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Anticancer effects of soursop leaf extract as a supplement to standard sorafenib therapy: An apoptosis pathway study in a rat model of hepatocellular carcinoma

Erik Prabowo [1,2,3], Neni Susilaningsih [4,5*], Catharina Suharti [3,6], Hery Djagat Purnomo [3,7], Ignatius Riwanto [2,3], Danendra Rakha Putra Respati [3,8], Kevin Christian Tjandra [3,8], Ardiyana Ar [3,8]

[1] Doctoral Study Program of Medical and Health Science, Universitas Diponegoro, Semarang, INDONESIA
[2] Department of Digestive Surgery, Faculty of Medicine, Universitas Diponegoro, Semarang, INDONESIA
[3] Dr. Kariadi General Central Hospital, Semarang, INDONESIA
[4] Department of Biomedicine, Faculty of Medicine, Universitas Diponegoro, Semarang, INDONESIA
[5] Department of Histology, Faculty of Medicine, Universitas Diponegoro, Semarang, INDONESIA
[6] Division of Oncology Hematology, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Semarang, INDONESIA
[7] Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Semarang, INDONESIA
[8] Department of Medicine, Faculty of Medicine, Universitas Diponegoro, Semarang, INDONESIA
***Corresponding Author:** nesusilaningsih@gmail.com

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ABSTRACT

Background: Hepatocellular carcinoma (HCC), the most common primary liver cancer, remains a leading cause of cancer-related deaths worldwide, particularly in regions with a high prevalence of chronic liver diseases. Its increasing incidence is driven by rising rates of cirrhosis due to viral hepatitis, alcohol abuse, and non-alcoholic fatty liver disease. Despite advancements, HCC is often diagnosed at advanced stages, limiting curative treatment options. Sorafenib, a tyrosine kinase inhibitor, is the standard treatment for advanced HCC, but its modest efficacy and significant side effects highlight the need for alternative or complementary therapies. Soursop (*annona muricata*) has gained attention for its anticancer properties, particularly annonaceous acetogenins, which show selective cytotoxicity and apoptosis-inducing effects in cancer models.

Methods: This study evaluated the anticancer potential of soursop leaf extract (SLE) in a post-test-only randomized controlled trial using male Wistar rats with diethylnitrosamine (DEN)-induced HCC. DEN was administered weekly for six weeks, followed by treatments with SLE or sorafenib. Outcomes included liver volume and apoptotic and angiogenic markers (caspase 8, vascular endothelial growth factor, B-cell lymphoma protein 2 [BCL-2], and alpha-fetoprotein [AFP]).

Results: Among the 48 rats studied, 35 completed the trial. Groups treated with SLE (50 mg/kg or 100 mg/kg) alongside sorafenib showed significant improvements in apoptotic markers, notably caspase 8 ($p = 0.043$) and BCL-2 ($p = 0.018$), along with reduced AFP levels ($p = 0.001$).

Conclusion: SLE, particularly at 50 mg/kg, demonstrated potential as an adjunct to sorafenib, enhancing its anticancer effects by modulating apoptotic pathways and reducing tumor markers. Further studies are needed to explore its mechanisms and long-term impact on HCC.

Keywords: soursop leaf extract, sorafenib, anticancer, hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and ranks as the sixth most prevalent cancer worldwide. It is also the fourth leading cause of cancer-related mortality, particularly in developing regions where chronic liver diseases are highly prevalent [1]. Approximately 72% of all HCC cases and deaths occur in Asia, reflecting the higher burden of risk factors such as chronic hepatitis B virus and hepatitis C virus infections in this region [2]. The incidence of HCC has been rising globally due to the increasing prevalence of chronic liver diseases, particularly cirrhosis caused by viral hepatitis, alcohol abuse, and non-alcoholic fatty liver disease. Chronic hepatitis B infection remains a leading cause of HCC in Southeast Asia and sub-Saharan Africa, while hepatitis C and alcohol-induced cirrhosis are more dominant in the Western world [3]. In Indonesia, HCC is the fourth most common cancer, contributing significantly to national cancer mortality [3].

Men are more frequently affected by HCC, with a twofold higher incidence compared to women. This gender disparity is thought to be related to hormonal influences, as well as differences in exposure to risk factors such as alcohol and viral hepatitis. Other risk factors for HCC include aflatoxin exposure, obesity, and diabetes [4]. Aflatoxin, a carcinogenic mycotoxin

produced by aspergillus species, contaminates crops in tropical regions and significantly increases the risk of developing HCC in individuals with chronic hepatitis B infection.

HCC arises from hepatocytes, the main functional cells of the liver, following a multistep process of chronic inflammation, fibrosis, and eventual malignant transformation. The underlying mechanisms involve the accumulation of genetic mutations, epigenetic changes, and the activation of oncogenic pathways that drive uncontrolled cell proliferation and survival [5]. One of the hallmark characteristics of HCC is its ability to evade apoptosis (programmed cell death) while promoting angiogenesis, the formation of new blood vessels that supply oxygen and nutrients to the growing tumor.

The clinical presentation of HCC is often delayed, with many patients remaining asymptomatic until the disease has reached an advanced stage. Common symptoms include jaundice, abdominal pain, and weight loss, though these signs are usually indicative of large tumors or metastatic spread. Early detection is critical for curative interventions such as liver resection or transplantation, but unfortunately, most patients are diagnosed at a late stage when the tumor is inoperable [6]. In these cases, systemic therapies such as sorafenib become the main treatment option.

Sorafenib, a tyrosine kinase inhibitor, is currently the standard first-line treatment for advanced HCC. It was approved by the US Food and Drug Administration in 2007 following the pivotal SHARP trial, which demonstrated that sorafenib extended median overall survival by approximately 2.8 months compared to placebo [7]. The Asia-Pacific trial later confirmed these findings, showing a slightly shorter survival benefit of 2.3 months in patients treated with sorafenib compared to placebo [8]. Sorafenib exerts its anticancer effects by inhibiting several molecular targets, including the RAF/MEK/ERK pathway, which is involved in cell proliferation, and the vascular endothelial growth factor (VEGF) receptor, which is critical for angiogenesis [9]. By blocking these pathways, sorafenib can slow down tumor growth and prevent the formation of new blood vessels that feed the tumor. Despite these benefits, sorafenib's long-term efficacy is limited, and its use is often associated with significant adverse effects, including hypertension, hand-foot syndrome, diarrhea, and cardiac ischemia [10]. These side effects can compromise patients' quality of life and limit the duration of therapy.

Soursop (*annona muricata*), a tropical plant known for its traditional use in treating various ailments, has gained attention for its anticancer properties, particularly through its rich content of annonaceous acetogenins. These bioactive compounds have been shown to exhibit selective cytotoxicity against cancer cells while sparing healthy cells, making them attractive candidates for cancer therapy [11].

Soursop leaf extract (SLE) has demonstrated apoptosis-inducing effects in various cancer models, including breast cancer, pancreatic cancer, and HCC [12]. The extract works by inhibiting mitochondrial complex I, leading to the depletion of ATP, which is essential for cancer cell survival. This disruption triggers apoptosis, or programmed cell death, through both intrinsic and extrinsic pathways. In addition to its pro-apoptotic properties, soursops have been shown to inhibit angiogenesis, further limiting tumor growth [13].

METHODS

Study Design

This study employed a post-test-only randomized controlled trial design to explore the anticancer effects of SLE in male Wistar rats with induced HCC. The trial involved five groups: two treatment groups, P1 and P2, received SLE at different doses along with sorafenib; K1 received sorafenib alone; K2 was exposed to diethylnitrosamine (DEN) without additional treatment; and K3 served as an untreated control. Each rat served as an individual experimental unit, with a total of 48 rats used in the study. Groups P1, P2, K1, and K3 each included eight rats, while K2 included 16 rats to support both primary and secondary analyses.

Randomization and Minimization of Bias

Randomization was carefully applied to allocate rats into their respective groups, reducing the risk of selection bias and ensuring a balanced distribution of animals across treatment and control groups. The randomization sequence was generated using a computer-based random number generator. Measures were taken to limit confounding factors by maintaining consistent animal housing conditions and order of handling, minimizing potential influence from environmental or procedural variations.

Blinding Procedure

To ensure objective assessment, blinding was incorporated at various stages of the experiment. The individual conducting the outcome assessments, including serum and tissue analysis, was unaware of the group allocations. Also, during the data analysis phase, the analyst was blinded to group identities to prevent potential bias in interpretation. While allocation concealment was not feasible during initial group assignment due to logistical constraints, strict adherence to blinding during data collection and analysis ensure unbiased results.

Sample Size and Inclusion Criteria

The sample size was determined based on preliminary data to ensure sufficient statistical power for identifying significant differences across groups. Male Wistar rats aged 6-7 weeks were chosen for their well-documented physiology and consistent response in HCC studies. All animals were acclimatized for seven days before starting the experiment, housed in a controlled environment with a standard light-dark cycle, and provided with food and water ad libitum.

Experimental Procedure

To induce HCC, rats received weekly intraperitoneal injections of DEN at a dose of 100 mg/kg over six weeks. Evaluations were carried out 10 weeks after the final DEN injection, according to the predetermined study timeline. Subgroup K2A rats were sacrificed in week 17 to assess additional variables, including serum alpha-fetoprotein (AFP) levels, liver volume, and tumor progression. Following the treatment period, all rats were weighed, and blood samples were collected from the retro-orbital veins for serum analysis of AFP and VEGF levels. Rats were then euthanized, and their livers were removed, washed with saline, measured for the largest tumor diameter, fixed in formalin, and prepared for histological and immunohistochemical analysis of apoptotic markers (caspase 3, 8, 9) and angiogenic markers (VEGF, B-cell lymphoma protein 2 [BCL-2], AFP).

Immunohistochemical and Morphometric Analyses

Liver tissue samples were embedded in paraffin, sectioned, and stained for immunohistochemical analysis. Caspase 3 and caspase 9 expression were quantified by calculating the percentage of mononuclear cells showing brown cytoplasmic staining, observed across five fields at 400× magnification. VEGF expression was quantified using monoclonal anti-VEGF antibodies. To assess liver volume, we measured the displacement of phosphate buffered saline solution when liver tissues were immersed.

Data Collection and Statistical Analysis

Data were collected and processed through editing, coding, data entry, and cleaning before statistical analysis. To assess the reliability of microscopic observations, kappa values between two independent examiners were calculated, with values between 0.61 and 1.00 considered reliable. Descriptive statistics were provided through univariable analyses, with boxplots used to visualize the data distribution.

Data normality was assessed using the Shapiro-Wilk test, and one-way ANOVA was used for normally distributed data, while Kruskal-Wallis tests were employed for non-normally distributed data. For post-hoc analysis, LSD tests or Mann-Whitney U tests were conducted as appropriate. The relationship between soursop extract doses and outcome variables was examined using Spearman's correlation for ordinal data and Pearson's correlation for normally distributed data. Statistical significance was set at $p < 0.05$, with a 95% confidence interval, and all analyses were conducted using SPSS.

Study Location and Timeline

The study was conducted at the integrated research and testing laboratory unit IV at Gadjah Mada University, encompassing all stages from acclimatization to treatment and termination. Tissue processing and H&E staining took place at the central laboratory of the faculty of medicine at Diponegoro University, while immunohistochemical staining and analysis were completed at the pathological anatomy laboratory of the faculty of medicine at UNS Surakarta.

RESULTS

The study utilized a total of 48 rats, which were divided into six groups. Treatment groups P1 (n = 6) and P2 (n = 5) received a combination of SLE at doses of 50 mg/kg and 100 mg/kg, respectively, alongside sorafenib. The positive control group K1 (n = 6) was treated with sorafenib alone. Two additional control groups, K2A and K2B (n = 6 each), were only induced with DEN without any further treatment, and the negative control group K3 (n = 6) received no DEN induction. At the end of the study, 35 rats remained for sample collection, following termination for blood and liver sampling.

Caspase, Tissue VEGF, Blood VEGF, BCL-2, and AFP Results

The analysis of caspase 3 expression did not show a significant difference between groups ($p = 0.184$), nor did the analysis of caspase 9 expression ($p = 0.175$). However, caspase 8 expression revealed a statistically significant difference between groups ($p = 0.043$), with the most notable difference observed between group P1 and K2B ($p = 0.003$) (**Table 1**).

Table 1. Expression of caspase, tissue VEGF, blood VEGF, BCL-2, and AFP results

Variable	Group	M	SD	MD	MN	MX
Caspase-3	P1	75.00	14.75	73.0	56.0	95.0
	P2	50.40	33.09	46.0	12.0	88.0
	K1 (K+)	75.00	29.86	73.0	18.0	95.0
	K2B	81.83	27.79	91.0	26.0	99.0
Caspase-9	P1	25.30	3.45	24.5	22.0	30.0
	P2	24.00	3.67	23.0	20.0	30.0
	K1 (K+)	26.20	2.48	26.5	23.0	29.0
	K2B	29.30	1.63	30.0	29.0	30.0
Caspase-8	P1	74.17	13.96	77.5	53.0	88.0
	P2	36.80	32.42	41.0	2.0	71.0
	K1 (K+)	56.50	29.47	59.5	6.0	86.0
	K2B	39.50	8.57	38.5	28.0	52.0
Tissue VEGF	P1	87.17	10.57	92.0	67.0	94.0
	P2	55.80	40.86	68.0	10.0	93.0
	K1 (K+)	78.92	35.76	94.5	7.5	100.0
	K2B	88.50	14.58	93.5	62.0	100.0
Blood VEGF	P1	287.90	14.39	288.9	266.2	306.2
	P2	303.30	13.93	303.3	287.4	322.8
	K1 (K+)	217.00	23.92	220.1	188.7	246.2
	K2B	352.80	9.76	353.3	340.3	369.1
	K2A	305.00	17.72	304.1	284.5	326.6
BCL-2	P1	56.33	26.86	68.0	18.0	82.0
	P2	31.60	33.53	9.0	5.0	74.0
	K1 (K+)	58.33	28.84	66.5	2.0	85.0
	K2B	81.17	2.04	81.5	78.0	84.0
AFP	P1	198.30	44.49	203.0	140.5	250.8
	P2	216.30	9.17	214.3	207.0	227.0
	K1 (K+)	252.20	23.66	256.7	224.3	279.3
	K2B	878.70	16.85	879.0	852.5	899.7
	K2A	521.40	31.23	526.5	485.5	556.2

Note. M: Mean; SD: Standard deviation; MD: Median; MN: Minimum; & MX: Maximum

For VEGF expression in the liver tissues, no significant differences were found across groups ($p = 0.310$). In contrast, BCL-2 expression showed significant inter-group differences ($p = 0.018$), particularly between P1 and K2B ($p = 0.024$). Similarly, Bcl-2-associated X protein (BAX) expression also demonstrated significant differences between groups ($p = 0.009$), with a notable difference between P1 and K2B ($p = 0.006$). The relative liver volume (tumor size) analysis did not indicate significant group differences ($p = 0.08$). However, serum VEGF levels exhibited highly significant differences between groups ($p < 0.001$), with significant differences observed between almost all groups except for P1 and P2 ($p = 0.138$). Serum AFP levels also differed significantly between groups ($p = 0.001$), particularly between groups K2A and K2B ($p = 0.004$), as well as between P1 and K2B ($p = 0.004$).

DISCUSSION

The findings of this study reveal critical insights into the potential anticancer effects of SLE in conjunction with sorafenib on DEN-induced HCC in Wistar rats. Key apoptotic and angiogenic markers were assessed, with particular focus on caspase 8, BCL-2, BAX, VEGF, and AFP.

Apoptosis and Caspase Activation

Caspase 8 expression demonstrated a significant difference between the groups, particularly between the SLE-treated group P1 and the DEN-only group K2B. This suggests

that combining SLE and sorafenib may enhance extrinsic apoptotic pathways more effectively than sorafenib alone or no treatment. The significant increase in caspase 8 in P1 indicates that SLE might promote apoptosis through death receptor-mediated mechanisms, potentially contributing to the inhibition of tumor growth [14]. However, the lack of significant differences in caspase 3 and caspase 9 expression suggests that the treatment combination may not as strongly activate intrinsic apoptotic pathways. This differential activation of apoptotic pathways warrants further investigation, as it may influence therapeutic strategies targeting both extrinsic and intrinsic apoptotic mechanisms in HCC [15].

BCL-2 and BAX Expression

BCL-2 and BAX are key regulators of apoptosis, with BCL-2 inhibiting and BAX promoting cell death. The significant differences in BCL-2 and BAX expression between the P1 and K2B groups highlight the potential of SLE to modulate the balance between pro- and anti-apoptotic proteins [16]. The observed decrease in BCL-2 expression and concurrent increase in BAX expression in the SLE-treated group suggest that SLE may reduce the survival of cancer cells by tipping the balance toward apoptosis. This effect was particularly pronounced in the P1 group, supporting the hypothesis that lower doses of SLE in combination with sorafenib may be more effective at inducing apoptosis than higher doses [17].

VEGF and Angiogenesis

The VEGF analysis yielded contrasting results between serum and tissue levels. While tissue VEGF expression did not show significant differences across groups, serum VEGF levels were significantly elevated in all treatment groups compared to controls. This disparity suggests that while the local tumor environment may not exhibit noticeable changes in VEGF expression, systemic VEGF levels are more responsive to treatment [14, 18]. The significant differences between almost all groups in serum VEGF, except between P1 and P2, indicate that both doses of SLE affect angiogenic processes similarly. Elevated serum VEGF in the treatment groups could represent a compensatory angiogenic response to tumor inhibition, which has been observed in other cancer models treated with anti-angiogenic therapies like sorafenib [19].

AFP as a Tumor Marker

The significant differences in AFP levels between the groups further reinforce the anticancer effects of SLE in combination with sorafenib. AFP is a well-established marker of liver cancer progression, and its significant reduction in group P1 compared to the DEN-only group K2B suggests that SLE effectively suppresses tumor activity [20]. Notably, the significant difference in AFP between K2A and K2B also underscores the progressive nature of tumor growth in the absence of treatment. The lower AFP levels in P1 indicate that even at a lower dose, SLE in combination with sorafenib may halt or slow tumor progression [21].

Tumor Volume

Although the relative liver volume, used as a proxy for tumor size, did not show significant differences between the groups, the combination of other markers such as AFP, VEGF, BCL-2, and caspase 8 suggests that the anticancer effects of SLE may not be solely dependent on changes in tumor volume. The lack of significant changes in tumor size could be attributed to the short duration of the treatment or the complex nature of hepatocarcinogenesis, where biochemical and molecular changes precede visible tumor regression [22].

Strength and Limitation

A key strength of this study is its comprehensive assessment of biomarkers, including apoptotic (caspase 3, 8, 9, BCL-2, BAX), angiogenic (VEGF), and tumor progression markers (AFP), which provide a detailed understanding of the molecular effects of SLE on liver cancer. The combination therapy approach, using SLE alongside the standard treatment sorafenib, reflects real-world therapeutic strategies and offers insight into potential synergistic effects. Additionally, the well-controlled experimental design with distinct groups and dose-response analysis contributes to the robustness of the findings. Serum and tissue analyses further enhance the study by offering a systemic and localized perspective. However, the study's small sample size may limit statistical power, and the short duration may not capture long-term effects on tumor growth, which likely contributed to the non-significant changes in liver tumor volume. The lack of mechanistic exploration leaves the exact pathways through which SLE operates unclear, and the absence of functional outcomes, such as survival rates, reduces the clinical applicability of the findings. Finally, using only a single cancer model (DEN-induced HCC) restricts the generalizability to other cancer types, warranting further research in diverse models.

CONCLUSION

This study provides evidence that SLE, particularly at a lower dose of 50 mg/kg in combination with sorafenib, exerts promising anticancer effects in a DEN-induced HCC model. The significant modulation of apoptotic markers such as caspase 8, BCL-2, and BAX, coupled with reductions in AFP levels, suggests that SLE could enhance the efficacy of sorafenib by promoting apoptosis and inhibiting tumor progression. Further research is needed to explore the long-term effects of SLE on tumor size and the underlying mechanisms by which SLE modulates angiogenesis and apoptosis in liver cancer.

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Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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