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NIGELLA SATIVA LOADED PLGA NANOPARTICLES: A PROMISING ALTERNATIVE THERAPEUTIC AGENT AGAINST CHRONIC SCHISTOSOMIASIS MANSONI

By

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Abstract

Praziquantel **(**PZQ) alone didn't improve histopathological damage of chronic schistosomiasis. *Nigella sativa* decreased the egg granuloma severity and histopathological changes in schistosomiasis. PLGA is regarded as an ideal polymer for drug delivery systems.

This study evaluated the effect of NSO, NSO-loaded PLGA nanoparticles alone and combined with PZQ on egg granuloma histopathology in *S. mansoni* Swiss Albino mice

A total of 48 mice were divided into 6 groups of 8 mice each: Control negative: neither infected nor treated; control positive: infected and not treated; NSO mice: treated with NSO; NP1 mice: treated with NSO/PLGANPs; NP2 mice: treated with a half dose of NSO/ PLGANPs; and NPP mice: treated with PZQ and half dose of NSO/PLGANPs. All mice were sacrificed for histopathological evaluation of Liver egg granuloma number and diameter, oogram pattern, type and state of egg granuloma in all mice groups

The results showed that NPP mice caused highest number of dead ova (91.63±1.41) followed by NP1 mice (14.88±2.03). Also, it caused the highest reduction in number (72.92%) and diameter (42.01%) of egg granuloma, followed by NP1 mice (67.53% & 34.42% respectively). The fibro-cellular granuloma was markedly increased from 15% in control positive to 63% & 43% in NPP & NP1 mice respectively. NPP mice showed the highest number of dead eggs (58%) than NP1 ones (28%) as compared to other groups and hydrobic hepatocytes degeneration was improved in all treated mice, with fewer inflammatory infiltrates in the liver.

Keywords: NSO, PLGA, *Schistosoma mansoni*, Egg Granuloma, Histopathology.

Introduction

In the 2030 roadmap for neglected tropical diseases (NTDs), WHO developed the goal of schistosomiasis elimination as a public health issue **(WHO, 2020).** Although PZQ is the best medication to treat all five schistosome species (Tesfie, 2020), it has a lot of disadvantages, such as poor pharmacokinetic profile, incomplete efficacy profile, big tablet size, and bitter taste (von Seidlein, 2015). Stronger evidence of PZQ resistance in *Schistosoma mansoni* has also been found (Pinto-Almeida, 2016). Also, the histological damage typical of chronic schistosomiasis is not resolved with PZQ alone. Therefore, new approaches that target infection-associated pathogenesis as well as parasites was required (Gouveia, 2018). *Nigella sativa* has been shown to have wide range of anti-helminthic and antiprotozoal properties. It also has the ability to enhance hepatic pathology in schistosomiasis treatment (Abououf, 2018). *Nigella sativa* oil has the potential to decrease ova deposited number in liver and intestine in *S. mansonai* infected mice. Also, NSO reduced the granuloma sizes and elevated the quantity of dead ova in intestinal wall (Mahmoud, 2002). Also, *N. sativa* extract led to damage and calcifications of the eggs in liver and spleen with decreasing granuloma size in *S. mansonai* infected hamsters (Fadladdin, 2022). Nano-delivery systems are fresh developing sciences using nanoparticles as diagnostic tools or to convey therapeutic drugs for certain targeted positions in an organized manner (Patra, 2018). The European Medicines Agency (EMA) and FDA have licensed PLGA nanoparticles in drug delivery systems, diagnosis, various fundamental and clinical research applica-

tions, as one of the most widely used synthetic polymers in biomedical field, along with biocompatibility and biodegradability (Martins, 2017).

This study aimed to evaluate the therapeutic effect of NSO loaded PLGA nanoparticles alone or combined with PZQ on the chronic schistomiasis *mansoni* in infected mice.

Materials and Methods

Study design: The study was carried out from September 2022 to April 2023, in *Schistosoma* Biological Supply Centre (SBSC), Theodore Bilharz Research Institute (TBRI) in Giza.

Experimental animals: Forty-eight laboratory-bred Swiss Albino mice (CDI strain) each weighed 18-20g was purchased (SBSP).

Mice were maintained during the study in an air conditioned room at 21ºC and allowed food with 24% protein. They were divided into six groups of eight mice each, two controls (negative and positive), and four infected treated mice. Treatment with NSO alone, NSO/PLGANPs full dose, NSO/PLGANPs, half dose, and a combined of half dose NSO/PLGANPs and PZQ were given. Parameters were tissue egg granuloma number and diameter, oogram pattern, type and state of tissue egg granuloma and liver egg granulomas histopathology.

Mice infection: Eight mice were left as control negative (neither infected nor treated), Groups 2-6 of mice were subcutaneously infected with freshly shed 60±10 cercariae/mouse from infected *B. alexandrina* snails, also purchased from SBSP, TBRI, Giza.

Treatments: Capsules of NSO (Baraka) were purchased from Pharco Egypt. The oil of each capsule was dissolved in 4ml corn oil and introduced orally to mice in a dose of 1140mg/kg.

Praziquantel (PZQ) tablets were purchased from EIPICO Pharmaceutical, Egypt, suspended in 2% Cremophore-El (Sigma-Aldrich Chemical Co, St. Louis, MO). Six-week post infection, PZQ was introduced orally by stainless steel cannula, at a dose of 500mg/kg body weight for 2 consecutive days.

PLGA solution preparation: PLGA with 46 770 molecular weight and a DL-lactide to glycolide copolymer ratio of 85:15 was obtained from Medisorb®, Du Pont Co., USA. 500mg of PLGA was dissolved in 12.5ml of mixture of acetone and dichloromethane, ethanol, or methanol; purified using an ultrafiltration and the nanoparticles mean diameter was measured by a laser particle analyzer.

Nigella sativa loaded PLGA nanoparticles (NS/PLGANPs) preparation (Murakami *et al*, 1999): It was prepared by adding PLGA nanoparticles solution to a 500mg/2ml solution of NSO, followed by NS/PLGANPs separation from the aqueous suspension by 30 minutes centrifugation at 20,000g and 14°C. The protein content in the supernatant (free NSO) was determined by the Bradford protein assay spectrophotometric method. The NSO encapsulation efficiency (EE) and loaded capacity (LC) of PLGA nanoparticles were calculated as follows: EE%= [(A-B)/A] ×100 %LC= [(A-B)/C] ×100. Where A= NSO total amount, B= NSO free amount and C= PLGA nanoparticles weight.

NS/PLGANPs characterization by SEM & histogram: SEM images showed that most particles were almost spherical with smooth surface morphology. SEM revealed that conjugating PLGA nanoparticles with NSO did not alter the morphology of nanoparticles alone, despite some nanoparticle aggregation after storage. Histogram showed the size distribution of NS/PLGANPs. Size distribution was determined by FTIR (Bates *et al*, 1978) as 40nm (46%), ~60nm (20%), and about 80-120nm (34%).

Experimental design: Mice were divided into six groups of eight mice each. Control negative: neither infected nor treated, control positive: infected, but not treated, NSO mice: treated with *N. sativa*, NP1 mice: treated with of NSO/PLGANPs full dose, NP2 mice: treated with NSO/PLGANPs half dose and NPP mice: treated with combined PZQ and NSO/PLGANPs half dose.

Treatment schedule: *N. sativa* oil (1140 mg/kg) was given daily to NSO mice. NSO/

PLGANPs (1140mg/kg) were given daily to NP1 mice, and NSO/PLGANPs (570mg/kg) were given daily to NP2 mice. Combined PZQ (500 mg/kg divided in half over 2 consecutive days) and NSO/PLGANPs (570mg/kg daily) were given to NPP mice. Treatment began in the 7^{th} week post infection and lasted for two weeks. All mice were gently euthanized at the 9^{th} week post-infection.

Tissue egg counts: After being weighed independently, liver and intestine were each put in a test tube with 5ml. of 5% KOH solution and incubated for 24 hours at 37°C until hydrolyzed. The digest was shaken and 3 samples were taken and 3 slides from each tissue were used to calculate the average number of ova (Cheever, 1968).

Oogram pattern: A part of small intestine was put into a petri-dish, cleaned and gently opened longitudinally along its length, and 1 cm three pieces each were separated, dried and comprised between a slide and a cover. This was microscopically examined for *S. mansoni* eggs, which were counted and classified as mature, immature, and dead ova based on developmental stages (Pellegrino, 1962).

Histopathological studies: a part of liver from each mouse was removed and immersed in 10% buffered formalin and proce- ssed for paraffin sectioning at 5µm stained with H & E and microscopically examined (Mangoud *et al*, 2004). To measure average of two lesion diameters at right angles to one another, the mean of each liver granuloma was calculated (von Lichtenberg, 1962).

Statistical analysis: STATA version 14.2 (Stata Statistical Software: Release 14.2 College Station, TX: StataCorp LP.) was used to analyze data. The mean, standard deviation, median, and range were used to depict quantitative data. ANOVA test combined with Bonferroni post-hoc test evaluated data. The Mann-Whitney test was used for pairwise comparisons and Kruskal-Wallis test was used for abnormally distributed data. Both Fisher exact and Chi-square tests were used to compare qualitative data displayed as numbers and percentages. Excel application created the graphs. A $P > 0.05$ was considered significant.

Ethical approval: Scientific Ethical Committee (MREC), Faculty of Medicine, Sohag University approved the study, with the IBR registration number (Soh-Med-21-04-12**).**

Results

Oogram pattern: NPP mice showed the highest increase in the mean dead ova number (91.63±1.41) followed by NP1 mice (14.88 ±2.03), and NSO mice (10.13±1.25), NP2 mice showed the lowest increase (9±1.31) in dead ova as compared to control. Also, NPP mice showed the highest reduction in mean mature ova number (8.38±1.41) followed by NP1 mice (38.75±0.71), NSO mice (40.5± 4.44), and NP2 mice (43.75±3.24). The mean immature ova number in NPP mice showed the highest reduction (0), NP1 & NP2 mice showed lowest reduction (45.13±2.53 & 47.33±2.66 respectively) as compared to control. But, NSO mice were not affected (49.38±4.62).

Tissue egg load: NPP showed highest reduction % in liver egg load (71.82%) followed by NP1 (39.02%), NP2 (24.67%), and then NS (17.27%). Also, NPP mice showed the highest reduction % in intestine egg load (73.16%) followed by NP1 (42.65%), NP2 (36.22%) mice, but NSO (35.94%) mice showed the lowest reduction % in liver and intestine egg load.

Granuloma number and diameter: The number was markedly decreased to 72.92%, 67.53% & 65.03% in NPP, NP1 & NP2 mice, respectively. The diameter was decreased to 42.01%, 34.42% & 31.88% in NPP, NP1 & NP2 mice, respectively. NSO mice showed the least reduction in granuloma number (48.03%) and diameter (28.21%) as compared to other treated mice.

Types of granulomas: Fibro-cellular granuloma was markedly increased from 15% in control positive to 63% in NPP & 43% NP1 mice. It increased to 35% in NP2 mice and to 25% in NSO mice. Cellular granuloma was markedly decreased from 85% in contr-

ol positive to 37% in NPP & 57% in NP1, to 65% in NP2 and to 75% in NSO mice.

NPP mice showed the highest degenerated eggs number (58%), but lowest intact ones (42%). NP1 mice showed more degenerated eggs (28%) and less intact ones (72%) as compared to NSO (22% & 78% respectively) and NP2 (17% & 83% respectively).

Liver egg granulomas in control positive mice were large and surrounded with heavy eosinophilic infiltration with macrophages, lymphocytes and thick collagen fiber dispositions. Granulomas in NSO mice were smaller, but demarcated from surrounding tissue compared to control positive. Granulomas in both NP1 & NP2 mice were the smallest with more packed inflammatory cells collagen fibers, but less eosinophil. Granuloma in NPP mice showed smallest diameter with few collagen fibers deposition and eosinophilia. Hepatocyte hydrobic degeneration was improved in all treatment mice, with reduced inflammatory infiltration in the liver tissues.

Details were given in tables (1, 2, 3, 4 & 5) and figures (1, 2, 3, 4, 5, & 6).

Table 1: Oogram pattern in *S. mansoni* infected mice treated 7 weeks post infection and sacrificed 2 weeks post treatment.

Mice group	Oogram pattern M± SD and P value		
	Immature ova	Mature ova	Dead ova
Control positive	48±2.97	47.13±3.31	4.88±1.55
NS	49.38±4.62	40.5±4.44(0.001)	10.13±1.25
P-value	1.00	0.001	<0.000
NP1	45.13±2.53	38.75±0.71)	14.88±2.03
P-value	0.60	<0.0001	<0.0001
NP2	47.33±2.66	43.75±3.24()	9±1.31
P-value	1.00	0.29	<0.0001
NPP	0	8.38±1.41)	91.63±1.41
P-value	<0.0001	(<0.0001	<0.0001

Table 2: Tissue egg load infected mice treated 7 weeks post infection and sacrificed 2 weeks post treatment.

Mice group	Liver egg load/gm M±SD (reduction %)	Intestine egg load/gm M±SD (reduction %)
Control positive	6884.3±980.9	8439.6±583.8
NS	5695.1±850.4 (17.27%)	5406.5±1182.4 (35.94%)
NP1	4198.3±750.9 (39.02%)	4839.8±489.9 (42.65%)
NP2	5185.9±450.6 (24.67%)	5382.4±229.9 (36.22%)
NPP	1940±345.9 (71.82%)	2264.9±489.0 (73.16%)

Table 3: Granulomas reduction % in infected mice treated 7 weeks post infection and sacrificed 2 weeks post treatment.

Mice group	Granuloma number M±SD (reduction %)	Granuloma diameter M±SD (reduction %)
Control positive	17.8±2.21	369.42±14.21
NS group	9.25±0.31 (48.03±3.2)	265.19±23.26 (28.21±2.1)
NP1 group	5.78±1.31 (67.53±5.1)	242.27±21.13 (34.42±3.4)
NP2 group	6.17±0.65 (65.03±4.3)	251.65±22.32 (31.88±3.2)
NPP group	4.82±1.24 (72.92±5.9)	214.24± 24.27 (42.01±4.2)

Table 4: Granulomas in *S. mansoni* infected mice treated 7 weeks post-infection and sacrificed 2 weeks post treatment.

Mice group	Cellular granuloma	Fibro- cellular granuloma	Fibrous granuloma
Control positive	121 (85%)	21 (15%)	0
NS	56 (75%)	19 (25%)	0
NP1	26 (57%)	20 (43%)	0
NP2	32 (65%)	17 (35%)	0
NPP group	14 (37%)	24 (63%)	0

Table 5: Eggs in *S. mansoni* infected mice treated 7 weeks after infection and sacrificed 2 weeks post treatment.

Mice group	Intact eggs	Degenerated eggs
Control positive	134 (94%)	9 (6%)
NS	58 (78%)	16 (22%)
NP1	33 (72%)	13 (28%)
NP2	41 (83%)	8 (17%)
NPP	16 (42%)	22 (58%)

Discussion

In the present study, NSO group showed marked increase in dead ova mean number (10.13±1.25) and moderate decrease in the

mature ova mean number of (40.5±4.44) as compared to control mice (4.88±1.55 & 47.13±3.31 respectively) without affection on number of immature ova. This agreed with Mahmoud *et al*. (2002), who found that NSO had a little eff-ect on the immature ova, but dramatically raised the quantity of dead eggs and decreased the number of mature ova (19-20%). But, the result disagreed with Abououf *et al.* (2018), who reported that NSO significantly increased the mean number of dead ova (4.08 times as cont-rol), but without effect on mature ova and significantly decreased immature ova percentage.

In the present study, NSO/PLGANPs significantly affected the female worms oviposition in NP1 mice, with markedly increased the mean dead ova (14.88±2.03) and decreased the mean mature ova (38.75±0.71). In NP2 mice treated with a half dose of NSO/ PLGANPs, the immature ova were hardly affected. This agreed with El-Menyawy *et al.* (2021), who found a highly significant decrease in the mature ova (8.50±5.648) and a highly significant increase in the mean dead ova (82.33±4.082) with 71 times as control) in TQ/ChNP treated mice, but immature ova were not affected (9.20±4.050). But, this disagreed with Elawamy *et al.* (2019), who detected that NS/ChNPs significantly increased the dead ova number from 3.4% in control mice to 32.5% in treated ones, and decreased the immature ova from 52% in control mice to 4% in treated ones.

In the present study, NPP treated mice only showed zero reduction in mean immature ova number compared to control (48±2.97) and significantly decreased the mean number of mature ova (8.38±1.41), but significant increase in the mean dead ova number (91.63±1.41). This agreed with Abououf *et al.* (2018), who reported that in mice received combined therapies, NSO enhanced the effects of PZQ, causing a substantial decrease in the mature ova number (1.8±4.02), and a high significant increase in the dead ova (98.2±4.02), with complete elimination of immature ova (0.0±0.0). This agreed with Mahmoud *et al.* (2002), who reported that when NSO was given with PZQ, mature ova increased to 85%, and dead ova decreased than with PZQ alone. Abo-Sheishaa *et al.* (2019) reported that PZQ-loaded PLGA treated mice showed significant increase in dead ova. Amer *et al.* (2022) found that PZQ-encapsulated niosomes caused a significant rise in dead eggs with complete elimination of immature ones.

In the present study, combination of NSO with PLGANPs augmented the NSO effect on eggs in liver either in NP1 mice with full dose or in NP2 mice with a half dose with reduction of 39.02% & 24.67% respectively. The NSO mice treated alone, reduction was 17.27%. The combined NSO and nanoparticles showed same effect on intestinal eggs in NP1 mice with reduction (42.65%), but with less effect in NP2 mice NSO treated with a half dose with a reduction (36.22%) that was more or less equaled to NSO treated mice (35.94%). Combined NSO/PLGANPs with PZQ in NPP mice significant increased the PZQ effect on ova in liver and intestine causing reduction (71.82% & 73.16% respectively). This agreed with Abououf *et al.* (2018), who reported that mice given NSO alone showed a high reduction in intestinal eggs (81.45%) and a moderate reduction in liver eggs (57.86%), but both NSO and PZQ therapies showed the great reduction in intestine and liver eggs (91.76% & 75.76%, respectively). Also, this agreed with Elawamy *et al.* (2019), who found that eggs reductions in liver (84.5%) and intestine (67.8%) in NS/ChNPs treated mice. El-Menyawy *et al.* (2021), who found that ova in liver and intestinal tissues with TQ/ChNP treated mice, were 73.295% & 72.89% respectively. But, the present results were higher than that of Mahmoud *et al.* (2002), who reported that mice treated with *N. sativa* alone reduced eggs in liver (33.7%) and intestine (33.2%), but mice treated with PZQ different doses showed reductions in liver and intestine eggs from 77.1% to 80.7% & 93.8 to 92.9%, respectively, proving the PLGA effect on NSO

and PZQ in decreasing eggs in tissues. This agreed with El Gendy *et al.* (2019), who reported that liposome encapsulated PZQ reduced eggs/gram in liver (99.3%) and intestine (99.5%). Also, Amer *et al.* (2022) found that PZQ-encapsulated niosomes raised the eggs reduction in liver (97.68%), and intestine (98.56%). Mokbel *et al.* (2020) reported that curcumin loaded gold-nanoparticles, caused eggs reduction (77.26%) in intestine and (83.85%) in liver, but Cur-GNPs combined with PZQ decreased eggs in intestine (73.77%) and liver (46.67%), which dis-agreed with the present study results.

In the present study, PLGA augmented the NSO effect on liver granulomas in NP1 and NP2 treated mice with reductions of 67.53% & 65.03% respectively. Also, it augmented the effect on liver granuloma diameters in both groups with reductions of 34.42% & 31.88% respectively, but NS mice treated by NSO showed reduction in granuloma number and diameter by 48.03% & 28.21% respectively. NPP mice showed the high reduction in mean diameter of granulomas with 72.92% & 42.01% respectively. Also, this was high than that of Sheir *et al.* (2015), who reported that the mean granuloma diameter decreased (32.2%) in mice treated by *N. sativa* and PZQ combined ones. Besides, Abououf *et al.* (2018), who found that granuloma size was reduced (26.69%) in NSO treated mice as compared to control, but comb ined therapies showed slightly significant reduction in granulomas diameter (27.06%). This agreed El Gendy *et al.* (2019), who reported that liposome encapsulated PZQ gave high significant reduction in number and diameter of liver granuloma (97.6% & 98.1% respectively), and Mokbel *et al.* (2020), who found that Cur-GNPs combined with PZQ, caused 70.1% reduction in granuloma size. But, this disagreed with El-Menyawy *et al.* (2021), who reported that the mean liver granulomas decreased (71.83%) in TQ/ChNP treated mice, and decreased in chitosan treated mice (40.84%). They added that TQ/ ChNP significantly reduced granuloma diameter (65.5±16.54), but chitosan-treated mice didn't cause reduction (119.1±32.60) as compared to control mice (125.6±20.88).

The present study results were also, high than that of Elawamy *et al.* (2019), who reported that compared to control, NS/ChNPs decreased the granuloma diameter (46.3%) and number (50.9%) and disagreed in that NS/ChNPs combined with PZQ that showed low reductions (41.3 & 32% respectively). Also, this disagreed with Mahmoud *et al.* (2002), who found that PZQ and *N. sativa* combined therapy didn't treat liver granuloma diameter.

In the present study, NPP showed marked increase in fibro-cellular granuloma (63%) and in degenerated eggs (58%) compared to control (15% & 6% respectively). The NSO/ PLGANPs full dose led to a high increase in fibro-cellular granuloma (43%) and in degenerated eggs (28%) in NP1 mice, but in NP2 mice with a half dose led to moderate increase in fibro-cellular granuloma (35%) and less increase in degenerated eggs (17%). NSO treatment led to less fibro-cellular granuloma (25%) and more degenerated eggs (22%). This agreed with Sheir *et al.* (2015), who found that combined *N. sativa* and PZQ reduced fibro-cellular granuloma compared to controls. Also, it agreed with El-Menyawy *et al.* (2021), who found that degenerated ova increased significantly in TQ/ChNP treated mice (90%) compared to control (5%), degenerated ova with chitosan (73%), and that TQ/ChNP treated mice led to less fibrocellular granulomas with deformed ova.

In the present study, liver egg control showed massive cellular granulomas with intact cellular miracidia inside and chronic inflammatory cells with high eosinophils. Also, there was focal atypical hyperplasia, and hydropic alteration in liver tissues. NSO treated mice showed fibro-cellular smaller granulomas with degenerated miracidia that were demarcated from surrounding tissues. NP1 & NP2 treated mice with combined PLGA with NSO enhanced liver granulomas, and fibro-cellular granulomas were smallest with

more inflammatory cells and collagen fibers, but less eosinophils, which improved hydrobic degeneration of liver. NPP mice showed least granuloma sizes, with fibro-cellular, eosinophilic infiltration, few collagen fibers deposited, less inflammation, and degenerated miracidia, with improved hydrobic degeneration of hepatocytes. This agreed with Gouveia *et al.* (2018), who found that combined NSO/PLGANPs & PZQ induced liver pathology, than PZQ alone in chronic schistosomiasis *mansoni*. Also, agreed with Abououf *et al.* (2018), who found that liver pathology in NSO-treated mice was improved, with mild hydrobic degeneration and small fibro-cellular granulomas, and that NSO & PZQ mice showed a slight improved in cloudy swelling, hydropic degeneration, and fibro-cellular granulomas. It agreed also, with El-Menyawy *et al.* (2021), who found that TQ/ChNP treated mice showed few degraded granulomas with deformed ova, and little improved liver, but with more collagen deposition and lobular inflammations.

Conclusion

PLGA nanoparticles enhance the activities of *N. sativa* oil (NSO/PLGANPs) against *Schistosoma mansoni* in infected mice.

Recommendation

The high effectiveness of NSO/ PLGANPs in treating *S. mansoni* infected mice as a drug delivery system must be tried with human schistosomiasis infected patients.

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Explanation of figures

Fig. 1: NS/PLGANPs character. a- SEM of NS/PLGANPs regularly, spherical with a smooth surface, b- Histogram showed mean size 50nm.
Fig. 2: Liver positive control showed a sizable cellular granuloma with chronic inflammatory cells, predominantly eosinophils, and cellular miracidium in egg (arrow), nearby hepatocytes exhibited hydropic degeneration and focal atypical hyperplasia. Fibro-cellular granuloma 15% and cellular granuloma 85%, a- Stained with hematoxylin-eosin (H & E, x100) and b- Stained with Masson's trichrome stain (MT, x100).
Fig. 3: NSO treated mice granuloma smooth, well-defined border and clearly separated from surrounding tissue. Fibro-cellular granuloma 25% & cellular granuloma75%, a- Stained (H & E, x100) and b- Stained (MT, x100).
Fig. 4: NP2 treated mice fibro-cellular granuloma 35% and cellular granuloma 65%, a- Stained (H & E, x100) and b, Stained (MT, x100).
Fig. 5: NP1 treated mice fibro-cellular granuloma 43% and cellular granuloma 57%, a- Stained (H & E, x100) and b- Stained (MT, x100).
Fig. 6: NPP treated mice fibro-cellular granuloma smooth, well-defined boundary, separated from surrounding tissue, with fewer eosinophils and collagen fibers, fibro-cellular granuloma 63%, and cellular granuloma 37%, a- Stained (H & E, x100) and b- Stained (MT, x100).