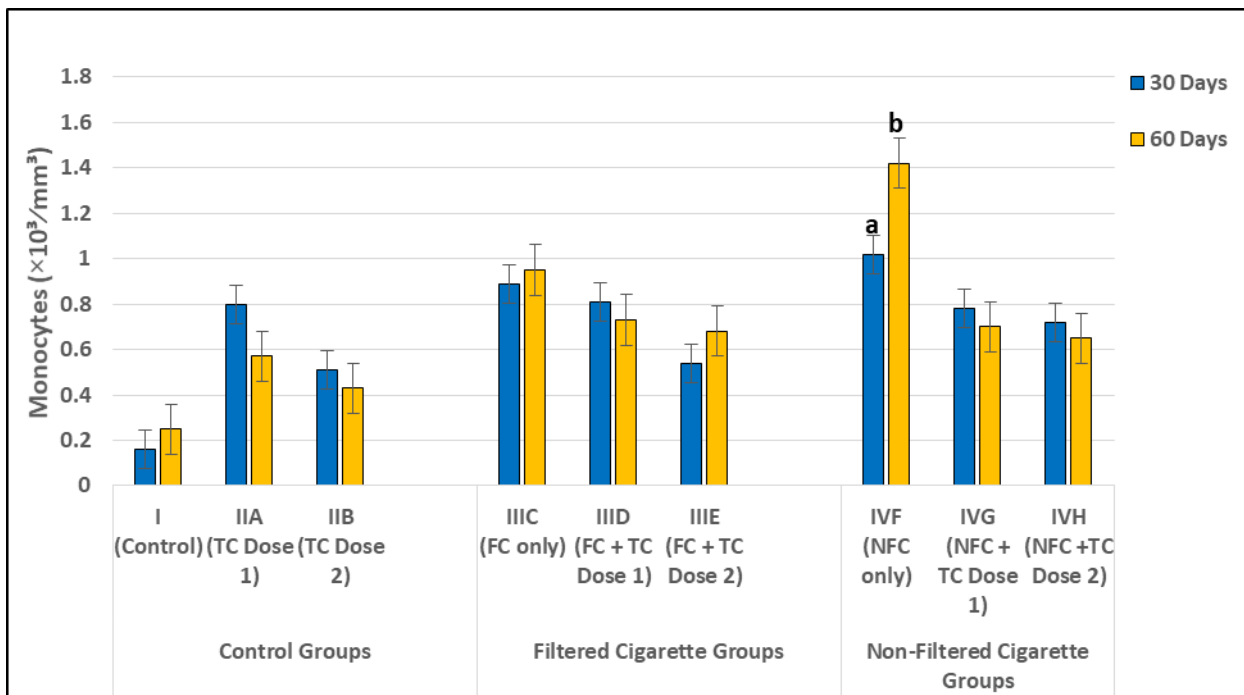


Figure 3. Effect of filtered and non-filtered cigarette smoke on monocytes ($\times 10^3/\text{mm}^3$) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; **a**-Significant difference in comparison to the control after 30 days ($p < 0.05$); **b**- Significant difference in comparison to the control after 60 days ($p < 0.05$); FC- Filtered cigarette; NFC- Non-filtered cigarette and TC- *Tinospora cordifolia*.

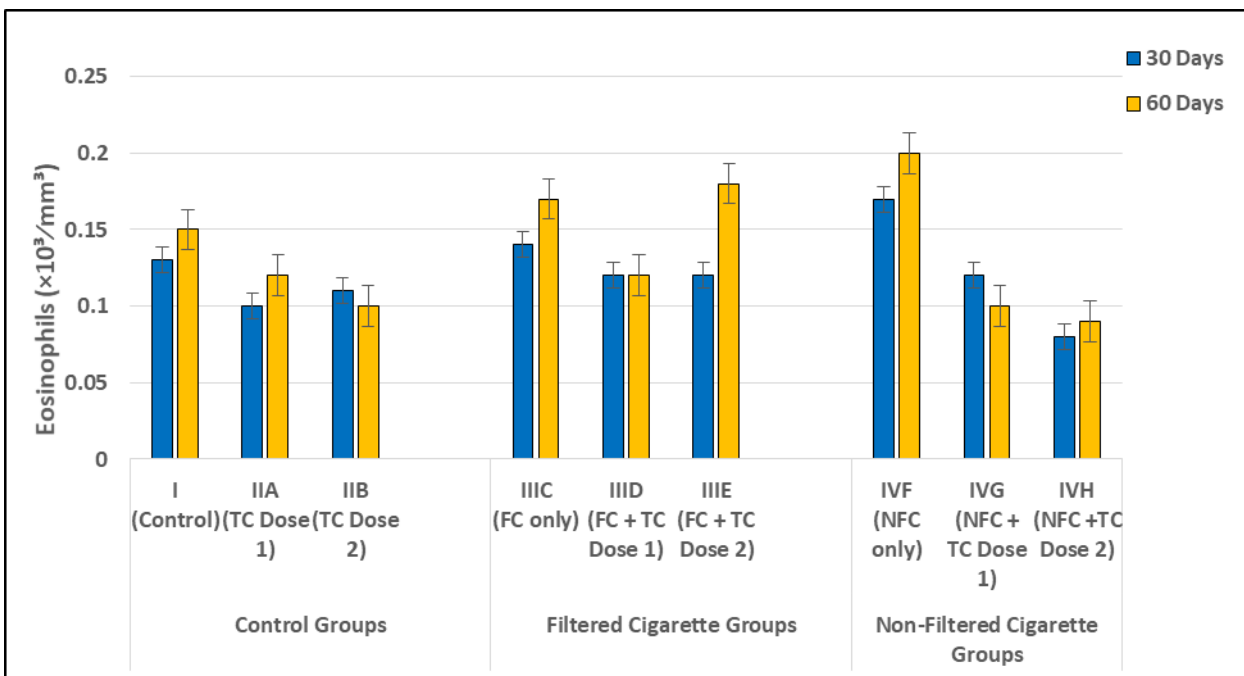


Figure 4. Effect of filtered and non-filtered cigarette smoke on eosinophils ($\times 10^3/\text{mm}^3$) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; FC- filtered cigarette; NFC- non-filtered cigarette and TC- *Tinospora cordifolia*.

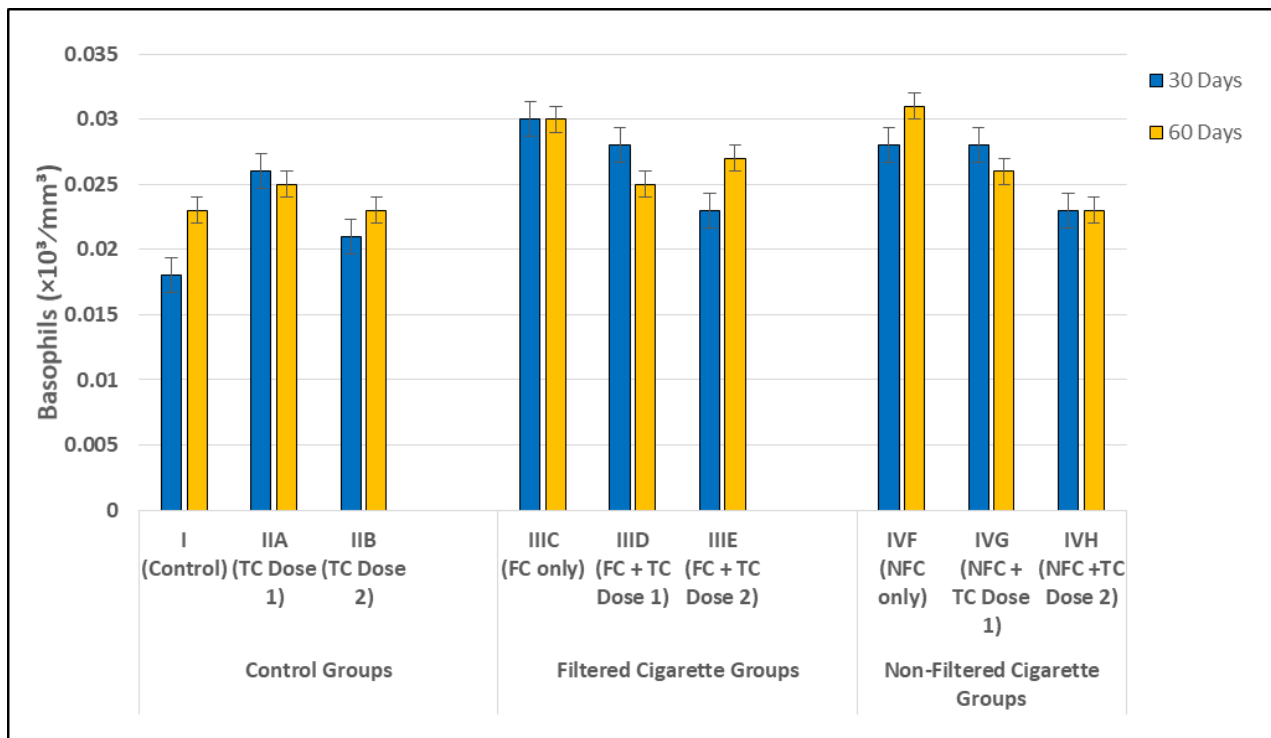


Figure 5. Effect of filtered and non-filtered cigarette smoke on basophils ($\times 10^3/\text{mm}^3$) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days. FC- Filtered cigarette; NFC- Non-filtered cigarette and TC- *Tinospora cordifolia*.

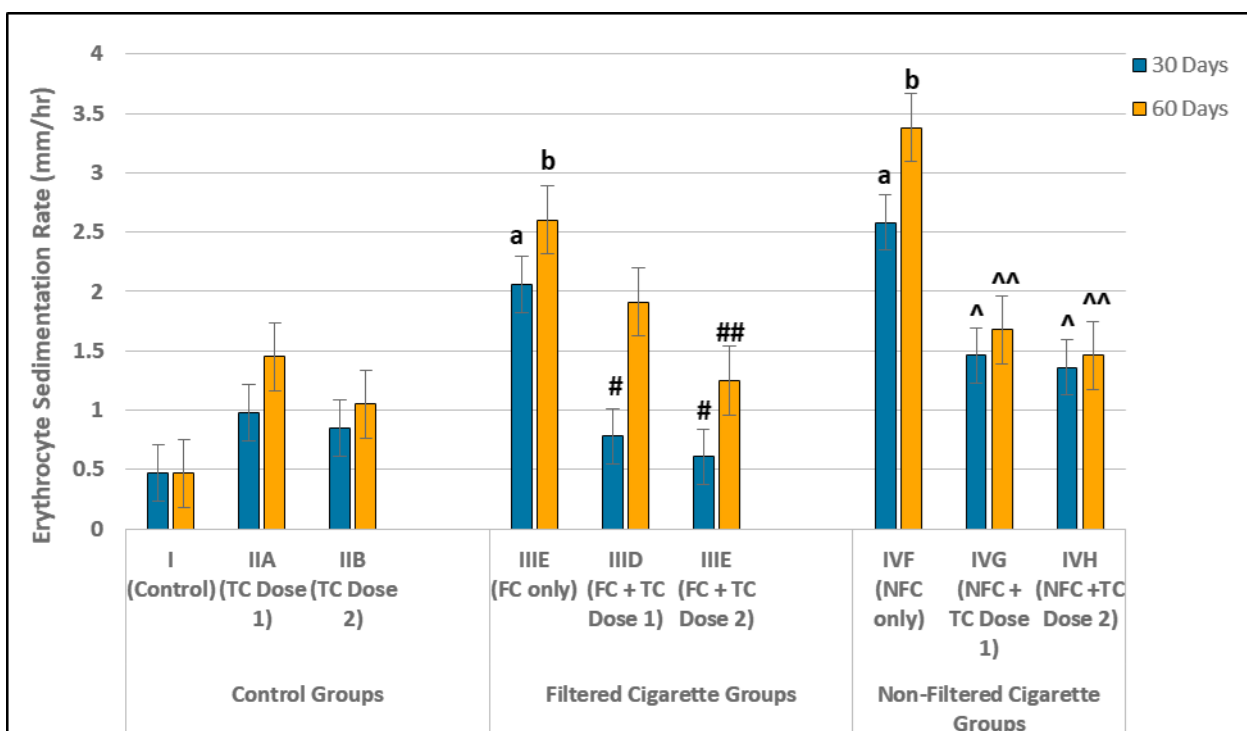


Figure 6. Effect of filtered and non-filtered cigarette smoke on erythrocyte sedimentation rate (mm/hr) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; **a**-Significant difference in comparison to the control after 30 days ($p < 0.05$); **b**- Significant difference in comparison to the control after 60 days ($p < 0.05$); **#**- Significant difference in comparison to Group IIIC after 30 days ($p < 0.05$); **##**- Significant difference in comparison to Group IIIC after 60 days ($p < 0.05$); **^**- Significant difference in comparison to Group IVF after 30 days ($p < 0.05$); **^^**- Significant difference in comparison to Group IVF after 60 days ($p < 0.05$). FC- Filtered cigarette; NFC- Non-filtered cigarette and TC- *Tinospora cordifolia*.

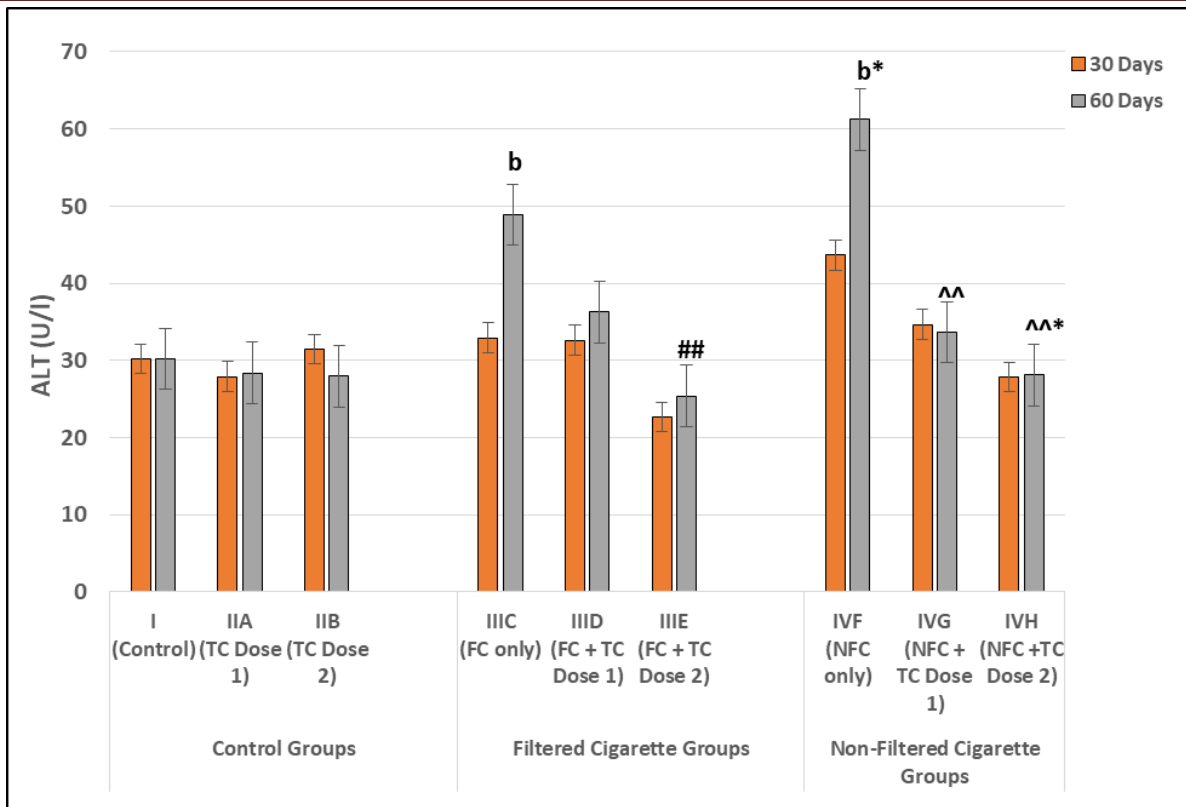


Figure 7. Effect of filtered and non-filtered cigarette smoke on alanine aminotransferase (ALT) (U/l) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; **b**- Significant difference in comparison to the control after 60 days ($p < 0.05$); **##**- Significant difference in comparison to Group IIIC after 60 days ($p < 0.05$); **^^**- Significant difference in comparison to Group IVF after 60 days ($p < 0.05$); *****- Highly significant ($p < 0.001$). FC- Filtered cigarette; NFC- Non-filtered cigarette and TC- *Tinospora cordifolia*.

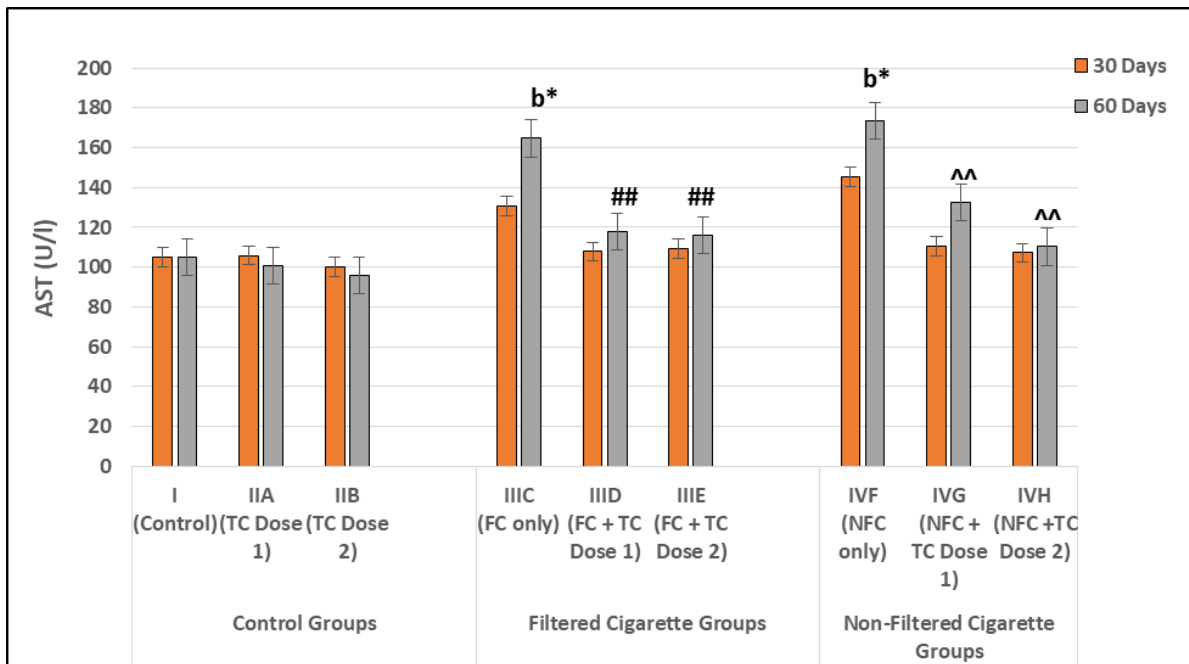


Figure 8. Effect of filtered and non-filtered cigarette smoke on aspartate aminotransferase (AST) (U/l) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; **b**- Significant difference in comparison to the control after 60 days ($p < 0.05$); **##**- Significant difference in comparison to Group IIIC after 60 days ($p < 0.05$); **^^**- Significant difference in comparison to Group IVF after 60 days ($p < 0.05$); *****- Highly significant ($p < 0.001$). FC- Filtered cigarette; NFC- Non-filtered cigarette and TC- *Tinospora cordifolia*.

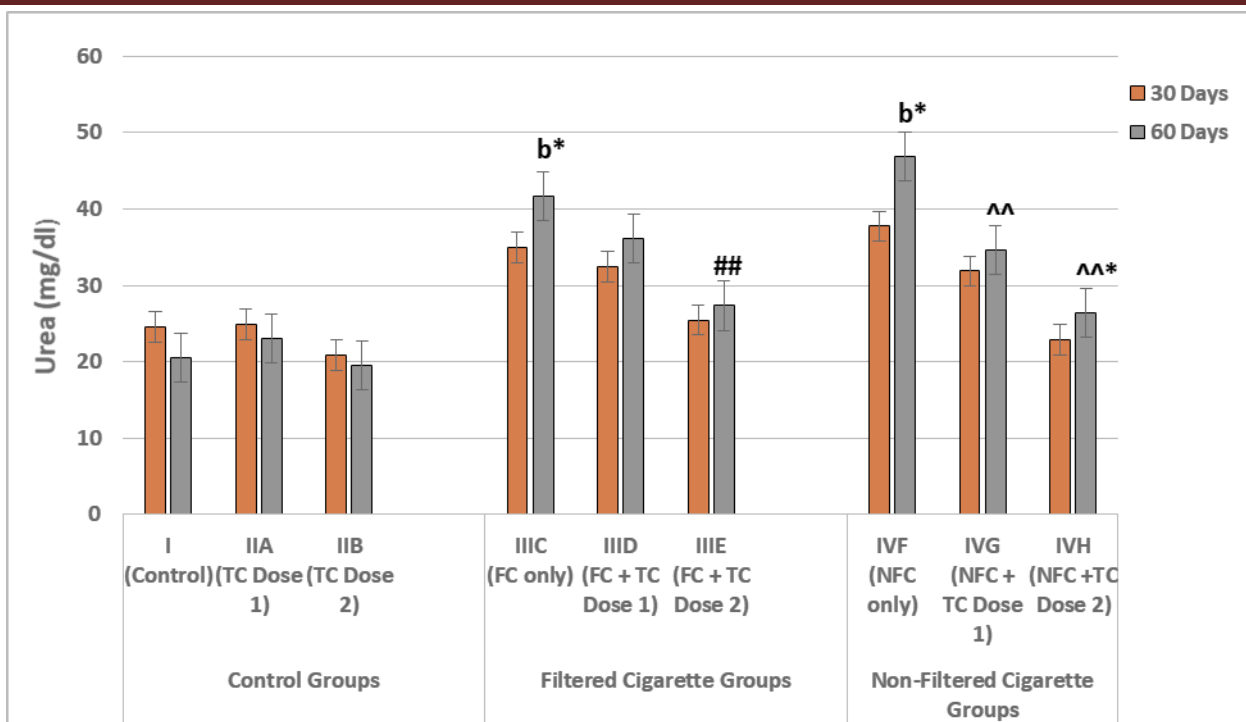


Figure 9. Effect of filtered and non-filtered cigarette smoke on urea (mg/dl) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; **b**- Significant difference in comparison to the control after 60 days ($p < 0.05$); **##**- Significant difference in comparison to Group IIIC after 60 days ($p < 0.05$); **^^**- Significant difference in comparison to Group IVF after 60 days ($p < 0.05$); *****- Highly significant ($p < 0.001$). FC- Filtered cigarette; NFC- Non-filtered cigarette and TC- *Tinospora cordifolia*.

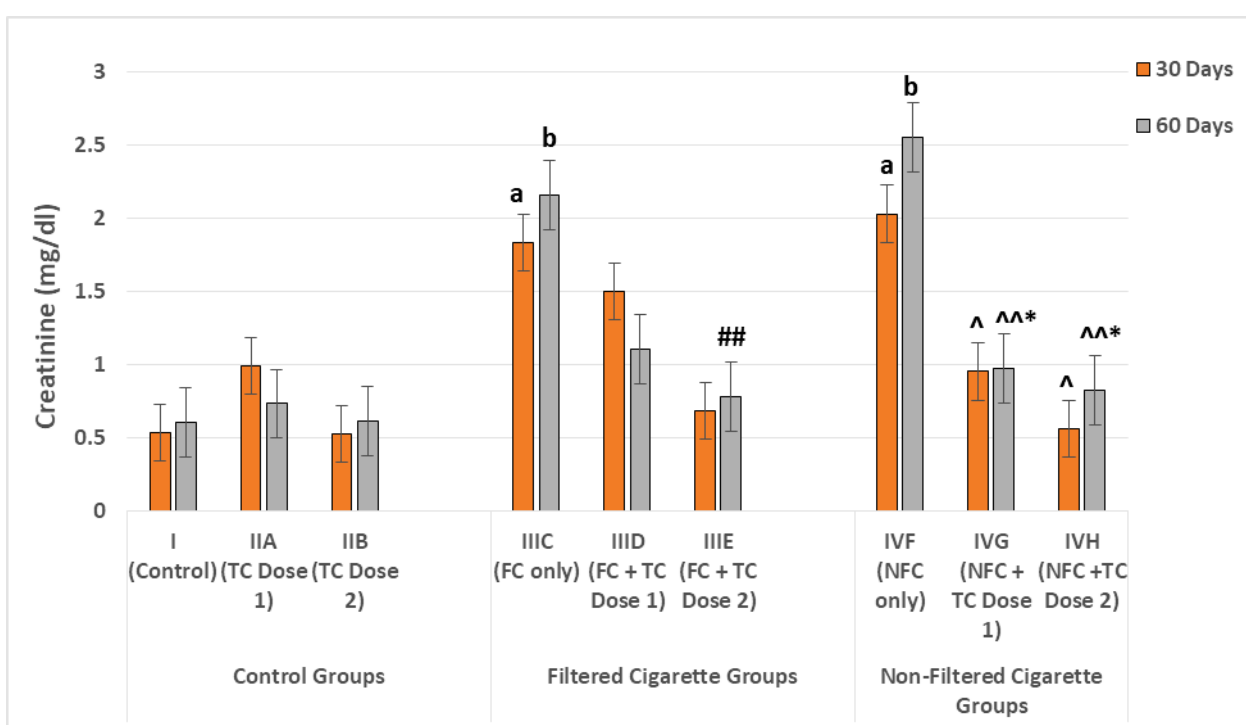


Figure 10. Effect of filtered and non-filtered cigarette smoke on creatinine (mg/dl) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; **a**-Significant difference in comparison to the control after 30 days ($p < 0.05$); **b**- Significant difference in comparison to the control after 60 days ($p < 0.05$); **##**- Significant difference in comparison to Group IIIC after 60 days ($p < 0.05$); **^^**- Significant difference in comparison to Group IVF after 30 days ($p < 0.05$); **^^***- Significant difference in comparison to Group IVF after 60 days ($p < 0.05$); *****- highly significant ($p < 0.001$). FC- Filtered cigarette; NFC- Non-filtered cigarette and TC- *Tinospora cordifolia*.

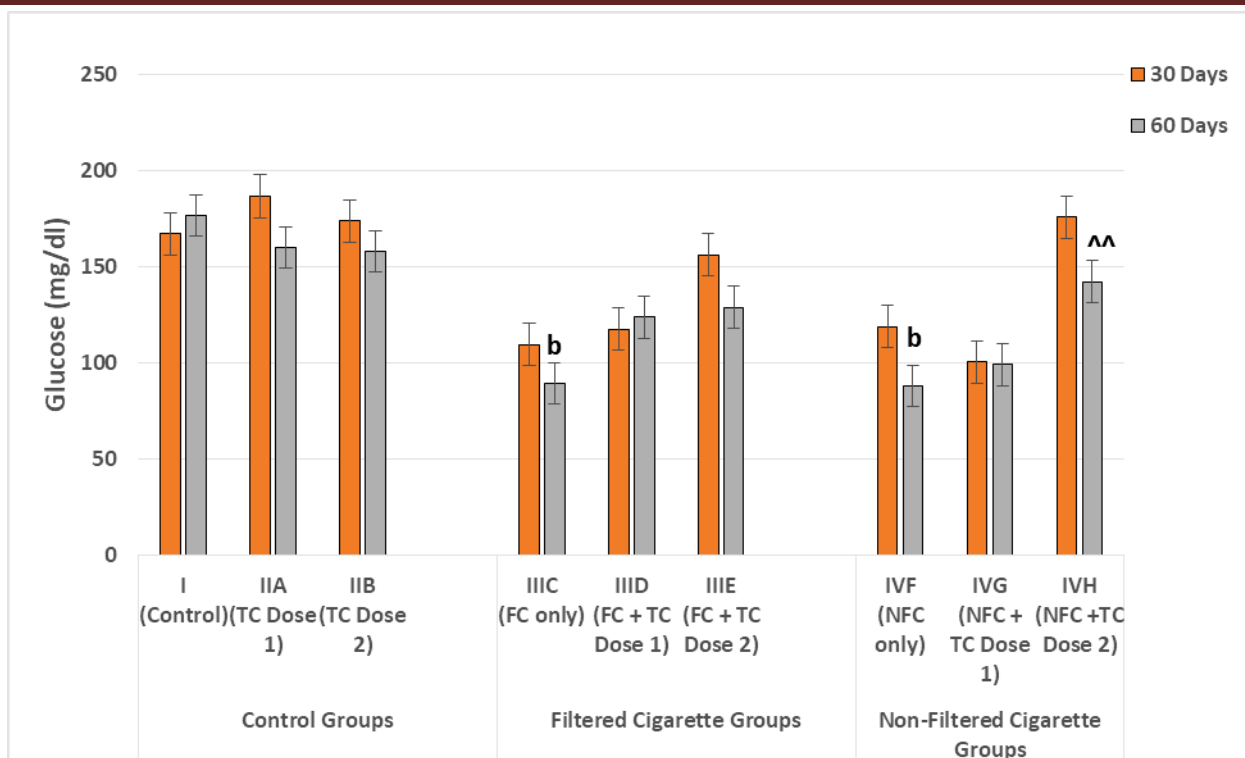


Figure 11. Effect of filtered and non-filtered cigarette smoke on glucose (mg/dl) in albino rats and the effect of *Tinospora cordifolia* after 30 and 60 days; **b**- Significant difference in comparison to the control after 60 days ($p < 0.05$); **^^**- Significant difference in comparison to the IVF group after 60 days ($p < 0.05$). FC- Filtered cigarette; NFC- Non-filtered cigarette and TC- *Tinospora cordifolia*.

Cite this Article:

Khushbu Tarangni Mathur, Geetesh Rawat, Geeta Maheshwari, "Effect of antioxidant activity of *Tinospora cordifolia* on the hemato-biochemical profile in Wistar rats exposed to passive smoking" *International Journal of Scientific Research in Modern Science and Technology (IJSRMST)*, ISSN: 2583-7605 (Online), Volume 3, Issue 3, pp. 32-53, March 2024.

Journal URL: <https://ijrmst.com/>

DOI: <https://doi.org/10.59828/ijrmst.v3i3.194>