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# Docking Study for Assessment of Anti-Cancer Potential of *Carica Papaya* Extract and *in-vitro* Evaluation of Anti-Cancer Activities

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## ABSTRACT

Carica papaya fruit extracts are subjected to phytochemical screening, molecular docking, and in vitro cytotoxicity testing in this investigation to determine their potential anticancer properties. Utilizing phytochemical profiling, the following compounds were discovered: alkaloids, tannins, flavonoids, terpenoids, phenols, and glycosides. According to the findings of Insilco molecular docking experiments, 1,11-dodecadiene is a potential ligand that possesses significant binding affinities to cancer-associated proteins such as EGFR (-5.3 kcal/mol), KRAS (-5.1), and MET (-4.8). ALK (-4.7 kcal/mol) and BRAF (-6.2) were also involved in the interaction between Silan amine n-phenyl and BRAF. The MTT assay demonstrated that the ethanolic extract exhibited a noteworthy cytotoxic effect on A549 lung cancer cells, as evidenced by an IC50 value of 120.85 µg/ml following a treatment period of 48 hours. Given these findings, it is reasonable to assume that the ethanolic extract of Carica papaya may possess anticancer effects. Therefore, it is necessary to conduct in vivo research and extract the active ingredient for medicinal purposes.

**Keywords:** *Carica papaya* fruits, GC-MS, bioactive compounds, molecular docking, in vitro cytotoxicity and lung cancer.

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## INTRODUCTION

The term "cancer" denotes a diverse array of disorders characterized by the unregulated proliferation of cells capable of metastasis. The metastasis of malignant tumours to other regions of the body may lead to substantial difficulties[1]. The most common symptoms include unexpected bleeding, coughing, and the creation of lumps, weight loss, and abnormalities in the gastrointestinal tract[2]. Cancer is primarily caused by mutations in genes, lifestyle choices, and environmental factors. The use of tobacco, obesity, poor food, inactivity, radiation, and infectious agents such as highly pathogenic virus (HPV), hepatitis B, and Helicobacter pylori all contribute to an increased chance of developing cancer. Malignancies are caused by environmental and lifestyle factors 90–95% of the time, while genetic abnormalities are responsible for 5–10% of all cases[3]. The screening, imaging, and biopsy procedures are used to diagnose cancer. Preventive strategies include refraining from smoking, maintaining a healthy diet, engaging in physical activity, obtaining vaccinations, and shielding oneself from the sun. According to the severity of the disease and the type of cancer that is present, medications, chemotherapy, radiation, and surgery may be used. Around the world, cancer claims the lives of roughly 10 million people in 2019. Increasing the likelihood of survival and treatment by early detection, genetic studies, and individualized treatment[4,5]. Lung cancer is a predominant cause of cancer-related mortality globally. Due to the uncontrolled proliferation of lung cells, the disease has the potential to spread. NSCLC and SCLC are the two subtypes that fall under this disease. The majority of lung cancer diagnoses are non-small cell lung cancers like adenocarcinoma, squamous cell carcinoma, and giant cell carcinoma. Although rare, malignant small cell lung cancer spreads quickly. About 85% of lung cancer cases are caused by smoking. which is caused by DNA mutations and tumors8. Nevertheless, the chance of developing lung cancer can be significantly increased by factors such as radon gas, air pollution, asbestos, occupational hazards, second-hand smoke, and hereditary predisposition[9,10]. Lung cancer progresses from the localized stage of stage I to the distant stage of stage IV. High-risk

patients can benefit from early detection using low-dose CT.

. Due to the fact that lung cancer in its early stages is typically asymptomatic, most instances are detected in advanced stages, when treatment choices are limited9. Lung cancer treatment depends on type and stage. Surgery is the best early treatment for NSCLC.but more advanced stages require chemotherapy, radiation, targeted therapy, and immunotherapy. The therapy of lung cancer has been altered as a result of the introduction of checkpoint inhibitors, which enhance the immune system's capacity to combat cancer cells11. Even though there have been advancements in therapeutic strategies, lung cancer continues to be a global health problem that calls for continued research and clinical development[10].

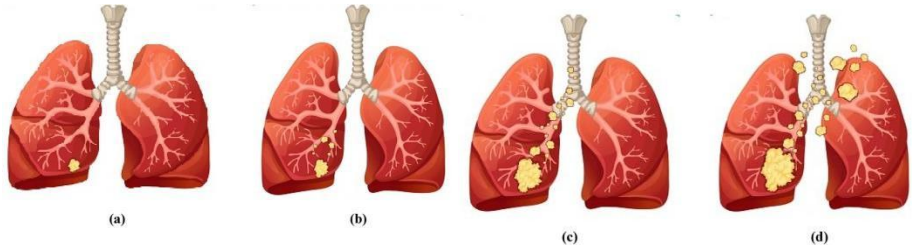



**Figure.1: Stages of Lungs cancer**

(**a**-Early Stage I (localized tumour), **b**-Stage II (spread to nearby lymph nodes), **c**-Stage III (advanced spread within the chest), and **d**-Stage IV (metastasis to distant organs).

Many medicinal plants exhibit potent anticancer properties, offering promising alternatives for cancer therapy. *One of the members of the Caricaceae family is the Carica papaya.*, is widely recognized for its therapeutic potential. Native to southern Mexico and Costa Rica, it has spread globally and thrives in diverse climates. The fruit, high in bioactive chemicals, including papain, among others, flavonoids, and alkaloids, has demonstrated significant anticancer potential. Studies suggest that papaya fruit extracts exhibit cytotoxic effects against lung cancer cells, it is a good contender for the treatment of cancer using natural methods. Its diverse phytoconstituents contribute to its pharmaceutical value, supporting its use in integrative cancer therapy[1,13].

## EXPERIMENTAL

### Material and methods

### Preparation of Extraction

The *Carica papaya* fruit was finely chopped and shade-dried for 10 days, followed by fine powdering. For 48 hours, 500 mg of powdered material was Soxhlet extracted in aqueous and ethanol solvents. The resulting crude extract was filtered through muslin cloth, separated, and dried using a tray dryer. The obtained extract was further analysed for phytochemical composition, GC-MS profiling, *in-vitro* anticancer activity and molecular docking studies to assess its potential interactions with lung cancer target proteins[14,15].

Qualitative Phytochemical Screening of ***Carica papaya*** **fruit**

The Carica papaya fruit extract was subjected to a qualitative phytochemical examination, which resulted in the identification of many bioactive components. These components included alkaloids, flavonoids, tannins, saponins, glycosides, terpenoids, steroids, carbohydrates, and proteins. There were phytochemical experiments carried out in a methodical manner[11,12].

1. Alkaloids (Wagner's Test)

In order to determine the presence of alkaloids, Wagner's reagent, which consists of iodine in potassium iodide solution, was applied to the extract. Using a precipitate that was a reddish-brown color, alkaloids were identified.

2. Flavonoids (Alkaline Reagent Test)

In order to determine the flavonoids, the extract was subjected to a treatment with 10% sodium hydroxide. Flavonoids were identified by a yellow color that became less clear as the acidity increased.

3. Tannins & Phenolic (Ferric Chloride Test)

The presence of tannins and phenolic was determined by mixing the extract with **1% ferric chloride ($FeCl_3$) solution. A blue-black or greenish coloration** confirmed their presence.

4. Saponins (Foam Test)

Saponins were detected by shaking the extract with distilled water. The formation of a **persistent froth lasting for at least 10 minutes** indicated a positive result for saponins.

5. Glycosides (Keller-Killiani Test)

**It was possible to identify cardiac glycosides with the use of ferric chloride, strong sulfuric acid, and glacial acetic acid solutions. Their presence was indicated by a ring of reddish-brown color near the contact.**

6. Terpenoids (Salkowski Test)

For the purpose of terpenoid detection, the extract was mixed with chloroform and sulphuric acid that had been concentrated. Terpenoids were distinguished by a bottom layer that has a reddish-brown consistency.

7. Steroids (Liebermann-Burchard Test)

Using acetic anhydride and concentrated sulfuric acid, the extract was examined to determine whether or not it contained steroids. The green or bluish-green hue that they possessed was significant in establishing their presence.

8. Carbohydrates (Benedict's test)

The presence of carbohydrates was determined by heating the extract with **Benedict's reagent.** A brick-red precipitate showed decreasing sugars.

9. Proteins (Biuret Test)

To detect proteins, the extract was treated with 1% copper sulphate and 10% sodium hydroxide. Violet hue indicated protein content.

## GC-MS Analysis

Utilizing GC-MS, the bioactive components that were present in the plant extract were identified. The three primary operations consisted of the following: Chromatographic analysis involves sample extract on GC column, component separation by analytical column, and target analyte detection by MS detector. For GC-MS analysis, the sample extract aliquot was reconstituted in 2 ml methanol. Analyses used SHIMADZU GC-MS-QP 2010 with a 0.25 µm DB-30.0 column. The oven was designed to maintain 70 degrees Celsius for five minutes, then climb by 10 degrees per minute to 200 degrees, then 5 degrees per minute to 280 degrees, and finally 35 minutes at 280 degrees. Mass spectrum analysis at 70 eV with 0.5-second scans and 40–1000 m/z. A 1.0 mL/min helium carrier gas flow was electrically managed. The samples that had been dissolved in ethanol were automatically administered. Within the scope of this inquiry, compounds that could provide support for the plant's traditional and commercial applications in herbal medicine were sought out[16].

## Molecular Docking Analysis

Through the use of cancer-related proteins, molecular docking studies were conducted in order to examine the possible anticancer properties of Carica papaya. The bioactivity of the ligands was taken into consideration, and their three-dimensional structures were obtained from Pubchem in the SDF format. The Protein Data Bank was accessed in order to retrieve the following genes: EGFR (4HJO), ALK (2XB7), KRAS (4EPV), MET (3DKF), and BRAF (4RZV). Before docking, the proteins were optimized by removing water molecules and heteroatoms while maintaining essential cofactors. This was done in order to prevent degradation. The molecular docking application MzDock, which is open-source, is being utilized in the docking experiment. At a physiological pH of 7.4, the MMFF94 force field was able to optimize the GC-MS chemical analysis. The location of the docking site was found to be at the co-crystallized ligand of the protein where a 4 Å buffer was present. PDBQT interaction profiles and output logs were generated as a result of docking simulations with nine different modes. The study used Lipinski's Rule of Five to determine drug-likeness, which requires less than five hydrogen bond donors, ten acceptors, and 500 Daltons of molecular weight. log P <5, and a maximum of one rule violation. This systematic approach helps assess the binding efficiency and potential anticancer properties of *Carica papaya* bioactive compounds[17-21].

## MTT Assay for In-vitro anticancer activities

MTT, also known as 2,5-diphenyltetrazolium bromide, is a sugar that is yellow in color and soluble in water. [4,5-dimethylthiazol-2-yl] is also known as MTT. Succinate dehydrogenase, an enzyme found in mitochondria, is responsible for hydrolysing the tetrazolium ring, which results in the formation of an insoluble purple formazan from MTT. There is a linear relationship between the number of viable cells and the amount of formazan that is produced. After a period of forty-eight hours, the MTT solution was diluted in phosphate-buffered saline (PBS) to a concentration of five milligrams per millilitre, and then it was added to each well. A four-hour incubation was then performed on the mixture at a temperature of 370 degrees Celsius. One hundred microliters of DMSO were used to dissolve the Formosan crystals after the MTT medium had been removed from the experiment. During the quantification process, a microplate reader was applied in order to detect the crystals at a wavelength of 570 nm. Two and twenty-three are the numbers[22,23].

## RESULT AND DISCUSSION

The impact of *Carica papaya* fruit extract was evaluated through phytochemical analysis, GC-MS profiling, molecular docking studies for anticancer potential, and in vitro assessment of anti-lung cancer effects.

**Table: 1 Phytochemical Evaluation of *carica papaya* extract**

| S.NO | Chemical constituent | Ethanol extract | Aqueous extract |
|---|---|---|---|
| 01 | Alkaloids | + | + |
| 02 | Glycoside | + | + |
| 03 | Flavanoids | + | + |
| 04 | Anthroquinone | + | - |
| 05 | Phenols | + | + |
| 06 | Tannins | + | + |
| 07 | Saponins | + | + |
| 08 | Steriods | + | - |
| 09 | Terpenoids | + | - |
| 10 | Protein | - | + |
| 11 | Amino acids | - | + |
| 12 | Carbohydrates | + | + |
| 13 | Phytosterols | + | - |

+ Positive, - Negative

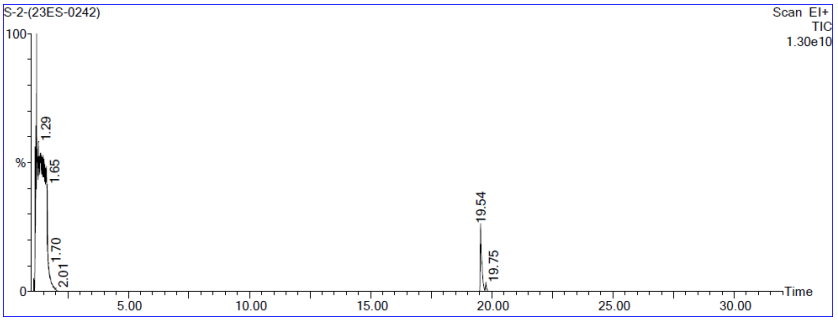
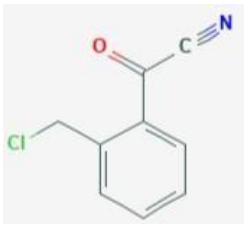



**Figure 2: GC-MS analysis for ethanol extract of *carica papaya* fruits extract**

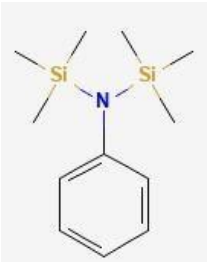
**Table 2: ligands of ethanol extract of *carica papaya***

| S. No | Compound Name | Retention Times (RT) | Area % | Molecular Formula (MF) | Molecular Weight (MW) |
|---|---|---|---|---|---|
| 1. | Chloromethyl Cyanide | 1.424 | 4.414 | $C_2H_2NCl$ | 75 |
| 2. | Chloromethyl Cyanide | 1.489 | 3.599 | $C_2H_2NCl$ | 75 |
| 3. | Chloromethyl Cyanide | 1.524 | 6.826 | $C_2H_2NCl$ | 75 |
| 4. | Silanamine, N-Phenyl | 1.629 | 16.702 | $C_6H_9NSi$ | 123 |
| 5. | 1-Propanethiol | 1.664 | 10.031 | $C_3H_8S$ | 76 |
| 6. | 1,11-Dodecadiene | 19.541 | 53.940 | C12H22 | 166 |

| | | | | | |
|---|---|---|---|---|---|
| 7. | 6-Hepten-1-Ol | 19.746 | 4.489 | C7H14O | 114 |




Chloromethyl Cyanide




Silanamine, N-Phenyl


1-Propanethiol

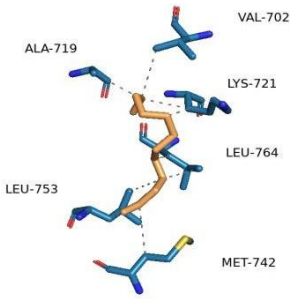
1,11-Dodecadiene


6-Hepten-1-Ol

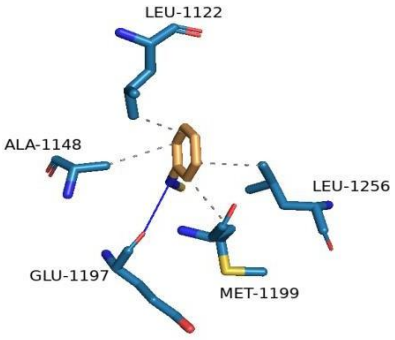
**Figure.3: Identified ligands from *carica papaya* fruits extract**

**Table 3: Dock Binding energies of the ligands interact with proteins**

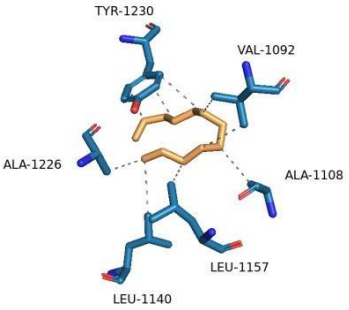
| S.No | LIGANDS | EGFR (4HJO) | ALK (2XB7) | KRAS (4EPV) | MET (3DKF) | BRAF (4RZV) |
|---|---|---|---|---|---|---|
| | | Kcl/mol | Kcl/mol | Kcl/mol | Kcl/mol | Kcl/mol |
| 1 | Chloromethyl Cyanide | -2.8 | -2.4 | -2.4 | -2.5 | -3.0 |
| 2 | Silanamine, N-Phenyl | -5.2 | -4.7 | -5.0 | -4.7 | -6.2 |
| 3 | 1-Propanethiol | -.26 | -2.4 | -2.4 | -2.7 | -3.0 |
| 4 | 1,11-Dodecadiene | -5.3 | -4.5 | -5.1 | -4.8 | -6.1 |
| 5 | 6-Hepten-1-Ol | -4.8 | -4.1 | -4.3 | -4.4 | -5.4 |



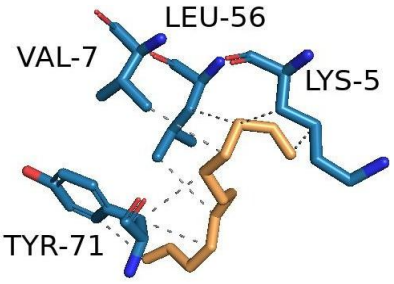

**(A)**



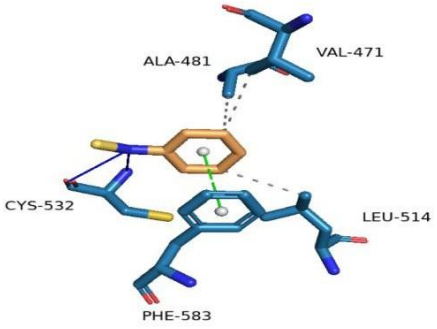

**(B)**




**(C)**




**(D)**




**(E)**

**Figure 4: Best Interaction between ligands with Protein (A) EGFR, (B) ALK, (C)KRAS, (D)MET and (D) BRAF**
{**A:** Interaction between ligands with EGFR(4HJO), Best Scored Ligand: 1,11 DODECADIENE)-Binding Score = -5.3
**B:** Interaction between ligands 2XB7, Best Scored Ligand: SILANAMINE, N-PHENYL)-Binding Score = -4.7
**C:** Interaction between ligands 3DKF, Best Scored Ligand: 1,11-DODECADIENE)-Binding Score = -5.1
**D:** Interaction between ligands 4EPV, Best Scored Ligand: 1,11-DODECADIENE)-Binding Score = -4.8
**E:** Interaction between ligands 4RZV, Best Scored Ligand: SILANAMINE, N-PHENYL)-Binding Score = -6.2}

**Table 4. Lipinski rules of five**

| S.No | LIGANDS | Lipinski's rule | | | | |
|---|---|---|---|---|---|---|
| | | Molecular weight (<500) | Hydrogen Bond Donor (<5) | Hydrogen Bond Acceptor (<10) | High Lipophilicity (<5) | Molar Refractivity (40-130) |
| 1 | Chloromethyl Cyanide | 75 | 0 | 1 | 1.39 | 112.11 |
| 2 | Silanamine, N-Phenyl | 123 | 0 | 1 | 1.25 | 53.1 |
| 3 | 1-Propanethiol | 76 | 1 | 1 | 1.24 | 44 |
| 4 | 1,11-Dodecadiene | 166 | 0 | 0 | 1.46 | 59.09 |
| 5 | 6-Hepten-1-Ol | 114 | 1 | 1 | 1.55 | 71.0 |

***In-Vitro* Anticancer Activities**

**Table 6: *In-vitro* A549 cell line response for different concentration**

| S.No. | Different Concentration of sample | | | | | Control |
|---|---|---|---|---|---|---|
| | 18.75 µg | 37.5 µg | 75 µg | 150 µg | 300 µg | |
| 1 | 0.467 | 0.402 | 0.325 | 0.254 | 0.165 | 0.543 |
| 2 | 0.465 | 0.403 | 0.321 | 0.251 | 0.163 | 0.546 |
| **Average** | 0.462 | 0.401 | 0.322 | 0.252 | 0.162 | 0.545 |

**Table 5: Percentage of cell inhibition for cell Cytotoxicity Effect of *carica papaya***

| S.No. | Different Concentration(µg/ml) | Percentage of Cell inhibition | IC 50 |
|---|---|---|---|
| 1 | 18.75 | 14.7 | 120.85µg/ml ($R^2$=0.9967) |
| 2 | 37.5 | 26.1 | |
| 3 | 75 | 40.8 | |
| 4 | 150 | 53.67 | |
| 5 | 300 | 70.03 | |

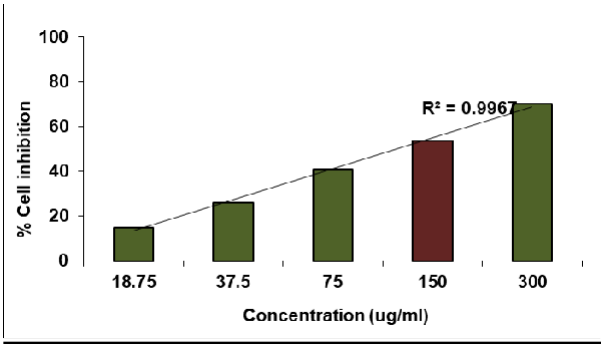


**Figure 5: Percentage of cell inhibition for different concentration**

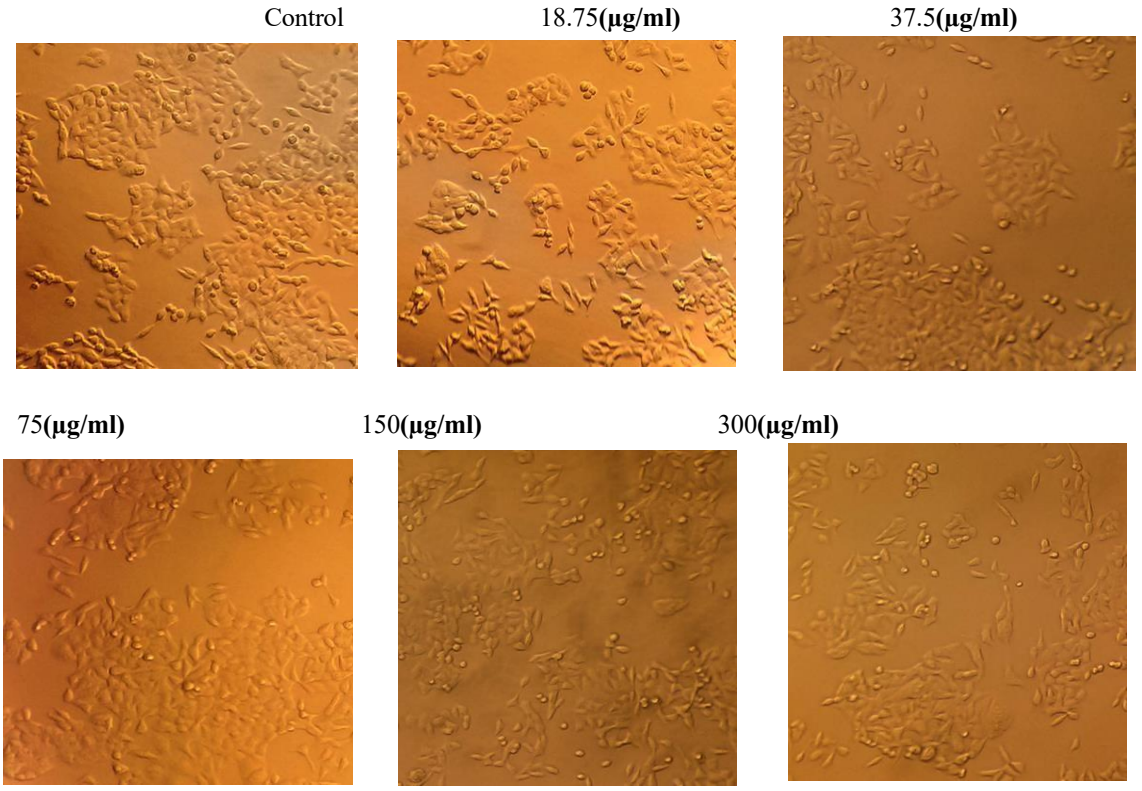



**Figure 6: Percentage of (*invitro* anti-cancer) cell Cytotoxicity Effect of *carica papaya***

## CONCLUSION

According to the findings of this research, the ethanolic and aqueous extracts of Carica papaya fruits include many different types of compounds, including alkaloids, tannins, saponins, flavonoids, terpenoids, phenols, glycosides, steroids, proteins, and amino acids. Using the MZ Dock software, molecular docking studies were performed on the ethanolic extract. The results showed that 1,11-Dodecadiene had a high binding to EGFR (-5.3 kcal/mol), KRAS (-5.1), and MET (-4.8). On the other hand, silanamine N-phenyl had a binding to ALK and BRAF (-4.7 and -6.2, respectively). In terms of binding affinity, 1,11-dodecadiene is the very best. The ethanolic extract had significant anticancer activity in A549 cell lines, as determined by the MTT test, which yielded an IC50 value of 120.85µg/mL after 48 hours of exposure. The ethanolic extract of Carica papaya has been shown to have strong anticancer effects, according to these findings. Given these promising results, In order to identify and define cancer-inhibiting drugs, it is recommended that in vivo research be conducted.

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**Conflict of Interests;**

The authors declare that there is **no conflict of interest** regarding the publication of this paper.

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