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COMPARATIVE CYTOTOXIC AND ANTIPROLIFERATIVE EFFECTS OF *ACTINIDIA DELICIOSA* EXTRACTS ON HEPG2 HEPATOCELLULAR CARCINOMA CELLS

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ABSTRACT

Herbal medicines derived from natural sources are gaining attention for their potential therapeutic roles in cancer treatment. This study evaluates the anticancer activity of various solvent extracts of *Actinidia deliciosa* (kiwi fruit) against the human hepatocellular carcinoma (HepG-2) cell line using MTT assay. Five extracts—aqueous, chloroform, ethyl acetate, hexane, and methanol—were tested at concentrations ranging from 25 to 125 µg/mL. Among these, the methanol extract showed the most potent cytotoxic effect with an IC_{50} value of 22.63 µg/mL after 48 hours. Cytomorphological analysis confirmed morphological changes in treated cells, indicating apoptosis. These results suggest that *A. deliciosa*, especially its methanol extract, holds promise as a potential natural anticancer agent.

INTRODUCTION

The health benefits of fruit consumption have been widely substantiated by epidemiological studies, largely attributed to their rich content of dietary fiber, proteins, vitamins, minerals, and bioactive phytochemicals. Among these, fruits from the *Actinidiaceae* family have long been recognized for their medicinal and therapeutic properties. Phytochemicals present in such fruits have demonstrated protective roles against a variety of ailments, including hepatitis, edema, wheezing, cough, diabetes, rheumatoid arthritis, gingival inflammation, hepatic injury, and several cancers such as gastric, breast, and esophageal. Additionally, they are known to alleviate conditions like mouth soreness, itching, urinary tract stones, and offer neuroprotective effects.

Notably, the efficacy of these phytochemicals often arises not from isolated compounds but from synergistic or additive interactions within complex mixtures found in whole food sources. This highlights the importance of evaluating whole extracts rather than individual constituents.

Hepatocellular carcinoma (HCC), also referred to as malignant hepatoma, is the most common form of primary liver cancer and ranks as the third leading cause of cancer-related deaths worldwide—after lung and stomach cancers . Global incidence estimates suggest over one million new cases annually. Major risk factors for HCC include chronic infections with hepatitis B and C viruses, aflatoxin exposure, liver cirrhosis, environmental pollutants, obesity, iron overload, and nitrosamine intake.

In recent years, there has been growing interest in identifying natural compounds with chemopreventive and anticancer properties, owing to their potent antioxidant and cytotoxic effects. Against this backdrop, the present study evaluates the anticancer potential of different solvent extracts of *Actinidia deliciosa* (kiwi fruit) against human hepatocellular carcinoma (HepG-2) cells in vitro.

2. LITERATURE REVIEW

Medicinal plants have long served as reservoirs of bioactive compounds for anticancer drug development. Cragg and Newman [1] emphasized the significance of plants as primary sources of anticancer agents, while Henriques et al. [4] documented the successful transition of natural product-derived compounds into clinical applications. Within this context, *Actinidia deliciosa* (kiwi fruit), a member of the Actinidiaceae family, has attracted increasing scientific attention for its rich profile of health-promoting phytochemicals, including flavonoids, phenolic acids, triterpenoids, and actinidin.

The cytotoxicity of *A. deliciosa* fruit extracts against HepG-2 liver cancer cells has been extensively evaluated using MTT assays. Methanol extracts showed the highest anticancer activity, with an IC_{50} value of 22.63 µg/ml, significantly outperforming chloroform (41.08 µg/ml), ethyl acetate (32.80 µg/ml), hexane (57.65 µg/ml), and aqueous extracts (57.87 µg/ml). This aligns with findings by Hashim et al. [27], where methanol effectively extracted key cytotoxic phenolics. Morphological observations revealed treated HepG-2 cells undergoing apoptosis-like changes, including shrinkage, rounding, and membrane disintegration [50].

Several studies corroborate the anticancer efficacy of various *Actinidia* species. Zuo et al. [12] reported antiproliferative effects from *A. kolomikta*, *A. arguta*, and *A. chinensis* extracts against multiple cancer cell lines. Similarly, Su et al. [37] and Zhang et al. [33] found that *Actinidia* root extracts induced

apoptosis via Mcl-1-mediated mechanisms. Other studies, such as by Fang et al. [31], highlighted the synergistic role of triterpenoids in suppressing HepG-2 growth both in vitro and in vivo.

Phytochemical investigations by Costa et al. [35] and Zhao et al. [41] revealed the presence of potent antioxidants and cytotoxic compounds in both the pulp and peel of *A. deliciosa*. Salama et al. [50] confirmed the antimicrobial, antioxidant, and anticancer activities of kiwi peel constituents, suggesting their utility in therapeutic formulations. Sivaraj et al. [42] and Singh and Patel [34] documented the higher antioxidant capacity in methanol and ethanol extracts of kiwi pulp, correlating this with enhanced cytotoxicity.

Beyond direct anticancer effects, kiwi fruit has also shown potential in green nanotechnology. Gao et al. [28] used kiwi extract to biosynthesize gold nanoparticles with notable antitumor properties. Studies by Lin et al. [29] and Dillard and German [26] emphasized the importance of phytochemical synergy in whole-food extracts over isolated compounds.

Comparative studies with other fruits and plants further reinforce the therapeutic potential of kiwi. Sun et al. [2] and McDougall et al. [3] reported strong antiproliferative activity in apples, cranberries, and strawberries. Similarly, Moongkarndi et al. [10] demonstrated that *Garcinia mangostana* induces apoptosis in breast cancer cells. Extracts from *Syzygium cumini* [5], *Solanum trilobatum* [8], and *Glossostemon bruguieri* [7] showed parallel cytotoxic effects, supporting the role of fruit-derived phytochemicals in cancer therapy.

Finally, kiwi's low toxicity toward normal cells makes it a promising candidate for further chemopreventive studies. Its ability to inhibit cancer cell proliferation while preserving healthy tissue integrity underscores the need for more in vivo validations and mechanistic studies. As noted by Newman and Cragg [23], the integration of such botanicals into mainstream oncology could redefine therapeutic approaches in the coming decades.

3. MATERIALS AND METHODS

3.1 Chemicals and reagents

All chemicals and reagents used in this study were of analytical grade. Dulbecco's Modified Eagle's Medium (DMEM), fetal bovine serum (FBS), penicillin, and streptomycin were purchased from HiMedia Laboratories (India). Other solvents and reagents, including methanol, chloroform, ethyl acetate, and hexane, were procured from Sigma-Aldrich and used without further purification.

3.2 Collection and Identification of Plant Material

Fresh kiwi fruits (*Actinidia deliciosa*), New Zealand variety, were obtained from the Koyambedu fruit market in Chennai, Tamil Nadu, India. The plant species was taxonomically authenticated by Prof. P. Jayaraman, Institute of Herbal Science, Plant Anatomy Research Centre (PARC), West Tambaram, Chennai, India, and a voucher specimen (No. PARC/2013/2120) was deposited for reference.

3.3 Preparation of Fruit Extracts

Table 1.Yield and Physical Characteristics of Solvent Extracts of Actinidia deliciosa

S. No.	*Solvent*	*Weight of Dried Extract (g)*	*Yield (%)*	*Colour*	*Consistency*
1	Aqueous	20	1.5	Dark brown	Paste
2	Chloroform	20	1.6	Dark brown	Paste
3	Ethyl acetate	20	1.5	Dark brown	Paste
4	Hexane	20	1.0	Dark brown	Paste
5	Methanol	20	2.0	Dark brown	Paste

The collected fruits were thoroughly washed and the pulp (endocarp) was separated (Fig. 1). The pulp was shade-dried for up to 20 days and then ground into a fine powder using a kitchen blender. Fifty grams of dried pulp powder was extracted separately with distilled water, chloroform, ethyl acetate, hexane, and methanol (1:5 w/v) by maceration at room temperature for 72 hours. The mixtures were filtered through Whatman No. 1 filter paper (Whatman™, Cat No. 1001-110) and concentrated under reduced pressure at 45–55°C using a rotary vacuum evaporator (ROLEX). The dried extracts were weighed, stored, and used for further biological assays.

3.4 Cell Line and Culture Conditions

The human hepatocellular carcinoma cell line (HepG-2) was obtained from the National Centre for Cell Science (NCCS), Pune, India. Cells were cultured in DMEM supplemented with 10% FBS, 100 U/mL penicillin, and 100 µg/mL streptomycin, and maintained at 37°C in a humidified atmosphere containing 5% CO_2.

3.5 MTT Assay for Cytotoxicity Evaluation

The cytotoxic potential of each solvent extract was assessed using the MTT assay as described by Mosmann (1983) [13]. HepG-2 cells (1×10^4 cells/well) were seeded into 96-well plates and incubated for 24 hours. After removing the medium, cells were washed with phosphate-buffered saline (PBS) and starved in serum-free DMEM for 1 hour. They were then treated with different concentrations (25, 50, 75, 100, and 125 µg/mL) of each extract and incubated for 24 and 48 hours.

Following incubation, 10 µL of MTT solution (5 mg/mL) was added to each well and incubated for an additional 4 hours. The medium was aspirated, and 100 µL of DMSO was added to dissolve the formazan crystals. Optical density (OD) was measured at 570 nm using a microplate reader. Cell viability was calculated using the following formula:

Cell Viability (%) = (OD of treated cells / OD of control cells) × 100

The IC_{50} values (concentration required to inhibit 50% of cell viability) were determined for each extract. The methanol extract showed the highest cytotoxic activity with an IC_{50} value of 22.63 µg/mL at 48 hours. In comparison, the IC_{50} values for chloroform, ethyl acetate, and hexane extracts were 41.09 µg/mL, 32.81 µg/mL, and 57.66 µg/mL, respectively. Based on this data, the methanol extract was selected for further investigations.

3.6 Cytomorphological Analysis

Morphological changes in HepG-2 cells were examined to assess the effect of the methanol extract. Cells (1×10^6 cells/mL) were cultured in 100 mm culture dishes and incubated for 24 hours. After replacing the medium, cells were treated with the methanol extract at the 48-hour IC_{50} concentration and further incubated for 48 hours. Morphological alterations were observed under an inverted phase-contrast microscope (Radical RTC-99) at 10× magnification.

3.7 Statistical Analysis

All experiments were performed in triplicate, and data were expressed as mean ± standard error (SE) from five independent observations. Statistical significance was evaluated using two-way ANOVA in SPSS software. Differences were considered statistically significant at $p < 0.05$.

4. RESULTS

4.1 Yield of Fruit Extracts

The extraction yield of *Actinidia deliciosa* pulp was highest in the methanol extract (2.0%), followed by chloroform (1.6%), ethyl acetate (1.5%), aqueous (1.5%), and hexane (1.0%). All extracts appeared as dark brown pastes in consistency (Table 1).

Table 1: Yield of solvent extracts of *A. deliciosa*

S. No.	Solvents	Weight of dried extract (g)	Yield (%)	Colour	Consistency

1.	Aqueous	20	1.5	Dark brown	Paste
2.	Chloroform	20	1.6	Dark brown	Paste
3.	Ethyl acetate	20	1.5	Dark brown	Paste
4.	Hexane	20	1.0	Dark brown	Paste
5.	Methanol	20	2.0	Dark brown	Paste

4.2 Standardization of Crude Extracts by MTT Assay

The cytotoxic potential of the five solvent extracts of *A. deliciosa* was evaluated against HepG-2 cells using the MTT assay at various concentrations (25–125 µg/mL) and time intervals (24 h and 48 h). A progressive decrease in cell viability was observed with increasing extract concentration in all treatments (Table 2, Fig. 1). Control cells maintained 100% viability. Among all extracts, the methanol extract demonstrated the most pronounced cytotoxicity, showing a steep decline in cell viability at higher concentrations.

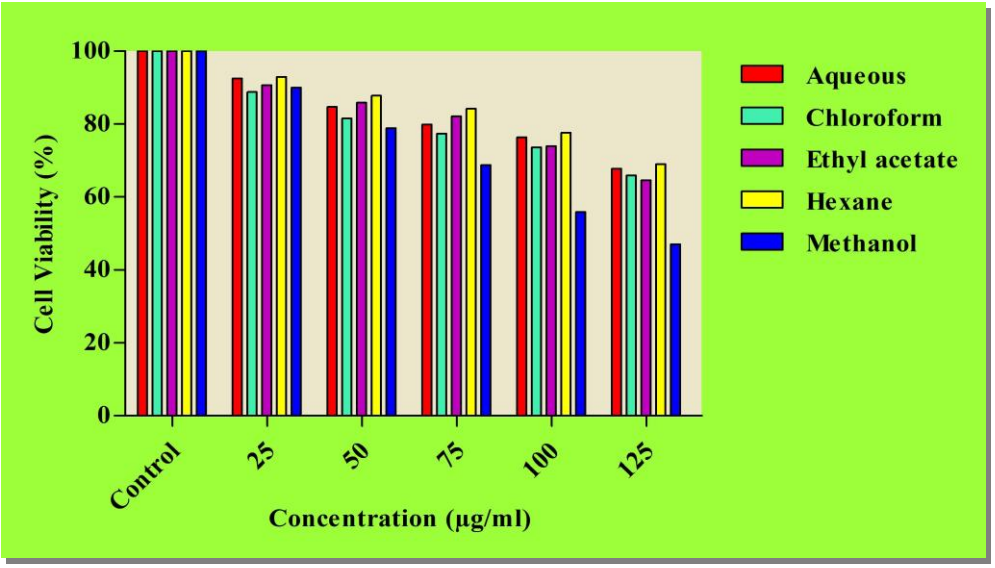

Fig. 1 : Per cent cell viability of HepG-2 cells when treated for 24 h with various extracts of *A. deliciosa*

Table 2: Per cent cell viability of HepG-2 cells when treated for 24 h with various extracts of *Actinidia deliciosa*

Concentration (µg/ml)	Aqueous	Chloroform	Ethyl acetate	Hexane	Methanol
Control (0)	100.00 ±0.00	100.00 ± 0.00	100.00 ± 0.00	100.00 ±0.00	100.00 ± 0.00
25	92.56 ± 0.84* (-7.44)	88.82 ± 0.59* (-11.18)	90.68 ± 0.51* (-9.32)	92.93 ± 0.58* (-7.06)	90.02 ± 0.45* (-9.98)
50	84.68 ± 0.71* (-15.32)	81.51 ± 0.35* (-18.49)	85.90 ± 0.50* (-14.11)	87.81 ± 0.55* (-12.19)	78.86 ± 0.55* (-21.14)
75	79.91 ± 0.35* (-20.09)	77.35 ± 0.61* (-22.65)	82.12 ± 0.97* (-17.87)	84.25 ± 1.99* (-15.75)	68.79 ± 1.01* (-31.21)
100	76.33 ± 0.84* (-23.67)	73.61 ± 0.45* (-26.39)	73.97 ± 0.50* (-26.03)	77.62 ± 1.08* (-22.38)	55.87 ± 0.44* (-44.13)
125	67.81 ± 0.59* (-32.19)	65.97 ± 0.54* (-34.03)	64.62 ± 0.56* (-35.37)	69.05 ± 0.51* (-30.95)	47.05 ± 0.50* (-52.95)

Values are mean ± S.E. of five individual observations. Values in parentheses are per cent change over control.

- Denotes per cent decrease over control.

*Values are significant at P<0.05.

Two-way ANOVA analysis confirmed statistically significant differences ($p < 0.05$) in cell viability both across extract types and concentrations (Table 2).

Table 3: Per cent cell viability of HepG-2 cells when treated for 48 h with various extracts of *A. deliciosa*

Concentration (µg/ml)	Aqueous	Chloroform	Ethyl acetate	Hexane	Methanol
Control (0)	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	100.00 ±0.00	100.00 ±0.00
25	59.97 ± 3.32* (-40.03)	53.17 ± 0.90* (-46.83)	53.21 ± 1.99* (-46.79)	60.19 ± 3.70* (-39.81)	45.23 ± 0.47* (-54.76)

50	54.70 ± 1.72* (-45.30)	48.24 ± 1.26* (-51.76)	42.92 ± 1.72* (-57.08)	55.28 ± 2.37* (-44.72)	40.71 ± 0.69* (-59.29)
75	39.77 ± 1.19* (-60.23)	36.66 ± 0.74* (-63.34)	34.69 ± 1.69* (-65.31)	38.03 ± 1.45* (-61.97)	32.65 ± 0.59* (-67.35)
100	34.14 ± 1.97* (-65.86)	33.18 ± 0.99* (-66.82)	31.92 ± 1.81* (-68.08)	35.28 ± 2.55* (-64.72)	28.07 ± 0.64* (-71.93)
125	30.14 ± 0.82* (-69.86)	30.03 ± 1.42* (-69.97)	26.83 ± 1.56* (-73.17)	32.56 ± 1.12* (-67.44)	24.38 ± 0.56* (-75.63)

Values are mean ± S.E. of five individual observations. Values in parentheses are per cent change over control.
- Denotes per cent decrease over control.
*Values are significant at P<0.05.

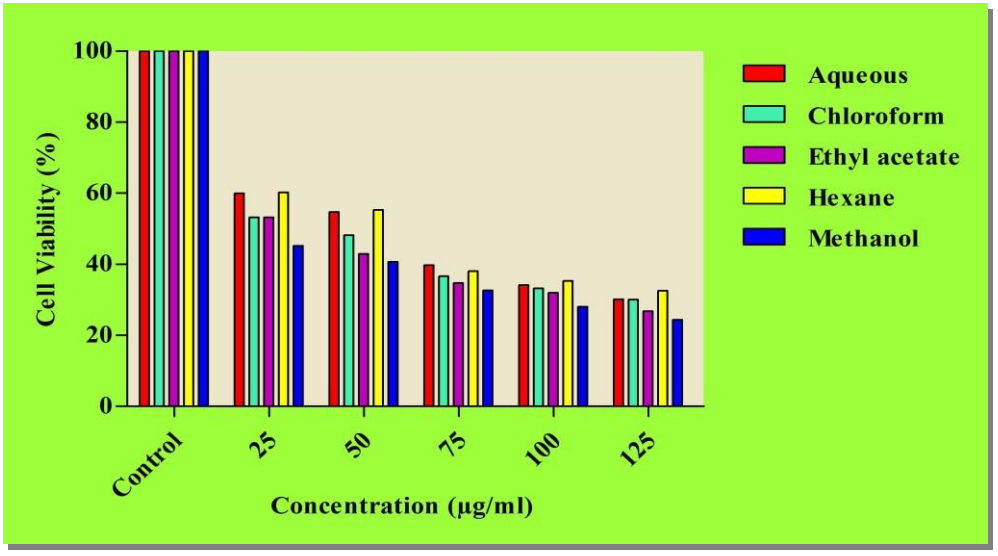

Fig. 2: Per cent cell viability of HepG-2 cells when treated for 48 h with various extracts of *A. deliciosa*

Further, the cytotoxic response was also assessed after 48 hours of treatment (Table 3, Fig. 2). A similar trend of concentration-dependent reduction in HepG-2 cell viability was noted, with the methanol extract again demonstrating the highest cytotoxicity at 125 µg/mL. ANOVA results corroborated the significant variability ($p < 0.05$) among treatments.

Table 4: Exact IC_{50} value of HepG-2 cells when treated with various extracts of *A. deliciosa*

Time (h)	IC_{50} value (µg/ml)				
	Aqueous	Chloroform	Ethyl acetate	Hexane	Methanol
24	194.16	183.66	176.30	201.94	116.64
48	57.87	41.08	32.80	57.65	22.63

The IC_{50} values calculated at 24 hours revealed that the methanol extract exhibited the strongest activity (116.64 µg/mL), followed by ethyl acetate (176.30 µg/mL), chloroform (183.66 µg/mL), aqueous (194.16 µg/mL), and hexane (201.94 µg/mL). At 48 hours, methanol extract exhibited a much lower IC_{50} value of 22.63 µg/mL, highlighting its potent time- dependent cytotoxicity. The IC_{50} values of the other extracts followed the trend: ethyl acetate (32.80 µg/mL) < chloroform (41.08 µg/mL) < hexane (57.65 µg/mL) < aqueous (57.87 µg/mL) (Table 4).

Collectively, these findings confirm that methanol extract of *A. deliciosa* possesses the most significant cytotoxic potential against HepG-2 cells and was therefore selected for further in-depth evaluation.

4.3 Cytomorphological Observation

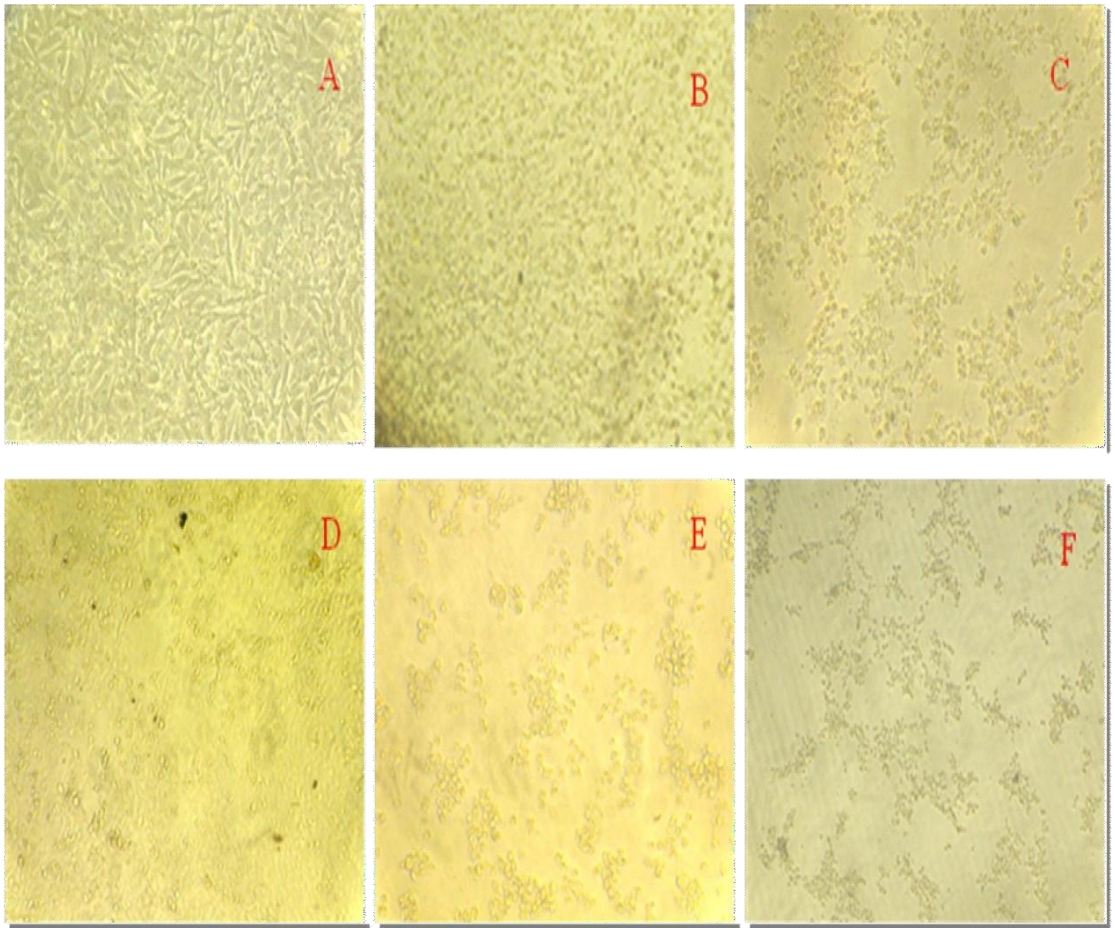

Plate 1: Cytomorphological Changes in HepG-2 Cells Treated with 48-Hour IC_{50} Concentrations of *Actinidia deliciosa* Extracts (10× Magnification)

(A) Untreated control cells showing normal polygonal morphology and confluent growth.
(B) Aqueous extract-treated cells.
(C) Chloroform extract-treated cells.
(D) Ethyl acetate extract-treated cells.
(E) Hexane extract-treated cells.
(F) Methanol extract-treated cells exhibiting pronounced cellular shrinkage and spherical morphology indicative of apoptosis.

Morphological changes in HepG-2 cells following treatment with 48-hour IC_{50} concentrations of the extracts were evaluated under an inverted phase-contrast microscope at 10× magnification. Control cells exhibited normal rounded and polygonal morphology with intact cell aggregates. In contrast, methanol extract-treated cells showed marked cytoplasmic shrinkage and transition to spherical morphology, indicative of apoptosis. The degree of morphological alteration was dose- and time-dependent, with the methanol extract inducing the most pronounced changes (Plate 1).

DISCUSSION

Cancer is a condition characterized by uncontrolled and abnormal cell proliferation. Despite advancements in treatment modalities such as chemotherapy, radiotherapy, and surgery, the disease continues to pose significant health challenges. While current therapies may prolong survival, they often come with limitations, including incomplete efficacy and severe side effects. Moreover, many chemotherapeutic agents target rapidly dividing cells indiscriminately, leading to toxicity in healthy tissues and organs.

Natural products derived from plants have long been recognized as valuable sources of therapeutic agents. They offer a wide array of bioactive compounds with diverse biological activities, including anticancer properties. Plants are capable of synthesizing a vast number of secondary metabolites, many of which have demonstrated potent cytotoxic activity against cancer cells while exerting minimal effects on normal cells.

The present study was conducted to evaluate the anticancer potential of different solvent extracts of *Actinidia deliciosa* (kiwi fruit) against human hepatocellular carcinoma (HepG-2) cells. Among the various solvent extracts tested—aqueous, chloroform, ethyl acetate, hexane, and methanol—the methanol extract displayed the strongest cytotoxic activity, with an IC_{50} value of 22.63 µg/mL after 48 hours of treatment. Other extracts showed higher IC_{50} values, indicating reduced efficacy compared to the methanol extract.

The enhanced anticancer activity observed in the methanol extract could be attributed to its ability to effectively extract and concentrate a broad spectrum of phytochemicals such as flavonoids, polyphenols, triterpenoids, and other bioactive constituents. Methanol, being a polar solvent, is known for its superior ability to solubilize phenolic compounds, which may contribute to its greater anticancer potential.

In addition to reduced cell viability, morphological changes characteristic of apoptosis were observed in HepG-2 cells treated with the methanol extract. These changes included cytoplasmic shrinkage and rounding of cells, suggesting that the extract not only inhibited proliferation but also induced programmed cell death. Such morphological alterations were more prominent in the methanol-treated group than in the other solvent groups.

The findings from this study suggest that the anticancer activity of *A. deliciosa* methanol extract may be due to the presence of active phytoconstituents that inhibit cancer cell growth and induce cell death through various mechanisms. The fruit has long been used in traditional medicine for treating conditions such as urinary tract stones, arthritis, and liver disorders. Its rich nutritional composition—including vitamins, minerals, flavonoids,

and phenolic acids—likely contributes to its therapeutic potential.

This investigation supports the use of *A. deliciosa* as a promising candidate for further research into plant-based anticancer therapies. The observed cytotoxicity, combined with low toxicity to normal cells, highlights its potential application in complementary cancer treatment strategies.

CONCLUSION

While synthetic and semi-synthetic drugs have proven effective in treating various diseases, their associated toxicity and side effects remain a concern. In contrast, herbal medicines offer a safer alternative with minimal adverse effects.

In this study, the anticancer activity of various solvent extracts of *Actinidia deliciosa* was assessed using the MTT colorimetric assay against HepG-2 cells. Among the tested extracts, the methanol extract demonstrated the most significant cytotoxic effect, showing 50% inhibition of cell viability at a concentration of 22.63 µg/mL after 48 hours. Other extracts such as ethyl acetate, chloroform, and hexane displayed less potency with higher IC_{50} values.

The results indicate that the methanol extract of *A. deliciosa* possesses strong anticancer activity and holds promise as a natural therapeutic agent. Further studies are needed to isolate, characterize, and understand the mechanisms of action of the active compound(s) responsible for this effect. This could lead to the development of safe, plant-based treatments for liver cancer and potentially other cancers.

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