IMMUNOMODULATORYACTIVITYOFLEAVESOF*RUMEXVESICARIUS*LINN.AND *SYMPLOCOSRACEMOSA*ROXB.

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ABSTRACT:Objective: In order to find out how Rumexvesicarius Linn. andSymplocosracemosaRoxb. leaves affect the immune system, we used the following methods:TheRumexVesicarius Linn. ethyl acetate and ethanolic extract, as well as the SymplocosracemosaRoxb. ethanolic and N-hexane extract, were given orally to rats at doses of 200 mg/kg/day and 400 mg/kg/day, respectively, based on their body weight. Evaluations of theThe carbon clearance test and the delayed type hypersensitivity test were used to measure the immunomodulatory action. The results demonstrated a substantial increase in phagocytic activity and DTH response in rats when the extracts of Rumexvesicarius Linn. andSymplocosracemosaRoxb. were administered orally at an experimental dosage ($P < 0.0001$). Acute toxicity and preliminary phytochemical screening are also part of the research. Results suggest that both humoral and cell-mediated immunity are significantly impacted by the immunomodulatory effects of the Rumexvesicarius Linn. andSymplocosracemosaRoxb. extracts, according to the study's conclusion.

Keywords:*Rumexvesicarius*Linn.,*Symplocosracemosa*Roxb.,CarbonClearanceTest,DelayedTypeHypersensitivitytest

INTRODUCTION: Theimmunesystemisaremarkablyversatiledefensesystemthathasevolvedtoprotectanimals frominvadingpathogenicmicroorganismstoeliminatethedisease. It is able to generate a multifarious varietyofcellsandmoleculescapableofspecificallyrecognizingandeliminatingvarietyofforeigninvaders[1].Itisnow beingrecognizedthatmodulationofimmunologicalresponsecouldprovide an alternative to conventional chemotherapyforavarietyofdiseasedconditionsofimpairedimmuneresponsivenessorwhenaselectiveimmunosup pression has to be induced in situationslikeautoimmunedisordersandorgantransplantation.

The modulation of the immune response by usingAyurvedicherbalmedicationsasapossibletherapeutic measure has now become a subject ofscientificinvestigation.Oneofthetherapeuticstrategies in Ayurvedic medicines is to enhance thebody'soverallnaturalresistancetothediseasecausing agent rather than directly neutralizing theagent itself [2]. Immunomodulation is the process ofmodifyinganimmuneresponseinapositive(immunostimulation)ornegativemanner(immunosuppressant)bya dministrationofadrugorcompound [3].

Therearemanyplantswhichareusedasimmunomodulators.*Heterostemmatanjorense*showsimmunostimulanta ctivityagainstAzathioprine administered rats[4]. The methanolicrootextractof*Withaniasomnifera*showsimmunostimulatoryactivitiesindexamethasoneinducedim munocompromisedmiceandinvitromodel [5]. The Methanolic leaf extract of *Moringaoleifera*showsanimmunostimulatoryeffecton

boththecell-mediatedandhumoralimmunesystems in the Wistar albino rats [6]. The methanolicleafextractsof*Cameroonian*medicinalplantspossess immunomodulatory activity [7].The ethanolicextractof*Sonerilatinnevelliensis*showedastimulatoryeffectonbothhumoralandcellularimmune functions in animal models [8]. *Caesalpiniasappan*shows the nonspecific immunomodulatoryeffectonmurineperitonealmacrophages[9].Theaqueousleafextractof*Ocimumbasilicum*Linn.i sa potent immunostimulant, stimulating specific andnonspecificimmunemechanisms.Theimmuno-stimulatoryactivityof*O.basilicum*isduetoflavonoids (quercetin), alkaloids, tannins, saponinglycosidesand phenoliccompounds[10].

The methanolic extract of *Trigonellafoenum*wholeplanthasshownsignificantimmunostimulatoryactivityinvariousmodelsofDrug-inducedmyelosuppression[11]. The flavonoids isolated fromfreshlyharvestedleavesof*Prosopisspicigera,Mimusopselengi*and*Terminaliaarjuna*showeddose dependent immunosuppressive activity [12]. Thecrude terpenoids extract from the leaves of *Emblicaofficinalis, Ficusracemosaand Strychnosnux-vomica* onhumanwholeblood stimulatedwithhepatitisBvaccine possessimmunosuppressiveactivity[13].

Theaqueousextractof*Leucasaspera*wasevaluatedincyclophosphamide-inducedimmunosuppressive mice and it shows prominentimmunostimulatoryeffect[14].Theleavesof*Calotropisgigantea*, *C. rotang*and *A. integrifolia*have an immunosuppressive activity of the variabledosesofcrudesaponin(0.625–2.5mg)onlymphocytes,monocytesandgranulocytes [15].

Triptolide, the active component of *Tripterygiumwilfordii*can be used alone or in combination withexisting therapeutic modalities as novel treatmentsforautoimmunedisorders,cancers,andforimmunosuppression [16]. The ethanolic extracts fromleavesof *Rhaphidophorakorthalsii*stimulateimmune cell proliferation, peripheral blood NK cellpopulation [17]. Cyclotides, ribosomally synthesizedplantpeptides havegrowth-inhibitingeffectsonprimary cells of the human immune system [18]. Theisogarcinol,activecompoundfrom*Garciniamangostana*L. inhibiteCalcineurin unique proteinphosphatase,playsanimportantroleinimmuneregulation in a dose-dependent manner [19]. Naturaltherapieshelptoregulatetheimmunesystem'saggressive behavior without suppressing necessarydefenses [20].

For this study we have selected two plants, *Rumexvesicarius*Linn.and*Symplocosracemosa*Roxb.

*Rumexvesicarius*Linn.(Chooka)belongstoperennialherbstothefamily Polygonaceae.Theplantisanerectusuallywithalongtaproot.Traditionallytheplantisusedasstomachic,Diuretic,usedforthedisordersofthelymphaticandglandularsystem,forbronchitis,asthma,constipation,dyspepsiaandthediseasesoftheliver. Plant leaves are rich in ascorbic acid, citricacid and tartaric acid, it also contains glycoside,alkaloid,flavonoids,tanninsandphenoliccompounds[21,22].

*Symplocosracemosa*Roxb. (Lodhra) belongs to thefamilySymplocaceae,isasmallevergreentreeupto 6 m tall. In traditional system it is mainly usedascardiotonic,antipyretic,antihelminticandlaxative properties. It is beneficial in billow fever,urinary discharge; pharmacologically it is used asantimicrobial,antidiarrhoeal,spasmogenicandheartdepressant.Theplantmainlycontainsmonomethylpelargonidingluocosides,loturidinealso contain oxalic acid, phytosterol, ellagic acidsandoleanolicacid[23,24,25].

MATERIALSAND METHODS:

PlantMaterial: Thefreshleavesof*Rumexvesicarius*and *Symplocosracemosa*Roxb.used inthis study, collected at the flowering stage (Month:August - November) from the local area of SangliandSatara,Maharashtrastate,Indiarespectivelyandauthenticatedby BotanicalSurveyofIndia,Pune, Maharashtra. (BSI/WRC/Iden./2015 dated 4-12-2015)

Extraction: The leaves were separated from freshstems and dried under shade at room temperatureuntilitbecomescompletelydry.Afterdryingleaves were subjected to size reduction. The shade-driedcoarselypowderedleaves(500g)weresubjectedto Soxhlet extraction.

A) *Rumexvesicarius*Linn.leavesweresubjectedtoSoxhletextractionwith95%ethanolandethyl

acetate to obtain ethanolic and ethyl acetate extractrespectively.

B) *Symplocosracemosa*Roxb.leaveswereSubjected to Soxhlet extraction with 95% ethanolandN-hexanetoobtainethanolicandN-hexaneextractrespectively.Theextractsobtainedweresubjected to the Rotary flash evaporator to removeexcessofsolventanddriedextractswerestoredinacoolplaceintightpackcontainerforfurtheruse.

Animals: Alltheexperimentswerecarriedoutusingmalealbinoratsofwistarstrain.Weightaround150-200gm.Theanimalsarefreetoaccessoffoodandwater,andtheywerehousedina natural (12 h each) light-dark cycle. The animalswereacclimatizedforatleast5daystothelaboratory conditionsbefore the experiment.Theexperimentalprotocolwasapprovedbytheinstitutionalanimalethicscommittee(IAEC/ABCP/09/2016-17)andthecareoflaboratoryanimal was taken as per the guidelines of CPCSEA,theministryofforestsandenvironmentgovernmentofIndia.

PreliminaryPhytochemicalScreening: Alltheextractsweresubjectedtopreliminaryphytochemicalscreeningusingthemethoddescribedby Kokate,TreaseandEvansforthedetection of various plants constituents. Test werecarriedoutforthepresenceorabsenceof Phytoconstituentslikeglycosides,flavonoids,saponins, alkaloids, carbohydrates, sterols, phenoliccompound and reducingcompounds[26,27,28].

Drugs and Chemicals: All the drugs and Chemicalwere of analytical grade while the other drugs wereprocured from - Levamisole (Johnson and JohnsonLtd.,) Cyclophosphamide (Biochem pharmaceuticalindustriesLtd.,)Colloidalcarbon(Indianink,CamelIndiaPvt.Ltd.,).

Selectionofdoses: AcuteToxicity studieswereperformedaccordingtotheorganizationforeconomiccooperationanddevelopment(OECD)guideline(425).Formacutetoxicitystudytherewas no mortality and physical/behavioral changesshowed after administration of all the extract over14 days at the dose of 2000 and 5000 mg/kg to adifferent group of rat weight around 150 - 200 gm.Theexperimentswereperformedaftertheexperimental protocols had been approved by theinstitutionalanimal ethical committee.

PharmacologicalScreening: Theimmuno-modulatory activity is carried out by using Carbonclearancetest.(TestforPhagocytosis)andDelayed-TypeHypersensitivityReaction.

Carbon Clearance Test: (Test for Phagocytosis):Procedure:

- Inthistest,animalsweredividedinto11groupcomprising6 animals ineach.

TABLE1:TREATMENTGROUPSOFCARBONCLEARANCETEST

Groups	Treatment	Doseandrouteofadministration
GroupI	Vehicle	10ml/kgP.O.
GroupII	Standarddrug(Cyclophosphamide)	50mg/kgP.O.
GroupIII	Standarddrug(Levamisole)	2.5mg/kgP.O
GroupIV	Ethylacetateextractofleavesof*Rumexvesicarius*L.(EARV-400)	400mg/kgP.O.
GroupV	Ethylacetateextractofleavesof*Rumexvesicarius*L.(EARV-200)	200mg/kgP.O.
GroupVI	Ethanolicextractofleavesof*Rumexvesicarius*L.(ERV-400)	400mg/kgP.O.
GroupVII	Ethanolicextractofleavesof*Rumexvesicarius*L.(ERV-200)	200mg/kgP.O.
GroupVIII	Ethanolicextractofleavesof *Symplocosracemosa*Roxb.(ESR-400)	400mg/kgP.O.
GroupIX	Ethanolicextractofleavesof*Symplocosracemosa*Roxb.(ESR-200)	200mg/kgP.O.
GroupX	n-hexaneextractofleavesof*Symplocosracemosa*Roxb.(NSR-400)	400mg/kgP.O.
GroupXI	n-hexaneextractofleavesof*Symplocosracemosa*Roxb.(NSR-200)	200mg/kgP.O.

- Carboninksuspensionwasinjectedviatailvein to each rat 48 hours after the five daystreatment
- Bloodsamples(25µl)werethenwithdrawnfromtheretro-orbitalplexuswithmildetheranesthesiaat5and15minafterinjectionofcolloidalcarboninklysedin0.1%sodiumcarbonatesolution (3ml).
- The optical density was measuredspectrophotometricallyat660 nm.
- Thephagocyticactivitywascalculatedusingthe followingformula[29,30].

$$K = \frac{\text{LogOD1} - \text{LogOD2}}{t_2 - t_1}$$

Where ODI and OD2 are the optical density at timet$_1$ and t_2, respectively.

Preparation of Carbon Ink Suspension: Camlinink was diluted eight times with saline and used forcarbon clearance test in a dose of 10 µl/gm bodyweightofrat[31].

Statistical Analysis: The result was expressed asmeanvalue±SEM.Thevariationinasetofdatahas been estimated by performing one-way analysisof variation (ANOVA). Individual comparison ofgroup mean value were done using Dunnet's test.The P value < 0.05, were considered statisticallysignificant.

Delayed Type of Hypersensitivity Reaction:Procedure:

- Inthistest,animalsweredividedinto11groupcomprising6 animals ineach.

TABLE2:TREATMENTGROUPSOFDELAYEDTYPE HYPERSENSITIVITY

Groups	Treatment	Doseandrouteofadministration
GroupI	Vehicle	10ml/kgP.O.
GroupII	Standarddrug(Cyclophosphamide)	50mg/kgP.O.
GroupIII	Standarddrug(Levamisole)	2.5mg/kgP.O
GroupIV	Ethylacetateextractofleavesof*Rumexvesicarius*L.(EARV-400)	400mg/kgP.O.
GroupV	Ethylacetateextractofleavesof*Rumexvesicarius*L.(EARV-200)	200mg/kgP.O.
GroupVI	Ethanolicextractofleavesof*Rumexvesicarius*L.(ERV-400)	400mg/kgP.O.
GroupVII	Ethanolicextractofleavesof *Rumexvesicarius*L.(ERV-200)	200mg/kgP.O.
GroupVIII	Ethanolicextractofleavesof*Symplocosracemosa*Roxb.(ESR-400)	400mg/kgP.O.
GroupIX	Ethanolicextractofleavesof*Symplocosracemosa*Roxb.(ESR-200)	200mg/kgP.O.
GroupX	N-hexaneextractofleavesof*Symplocosracemosa*Roxb.(NSR-400)	400mg/kgP.O.
GroupXI	N-hexaneextractofleavesof*Symplocosracemosa*Roxb.(NSR-200)	200mg/kgP.O.

- Immunized Rat with 0.1ml of 20% SRBCS innormalsaline intraperitoneally on14th day ofthe study. On day 21st, animals from all groupsget challenge with 0.03 ml of 1% SRBCs in subplantar region of the right hind paw. Footpadreaction was assessed after 24 hrs*i.e.* on the22nd day.Increaseinfootpadedemawasmeasuredwith thehelp of verniercaliper [29].

AntigenicMaterial:

PreparationofSheepRBCs: SheepbloodwascollectedinsterileAlsever'ssolutionin1:1proportion,Alsever'ssolution(freshlyprepared)blood was kept in the refrigerator and processed forthepreparationofSRBCsbatch,bycentrifugationat2000rpmfor10minandwashingwithphysiologicalsaline4-5timesandthensuspendinginto bufferedsalineforfurther use[31].

CompositionofAlsever'sSolution:

TABLE3:COMPOSITIONOFALSEVER'SSOLUTION

Chemicals	Quantity(g/L)
SodiumChloride	4.2
SodiumCitrate	8.0
Citricacidanhydrous	0.55
Glucose	20.5
Distilled waterq.s.	1000ml

Statistical Analysis: The result was expressed asmean value ± SEM. The variation in a set of datahas been estimated by performing one-way analysisof variation (ANOVA). Individual comparison ofgroup mean value were done using Dunnett's test.The P value < 0.05, were considered statisticallysignificant.

RESULT:

AcuteOralToxicityStudy: Acuteoraltoxicitywas carried out by the up-down method. It is foundthat all extract (EARV, ERV, ESR and NSR) weresafeatlimitdose 4000mg/kg and2000mg/kg,with no mortality and physical/behavioral changes.1/10th of this dose *i.e.* 400 mg/kg and 200 mg/kgwereused in thesubsequent study.

Preliminary Phytochemical Study: The presenceofvariousphytoconstituentsoftheextractwasdetected by phytochemical screening. The EARVfound to contains Alkaloids, Flavonoids, Tannins,Sterols,CarbohydrateandVitaminC.ERVcontains Alkaloids, Flavonoids, Carbohydrate andVitaminC.ESRfoundtocontainCardiacglycoside,Flavonoids,Alkaloids,TanninsandCarbohydrate.NSRcontainscardiacglycoside,alkaloidsand steroids.

Carbon Clearance Test: Effect of EARV, ERV,ESR, and NSR on the phagocytic activity by thecarbonclearancetestisshowninTable4.Thephagocyticactivityofthereticuloendothelialsystemisgenerallymeasuredbytherateofremoval of carbon particles from the bloodstream.IncarbonclearancetestEARV,ERVandESR,

TABLE4:RESULTOFCARBONCLEARANCE TEST

treatedallgroupsexhibitedsignificantlyhighphagocytic index (P < 0.0001) when compared withcontrol group. While NSR treated group showed asmallincreaseintheirphagocyticindexwhencomparedwithcontrolgroup.Thisindicatesstimulationofthereticuloendothelial system.

S.no.	Groups	Treatments	Doseandrouteofadministration	Phagocytic index(Mean± SEM)
1	I	Control	10ml/kg(P.O.)	0.0312±0.0005
2	II	Standard(Cyclophosphamide)	50mg/kg(P.O.)	0.0206±0.0005****
3	III	Standard(Levamisole)	2.5mg/kg(P.O.)	0.0573±0.0003****
4	IV	Ethylacetateextractofleavesof *Rumexvesicarius*L.(EARV-400)	400mg/kg(P.O.)	0.0530±0.0004****
5	V	Ethylacetateextractofleavesof *Rumexvesicarius*L.(EARV-200)	200 mg/kg(P.O.)	0.0492±0.0004****
6	VI	Ethanolicextractofleavesof*Rumex vesicarius*L.(ERV-400)	400mg/kg(P.O.)	0.04566±0.0005****
7	VII	Ethanolicextractofleavesof*Rumex vesicarius*L.(ERV-200)	200mg/kg(P.O.)	0.0414±0.0003****
8	VIII	Ethanolicextractofleavesof *Symplocosracemosa*Roxb.(ESR-400)	400mg/kg(P.O.)	0.0391±0.0003****
9	IX	Ethanolicextractofleavesof *Symplocosracemosa*Roxb.(ESR-200)	200mg/kg(P.O.)	0.0363±0.0004****
10	X	N-hexaneextractofleavesof *Symplocosracemosa*Roxb.(NSR-400)	400mg/kg(P.O.)	0.0350±0.0002****
11	XI	N-hexaneextractofleavesof *Symplocosracemosa*Roxb.(NSR-200)	200mg/kg(P.O.)	0.0327±0.0002

Valuesareexpressedas(Mean±SEM).N=6****P<0.0001.StatisticallysignificantwhencomparedwithcontrolgroupbyANOVAfollowed byDunnett'stest.

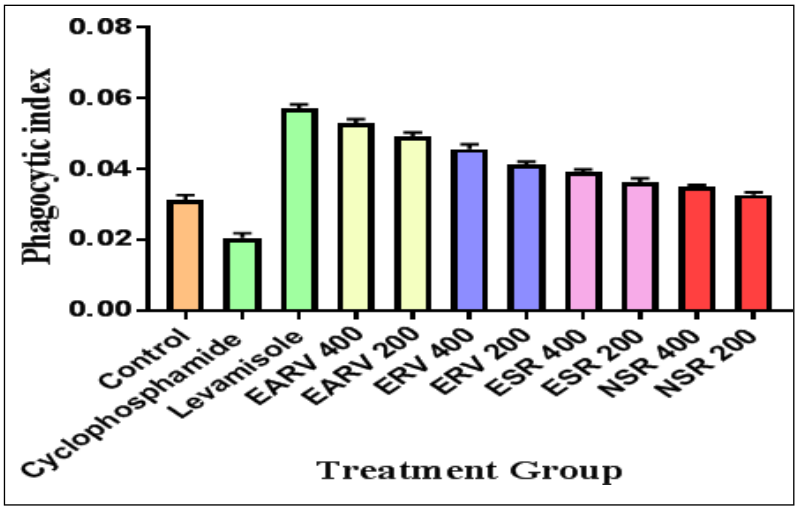

FIG.1:GRAPHICALREPRESENTATIONOFCARBONCLEARANCETEST

DelayedTypeofHypersensitivityReaction: Effect of EARV, ERV, ESR and NSR on the cell-mediated immune response by DTH induce footpadedemaisshowninTable5.AlltreatedgroupEARV,ERVandESRshowedthesignificantly($p < 0.0001$) potentiating DTH response in terms ofincreaseinthemeandifferenceofpawedemawhencompared with control group. It indicates activationof the cellular immune system. While NSR treatedgroup showed a small increase in footpad oedemawhencomparedwithcontrolgroup.Cyclo-phosphamidetreatedgroupshowedasignificantdecreaseinthemeandifferenceofpawedemawhencompared with control group.

TABLE5:RESULTOFDTH

S. no.	Groups	Treatments	Dose and route ofadministration	MeanDifferenceinPawedema(Mean±SEM)
1	I	Control	10ml/kg(P.O.)	1.508±0.0316
2	II	Standard(Cyclophosphamide)	50mg/kg(P.O.)	0.59±0.0513****
3	III	Standard(Levamisole)	2.5mg/kg(P.O.)	4.56±0.0594****
4	IV	Ethylacetateextractofleavesof*Rumex vesicarius*L.(EARV-400)	400mg/kg(P.O.)	4.20±0.0545****
5	V	Ethylacetateextractofleavesof*Rumex vesicarius*L.(EARV-200)	200mg/kg(P.O.)	3.66±0.123****
6	VI	Ethanolicextractofleavesof*Rumex vesicarius*L.(ERV-400)	400mg/kg(P.O.)	3.22±0.0519****
7	VII	Ethanolicextractofleavesof*Rumex vesicarius*L.(ERV-200)	200mg/kg(P.O.)	2.51±0.0586****
8	VIII	Ethanolicextractofleavesof*Symplocos racemosa*Roxb.(ESR-400)	400mg/kg(P.O.)	2.29±0.0152****
9	IX	Ethanolicextractofleavesof*Symplocos racemosa*Roxb(ESR-200)	200mg/kg(P.O.)	2.08±0.0345****
10	X	N-hexaneextractofleavesof*Symplocos racemosa*Roxb (NSR-400)	400mg/kg(P.O.)	1.90±0.0085****
11	XI	N-hexaneextractofleavesof *Symplocos racemosa*Roxb.(NSR-200)	200mg/kg(P.O.)	1.74±0.02986*

Valuesareexpressedas(Mean±SEM).n=6****P<0.0001.StatisticallysignificantwhencomparedwithcontrolgroupbyANOVAfollowed byDunnett'stest.

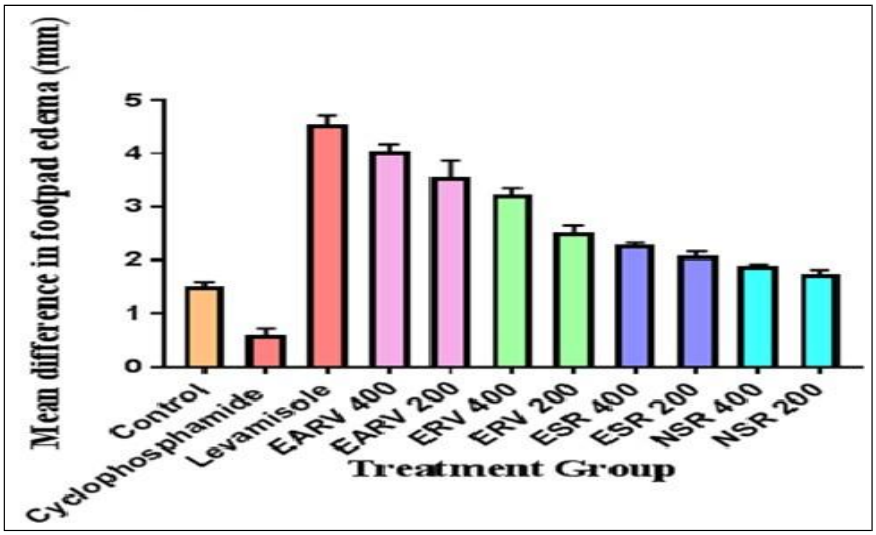

FIG.2:GRAPHICALREPRESENTATIONOFDTH

DISCUSSION: Theimmunesystemisaremarkablyversatilesystemthathasevolvedtodefend itself against a vast range of harmful agents.Itisable togenerate anenormous variety of celland molecules capable of specifically recognizingandeliminatingavarietyofforeigninvaders.Immunomodulatorsareanaturalorsyntheticsubstance that helps to regulate or normalize theimmunesystem.Immunomodulatorscorrectimmunesystemsthatareoutofbalance.Andimmunomodulation is a process which can alter theimmunesystemspecificallyimmunostimulationandimmunosuppressant.

Thepresentstudywasdesignedtoexploretheimmunomodulatoryactivityof*Rumexvesicarius*Linn. and*Symplocosracemosa*Roxb. In this studyCarbonClearanceTestandDelayedTypeHypersensitivity testwereselectedforevaluationof immunomodulatory activity of *Rumexvesicarius*Linn.and*Symplocosracemosa*Roxb.

According to SmrithiTripathi*et al*., the Phagocyticactivity of reticuloendothelial system was assayedbycarbonclearancetestphagocyticindexwascalculatedastherateofcarboneliminationofreticuloendothelialsystem.

In the present study after oral administration of alltheextract(EARV,ERV,ESRandNSR)atanexperimentaldose(400mg/kgand200mg/kg)showedasignificantincreaseinthephagocyticindex ($P < 0.0001$) when compared with controlgroup. Increase in phagocytic activity indicates thattherewasstimulationofreticuloendothelialsystem.

According to N. L. Dashputre*et al*., Cell-mediatedimmunityinvolvestheinteractionofeffectorsmechanism carried out by T lymphocytes and theirproducts(lymphokines).DTHrequiredspecificrecognition of antigen by activated T lymphocytes,whichsubsequentlyproliferateandreleasecytokines.Theseinturnincreasevesselpermeabilitycause vasodilatation,macrophageaccumulation, and activation promoting phagocyticactivityandincreasedconcentrationoflyticenzyme for more effective killing. The delay in theonset of the response reflects the time required forthecytokinestoinducetherecruitmentandactivationofmacrophages.ThereforeincreaseinDTH response after oral administration of all theextract(EARV,ERV,ESRandNSR)atexperimentaldose(400mg/kgand200mg/kg)showedasignificantincreaseinfootpadedema($P < 0.0001$)whencomparedwithcontrol.Itisindicatestimulationofthecell-mediatedimmunity.

ThePresentstudyrevealedthatethylacetateextract of *Rumexvesicarius*Linn. showed highestimmunomodulatoryactivity.

Inthisstudy,theoverallorderofimmuno-modulatoryactivitywasestablishedasEARV>ERV >ESR>NSR.

CONCLUSION: Both humoral and cell-mediated immunity were found to be significantly impacted by the present study'sethanolic and methyl acetate extracts of Rumexvesicarius Linn. andSymplocosracemosaRoxb. leaves, respectively. This was attributed to the following mechanisms:

- The activation of T-cells, which mediated the DTH response;
- The activation of the reticuloendothelial system.
- Raise the efficiency of the macrophage system's monocytes.

Additionally, when comparing the immunomodulatory activity of the four extracts (EARV, ERV, ESR, and NSR), the ethyl acetate extract of Rumexvesicarius Linn. leaves (EARV) exhibited the highest activity at the experimental dosage. As a whole, EARV is more immunomodulatory than ERV, ESR is more immunomodulatory than NSR, and so on. Its precise immunomodulatory effect mechanism may be determined by a thorough examination.

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