

Critical Evaluation of Papaya Leaf's Role as a Natural Platelet Booster Formulation of Syrup

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ABSTRACT:-

Medicinal herbs synthesize a variety of active chemicals, primarily secondary metabolites. The antibacterial properties are mostly attributed to these secondary metabolites. These pharmacologically active compounds function as reservoirs for antimicrobial agents, either alone or in combination with other inactive compounds. These antimicrobial compounds lessen the negative effects of synthetic antimicrobial agents in addition to being highly effective against infectious illnesses. Papaya trees are semiwoody, grow quickly, yield latex, and often have a limited lifespan. According , the cultivars are identified by the number of main veins on the leaves, the types of stomata, the color of the petiole, the number of lobes at the leaf margins, the form of the leaves, and the structure of the wax on the leaf surface. Most tropical and subtropical lowland areas, including Hawaii, Australia, and South-East Asia, are home to carica papaya L. cultivation. The leading emerging nations that grow papayas are Nigeria, Thailand, Indonesia, Mexico, India, and Lopes.

In comparison to other elements, higher concentrations of oxygen (87%), calcium (4.47%), magnesium (3.37%), and potassium (1.49%) were discovered. Other elements present in smaller amounts include silicon, aluminum (0.805%), phosphorus, chloride, sulfur, sulphur, stannous, and strontium. Additionally, the element chromium (0.0129%) has been measured. The leaves have seven enormous, strongly palmately lobed lobes that measure between 50 and 70 cm (20 and 28 in) in diameter. The trees are dioecious, with latex present throughout. The stamens of the five part, highly dimorphic flowers fuse to the petals of the male flowers. Female flowers still have five twisted petals and a superior ovary. Flowers, both male and female, stay in the leaf axils. As a protease with versatile biocatalytic properties, caricapapayalipase (CPL) has emerged. Its many uses include the modification of fats and oils, which allows a variety of acids and alcohols to be used as substrates for esterification and inter-esterification reactions,[44] as well as the asymmetric resolution of various non-steroidal anti-inflammatory drugs (NSAIDs) and non-natural Papain (less than 10%), chymopapain A and B (26–30%), glycyendo peptidase III and IV (23–28%), and caricain (14–26%) are the four types of cysteine proteases found in papaya proteases.

INTRODUCTION:-

Medicinal plants are widely distributed throughout the world but most abundantly in tropical countries. This mosquito-borne illness is caused by infection with any of the antigenically different dengue virus serotypes, which are single positive stranded RNA viruses that belong to the Flavivirus genus and the Flaviviridae family. Approximately 25% of contemporary medications are thought to be derived, either directly or indirectly, from higher plants. Consequently, the development of several new medications and non-drug compounds has been facilitated by herbal therapy. A person must take the prescribed dose over a predetermined period of time in order to receive the desired benefit from herbal medications. While most people assume that most herbal preparations are safe to eat, some herbs, such as the majority of physiologically active compounds, may be hazardous when combined with other substances.

Dengue virus is a member of the Flaviviridae family. The main or predominant vector that transmits dengue from person to person is the flavivirus. The World Health Organization (WHO) has determined that 2.5 billion individuals, or 40% of the world's population, are infected with dengue (WHO,2009).

The earliest recorded case of dengue fever was described as "water poison" in a Chinese medical encyclopedia from the Jin Dynasty (265–420 AD), and it was directly linked to flying insects. As there is no delicate remedial treatment, it can be cured with appropriate supportive care or medication supervision and close observation for potential risks, complications, or patient phases that can also be treated with cautious fluid delivery.

Because of its high starch and carbohydrate content, the unripe pulp of *Carica papaya* is considered a fruit high in carbohydrates. About 43% of the starch in unripe *Carica papaya* fruit is present [3]. The pharmaceutical sciences make use of starch as a multipurpose excipient. The starch's disintegration activity is due to its swelling property. Disintegrating agents are hydrophilic compounds that absorb water, expand, and cause tablet disintegration when they come into touch with saliva or gastric fluid [4]. One of the most often utilized excipients in the production of solid dosage forms is starch, which is employed as a filler, binder, and disintegrant. While corn starch is a commonly utilized starch in pharmaceutical formulations, different botanical sources of starches have demonstrated distinct functional characteristics, including

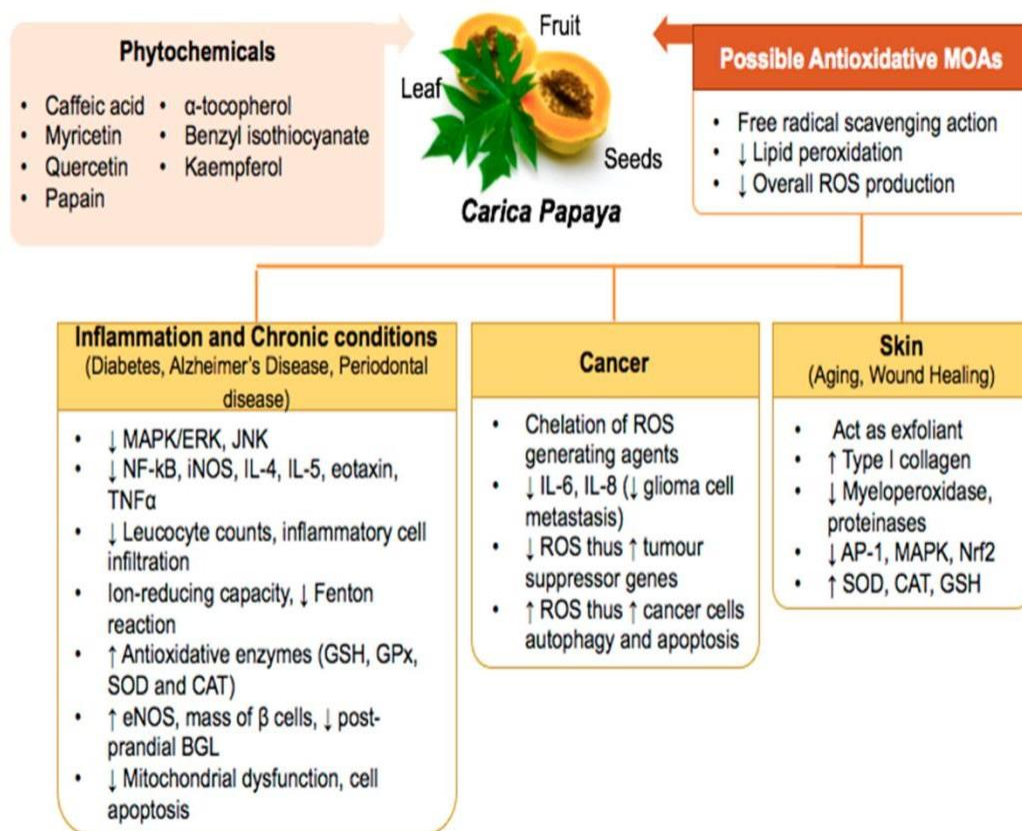
PLANT DESCRIPTION:-



Papaya was discovered to be distributed historically from Mexico to Panama, and during the 16th-century Spanish explorer Don Francisco Marine's exploration of the Caribbean and the Philippines, it later spread from the Philippines to Malaysia, India, and other Asean countries (33,36,37). The Caricaceae family includes *Carica papaya* L. It develops as a single, unbranched trunk and has a lifespan of roughly five to 10 years. It is a perennial herbaceous plant with a milky latex that can reach a height of 12 meters. It bears fruit all year round and its fruits range in weight from 1,000 to 3,000 grams. The leaves have hollow petioles, are up to 75 cm wide, and have five to nine segments on the blades. They are also palmately lobed. The inflorescences, which are located in the leaf axils, give birth to the flowers. According to *carica papaya* L.(38,39). fruits resemble melon and have smooth, green skin that becomes yellow or orange when ripe. They typically contain more than 1,000 seeds.

Family:-Caricaceae **Genus:-** *Carica* L **Species:-** *Carica papaya* L

MEDICINAL PROPERTIES:-



Papaya latex is externally used to burns and scalds and is highly helpful in treating dyspepsia, whooping cough, diarrhea, and bleeding hemorrhoids, according to Reed [57]. Papaya juice helps reduce colon infections by removing mucus, pus, and inflammation. Ripe fruit has carminative, diuretic, expectorant, sedative, and preventative properties against ringworm, dysentery, and skin ailments.

Additionally, papaya has therapeutic benefits against a range of clinical conditions. The unripe fruit is used as a treatment for impotence and ulcers;[58,59] it can show bacterio static activity against human intestinal infections; and it helps women experience less erratic menstruation and encourages natural menstrual flow.It is advised for managing the most common issue of dandruff in hair. While the yellow leaf contains iron, the green leaf offers an adaptable source of critical and needed minerals.[60] It is used to eliminate venom from snakebite and may work in concert to shrink enlarged liver and spleen. Papaya fruit juice is recommended to treat gastrointestinal disorders; it is believed to include some immune stimulating and antioxidant substances [54, 54].

Mechanism of Action :-

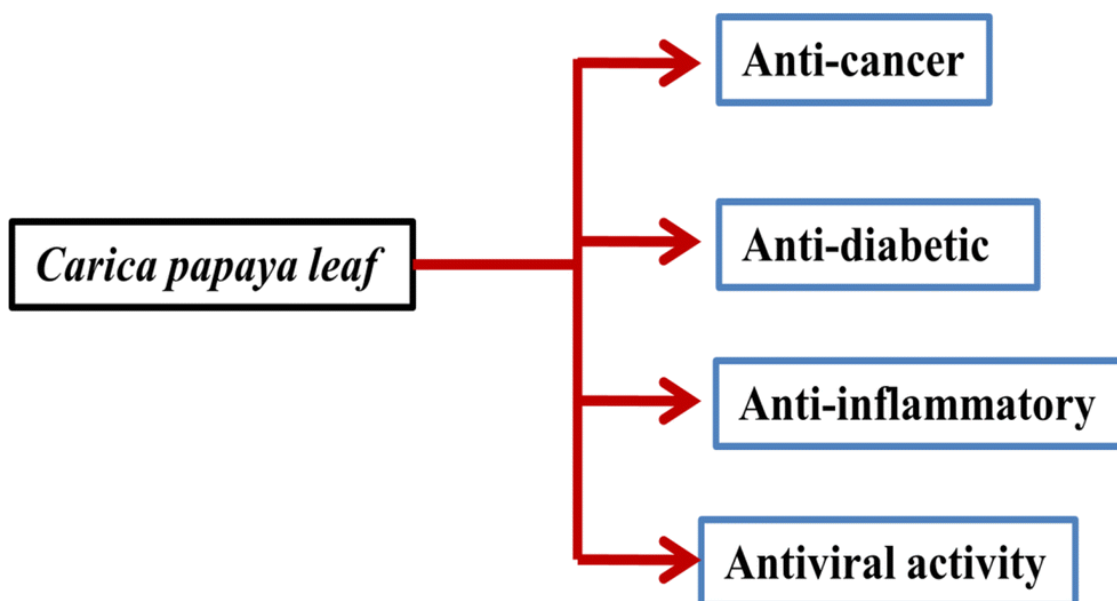


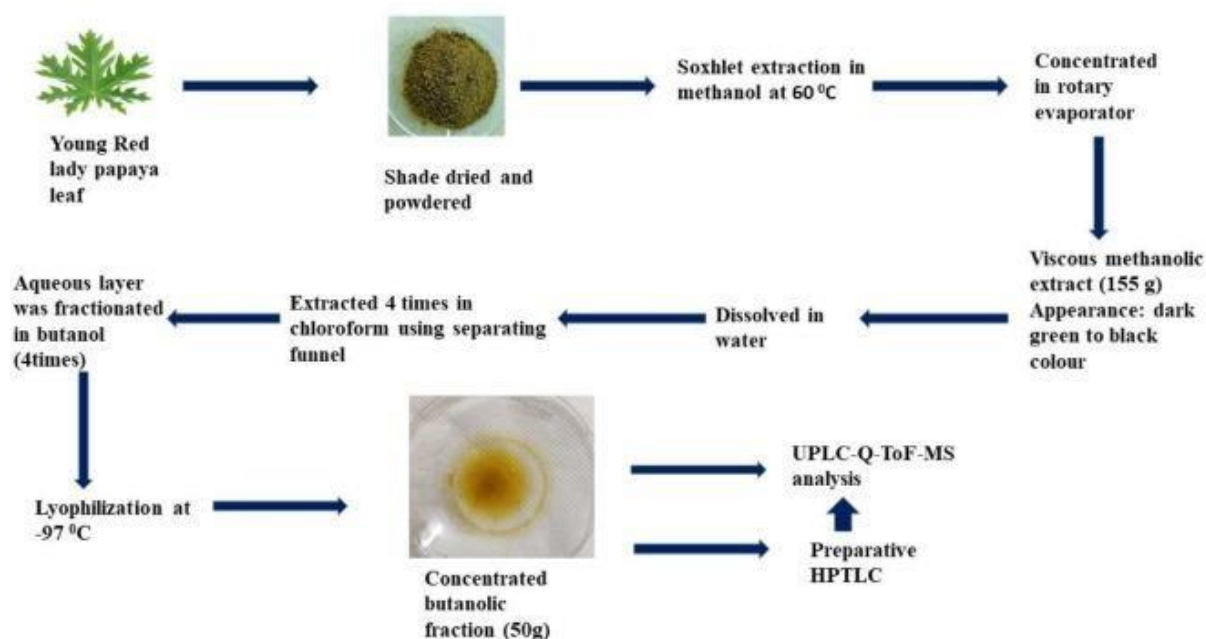
Figure. C papaya's mechanism of action in modulating thrombocytopenia

Numerous studies have demonstrated that C. papaya leaf enhances platelet formation through gene expression activities .The effect of C. papaya leaf extract boosted the activity of specific genes, such as arachidonic acid 12-lipoxygenase (ALOX-12) and platelet-activating factor receptor (PTAFR).As seen in Figure 1, the high expression of particular gene expression induces the bone marrow to manufacture more megakaryocytes. These megakaryocytes are the stem cells that produce platelets; when they mature, they divide into tiny pieces known as platelets, which increases the number of platelets and their aggregation in the bloodstream [61,62,63].

According to a recent experimental investigation, the for this mechanism of action of C. papaya leaf is attributed to carpaine [161].The leaf juice of C. papaya helps to express more CD110 receptors on megakaryocytes, which are useful in preventing thrombocytopenia brought on by chemotherapy [64]. C. papaya leaf can also be used to treat thrombocytopenia by lessening the breakdown of platelets. Flavonoids found in C. papaya leaves bind to the proteases in the viral assembly—the virus's functional and replicating units—to stop viral growth.

As seen in Figure 2, this procedure maintains normal hematocrit levels while minimizing platelet damage. Additionally, the leaf extract has antioxidant and free radical scavenging qualities that hinder 6 | P a g e degradation and stop hemolysis and bleeding. By raising the activities of ALOX-12 and PTFAR by 15 and 13–14 folds, respectively, these extracts also increase platelet generation [65].

Materials and Methods:-



Plant material:-The aqueous extract of carica papaya leaves was produced by sonicating the powdered leaf material in water at 37° C. **Animals:-**Albino For the investigation, wistar rats (100–125g) of both sexes were employed. They were kept in a standard environment with constant lighting and temperature, given a standard feed, and had unlimited access to water. The Institutional Animal Ethics Committee authorized the experimental protocol. Platelet

augmentation activity:-The rats were split up into four groups, each containing six animals: For fifteen days, Group I received saline (10ml/kg p.o). Group II, which was the toxicant group, received cyclophosphamide (50mg/kg s.c). for three days in a row. Group III received Carica papaya leaf aqueous extract (400 mg/kg p.o.) for fifteen days along with cyclophosphamide (50mg/kg s.c).

Group IV received Carica papaya leaf aqueous extract (800 mg/kg p.o.) for fifteen days along with cyclophosphamide (50mg/kg s.c). On the first, fourth, seventh, and eleventh day of the trial, blood was extracted from the retroorbital plexus after the animals were given ether for mild anesthesia. The platelet count was then calculated using an automated cell counter, the Coulter Act-Diff[31] (Patrick and Singh, 2011). The capillary method was used to determine the blood's clotting time on the fifteenth day.

LITERATURE OF THE RESEARCH :-

Nor zahirah Binti Ahmad et.al(2022):-Scientists and the general public are very interested in the possible therapeutic benefit of *Carica papaya* leaf juice in treating dengue-related symptoms. There isn't enough verified data available right now regarding its juice form. As a result, the purpose of this scoping review is to evaluate the scientific data that is currently available about the effectiveness of *C. papaya* leaf juice in treating dengue. Using preset keywords, a methodical search was conducted on two electronic databases (PubMed and Google Scholar).The identified, filtered, and evaluated search results were used to determine the relationship between *C. papaya* and the relief of dengue-related illnesses

Seemal Munir et.al(2022):- A low platelet count of less than $150 \times 10^3/\mu\text{L}$ in blood is known as thrombocytopenia, a clinical manifestation that causes unbalanced hemostasis and multiple 10 | P a g e deadly consequences. The underlying causes differ widely, but ultimately they disrupt the synthesis of platelets and encourage their decomposition, which results in mortality. Scientific research supports the special therapeutic and medicinal properties of *carica papaya* leaf against thrombocytopenia. Minerals and secondary metabolites found in leaves, such as quercetin and carpaine, encourage the formation of new platelets, prevent the destruction of existing ones, and preserve the membrane of existing platelets by reducing viral proteases and promoting the expression of certain genes.

BK Srikanth et.at(2022):- CPLE syrup significantly increases the platelet count in pediatric DF patients and is well tolerated.

Md. Moklesur Rahman Sarker et. Al (2021):-Directorate General of Bangladesh Health Services. Serious bleeding and hemorrhaging caused by a drop in platelets to hazardous levels killed most of the patients. In light of this, the purpose of this research is to critically examine the preclinical and clinical data supporting the use of *Carica papaya* L. leaves in the treatment of dengue fever. One of the main illnesses that frequently accompany dengue infections is thrombocytopenia. Furthermore, dengue sufferers are concerned about infection and immune system dysfunction. All of the research on *Carica papaya* L.'s potential to treat dengue fever in three areas—antiviral activity, thrombocytopenia prevention, and immune system enhancement—is compiled in this study.

C. Nandini et.al(2021):-Ethno pharmacological relevance: *Carica papaya* leaf juice/decoction has been in use in folk medicine in Sri Lanka, Malaysia and in few parts of India for enhancing the platelet counts in dengue. In Siddha medicine, a traditional form of medicine in India, *papaya* leaf juice has been used for increasing the platelet counts. *Papaya* leaf has been reported to enhance blood volume in ancient Ayurveda books in India. *Carica papaya* leaf is well known for its platelet enhancement activity. Although many preclinical and clinical studies have demonstrated the ability of *papaya* leaf juice for platelet enhancement, but the underlying mechanisms are still unclear.

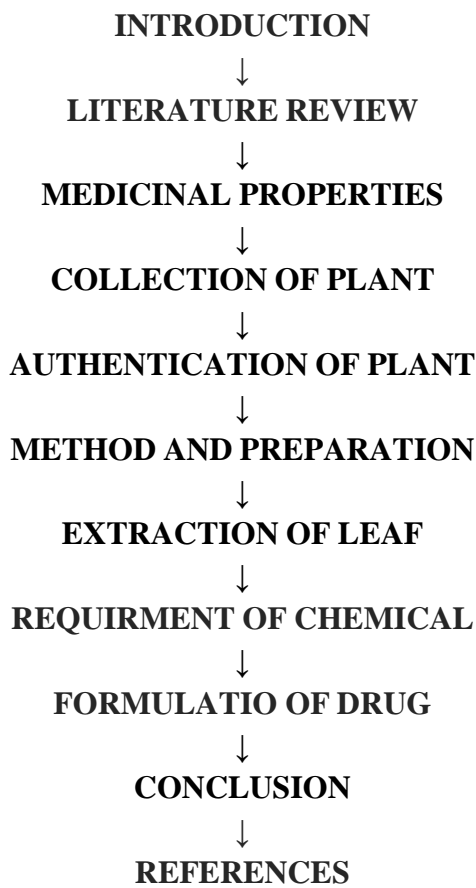
A. E. AJIBOYE et.al(2020):-Numerous infections are known to be caused by microorganisms, and the emergence of multidrug resistant bacteria has made it necessary to employ plants as a treatment for a number of illnesses brought on by *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*, among other bacteria, increasing rates of morbidity and mortality. It is anticipated that certain diseases will be inhibited by the functional elements innate to these plants. Therefore, the purpose of this study was to ascertain the crude extracts of *Carica papaya* leaf's antibacterial activity and phytochemical screening against certain pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*.

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Venugopal K.et.al(2018):-The classic laboratory finding of dengue fever is thrombocytopenia, which, when significantly reduced, manifests as bleeding. As a result, the patient and their loved ones get terrified about the potential for severity, which can result in a number of problems including bleeding tendencies. The only conclusive treatment is platelet transfusion, which should only be used in extreme situations where bleeding symptoms are present. A prophylactic transfusion of platelets is not very helpful unless the cell count falls below 10,000/cumm. It is uncertain how *Carica papaya* leaf extract (CPLE) improves platelets, however it is thought to play a part. Therefore, the purpose of this study is to assess how CPLE might help with dengue thrombocytopenia.

Apurva Priyadarshi et.al(2018):-*Papaya* (*Carica papaya* Linn.) is well known for its nutritional as well as medicinal value since long time. The medicinal properties of fruit and other parts of *papaya* are well known in the different system of traditional medicine including Ayurveda. Its various parts has been reported for various disease conditions viz. fever, swellings, jaundice, gonorrhoea, bilious fever, itches, eczema, and rheumatism cold, headache, whooping cough, asthma, chicken pox, and bronchitis in various traditional literature.

PLAN OF THE WORK



Aim and Objectiv:-

Aim:

The objective is to create and evaluate herbal tablets that can effectively treat dengue fever by reducing symptoms and possibly preventing the virus from replicating.

Objective:-

Identification of Herbal Ingredients:- To choose herbs with proven anti-dengue effects, conduct a thorough literature review and confer with specialists in herbal medicine.

Formulation Development:- To guarantee stability, bioavailability, and patient acceptance, formulate herbal tablets using the chosen herbs and suitable excipients.

Physicochemical Characterization:- To guarantee consistency and quality, examine the formed tablets for a range of physicochemical characteristics, such as weight variation, hardness, friability, disintegration time, and content homogeneity.

In vitro Release Studies:- To comprehend drug release kinetics and adjust the formulation for desired release characteristics, assess the in vitro release profile of the active ingredients from the herbal tablets using a dissolving instrument.

Anti-Dengue Activity Assessment:- Using cell culture models, evaluate the manufactured tablets' effectiveness against the dengue virus in vitro by monitoring criteria including inhibition of viral replication and reduction of viral load.

Optimizing Formulation:- To increase effectiveness and guarantee repeatability, optimize the formulation based on the findings of physicochemical characterisation and anti- dengue activity assessment.

Documentation and Regulatory Compliance:- In order to guarantee that herbal product regulations are followed, create thorough documentation of the formulation procedure, characterization findings, and safety evaluations.

Stability tests:- To ensure shelf life and preserve medicinal efficacy, conduct stability tests to assess the formed tablets' long-term stability under varied storage settings.

DRUG PORFILE:-

Drug Overview: Herbal Tablets for the Treatment of Dengue

Name:- Herbal Dengue tablet

Composition:-

- Active Components: Herbal extracts that have been shown to have anti-dengue effects, such as but not restricted to:
- The(King of Bitters), *Andrographis paniculata*
- Papaya carica,(papaya leaf)
- Tulsi's (*ocimum sanctum*)
- Neem,(*Azadirachta indica*)
- Ingredients: microcrystalline cellulose, lactose, sodium croscarmellose, magnesium stearate, and colloidal silicon dioxide;
- curcuma longa (turmeric)

Dosage form:-Tablets for oral administration

Mechansim of action:-

- The herbal pills' active constituents have a range of pharmacological characteristics, such as antioxidant, immune modulatory, antiviral, and anti-inflammatory actions.
- The antiviral properties of *Andrographis paniculata* include suppression of viral replication and adjustment of the host immune response.
- The extract from carica papaya leaves has anti-inflammatory and platelet-stimulating qualities that can treat dengue symptoms.
- The immune modulatory properties of *Ocimum sanctum* and *Azadirachta indica* strengthen the body's defenses against viral infections.
- Due to its anti-inflammatory and antioxidant qualities, curcuma longa may be able to lessen the inflammatory reaction brought on by a dengue infection.

Pharmacokinetics:-

- Absorption: Individual physiology and formulation qualities, among other things, can have an impact on how well active ingredients are absorbed from the gastrointestinal system.
- Distribution: Tissue perfusion and protein binding are two mechanisms that affect how herbal ingredients are distributed throughout the body.
- Metabolism: The liver uses a number of different metabolic processes to break down the components of herbs.
- Excretion: The biliary and renal systems are principally responsible for the excretion of metabolites.

Formulation Characteristics:-

- Tablet Size: Designed to be easily administered, tablets have a standard size.
- Weight Variation: To guarantee precise dosage, tablets should weigh the same. toughness: Just the right amount of toughness to endure handling and transit without crumbling.
- Friability: Low friability to avoid breaking when being handled.
- Disintegration Time: Quick disintegration ensures effective medication absorption and release.
- Uniformity of Content: Each tablet's active components are distributed consistently for consistent dosage delivery.

Preclinical Studies:-

- Studies conducted in vitro show that some herbal extracts have antiviral properties against the dengue virus.
- Research conducted on animals suggests that the herbal preparation is safe and effective in reducing dengue symptoms and enhancing therapeutic results.

Clinical Studies:-

- A small number of clinical trials support the effectiveness of herbal medicines, including the specific herbs included in the formulation, in reducing the symptoms of dengue fever and raising platelet counts.
- Additional randomized controlled trials are necessary to assess the herbal pills' safety and effectiveness in human subjects.

Safety Profile:-

- Preclinical research and conventional usage have led to the general consensus that it is safe.
- In susceptible people, adverse effects may include moderate gastrointestinal issues or allergic responses.
- There is a lack of long-term safety evidence, which calls for additional analysis.

Regulatory Status:-

- adherence to legal requirements for herbal goods in the intended market, including proof of efficacy, safety, and quality assurance procedures.
- Market authorization may involve registration and regulatory authority approval.

Methodology:-

Instruments and supplies:-

Digital scales (AND G-120), an oven, a funnel, calipers, a flow meter, stopwatches, a tablet printer (Delta), a desiccator, a disintegration tester (Vanguard Pharmaceutical Machinery Inc., USA), a spectrophotometer ultraviolet-visible (UV-Vis) (Optizen), a furnace (Ney), a vacuum dryer (Ogawa), and glass tools were among the instruments used.

PVP K-30, Avicel pH 102, Ac-Di-Sol, talc and magnesium stearate, sodium chloride 10%, iron (III) chloride, hydrochloric acid, sodium acetate 1M, methanol, magnesium powder, reagent Mayer, Bouchardat, Dragendorff, quercetin, and aluminum chloride 10% were the materials used. Every chemical that was used was analytical grade.

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