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Formulation and Evaluation of Polyherbal Extract Used in Prognosis of Pulmonary Embolism

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ABSTRACT:
Pulmonary embolism (PE) is a common and potentially deadly form of venous thromboembolic disease. It is the third most common cause of cardiovascular death and is associated with multiple inherited and acquired risk factors as well as advanced age. It is the condition in which one or more arteries in the lungs become blocked by a blood clot causing various chronic symptoms is said to be pulmonary embolism and there are various allopathic medications are currently available on the management of the emboli including the various clot dissolvers(thrombolytics) and blood thinners (anticoagulants) also surgical processes are performed according to the sevearity. But there is a herbal aspects which is useful as well in case of prognosis of the various kind of emboli including pulmanary emboli and it shows numerous health benefits along with its physiological activity with minimum or less
side effects

ABBRIVATIONS :-

PE. :- pulmonary embolism
DVT. :- deep vein thrombosis
VTE. :- venous thromboembolism
PVR. :- Pumanary vascular resistance
PAP :- pulmonary arterial pressure
RV. :- right ventricle
LV :- left ventricle
CQ. :- cardiac output
CTOA. :-Computer tomographic pulmonary angiography
ABG. :-Arterial blood gas analysis
MRA. :- magnetic resonance angiography

INTRODUCTION:-

An embolism is a blocked artery caused by a foreign body, such as a blood clot or an air bubble.The body's tissues and organs need oxygen, which is transported around the body in the bloodstream.If the blood supply to a major organ – such as the brain, heart or lungs – is blocked, the organ will lose some or all of its function.

There are various conditions occurs due to clot including

1. stroke
2. pulmonary embolism

The formation of an unwanted blood clot needs to be attended immediately as it may be a serious condition. Symptoms of blood clot depends on the place where the clot is formed while in some people the clot may not exhibit any symptoms. Natural remedies for blood clots can help you get relief from the conditions

MECHANISM OF BLOOD CLOTTING:-

Blood Coagulation:-

Blood coagulation or clotting is an important phenomenon to prevent excess loss of blood in case of injury or trauma. The blood stops flowing from a wound in case of injury. The blood clot or 'coagulum' is formed by a network of fibrin threads. In this network, deformed and dead formed elements (erythrocytes, leukocytes and platelets) get trapped.

Factors Involved in Blood Coagulation :-

Coagulation factors involved in the blood clotting process.

Coagulation of blood occurs through a series of reactions due to the activation of a group of substances called clotting factor

Blood coagulation pathway :-

Platelet Activation:-

The blood circulating in the blood vessel does not clot under normal circumstances. The blood coagulation process is stimulated when there is any damage to the endothelium of blood vessels. It leads to platelet activation and aggregation.

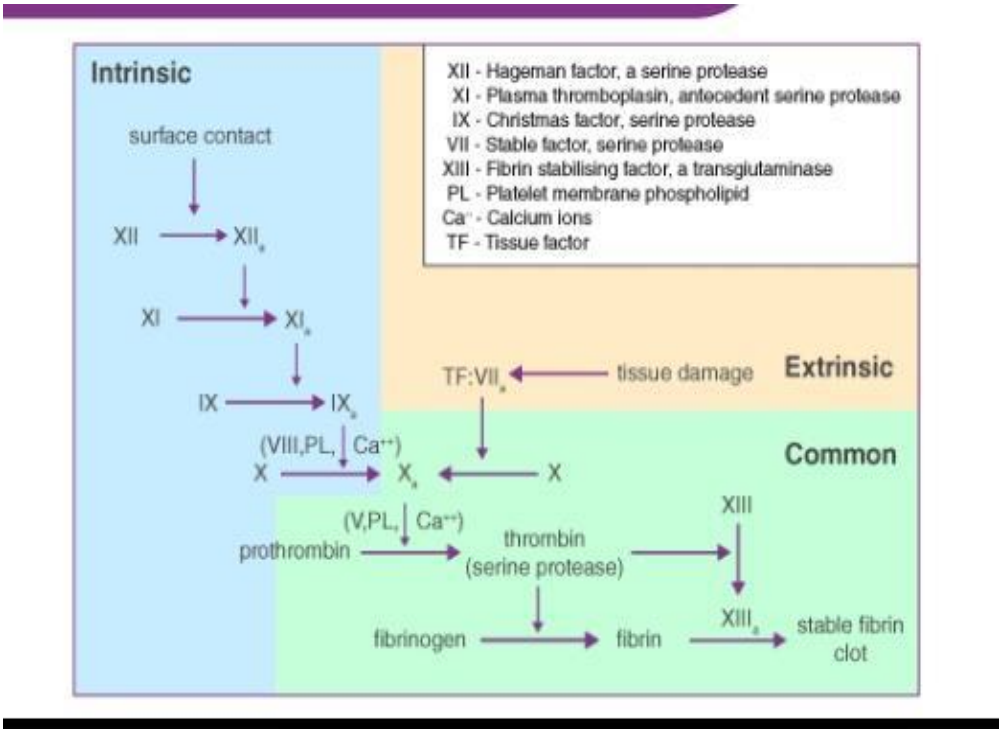

Fig 1) Blood coagulation pathway.

Blood coagulation cascade:-

The three main steps of the blood coagulation cascade are as follows:

1. Formation of prothrombin activator.
2. Conversion of prothrombin to thrombin.
3. Conversion of fibrinogen into fibrin.

DISEASE OVERVIEW:-

What is emboli:-

A blood clot that forms in a blood vessel in one area of the body, breaks off, and travels to another area of the body in the blood is called an embolus. An embolus can lodge itself in a blood vessel. This can block the blood supply to a particular organ. This blockage of a blood vessel by an embolus is called an embolism.

A clot can travel in the bloodstream before it gets stuck and starts to block the blood flow to an organ or a limb.

Fat

A fracture to a long bone, such as a thigh bone, can lead to fat particles within the bone being released into the bloodstream. Fat particles can also sometimes develop following severe burns or as a complication of bone surgery.

Air

Embolisms can also occur if air bubbles or other gases enter the bloodstream.

Air embolisms are a particular concern for scuba divers. If a diver swims to the surface too quickly, the change in pressure can cause nitrogen bubbles to form in their bloodstream and become trapped in a blood vessel. This blockage can cause decompression sickness, which is often referred to as "the bends".

Cholesterol

In people with severe atherosclerosis (narrowed arteries caused by a build-up of cholesterol), small pieces of cholesterol can sometimes break away from the side of a blood vessel, resulting in an embolism.

Amniotic fluid

In rare cases, amniotic fluid – which surrounds and protects a baby inside the womb – can leak into the mother's blood vessels during labour, causing a blockage. This can lead to breathing problems, a drop in blood pressure and loss of consciousness.

Pathophysiology of pulmonary embolism:-

Pulmonary embolism (PE) occurs when there is a disruption to the flow of blood in the pulmonary artery or its branches by a thrombus that originated somewhere else. In deep vein thrombosis (DVT), a thrombus develops within the deep veins, most commonly in the lower extremities. PE usually occurs when a part of this thrombus breaks off and enters the pulmonary circulation. Very rarely, PE can occur from the

embolization of other materials into the pulmonary circulation such as air, fat, or tumor cells.[1] The spectrum of PE and DVT combined is referred to as venous thromboembolism (VTE).

There are three types of pulmonary embolism

- Acute
- Subacute
- Chronic

Pulmonary embolism occurs when clots break off and embolize into the pulmonary circulation.

Pulmonary emboli are typically multiple, with the lower lobes being involved more frequently than the upper, and bilateral lung involvement being more common.[13]

Large emboli tend to obstruct the main pulmonary artery, causing saddle embolus with deleterious cardiovascular consequences. In contrast, smaller sized emboli block the peripheral arteries and can lead to pulmonary infarction, manifested by intra-alveolar hemorrhage. Pulmonary infarction occurs in about 10% of patients.

PE leads to impaired gas exchange due to obstruction of the pulmonary vascular bed leading to a mismatch in the ventilation to perfusion ratio because alveolar ventilation remains the same, but pulmonary capillary blood flow decreases, effectively leading to dead space ventilation and hypoxemia.

Also, mediators, such as serotonin, are released, which cause vasospasm and further decreased pulmonary flow in unaffected areas of the lung. Local accumulation of inflammatory mediators alters lung surfactant and stimulates respiratory drive resulting in hypocapnia and respiratory alkalosis.

In PE, pulmonary vascular resistance (PVR) increases due to the mechanical obstruction of the vascular bed with thrombus and hypoxic vasoconstriction. Pulmonary artery pressure (PAP) increases if thromboemboli occludes greater than 30% to 50% of the total cross-sectional area of the pulmonary arterial bed.

Increased PVR increases the right ventricular afterload, which impedes right ventricular outflow, which, in turn, causes right ventricular dilation and flattening or bowing of the interventricular septum. The desynchronization of the ventricles may be increased by the development of the right bundle branch block. The decreased RV outflow and concomitant RV dilation reduce left ventricular filling, thereby compromising cardiac output.As a result, LV filling is reduced in early diastole, and this leads to a reduction in the cardiac output (CO), and cause systemic hypotension and hemodynamic instability. Right ventricle (RV) failure due to acute pressure overload is the primary cause of death in severe PE. Given the above pathophysiological considerations, clinical symptoms, and signs of overt RV failure and hemodynamic instability, are indicative of a high risk of early (in-hospital or 30 day) mortality.

Symptoms

Pulmonary embolism symptoms can vary greatly, depending on how much of your lung is involved, the size of the clots, and whether you have underlying lung or heart disease.

Common symptoms include:

Shortness of breath. This symptom usually appears suddenly. Trouble catching your breath happens even when resting and gets worse with physical activity.

Chest pain. You may feel like you're having a heart attack. The pain is often sharp and felt when you breathe in deeply. The pain can stop you from being able to take a deep breath. You also may feel it when you cough, bend or lean over.

Fainting. You may pass out if your heart rate or blood pressure drops suddenly. This is called syncope.

Other symptoms that can occur with pulmonary embolism include:

- A cough that may include bloody or blood-streaked mucus
- Rapid or irregular heartbeat
- Lightheadedness or dizziness
- Excessive sweating
- Fever
- Leg pain or swelling, or both, usually in the back of the lower leg
- Clammy or discolored skin, called cyanosis.

Causes :-

Pulmonary Embolism Causes

The most common cause of a pulmonary embolism is a the breaking off of a blood clot in your leg's deep veins, known as deep vein thrombosis (DVT).

Air bubbles

- Tumors
- Cancer
- Heart disease

Health history of blood clots

- Long-term use of birth
- Control pills
- Fracture of lower limb
- Hospitalization for heart failure or atrial fibrillation/flutter within the previous three months
- Hip or knee replacement
- Major trauma
- History of previous venous thromboembolism
- Central venous lines
- Chemotherapy
- Congestive heart failure or respiratory failure
- Hormone replacement therapy
- Oral contraceptive therapy
- Postpartum period
- Infection (specifically pneumonia, urinary tract infection, and HIV)
- Cancer (highest risk in metastatic disease)
- Thrombophilia

- Bed rest greater than three days
- Obesity
- Pregnancy

Complications :-

- Recurrent thromboembolism
- chronic thromboembolic pulmonary hypertension.
- cardiogenic shock.

Diagnosis :-

Arterial blood gas analysis(ABG)
Brain natriuretic peptide
D dimer
Electrocardiography
Cheast radiocardiograph
Computer tomographic pulmonary angiography (CTOA)
Lung scientigraphy
Pulmonary angiography
Magnetic resonance angiography (MRA)
Echocardiography
Compression ultrasonography

Treatment :-

A)Initial management
1) supportive measures
2) anticoagulation
3) reperfusion stratergy

- Thrombolysis
- Catheter directed treatment
- Surgical embolectomy
- Vena cava filters

B) chronic treatment and prevention of recurrance

:-HERBAL APPROACH:

ZINGIBER OFFICINALAE (GINGER):

Fig 2) ZINGIBER OFFICINALE

Kingdom :-Plantae
Order :-Zingiberales

Family :-Zingiberaceae
Genus :-Zingiber
Species :-Z. officinale
Chemistry of Ginger :-
Chemical makeup of zinger the gingerly were found to be the primary active ingredients in fresh ginger rhizomes, and [7] gingerol [5-hydroxy-1-(4-hydroxy-3-methoxy phenyl) decan-3-one is the most prevalent gingerol in the series (Table 1). The powdered rhizome is made up of 3-6% fat, 9% protein, 60–70% carbs, 3- 8% crude fibre, 8% ash, and 2-3% volatile oil. Alpha-farmesene, camphene, beta-phellandrene, curcumene, cineole, geranial acetate, terphineol, terpenes, borneol, geraniol, limonene, and linalool are among the main mono- and sesquiter-pene components of volatile oil. Alpha-zingiberene, which makes up 30–70% of the oil, beta-sesShogaol, a dehydrated form of gingerol.

CURCUMA LONGA(TURMERIC):

Fig3) CURCUMA LONGA

Kingdom :-Plantae
Order :-Zingiberales
Family :- Zingiberaceae
Genus :-Curcuma
Species :-C. longa
Chemistry of Turmeric:-
Turmeric contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). Phenolic diketone, curcumin (diferuloylmethane) (34%) is responsible for the yellow colour, and comprises curcumin I (94%), curcumin II (6%) and curcumin III (0.3%). Other phenolic diketonesdemethoxycurcumin and bis-demethoxycurcumin have also been isolated from the rhizomes of Curcuma longa. Presence of tumerones (a and b), curdione, curzerenone, mono- and di-demethoxycurcumin have been reported in the rhizomes. The essential oil (5.8%) obtained by steam distillation ofrhizomes has a- phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%)[40]The essential oils of leaves of C. Longa have been analyzed by GLC (Perkina Elmer auto-system fitted with capillary column carbowax 20 m of 50 mlength flux ionization detector) and was reported to contain Î±-pinene, Î2-pinene, sabinene, myrcene, a-phellandrene, 1,8-cineole, p-cymene, C8-aldehyde, linalool, caryophyllene, geraniol and methyl heptanone.

AZARDIRACHTAINDICA(Neem) :-:

Fig. 4) AZARDIRACHTAINDICAI

Kingdom :-Plantae
Order :-Sapindales
Family :-Meliaceae
Genus :-Azadirachta
Species :-A. indica
Chemistry of Neem :-

Nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin are the other active ingredients, with azadirachtin being the most significant. N-hexacosanol, amino acids, ascorbic acid, 6-desacetylnimbinene, nimbandiol, nimbolide, 7-desacetyl-7-benzoylazadiradione, 7- desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol are all components found in leaves.[55]Polyphenolic flavonoids isolated from freshly harvested neem leaves include quercetin and ß-sitosterol, which are known to have antimicrobial and antifungal activities[56]Its seeds contain beneficial substances including azadirachtin and gedunin.

GLYCYRRHIZA GLABRA (liquorice) :-

Fig.5) GLYCYRRHIZA GLABRA

Kingdom :-Plantae
Order :-Fabales
Family :-Fabaceae
Subfamily :-Faboideae
Genus :-Glycyrrhiza
Species :-G. glabra
Chemistry of glycyrrhiza glabra :-

Isolatedfrom the roots of Glycyrrhiza glabra, including a water-soluble, biologically active complex that accounts for 40–50% of total dry material weight. This complex is composed of triterpene, saponin, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, asparagines, bitters, essential oil, fat, female hormone estrogen, gums, mucilage (rhizome), protein, resins, starches, sterols, volatile oils, tannins, glycosides, and various other substances. Glycyrrhizin , a triterpenoid compound, accounts for the sweet taste of licorice root. This compound represents a mixture of potassium-calcium-magnesium salts of glycyrrhizic acid that varies within a 2–25% range. Among the natural saponin, glycyrrhizic acid is a molecule composed of a hydrophilic part, two molecules of glucuronic acid, and a hydrophobic fragment, glycyrrhetic acid . The yellow color of licorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin and other compounds.

The isoflavones, glabridin and hispaglabridins A and B have significant antioxidant activity , and both glabridin and glabrene possess estrogen-like activity

OCIMUM TENUIFLORUM (Tulsi):-

Fig6)

Kingdom :-Plantae
Order :-Lamiales
Family :-Lamiaceae
Genus :-Ocimum
Species :-O. tenuiflorum

Chemistry of Ocimum tenuifolium :-

Phytochemical studies have shown that oleanolic acid, ursolic acid rosmarinic acid, eugenol ,carvacrol, linalool, and β-caryophyllene are some of the main chemical constituents of Tulsi.

MENTHA PIPERITA (papermint) :-

Fig 7) MENTHA PIPERITA

Kingdom :-Plantae
Order :-Lamiales
Family :-Lamiaceae
Genus :-Mentha
Species :-M. × piperita
Chemistry of Mentha piperita :-
The main constituents were menthol (40.7%) and menthone (23.4%). Further components were (+/-)-menthyl acetate, 1,8-cineole, limonene, beta-pinene and beta-caryophyllene.

BACOPA MONERI (Bramhi) :-

Fig 8) BACOPA MONERI

Kingdom :-Plantae
Order :-Lamiales
Family :-Plantaginaceae
Genus :-Bacopa
Species :-B. monnieri
Chemistry of Bacopa moneri :-
Nicotin,D-Mannitol,Bacoside,Bacopasaponin A,Bacopasaponin B,Bacopasaponin C,Bacopasaponin D,Bacopasaponin E Bacopasaponin F,Bacopasaponin G,Bacopaside I,Bacopaside II,Bacopaside III,Bacopaside IV, Bacopaside V,BacopasideVII,BacopasideXII,Plantainoside B, Betulinic acid Cucurbitacin, CucurbitacinB, CucurbitacinC, Cucurbitacin D Cucurbitacin EStearic acid Rosavin,3,4Dimethoxycinnamic acid,corbic acid,Asiatic acid,Brahmic acid ,Wogonin,Oroxindin,Loliolide,Stigmasterol,,β-sitosterol,Ebelin lactone,Stigmastanol ,Bacosterol,Bacosine, Heptacosane ,Octacosane,Nonacosane, Triacontane4, Hentriacontane, Dotriacontane,Apigenin ,Quercetin,Ursolic acid,Luteolin,Asiaticoside,Bacopaside,Bacopaside.

ALLIUM SATIVUM (garlic) :-

Fig 9) ALLUM SATIVUM

Kingdom :-Plantae
Order :-Asparagales
Family :-Amaryllidaceae
Subfamily :-Allioideae
Genus :-Allium
Subgenus :-A. subg. Allium
Species :-A. sativum
Chemistry of allium sativum :-
The major active components of garlic are its organosulfur compounds, such as diallyl thiosulfonate (allicin), diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), E/Z-ajoene, S-allyl-cysteine (SAC), and S-allyl-cysteine sulfoxide (alliin).

Formulation table per 100ml :-

Sr no.	Name of ingredient.	quantity taken
1.	Tulsi.	-. 3 gm
2.	Ginger	-. 3 gm
3.	Liquorice.	- 3 gm
4.	Turmeric.	-. 2 gm
5.	Papermint.	-. 2 gm
6.	Bramhi.	- 2 gm
7.	Garlic.	- 2 gm
8.	Neem.	-. 1 gm
9.	Sodium benzoate	- qs

Materials and method :-
Ingredients used :-
1) Tulsi :-
Tulsi is known to have blood-thinning properties and it should not be taken by people who are already on anti-clotting medications.
Used part :- leaves

Qty. :- 3 gm

2) **Ginger :-**

Ginger contains gingerols and shogaols that prevent blood cells from clotting and acts as a natural blood thinner.

Also a good antioxidant.

Used part :- Root powder

Qty. :- 3gm

3) **Liquorice**:-

Licorice is derived from the root of the plant, Glycyrrhiza glabra. The components of its extract inhibit the P450 system enzymes that metabolize Warfarin, inhibit thrombin, and prolong fibrinogen clotting times.Studies of licorice have demonstrated properties that can theoretically potentiate anticoagulants.

Part used :- Root powder

Qty :- 3 gm.

4) **Turmeric** :-

Curcumin is an active ingredient in turmeric and appears to have anti-inflammatory and blood-thinning or anticoagulant properties.

Part used :- Root powder

Qty. :- 2gm

5) **Papermint :-**

Increase blood flow and heat to
the area and intensify
Inflammation.
It contains salicylates that is
natural blood thinner.

Part used :- leaves

Qty :- 2 gm

6) Bramhi :-

Antioxidant and neuroprotective: Brahmi is rich in antioxidant compounds that terminate the attack of free radicals and thus reduce the risk of neurodegenerative disorders. Increases Cerebral Blood Flow: Bacopa increases blood flow to the brain.

Part used :- leaves powder

Qty. :- 2gm

7) **Garlic :-**

Garlic is extremely beneficial to the entire cardiovascular system. Chemicals named alliin, allinase, and allicin present in garlic improve blood circulation by thinning the blood.

Part used :- fresh bulb of garlic

Qty :- 2 gm

8) **Neem :-**

Neem leaf extracts might have
potential to help lower blood
preessure.Reduse clotting and
strains on the circulatory system.
Lowers the level of bad

Cholesterol.
Part used :- leaves powder
Qty. :-1 gm
9) **Sodium benzoate :-**
Used as preservative . Prevent from microbial attack. Slow down changes in PH , colour ,tatse , smell ,etc .
Qty. :- q.s

Fig 10) Formulation ingredients

Phytochemical screening :-
Qualitative phytochemical analysis for secondary metabolites was carried out for the crude extracts as per standard methods.

a) Saponin:-
5ml distilled water was added to 1ml plant extract and then shaken well, froth formation took place. Stability of froth confirms the presence of saponin in plant extract.

b) Tannin:-
1ml 5% FeCl3 was added to 1ml plant extract. Appearance of dark blue, black or dark green confirms presence of tannin in plant extract.

c) Flavonoid:-
2ml 1% NaOH was added to 1ml plant extract, presence of yellow colour indicates the in plant extract.

d) Carbohydrate:-
1ml Fehling A and 1ml Fehling B was added to 2ml plant extract and then test tube was heated in water bath for 20 min. Appearance of red precipitate confirms the presence of carbohydrate in plant extract.

e) Protein:-
1ml of 1% CuSo4 and 1ml of 1% NaOH was added to 2ml plant extract. Appearance of purple color confirms the presence of protein in plant extract.

f) Alkaloid :-
1ml iodine was added to 1ml plant extract. Appearance of reddish brown precipitate confirms the presence of alkaloid in plant extract.

g) Starch :-

1ml iodine was added to 1ml plant extract. Appearance of blue or black color confirms the presence of starch in plant extract.

h) Fat Test:-

1mL of distilled water and few drops of ethanol were added to 1mL of plant extract. The white color precipitate formed showed the presence of fat in the plant extract.

i) Terpenoid Test:-

250µl chloroform was added to 500 µl plant extract then 625 µl Conc. H_2SO_4 was added to the solution. Reddish brown ppt, of the solution confirms presence of terpenoids.

Procedure :-

- Weigh accurately all the ingredients
- All the ingredients are added in RBF.
- 500 ml water added in the RBF.
- Reflux condenser is attached and all mixed material boiled for 3 hours.
- Boil until the one fourth part of solution is remained the liquid extract was cooled and filtered.
- The sodium benzoate added q.s.

Flowchart of procedure :- fig 11)

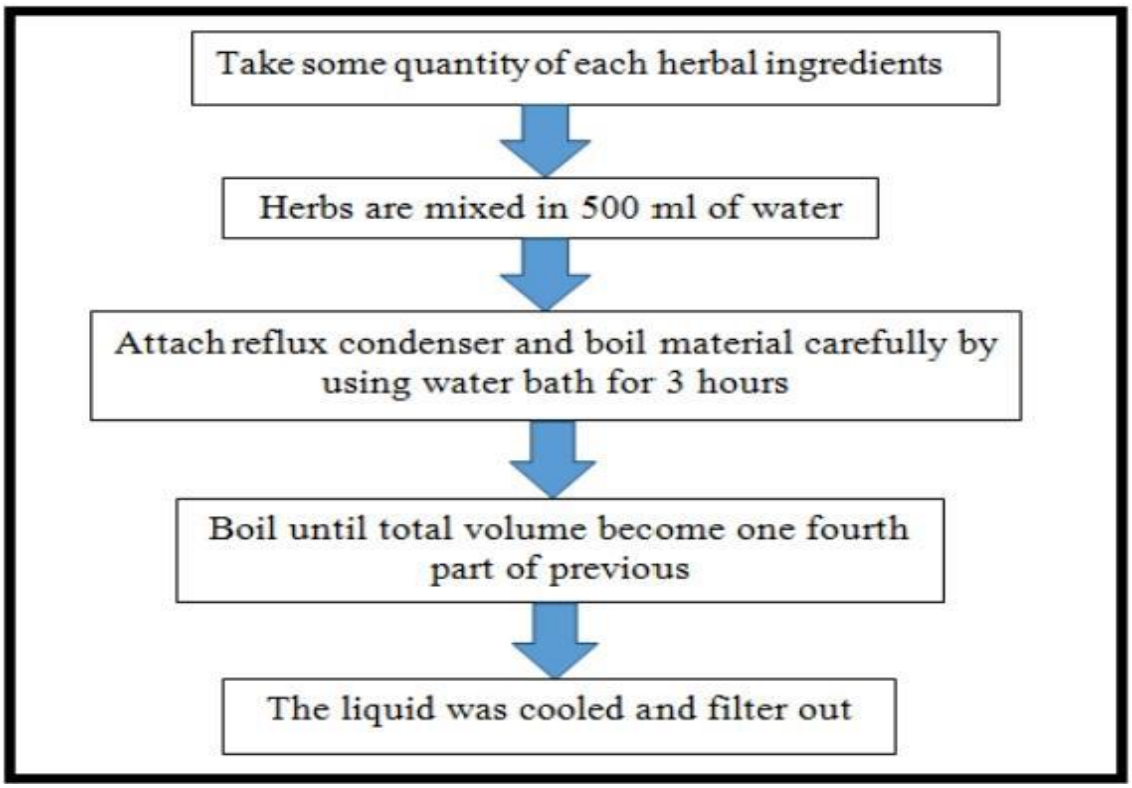

Fig 12) preparation of Formulation

Post formulation evaluation parameters of final extract.

A)Test Procedure Colour examination

1. 5 ml of prepared syrup was taken on a watch glass
2. Watch glass placed against white background in white tube light.
3. Colour was observed by naked eyes.

B)Odour examination

1. 2ml of prepared syrup was taken and smelled by individually
2. The time interval between 2 smelling was 2 minutes to nullify effect of previous smelling

C)Taste examination

1. A pinch of final syrup was taken and examined on taste buds of the tongue.

D) Stability study

1. Final syrup was taken in amber colour bottle.
2. Kept at accelerated temperature at 40oC, Room temperature and 47oC respectively.
3. Sample was tested all physicochemical parameters and turbidity at the interval of 24 hours, 48 hours and 72 hours t

RESULTS:-

Post formulation evaluation parameters :-

Organoleptic evaluation :-

Test	Observed value
Colour	Yellowish-Brown
Odour	Aromatic
Taste	Slightly pungent

Table 1) organoleptic evaluation

Stability testing :-

Time Duration (Hour)	Temperature (^{O}C)	Turbidity	Colour/Odour
24	4 ^{0}C	No Turbidity	No Change
24	RT	No Turbidity	No Change
24	47 ^{0}C	No Turbidity	No Change
48	4 ^{0}C	No Turbidity	No Change
48	RT	No Turbidity	No Change
48	47 ^{0}C	No Turbidity	No Change
72	4 ^{0}C	No Turbidity	No Change
72	RT	No Turbidity	No Change
72	47 ^{0}C	No Turbidity	No Change

Table 2) stability testing

Test for phytochemical screening:-

Name of phytochemical.	Test result
Saponin.	:- Positive
Tanin.	:-. Positive
Flavonoid.	:-. Positive
Carbohydrate.	:-. Positive
Protein.	:- Positive
Alkaloid.	:-. Positive
Starch.	:- Positive
Fat.	:-. Positive
Terpenoid.	:-. Positive

DISCUSSION :-

In today's era the herbal products are the symbol of safety in contrast to the synthetic drugs which are regarded as unsafe due to multiple adverse and side effects .Although, herbs had been priced for their medicinal, flavouring and aromatic qualities for centuries. It's time to promote them globally.The prepared polyherbal extract have the property to lysis the clot formed and might be used in the prognosis of pulmonary embolism. The extract shows the blood thinning properties as well as the research shown that the herbs included in above extract are showing blood thinner, Antioxidant , Anti-inflammatory activities additionally and to minimise the side effects the quantity of drugs taken less as compared to the formulations which are surveyed.

CONCLUSION:-

Polyherbal extract showing the clot dissolving , blood thinning and Antioxidant activity for the prognosis of pulmonary embolism were prepared and stability were studied,and the results obtained are as per the desired standards. However more work need to be done in this perticular area to enhance the compliance.We will able to standardize the formulation and it's specificity with the users with the use of many factors like colour,taste, aroma etc.

Fig13) Formulation

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