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EXPLORING THE ANTICANCER, ANTI-INFLAMMATORY, AND ANTIOXIDANT PROPERTIES OF *PARKIA BIGLOBOSA* SEED LIQUOR

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ABSTRACT

Background: Cancer remains a major cause of morbidity and mortality globally. Oxidative stress and inflammation play key roles in cancer pathophysiology. Challenges associated with conventional management are driving the search for alternatively safer, more effective, and accessible cancer therapies. This study aimed to investigate the liquor from *Parkia biglobosa*, used traditionally to manage various diseases for its antioxidant, anti-inflammatory, and anticancer activities. **Methods:** Freeze-dried extract of *P. biglobosa* seed liquor (PBL) and a hydroethanolic fractionated (HPBL) were prepared. Qualitative phytochemical screening of PBL, High-performance liquid chromatographic fingerprinting of the extracts, and assays for extracts' antioxidant, anti-inflammatory and cytotoxic activities against human prostate cancer (PC-3), human T-lymphoblastic leukemia (Jurkat), and human colon cancer (HCT-15) cancer cell lines were done. **Results:** The quantitative phytochemical screening showed that both PBL and HPBL contained flavonoid and phenolic substances as well as glutathione. HPBL had stronger antioxidant activity compared to PBL. The extracts also demonstrated significant anti-inflammatory activities. Moderate to weak cytotoxicity was measured with PBL for PC-3, Jurkat, and HCT-15 (IC_{50} values, 33.09, 77.88, and > 1000 µg/mL, respectively) and this was similar to HPBL (IC_{50} values, 45.08

μg/mL, >1000 μg/mL, and >1000 μg/mL, respectively). Neither PBL nor HPBL was cytotoxic to normal cells. The selectivity indices of PBL were 12.84 and 30.22 in Jurkat and PC-3 cells, respectively, and the selectivity index of HPBL was 22.18 in Jurkat cells. **Conclusion:** These findings provide empirical evidence for the anti-inflammatory, antioxidant, and anticancer properties of *Parkia biglobosa* liquor.

KEYWORDS: *Parkia biglobosa*, phytochemicals, antioxidant, anti-inflammatory, anticancer.

INTRODUCTION

Cancer poses a public health challenge globally and was ranked as the first or second leading cause of mortalities in 112 out of the 183 countries profiled.[1] In the year 2020, 19.3 million new cases and nearly 10 million cancer-related mortalities were projected.[2] Although low- and middle-income countries (LMICS) do record fewer cancer cases, these geographic areas contribute about 65% of cancer deaths globally.[1,3]

Chronic inflammation has been identified to play numerous roles in all stages of cancers of the lung, breast, and colorectum, the leading causes of new cancer cases and cancer death.[2,4] The intrinsic pathway of inflammation in these tumuors are initiated by mutations resulting from neoplastic cells that recruit and activate inflammatory cells. Infections, autoimmune conditions, environmental exposure, and poor lifestyle habits trigger the extrinsic pathways.[5]

Reactive oxygen species (ROS) play double-edged roles in cancer.[6] The tumor-promoting activities of ROS include its ability to influence cellular signaling pathways that contribute to tumor development and drug resistance in cancer.[7,8] Additionally, the mutation of the DNA and the impairment in the functionality of DNA repair enzymes by ROS can result in the accumulation of cellular mutations over time and ultimately, cancer.[8]

The mainstream management of cancer is chemotherapy, radiotherapy, and surgery, used in isolation or in combination.[9] The hurdle of dosage selection, adverse side effects, non-specificity of radiotherapy and chemotherapy, drug resistance, and limitations of surgical treatments are some of the drawbacks that limit the use of these conventional treatments.[10–12] Hence, research on monoclonal antibodies, stem cell therapy, gene therapy, and natural antioxidants are some of the current foci for safe and effective cancer therapy.[9]

In many LMICS, access to conventional and novel treatment modalities is a challenge, hence, many rely on herbal medicines due to their accessibility, affordability, and perceived safety.[13,14] Research over the years have identified plants as reservoirs of complex bioactive principles for cancer prevention and management.[15] Therefore, plant biodiversity is under extensive scientific investigation for safe, and effective agents to address the challenges associated with cancer therapy.[14]

Parkia biglobosa (Jacq.) R. Br. ex G. Don (Fabaceae), known as the African locust bean tree, is a perennial leguminous plant cultivated in parts of Africa, Asia, and South America.[16] Standing at 20 m high, the umbrella-crown-shaped tree has about 13–60 pairs of bipinnated dark green leaflets attached to a long rachis.[17] Different parts of the plant are used for various purposes, including anticancer remedy.[13,18] The plant has antioxidant, anti-hypertensive, anti-diabetic, anti-inflammatory, and anti-infective activities.[18] While some parts and preparations of *Parkia biglobosa* have been investigated for their anticancer properties, the seed liquor, a major by-product of *Parkia biglobosa* cake has not been studied. In this paper, we describe the antioxidant, anti-inflammatory and anticancer activities of the seed liquor of *Parkia biglobosa*.

MATERIAL AND METHODS

Chemicals and Reagents

Roswell Park Memorial Institute (RPMI-1640) medium, Dulbecco's Modified Eagle Medium (DMEM), 10% Fetal Bovine Serum (FBS), Bovine Serum Albumin (BSA), Trypsin, EDTA, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) were purchased from Sigma Chemical (Missouri, USA). The African green monkey kidney (Vero, normal), PC-3, Jurkat, HCT-15 cell lines were obtained from the RIKEN BioResource Center Cell Bank (Japan). All other reagents and chemicals used were of analytical grade and obtained from standard suppliers.

Sample Collection and Preparation

The raw seeds of *P. biglobosa* were purchased from the Yendi market (GPS coordinate: 9.44075698464707, -0.007624959637879167). The seeds were authenticated and assigned a voucher specimen number CPMR 5202 by Mr. Peter Atta-Adjei Jnr., a taxonomist at the Center for Plant Medicine Research, Mampong-Akuapem, Ghana. Two hundred grams of raw seeds were boiled over medium heat for a period of 16.5 h, with a total volume of 7 L of water added intermittently. The liquid portion was filtered, frozen at -20 °C, and then freeze-

dried (PBL) using a Labconco Freezone 6 Freeze Dryer (Missouri, USA). Twenty grams of PBL was redissolved in 200 mL of 70% (v/v) ethanol for 72 h (2x) and filtered out. The ethanolic component of the filtrate was evaporated using a rotary (Ecodyst EcoChyll S, North Carolina, USA), frozen and freeze-dried to obtain the hydroethanolic (HPBL) residues.

High-performance liquid chromatography (HPLC) fingerprinting

An HPLC fingerprint was developed for PBL and HPBL using the gradient elution method as previously described (19) with slight modifications. Twenty microliters of 1 mg/mL sample was introduced into a Shimadzu C18 column. The temperature of the column was kept constant at 40 °C, and the eluent, comprising methanol and 1% phosphoric acid, in a 60:40 ratio, was allowed to flow at a rate of 0.7 mL/min.

Phytochemical screening

PBL (50 mg/mL) was screened for the presence of saponins, alkaloids, tannins, flavonoids, and terpenoids as previously described[20] with slight modifications.

Test for saponins

Two milliliters of the PBL solution was vigorously shaken. The persistence of a stable froth lasting beyond 10 min indicated the presence of saponins.

Test for tannins

The presence of tannins was tested by adding a few drops of 0.1% $FeCl_3$ to 2 mL of the sample solution after boiling. The formation of a blue-black color suggests the presence of tannins.

Test for flavonoids

One milliliter of diluted NH_4OH was added to 1 mL of the PBL solution. The gradual disappearance of the yellow coloration formed at room temperature after the addition of a few drops of concentrated H_2SO_4 confirms the presence of flavonoids.

Test for alkaloids

To 1 ml of the PBL solution, 2 mL of 1% HCL in 70% ethanol was added and allowed to boil. A volume of 400 µL of 10% (v/v) NH_4OH and 1 mL of chloroform was added and shaken, followed by the extraction of the chloroform layer by the addition of 2 mL of acetic acid. To the chloroform layer, a few drops of Mayer's reagent were added. The formation of a cream-like or whitish precipitate confirms the presence of alkaloids.

Test for terpenoids

One milliliter of chloroform was added to 1 mL of the PBL solution. The appearance of a reddish-brown color after the gentle addition of 2 mL of concentrated H_2SO_4 indicates the presence of terpenoids.

Determination of antioxidant activities

DPPH Radical scavenging activity

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was used to determine the total antioxidant activity of PBL and HPBL.[21] A volume of 100 µL of 0.5 mM DPPH solution was added to 100 µL of PBL (concentration range 0.3125 mg/mL to 20 mg/mL) in a 96-well plate. The plate was incubated in the dark at room temperature (26 °C) for 20 min. The absorbances were measured at a wavelength of 517 nm using the plate reader (Tecan Infinite M200 Pro, Austria) against a blank solution of water and methanol only. Ascorbic acid solution served as the positive control, while a mixture of 100 µL of 0.5 mM DPPH solution and 100 µL of methanol was used as the negative control. The assays were repeated using two-fold serially diluted HPBL. Triplicate experiments were performed. The percent antioxidant activity was calculated with the formula:

$$\% \text{ Antioxidant Activity} = \frac{A(blank) - A(sample)}{A(blank)} x\ 100\%$$

where A (blank) is the blank absorbance and A (sample) is the absorbance of PBL or HPBL sample or ascorbic acid. The 50% effective concentration (EC_{50}) was determined from a graph of % antioxidant activity plotted against Log of the concentration (mg/mL) of the sample, using GraphPad prism version 8.0.1 (GraphPad Software Inc., San Diego, CA, USA).

Total flavonoid content

The colorimetric method was used to quantify flavonoid content in HPBL and PBL.[22] A reaction mixture of 100 µL of 2% $AlCl_3$ and extract concentrations (20, 10, and 5 mg/mL) were added to separate wells of a 96-well plate and incubated at room temperature (26 ^oC) for 20 min. The blank and standard in this assay were methanol and quercetin, respectively. All experiments were done in triplicate, and the absorbances were read using a Tecan Infinite M200 Pro at a wavelength of 415 nm. The total flavonoid concentrations were estimated from a calibration curve plotted using quercetin.

Determination of total phenolic content

The Folin-Ciocalteu assay was used to quantify the total phenolic content of PBL and HPBL with slight modifications.[22] For this assay, 50 µL of Folin-Ciocalteu reagent, 750 µL of distilled water, and 10 µL of 20, 10, or 5 mg/mL of the extracts were thoroughly mixed in separate wells of a 24-well plate in triplicate and then incubated in the dark for 8 min. To each well, 150 µL of 4 M Na_2CO_3 was added and then incubated for an additional 2 h at room temperature. The absorbance was measured at a wavelength of 750 nm using the Tecan Infinite M200 Pro. The serially diluted concentration of gallic acid solutions (0.0078 mg/mL to 5 mg/mL) tested concurrently was used to plot the standard calibration curve and used to determine the total phenolic content of extracts in mg of gallic acid equivalents (GAE) / g extract.

Reduced glutathione level estimation

The amount of GSH in the extract was quantified using the o-phthalaldehyde (OPA) conjugation method.[23,24] A stock GSH solution (1 mg/mL) was diluted to obtain a concentration range of 0.02 mg/mL to 0.100 mg/mL of GSH solution. Aliquots of 50 µL of different concentrations of GSH solution and 50 µL of PBL and HPBL (5, 10, and 20, mg/mL) were transferred into separate wells of a 96-well plate. To each well, 10 µL of 10 mg/mL OPA and 50 µL of 0.1 M sodium phosphate buffer (pH 8) were added, and the plate was incubated for 15 min at room temperature in the dark. The fluorescence was measured at an excitation wavelength of 460 nm and an emission wavelength of 350 nm using the Tecan Infinite M200 Pro. The GSH levels in PBL and HPBL were calculated from the standard calibration curve plotted for the GSH standard.

In vitro Anti-Inflammatory Assay

Bovine serum albumin (BSA) denaturation model

The bovine serum albumin denaturation assay was used for the anti-inflammatory assay.[25] Three concentrations (31.25 µg/mL, 62.5 µg/mL, and 125 µg/mL) of the test sample (PBL or HPBL) and the standard sample (Diclofenac sodium) were prepared. To each tube containing 10 µL of different concentrations of PBL, HPBL, or diclofenac sodium, 90 µL of 0.5% w/v BSA was added. For the negative control, the BSA solution was added to distilled water or vehicle. The colour control solution had 90 µL of distilled water added to 10 µL of the different concentrations of diclofenac, PBL, or HPBL. The solutions were heated at 37 °C for 20 min and then for another 30 min at 57 °C. Subsequently, 500 µL of phosphate saline

buffer (pH 6.6) was added to each tube, and then the contents of the tubes were transferred into a 96-well plate. Absorbance was read at 320 nm using the Tecan Infinite M200 Pro. The % protein denaturation inhibition was computed as:

$$\text{Percentage inhibition} = 100 - \left(\frac{A(Test\ solution) - A(Colour\ control\ solution)}{A(Negative\ control)} x\ 100\%\right)$$

Cell Culture and Cytotoxicity assay

The cancer cell lines (Jurkat, PC-3, and HCT-15) were cultured in 25 cc culture flasks using 5 mL of RPMI-1640 and DMEM for the Vero cell line. The media were supplemented with 10% FBS and 1% penicillin-streptomycin. The culture flask was incubated at 37 °C in the presence of 5% CO_2. The MTT assay was used to determine the cytotoxic activity of the PBL and HPBL as described.[26] The cell lines were treated with five serially diluted concentrations (62.5 µg/mL to 1000 µg/mL) of the extracts for 72 h in triplicate. Curcumin was used as the positive control. After the 72-h incubation period, 20 µL of 2.5 mg/mL MTT solution was added to the wells of the 96-well culture plate and incubated for an additional 4 h. To each well, 150 µL of acidified isopropanol was added, and the absorbance was read at a wavelength of 450 nm after overnight incubation. The 50% inhibitory concentration (IC_{50}) values were determined from the graph of percentage viability of cell lines plotted against concentrations of extracts or curcumin, and the selective index (SI) was calculated as the ratio of the IC_{50} value in Vero cells to the IC_{50} of the cancer cells.

Statistical analysis

The one-way analysis of variance followed by Tukey`s multiple comparison test was used to determine statistical differences between the extracts and the positive control of the IC_{50} and EC_{50} values. For the quantitative phytochemical screening, the student t-test was used to determine statistical differences between the HPBL and PBL. A two-way ANOVA was used for the statistical analysis of percentage inhibitory values for the anti-inflammatory assay. A ρ-value of less than 0.05 was considered statistically significant.

RESULTS

HPLC Fingerprinting

The chromatograms obtained showed ten peaks between the retention time of 6.8 to 22.4 min for PBL and seven peaks between the retention time 6.8 to 31.1 min for HPBL. The retention times and peak areas have been shown in Tables 1 and 2.

Table 1: Retention time and peak areas of PBL.

Peak Number	Retention Time (min)	Peak Area (mUA)
1	6.8	27956
2	7.5	280222
3	8.0	610814
4	9.6	165323
5	13.0	16240
6	15.6	815162
7	21.3	14271
8	21.5	1396
9	21.8	3608
10	22.4	1205

Table 2: Retention Time and Peak areas of HPBL.

Peak Number	Retention Time (min)	Peak Area (mUA)
1	6.8	348162
2	7.5	238164
3	8.0	492546
4	12.5	1209929
5	22.7	15878
6	24.8	5427
7	31.1	4299

Phytochemical screening

The results of phytochemical tests showed the presence of all phytochemicals screened for except saponins in PBL (Table 3).

Table 3: Phytochemical composition of *P. biglobosa* seed liquor.

Phytochemical component	Results
Alkaloids	+
Flavonoids	+
Saponins	-
Tannins	+
Terpenoids	+

(+) denotes the presence of the specified phytochemical (-) denotes the absence of the specified phytochemical.

DPPH Radical Scavenging Activities

The EC_{50} values for free radical scavenging activities obtained from the plotted curves were 0.968 ± 0.203 ($P<0.01$), 0.270 ± 0.067 ($P<0001$) and 0.0067 ± 0.0006 mg/mL, for PBL, HPBL and ascorbic acid, respectively.

Total Phenolics, Glutathione and Flavonoid Content

There was an appreciable amount of phenolics and flavonoids in PBL and HPBL as confirmed by the qualitative analysis of phytochemicals of the PBL in Table 3 as well as a measurable amount of Glutathione (Table 4).

Table 4: Total phenolic, Flavonoid and Glutathione content in PBL and HPBL.

Extract	Total Phenolic content (GAE/100 g) ns	Flavonoid content ([QUER] mg /g) **	Glutathione ([QUER] mg / g, ****
PBL	760.11 ± 24.79	20.33 ± 1.93	2.29 ± 0.02
HPBL	800 ± 6.20	12.21 ± 1.69	1.45 ± 0.05

Values are presented as mean ± SD (n=3), ns > 0.05, **= P< 0.01, ****= P < 0.0001 represents the statistical significance between the HPBL and PBL.

***In vitro* protein denaturation assay using bovine serum denaturation method**

As illustrated in Figure 1, the test samples (PBL and HPBL) and the positive control (Diclofenac sodium) showed concentration-dependent protein denaturation inhibitory activity. The highest percentage of protein denaturation inhibitory activity was measured in HPBL.

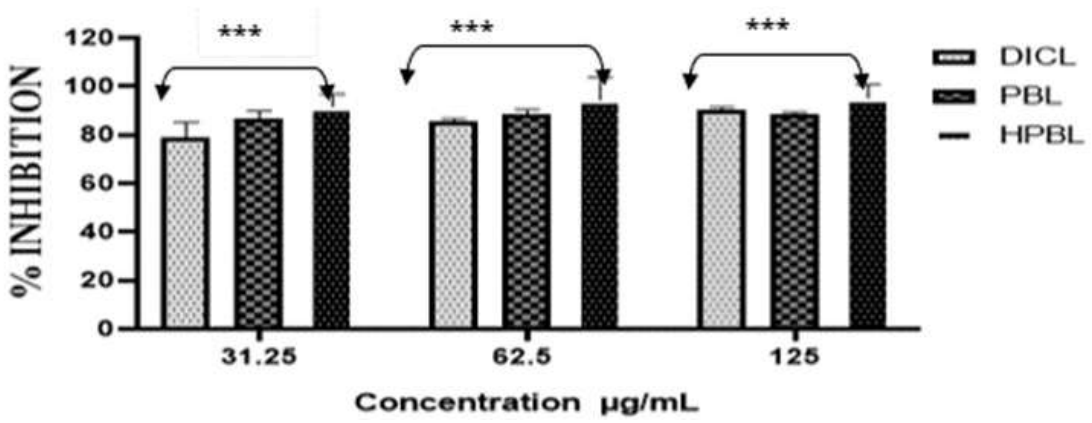

Figure 1: The percentage protein denaturation inhibitory effects of Diclofenac sodium, HPBL and PBL. *, represents statistical difference between test samples and the positive control, Diclofenac sodium (p < 0.001).**

Effects of *P. biglobosa* extracts on cancer cells

The results of the cytotoxicity tests are presented in Table 5. Compared to Vero cells, IC_{50} values for curcumin, PBL and HPBL were significantly lower for all the cancer cell lines tested. The PBL had good SI in PC-3 and Jurkat cell lines while HPBL showed good SI only in Jurkat cells.

Table 5: IC_{50} and S.I values of Curcumin, PBL and HPBL in JURKAT, PC-3, and HCT-15 cell lines.

Cell Line	Curcumin		PBL		HPBL	
	IC_{50}, µg/mL	SI	IC_{50}, µg/mL	SI	IC_{50}, µg/mL	SI
Jurkat	0.91(±0.10)	18.10	77.88 (±5.23) ***	> 12.84	45.08 (±2.51) **	> 22.18
PC-3	1.71(±0.09)	9.6	33.09 (±2.17) ****	>30.22	>1000	-
HCT-15	1.83	9.00	>1000	-	> 1000	-
VERO	16.47		>1,000		>1,000	

Numbers in parentheses are SDs. ****($p< 0.0001$), *** ($p<0.001$) and **($p<0.01$) represent statistical significance between the IC_{50} of the test sample and the positive control, Curcumin.

DISCUSSION

Plant medicine is a primary source of novel, effective drugs, pharmacophores, or chemotypes (27). Research on plant medicine in cancer is aimed at discovering potentially effective, safe, and accessible anticancer drugs.[15] *Parkia biglobosa* is one of the many plants used traditionally in cancer management.[13,18] To address the paucity of scientific data on the anticancer properties of *P. biglobosa*, this study sought to investigate liquor prepared from the seeds of the plant for anticancer properties. The traditional method was used for the preparation of the seed liquor.

The presence or absence of some phytoconstituents in PBL presented in Table 3 conforms to previous reports.[28,29] These variations may be attributed to the differences in the plant processing, extraction method, phytochemical screening protocols, and geographical distribution of the seeds collected. The presence of these phytochemicals in the liquor could account for its medicinal properties as phenolic, flavonoid and GSH are reported to have anticancer, antioxidant, and anti-inflammatory activities.[30,31]

Fingerprints, such as the HPLC fingerprint of *P. biglobosa*, along with several other fingerprints for extracts, are essential for the unambiguous recognition of unknown samples.[32] HPLC fingerprinting is useful for purposes of quality control, identification, characterization, purification, isolation, and quantification of phytoconstituents.[32] The data generated from the chromatograms developed in this study could also serve as quality control and reference material for future characterization and isolation of the bioactive principles in *P. biglobosa* liquor.

Glutathione, flavonoids, and phenolics are primarily antioxidant compounds capable of mopping up free radicals.[31] The levels of these substances observed were consistent with

previous findings.[24,29,33] The EC_{50} values recorded for HPBL and PBL, respectively, indicate the strong antioxidant capacity and potential therapeutic benefits of *P. biglobosa* seed liquor.[34] However, the formation of 6-and-8-glutathionyl quercetin adducts between glutathione and flavonoid compounds like quercetagetin containing additional OH at C6 of the A ring, which neutralizes their antioxidant activities, may reduce the potential antioxidant effects of PBL and HPBL.[35]

Denatured cellular and extracellular proteins precipitate inflammation and contribute to chronic diseases associated with inflammation, such as cancer and arthritis.[36] The protein denaturation inhibitory assay is based on the principle that compounds that can inhibit the denaturation of inflammatory proteins *in vitro* can induce an anti-inflammatory response.[36] The inhibition of protein denaturation using the bovine protein denaturation method by both PBL and HPBL may imply the presence of compounds that prevent the breakdown of proteins and could translate into anti-inflammatory activity.[25,36] In this study, HPBL produced the highest anti-inflammatory responses, and even compared to the standard compound diclofenac sodium. The anti-inflammatory effects of natural compounds such as curcumin and quercetin may contribute to their anticancer activities,[37] hence, the anti-inflammatory effects of HPBL and PBL may translate to anticancer activities. Additionally, the strong anti-inflammatory activity in this study explains the rationale for the traditional usage of *P. biglobosa* liquor in some parts of northern Ghana to manage arthritis.

The cytotoxic activities of the extracts accessed against three cancer cell lines showed that HPBL was moderately cytotoxic against Jurkat cells only, and PBL was moderately cytotoxic against Jurkat and PC-3 cells. The selective cytotoxic activities of *P. biglobosa* against some cancer cell lines are consistent with previous findings on *P. biglobosa*.[38,39] However, compared to the literature, the liquor recorded lower IC_{50} values, indicating a more cytotoxic effect on cancer cells.[38,39] For compounds to be considered promising therapeutic candidates, they should be selectively toxic to cancer cell lines without harming normal cell lines, and this can be determined if the SI value is greater than 2.[40] The SIs obtained in this study suggest that the phytoconstituents in PBL were selective for Jurkat and PC-3 while HPBL was selectively cytotoxic to Jurkat cancer cells.

CONCLUSION

This study has shown that PBL is selectively cytotoxic against PC-3 and Jurkat cell lines while HPBL is selectively cytotoxic to Jurkat cells. PBL and HPBL contain phenolics,

flavonoids, and glutathione and have antioxidant and anti-inflammatory properties. These properties may partly account for its anticancer property of cytotoxicity. These results suggest that *Parkia biglobosa* seed liquor could be a potential source of bioactive anticancer compounds, and should be further investigated.

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