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Elucidating the anti inflammatory potential of bio active hydrogel from *Carica papaya* leaf extracts using combination of *in silico* and *in vitro* methods

Research Article

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Abstract

The investigation on medicinal plants have been gaining importance around the world especially in Asian nations due to the presence of wide range of bioactive phytochemicals. The presence of diverse bioactive compounds makes medicinal plants more demandable for curing several diseases, such as inflammatory diseases, and diabetes. *Carica papaya* is one such plant found very commonly throughout the country and reported to have a massive traditional properties. The present study addresses the in vitro and in silico study of the plant leaf extract for a potential anti inflammatory effect. The plant showed adequate anti-inflammatory effect through in silico and in vitro models. The compounds identified by GC-MS are put through molecular docking studies and virtual toxicity studies. Out of all the compounds, pigenin (-9.9 kcal/mol), quercetin (-9.4 kcal/mol), and kaempferol (-9.2 kcal/mol) have the best binding energy as compared to the standard diclofenac indicating that the extract can find its usage as anti-inflammatory drug. Further the claim was confirmed by in vitro study using BSA method. As compared to standard diclofenac (IC50: 0.47 mg/ml) the IC50 value of papaya extract was found to be only 0.198 mg/ml indicating a significant increase in inhibition at low concentration of the extract. A set of hydrogel formulations were designed to deliver the extract and it was found that formulation F3 containing 0.5% w/v extract was the most suitable with pH of 7.02 and spreadability of 15.11 gcm/s. Hence, a highly potent natural anti-inflammatory formulation is reported to be developed in this study.

Keywords: *Carica papaya,* Leaf extract, Molecular Docking, Toxicity study, Anti-inflammatory assay.

Introduction

Traditional medicine has been widely used around the world especially in Asian developing nations due to their ease of accessibility, inexpensiveness and safe in nature. Around three quarter of the world are directly or indirectly dependent on natural products/ traditional medicine to combat most of the chronic as well as lethal diseases (1). As per WHO reports around 21000 plant species been identified which have potential to act against diseases since then isolation of specific compounds. Plant derived drugs have always been considered as a safer option for development of new drugs as compared to chemically synthesised drugs as it exerts several adverse effects on health (2). Over the years several compounds from natural origin have been approved by the Food and Drug Administration (FDA) for multiple diseases including chronic and lethal diseases like cancer, diabetes, cardiovascular diseases, inflammations, haematological issues etc (3).

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The experimental plant in this study, *Carica papaya*, is a well-known and traditionally established plant from the family Caricaceae, is well distributed in the entire Indian subcontinent including West Bengal. It has been traditionally used as carminative, stomachic and in cases of increased bilirubin. Thus, these many potentials lead to exploration of the plant in chronic diseases like inflammation (4).

Chronic inflammation is a condition where the body's immune system remains in a state of heightened activity, even when there's no immediate threat. This prolonged response can lead to tissue damage, organ dysfunction, and a host of serious health problems. While acute inflammation is a normal and necessary process to fight off infections or injuries, chronic inflammation can become a self-perpetuating cycle, contributing to conditions such as heart disease, arthritis, diabetes, and even certain types of cancer (5). It is quite difficult and time-consuming to establish a raw compound as a drug by analysing its specific target, effectiveness, drug-likeness, pharmacokinetics activity, toxicity and drug-protein interaction. However, these challenges have been efficiently resolved by a computational method known as computer-aided drug design (CADD) where molecular docking, and in vitro studies (6). Hence, the present study explored the *in vitro* as well as *in silico* anti inflammatory activity of *Carica papaya*. Thus, the phytochemicals in its extract

were qualitatively screened, and the extract's inflammatory activity was assessed.

Materials and methods

Details of plants

Carica papaya L. belongs to the Caricaceae family and is a very nutritious and medicinally valuable fruit crop found in tropical and subtropical regions worldwide. The market demand for tropical fruits like papaya has significantly increased over the previous few decades. This fruit has increased in popularity because to its high nutritional value, production, and year-round availability. *C. papaya* have shown multiple pharmacological properties in the past including its effect against inflammation, so in this work a detailed insight regarding *in vitro* and *in silico* effects effects especially for the variety found in West Bengal is observed (3) (7).

Collection and extraction of plant material

The authenticated leaves of *C. papaya* were procured from West Bengal State Medicinal Plants Board, Kalyani, West Bengal (4). The leaves were sun dried and extracted in methanol using ultrasonic extraction method. The plant materials were steeped in the solvent methanol for a period of 1h followed by sonication in ultrasonic bath at 15 kHz (Vinayak Enterprise). The extract was filtered, dried under vacuum to remove all the traces of alcohol and stored for further use (8).

Phytochemical Screening

As per various standard literature, various chemical tests for various phytochemical categories like alkaloids (Wagner and Dragendorff's test), flavonoids, cardiac (Baljet's Test), saponin (Froth test) and anthraquinone glycosides (Bortrager Test), fixed and volatile oils (Sudan III dye test), proteins (Millon's test), mucilages and carbohydrate (Molisch Test), were performed on the extract.(5) All the tests were carried out to ascertain the presence of these groups of primary and secondary metabolites present in *C. papaya*

Insilico docking studies

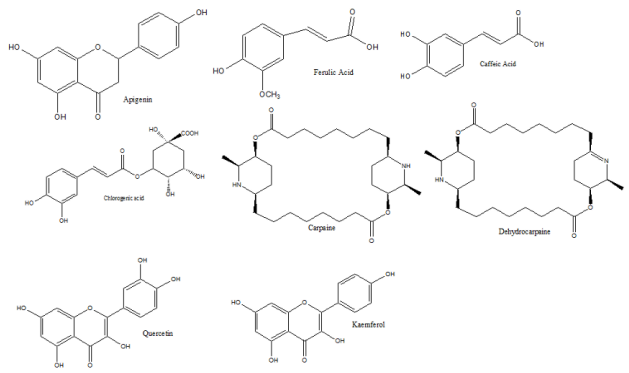
Ligands preparation and optimisation

According to reports of Khor et al., all ten reported ligands observed by his team under GCMS in *C. papaya* leaf were drawn in Chem Draw Professional 15.0 (Fig. 1). The ligands' three-dimensional structures were generated using Open Babel and stored in SDF format for further preparation and molecular docking studies (9).

COX 2 inhibitor protein preparation and optimization.

The protein data bank revealed the crystallographic structures of Vioxx bound to human COX-2 (PDB ID: 5KIR). The protein was prepared for molecular docking by removing the water molecules, and then polar hydrogen atoms were supplied using the BIOVIA Discovery Studio 2021 Client application to fix the ionisation of the amino acid residues (10).

Fig 1. Ligands from *C. papaya*



Molecular docking analyses and visualisation

The PyRx application was used to perform molecular docking using the Auto dock Vina tool once the proteins were saved in pdb format and loaded. The PyPx stability test was used to identify which conformer was the most stable. The experiment used a grid with dimensions of 57.02 Å x 66.94 Å x 51.40 Å. The intermolecular interactions of ligands derived from *C. papaya* leaf(6) , with the residues of the COX -2 protein were discovered and visualised using the Discovery Studio 2021 Client program (11).

Toxicity prediction

The top-scoring ligands were tested for toxicity in human cells using the ProTox III software (https://tox-new.charite.de/protox_III). The website accepts a two-dimensional chemical structure as input and returns the possible toxicity profile of the substance for 10 models with confidence scores. (12).

In vitro Anti inflammatory assay

Preparation of reference drug (positive control)

NSAID like diclofenac was used as reference drugs. Diclofenac tablet was crushed into fine powder. From the powder 0.2 g equivalent of diclofenac drug powder was measured using a digital analytical balance (Satorius) and was added to 20.0 ml of distilled water, respectively. The solution was mixed well using a vortex mixer (Remi).

Serial dilutions

The dried *C. papaya* leaf extract and the reference medication were serially diluted in distilled water in concentration ranging(7) from 0.1 mg/ml to 1 mg/ml. Each sample had 5.0 mL of total volume. Reaction mixtures were made with 2.8 ml of phosphate-buffered saline (pH 6.4) and 0.2 ml of Bovine Serum Albumin (BSA)(8) . Then, 2 ml of *C. papaya* extract from each concentration was gently added into the reaction mixtures. A similar approach was utilized for the reference medication, and they served as positive controls in this investigation. In addition, distilled water was employed as the negative control (13).

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Inhibition of protein denaturation

Reaction mixtures were incubated in a water bath at 37°C ± 2°C for 30 minutes, then heated to 70°C for 15 minutes. The reaction mixture was then allowed to cool to room temperature for 15 minutes. The absorbance of the reaction mixture before and after denaturation was measured at 680 nm using a UV spectrophotometer (Shimadzu 1900i). Each test was done three times, and the average absorbance was recorded (14). The percentage of inhibition of protein was determined on a percentage basis with respect to control using the following formula.

$$\%Inhibition = \left(\frac{Absorbance of control - Absorbance of test}{Absorbance of control}\right) \times 100.$$

Preparation of hydrogel

Hydrogel is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrophilic polymer like tragacanth gum and gelatin were selected and 0.1 N NaOH was used as cross linking agent. The gelatin in same proportions along with tragacanth dissolved in water forms a colloidal solution. 5% solution of Gelatin in constant 10% tragacanth forms a stable gel with good mechanical strength.

The topical hydrogels using different proportions were prepared as follows:

1. Hydrogels were manufactured using different concentrations of polymeric colloidal solutions.
2. Same volumes (9) of Gelatin (5% w/v) and Tragacanth (10% w/v) colloidal dispersions were prepared using distilled water containing 0.1N NaOH.
3. After complete dispersion, both the polymer solutions were kept in dark for 24 h for complete swelling.(10)
4. Different concentrations of plant extracts (0.1%, 0.25%, 0.5%, 1% w/v) were added in the colloidal dispersion
5. Dispersions of polymers and extracts were made using magnetic stirrer at 350rpm (Remi RG1, Remi India). After dispersing gelatin (5% w/v) in distilled water containing 0.1N NaOH, colloidal dispersion of tragacanth gum (10% w/v) was added to it under magnetic stirring. After the swelling period of 24 h, 0.1%, 0.25%, 0.5%, 1% w/v extracts were added in were added in different formulations to generate four formulations F1-F4. The magnetic stirring continues until a homogeneous dispersion of gel is obtained (15).

Evaluation of hydrogel

Physical appearance

The physical appearance and homogeneity of the prepared gels were tested by visual observations. The marketed formulation was considered as reference.

Spread ability test

Spread ability can be determined by applying the gel over an even surface and observed for the gritty nature of the hydrogel if present.

pH determination

The pH of the gel formulations was determined by using a pH meter. For pH determination, 1% of hydrogel formulation in deionised water was prepared and pH was determined.

Stability Studies

The stability of the gels were assessed by storing it in cool dry place for a period upto 6 months as per ICH guidelines. For six months, accelerated stability tests were conducted at 40 C±2 C and 75% ± 5% relative humidity (0, 1, 3, and 6 months). In addition to measuring the drug concentration and pH, the hydrogel was physically assessed for colour, grittiness, and synerisis/phase separation (16).

Statistical analysis

The values are expressed as the mean ± standard error of the mean. The result is also expressed as an IC50 value. The IC50 value was calculated using logarithmic regression analysis.

Results and Discussion

Extract yield

The extracts were allowed for drying under vacuum in rota evaporator (Dlab D125)(11) and the % yield was calculated. And the % yield was found to be 8.89%. The dried extract was kept in airtight container for further use.

Chemical Tests

Various chemical tests were performed, revealing the presence of various phytoconstituents in the methanolic extract of depicted in Table 1.

Table 1: Presence of phytoconstituents in the extract (12)

Chemical tests	Phytoconstituents
Alkaloid	Present
Volatile oil	Absent
Fixed Oil	Present
Protein	Present
Carbohydrate	Present
Flavonoids	Present
Glycoside a. Anthraquinone b. Saponin c. Cardiac	 Absent Present Absent (13)
Gums and Mucilage	Absent

In silico* studies of *C. papaya

PyRx docking was used to establish binding affinities and critical interactions between the crystallographic structures of Vioxx bound to human COX-2 (PDB ID: 5KIR) and phytochemical ligands extracted from the leaves of C. papaya. The binding affinity of the produced ligands was compared to that of the typical inflammatory medication diclofenac. Table 1 illustrates the binding affinity derived from the protein bound ligands and the standard medication, Diclofenac (17). The binding affinity of the active phytochemicals present in *C. papaya* leaf(14) varied from -9.9 to -7.3 kcal/mol. The Discovery Studio 2021 Client program was used to visualise the molecular interactions between the most active ligands and the active site

targeting COX-2 protein (Figures 2 and 3). The Table 3 shows the two most active compound and their interacting amino acids in specific protein pocket. These two samples showed the expected interactions with amino acids in the protein's active region, indicating strong antagonistic characteristics against the COX-2 protein, which targets the COX 2 receptor(15) . Apigenin had the highest binding affinity for the protein 5KIR, at -9.9 kcal/mol, followed by Quercetin (9.4 kcal/mol). The ligand with values lowest binding affinity was observed in Citropen (-7.3 kcal/mol). As compared to the commonly used COX 2 inhibitor(16) drug Diclofenac (-8.4 kcal/mol), the binding affinities of three natural compounds (Apigenin, Quercetin, Dehydrocarpaine II) derived from *C. papaya* were found to be higher indicating their future usage in inhibition of inflammation. The drug target prediction using top scoring ligands showing all three of them is having COX inhibition properties (18,19) (Table 1). The same set of ligands were studied for their toxicity using ProTox II software showed Apigenin, Quercetin, Dehydrocarpaine II had a predicted class 4 to class 5 toxicity with higher LD50 ranging between 900-4500 mg/kg values indicating their safe usage in human.

Table 2: Binding affinity of ligands in 5KIR protein

Ligands	Binding Affinity (cΔG in kcal/mol)
	5KIR
Apigenin	-9.9
Ferulic acid	-7.9
Caffeic acid	-8.4
Chlorogenic Acid	-8.0
Carpaine	-7.8
Dehydrocarpaine I	-7.9
Dehydrocarpaine II	-8.9
Kaemferol	-9.2
Quercetin	-9.4
Citropen	-7.3
Diclofenac	-8.4

Fig.2 : Interaction diagram of Apigenin

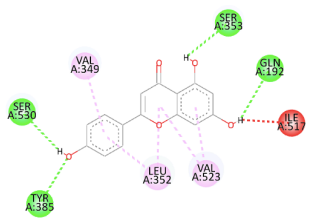
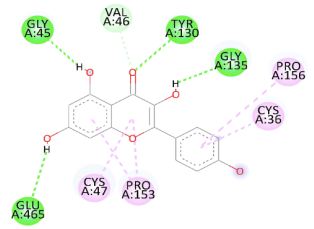


Fig.3: Interaction diagram of Quercetin



In vitro anti-inflammatory assay

The anti-inflammatory properties of *C. papaya* were tested against denaturation of Bovine Serum Albumin(18) . The extract showed the maximum inhibition rate at a concentration of 0.25 mg/ml (µg/ml). All inhibitions are documented in Tables 4 and 5 below. In compared *to C. papaya* extracts (0.198 mg/ml), the inhibition rates of the reference medication were found to be lower (0.47 mg/ml). Thus, data suggests that *C. papaya* extract may have anti-inflammatory properties (20).

Table 3: Binding interactions of the most potent molecules against 5KIR protein (17)

Compound Name	Active Amino Acids	Bond Category
Apigenin	Ser A:530	Carbon hydrogen
	Ser A: 353	Carbon hydrogen
	Gln A:192	Carbon hydrogen
	Tyr A:119	Carbon hydrogen
	Val A:349	Pi-Alkyl
	Val A: 523	Pi-Alkyl
	Leu A:352	Pi-Alkyl
	Ile A:517	Donor Donor bond
Quercetin	Gly A: 46	Carbon hydrogen
	Gly A: 135	Carbon hydrogen
	Tyr A: 130	Carbon hydrogen
	Glu A: 465	Carbon hydrogen
	Val A: 46	Van der Waal's force
	Pro A:156	Pi-Alkyl
	Cys A:36	Pi-Alkyl
	Cys A: 47	Pi-Alkyl
	Pro A: 153	Pi-Alkyl

Table 4: IC50 value of the standard Diclofenac against inflammation

Concentration(mg/ml)	% inhibition	IC50 value
0.1	0.12	0.47 mg/ml
0.25	23.37	
0.5	56.14	
1	83.92	

Table 5: IC50 value of the C. papaya leaf extract against inflammation

Concentration(µL)	% inhibition	IC50 value
0.1	0.79	0.198 mg/ml
0.25	81.81	
0.5	47.43	
1	43.19	

Evaluation of hydrogel

The results of spreadability, pH and Physical appearance of all four formulations are presented in Table. 5. The physical appearance of all the formulation appeared to be same for all F1 to F4 formulation ie, greenish brown in colour. The spreadability of the formulations ranged between 12.84-15.11 gcm/s, with F3 containing 0.5% w/v extract had the highest spreadability. A similar trend was observed for pH. The pH ranged between 6.92 – 7.34 with F3 found to have 7.02 pH value (Table 6). In compliance with ICH requirements, accelerated stability experiments were carried out, and the impact of temperature and relative humidity on the final formulation was examined. The stability of hydrogel was demonstrated by the results of these investigations, as shown in Table 7 (19) (21).

Table 6: Evaluation of hydrogel formulations

	Physical Appearance	Spreadability (gcm/s)	pH
F1	Greenish Brown; smooth to touch	12.84	7.34
F2	Greenish Brown; smooth to touch	13.19	7.19
F3	Greenish Brown; smooth to touch	15.11	7.02
F4	Greenish Brown; smooth to touch	14.47	6.92

Table 7: Stability study of hydrogel preparation (F1-F4)

Time	Phase Separation	Gritiness	Color
0	No	None	No Change
3	No	None	No Change
6	No	None	No Change

Discussion

From the above-mentioned results, it can be observed that % extractive value of the extracts were found to be 8.89% (for methanolic extract). The phytochemical tests using the mentioned experiments yielded the presence of alkaloid, glycosides, flavonoids, saponin glycosides along with fixed oils, proteins and carbohydrates indicating the extracts to be phytochemical rich and can find potential usage in multiple disease conditions as well as in nutraceuticals alike.(20) As reported by Khor *et al*., 2021, the GCMS of the reported extract(21) yielded many potent compounds under flavonoid categories (Apigenin, Ferulic Acid, Caffeic Acid, Chlorogenic acid, Carpaine, Dehydrocarpaine I & II, Kaemferol, Quercetin, and Citropen) which may be explored for their anti-inflammatory properties. In silico studies on these flavonoid compounds yielded that apigenin (-9.9 kcal/mol), quercetin (-9.4 kcal/mol), and kaempferol (-9.2 kcal/mol) have the best binding energy as compared to the standard diclofenac indicating that the extract can find its usage as anti-inflammatory drug (22). Further the claim was confirmed by in vitro study using BSA method. As compared to standard diclofenac (IC50: 0.47 mg/ml) the IC50 value of papaya extract was found to be only 0.198 mg/ml indicating a significant increase in inhibition at low concentration of the extract (23). Thus, all the evidence confirm that the presence of flavonoid compounds prompts the extract to have anti-inflammatory properties. A hydrogel formulation using gelatin and Tragacanth was prepared using varied amount of the extract. The formulation containing 0.5% w/v, extract was found to have the best spreadability and most neutral pH indicating its further use for stable delivery of the extracts as anti-inflammatory drug. With further research a pre-clinical and clinical data set can be prepared so that it can provide greater beneficiary to human.

Conclusion

Through this study, an excellent anti-inflammatory activity of *C. papaya* leaf extracts was observed by in vitro process. More over GCMS studies showed around ten bioactive agents present in the extracts including Apigenin, Ferulic Acid, Caffeic Acid, Chlorogenic acid, Carpaine, Dehydrocarpaine I & II, Kaemferol, Quercetin, and Citropen. To increase the confidence of the obtained result, in silico analysis was performed, which included toxicology analysis, and molecular docking which also ensured the anti-inflammatory properties of this plant. A set of hydrogel formulations were designed to deliver the extract and it was found that formulation F3 containing 0.5% w/v extract was the most suitable. Hence, a highly potent natural anti-inflammatory formulation is reported to be developed in this study.

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