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Research Article

Anticancer Effects of *Bumelia sartorum* Stem Bark Extracts on Human Lung Carcinoma Cell Line

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Abstract

Lung cancer has remained one of the most prevalent and lethal malignancies worldwide for several decades. Despite the availability of various therapeutic interventions, there is still an urgent need for novel treatment strategies, with phytotherapy emerging as a promising alternative. In this study, the effects of B. sartorum stem bark extracts on the viability of human lung carcinoma cell lines were evaluated to assess their potential anti-cancer activity. Additionally, the chemical profile of the dichloromethane extract was analysed. Extracts obtained through liquid-liquid partition with dichloromethane and ethyl acetate demonstrated significant inhibitory effects on the viability of lung cancer cell lines, contributing to the search for new therapeutic agents for next-generation chemotherapeutic development.

Keywords: *Bumelia sartorum*, Anticancer, Lung cancer, Cell viability, Phytochemistry, Sapotaceae, Procyanidins, Ethnopharmacology, Epicatechin, Chemotherapy resistance

Abbreviations: DMSO: dimethyl sulfoxide; EC: epicatechin; ECG: epicatechin-3-gallate; EGC: epigallocatechin; EGCG: epigallocatechin-3-gallate; EMT: epithelial-mesenchymal transition; GC-MS: gas chromatography-mass spectrometry; GTCs: green tea catechins; JAK2: Janus kinase 2; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide; RT: retention time; STAT3: signal transducer and activator of transcription 3

Introduction

Cancer represents a major public health challenge and remains one of the leading causes of mortality worldwide. In 2020, it accounted for approximately 10 million deaths, corresponding to nearly one in six fatalities [1]. The term "cancer" encompasses a group of diseases characterized by uncontrolled and dysregulated cellular proliferation, which can affect any part of the body. This unregulated growth often leads to local invasion of adjacent tissues and may result in the dissemination of malignant cells to distant sites a process known as metastasis, which is the primary cause of cancer-related mortality. Other commonly used terms include malignant tumors and neoplasms [2]. Lung cancer has remained one of the most prevalent malignant tumors for several decades, ranking as the second leading cause of cancer-related mortality worldwide [1]. In some developed countries, it has become the primary cause of cancer-related deaths [2]. In Brazil, recent statistics from 2023 indicate that lung cancer is the third most common cancer among men and the fourth most common among women, according to data from the National Cancer Institute [3]. Approximately one-third of cancer-related deaths are attributed to risk factors such as tobacco use, high body mass index, excessive alcohol consumption, inadequate fruit and vegetable intake, and a sedentary lifestyle. Additionally, air pollution is a well-established risk factor, particularly associated with lung cancer incidence [1]. Despite the availability of various cancer treatment modalities, including radiation therapy, surgery, immunotherapy, endocrine therapy, and gene therapy, chemotherapy remains the most widely utilized approach in cancer management [4].

However, chemotherapy resistance remains a major challenge to the effectiveness of cancer treatment. It is well established that certain lung tumors, for example, exhibit intrinsic resistance to

chemotherapy, while others that initially respond favorably may later develop acquired resistance [5,6]. Consequently, there is an urgent need to develop novel therapeutic strategies, with phytotherapy emerging as a promising alternative. *Bumelia sartorum Mart*. (Sapotaceae) is a Brazilian plant popularly known as "quixaba", "quixabeira" or "rompe-gibão", which occurs sporadically from northern Minas Gerais to Piauí. In traditional medicine, its stem bark is used in preparations to treat several health conditions, including diabetes mellitus and inflammatory disorders [7,8], ulceration [9], bacterial infections [10,11], and cancer [12].

Phytochemical analyses have identified the presence of triterpenoids and steroids, including (2β,3β,4α)-2,3,23-trihydroxyoleana-5,12-dien-28-oic acid and bassic acid, the latter identified as a hydrolysis product from the ethanol extract [7,13]. Previous studies have reported a significant concentration of polyphenolic compounds in the polar extracts of *B. sartorum*, such as catechin, epicatechin, and type-B procyanidins [11,12]. However, the chemical profile of the apolar fractions remains poorly investigated. In this study, the effects of *B. sartorum* stem bark extracts on the viability of human lung carcinoma cell lines were evaluated to assess their anticancer potential, representing a possible alternative for the development of new chemotherapeutic drugs. Furthermore, the chemical composition of the dichloromethane extract was analyzed.

Materials and Methods

Plant Material

According to our previous study [8], *B. sartorum* Mart. was collected in Cabrobó, Pernambuco State (08º30' S; 39º18' W) during the Brazilian summer. A representative sample was deposited in the herbarium of the Institute of Biology (RFA-34154), Federal University of Rio de Janeiro. A methanol crude extract was obtained from the ground bark by maceration for 7 days at room temperature. From this, n-hexane, dichloromethane, ethyl acetate, and n-butanol fractions were obtained through liquid-liquid partition. Consistent with the traditional use of this plant, an aqueous extract was also prepared by boiling 20 g of ground bark in 1 L of water for 15 minutes. The resulting material was then frozen and lyophilized using a Labconco® lyophilizer.

Chemical Profile of Dichloromethane Extract

Gas Chromatography-Mass Spectrometry (GC-MS) analysis of the dichloromethane extract was performed on a GCMS-QP2010 Plus (Shimadzu) under the following conditions: 70 eV electron impact, source temperature 200°C; DB-5MS column (J&W, 25m × 0.25mm, 0.25µm film thickness); injection temperature 270°C, interface temperature 230°C; carrier gas: He, flow rate 1.0 mL/min in constant flow mode; splitless injection. The column temperature program was as follows: 60°C for 1 min, ramped to 290°C at a rate of 5°C/min, and held at 290°C for 20min. Substances were identified by comparing their mass spectra with those in the NIST05s. LIB MS library and using the Kovats indices of n-alkane standards.

Cell Lines and Culture

NCI-H460 [H460] (ATCC®) is a human large-cell lung cancer cell line. All cell cultures were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum and incubated at 37°C in a 5% CO_2 atmosphere.

3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) Assay

Cell viability was determined by the conversion of MTT to formazan via mitochondrial activity. Following the method described by Ruela and collaborators [12], H460 cells were seeded at a density of 1.5×10^4 cells/mL in a sterile 96-well plate. After overnight incubation, cells were treated with serial concentrations of plant extracts (50, 125, 250, and 500µg/ml) and incubated for 48 hours. Then, 20µl of 5 mg/mL MTT (Sigma®) solution was added to each well and incubated at 37°C for 4 hours. The media were removed, and formazan was dissolved in DMSO. The optical density was measured at 570 nm using a microplate reader. Three replicates per condition were performed, and data averages from three or more separate experiments are presented. The control Culture (Ct) was prepared without the extracts. To assess potential color interference from the samples, blanks were prepared with 180µL of medium and 20µL of each extract. Cell viability was expressed as the percentage of control values, with the control values considered as 100% and blank values subtracted.

Statistical Analysis

The results are expressed as the mean ± standard deviation of three or more independent experiments. Data comparison was performed using either Student's t-test or ANOVA, followed by the Tukey post hoc test, with statistical significance considered for differences when $p < 0.05$. The analyses were conducted using GraphPad Prism® software.

Results and Discussion

The effects of *B. sartorum* extracts on H460 cell viability are shown in (Figure 1). The methanol crude extract exhibited a dose-dependent inhibition of cell viability, with reductions of 92.2% and 98.6% observed at concentrations of 250 and 500µg/mL, respectively ($p<0.001$). In contrast, the aqueous extract, prepared based on traditional knowledge, demonstrated minimal inhibition at 500µg/mL, with a 35.66% decrease in viability ($p<0.01$). A more pronounced reduction in cell viability was observed with the dichloromethane and ethyl acetate extracts. Both extracts induced approximately 50% inhibition at 125µg/mL ($p<0.01$) and 100% inhibition at 250µg/mL ($p<0.001$).

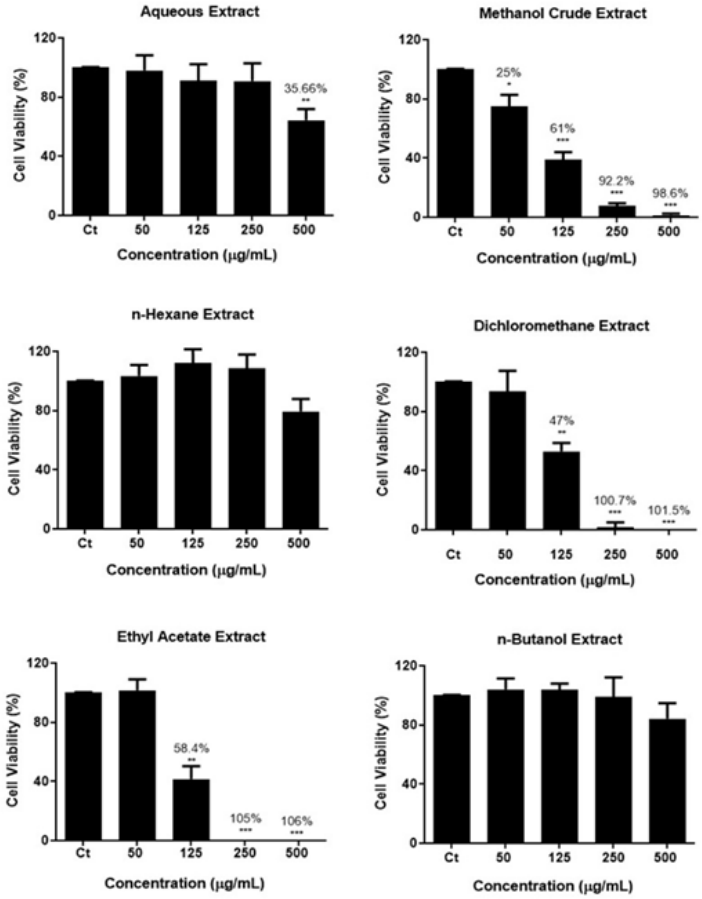

Figure 1: Effect of *Bumelia sartorum* extracts on H460 cell line viability. The results represent the mean ± standard deviation of three independent experiments, each performed in triplicate. The values on the bars indicate the percentage of viability inhibition. *p < 0.05; **p < 0.01; ***p < 0.001 (ANOVA followed by Tukey test).

As previously reported by Ruela and collaborators [11], the phytochemical profile of the ethyl acetate extract revealed a high concentration of polyphenolic compounds, with epicatechin, catechin, procyanidin B, and ellagic acid identified as the predominant constituents. These compounds may contribute to the observed inhibitory effects on H460 cells. Phytochemical analysis of the dichloromethane extract (Figure 2) revealed the presence of three predominant compounds with similar retention times at 28.4, 31.8, and 31.9 minutes. The identification of these compounds was facilitated by comparison with the NIST05s.LIB MS Library and the Kovats indices of n-alkane references (Table 1), leading to the identification of these substances as the methyl esters of palmitic acid (hexadecanoic acid), linoleic acid (9,12-octadecadienoic acid), and oleic acid (9-octadecenoic acid), respectively. Additionally, several methyl esters of phenolic acids were identified, including 4-hydroxybenzoic acid (RT: 17.4 min), vanillic acid (RT: 19.9 min), veratric acid (RT: 20.8 min), and protocatechuic acid (RT: 22.8 min). These findings suggest the potential for a synergistic interaction between fatty acids and phenolic acids, which may contribute to the observed antitumor activity of this extract.

Table 1: Kovats Index values for the methyl esters of major compounds identified in the dichloromethane extract of *Bumelia sartorum*, along with the respective reference values.

Compound	IK*am*	IK*ref*	Reference
palmitic acid	1925	1927	[14]
linoleic acid	2091	2092	[15]
oleic acid	2097	2103	[16]
4-hydroxybenzoic acid	1541	1549	[17]
vanillic acid	1511	1525	[18]

veratric acid	1586	NA	-
protocatechuic acid	1669	NA	-

Table Abbreviations: IKam: Kovats Retention Index; IKref: Kovats reference; NA: not applicable.

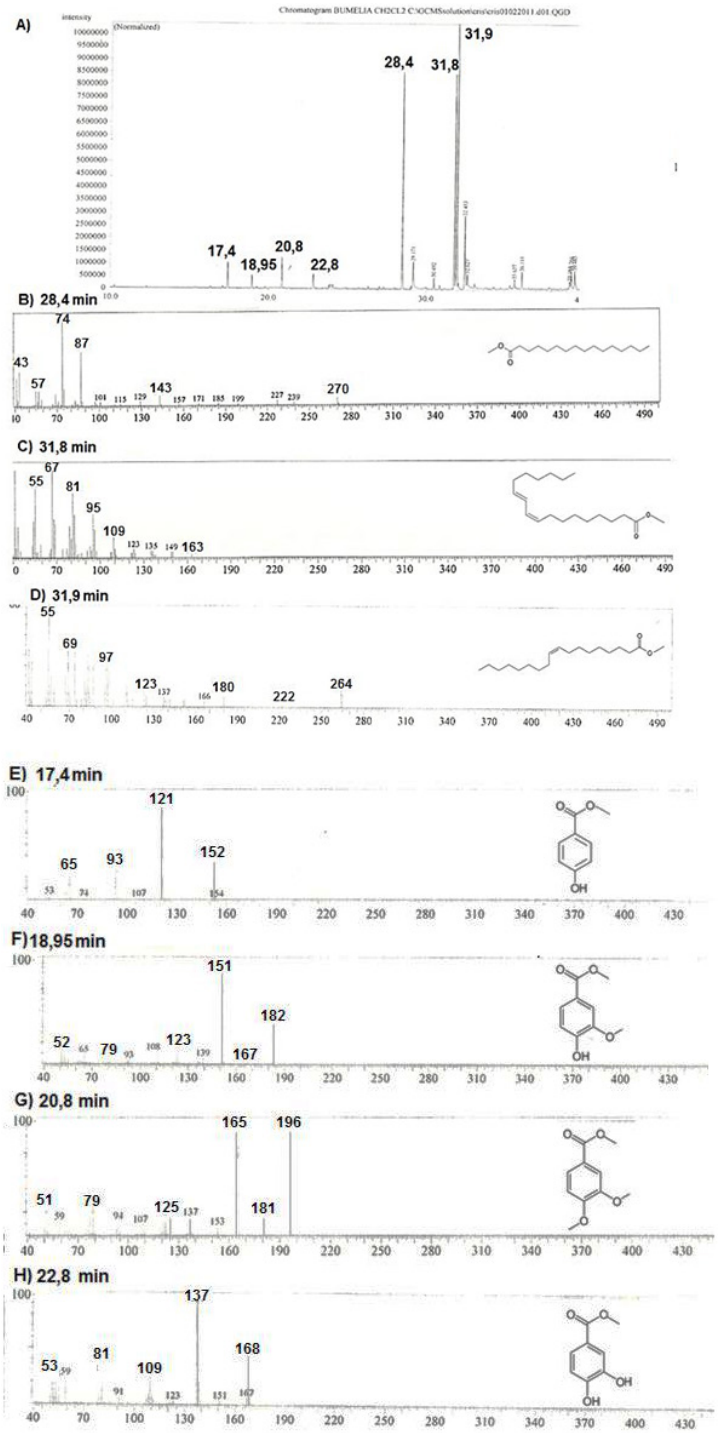

Figure 2: GC-MS analysis of *Bumelia sartorum* dichloromethane extract **(A)** With the corresponding chemical structures of the methyl esters derived from the following acids: palmitic acid **(B)**, linoleic acid **(C)**, oleic acid **(D)**, 4-hydroxybenzoic acid **(E)**, vanillic acid **(F)**, veratric acid **(G)**, and protocatechuic acid **(H)**.

The efficacy of linoleic, oleic, and palmitic acids as potential antitumor agents has been extensively documented in the scientific literature. Nutritional and epidemiological studies have suggested an association between cancer progression and the fatty acids consumption, although the underlying mechanisms remain incompletely understood [19,20].

The beneficial effects of both saturated and unsaturated free fatty acids on carcinogenesis have been reported across various tumor cell lines [21,22]. Additionally, modifications of fatty acids through conjugation with existing anticancer agents and heterocyclic moieties via condensation reactions have been shown to alter their biological activity, enhance tissue selectivity, and modify drug delivery mechanisms. These structural modifications may improve chemotherapy efficacy while reducing toxicity, as demonstrated in both *in vitro* and *in vivo* studies [23-26]. Such modifications could be pivotal in unlocking the full therapeutic potential of fatty acids in cancer treatment. Concerning the constituents identified in the ethyl acetate extract, numerous studies have reported the antitumor properties of polyphenolic compounds. Cheng and colleagues conducted a comprehensive review on the inhibitory activities of Green Tea Catechins (GTCs) against various forms of tumorigenesis, highlighting their suppressive effects on cancer cell progression, metastasis, and angiogenesis [27], as supported by extensive literature.

These compounds demonstrate significant anti-carcinogenic and anti-mutagenic potential in a range of human cancers, including those of the breast, esophagus, prostate, stomach, small intestine, colon, liver, and lung [28,29]. The four major green tea GTCs are (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epigallocatechin-3-gallate (EGCG) [30]. Among these, EGCG exhibits the most potent inhibitory activity, followed by ECG, EGC, and EC [31,32]. Notably, mixtures of catechins have been found to exhibit superior anti-tumor effects compared to pure EGCG, likely due to synergistic interactions between the individual catechins [33-35]. Fujiki and group further investigated various combinations of EGCG and anticancer drugs, observing that these combinations promoted synergistic anticancer effects in both *in vitro* and *in vivo* models [33].

The study conducted by Wu and collaborators demonstrates that proanthocyanidins can effectively inhibit proliferation, invasion, metastasis, clonogenic formation, and Epithelial-Mesenchymal Transition (EMT) in non-small cell lung cancer (A549 cell line). Additionally, these compounds induce apoptosis and cause G2/M phase cell cycle arrest. It is proposed that these effects are mediated through the inhibition of the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) signaling pathway [36]. The potent antitumor activity of procyanidin B1 was elucidated by Lei and group through in vivo studies conducted in a mouse xenograft model, demonstrating that the compound significantly inhibited tumor growth. This effect appears to be associated with the induction of apoptosis and cell cycle arrest at the S phase, mediated by an upregulation of the pro-apoptotic proteins caspase-3 and BAX, alongside a downregulation of the anti-apoptotic protein Bcl-2. The authors suggested that procyanidins represent a novel class of plant-derived compounds, with potential for development as anticancer drugs [37].

Conclusion

The results indicate that an ethnopharmacological approach can be effective in selecting plant species for investigation. Extracts obtained through liquid-liquid partition with dichloromethane and ethyl acetate the first previously described as rich in linoleic, oleic, and palmitic acids, and the second rich in catechins, epicatechins, and procyanidins demonstrated significant inhibitory effects on the viability of lung cancer cell lines. This is the first report of the presence of fatty acids in this plant. The study suggests that *Bumelia sartorum* may serve as a promising candidate for the development of novel therapeutic agents for cancer treatment, particularly lung cancer. However, further research is needed to assess the practical implications of its therapeutic application.

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Conflict of Interest

The authors have no conflict of interest.

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