Section A-Research paper
ISSN 2063-5346

Assessment of oral toxicity study for functionalized tamarind for safer use in drug delivery system

Deshmane Gorakh*, Dhawale Shashikant, Dhonde Satish
School of Pharmacy, S.R.T.M. University, Nanded-431606, MS, India
*** Corresponding Author**
Deshmane Gorakh
School of Pharmacy, S.R.T.M. University,
Nanded-431606, MS, India
E-mail:gorakh.deshmane.gd@gmail.com

Abstract

Background: In the pharmaceutical industry, tamarind is often utilized as a mucoadhesive polymer, a naturally occurring polysaccharide that is derived from tamarind seed. However, tamarind's organic application in drug delivery is limited but, its functionalization has shown to enhance its functionality. The contemporary paintings were created with the intention of evaluating the tamarind's observed oral toxicity. IR and mass spectroscopy have almost completely evaluated the functionalized and unmodified tamarind.

Results: The experiments confirmed and predicted that sulphonation and thionation of pure tamarind results in effective functionalization. The functionalized and pure tamarind's oral toxicity was tested in albino Wistar rats. Data obtained revealed a notable distinction between Hb and platelet levels. When compared to natural tamarind, functionalized tamarind did not exhibit any acute oral toxicity.

Conclusions: The functionalized tamarind is a unique, risk-free, and efficient carrier for the oral administration of medicines.

Keywords: Tamarind, Sulphonation, Thionation, Acute inhalation toxicity study, Kidney function test, Liver function test, Haemogram.

Introduction

In view of remarkable properties, such as biodegradability, biocompatibility in Nature, and expanding while they interact with fluid media, ordinary polymers or gums have been used in the design of transport and controlled release dosage systems. Tamarind (Tamarind indica L.) belongs to the Leguminosae family of plants [1].The oil obtained from its seeds is rich in eicosanoic grease acids, such as palmitic, oleic, and linoleic acids, with the most notable fixations relating to linoleic corrosive and palmitic corrosive [2]. Tamarillo seed polysaccharide (TP), a polymer with a wide range of functions, with a particle load of 700–880 kDa [3], about 65% of TP is made out of tamarind seeds [4]. Glucose, xylose, and galactose in the ratio of 80:2.25:1 make up the substance components of TP [6]. A distinct polymer with distinctive properties, TP is regarded as a galacto-xyloglucan and is valuable in the pharmaceutical industry. It was found that tamarind gum developed into a considerably thick, mucoadhesive, and biocompatible ordinary polymer that may be used for visual medicine delivery bases assisted discharge drug conveyance frameworks, and size systems.

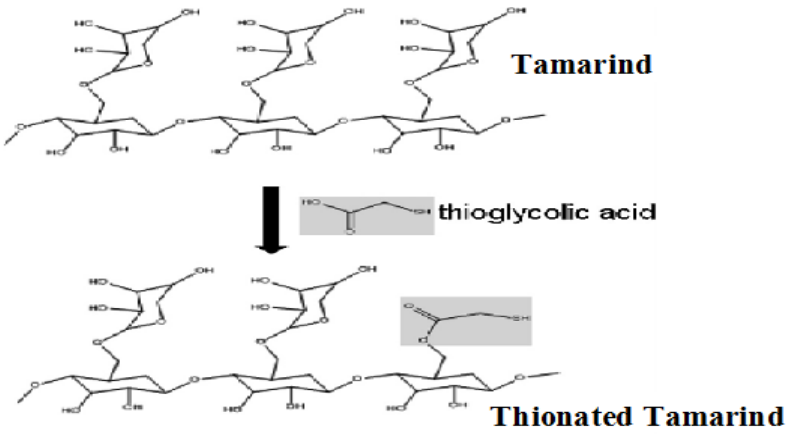
[7]. As a vehicle for ocular medications, TP is a desirable candidate due to its distinctive features [8]. For ophthalmic use in dry eye circumstances, mixtures of synthetic tears and hyaluronic acid are used [9]. For the obvious utilization hydrophilic and hydrophobic anti-microbials, TP can be used in drug delivery frameworks [10]. Tamarind seed polysaccharide is made of gelatin that has a high methoxyl content material about 6.8% to 8.37%, which improves gel strength and hotness dependability [11]. It possesses high consistency, broad pH resilience, non-carcinogenicity, mucoadhesive nature, and biocompatibility properties [12]. In addition, it disperses in hot water to form an extraordinarily thick gel that can be used as an adhesive arrangement despite being insoluble in natural solvents [13,14]. Better than organic product gelatins, TP has the distinctive ability to create gels with sugar packs in a wide pH range that are also not affected by effervescence in an impartial fluid arrangement, even if bubbled for a considerable amount of time [15].It has been shown as a thickener with mucomimetic and mucoadhesive properties that can produce hydrogels. As such, this research study sought to combine tamarind modification to alter their properties and minimizing toxicity for the prospective future advancement of drug delivery systems.

Methods

Tamarind powder was purchased from Unique Eco Export Coimbatore, Tamilnadu, India. All the opposite chemical compounds used for synthesis had been procured from Sigma Aldrich Chemicals Inc., Bangalore, India, and distilled water turned into prepared from deionized water in the lab.

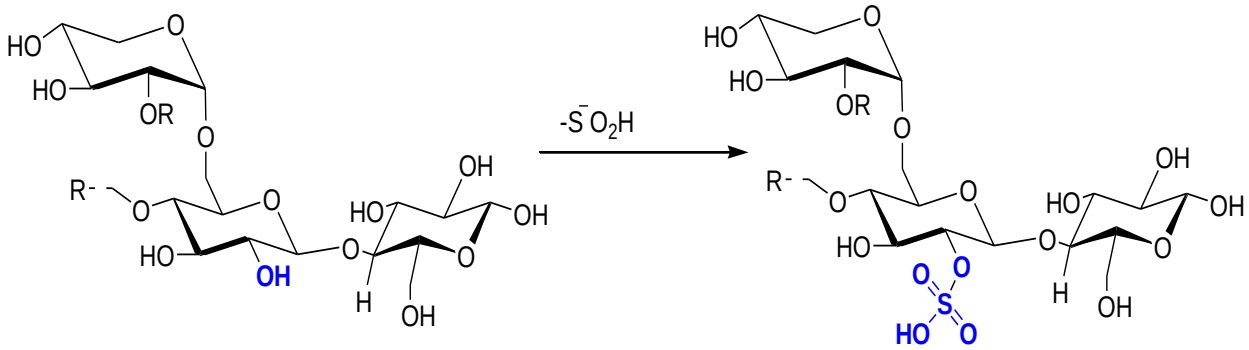
Thionation of Tamarind

The hydroxyl institutions of the beta-galactose moieties of tamarind and the carboxyl institution of thioglycolic acid formed ester bonds, which allowed tamarind to be covalently linked to the acid. The product appeared to be an off-white, odorless powder that was soluble in water when it had fully dried. This synthesis produced a normal yield of 40.80% of the tamarind that was used. Both the water and methanol can dissolve thioglycolic acid. Thiolated tamarind could be sufficiently purified by precipitation with methanol from an aqueous solution and subsequent washing with the help of overnight storage of the precipitate. The number of thiol companies per gram was calculated using Ellman's method. [16]



Sulphonation of Tamarind

Sulfonation was carried out in accordance with the method established by Vasconcelos *et al*. [17] and Wang and Zhang *et al.*[18], with slight modification, tamarind polymer (50 mg) was dissolved in dimethyl sulfoxide (DMSO, 10 mL) over the course of 24 h at room temperature with vigorous stirring. The solution was then agitated for 2 h at room temperature using pyridine (10 mL).Following the addition of 4 mL of chlorosulfonic acid dropwise, the mixture was placed in an ice bath for 2 h before being left at 4^{o}C for 15 h. By adding ice-cold water (5 mL), sulfonation is stopped. The mixture is then neutralized by adding sodium bicarbonate (10%, v/v), and the process is repeated until all CO_2 has been eliminated. The resulting solution was severely dialyzed against distilled water for 6 days before being lyophilized to produce a product known as. The method was followed the Mendes *et al.* [19] technique with a few minor modifications. Sulfonated polymer samples were first hydrolyzed with strong hydrochloric acid (12.23 mol L-1) in a thermostatic bath at 100^{o}C for 10 min. Then, verified tubes containing 3 have received 0.2 mL of the sulfonated polymer hydrolysates. 8 mL of trichloroacetic acid (TCA, 3% w/v) have been added, followed by 1 mL of protective solution (6 g NaCl, 0.5 mL concentrated HCl, 0.1% gelatin (w/v), and 47 mL of distilled water), and.03 g of barium chloride. After being shook ferociously for 1 min, the tubes were left inactive for 15 min. At 420 nm, the resultant barium sulphate endured spectrophotometric quantification.



Characterization of Tamarind and functionalized tamarind

With an FTIR-8400; Shimadzu Corporation, Kyoto, Japan equipped with a diffuse reflectance extra (DRS-8000; Shimadzu Corporation, Japan) and an information station, the IR spectra of natural and functionalized tamarind were examined from 4,000 to 400 cm1 to assess the polymer's ability to capture Medicare. By using sample compressed KBR CDs, around 2 to 3 mg exams have been set up. The determination of ions' mass-to-charge ratios can be done analytically using mass spectrometry (MS). The results are typically shown as a mass spectrum, an intensity plot as a measure of the mass-to-charge percentage, and a way to roughly determine the molecular weight of the chemical. All of the characteristics (IR, NMR, Zeta potentials, and mass spectroscopy) that were investigated were carried out in accordance with the most recent, current methods for each. [20][21]

Acute oral toxicity study of Tamarind and surface functionalized tamarind

Experimental design

The research experiment was carried out on healthy Wistar albino rats weighing 180 to 250 g purchased from National Institute of Biosciences, Pune, India for the measurement of tamarind and functionalized tamarind toxicity. They were trained in cages with a 12 h dark/light cycle, controlled humidity (44–55%), and unrestricted access to food and tap water. Study was carried out according to the Organization for Economic Cooperation and Development's (OECD 2001) criteria with approval from the Institutional Animal Ethics Committee. Animals were grouped into four group (n=6) and overnight fasted with access to water only before initiation of study. Oral distilled water was administered to the control group. Pure tamarind, sulphonated tamarind, and thionated tamarind have been administered orally to other groups at various amounts .Following the initial dose, daily metrics such as body weight, food intake, and water intake were observed. The blood samples taken after 28 days to determine the hematological parameters, which were determined using optical microscope after staining. At the conclusion of the procedure and in accordance with protocol, the animals were put to sleep using CO_2, and one animal from each group was randomly chosen for euthanasia in order to examine the tissue's macroscopic exterior features in the areas of the heart, kidney, and lung. These tissues were painstakingly taken out, fixed in buffered formalin (10%), and then embedded in paraffin wax. Hematoxylin-stained histology sections (5 m thick) were seen under a light microscope. The parameters assessed for the toxicity studies were as; [22]

Daily parameters:	Body weight, food intake, and water intake
Last day parameters:	
Hematology:	RBC, WBC, Hb, Platelet, PCV, MCV, MCH, MCHC.
Liver function tests:	GGTP, Total protein, albumin, globulin, SGOT, SGPT, ALP, Total Bilirubin, conjugated bilirubin, unconjugated bilirubin.
Kidney function tests:	Creatinine, (BUN) Blood urea nitrogen Sodium, potassium, urea, chloride, calcium, bicarbonate, phosphorus, uric acid.
Histopathology:	Sacrificing the animals at end of study, organs were removed, weighed and finally processed for histopathology of kidney, heart, and liver.

Results and discussion

IR Spectroscopy

Sulpha and thio groups with oxygen were present, according to the IR data. Some absorption peaks in both pure and functionalized tamarind were in the same location, such as 2397.08 cm-1 in pure tamarind and 2394.19 cm-1 in functionalized tamarind, which represent comparable functional groups. In the spectra of functionalized tamarind, more absorption peaks were seen. It suggests that the tamarind may successfully be functionalized. The results of the current experiment using pure tamarind have shown that IR spectra were very useful for elucidating functioning at the surface. There were no observable distinctive absorption peaks in pure tamarind. Wave numbers 2500.04 (-SH), 1076.06 (C-O), 1396.89 (SO3H),

1691.27 (C=O), 3097.12 (CSP2-H), and 3287.07 cm-1 in the spectra showed intense bands (-OH). The acquired IR spectra of pure and functionalized tamarind are displayed in figure 1.

Figure 1. IR interpretation of pure (PT), Sulpho (ST) and thio (TT) functionalized tamarind

Mass spectroscopy

After being subjected to sulfonation and thionation, the tamarind's graphitic structure was still there according to the results of mass spectroscopy. Figure 2 shows the results for the functionalized tamarind group, which exhibited a mass change of 2800 m/z as opposed to the results for the pure tamarind group, which showed a mass change of 1500 m/z. This showed that the highest mass to charge ratio in the mass spectrum was produced as a result of the loss of an electron from a molecule, and it was concluded that after functionalization, molecular weight was increased in comparison to pure tamarind because of the attachment of functional groups to the tamarind, which confirms the functionalization.

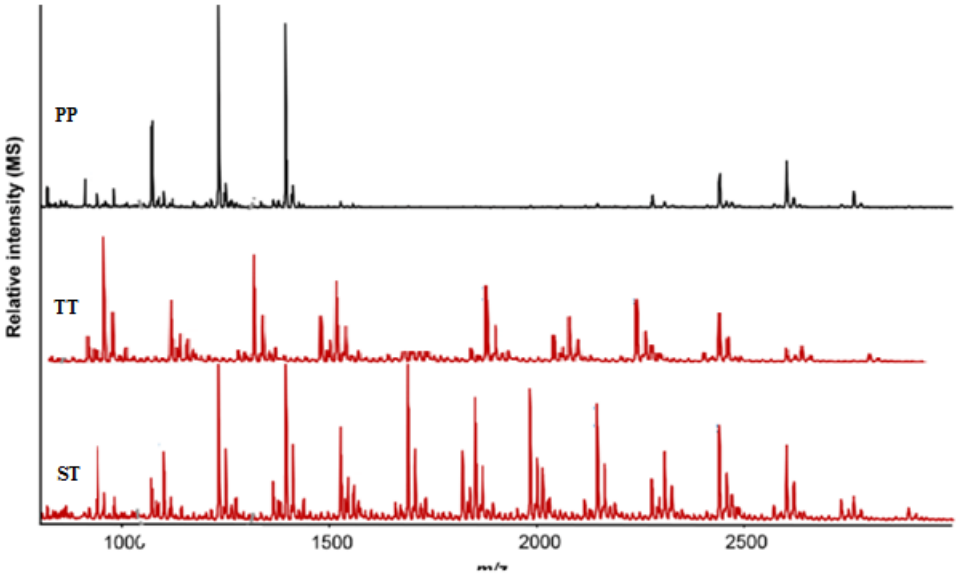


Figure 2: Mass spectroscopy of pure sulphonated and thionated tamarind

Nuclear magnetic resonance (NMR)

We investigated the 1H NMR spectra of tamarind and thiolated tamarind in order to examine the possibility of tamarind alteration (Fig. 3). The bulk of tamarind and thionated tamarind chemical changes were between 50 and 150 ppm, as seen in Fig. 3. Thionated tamarind's NMR spectra displayed singlets similar to tamarind but with additional singlets at 183.This outcome validates tamarind's thiolation. Sulfonated tamarind's NMR spectra revealed singlets similar to tamarind but with extra singlets at 163 because of (SH). This outcome validates tamarind's thiolation.

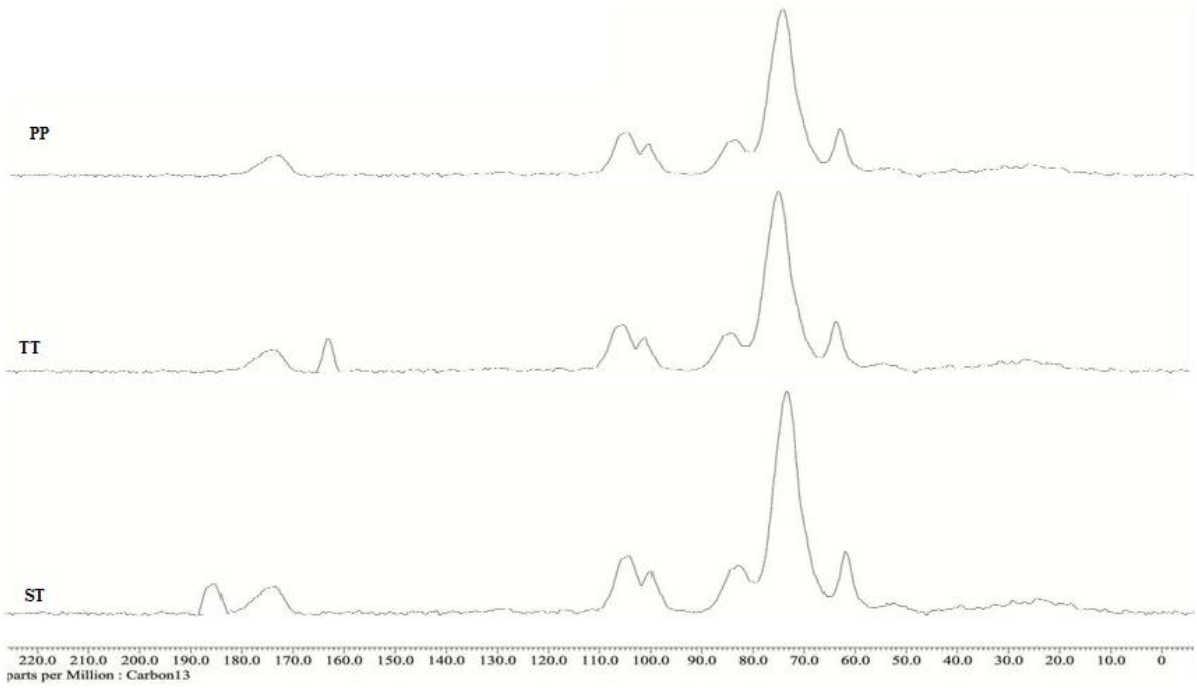


Figure3. NMR spectra of pure sulphonated and thionated tamarind

Zeta potential measurements

Zeta potential measurements of tamarind and thionated tamarind showed anionic characteristics in distilled water with values of 20.7 1.67 mV and 22.2 2.64 mV, respectively. Zeta potential was determined to be negative and was altered by thionation to a higher negative value. This could occur as a result of the existence of many OH groups in anionic structures. Figure 4 shows tamarind's zeta potential upon sulphonation was 32.7 1.67 mV.

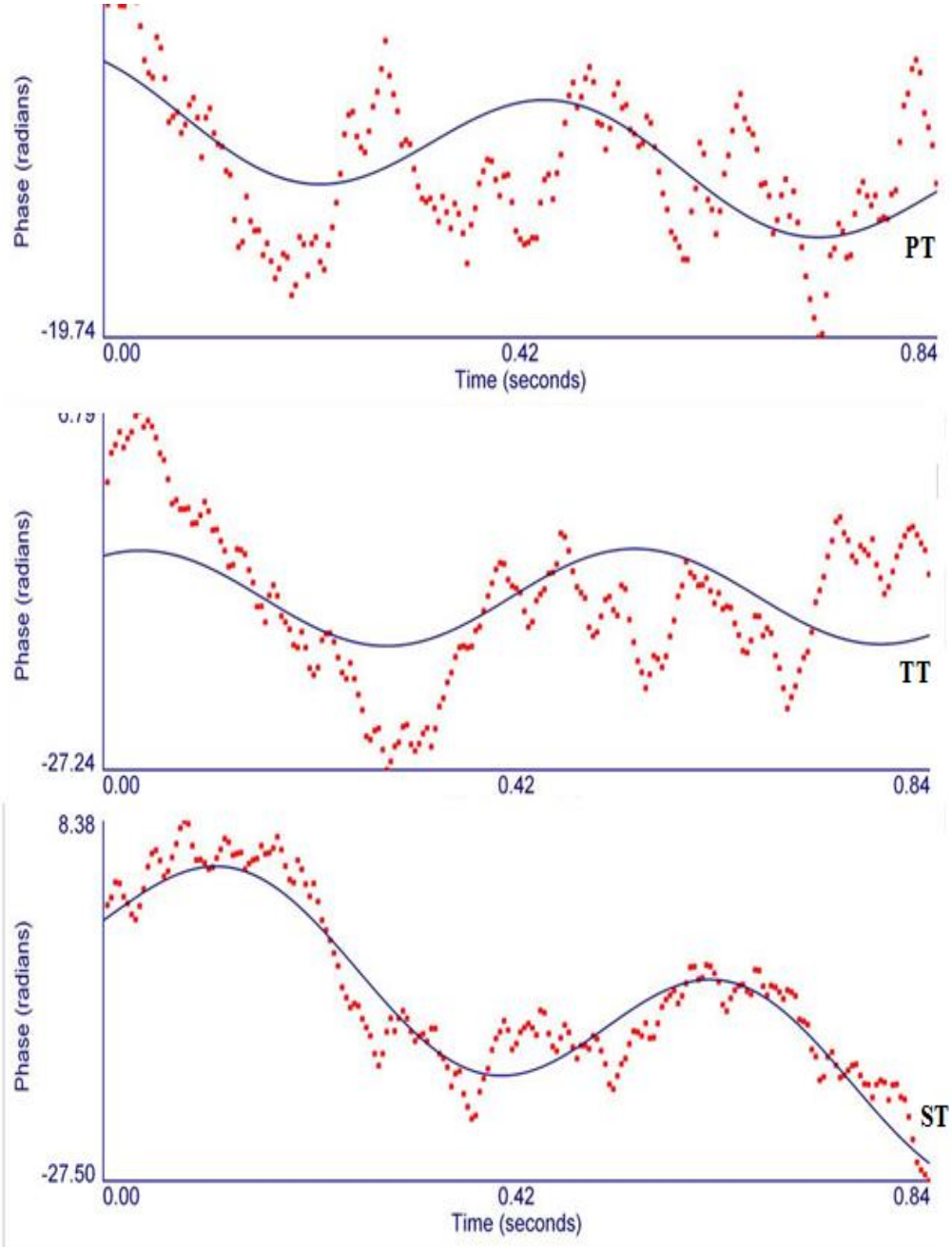


Figure 4. Zeta potential of pure sulphonated and thionated tamarind

Daily parameters

Body weight

After 28 days in the pure tamarind group, both the male and female Wistar rats showed variance in body weight, however the functionalized tamarind group and control group showed little difference. The results were shown in table 1.

Table 1.: Bodyweight (in gm)

Days	Control	PT	TT	ST
0	180	194	170	194
1	193	198	175	198
2	199	204	172	204
3	203	204	178	204
4	205	206	181	206
5	202	207	187	207
6	213	207	186	207
7	219	208	192	208
8	216	210	191	210
9	222	212	195	212
10	228	214	198	214
11	224	216	201	216
12	225	218	206	218
13	230	220	206	220
14	234	220	209	220
15	234	222	211	222
16	234	223	214	223
17	234	221	233	221
18	234	222	234	222
19	231	225	230	225
20	246	220	243	220
21	248	221	247	221
22	239	223	238	223
23	242	223	240	223
24	243	220	241	220
25	245	222	240	222
26	243	223	243	223
27	243	224	244	224
28	244	224	244	224

Water intake

The results revealed that after 28 days in the pure tamarind group, Wistar rats' water intake changed little, whereas the functionalized tamarind group exhibited minimal variation. The results were as per shown in table 2.

Table 2 : Water intake (in ml).

Days	Control	PT	TT	ST
1	150	150	140	150
2	140	140	110	140
3	150	150	115	150
4	140	160	125	160
5	160	185	105	185
6	180	210	100	210
7	160	130	85	130
8	140	160	110	160
9	125	135	95	135
10	150	140	100	140
11	140	130	100	130
12	130	120	130	120
13	180	220	100	220
14	150	140	90	140
15	110	80	85	80
16	165	150	110	150
17	145	170	100	170
18	140	160	115	160
19	145	165	105	165
20	225	225	155	225
21	160	170	155	170
22	150	180	155	180
23	140	180	130	180
24	170	190	175	190
25	160	175	160	175

26	150	170	160	170
27	155	170	165	170
28	160	160	155	160

Food intake

The results showed that there was a notable modification in the Wistar rats' daily food intake after 28 days in the pure tamarind group, but the functionalized tamarind group exhibited insignificant alteration in comparison to the control group, as shown in table 3

Table 3.: Food intake (in gm)

Days	**Control**	**PT**	**TT**	**ST**
1	86	75	82	75
2	77	67	87	67
3	145	74	91	74
4	140	79	95	79
5	107	98	95	98
6	116	104	91	104
7	82	47	78	47
8	103	70	96	70
9	70	36	73	36
10	75	49	84	49
11	80	60	90	60
12	82	72	85	72
13	79	56	91	56
14	85	55	88	55
15	70	49	70	49
16	72	53	79	53
17	69	45	70	45

18	70	55	65	55
19	67	47	72	47
20	96	89	89	89
21	98	83	75	83
22	81	85	81	85
23	89	67	72	67
24	83	88	81	88
25	65	67	65	67
26	81	86	76	86
27	83	84	77	84
28	86	81	80	81

Last day parameters

After 28 days, all of the last day's parameters were examined, including the hematological parameters (Hb, WBC, RBC, platelets, PCV, MCV, MCH, and MCHC), liver function test (GGTP, total protein, albumin, globulin, alkaline phosphatase, SGPT, SGOT, total Bilirubin, conjugated bilirubin, and unconjugated bilirubin), and the kidney.

Haemogram

The findings of looking at all the significant hematological parameters in all the groups were shown in table 4. The study findings showed that the sulphonated group's hemoglobin and platelets differed significantly from those of the control group. The other parameters (WBC, RBC, PCV, MCV, MCH, and MCHC) barely changed after functionalization with the thiol group. Finally, neither the control group nor the functionalized group's hemograms underwent any changes. [22]

Table No 4. Hematological parameters

Sr	**Parameter**	**Control group**	**PT group**	**TT group**	**ST group**
1.	Hb	13 ± 0.29	13 ± 0.92	13 ± 0.47	14 ± 0.28
2.	WBCs	14975 ± 2145	13775 ± 2027	14050 ± 805	39533 ± 15990
3.	RBCs	6.4 ± 0.2	6.4 ± 0.47	6.6 ± 0.15	6.9 ± 0.18
4.	Platelets	656250 ± 54442	494250 ± 135067	813500 ± 117330	893667 ± 59179
5.	PCV	39 ± 1.3	39 ± 2.6	39 ± 1.4	39 ± 1.1

6.	MCV	61 ± 1.70	61 ± 0.79	59 ± 0.94	57 ± 0.52
7.	MCH	20 ± 0.34	20 ± 0.31	20 ± 0.26	20 ± 0.26
8.	MCHC	34 ± 0.50	33 ± 0.23	35 ± 1.10	35 ± 0.24

Liver function test

All the three groups underwent all significant elements of the liver function test, and the findings were displayed in table 5. The control group's albumin and total bilirubin count varied significantly from that of the functionalized groups for sulphonation and thionation, according to the results. Only the sulphonation tamarind group demonstrated any discernible variation in other liver function metrics. But as compared to the control group, there was no variation in the count of group functionalized with thionation.

Table No 5 Significant elements of the liver function test

Sr.	**Parameters**	**Control group**	**PT group**	**TT group**	**ST group**
1.	GGTP	9 ± 0.71	10 ± 2.6	10 ± 2.6	7.5 ± 0.65
2.	Total Protein	7.9 ± 0.24	10 ± 0.08	10 ± 0.08	7.7 ± 0.11
3.	Albumin	0.99 ± 0.06	0.86 ± 0.11	0.86 ± 0.11	1.1 ± 0.06
4.	Globulin	6.9 ±0.2	6.6 ± 0.14	6.6 ± 0.14	6.6 ± 0.1
5.	Alkaline phosphatase	182 ± 19	243 ± 74	243 ± 74	162 ± 56
6.	SGPT	89 ± 6.6	87 ± 6.8	87 ± 6.8	73 ± 3.4
7.	SGOT	270 ± 8.5	173 ± 39	173 ± 39	303 ± 51
8.	Total Bilirubin	0.18 ± 0.039	0.22 ± 0.039	0.22 ± 0.039	0.25 ± 0.035
9.	Conjugated Bilirubin	0.045 ± 0.023	0.043 ± 0.012	0.043 ± 0.012	0.073 ± 0.03
10.	Unconjugated bilirubin	0.14 ± 0.056	0.17 ±0.049	0.17 ±0.049	0.2 ± 0.039

Kidney function test

Relevant kidney function test parameters were examined in each group, and the outcomes were shown in table 6. The results showed that there was a significant difference in creatinine, BUN, and urea acid count between the ST group and control group, and this difference was functionalized with thionation group, which also showed a negligible

difference in other kidney parameters. However, group 3 and control showed a constant level of all parameters.

Table 6.: Kidney function major parameter comparison with control and test group

Sr.	Parameter	Control group	PT group	TT group	ST group
1.	Creatinine	0.47 ± 0.022	0.41 ± 0.051	0.46 ± 0.022	0.41 ± 0.051
2.	Sodium	146 ± 0.75	145 ± 0.96	147 ± 0.65	145 ± 0.96
3.	Potassium	4.6 ± 0.14	5 ± 0.36	4.7 ± 0.17	5 ± 0.36
4.	Chloride	99 ± 0.48	100 ± 1	100 ± 0.71	100 ± 1
5.	Urea	43 ± 3	66 ± 25	41 ± 0.41	66 ± 25
6.	BUN	20 ± 1.4	19 ± 0.77	19 ± 0.19	19 ± 0.77
7.	Bicarbonate	24 ± 1.9	22 ± 0.61	24 ± 0.89	22 ± 0.61
8.	Calcium	9.3 ± 0.18	9.1 ± 0.065	7.3 ± 2.2	9.1 ± 0.065
9.	Phosphorus	7.5 ± 0.36	7.7 ± 0.49	7.6 ± 0.23	7.7 ± 0.49
10.	Uric acid	0.97 ± 0.30	1.5 ± 0.34	1.4 ± 0.15	1.5 ± 0.34

Histopathology

After 28 days, a histopathology analysis of pure and functionalized tamarind groups on vital organs such the liver, heart, and kidney were carried out. The outcomes of the observed results were compared to the control groups. Figure 5 (a) showed that functionalized tamarind had liver tissue damage and that ulceration had resulted, as evidenced by the presence of tiny red blood clots inside the structure. After oral administration, there were no further functionalization variances among the pure tamarind as compared to the control group. The histopathology of the heart's findings, which were depicted in figure 5 (b), indicated that 5 mg/kg of pure and functionalized tamarind had no discernible effects when compared to the control group. However, in figure 5 (c) the histopathology of the kidney showed that oral tamarind in rats caused significant tubular necrosis, which was further characterized by the death of tubular epithelial cells of the kidney and interstitial nephritis, that is swelling in between the kidney tubules, at a dose of 5 mg/kg on 28^{th} day. Whereas no difference was seen in functionalized tamarind compared to the control group. [23] [24]

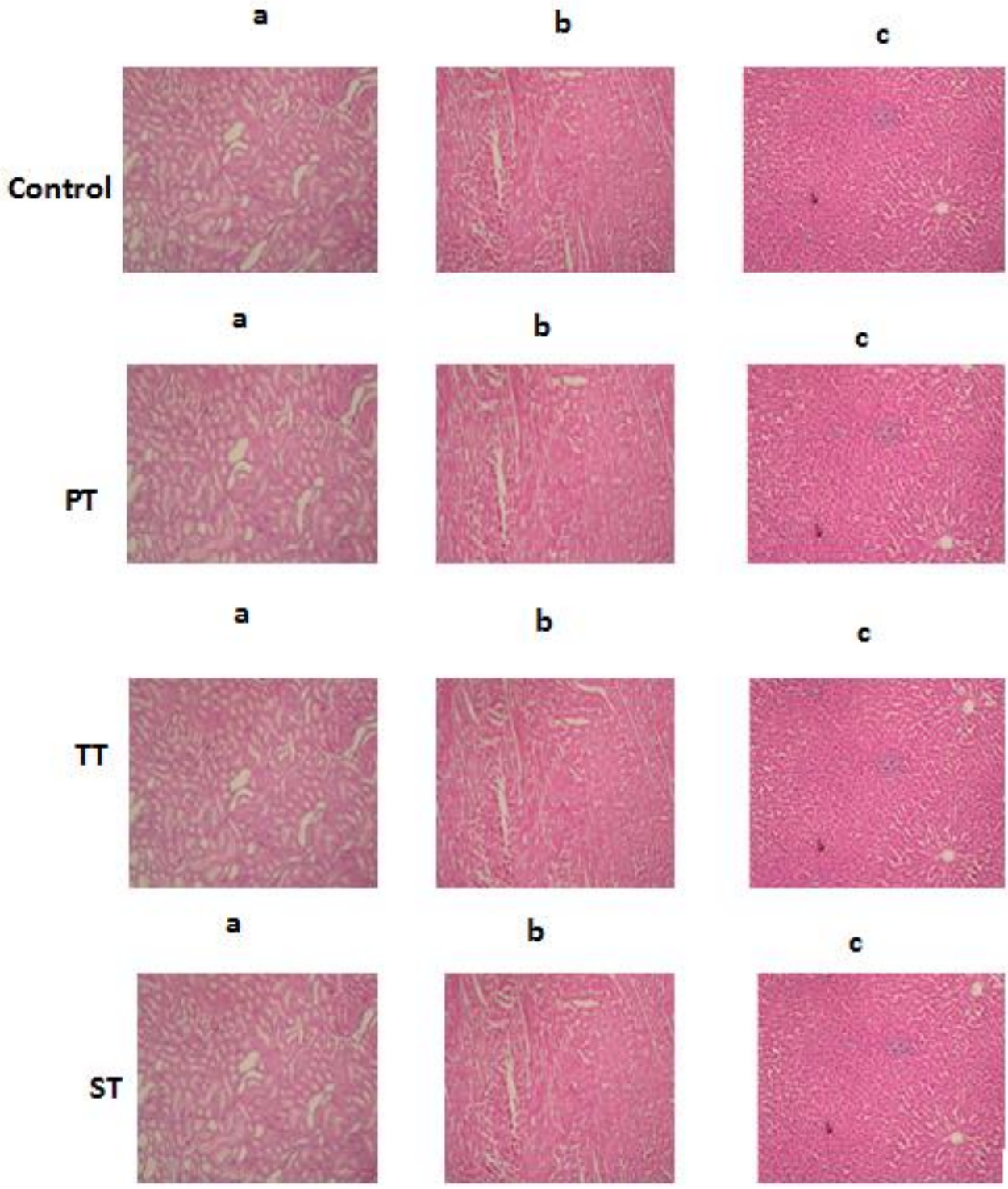


Figure. 6: Histopathology **a)** Liver **b)** Heart, and **c)** Kidney

Overall Toxicity Study

In-vivo toxicity tests with functionalized and pure tamarind were studied in the current research work. The justification for these specific tests was based on the criteria;daily parameters, histopathology, Hb, WBC, RBC, platelets, PCV, MCV, MCH,MCHC, liver function test and kidney function test. The results of these acute studies did not demonstrate

any significant changes or hazard potential in rats after acute oral exposure to the functionalized tamarind, and there was no significant size dependent toxicity.

Conclusions

Sulphonation and thionation of tamarind were effectively used to functionalize the fruit in order to test its oral toxicity while taking into account numerous factors that are known to predict toxicity. It was shown that tamarind's functionalization decreased its oral toxicity. Furthermore, it can be deduced that functionalized tamarind is a secure oral biodegradable polymer that has the potential to be used in oral drug delivery systems.

Acknowledgements

The authors are thankful to the Research Centre, School of Pharmacy, S.R.T.M. University, Nanded, India for providing research facilities. The authors are grateful to the Sudhakarrao Naik Institute of Pharmacy, Pusad Dist Yavatmal, Maharashtra for providing laboratory animal research facilities. Authors would like to thank Dhande Pathlab Diagnostic Pvt. Ltd. Pune, India for their kind support during hematological and all other lab studies.

Author's contributions

D carried out all experimental work, analysis, interprets the study results, and inscribed the major part of manuscript. SCD was associated in supervising and advising experimental work. All authors go through the manuscript in detail and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval

All the experimental animals were procured from and study protocol was approved by the Institutional animal ethical committee (Approval No.: CPCSEA/IAEC/CP-PL/21/2022), animal care and handling were followed as per the CPCSEA guidelines from ministry of animal husbandry in India.

Consent for publication

Not Applicable

Competing interests

The authors declare that they have no competing interests.

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