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Plant-Derived Bioactive Constituents from *Beta vulgaris* and *Triticum aestivum* Induce Apoptosis in A549 Lung Adenocarcinoma Cells: Phytochemical and Antioxidant Insights

Devanshi Rajput[1], Swati Makwana[1], Payal Sargara[2], M. Nataraj[3]

[1]P.G. Department of Biosciences, Sardar Patel University, Vallabh Vidyanagar, Gujarat, India
Corresponding Author: Devanshi Rajput[1]

Abstract: ***Lung cancer remains one of the leading causes of cancer-associated deaths worldwide, underscoring the urgent need for safer and more effective therapeutic alternatives. In this context, plant-derived bioactive compounds have gained increasing attention as potential anticancer agents due to their therapeutic efficacy and lower toxicity. The present study evaluated the phytochemical composition, total phenolic content, antioxidant potential, and anticancer activity of Beta vulgaris L. (beetroot sprouts) and Triticum aestivum L. (wheatgrass) extracts against human lung adenocarcinoma (A549) cells. The Cytotoxic effects were assessed using the MTT assay, while apoptosis induction was examined through Acridine Orange/Ethidium Bromide (AO/EB) staining and DNA fragmentation analysis by agarose gel electrophoresis. Phytochemical screening revealed the presence of diverse secondary metabolites in both plant extracts. Notably, Triticum aestivum L. exhibited a substantially higher total phenolic content (12.31 mg/g GAE) than Beta vulgaris L. (3.91 mg/g GAE). Both extracts demonstrated marked antioxidant and anticancer activities; however, Triticum aestivum L. showed greater cytotoxic potency, with a significantly lower IC_{50} value (39.58 µg/mL) compared to Beta vulgaris L. (963.58 µg/mL) in the MTT assay. Morphological changes were observed through AO/EB staining, along with DNA fragmentation patterns, which confirmed apoptosis in treated A549 cells. Overall, the results indicate that bioactive metabolites present in Beta vulgaris L. and Triticum aestivum L. possess notable antioxidant and apoptosis-inducing properties, highlighting their potential as natural therapeutic agents against lung cancer.***

Keywords: *Beta vulgaris*, *Triticum aestivum,* Ao/EB staining, Lung Adenocarcinoma cell line (A549), MTT assay

1. Introduction

Cancer, a major global health challenge, is characterised by the dysregulation of cellular proliferation and the accumulation of genetic damage[23]. These processes drive uncontrolled growth and genomic instability, ultimately leading to invasive tumors that disrupt tissue function and cause life-threatening complications[22]. The etiology of cancer is multifactorial, encompassing environmental, biological, and hereditary factors[19]. Despite chemotherapy remaining a cornerstone of cancer treatment, its clinical application is frequently limited by severe side effects, drug interactions, and the emergence of chemoresistance[18]. These challenges underscore the need for safer and more effective therapeutic alternatives. In contrast to conventional treatments, plants offer a promising source of biologically active natural compounds that can be used either as standalone therapeutic agents or as the basis for developing modified derivatives with improved efficacy and reduced toxicity in cancer treatment[17]. Plant-derived compounds, therefore, represent a promising avenue for discovering novel anticancer agents.

Recognising the rich biodiversity of the plant kingdom as a promising source for novel chemopreventive agents, our research aims to explore the chemopreventive potential of two widely recognised species—*Beta vulgaris* L. and *Triticum aestivum* L., renowned for their rich phytochemical profiles. *Beta vulgaris L.* (beetroot) is a rich source of betalains, particularly betacyanins and betaxanthins, along with phenolic compounds, flavonoids, and ascorbic acid, which collectively contribute to its potent antioxidant and free radical scavenging properties[5]. The Phytochemical investigation of *Beta vulgaris L*. has revealed its biological activities, such as antifungal, antibacterial, antimutagenic and antidiabetic[2]. Betalains have been reported to induce apoptosis, inhibit proliferation, and modulate signalling pathways such as PI3K/Akt and MAPK in various cancer models [4]. Similarly, *Triticum aestivum L.* (wheatgrass) contains phenolic acids and flavonoids, which exhibit strong antioxidant and detoxifying activities [3]. These phytochemicals can suppress tumor progression by reducing oxidative stress, enhancing cellular antioxidant defence, and triggering apoptotic mechanisms in malignant cells. To elucidate their potential mechanisms of action, we conducted a comprehensive analysis, including qualitative phytochemical screening, antioxidant assays, cytotoxicity evaluation against A549 lung carcinoma cells and DNA fragmentation pattern study.

2. Materials and Method

2.1 Plant Material and Extract Preparation

To prepare plant extracts, fresh beetroot sprouts (*Beta vulgaris L.*) and wheatgrass (*Triticum aestivum L.*) were collected, washed thoroughly to remove debris, and shade-dried at room temperature to preserve heat-sensitive compounds. The dried material was ground into a fine powder using a grinder. For extraction, 20 g of each powdered sample was macerated in 200 mL methanol: water (7:3, v/v) solution for 24 h at ambient conditions with intermittent shaking. The extracts were filtered, and the filtrates were concentrated under reduced pressure to obtain crude residues, which were stored at 4 °C until further use [24].

2.2 Phytochemical Analysis

Preliminary phytochemical screening of the plant extracts was carried out to identify the presence of bioactive secondary metabolites, following standard qualitative procedures [16]. Assays included Mayer's reagent for alkaloids, lead acetate for flavonoids, foam test for saponins, ferric chloride test for phenols, and other standard procedures for tannins, terpenoids, coumarins, emodins, cardiac glycosides, and polyphenols.

2.3 Total Phenolic Content

Plants use phenolic acids to develop, grow, stabilise against pathogens, and respond to abiotic stress, defining them as essential secondary metabolites in plant physiology [15].Additionally, earlier studies confirm their protective role against UV radiation and pathogens due to their redox properties [14].

This study aims to analyse the total phenolic content in selected samples, providing insights into their antioxidant capacity and potential health benefits. The Total Phenolic Content (TPC) of the extracts was determined using the Folin–Ciocalteu colorimetric method [21]. A standard calibration curve was prepared using gallic acid (100–500 µg/mL) dissolved in DMSO from a 100 mg/mL stock solution. Briefly, 25 µL of plant extracts (10 mg/mL) and standard solution were mixed with 250 µL Folin–Ciocalteu reagent and incubated for 5 min. Then, 750 µL of 20% sodium carbonate solution was added, and the volume was adjusted to 5 mL with distilled water. The mixture was kept in the dark at room temperature for 2 h. Absorbance was recorded at 760 nm, and TPC was expressed as mg gallic acid equivalent (GAE)/g extract, based on a standard curve prepared using gallic acid.

2.4 Antioxidant Activity by DPPH Assay

The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay is routinely used to assess antiradical properties. This assay is based on the principle that DPPH, on accepting a hydrogen (H) atom from the scavenger molecule, i.e. antioxidant, results in reduction of DPPH to $DPPH_2$, the purple colour changes to yellow with concomitant decrease in absorbance that can be quantified spectrophotometrically [1].

The antioxidant potential of the extracts was determined by their ability to scavenge the stable DPPH (2,2-diphenyl-1-picrylhydrazyl) radical, as described by [20]. A 0.1 mM DPPH solution in methanol was prepared freshly. For the assay, the plant crude extracts were dissolved at a concentration of 1 mg/mL and compared against a 1 mg/mL ascorbic acid standard, a known antioxidant.

Standard solutions were prepared by serial dilution of the stock solution (1000 µg/mL) using methanol to obtain concentrations ranging from 100 to 1000 µg/mL, maintaining a final volume of 1 mL for each solution. Sample solutions (10–50 µg/mL) were similarly prepared by diluting the plant crude extract in the extraction solvent to a final volume of 1 mL. For both standards and samples, 500 µL of each solution was transferred into amber tubes, followed by the addition of 1500 µL of DPPH reagent. A reagent blank containing only DPPH was included as a control. All tubes were incubated in the dark at room temperature for 30 minutes. After incubation, the absorbance was measured at 517 nm using a UV-Vis spectrophotometer [7]. The percentage inhibition of DPPH radical scavenging was calculated using the following formula: %Inhibition = Absorbance of control- Absorbance of sample/ Absorbance of control*100 [25].

2.5 Anticancer Activity by MTT Assay

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay is widely employed in vitro colorimetric method for assessing cell viability, particularly in evaluating the anticancer activity of plant extracts. This assay leverages the metabolic activity of living cells [8].

The core principle involves the enzymatic reduction of yellow MTT tetrazolium salt into purple formazan crystals by mitochondrial dehydrogenases in metabolically active cells. The intensity of the purple colour, measured spectrophotometrically, is directly proportional to the number of viable cells, making it a reliable indicator of cell health, proliferation, and cytotoxicity [12].

2.6 Culturing of Human Lung Carcinoma Cells (A549)

The Human lung adenocarcinoma cells (A549) were procured from NCCS, Pune, India. The cells were grown in Minimum Essential Medium (MEM) (AL047S Himedia) supplemented with 10% Fetal Bovine Serum (FBS) (RM10832 Himedia) along with 2.5% antibiotics solution (5000 units Penicillin, 5mg Streptomycin and 10mg Neomycin per ml in Citrate buffer) (A028 Himedia). The cells were maintained as a monolayer culture in an incubator at 37 °C with 5% CO2 and 95% air [11].

2.7 Evaluation of Cytotoxic Effects of Plant Extracts on A549 Cells using MTT Assay

The A549 cells were seeded in 96-well plates at 6,000–10,000 cells/well and allowed to adhere for 24 h. Cells were then treated with serial dilutions (3.9-8000 µg/mL) of *Beta vulgaris* and *Triticum aestivum* extracts in triplicate and incubated for 24 h in a CO_2 incubator. Following treatment, 5 µL of MTT solution (5 mg/mL in PBS) was added to each well, and plates were incubated for 90 min at 37 °C in the dark. Absorbance was recorded at 570 nm with a reference at 690 nm using a microplate reader (SpectraMax M2e, Molecular Devices)[6].

2.8 Evaluation of Apoptosis in A549 Cells Using Acridine Orange/Ethidium Bromide (AO/EB) Dual Staining

Morphological and viability changes in A549 cells following plant extract treatment were assessed using acridine orange/ethidium bromide (AO/EB) dual staining. For this, A549 cells were cultured in 50 mL YEG broth at 37 °C with shaking for 24 h. The culture was then treated with 500 µL of plant extract (100 mg/mL) and incubated for the next 24 h under the same conditions. Subsequently, 10 mL of treated culture was centrifuged at 8,000 rpm for 10 min at 4 °C, and the pellet was washed twice with PBS before resuspension in 1 mL PBS. For staining, 10 µL of the suspension was mixed

with 5 µL of AO/EB (1:1) and incubated at room temperature for 10 min. A 10 µL sample was then mounted on a slide and examined under a fluorescence microscope[10]. Thus, this staining approach enables visualisation of treatment-induced changes in cell morphology and membrane integrity, allowing discrimination between viable and apoptotic cells.

2.9 DNA Isolation of Treated Lung Cancer Cells (A549) and Analyzing DNA Integrity on Agarose Gel Electrophoresis

The cells were harvested from T-75 flasks using trypsin, centrifuged at 1200 rpm for 10 min at 10 °C, and washed twice with 10 mL 1× PBS. The pellet was resuspended in 10 mL DNA buffer, centrifuged again, and the supernatant was discarded. For lysis, 3 mL DNA buffer, 125 µL Proteinase K (10 mg/mL), and 400 µL 10% SDS were added, and the mixture was incubated overnight at 45 °C. Lysates were extracted with phenol (1.8 mL), followed by sequential chloroform–isoamyl alcohol extractions (1.8 mL each), with centrifugation at 3000 rpm for 10 min at 10 °C after each step. DNA was precipitated by adding 1/10 volume of 3 M sodium acetate (pH 5.2) and absolute ethanol, then spooled using a sterile glass pipette and washed in 70% ethanol. The DNA pellet was centrifuged at 14,000 rpm for 20 min, dried in a Speed Vac for 5 min, and dissolved in 300–500 µL sterile water by overnight incubation at 37 °C [9]. DNA concentration was measured using a Nanodrop, and integrity was verified on 1% agarose gel in 1× TAE buffer.

3. Results and Discussions

3.1 Percentage Yield of Plant Extract

The percentage yield of a plant's extract was calculated to determine the quantity of extract obtained from the raw plant material, expressed as a percentage (Table 1). This value was useful in evaluating the efficiency of the extraction process and the yield of bioactive compounds.

The percentage yield was calculated using the formula:
% yield = Final weight of sample extracted (g) / Initial weight of the sample (g) *100

Table 1: %Yield of plants' crude extract in different solvent

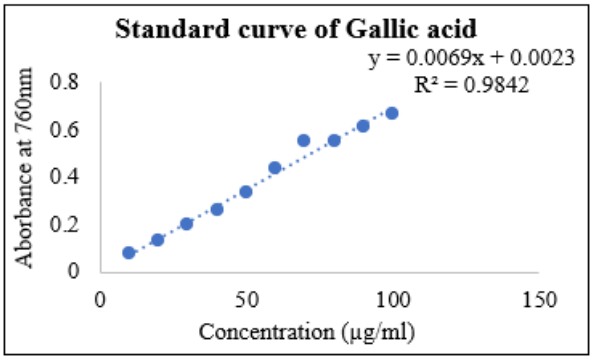
Plant part	Solvent (Methanol: water)
Beta vulgaris L. (Beetroot sprouts)	30%
Triticum aestivum L. (Wheatgrass)	30%

3.2 Phytochemical Screening

Qualitative phytochemical analysis of *Beta vulgaris L.* and *Triticum aestivum L.* extracts revealed the presence of broad-spectrum bioactive secondary metabolites, including alkaloids, tannins, terpenoids, flavonoids, coumarins, steroids, cardiac glycosides, phenols, polyphenols, and saponins. In contrast, emodins were absent in both extracts, as indicated by a negative result in the ammonia test. The abundant presence of these bioactive compounds supports the potential therapeutic efficacy of both plants.

3.3 Total Phenolics by FCR Reagent

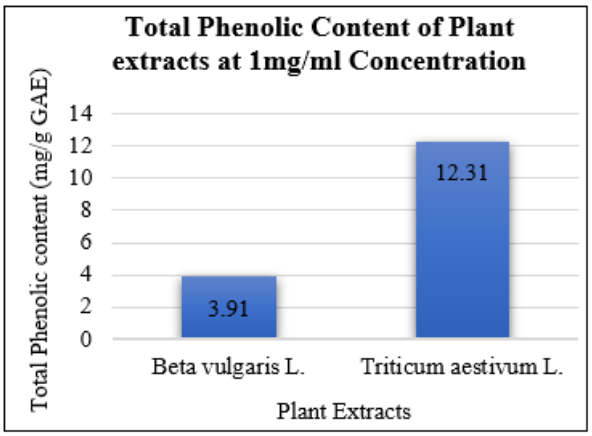
The phenolic content was determined from a standard curve of gallic acid in DMSO (Graph 1). The total phenolic content in crude extracts of *Beta vulgaris* and *Triticum aestivum* was found to be 3.91mg/g GAE and 12.31mg/g GAE (Graph 2).



Graph 1: Standard curve of Gallic acid

Table 2: Phytochemical tests of plants extract in Methanol: Water

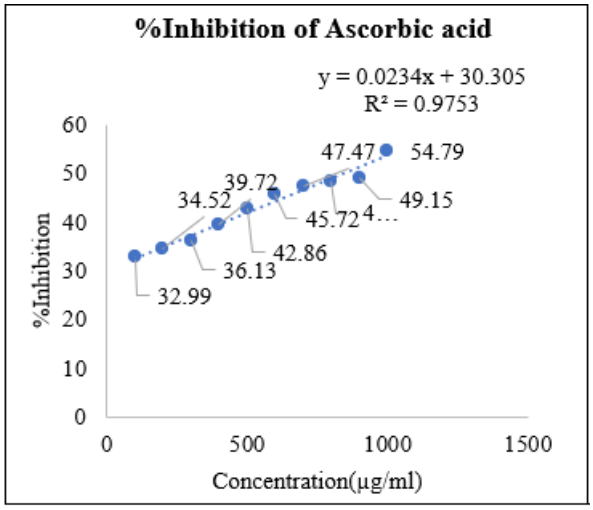
Secondary Metabolites	Test Name	Beta vulgaris (Beetroot sprouts)	Triticum aestivum (Wheatgrass)
Alkaloids	Mayer's Test	Positive	Positive
Flavonoids	Lead Acetate Test	Positive	Positive
Tannins	Ferric Chloride Test	Positive	Positive
Saponins	Foam Test	Positive	Positive
Terpenoids	Salkowski Test	Positive	Positive
Coumarins	UV Fluorescence Test	Positive	Positive
Emodins	Ammonia Test	Negative	Negative
Phenols	Ferric Chloride Test	Positive	Positive
Polyphenols	Lead Acetate Test	Positive	Positive
Cardiac Glycosides	Legal Test	Positive	Positive



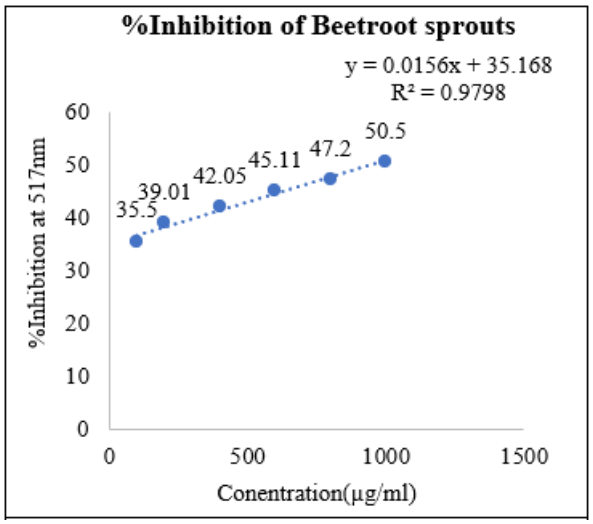
Graph 2: Total Phenolic Content of plant's crude extracts

3.4 Antioxidant Activity by DPPH Assay

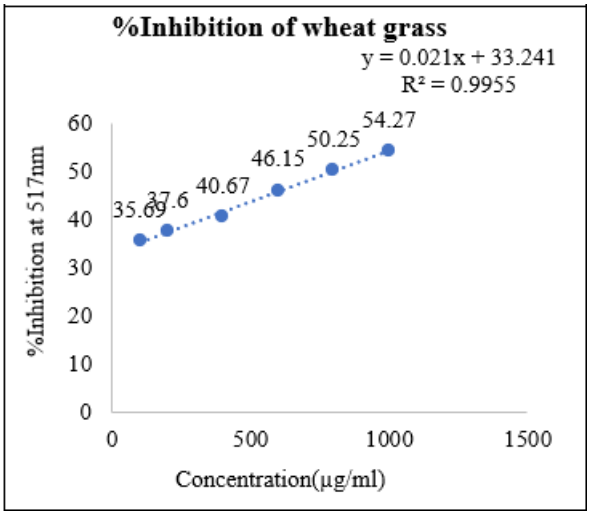
The detection of diverse secondary metabolites, particularly phenols, flavonoids, and tannins, in the extracts of *Beta vulgaris* and *Triticum aestivum* provided a strong basis for the investigation of their antioxidant potential through DPPH radical scavenging assay.



Graph 3: %Inhibition of Ascorbic acid standard



Graph 4: %Inhibition of *Beta vulgaris* L. (Beetroot sprouts)



Graph 5: %Inhibition of *Triticum aestivum L.* (Wheatgrass)

The antioxidant activities of the ascorbic acid standard, *Beta vulgaris L.* (beetroot sprouts), and *Triticum aestivum L.* (wheatgrass) extracts were evaluated using the DPPH free radical scavenging assay. Ascorbic acid, used as a positive control, exhibited a concentration-dependent increase in DPPH radical scavenging activity, with an IC_{50} value of 841.66 µg/mL (Graph 3). Similarly, the plant extracts demonstrated notable antioxidant activities. *Beta vulgaris* extract showed an IC_{50} value of 950.76 µg/mL (Graph 4), indicating a moderate free radical scavenging capacity comparable to that of the standard, whereas *Triticum aestivum* extract exhibited a stronger antioxidant activity, achieving an IC_{50} value of 789.04 µg/mL (Graph 5).

These results suggest that both *Beta vulgaris* and *Triticum aestivum* possess significant antioxidant potential, with *Triticum aestivum* demonstrating slightly superior radical scavenging ability.

3.6. Anticancer Activity by MTT Assay

The cytotoxic effects of *Beta vulgaris L.* (beetroot sprouts) and *Triticum aestivum L.* (wheatgrass) extracts on human lung adenocarcinoma (A549) cells were assessed by morphological observations under a 20× objective lens following MTT assay treatment.

Figure 1: Morphological characteristic of untreated A549 cells (control)

Figure 2: Morphological changes in A549 cells treated with *Beta vulgaris L.* extract at the IC_{50} concentration (963.58 µg/mL)

Figure 3: Morphological changes in A549 cells treated with *Triticum aestivum L.* extract at the IC_{50} concentration (39.58 µg/mL).

In the untreated control group (Figure 1), A549 cells appeared healthy, displaying a typical elongated spindle-shaped morphology with high confluency and strong adherence to the culture surface. Treatment with *Beta vulgaris* extract (IC_{50}: 963.58 µg/mL) (Figure 2) resulted in noticeable morphological alterations, including cell shrinkage, membrane blebbing, and a reduction in overall cell density, indicating cytotoxic effects and initiation of apoptosis. A more

pronounced cytotoxic effect was observed in cells treated with *Triticum aestivum* extract (IC_{50}: 39.58 µg/mL) (Figure 3), where a significant reduction in viable cells was evident. Cells exhibited severe rounding, detachment from the surface, and fragmented morphology, suggesting advanced stages of cell death. These observations, consistent with the MTT assay results, confirm that both plant extracts exert cytotoxic effects on A549 cells, with *Triticum aestivum* exhibiting greater anticancer potency compared to *Beta vulgaris*.

3.7 Evaluation of Apoptosis in A549 Cells using Acridine Orange/ Ethidium Bromide (AO/EB) Dual Staining

The effect of *Beta vulgaris L.* and *Triticum aestivum L.* extracts on the viability and apoptosis of A549 lung adenocarcinoma cells was assessed by dual staining with Acridine Orange/Ethidium Bromide (AO/EB) and visualised under a fluorescence microscope.

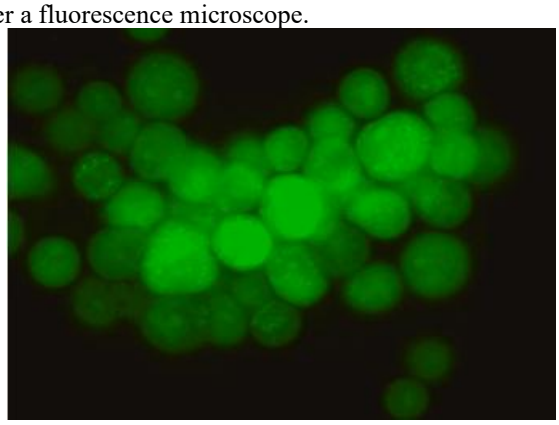


Figure 4: Morphological characteristics of untreated A549 cells (control) after 24 hours of incubation, observed under a 20× objective lens. Cells display typical spindle-shaped morphology with intact cellular architecture.

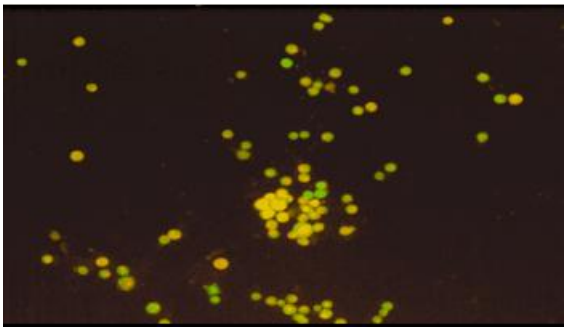


Figure 5: Morphological changes in A549 cells treated with *Beta vulgaris* (beetroot sprouts) extract at the IC_{50} concentration (963.58 µg/mL) after 24 hours, observed under a 20× objective lens. Visible cellular shrinkage and loss of adherence indicate cytotoxic effects

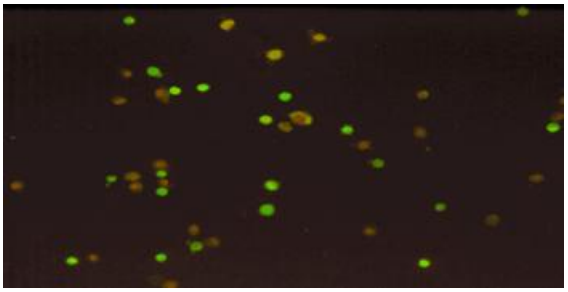


Figure 6: Morphological changes in A549 cells treated with *Triticum aestivum* (wheatgrass) extract at the IC_{50} concentration (39.58 µg/mL) after 24 hours, observed under a 20× objective lens. Treated cells show marked morphological alterations compared to control.

In the untreated control group (Figure 4), the majority of cells fluorescence green, indicating viable and healthy cells with intact membranes. Cells treated with *Beta vulgaris* extract (Figure 5) showed a significant increase in orange/red fluorescence. This suggests the induction of apoptosis, characterised by compromised membrane integrity. A higher number of early and late apoptotic cells was observed compared to the control.

Similarly, treatment with *Triticum aestivum* extract (Figure 6), resulted in a marked increase in apoptotic cells, as evidenced by bright orange and red fluorescence. Compared to *Beta vulgaris*, *Triticum aestivum* treatment demonstrated a slightly higher proportion of apoptotic cells, indicating its stronger pro-apoptotic potential on A549 cells.

3.8. DNA Isolation of Treated Human Lung Adenocarcinoma (A549) Cells

The effects of plant-derived metabolites on human lung adenocarcinoma cells were assessed by analysing DNA fragmentation through agarose gel electrophoresis (Figure 7). Lane 1 represents the DNA ladder, confirming the molecular weight markers for comparison. Lane 2 shows untreated control cells, where intact, high-molecular-weight DNA is observed, indicating no DNA fragmentation. In contrast, Lane 3 shows cells treated with *Triticum aestivum L.* extract, displaying a characteristic DNA smear pattern and fragmented bands, indicating extensive DNA degradation typically associated with apoptosis. Lane 4 contains DNA from cells treated with *Beta vulgaris* extract, which also displayed DNA fragmentation. Overall, treatment with both plant-derived metabolites induced DNA fragmentation in lung adenocarcinoma cells, suggesting a pro-apoptotic effect, with *Triticum aestivum* demonstrating a more pronounced activity.

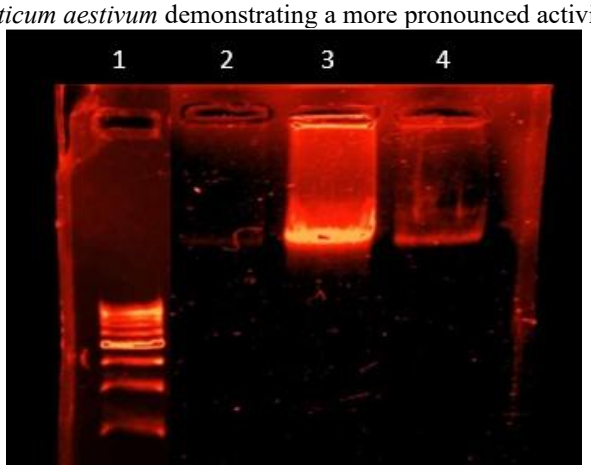


Figure 7: Agarose gel electrophoresis of genomic DNA extracted from A549 cells treated with plant extracts

4. Conclusion

The study demonstrated that extracts from *Beta vulgaris* (beetroot sprouts) and *Triticum aestivum* (wheatgrass) possess potent antioxidant and anticancer properties against human lung adenocarcinoma (A549) cells. Both extracts exhibited significant cytotoxic effects, as evidenced by MTT assay,

AO/EB staining, and DNA fragmentation analysis. Notably, *Triticum aestivum* exhibited stronger anticancer activity, reflected by its lower IC_{50} value and more pronounced DNA fragmentation. These findings underscore the potential of *Beta vulgaris* and *Triticum aestivum* as sources of bioactive compounds for the development of novel, plant-based therapies for lung cancer. Further investigations are warranted to isolate the active constituents and elucidate the underlying molecular mechanisms of their anticancer effects.

Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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