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Anticancer Activity of n-Hexane and Acetone Leaf Extracts from *Delonix regia* (Gul Mohar) on HeLa (Cervical) and Prostate Cell Lines

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ABSTRACT:

Objective: The purpose of this study was evaluation of the anticancer activity of n-hexane and acetone leaf extracts obtained from *Delonix regia* on BJ (normal fibroblast), cervical (HeLa), and prostate cell lines.

Study Design and Setting: This in vitro study was designed to assess the cytotoxic effects of leaf extracts from *D. regia*. The leaves were harvested, dried, and then subjected to extraction using hexane and acetone. The resulting extracts were concentrated and prepared for analysis. The effects of these extracts were evaluated on HeLa and prostate cell lines under standard laboratory conditions.

Methodology: MTT colorimetric assay was used to evaluate the cytotoxic activity of leaf extracts. Cell cultures were prepared and introduced into the plates. Different concentrations of extracts were added, and reduction of MTT to formazan within cells was measured. The cytotoxicity was monitored as the concentration causing 50% growth inhibition (IC_{50}) for cell lines.

Results: Results show that the acetone extract exhibits moderate inhibition (36.29%) on cervical cell lines, while the n-hexane extract demonstrates higher inhibition (55.84%) on the same cell line. However, both extracts are inactive on prostate cell lines. On BJ cell lines, both extract showing significant inhibition (69.68% & 61.32%) respectively.

Conclusion: In conclusion n-hexane extracts of *D. regia* exhibited more cytotoxic activity than acetone leaf extract. Although, *D. regia* possessed some anticancer activity potential however its efficacy is not comparable to doxorubicin. The study suggests further exploration of acetone and n-hexane extracts from *D. regia* as potential anticancer agents.

Keywords: Acetone, Anticancer, *Delonix regia*, HeLa, Leaf extract, n-Hexane, Prostate cell lines

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INTRODUCTION:

In recent years, natural compounds derived from plants have emerged as highly capable candidates for cancer treatment. These compounds show minimal harm to healthy cells as selectively targeting tumor cells, owing to their minor side effects, inherent biological activity, structural complexity, and chemical diversity.[1] Flavonoids, terpenoids, alkaloids, and phenols are among the various organic compounds derived from plants that possess anti-tumor properties. These compounds have been shown to impede tumor cell progression, inhibit telomerase activity, regulate apoptosis, halt angiogenesis, boost immunity, modulate resistance-causing signaling pathways, and more.[2,3] Currently, the basis of cancer treatment includes radiotherapy, immunotherapy, locally targeted therapy, and surgical resection. Traditional therapies are effective for early-stage cancer; however, they often entail significant side effects, drug resistance, frequent recurrences, and metastases, rendering them less successful for locally advanced or metastatic cervical cancer.[4]

Prostate cancer ranks among the most prevalent types of cancer globally, particularly affecting Western societies. Around 1.1 million men globally diagnosed with prostate cancer in 2012, constituting nearly 15% of all cancers. The 70% of these cases occurred in more developed nations, due to widespread prostate-specific antigen (PSA) testing and subsequent biopsies. Prostate cancer accounted for 307,000 estimated deaths in 2012, making it the 5th leading cause of cancer-related death in men, comprising 6.6% of total male deaths.[5] Moreover, common medications prescribed for cervical cancer have been associated with various side effects and drug resistance.[6] Cisplatin, one of the most potent

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anticancer drugs, can encounter resistance mechanisms.[7] Similarly, 5-fluorouracil, used in cervical cancer treatment, has been linked to side effects and resistance.[8] Thus, there is a pressing need to develop medications for cervical cancer with improved safety profiles and efficacy.

The *Delonix regia* tree, commonly known as Gul mohar, Royal Poinciana, or Flamboyant, is native to Madagascar. It was first identified by botanist Wensel Brojer in its natural habitat during the early 19th century. Since then, *D. regia* has spread widely across subtropical and tropical regions around the world and is extensively cultivated, particularly as a decorative garden and avenue tree in Pakistan. Although originally from Madagascar, this species has adapted to various climates and is renowned for its vivid foliage and striking flowers, enhancing landscapes globally.[9] *Delonix regia* is renowned for its medicinal properties, which are attributed to its active compounds and secondary metabolites with notable biological significance. The entire plant is considered to have medicinal potential, with its various constituents providing diverse therapeutic benefits. The botanical name "Delonix" suggests visibility, while "regia" denotes regal magnificence, reflecting the tree's grandeur and its significance within its ecosystem.

The primary plant constituents include essential nutrients such as common sugars, amino acids, proteins, and chlorophyll. Although these are crucial for plant growth, they typically do not possess significant medicinal properties. In contrast, secondary plant metabolites, which include alkaloids, terpenoids, saponins, phenolic compounds, flavonoids, and tannins, are essential for various biological and pharmacological activities. These secondary metabolites are vital for plant defense and ecological interactions and are often used in both traditional and modern medicine due to their diverse and potent bioactive properties.[10, 11]

Traditionally, its flowers have been used to treat various diseases such as malaria, rheumatoid arthritis, constipation, pneumonia, diabetes and inflammation.[12] Extracts from its leaves exhibit anti-inflammatory, anti-hyperglycemic, anti-microbial, anti-oxidant, hepato-protective and cytotoxic effects, while stem bark extracts possess antioxidant and antimicrobial activities.[9,13,14] Despite its ornamental value, *D. regia* harbors significant medicinal potential, prompting research into its anticancer properties beyond its traditional uses.

Different parts of *D. regia* contains different phytochemicals associated with different pharmacological activity. In leaves the most abundant phytochemical constituents are flavonoids, amino acid, alkaloids, saponins, glycosides, proteins, carbohydrates, diterpenes, and steroids. This study was design to evaluate the anticancer potential of *Delonix regia* leaf extracts using both polar (acetone) and non-polar (n-hexane) solvents. The main goal was to understand how these different solvents affect the extraction of bioactive compounds from the leaves and to assess their impact on inhibiting cancer cell growth. By comparing the anticancer effects of the extracts from these solvents, the research aimed to identify which extract holds the most promise for therapeutic applications. Ultimately, this study seeks to offer valuable insights into the effectiveness of *D. regia* leaf extracts in cancer treatment and contribute to the development of new, plant-based anticancer therapies.

METHODOLOGY:

This research was approved by the Institutional Review and Ethical Board (IREB) of Baqai Medical University, Ref. No. BMU-IREB-03-2023 dated 02-08-2023.

This was an in-vitro study. The experimental investigation was conducted at the Department of Pharmacology and Therapeutics, Baqai Medical College and University of Karachi (HEJ), utilizing in vitro methodologies spanning a period of six months from March 2023 to September 2023.

D. regia leaves were brought from the local garden of Karachi University. Subsequently, the plant underwent identification and authentication processes at the herbarium of the Botany Department of Karachi University, where it was assigned voucher number 97626.

Freshly harvested *D. regia* leaves were collected and carefully sorted. They were cleaned using tap water to remove any dirt, then rinsed with distilled water to eliminate contaminants. Afterward, the leaves were air-dried, sliced on a cutting board, and finely pulverized using a blender. The resulting powder was subjected to extraction using n-Hexane and Ethanol solvents in a Soxhlet apparatus. The extracted solution was concentrated using a rotary vacuum evaporator and then stored in a desiccator to maintain its integrity and prolong its shelf life, ensuring its suitability for potential applications. [15,16,17,18]

For determination of anticancer activity MTT (3-[4, 5-dimethylthiazole-2-yl]-2, 5-diphenyl-tetrazolium bromide) colorimetric assay was performed according to previously described protocol.[19] Cytotoxic activity of extracts was assessed in 96-well micro-plates. Cells including BJ (fibroblast), HeLa (cervical cancer), and prostate cell lines were cultured in minimum essential medium eagle supplemented with 5% fetal bovine serum (FBS), 100 IU/ml of penicillin, and 100 µg/ml of streptomycin in 75 cm^2 flasks, and maintained in a 5% CO_2 incubator at 37°C. Exponentially growing cells were harvested, counted with a haemocytometer, and diluted to a concentration of $6x10^4$ cells/ml in a specific medium. Cell suspensions were then introduced into 96-well plates (100 µL/well).

Following overnight incubation, the medium was replaced with 200 µL of fresh medium containing various concentrations of compounds (1-30 µM). After 48 hours, 200 µL of MTT solution (0.5 mg/ml) was added to each well and further incubated for 4 hours. Subsequently, 100

µL of DMSO was added to each well to dissolve the formazan granules formed by MTT reduction. The extent of MTT reduction within cells was quantified by measuring the absorbance at 570 nm using a microplate reader (Spectra Max plus, Molecular Devices, CA, USA). The cytotoxicity of the compounds was assessed by determining the concentration causing 50% growth inhibition (IC_{50}) for HeLa cells. The percent inhibition was calculated using the following formula:

Percent inhibition = 100-((mean of O.D of test compound – mean of O.D of negative control)/ (mean of O.D of positive control – mean of O.D of negative control)*100).

The results (Percent inhibition) were processed by using Soft- Max Pro software (Molecular Device, USA).[19]

RESULTS:

The table presents the anticancer activity of leaf extracts from *D. regia* on HeLa and prostate cell lines, along with BJ cell lines, in comparison with the standard drug doxorubicin. The results are outlined below: The cutoff value for significant inhibition is set at 50%. Results show that the acetone extract exhibits moderate inhibition (36.29%) on HeLa cell lines, while the n-hexane extract demonstrates higher inhibition (55.84%) on the same cell line (Table 1). However, both extracts are inactive on prostate cell lines, with the acetone extract showing some activity (5.24%) and n-hexane extract exhibiting (18.29%) activity (Table 2). On BJ cell lines, both extract showing significant inhibition (69.68% and 61.32%) respectively (Table 1). In contrast, doxorubicin displays significant inhibition on all cell lines tested, surpassing the 50% cutoff value, with notable potency observed in both inhibition percentages and IC_{50} values.

DISCUSSION:

This study demonstrates the anticancer properties of n-hexane and acetone leaf extracts from *Delonix regia* (Gul Mohar) across HeLa, prostate, and BJ (normal fibroblast) cell lines, offering important insights into their possible therapeutic uses and limitations.

This study showed that leaf extracts of n-Hexane of *D. regia* demonstrated higher inhibition ((55.84%) on cervical cancer cells compared to the acetone extract (36.29%). This suggested that the n-hexane extract may contain more potent and bioactive anticancer components which were effective in targeting cervical cancer cells. However it lacked significant activity against prostate cancer cells which suggested that active compounds are not effective this type of cancer cell line. Interestingly, n-hexane extracts exhibited significant inhibition on BJ normal fibroblast cell lines, showing 69.68% inhibition. The significant inhibition on normal cells is less desirable from a therapeutic perspective, so this need careful monitoring. In our previous study, GC-MS (Gas Chromatography-Mass Spectrometry) analysis showed that n-hexane extracts of leaf of *D. regia* contained phytol, di-iso-octyl ester, lupeol, Squalene, 2,6,10,15-tetramethyl-, Pentadecan, nonacosane, 1, 30-triacontanediol, Hexadecane, 2,6,11,15-tetramethyl, Heptadecane 2,6,10,15-tetramethyl-, Tetra- and tri- acontane, Phthalic acid, butyl tetradecyl ester, Vitamin E, Heneicosane, Triacontane and á-Amyrin. In which Heptadecane 2, 6, 10, 15-tetramethyl, Phytol, Heneicosane, squalene, Triacontane, lupeol reported to had anticancer and antineoplastic activities.[20, 21]

The acetone extract exhibited moderate inhibition on HeLa cell lines, however, it lacked considerable activity against prostate cancer cells. Especially, it showed some inhibition on BJ cell lines, indicating a potential impact on non-cancerous cells, possibly through cytostatic effects. In our previous study through GC-MS examination we determined that the *D. regia* leaf extract with acetone contains many phyto-constituents which included phytol, squalene, á-amyrin, lupeol, Vitamin E, Stigmasterol and â Sitosterol. In which phytol, squalene and lupeol are associated with anticancer/anti-tumor activities.[20, 21]

Table 1: Anticancer activity of leaf extracts from *Delonix regia* on cervical (HeLa) cell lines compared with BJ and standard drug (Doxorubicin)

Sample Code	Conc. (µM)	HeLa cell lines		BJ cell lines	
		% Inhibition	IC_{50}±SD	% Inhibition	IC_{50}±SD
Acetone extract	30	36.29	Inactive	69.68	14.51±0.18
n-Hexane extract	30	55.84	26.32±0.48	61.32	19.62±0.21
Doxorubicin (Standard)	30	98.7	1.13±0.16	93.68	0.16±0.19

Table 2**:** Anticancer activity of leaf extracts from *Delonix regia* on prostate cell lines compared with BJ and standard drug (Doxorubicin)

Sample Code	Conc. (µM)	HeLa cell lines		BJ cell lines	
		% Inhibition	IC_{50}±SD	% Inhibition	IC_{50}±SD
Acetone extract	30	05.24	Inactive	69.68	14.51±0.18
n-Hexane extract	30	18.29	Inactive	61.32	19.62±0.21
Doxorubicin (Standard)	30	80.8	1.18±0.21	93.68	0.16±0.19

The differences in activity may stem from variations in the composition and their concentration of bioactive compounds and their mechanisms of action in acetone and n-hexane extracts. n-Hexane contained more anti-cancer components than acetone extracts.

In contrast, doxorubicin which is well established anticancer drug, displayed potent anticancer activity across all cell lines tested. Its efficacy against cervical, prostate as well as BJ cell lines, highlighted its broad-spectrum cytotoxicity, further supported by low IC_{50} values.

The comparison between the leaf extracts and doxorubicin emphasized the superior efficacy of the standard drug in inhibiting cancer cell growth across all cell lines. Whereas the leaf extracts illustrated some level of inhibition on cervical cancer cells, they displayed limited activity against prostate cancer cells and BJ cell lines compared to doxorubicin.

A previous study demonstrated that the methanol extract of *D. regia* leaves exhibited cytotoxic activity against the HepG2 (human liver carcinoma) cell line, which was due to presence of different flavonoid glycosides. These flavonoids had potential anticancer as well as anti-oxidant activities.[22] Additionally, research conducted by El-Sayed et al., (2011) showed that the ethanolic extract of *D. regia* flower also possessed cytotoxic activities against the HepG2 cell line and linked it due to rich contents of flavonoids.[23] Ursolic acid, quercetin and its 3-o-rhamnoside compounds, â-sitosterol and its glucoside present in ethanolic extract of *D. regia* flower possessed significant cytotoxicity when anticancer activity was checked alone. Methanol extract, aqueous and chloroform fractions of stem bar of *D. regia* also possessed cytotoxicity monitored in tadpole model. The order of cytotoxic activity was chloroform fraction, methanol extract and aqueous fraction respectively.[24]

This study aligns with previous findings and supports the cytotoxic potential of *Delonix regia*, likely due to its diverse flavonoid content. The link between antioxidant activity and anticancer effects is crucial here. Oxidative stress, caused by an imbalance of reactive oxygen species (ROS) and antioxidants, can lead to DNA damage, mutations, and cancer progression. The antioxidant compounds in *Delonix regia* help mitigate this oxidative stress by neutralizing ROS, thus protecting healthy cells from damage and potentially preventing their transformation into cancerous cells. By reducing oxidative stress, these compounds contribute to maintaining cellular health and reducing cancer risk, reinforcing the anticancer activity observed in various extracts of *Delonix regia*. Therefore, compounds or treatments that reduce oxidative stress can also help to inhibit tumor promotion.[23, 25]

This research had few limitations. Study was carried out entirely in vitro using cell cultures to evaluate the anticancer properties of acetone and n-hexane extracts from *Delonix regia* leaves. As a result, the study may not necessarily reflect their effectiveness or safety in animal models or humans. Further exploration of acetone and n-hexane extracts from *D. regia* as potential anticancer agents in animals is needed. Comparative study can also be performed using other solvents like aqueous and methanolic solvents using other cell lines of cancer. Specific bioactive compounds within the leaf extracts and their interactions with cancer cells could provide valuable insights for the development of novel anticancer therapies. Combining leaf extracts with conventional chemotherapeutic agents could enhance treatment outcomes.

CONCLUSION:

In conclusion, acetone and n-hexane extracts showed moderate inhibition on cervical cell lines, however no activity observed on prostate cell lines. Doxorubicin, however, illustrated significant inhibition on all tested cell lines. Although, *D. regia* possesses some anticancer activity potential however its efficacy is not comparable to doxorubicin. The study suggests further exploration of acetone and n-hexane extracts from *D. regia* as potential anticancer agents in animals.

Authors Contribution:
Saeed Ahmed Sheikh: Study conception and design, performed all experiments, writing
Asif Ahmed: Study conception and design, supervisor
Asadullah: Helped in experimenting and data collection
Shazia Nawaz: Manuscript writing, review and proof reading of article

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