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Original article

Anticancer efficacy and Xenobiotic role of Withaferin A and combination of Paclitaxel -Withaferin A on Benz (a) pyrene induced lung cancer in Wistar rat

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Abstract

Lung cancer is a leading cause of cancer-related morbidity and mortality globally and current chemotherapy treatment protocols have not yielded the desired results, thereby leaving room for alternative therapies. The present study aimed at the chemotherapeutic effect of Withaferin A when combined with paclitaxel against benz (a)pyrene (B(a)P) induced lung cancer in male Wistar rats. Experimental lung carcinogenesis was induced using the chemical B(a)P and subsequently treated with the combination of paclitaxel, Withaferin A and paclitaxel + Withaferin A. Treatment was evaluated for effects by examining xenobiotic-metabolizing enzymes and Phase I and Phase II detoxification systems. B (a) P administration led to significant changes in Phase I enzymes such as cytochrome P450, cytochrome b5 and NADPH–cytochrome c reductase, suggesting an increased metabolism of carcinogenic compounds and impairment of microsomal enzyme function. Changes were also seen in Phase II detoxification enzymes such as glutathione-S-transferase (GST) and UDP-glucuronosyltransferase (UDP-GT) which indicated that the detoxification capacity was impaired during carcinogenesis. Treatment with paclitaxel and Withaferin A alone was effective in improving these biochemical changes, but the combination of the two was more effective in restoring enzyme activities to control levels. The results show that overall, Withaferin A can improve the therapeutic effectiveness of paclitaxel by altering the metabolism of xenobiotics and the ability of the cells to detoxify.

Keywords: *Withaferin A, Paclitaxel, Benzo (a) pyrene, Lung cancer, Cytochrome P450.*

Introduction

Lung cancer is one of the most common and fatal malignancies worldwide, affecting both men and women. Despite advances in diagnosis and treatment, its incidence and mortality remain high. Tobacco smoking is the principal risk factor for lung cancer, and cigarette smoke contains numerous established carcinogens. Among these carcinogenic constituents, polycyclic aromatic hydrocarbons (PAHs), particularly benzo(a)pyrene [B(a)P], play an important role

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in the initiation and progression of lung carcinogenesis [1-3]. The World Health Organization has identified lung cancer as one of the most frequently occurring cancers globally. Its incidence continues to increase in several developing countries, partly because of the continuing spread of tobacco use. Among the carcinogenic compounds present in tobacco smoke, B(a)P is of particular importance because it requires metabolic activation to exert its mutagenic and carcinogenic effects. B(a)P is bio activated primarily by cytochrome P450 (CYP) enzymes. The initial metabolic step involves the formation of B(a)P-7,8-epoxide, which is subsequently hydrolyzed by epoxide hydrolase (EH) to form B(a)P-trans-7,8-dihydrodiol (7,8-diol). Further oxidation by CYP enzymes generates the highly reactive ultimate carcinogen, (±)-B(a)P-r-7,t-8-dihydrodiol-t-9,10-epoxide (BPDE). Paclitaxel, a taxane-class antineoplastic agent, was originally isolated from the bark of the western yew tree, Taxus brevifolia. It subsequently demonstrated significant antitumor activity and underwent extensive clinical development because of its efficacy against several malignancies, including lung cancer. Paclitaxel exerts its antitumor effect primarily by interfering with microtubule dynamics and inhibiting normal mitotic progression, ultimately leading to cell-cycle arrest and cancer-cell death [4,5]. Although paclitaxel is an effective chemotherapeutic agent, its clinical use is associated with several adverse effects, including neutropenia, peripheral neuropathy, and hypersensitivity reactions.

Withaferin A is a naturally occurring steroidal lactone derived from Withania somnifera (L.) Dunal (Solanaceae), commonly known as Ashwagandha. Withania somnifera is an important medicinal plant widely used in Ayurveda, the traditional system of medicine in India, and has historically been employed as a remedy for a variety of ailments. Withaferin A is considered one of the major bioactive constituents of the plant and has attracted considerable attention because of its reported antioxidant, anti-inflammatory, immunomodulatory, and antitumor properties [6,7]. Recent studies have demonstrated that Withaferin A possesses significant anticancer activity against lung cancer cells and may affect pathways involved in proliferation, apoptosis, epithelial-to-mesenchymal transition, cancer stem-cell characteristics, and metastasis [8,9] and also minimize the side effects.

MATERIALS AND METHODS

Healthy male Wistar rats (150-200gms) were used throughout the study. The animals were purchased from mass biotech, Chengalpattu, India, and maintained in a controlled environmental condition of temperature and humidity on alternatively 12 hr light/dark cycles. All animals were fed standard pellet diet and water *ad libitum.* This research work on Swiss albino mice was sanctioned and approved by the Institutional animal ethical committee.

The animals were divided into **FIVE** groups and each group consists of six animals.

Group I : Control animals treated with corn oil (vehicle) orally.

Group II : B(a)p treated (50 mg/kg body weight dissolved in corn oil, orally) twice weekly for 4 successive weeks to induce lung cancer.

Group III : Lung cancer bearing animals (after 12 weeks of induction) treated with paclitaxel (33mg/kg b.wt, i.p) for four weeks.

. Group IV : Lung cancer bearing animals treated with paclitaxel (as above) along with *Withaferin A* (400 mg/kg b.wt) orally for four weeks.

Group V : Control animals treated with paclitaxel along with *Withaferin A* (as above).

At the end of the experimental period, the animals were fasted overnight and euthanized by cervical decapitation. Blood samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA) for the separation of plasma and into tubes without anticoagulant for serum separation. The blood samples were subsequently used for the estimation of various hematological and biochemical parameters. Following blood collection, the lung and liver tissues were carefully excised from all experimental animals, immediately washed with ice-cold physiological saline to remove adhering blood, and processed for further biochemical and histopathological analyses

Sources of Chemicals

Benzo(a)pyrene, was obtained from Sigma Chemical Company, St. Louis, MO, USA. Paclitaxel was purchased from Dabur India Ltd, Solan, India. *Withania somnifera* root powder was purchased from Indian Medical Practitoners Co-operative Pharmacy & Stores Ltd, Chennai, India. *Withaferin A* was extracted in 95% v/v ethanol in a hermetically closed glass vessel for 4 days at 37^{o}C under occasional shaking. The ethanolic extract was then filtered through a Whatman filter paper #4 and evaporated in a rotary evaporator under reduced pressure at 60^{o} C.

Biochemical Analysis

The activity of NADPH-cytochrome C reductase was assayed by the method of Phillips and Langdon (1962). The UDP-Glucuronyl transferase was estimated by the method of Issalbacher *et al.* (1962) modified by Hollman and Touster (1962). Glutathione S-transferase was assayed by the method of Habig *et al.* (1974).

Statistical Analysis

The data for each variable are expressed as mean ± standard deviation (SD). Statistical significance among the groups was assessed using one-way analysis of variance (ANOVA), followed by the least significant difference (LSD) test for multiple comparisons. A *p*-value of less than 0.05 was considered statistically significant

Results

Phase I enzymes

Table 1 shows the effect of paclitaxel along with *Withaferin A* on the activities of Phase I enzymes such as Cyt P_{450}, Cyt b_5 and NADPH Cyt C reductase in the lung of control and experimental animals. The activities of phase I enzymes were found to be significantly ($p<0.001$) increased in cancer bearing group II animals when compared with the control group (G-I). Paclitaxel (G-III) treatment caused a significant ($p<0.001$; $p<0.01$) decrease in the activity of these enzymes Cancer bearing group treated with a combination of paclitaxel and *Withaferin A* (G-IV) showed a much significant ($p<0.001$) decrease in the activities of these enzymes when compared with the cancer-induced group. However, there found to be no significant difference in the activities of these phase I enzymes between the control animals and the control animals treated with the paclitaxel and *Withaferin A* (G-V).

Table 1. Antitumor Efficacy of paclitaxel along with *Withaferin A* on phase I enzymes in lung of control and experimental animals

Particulars	Group I	Group II	Group III	Group IV	Group V
Cytochrome P_{450}	0.58 ± 0.05	0.88 ± 0.08^{a*}	0.79 ± 0.07^{b*}	0.69 ± 0.06^{b*}	0.63 ± 0.06
Cytochrome b_5	0.39 ± 0.04	0.59 ± 0.05^{a*}	0.52 ± 0.05^{b*}	0.41 ± 0.04^{b*}	0.40 ± 0.04
NADPH Cytochrome C reductase	142.00 ± 14.00	215.00 ± 21.00^{a*}	188.00 ± 18.00$^{b@}$	151.00 ± 9.00^{b*}	145.00 ± 14.00

Each value is expressed as mean □ SD for six mice in each group.
Cytochrome P_{450} and Cytochrome b_5 - nmol/mg protein.
NADPH Cytochrome C reductase - nmol of Cytochrome C reduced/min/mg protein.

a: Group II compared with Group I.
b: Group II compared with Group III and IV.
Statistical significance: * $p<0.001$ $^{@}$ $p<0.01$ $^{\#}$ $p<0.05$

Table 2 represents the effect of Paclitaxel along with *Withaferin A* on the activities of Phase I enzymes such as Cyt P_{450}, Cyt b_5 and NADPH Cyt C reductase in the liver of control and experimental animals. The activities of these phase I enzymes were found to be significantly ($p<0.001$) increased in cancer bearing group II animals when compared with the control group (G-I).

Administration of paclitaxel (G-III) caused a significant ($p<0.001$; $p<0.01$) decrease in these enzyme activities when compared with cancer bearing animals. Animals treated with paclitaxel and *Withaferin A* (G-IV) showed a very significant ($p<0.001$) decrease in the activities of these enzymes when compared with the cancer-induced group. However, there found to be no significant difference in the activities of these phase I enzymes between the control animals and the control animals treated with the combination of paclitaxel and *Withaferin A* (G-V).

Table 2. Antitumor Efficacy of paclitaxel along with *Withaferin A* on phase I enzymes in liver of control and experimental animals

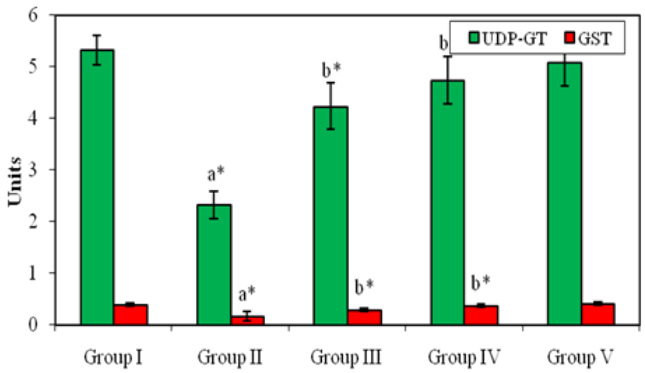
Particulars	Group I	Group II	Group III	Group IV	Group V
Cytochrome P_{450}	0.70 ±0.07	0.91 ± 0.09^{a*}	0.77 ± 0.0^{b*}	0.83 ± 0.04$^{b@}$	0.69 ± 0.06
Cytochrome b_5	0.47 ± 0.04	0.72 ± 0.07^{a*}	0.62 ± 0.06$^{b@}$	0.52 ± 0.05^{b*}	0.46 ± 0.04
NADPH cytochrome C reductase	159.00 ± 15.00	209.00 ± 20.00^{a*}	179.00 ± 17.00$^{b@}$	175.00 ± 16.00^{b*}	165.00 ± 14.00

Each value is expressed as mean ± SD for six mice in each group.
Cytochrome P_{450} and Cytochrome b_5 - nmol/mg protein.
NADPH Cytochrome C reductase - nmol of Cytochrome C reduced/min/mg protein.
a: Group II compared with Group I; b: Group II compared with Group III and IV.
Statistical significance: * p<0.001 @ p<0.01 # p<0.05

Phase II enzymes

Fig. 1 depicts the effect of paclitaxel along with *Withaferin A* on the activities of Phase II enzymes such as UDP, GST and QR in the lung of control and experimental animals. The activities of these phase II enzymes were found to be significantly (p<0.001) decreased in cancer bearing group (G-II) when compared with the control animals (G-I). On treatment with paclitaxel (G-III) there found to be a significant increase in these enzyme activities when compared with cancer bearing animals. Paclitaxel and *Withaferin A* treated animals (G-IV) showed a much significant (p<0.001) increase in the activities of these enzymes when compared with the cancer-induced group. However, there found to be no significant difference in the activities of these phase II enzymes between the control animals and the control animals treated with both paclitaxel and *Withaferin A* (G-V).

Fig.1 Antitumor efficacy of paclitaxel along with *Withaferin A* on the phase II enzymes in lung of control and experimental animals

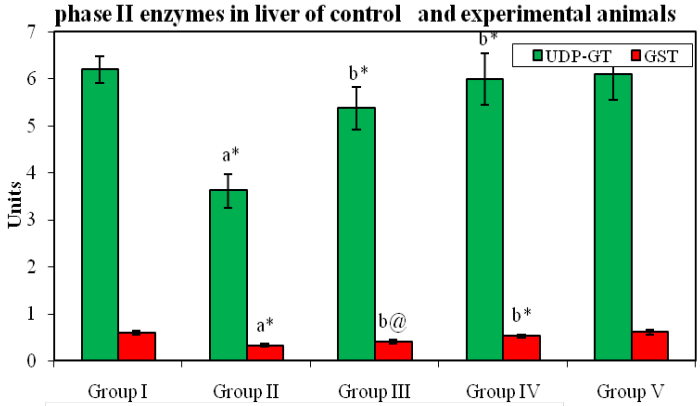


Units
UDP - Glucuronyl transferase - Units/min/mg protein
GST - mmol of CDNB conjugated/min/mg protein
Each value is expressed as mean + SD for six mice in each group
a : Group II compared with Group I; b : Group II compared with

Fig.2 shows the effect of paclitaxel along with *Withaferin A* on the activities of Phase II enzymes in the liver of control and experimental animals. The activities of UDPGT and GST were found to be significantly (p<0.001)

decreased in cancer bearing group II animals when compared with the control group (G-I). Paclitaxel (G-III) treatment caused a significant ($p<0.001$; $p<0.01$) increase in these enzyme activities when compared with cancer bearing animals. Cancer bearing group treated with a combination of paclitaxel and *Withaferin A* (G-IV) showed a highly significant ($p<0.001$) decrease in the activities of these enzymes when compared with the cancer-induced group. However, there found to be no significant difference in the activities of these phase II enzymes between the control animals and the control animals treated with the combination of paclitaxel and *Withaferin A* (G-V).

Fig.2 Antitumor efficacy of paclitaxel along with *Withaferin A* on the phase II enzymes in liver of control and experimental animals



Units
UDP - Glucuronyl transferase - Units/min/mg protein
GST - mmol of CDNB conjugated/min/mg protein
Each value is expressed as mean + SD for six mice in each group
a : Group II compared with Group I; b : Group II compared with

Discussion

Lung cancer is one of the leading causes of cancer-related mortality worldwide. Despite considerable advances in the understanding of the molecular and biological mechanisms underlying lung cancer, the development of effective therapeutic strategies remains a major challenge. Nevertheless, the emergence of therapies targeting specific biological abnormalities associated with lung cancer has provided new opportunities for improving treatment outcomes [7]. Antioxidant defense mechanisms constitute an important component of cellular protection against oxidative stress and can broadly be categorized into prevention, interception, and repair mechanisms. Different tissues and organs possess distinct antioxidant defense systems depending on their physiological and metabolic requirements [10, 11].

The “war against cancer” remains far from over, highlighting the continuing limitations of conventional anticancer therapies in reducing cancer-related mortality. Although advances in chemotherapy have resulted in prolonged survival and improved quality of life in some lung cancer patients, the overall therapeutic benefits remain limited, particularly in advanced disease [7]. These limitations emphasize the need for novel therapeutic approaches and combination strategies that can improve treatment efficacy while minimizing adverse effects.

Phase I biotransformation reactions primarily include oxidation, reduction, and hydrolysis, which generally convert lipophilic xenobiotics into more polar metabolites. Cytochrome P450 (CYP) enzymes represent the major group of Phase I enzymes involved in the metabolism of a wide range of endogenous and exogenous compounds. Cytochrome P450 functions as a terminal oxidase in the microsomal electron transport system and plays an important role in the metabolism of numerous xenobiotics [12]. However, CYP-mediated metabolism may also result in the metabolic activation of several chemical carcinogens, including polycyclic aromatic hydrocarbons (PAHs), thereby generating reactive intermediates capable of inducing cellular and DNA damage [3,12]. Alterations in the microsomal monooxygenase system have been reported during carcinogenesis, and CYP enzymes have been implicated in the metabolism and activation of carcinogenic compounds associated with lung cancer. Such changes suggest that tumor development and exposure to carcinogens can substantially influence xenobiotic-metabolizing enzyme systems [3,12].

In the present study, the activities of Phase I enzymes, namely cytochrome P450, cytochrome b5, and NADPH–cytochrome c reductase, were significantly altered in lung cancer-bearing animals. The increased activities observed in the cancer-bearing group may reflect enhanced xenobiotic metabolism and metabolic activation of carcinogenic compounds during B(a)P-induced lung carcinogenesis. Treatment with paclitaxel and Withaferin A, particularly in combination, restored these enzyme activities toward the values observed in the control animals. These findings suggest that the combination treatment may modulate the altered microsomal enzyme system associated with B(a)P-induced carcinogenesis and may contribute to its chemopreventive and chemotherapeutic effects [3,12].

The induction of Phase II detoxification enzymes is widely recognized as an important cellular defense mechanism against endogenous and exogenous toxic compounds, including reactive oxygen species and chemically reactive carcinogenic metabolites. Phase II enzymes facilitate the conjugation and subsequent elimination of electrophilic compounds generated during Phase I metabolism. The chemotherapeutic and chemopreventive actions of certain compounds may therefore involve multiple biochemical mechanisms, including modulation of drug-metabolizing enzymes and enhancement of antioxidant defenses. Some chemopreventive agents have been described as bifunctional inducers because they can modulate both Phase I and Phase II detoxification enzymes [12].

UDP-glucuronosyltransferase (UDP-GT) and glutathione-S-transferase (GST) are important components of the Phase II detoxification system and are frequently used as biochemical indicators of cellular responses to carcinogen exposure and oxidative stress. Antioxidant systems, together with Phase II enzymes such as GST and non-enzymatic water-soluble antioxidants, provide an important defense against oxidants and reactive metabolites generated from procarcinogens. Alterations in antioxidant defense mechanisms can contribute to oxidative stress and may influence cellular responses during carcinogenesis [10].

GSTs comprise a family of detoxification enzymes that catalyze the conjugation of reduced glutathione (GSH) with a broad range of electrophilic and hydrophobic compounds. This conjugation generally produces more water-soluble metabolites that can be readily eliminated through the bile or urine. GSTs can also participate in the detoxification of several carcinogenic electrophiles by facilitating their conjugation with GSH. Consequently, induction of GST and related detoxification pathways may increase the capacity of cells to inactivate potentially harmful electrophilic metabolites [12].

In the present investigation, treatment with paclitaxel and Withaferin A resulted in increased activities of UDP-glucuronosyltransferase and GST compared with the untreated cancer-bearing animals. The stimulation of these Phase II enzymes may enhance the detoxification and elimination of reactive metabolites generated during B(a)P-induced carcinogenesis. The increased GST activity observed following Withaferin A treatment is consistent with the reported ability of Withaferin A to activate cellular antioxidant and cytoprotective pathways, including the Keap1/Nrf2 pathway, which regulates antioxidant and Phase II detoxification responses [13]. Enhancement of Phase II enzyme activities may therefore represent one of the possible mechanisms underlying the anticarcinogenic and chemotherapeutic potential of paclitaxel and Withaferin A.

Overall, the present study was undertaken to evaluate the chemotherapeutic efficacy of Withaferin A in combination with paclitaxel against B(a)P-induced lung cancer in male Swiss albino mice. The findings indicate that B(a)P-induced lung carcinogenesis was associated with marked alterations in xenobiotic-metabolizing and detoxification enzymes. In particular, alterations in the activities of Phase I enzymes were accompanied by changes in Phase II detoxification enzymes. Treatment with paclitaxel and Withaferin A, particularly their combination, effectively modulated these enzyme activities toward normal levels. The observed restoration of cytochrome P450, cytochrome b5, and NADPH–cytochrome c reductase activities, together with enhancement of GST and UDP-GT activities, suggests improved regulation of xenobiotic metabolism and detoxification [3].

Conclusion

This study provides an example of significant changes in xenobiotic metabolizing enzymes, antioxidants, as well as Phase I and Phase II detoxification systems in lung carcinogenesis caused by B(a)P. An increase in the activity of Phase I enzymes, such as cytochrome P450, cytochrome b5 and NADPH cytochrome c reductase, indicate more metabolic activation of carcinogenic compounds and impaired normal microsomal enzyme activity during the development of the tumour. On the other hand, changes in Phase II enzymes, especially UDP-

glucuronosyltransferase and glutathione-S-transferase, suggest decreased detoxification and elimination of reactive metabolites. These biochemical changes were improved with either paclitaxel alone, or Withaferin A alone, and more markedly with paclitaxel and Withaferin A together, compared to untreated controls. The increased activity of detoxification enzymes (Phase II) along with better regulation of xenobiotic metabolism indicates that Withaferin A might synergize the antitumor activity of paclitaxel by reinforcing cellular defense and detoxification systems. Based on these results, Withaferin A is a promising natural product for use as a chemosensitizer in conventional chemotherapy. On a global level, the synergism of Withaferin A and paclitaxel might be a promising therapeutic approach for chemically-induced lung carcinogenesis by acting as a multifaceted modulatory effect on the carcinogen metabolism, detoxification pathways, and cellular protective mechanisms.

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