FORMULATION AND EVALUATION OF HERBAL TABLET CONTAINING POLMACOXIB FOR THE TREATMENT OF MONKEYPOX VIRUS

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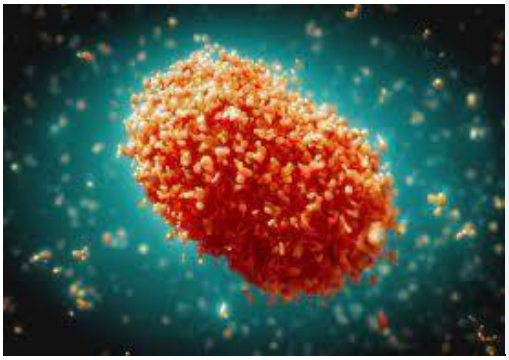
ABSTRACT:
This study aims for formulation and evaluation of herbal drug formulation consist Sarracenia purpurea, Kanchnar guggulu, Lemon balm and incorporating Polmacoxib an anti-inflammatory drug suppresses the production of pro-inflammatory substances (Prostaglandins) by inhibiting certain enzymes involved in inflammation which was found to be novel and versatile to enhance treatment outcome of monkey pox virus. As herbal components sarracenia purpurea inhibit viral transcription and replication, sarapin extract of sarracenia purpurea include of phenolic glycosides, flavonoid glycosides and iridoids inhibit initial virus trancription in humans. Kachnar gugglu inhibiting replication of virus in host cell and prevent spreading exhibit by Lemon balm. The formulation was prepared using direct compression method, the formulation has potential antiviral and immuno-modulatory properties, aiming to create a synergistic effect in combating the virus and managing associated. This research highlights the potential of integrating Polmacoxib with herbal constituents to develop a synergistic therapeutic approach against Monkeypox.
Keywords: Monkey pox, Anti-inflamation, Cox-II, NSAID, herbal

1. INTRODUCTION:

Monkeypox is a zoonotic infection. disease caused by the Monkeypox virus which belongs to genus Orthopoxvirus and Family Poxviridae and Sub-family Chordopoxvirinae. It is a double-stranded deoxyribonucleic acid (dsDNA) virus. It is similar to smallpox with less fatality rates by 10%. Monkeypox is described as an enveloped, pleomorphic and dumbbell-shaped core with lateral bodies. It was first identified in 1958 during studies of pox like virus in State Serum Institute in Copenhagen, Denmark. In NIGERIA, the last case of monkeypox was seen 46 years ago. A recent case was registered in 2017 in Nigeria. After that in 24 states total 228 cases were suspected. Now, Since April 2022 many cases of monkeypox virus have been noted throughout the world. It was declared a global outbreak on 23rd July 2022 by the WHO. In non-endemic countries total 15000 cases of monkeypox virus have been registered till now. In INDIA, on 15th July 2022, 1st case of monkeypox virus was recorded in Kerala. Monkeypox is not a fast spreading disease. There has been no death in 6000 cases noted this year. Recently the 4th case of monkeypox in India was recorded in Delhi on 24th July 2022. It is a self-limited disease. The symptoms last from 2-4 weeks. Anti-viral drugs for smallpox are licensed for monkeypox treatment. The symptoms are mostly similar to smallpox.[1]



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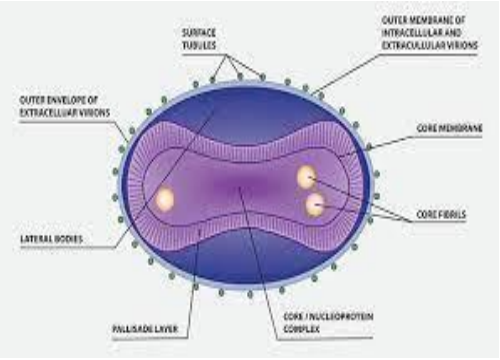

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1. *Kanchnar gugglu:*

Kanchnar (Bauhinia variegata) Family:Fabaceae	guggulu (*Cammiphora wightii)* Family: Burseraceae.

Mixture of powders of kanchnar and guggulu. *Kanchnar guggulu* is used to treat swollen lymph nodes, cystic swelling and also tumors. In kanchnar guggulu, myrcene, alpha-pinene, methyl chavinol and 1, 8-cineole are the essential oil compound.

Mechanism of action: *Kanchnar guggulu* has anti-inflammatory properties and also anti-viral properties hence it reduces swelling in lymph nodes.

2. *Sarracenia purpurea:*

Family: Sarraceniaceae

It is also known as purple pitcher plant, northern pitcher plant, turtle socks and side-saddle flower, is a carnivorous plant. It is used as medicinal plant to treat viruses in Orthopoxvirus family, including smallpox and monkeypox. The extract of Sarracenia purpurea is known as Sarapin consists of phenolic glycosides, flavonoid glycosides and iridoids.

Mechanism of action: Sarracenia purpurea inhibits the early transcription of the viral cells and prevent the further replication of virus.

3. Lemon balm (*Melissa officinalis*)

Family: lamiaceae

It is used as essential oil and also has medicinal properties. It inhibits viral replication in the body. It also acts as an anti-oxidant. Lemon balm has pleasant smell and taste of mint and lemon; hence it can be used as a flavoring and masking agent. *Lemon balm* consists of rosmarinic acid, oleanolic acid and ursolic acid.Mechanism of action *Lemon balm* inhibits replication of virus in host cell and prevent its further spreading.

Polmacoxib:

Polmacoxib (CG100649) an its chemical name 4-{3-(3-fluorophenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-2-furanyl}benzenesulfonamide is selective non-steroidal anti-inflammatory drug NSAID, also known as CG100649.Polmacoxib long-acting a novel non-steroidal anti inflammatory disease(NSAID), an selective COX-2 and Carbonic anhydrase (CA) subtype (CA I/II) inhibitor. It is a specially designed cox-2 preferential NSAID that appears to have retained analgesic and anti-inflammatory effects similar to cox-2 while providing certain of the negative cox-1 inhibition actions to a lesser degree. its safety and efficacy would be evaluated in human clinical trials, while other coxibs such as Celecoxib, Rafecoxib ,Valdecoxib.

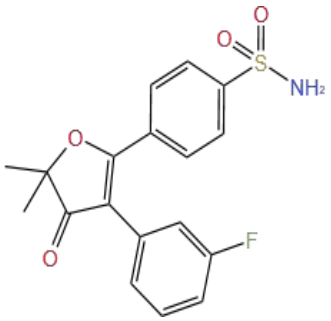


Fig.1 Structure of Polmacoxib

Inhibiting the Cyclooxygenase (COX) enzymes including both COX-I and COX-II inhibitors Non-steroidal anti inflammatory drug aka NSAIDs suppressing inflammation and pain. There are few studies which showed that the COX-1 inhibiting species cause Gastrointestinal adverse effects and COX-II inhibitors caused certain Cardiovascular disorders as adverse effects in patients.[10] Polmacoxib suppresses the production of proinflammatory substances (prostaglandins) by inhibiting certain enzymes involved in inflammation, results in a reduction in inflammation. lower dosage administration of Polmacoxib 2mg this reduced adverse effects of GI disorders and have least effect on carbonic anhydrase in the circulatory system.

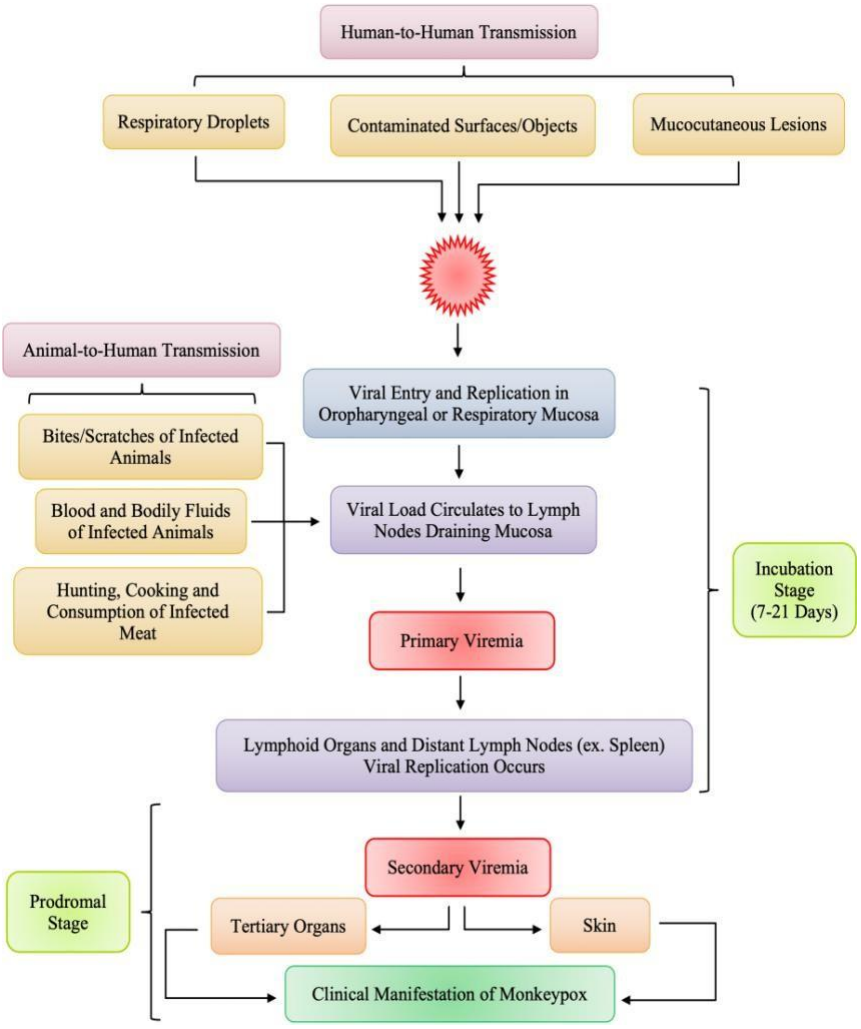
Reduction of Prostaglandin enzyme-2 (PGE2) Level:	Lower inflammation: Decrease swelling, redness, and immune-mediated tissue damage. Relieve pain: Prostaglandins are major contributors to pain and fever.

MECHANISM OF ACTION OF MONKEYPOX VIRUS:

When the virus enters the cell, it undergoes two processes Early transcription and uncoating. The early transcription stage then goes into early translation and intermediate transcription. While the uncoating stage forms double stranded DNA and intermediate transcription occurs. After this the genome replication takes place and then late transcription occurs. Late transcription forms a viral assembly and then maturation of the virus takes place.

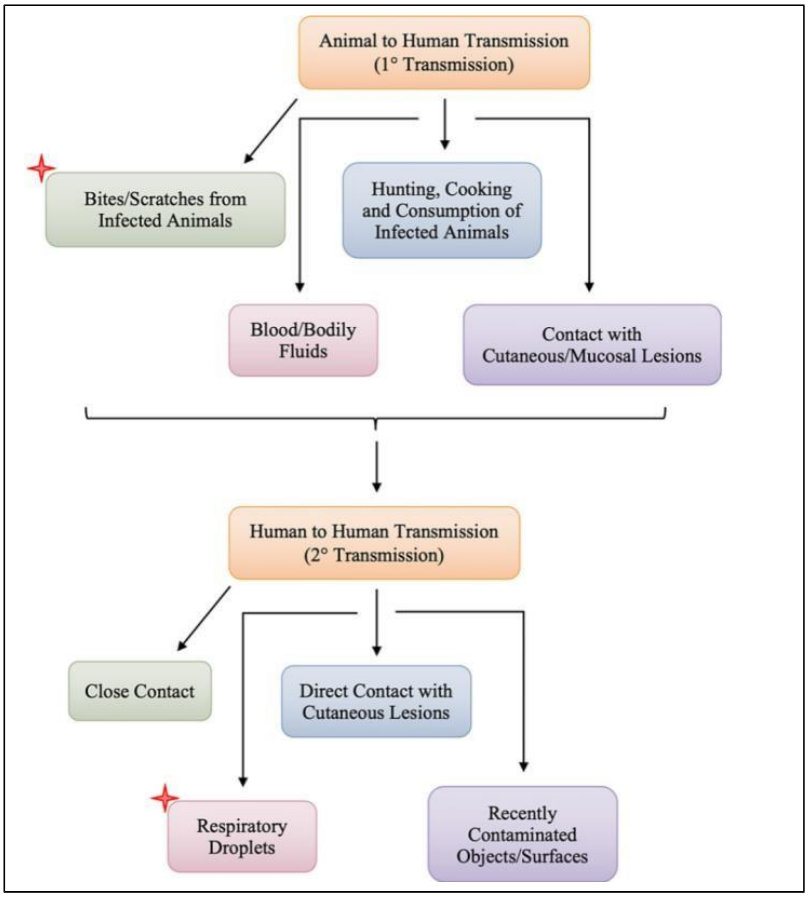
PATHOGENESIS:

Monkeypox follows the same pathogenesis as smallpox. It begins with exposure to the oropharyngeal as a host. The monkeypox virus replicates at the inoculation site in person to person transmission. The virus enters the oropharyngeal or respiratory mucosa and replicates. After that the viral load enters lymph nodes draining mucosa. It enters primary viremia where viral replication occurs in lymphoid organs and distinct lymph nodes. The incubation period of primary viremia is 7-12 days. From primary viremia, it enters into secondary viremia where the clinical manifestation of monkeypox occurs in tertiary organs and skin. In animal to human transmission, it spreads from biting or scratches of the infected animal, blood and bodily fluid of the infected animal hunting, cooking and consuming infected meat. From there it enters directly into lymph nodes draining mucosa, followed by primary and secondary viremia.[1]



CAUSES:

Animal-to-human transmission known as 1˚ transmission, is caused by bites and scratches of infected animals, blood or bodily fluids of infected animals, consumption of infected animals and contact with cutaneous or mucosal lesions. In human to human transmission which is also known as 2˚ transmission, is caused by close contact, respiratory droplets, contact with cutaneous lesions and contamination from recently infected surfaces or objects.[1]



SIGNS AND SYMPTOMS:

Table1. Sign and Symptoms of Monkeypox[1]

CNS	Headache
THROAT	Sore throat
SYSTEMATIC	Fever
	Chills
	Vomitting
SKIN	Rashes
LYMPH NODES	Adenopathy
MUSCLES	Myalgia
OTHERS	Hypoalbuminemia
	Increase Blood, Urine, Nitrogen level
	Leukocytosis
	Thrombocytopenia

STAGES OF VASCULO-PUSTULAR RASHES:

There are six stages in Vasculo-pustular rashes which are:

Table2. Stages of Vasculo-pustular rashes.[1]

S.no.	Stages	Description
1.	Enanthem	Enanthem are the first lesions to develop on the tongue and in the mouth.
2.	Macules	Flat lesions that begin on face and spreads to arms, legs and then hands and feet
3.	Papules	Flat lesions progress to raise
4.	Vesicles	Raised lesions become filled with clear fluid becoming vesicles
5.	Pustules	Lesions become filled with opaque fluid
6.	Crusting	Pustules begin to crust and then fall off leaving scars

DIAGNOSIS:

Monkeypox is rare and first seems like measles and chickenpox but is distinguished by swollen lymph nodes. To diagnose, a tissue from lesion is taken and sent for Polymerase chain reaction (PCR) testing. And also, blood test is done to check antibodies formed against monkeypox virus.The evaluation of monkeypox involves thorough medical history taking, clinical examination, and laboratory confirmation. Key history points include travel to endemic areas, contact with infected animals, or caring for an infected person. Diagnosis must be confirmed through laboratory findings due to the wide range of differential diagnoses for acute rash with nonspecific symptoms (e.g., fever, headache, myalgia).Lymphadenopathy in the prodromal stage is a venerated sign of monkeypox which helps differentiating it from varicella and variola.

Infectious diseases	**Non-infectious conditions**
Varicella (chickenpox), Measles, molluscum contagiosum, scabies, syphilis, bacterial skin infections, drug allergies and sexually transmitted infections such as herpes simplex virus, chancroid, lymphogranuloma venereum (LGV) and granuloma inguinale.	Behcet's disease, squamous cell carcinoma, recurrent aphthous stomatitis.

SIDE EFFECTS:

Pain at site of injection, redness, headache, fatigue, nausea, chills, rashes, lymph nodes swelling, myocarditis, pericarditis. [3]

TREATMENT:

There is no such specific treatment for monkeypox disease. But the symptoms can be treated with supportive medications.

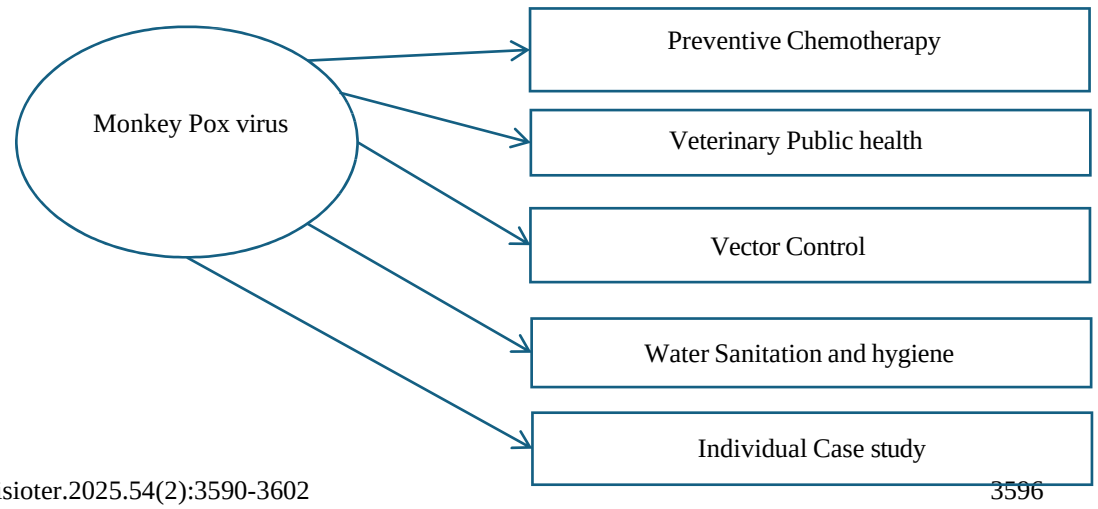
Table 3: Supportive treatment of symptoms of monkeypox virus.[2]

SYMPTOMS	SUPPORTIVE TREATMENT
Respiratory distress/ Bronchopneumonia	Oral/ I.V. antibiotics for prophylaxis, nebulizer treatments, non- invasive ventilation
Sepsis	Oral/ I.V. antibiotics, supplemental oxygen, corticosteroids, insulin
Gastrointestinal mouth and throat ulcers	Oral/ I.V. antiemetic and anti-diarrheal medications, Oral/ I.V. rehydration
Fever	Antipyretic medication, external cooling
Superinfection skin	Oral/I.V. antibiotics, incision, and drainage, advanced wound management
Lymphadenopathy	Oral/ I.V. anti-inflammatory/ analgesic medications
Corneal infection	Ophthalmic antibiotics/ antivirals and corticosteroids
Skin scaring/ Cellulitis/ skin lesions	Application of moist occlusive dressings to promote re-epithelization
Adenopathy (Inflammation in lymph nodes)	Polmacoxib (2mg) non-steroidal anti-inflamation drug

PREVENTION:

Smallpox vaccine provide prevention from monkeypox virus. Prevention depends on decreasing contact with animals and infected person. Wash hands with soap and water frequently. Perform safe sex, using condom and dental dams. Wear a mask covering nose and mouth. Wearing PPE kit while taking care of infected person. Clean and disinfect touched surfaces.[3]

STRATIGIES TO PREVENT MONKEY POX:



MATERIAL AND METHODS:

The methods used for tablet preparation are: Dry granulation, Wet granulation and Direct compression. For the formulation of herbal tablet direct compression is used.

Direct compression:

Direct compression is a process where the powdered material are directly compressed into tablet without drying of the compounds. [8, 9, 10]

Steps involved in direct compression:

Mixing: All the 3 ingredients i.e. *Sarracenia purpurea, Kanchnar guggulu and Lemon balm* were mixed together in a motor pastel.

Screening: The mixture was passed through the sieve to obtain uniform size and shape particles.

Compression: The mixture was then filled in the die and compressed to form tablet.

TABLET FORMULATION:

Table 4: Standard dose per day

Sr. No.	Herbal ingredients	Quantity per day
1.	*Sarracenia purpurea*	15 milligrams
2.	*Kanchnar guggulu*	1 grams
3.	*Lemon balm*	1.5 grams

EVALUATION PARAMETERS:

1. ORGANOLEPTIC PROPERTIES:

Consumer acceptance, Control of lot-to-lot uniformity, Monitoring trouble-free manufacturing.It Consists of organoleptic properties such as colour, odour and taste. Colour is vital means of identification of many pharmaceutical tablets and is also important for consumer acceptance. The colour of the tablet must be uniform within a single tablet and also from tablet to tablet. Reflectance spectrophotometry, tristimulus colorimetric measurements are used to measure colour uniformity in tablet, Odour is also important for consumer acceptance and can provide an indication to the quality of tablets.

2. SHAPE AND SIZE:

It can be dimensionally described and controlled. The size and shape should be acceptable by the consumer. The size of the tablet should be such that the patient could easily swallow the tablet. The shape of the tablet should be such that it easily flows down the throat without causing any problem. It should not be difficult in swallowing. [11]

3. WEIGHT VARIATION:

Weight 10 tablets individuallyCalculate average weight of tablets.Compare the individual weight with the average weight.Calculation % weight variation.

Weight variation= (IV-AW)/AW x 100

4. FRIABILITY TEST:

20 tablets was taken initial weighed, placed in friabilator and rotate at 25rpm or 100 rpm for 4 minutes.After 4 minutes, final weight of tablet and % friability was calculated.

%Friability = W1-W2/W1x100

5. HARDNESS TEST:

Hardness of the tablet was performed by using Monsanto tester. The hardness is measured by the unit Kg/cm^2. Official standard for hardness is 5-8 kg/cm^2.

6. DISSOLUTION TEST:

The administration of tablets via oral route is most effective means of delivering treatment in the patients. When a dosage form is swallowed, the rate at which it releases active ingredient is critical to ensure that the drug is delivered properly. The rate at which the drug is dissolved is known as dissolution rate. [13]

In USP, there are 4 dissolution apparatus:

USP Dissolution Apparatus 1- Basket (37˚C)

USP Dissolution Apparatus 2- Paddle (37˚ C)

USP Dissolution Apparatus 3- Reciprocating cylinder (37˚C)

USP Dissolution Apparatus 4- Flow Through Cell (37˚ C)

In IP, there are 2 dissolution apparatus:

- Type I: Paddle type apparatus
- Type II: Basket type apparatus

7. DISINTEGRATION TEST:

Tablet was placed in each tube, the basket rack is positioned in a beaker contain water(1 litre), stimulated gastric fluid or stimulated intestinal fluid at 37˚C $\pm$ 2˚C. Tablet should remain 2.5 cm below the surface of the liquid on upward movement and not closer than 2.5cm from the bottom of the beaker.The basket assembly move up and down through a distance of 5-6cm at frequency of 28-32 cycles per min.Note the time taken by the tablets to disintegrate from the glass tube.

BENEFITS OF AYURVEDIC MEDICINE FOR MONKEYPOX:

Ayurveda is non-toxic and with lesser side effects as it is natural and plant based. Allopathic medications and drugs may cause severe side effects hence Ayurveda can be recommended as a way of curing with no or less side effects. Monkeypox vaccine used cannot be given to patients with eczema and during pregnancy but in such conditions as ayurvedic medication can be given to any non-allergic patient. There are many ayurvedic herbs which can be used for treatment of monkeypox as they treat all the symptoms. Nowadays, Ayurveda is mostly preferred by people and is trending in Indian market.

RESULTS:

Table 5: Observation of evaluation parameters

Sr. No.	Evaluation parameters	Observation	Instrument used	Standard criteria
1.	Organoleptic properties	Colour: Greenish brown Odour: Characteristic Taste: Bitter	--------	-----
2.	Shape and size	Shape: Round biconvex Size: Standard (Medium)	---------	------
3.	Weight variation	± 2.77%	Weighing scale	(+ or -) 5%
4.	Friability test	0.55%	Friabilator	0.5 to 1%
5.	Hardness test	Tablet 1: 7.5 Kg/cm^2 Tablet 2: 7 Kg/cm^2 Tablet 3: 8 Kg/cm^2	Monsanto tester	5-8 kg/cm^2
6.	Dissolution test	73% in 40 mins	Paddle apparatus	75% in 40 mins
7.	Disintegration test	In stomach: 1hr 15 mins In intestine: 47 mins	Disintegrating apparatus	15- 60 mins

RATIONALE OF RESEARCH:

There is no treatment yet of monkeypox virus. Vaccine for smallpox is used as monkeypox is similar to smallpox. Antiviral drugs to treat the symptoms can be given. There is no ayurvedic treatment available for monkeypox. Hence, by reviewing many articles and references the combination of three herbal plants, *Sarracenia purpurea*, *Kanchnar guggulu* and *Lemon balm*, an ayurvedic tablet is prepared which treats all the symptoms of monkeypox virus. *Sarracenia purpurea* extract called Sarapin is used for treatment of smallpox and also treats mostly all symptoms of monkeypox virus and also inhibits replication of virus in body. *Kanchnar guggulu* is used for treatment of swollen lymph nodes (lymphadenopathy), which distinguishes monkeypox from smallpox. *Lemon balm* inhibits viral replication in the body and also has a pleasant odour and taste which can be used for masking the taste and odour of the formulation. All these three herbal plants can be used for treatment of monkeypox

DISCUSSION:

Monkeypox is an infection which is now becoming global concern as it is spreading in regions of western hemisphere and has 0.5% case fatality ratio. Monkeypox spreads with human to human transmission and animal to human transmission trough blood, respiratory droplets or direct contact with lesions. It is an endemic, there is no treatment of monkeypox virus available hence smallpox vaccines and anti-viral medications are used for treatment of monkeypox. As allopathic treatment causes toxicity and adverse drug reactions, a study on ayurvedic treatment has been done to prevent toxicity and side effects. Study on herbal plants like *Sarracenia purpurea*, *Kanchnar guggulu* and *Lemon balm* has been done. The extract of Sarracenia purpurea called Sarapin is used to inhibit viral transcription and replication. Chemical constituents of kanchnar guggulu is used for swollen lymph nodes. Lemon balm is used as flavoring agent, masking agent and also inhibits viral replication in the host cell. The evaluation parameter of tablet are performed for better stability, efficacy and effectiveness of formulation. The organoleptic properties of the tablet i.e. the colour, odour and taste of the tablet are seen for consumer acceptance. The weight variation of the tablet is $\pm$ 2.77% which comes under standard criteria hence, it is acceptable. The friability of the test is 0.55% which comes under the criteria of 0.5- 1% hence, the friability is acceptable. The hardness of the tablets was 7.5, 7 and 8 Kg/cm^2 and the standard criteria is between 5- 8 Kg/cm^2 hence, the hardness is also acceptable. The dissolution test was performed and the results were 73% in 40 mins which is under standard criteria hence, the results are acceptable. The disintegration time of the tablet is 47 mins in intestine (pH=6.8) and 1hr 15 mins in stomach (pH=2-3) which comes under standard criteria of 15-60 mins hence, disintegration time is also acceptable. So, all the evaluation parameters are acceptable.

Polmacoxib nonsteroidal anti inflammatory first in class act by inhibiting cyclooxegenase enzme (COX-2) and Carbonic anhydrase (CA-I/II) prone toward inhibition of Prostaglandin enzyme-2 (PGE2), which is responsible of inflammation. It lower chance of gastroinstestinal infection and Cardiaovascular adverse effect simultaneously due to its lower dose admistration.

CONCLUSION:

After literature survey of review articles on monkeypox virus, its pathogenesis, causes and symptoms, study of herbal plants like *Sarracenia purpurea, Kanchnar guggulu* and *Lemon balm,* study of tablet preparation and its evaluation parameters has been done. The study shows that herbal plants like *Sarracenia purpurea, Kanchnar guggulu* and *Lemon balm* can be used to treat monkeypox virus as they inhibit viral transcription and replication. Tablet formulation is done by direct compression method. All the evaluation parameters like weight variation, hardness, friability, dissolution and disintegration were performed and the results are under standard criteria hence, it is acceptable. As the tablets meet the requirement for treatment of monkeypox virus and all the evaluation parameters are acceptable which shows that the tablet are optimum for treatment. In future, these tablets can be used for the treatment of monkeypox virus.

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