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EMBLICA OFFICINALIS ENHANCES CARDIAC TISSUE REGENERATION IN TADPOLES OF THE FROG RANA CYANOPHLYCTIS (SCHNEIDER)

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Keywords:

Emblica officinalis, cardiac tissue regeneration, *in vivo*

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ABSTRACT: *Emblica officinalis* and its derivative (Ascorbic acid) have profound effect on development and regeneration and are widely used in the Indian System of medicine for the treatment of different type of disease. Here, we discussed the comprehensive account of the effect of aqueous extract of the fruit of *E.officinalis* with special reference to cardiac tissue regeneration in frog tadpoles. *E.officinalis* was found to be a good model to accelerate regeneration ability of infracted cardiac cells which further give rise to intact cardiac part (intact ventricle part) in all mode of experiment employed i.e insitu (*in vivo*), in transplantation setup and in culture medium. The most spectacular case was rhythmic beating of implanted cardiac tissue at ectopic site of tail of *E.officinalis* treated tadpoles. The *E.officinalis* supplemented cultures were also appeared to be a suitable for investigating the changes occurred during regeneration and differentiation of cardiac muscles.

INTRODUCTION: Amla (*Emblica officinalis*) is considered as vital drug in Ayurveda- an Indian indigenous system of medicine. It has its beneficial role in cancer, diabetes, liver treatment, heart trouble, ulcer, anemia and various other diseases. Ascorbic acid is a chemical constituent of *E.officinalis*. Treatment of ascorbic acid markedly increased the proportion of Enhanced green fluorescent protein (EGFP) positive cells containing cardiac myocytes[1]. It also increases the proliferation of cardio progenitor cells via the mitogen-activated protein kinases-extracellular signal-regulated kinases (MAPK-ERK) pathway by promoting collagen synthesis. In addition, Ascorbic acid induced cardiomyocytes showed better sarcomeric stimulation[5].

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Chronic administration of *E.officinalis* produces myocardial adaption by augmenting endogenous antioxidants and protect rat heart from oxidative stress associated with IRI[10]. Banot et al.[1] reported that *E.officinalis* induced lens regeneration in different developmental stages of the toad *Bufo meleanstitus*. Juce of *E.officinalis* may be beneficial for the treatment of myocardial damage associated with type-1 diabetes mellitus[12]. Ojha et al [9] studied the cardioprotective effect of *E.officinalis* on induced cardiotoxicity in rats and the result obtained conform the restoration of hemodynamic and left ventricular function along with significant preservation of antioxidents.

Emblica increase cellular proliferation and cross linking of collagen at the wounded site. It accelerate wound concentration and closure[13]. It was also reported by several workers that chemicals or drugs which accelerate dedifferentiation and proliferation of cells are beneficial to regeneratio[2, 3, 4, 6, 7, 8, 11, 15]. The cited references motivate to explore more knowledge

regarding the role of Emblica in cardiac regeneration.

MATERIALS AND METHODS:

Experimental animals employed:

Young (3 toe stage) tadpoles of the frog, *Rana cyanophlyctis* were used as experimental animals. Tadpoles were fed on half boiled spinach leaves. Tadpoles were anaesthetized in 1:2000 MS222 solution before operation and fixation. Experiments were conducted at room temperature (35^0C -37^0C).

Preparation of Emblica solution:

Fine meshed fruits of *Emblica officinalis* (100g) was mixed with two liter of tap water and kept for 24 hours. The solution was boiled in pressure cooker. The vapours of such solution were condensed to get its watery form and were collected in sterilized beaker. This extract was treated as standards solution (Aqueous Extract of *Emblica officinalis*).

To study the effect of *Emblica officinalis* on cardiac tissue regeneration, three experiments were conducted.

Experiment I: *In vivo* study of *Emblica officinalis* on heart regeneration.

Animals employed: 60 young 3 toe stage tadpoles of the frog, *Rana cyanophlyctis.*

Operation:

Anesthetized tadpoles were secured ventral side up in a slotted moist cotton pad. Sterilized forceps were used to penetrate the skin, muscles and pericardial sac. A tip of ventricle (almost 20 %) was cut with irridectomy scissors (**Fig. 1**). After surgery tadpoles were immediately returned to either tap water (for control group) or *E.officinalis* (5 ml of standard solution/500ml of tap water) solution for treated group.

The operated animals were preserved at different time intervals in Bouin's solution for histological evaluation. Experiments were terminated on day 20 after operation.

Experiment II: Study of cardiac tissue regeneration at ectopic site of tail of frog, *Rana cyanophlyctis* under the influence of *Emblica officinalis*.

Animals employed: 60 young 3 toe stage tadpoles of the frog, *Rana cyanophlyctis.*

Operation:

Preparation of Explants:

Meshed ventricular parts of heart of young (3 toe stage) tadpoles were used as explants. For this purpose ventricular parts of heart were taken out from 5 donor young tadpoles, pooled them in 2 ml saline solution and meshed or subjected to homogenization and there after tissue were used as explants.

Preparation of Recipients:

Young (3 toe stage) and mature (5 toe stage) tadpoles were treated as recipients or host animals. The animals were anesthetized (1:4000 MS222 solution Ethyl-m-amino benzoate methane sulfonate) before operation.

Implantation:

A pit of about 1mm deep was made by a sharp sterile needle at mid lateral position (towards the trunk) of the tail and a pin head size meshed cardiac tissue implanted into the pit on recipient tadpoles tail (**Fig. 7).** After insertion of the cardiac tissue explant, skin flap was covered over it. Half of the operated tadpoles were reared in *Emblica officinalis* solution for first 3 days and then transferred in tap water. Remaining were not treated with *E. officinalis* . Operated tadpoles of both series were fixed in Bouin's solution for 24 hours on day 5, 10 and 20 after operation for histological evaluation.

Experiment III:

In vitro study of cardiac tissue regeneration in *Emblica officinalis* supplemented culture medium.

Preparation of Explants:

Meshed ventricle tissue of young tadpole was employed as explant. For this purpose three toe stage young tadpoles were immersed in 1% Euclorine solution for 30 sec., rinsed thrice in sterile Holtfreter's solution and anaesthetized with MS 222 (Sandoz) 1:2000.

Operation:

Operations were carried out in sterile Holtfreter's solution containing 100 U/ml penicillin, 100 µg/ml streptomycin and 0.25 µg/ml Fungizone (GIBCO). During operation, the heart of young tadpole was exposed out by making a cut on an anterior ventral surface of skin and then the tip of ventricle was incised. In the same way, the ventricular tips from ten young tadpoles were pooled and meshed in Leibovitz (L-15) culture medium. The removed meshed tissue was rinsed four times in Leibovitz (L-15) diluted with sterile water (2:1) and containing 100 U/ml penicillin and 100 µg/ml streptomyocin. This meshed cardiac tissue (ventricle tissue) was treated as explant.

Culture method:

Meshed cardiac tissues (explant) were placed in a sterlized plastic organ culture dish (35x10 mm Falcon plastics) with culture medium. *Emblica officinalis* (0.1 ml of *E. officinalis* in 100 ml culture medium) was supplemented to the culture medium for treated group. The culture medium was renewed on every 2nd day. Cultures were terminated after 5, 10, 15 and 40 days of inoculation.

Histological method:

Culture were fixed in 95% chilled ethanol (at 4ºC), embedded in paraffin, cut into 7 µm, serial sections and stained with Haemotoxyline and counter stain with eosin.

TABLE 1: THE INFLUENCE OF *E.OFFICINALIS* ON HEART REGENERATION IN TADPOLES OF THE FROG, *RANA CYANOPHLYCTIS*

Series	Developmental Stage on the day of operation	Group	No. of animals employed	Day of preservation	No. of animals Preserved	Percentage of Regeneration	
						Regenerates (lost part)	Non regenerates
SI: Heart regeneration *in vivo* (Tadpoles with amputated heart)	Young (3 toe stage) tadpoles	C1 : (Control operated animals reared in water D0 - D20 =Water)	40	5 10 20	10 10 20	30%	70%
		T1 : *E. officinalis* treated (D0 - D3 =*E. officinalis* D4 - D20 =Water)	40	5 10 20	10 10 20	50%	50%
	Mature (5 toe stage) tadpoles	C2 : (Control operated animals reared in water D0 - D20 =Water)	40	5 10 20	10 10 20	20%	80%
		T2 : *E. officinalis* treated (D0 - D3 = *E. officinalis* D4 - D20 =Water)	40	5 10 20	10 10 20	40%	60%
SII: Ectopic heart regeneration (Tadpoles with meshed cardiac tissue explants in a	Young (3 toe stage) tadpoles	C3 : Control (operated animals reared in water D0 - D20 =Water)	40	5 10 20	10 10 20	30%	70%
		T3 : *E. officinalis* treated	40	5 10	10 10	50%	50%

pit made on their tail)		(D0 - D3 = *E. officinalis* D4 - D20 =Water)		20	20		
		C4 : Control (operated animals reared in water D0 - D20 =Water)		5 10	10 10		
	Mature (5 toe stage) tadpoles		40	20	20	20%	80%
		T4 : *E. officinals* treated D0 - D3 = *E .officinalis* D4 - D20 =Water		5 10	10 10		
			40	20	20	40%	60%

TABLE 2: INFLUENCE OF *E.OFFICINALIS* ON MESHED CARDIAC TISSUE REGENERATION IN CULTURE MEDIUM

Mode of Experiments	Group	Days of Culture	No. of Culture vessels examined	Status of Cardiac tissue regeneration(Number)					Percentage of cardiac tissue regeneration
				Explant with undifferentiated cell mass	Explant With differentiating cardio myocytes	Explant with cardio myo fibrils	Explants with differentiated cardic muscles	Un identified Structure	
Meshed cardiac tissue(tip of ventricle) inoculated in culture medium	A (Control) Explant tissue inoculated in culture medium	5	30	05	-	-	-	28	25%
		10	30	-	03	-	-	27	
		15	30	-	02	03	01	23	
		40	30	08	04	05	07	10	
	B (*E. officinails* treated group) Explant tissue inoculated in culture medium supplemented with *E. officinalis*	5	30	12	-	-	-	20	45%
		10	30	-	10	06	04	18	
		15	30	-	8	09	06	07	
		40	30	-	2	06	10	10	

RESULTS: The results obtained are presented in **Table 1** and **2.** The findings offer a useful opportunity to study the effect of *E.officinalis* on cardiac tissue regeneration in all three modes of experiments- *in vivo, invitro* and transplantation setup. *E.officinalis* was found to be a good model to accelerate the percentage of cardiac tissue regeneration; it was 50% in comparison to 30% in untreated control group tadpoles (**Table 1**).

In case of *in vivo* study, blastema like structure was reported to develop on amputation site on day 10 (**Fig.2**). On day 20 after amputation, lost part of ventricle was developed in 50% cases of *E.officinalis* treated tadpoles (**Fig.3**). Histological observation of amputated heart revealed that following amputation, cardiomyocytes become to detach from one another, creating large intercellular space (**Fig.4**).

The proportion of these structurally altered, cardiomyocytes increased by day 10 to15. In case of *E. officinalis* treated tadpoles, it was reported that, accumulation of dedifferentiated cells near the edge of lesions begins and consequently blastema is formed (**Fig.4**). The source of blastema cells is

still not well-known.; either from the dedifferentiation of resident injured cardiac tissue or from the resident progenitor cells. By day 5 the wound showed proper healing whereas by day 10 wound showed rapid resolution of granulation tissue and a restoration of normal myocardial architecture. By day 20 amputated heart showed little or no scar in the wound area particularly in *E.officinalis* treated cases. Myocardium was strikingly looking normal by day 20 (Figs-3,5&6) in 50% cases while in remaining cases there was little evidence of myocardial replacement.

The result obtained from transplantation set-up mode of experiment are presented in **Table1**. Here also *E.officinalis* was found to accelerate the percentage of cardiac tissue regeneration .The declining trend of regeneration with the age of animal was found similar to that of *in vivo* study (**Table 1**). Histological changes occurred in grafted cardiac tissue showed that engrafted cardiac tissue extract lost its identity in most of the control recipient operated tadpoles. Where as in *E. officinalis* treated host tadpoles engrafted tissue showed good vascularization and even normal cardiac beating in majority of cases (**Fig.8** and **9**). It seems that *E. officinalis* solution enhanced the differentiation of implanted meshed cardiac tissue even at ectopic site (tail) consequently transplanted cardiac tissue differentiated like miniature ectopic heart on the tail (**Fig.8** and **9**). Histological study showed normal progressive differentiation of cardiomyocytes to cardiomyofibrils (**Fig. 10, 11** and **12**).

Result from the *in vitro* study of cardiac tissue regeneration mode of experiment showed that the ability of cardiac tissue regeneration in culture medium too. Percentage of cardiac tissue regeneration was higher in *E.officinalis* supplemented culture medium (**Table 2**). On day 40 after inoculation of meshed cardiac tissue in culture medium supplemented with *E.officinalis* solution, showed differentiation and good growth (**Fig.13** and **14**). These inoculated tissues showed cardiac beating on day 40 (**Fig. 14**). Histological examination showed that the changes occurred during cardiac tissue regeneration was almost similar in both *in vivo* and *in vitro* (**Fig.15, 16** and **17**).

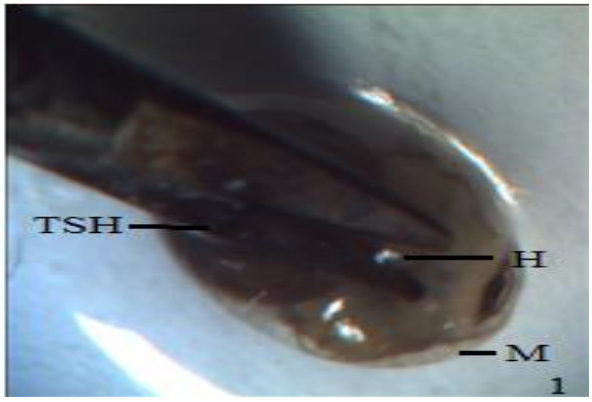

FIG.1: PHOTOGRAPH SHOWING LEVEL OF AMPUTATION (SURGICAL REMOVAL OF THE TIP OF THEVENTRICLE REGION OF THE TOAD TADPOLES, (20 X)

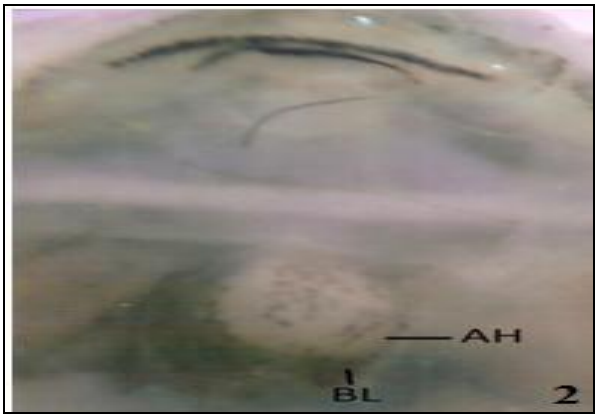

FIG.2: PHOTOGRAPH OF AMPUTATED HEART OF *E.OFFICINALIS* TREATED GROUP (10 DAYS OLD) YOUNG TADPOLES SHOWING BLASTEMA AT WOUNDED SITE, (20 X)

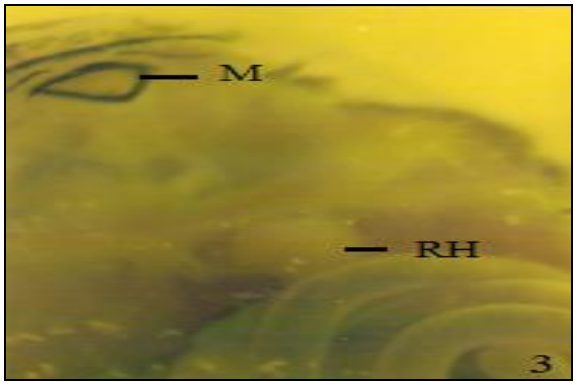

FIG.3: PHOTOGRAPH SHOWING COMPLETE REGENERATION OF VENTRICLE PART OF THE HEART OF *E.OFFICINALIS* TREATED (20 DAYS OLD) YOUNG TADPOLES (20X)

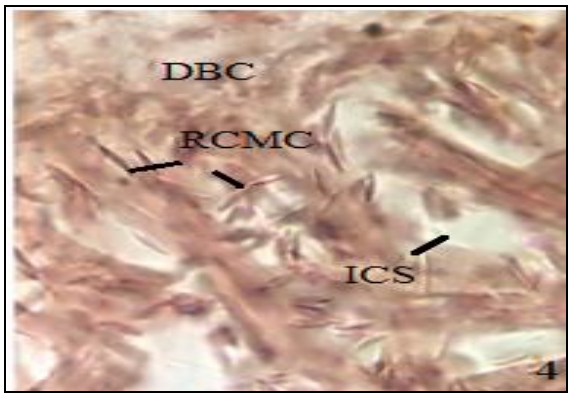

FIG.4: MICROPHOTOGRAPH OF A SECTION PASSING THROUGH THE AMPUTATED HEART OF *E.OFFICINALIS* TREATED YOUNG TADPOLES (5 DAYS OLD) SHOWING DEDIFFERENTIATION OF DBC IN TO CARDIOMYOCITES,(100X).

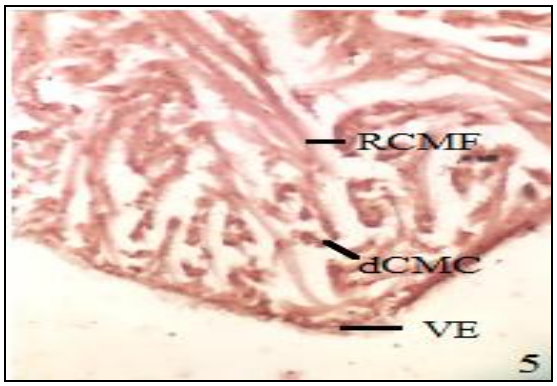

FIG.5: MICROPHOTOGRAPH OF A SECTION PASSING THROUGH THE AMPUTATED HEART OF ARJUNA TREATED YOUNG TADPOLES (10 DAYS OLD) SHOWING DIFFERENTIATION OF CARDIOMYOCYTES INTO CARDIOMYOFIBRIL (100X).

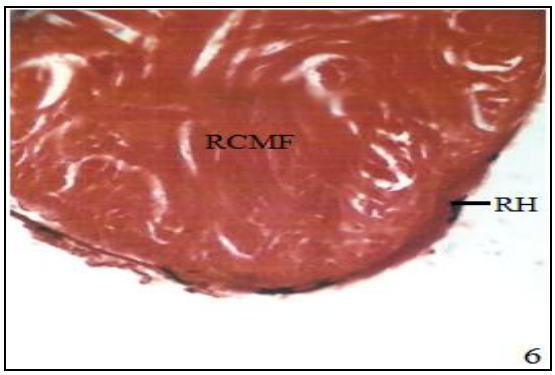

FIG.6: MICROPHOTOGRAPH OF A SECTION PASSING THROUGH THE AMPUTATED HEART OF *E.OFFICINALIS* TREATED YOUNG TADPOLES (20 DAYS OLD) SHOWING COMPLETE REGENERATION OF LOST PART OF THE VENTRICLE (100X).

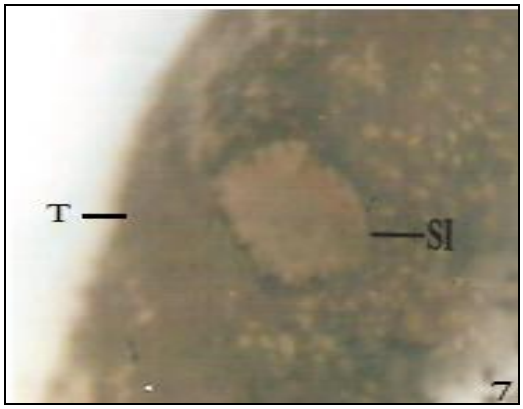

FIG.7: PHOTOGRAPH SHOWING THE SITE OF IMPLANTATION OF MESSED TISSUE. MESHED CARDIAC TISSUE WAS IMPLANTED INTO A PIT MADE ON MID-LATERAL POSITION OF TAIL OF THE HOST TADPOLE (20X).

FIG. 8 AND 9: PHOTOGRAPHS OF CARDIAC TISSUE IMPLANTS ON ECTOPIC SITE (MID-LATERAL POSITION OF TAIL). ALL FIGURES SHOWING DEVELOPMENT, DIFFERENTIATION AND GROWTH OF THE IMPLANTS. (20X)

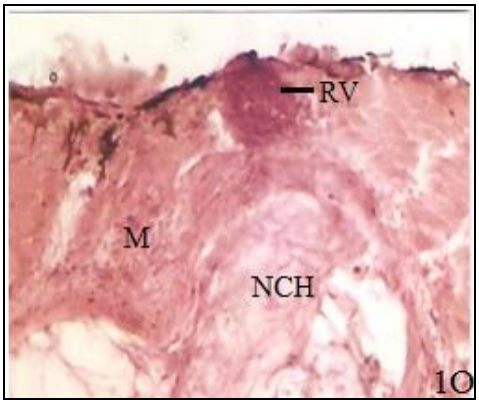

FIG. 10: MICROPHOTOGRAPH OF A 5 DAYS OLD SECTION PASSING THROUGH THE IMPLANTED VENTRICULAR TISSUE ON RECIPIENT *E.OFFICINALIS* TREATED TADPOLE'S TAIL SHOWING REGENERATION OF VENTRICLE PART (100X).

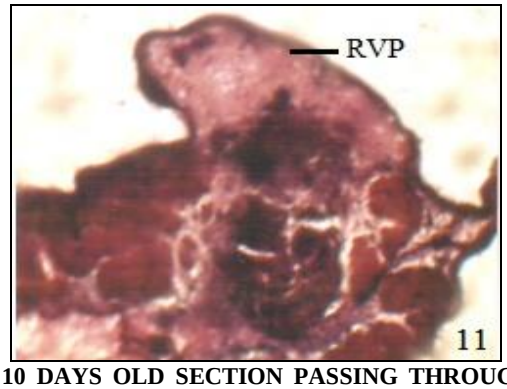

FIG.11: MICROPHOTOGRAPH OF A 10 DAYS OLD SECTION PASSING THROUGH THE IMPLANTED VENTRICULAR TISSUE ON RECIPIENT *E.OFFICINALIS* TREATED TADPOLE'S TAIL SHOWING ALMOST REGENERATION OF VENTRICLE PART FROM THE TRANSPLANTATION SITE (100X).

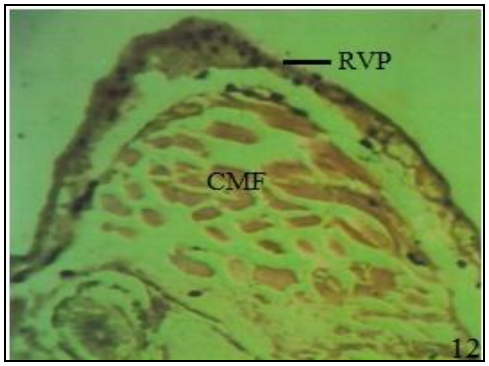

FIG.12: MICROPHOTOGRAPH OF A 20 DAYS OLD SECTION PASSING THROUGH THE IMPLANTED VENTRICULAR TISSUE ON RECIPIENT *E.OFFICINALIS* TREATED TADPOLE'S TAIL SHOWING REGENERATION AND DIFFERENTIATION OF CARDIAC TISSUE (100X).

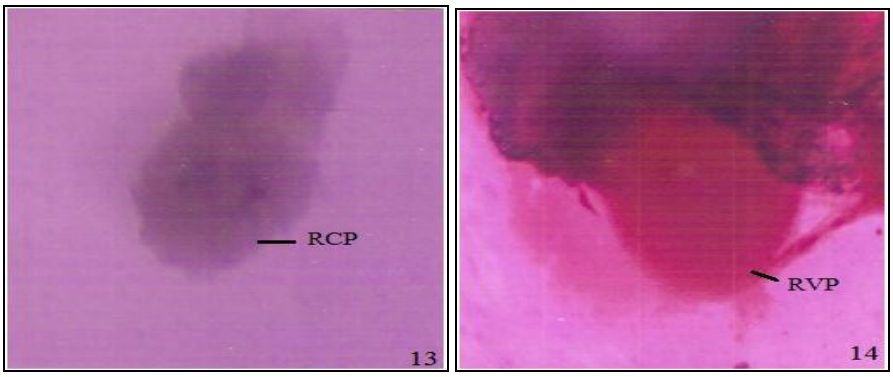

FIG.13 AND14: MICROPHOTOGRAPH OF A SECTION PASSING THROUGH THE 15&40 DAYS OLD EXPLANTS AFTER INOCULATION IN CULTURE MEDIUM SUPPLEMENTED WITH *E.OFFICINALIS* SHOWING COMPLETE REGENERATION OF CARDIAC TISSUE (VENTRICULAR PART).(10X)

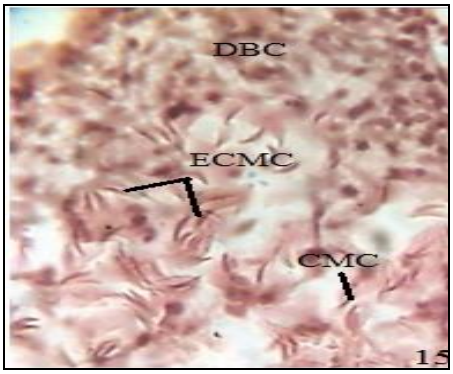

FIG.15: MICROPHOTOGRAPH OF A SECTION PASSING THROUGH THE 10 DAYS OLD EXPLANT AFTER INOCULATION IN CULTURE MEDIUM SUPPLEMENTED WITH *E.OFFICINALIS* SHOWING DEDIFFERENTIATION OF DBC IN TO CARDIOMYOCITES,(100X).

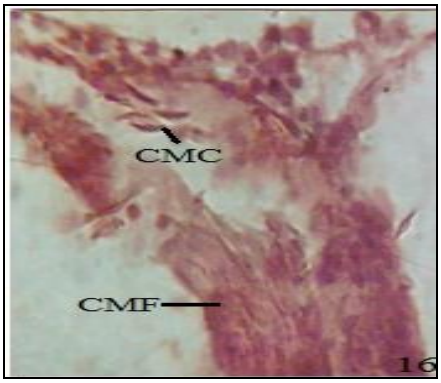

FIG.16: MICROPHOTOGRAPH OF A SECTION PASSING THROUGH THE 15 DAYS OLD EXPLANT AFTER INOCULATION IN CULTURE MEDIUM SUPPLEMENTED WITH *E.OFFICINALIS* SHOWING DIFFERENTIATION OF CARDIOMYOCYTES INTO CARDIOMYOFIBRILS (100X).

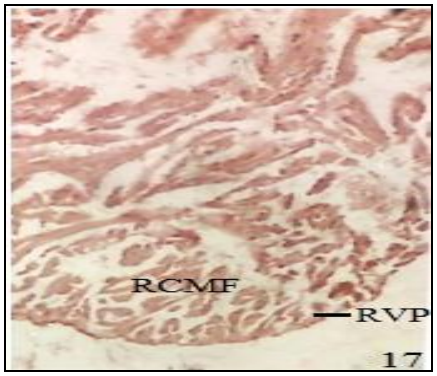

FIG.17: MICROPHOTOGRAPH OF A SECTION PASSING THROUGH THE 40 DAYS OLD EXPLANT AFTER INOCULATION IN CULTURE MEDIUM SUPPLEMENTED WITH *E.OFFICINALIS* SHOWING COMPLETE REGENERATION OF CARDIAC TISSUE (VENTRICULAR PART).(100X)

DISCUSSION AND CONCLUSION:

The present result shows that *E. officinalis* affect the regeneration of cardiac tissue in the tadpoles of frog *Rana cyanophlyctis* in all three modes of experiments (*in vivo*, transplantation and *in vitro*). Similar results have also been reported by Jangir et al.[678] in cardiac tissue regeneration in anuran amphibians. The mechanism of *E.officinalis* on cardiac tissue regeneration is still not clear. However, Sumitra et al[13] reported that Emblica increase cellular proliferation and cross linking of collagen at the wound site and thus leading to the rapid healing of wound. It is also reported that *E. officinalis* enhance lens regeneration in frog, *Rana cyanophlystitus*[1].

Takahashi et al.[14] reported that treatment of ascorbic acid (a major constituent of Emblica) markedly increase the proportion of cardiomyocytes in infracted cardiac part of mice *in vivo*. Patel et al.[12] reported that *E. officinalis* may be beneficial for the treatment of myocardial damage associated with type-1 diabetes mellitus.

In present study, *E. officinalis* might have enhanced dedifferentiation of myocardial tissue cells of tadpoles of *Rana cyanophlyctis* resulting in regeneration of cardiac tissue in all three mode of experiment. This suggests that *Emblica officinalis* may act as a good model employed for investigation of the molecular mechanisms responsible for cardiac tissue regeneration. Heart regeneration appears to be a suitable system for such investigation. This discovery opens the possibility that researchers may one day enhance the endogenous regenerative capacity of mammals including man by inducing cellular dedifferentiation *in vivo*.

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