KALC 2022 Korean Association for Lung Cancer International Conference
November 10-11, 2022 | Lotte Hotel World, Seoul, Korea

Dual Inhibitory Effects of Resveratrol in Tobacco-Carcinogen Induced Lung Cancer Via Down-Regulation of PI3K/Akt/mTOR pathway

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Introduction

- Lung cancer is a major disease worldwide. Lung cancer accounts for 17% and 9% of all cancers in men and women, respectively, and represents 19% of all cancer-related deaths.
- An estimated 2.1 million peoples are diagnosed with lung cancer annually, and 1.8 million peoples had died till 2018.
- Of all the cases of lung cancer, 80% to 90% are caused by smoking cigarettes.
- Tobacco smoke comprises more than 60 harmful cancer-causing mediators. Among the elements of smoke, benzo(a)pyrene (B(a)P) plays an important role in lung malignancy.
- It metabolically activates into benzo(a)pyrene-7,8-diol-9,10-epoxide that responds through DNA adduct with the development of the disease.
- Benzo(a)pyrene (BaP), a polycyclic aromatic hydrocarbon (PAH) and well-known environmental pollutants.
- The toxic effects of BaP are attributed to increased generation of free radicals and the development of a state of oxidative stress.
- DNA damages mediated by oxidative stress play critical roles in the processes of carcinogenesis and aging.
- it is usually generated by incomplete combustion of organic substances such as automobile exhaust, fossil fuels and most importantly, cigarette smoke.

- Human exposure can occur through inhalation, ingestion, and also by dermal route . BaP can be metabolized in the cells and its metabolites may be involved in the onset of carcinogenic processes.
- The metabolic activation of BaP by the CYP1A1 enzyme can produce reactive oxygen species (ROS) that can also react with DNA to produce DNA adducts.
- Phosphoinositide 3- kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathways is considered as the singling pathway which activates the diverse cellular function viz., survival, cell expansion, vesicular transport and proliferation and found frequently dysregulated pathway in lung cancer.
- Consequently, flavonoids-based inhibitors play a key kinase role in the pathway including mTOR, PI3K and AKT, have been extensively scrutinized in targeting the oncology in recent years.
- The common pathway to PI3K-Akt-mTOR used to target during the lung cancer therapy. Therefore, the current study was aimed to peruse the resveratrol as dual PI3K/mTOR for lung cancer.

Objectives

- OBJECTIVES:-
- To isolate the resveratrol from the grapes.
- Benzo(a)pyrene (B(a)P) was used for the induction the lung cancer in the experimental rats.
- To estimate the Pro-inflammatory cytokines, Inflammatory mediator and antioxidant parameters for explore the possible mechanism of action.
- To estimate the PI3K/Akt/mTOR pathway for explore the possible mechanism of action.

Material and methods

- The rats were divided into six groups and each group contained six rats:
- The rats were divided into following group as follows-
- Gp-I: normal control received only vehicle;
- Gp-II: B(a)P (50 mg/kg b.wt.)
- Gps-III–V B(a)P (50 mg/kg b.wt.) + Resveratrol (5, 10 and 20 mg/kg)
- The experimental animals were received Benzo(a)pyrene (B(a)P) (Starting at 4 to 22 weeks after administration of B(a)P, the rats were given resveratrol). The lungs were harvested, transferred to 70% alcohol, and evaluated for tumors before embedding in paraffin for histology.

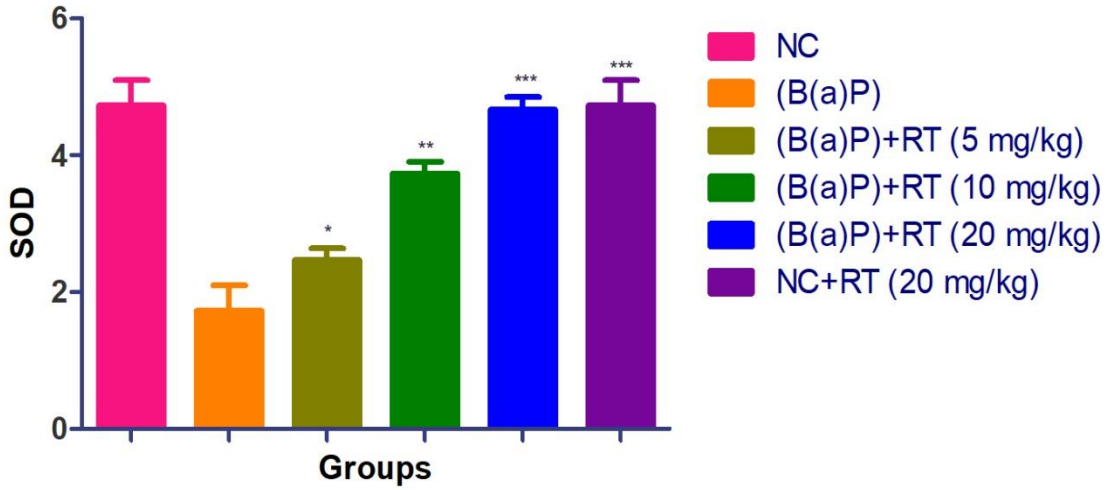
Table 1: Effect of Resveratrol on body weight

Treatment	Initial Body Weight	Final Body Weight
NC	125.43±3.45	283.73±6.03
B(a)P	132±2.93	302.2±17.54
B(a)P+RT (5 mg/kg)	135.34±3.82	254.34±12.3
B(a)P+RT (10 mg/kg)	132.4±5.43	265±11.27
B(a)P+RT (20 mg/kg)	136±3.45	273.45±9.83
NC+RT (20 mg/kg)	123.56±3.67	293.03±5.06

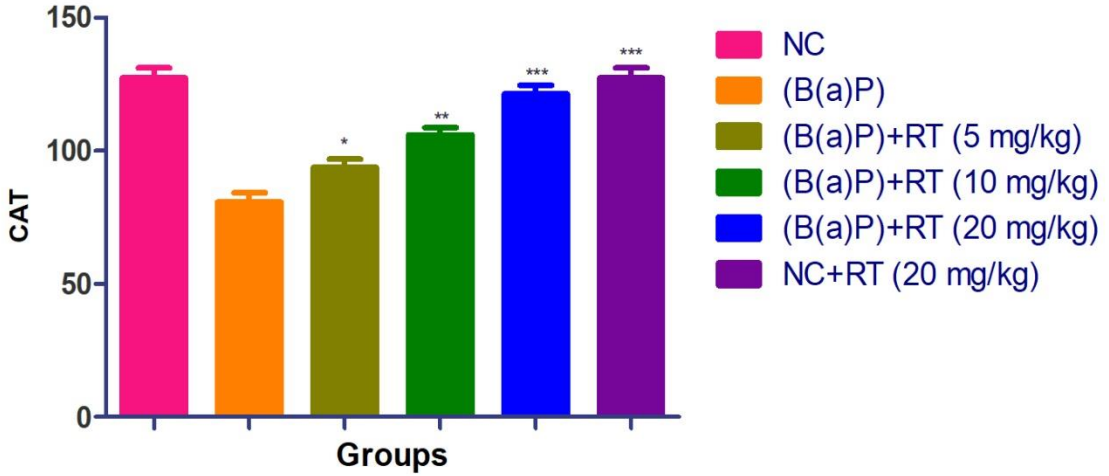
Table 2: Effect of Resveratrol on tumor

S.No	Groups	No of rats with tumors/total rats	Tumor incidence (%)	Total Tumor burden (g)	Inhibition (%)
1	NC	12/12	-	-	-
2	**B(a)P**	10/10	100	92.5	-
3	**B(a)P+RT (5 mg/kg)**	9/11	81.82	78.7	28
4	**B(a)P+RT (10 mg/kg)**	6/10	60	35.4	81
5	**B(a)P+RT (20 mg/kg)**	2/11	18.18	1.2	98
6	**NC+RT (20 mg/kg)**	12/12	-	-	-

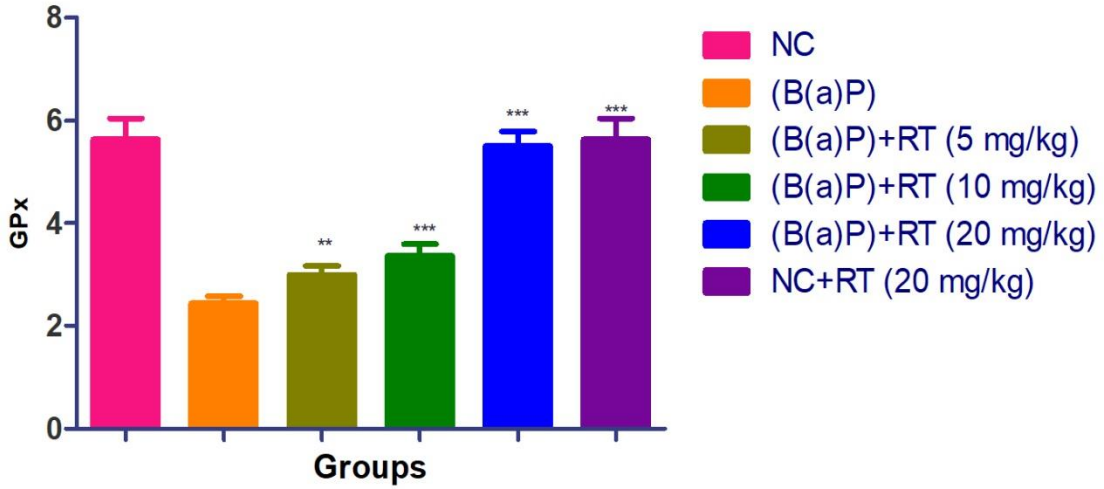
a


SOD
Groups
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

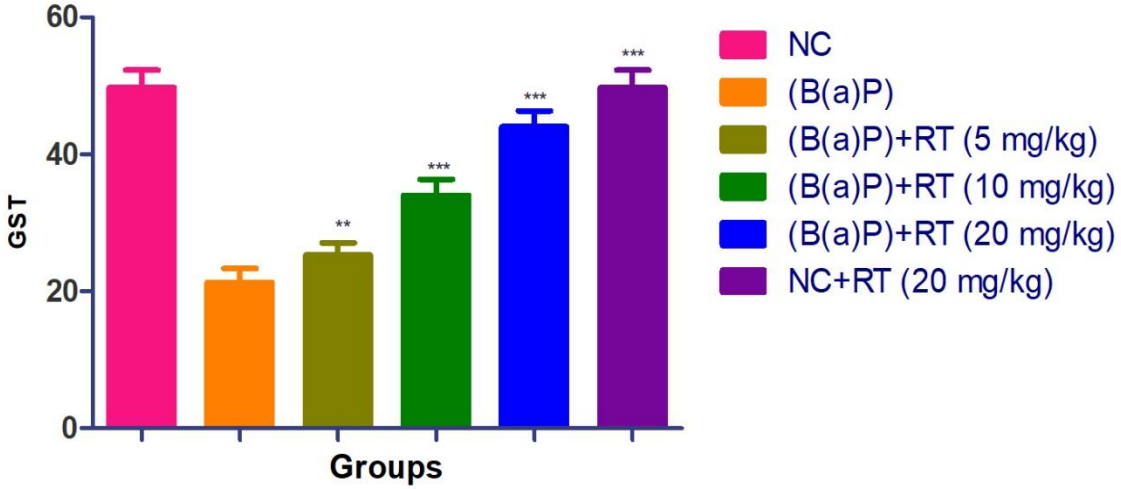
b


CAT
Groups
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

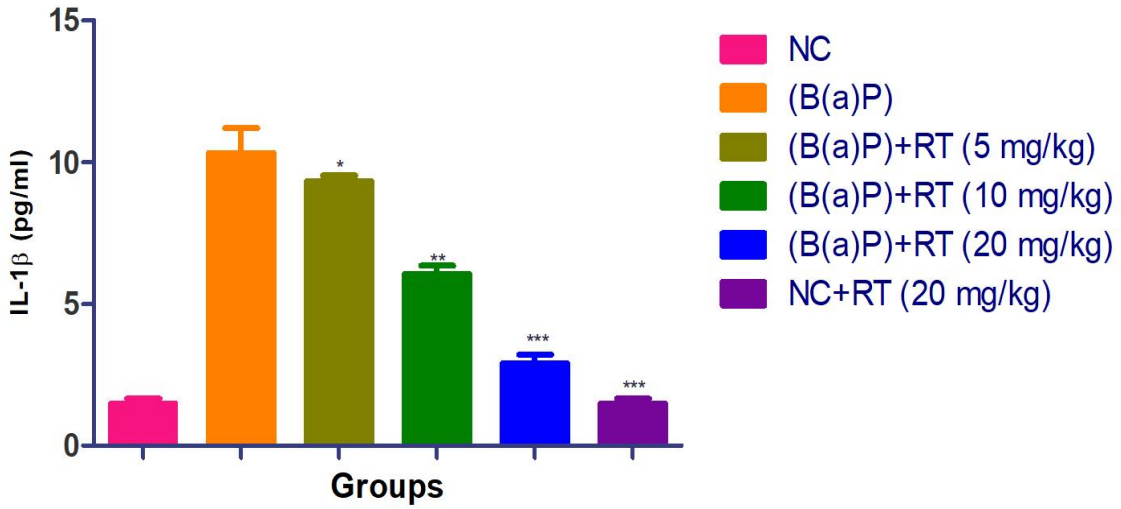
c


GPx
Groups
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

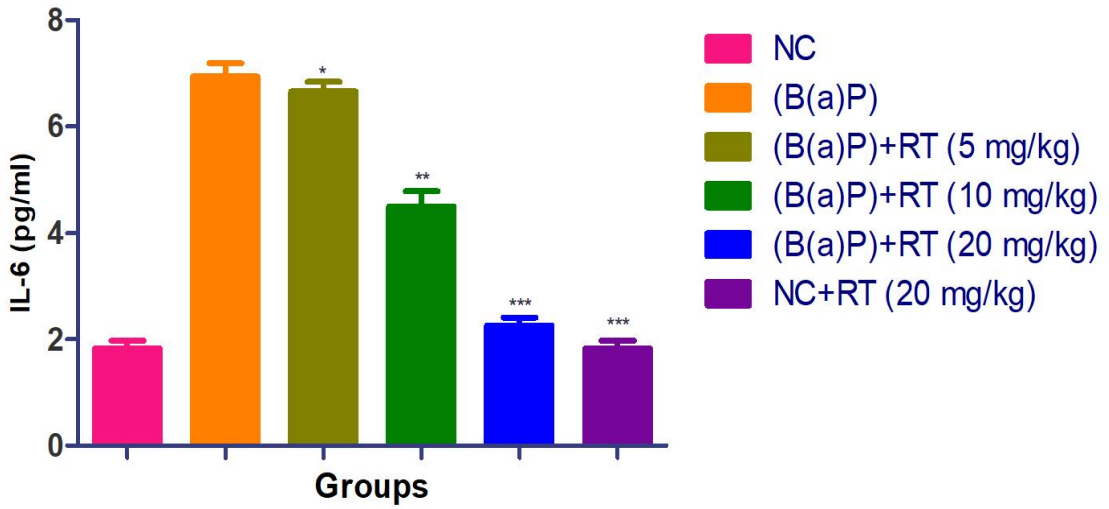
d


GST
Groups
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

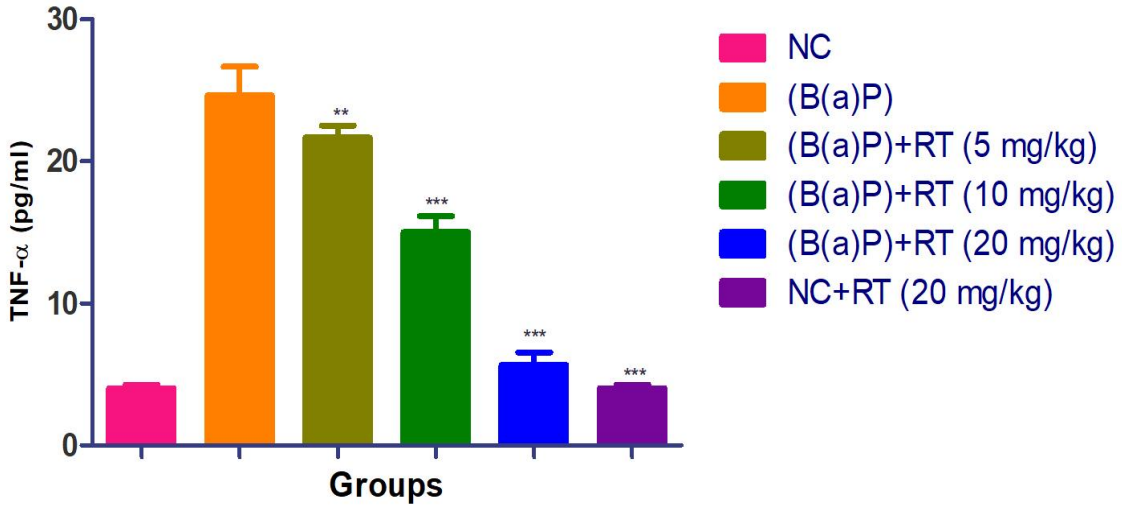
a


15
10
5
0
IL-1β (pg/ml)
Groups
*
**
***
***
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

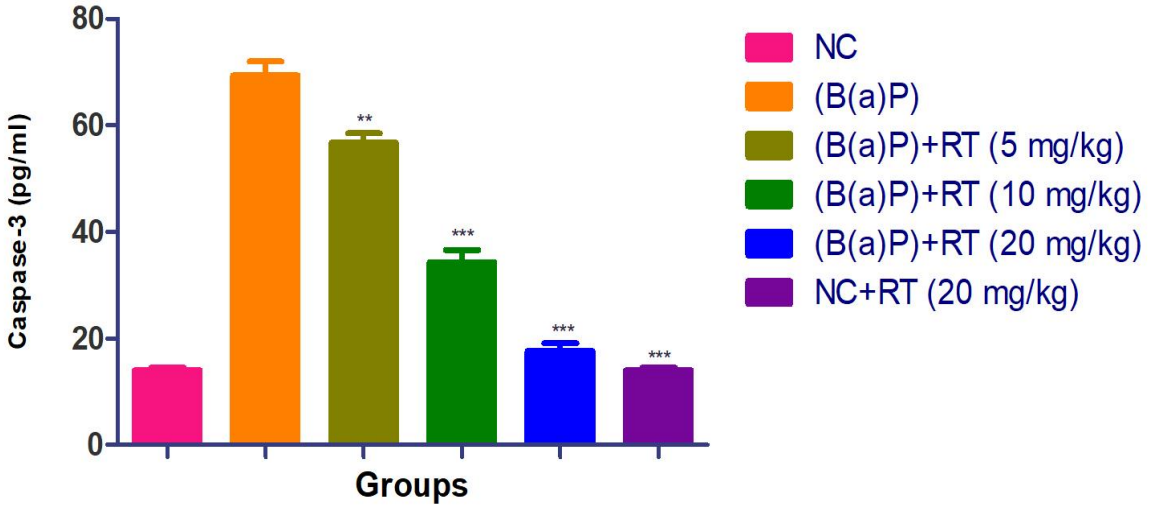
b


8
6
4
2
0
IL-6 (pg/ml)
Groups
*
**
***
***
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

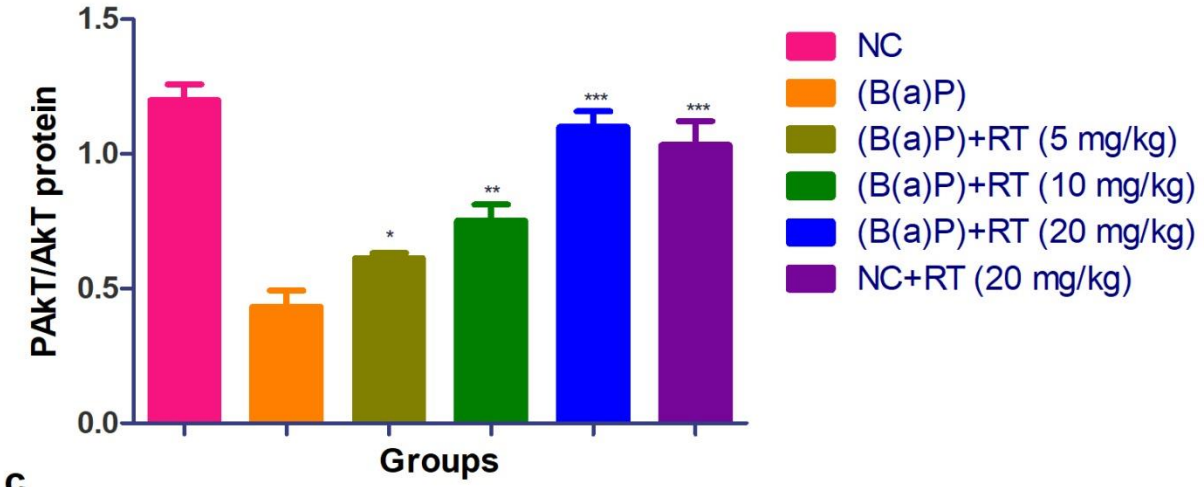
c


30
20
10
0
TNF-α (pg/ml)
Groups
**
***
***
***
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

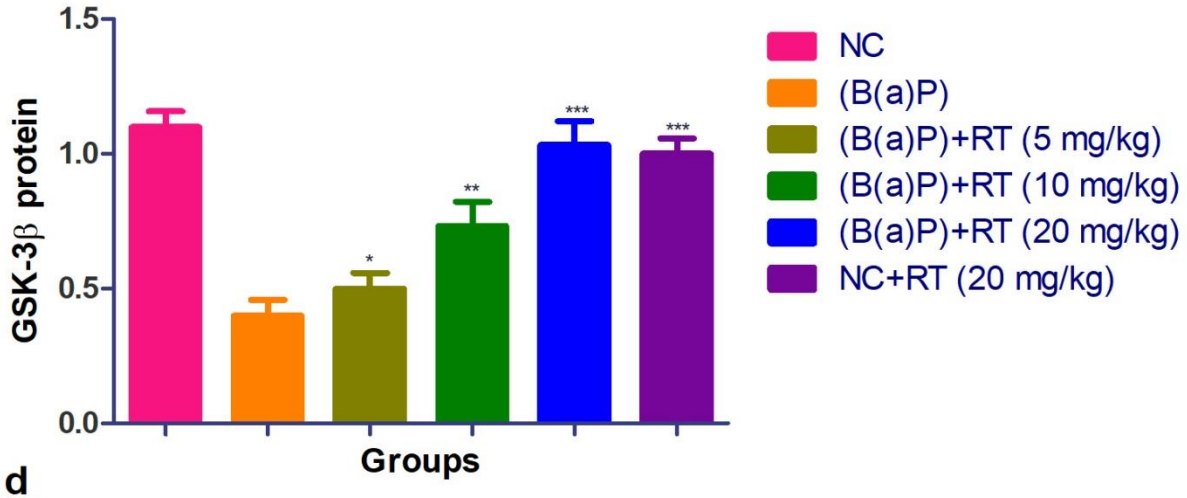
d


80
60
40
20
0
Caspase-3 (pg/ml)
Groups
**
***
***
***
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

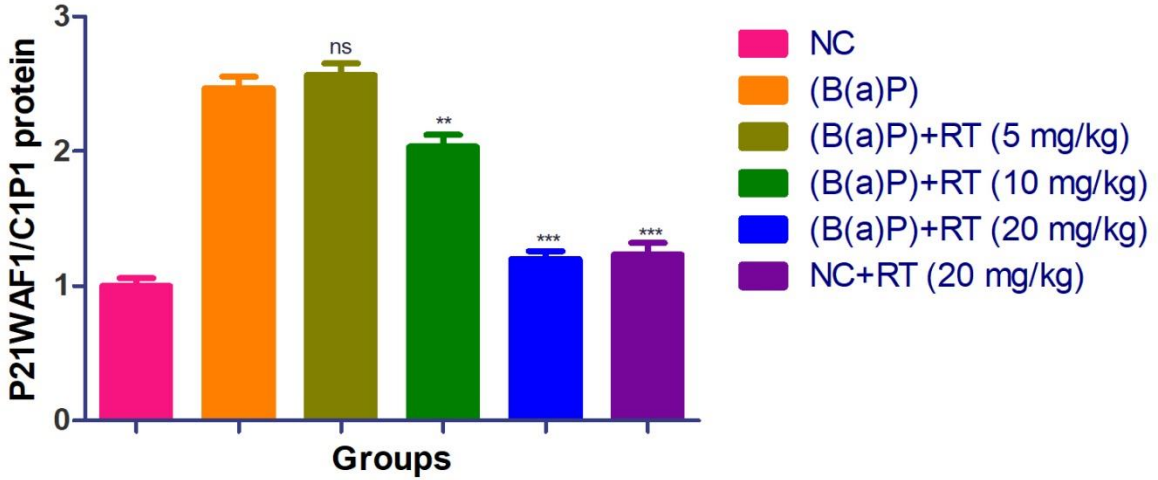
a


PAkT/AkT protein
1.5
1.0
0.5
0.0
*
**
***
***
Groups
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

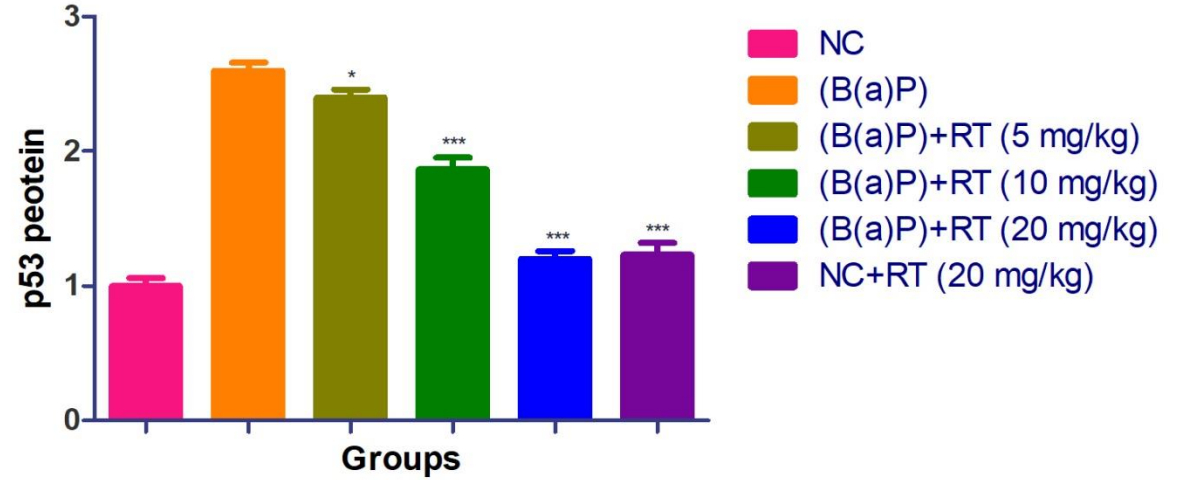
b


GSK-3β protein
1.5
1.0
0.5
0.0
*
**
***
***
Groups
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

c


P21WAF1/C1P1 protein
3
2
1
0
ns
**
***
***
Groups
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

d


p53 peotein
3
2
1
0
*
***
***
***
Groups
NC
(B(a)P)
(B(a)P)+RT (5 mg/kg)
(B(a)P)+RT (10 mg/kg)
(B(a)P)+RT (20 mg/kg)
NC+RT (20 mg/kg)

Conclusion

- Resveratrol successfully isolated from the grapes.
- Finally, the structure of Resveratrol was characterized via using the various spectroscopy techniques.
- Resveratrol showed that the lung protective effect in in tobacco-carcinogen induced lung cancer via down-regulation of PI3K/Akt/mTOR pathway in rats.
- Resveratrol down-regulated the antioxidant parameter.
- Resveratrol exhibited the reduction level of pro-inflammatory cytokines and apoptosis marker.
- Resveratrol altered the antioxidant, inflammatory and apoptotic parameters at dose dependent manner.
- Finally, Resveratrol altered the antioxidant, inflammatory and apoptotic parameters via PI3K/AKT/GSK-3β pathway in rats.