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RESEARCH PAPER

Investigate the Impact of Propolis-Loaded Lipid Nanoparticles (PLNs) on Antioxidant Activity in Male Rats

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ABSTRACT

The aims of study is detecting the impact antioxidant Propolis-loaded lipid nanoparticles (PLNs) in male rats. Sixty-four male mature male Wister rats (aged 90 days and weighted 148±10 g) divided four group. Group 1 were Control group drenched with distilled water for (28) days and Second group were administered Propolis extraction (PL) (10 mg\kg\day), third group administered with free LNPs (20mg \ Kg) and the fourth group administered with LNPs-PL (20mg\ kg \day). The result of X-Ray diffraction of LNPs-PL in major peak at 28.56° in the diffract to gram has moved to a lower 2θ value. The Zeta Potential (ZP) values of all formulations prepared were measured to be negative. The result indicates that the ZP ranges between 33.7 mV to -48.7 mV with the smallest size comprising the PLNs. The PDI value in the case of LNPs- PL were 0.265. The change in liver enzyme indicated a significant increase (P 0.05) in the expression of gene of Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and Alkaline phosphatase (ALP) in G4 group in comparison of control group (G1) 14 and 28 days later. The results also indicated that G2 group recorded a significant increment (62 C (P600.05)) after a period of 28 days compared to the same group after 14 days. Whereas, the transcript output of the Antioxidants revealed that there was a significant reduction (P Effect on Shell deformities on the gene expression of Super Oxide Dismutase (SOD1) in the G4 group than in the control group (G1), after 14 and 28 days. The results also indicated a huge reduction (P14 days as compared with G4 group after 28 days (P 0.05).

How to cite this article
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INTRODUCTION

Propolis is a resinaceous complex made by honeybees using the extracts of various plant resources loaded with bioactive compounds (flavonoids, phenolic acid, and esters). It has very diverse pharmacological effects, such as possessing antioxidant, antimicrobial, anti-inflammatory, and anticancer properties. Yet, low water solubility and bioavailability, as well as chemical instability, are the main limitations to the potential of propolis as a therapeutic agent. In overcoming these shortcomings, lipid-based delivery systems have

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signified as a viable method of improving stability, solubility and targeted delivery of propolis-derived compounds [1]. Nanoparticles (NP) are colloidal particles loaded with active chemicals that had been dissolved, entrapped, adsorbed, or adhered to the particle [2]. Some of the advantages associated with the use of nanotechnology in phytoceuticals are easy to manufacture as prolonged release systems, better permeability, better physicochemical stability, better tissue dispersion, and enhanced solubility and bioavailability. ROS and other oxidative stress-induced intermediates Death, prolongation of chronic inflammatory responses, and fibrogenesis, especially hepatic chronic wound healing and liver fibrogenesis, are all affected by ROS and other oxidative stress-induced intermediate [3]. Patients with HCV infection had lower levels of antioxidants and higher amounts of ROS/RNS [4]. It has been discovered that individuals who are overheated may benefit greatly from antioxidant therapy. Still, it appears that traditional antioxidants such as vitamins C and E are ineffective [5]. The goal of this experiment was to determine the impact of antioxidant Propolis-loaded lipid nanoparticles (PLNs).

MATERIALS AND METHODS

Animals and Housing

In this investigation, sixty-four adult male Wister rats weighing 150±10 g and 90 days old were utilized. Throughout the experiment, a 12-hour light/dark cycle was observed, with the light turning on at 6:00 a.m. and off at 6:00 p.m. The room temperature was kept at 23 ± 2 ºC.

Experimental design

The subsequent treatment was given to sixty-four male Wister rats for a total of twenty-eight continuous days when they were randomly split into two equal groups of fifteen animals each [6]:

first group(G1): will be kept without treatment as negative control.

2- Second group(G2): Will be orally administered Propolis extraction (PL)

(10 mg\kg\day) for 28 days

3- Third group (G3): Will be orally administered with free LNPs (20mg \ Kg) for 28 days.

4- Forth group (G4): will be orally administered with LNPs-PL (20mg\ kg \day) for 28 days. The following two subgroups will be formed from the second group:

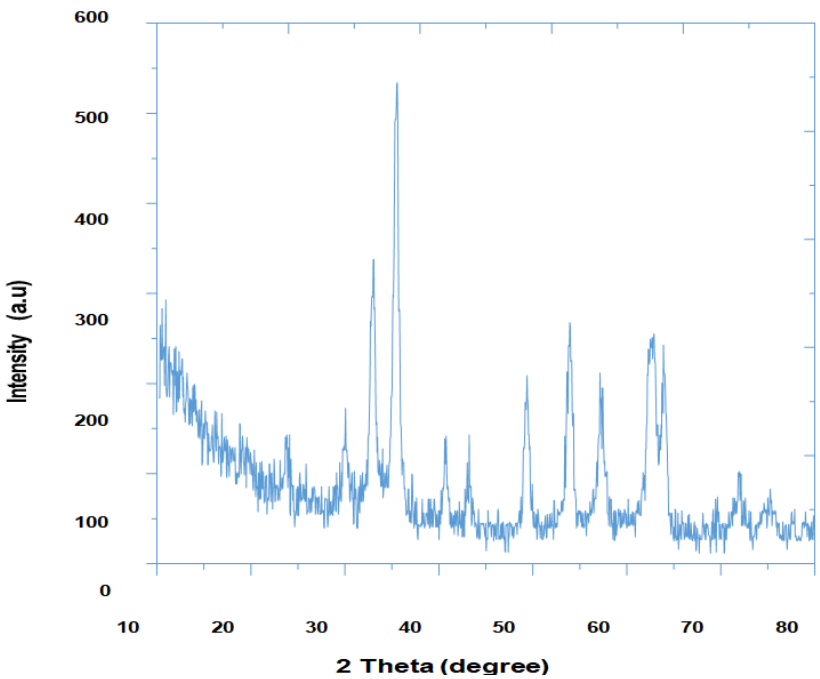


Fig. 1. XRD of LNPs-PL surface

Table 1. Primers of 18S rRNA gene of Entamoeba species

Prime name	Sequence (5'-3')	Product Size	Reference
AST	AGATGACTTGGGCAAAGGTG AATCACACCACAAGCCAAGC	563 bp	
ALT	ATTTGACCAGCGTGCCATAG AACAGCCTTCGGTTTTGGTC	587 bp	
ALP	ATGTGTGAGGCTTGATGGGG AATGGAAGGTCAGCCATGGG	531 bp	
GSS	GCCACCACCTGCTTCAAAAG GAGGCCAGCAACAGGTTTTG	114 bp	[9]
GAPDH	TCGTATTGACCAAGGCCACC CAGGGTGTTTAGGGGAGCAG	136 bp	

A- Subgroup 1: Following a 14-day course of therapy, eight male rats will be slaughtered.

B- Subgroup 2: Following a 28-day course of therapy, eight male rats will be slaughtered.

During the entire trial, male rats have been observed. A 0.3 ml ketamine + 0.1 ml xylazine injection per kg body weight intraperitoneally was used to anesthetize male rats at the conclusion of each treatment and control subgroup session. Male liver samples were taken and immediately stored at -70 ºC to assess the mRNA expression levels of GSS and GAPDH, the housekeeping gene, using a q RT-PCR approach based on Syber Green dye. The kidney, liver, and samples have been removed, and they are kept at 10% formaline until the tissues are processed.

Particle size and zeta potential

Dynamic light scattering method (ZetaSizer Nano-ZS) was used to determine the particle size, polydispersity index and zeta potential of the SLNs formulations [7].

Determination of Encapsulation and Loading Efficiency

EE can be referenced as the percentage of total quantity of the PL received through the formulation after doing the procedure. Loading capacity (LC) of the stimulation mass of entrapped GO to the total mass of lipid (stearic acid). EE and LC were calculated as was explained above. The 10 mg LNPs-PL formulations were well weighed by dissolving them with 10 ml methanol. This was followed by centrifuging of the samples at 9,000 rpm within 30 minutes. The use of a UV Vis spectrophotometer (T80+ UV/VIS Spectrophotometer, PG Instruments Ltd.).

Differential scanning calorimetry (DSC)

DSC scans of PL and LNPs-PL were carried out in a Mettler DSC 821e (Mettler Toledo, Germany). Five mg of the samples were placed into aluminum oxide pans, sealed, and subjected to analysis. As a guide, an empty aluminum pan was used. DSC was done at a 25 to 250 °C temperature range at the rate of 5 °C/min under N2 flow and the melting point of SLN dispersions was compared to the bulk lipid [8].

The primers

The study used primers for the housekeeping gene GAPDH and the target genes for glutathione gene expression, glutathione GSH gene primers.

These primers were created using the online Primer 3 creation tool and the NCBI Gene Bank database. With help from the Bioneer firm in Korea, the primers were used to quantify the levels of gene expression using the q RT-PCR technique based on SYBER Green DNA binding dye (Table.1) . The manufacturer's instructions were followed when using the genotyping isolation DNA.

1. Glutathione synthetase (GSH) in Rattus norvegicus, mRNA; NCBI reference sequence: NM_012962.1

2- Gamma-glutamyltransferase (ALT) from Rattus norvegicus, mRNA; NCBI Reference Sequence: NC_051342.1

3- Glutamic-oxaloacetic transaminase 2 (AST) in Rattus norvegicus, mRNA; NCBI Reference Sequence: NC_051354.1

4- NCBI Reference Sequence: NC_051340.1; Rattus norvegicus alkaline phosphatase, biomineralization (ALP), mRNA

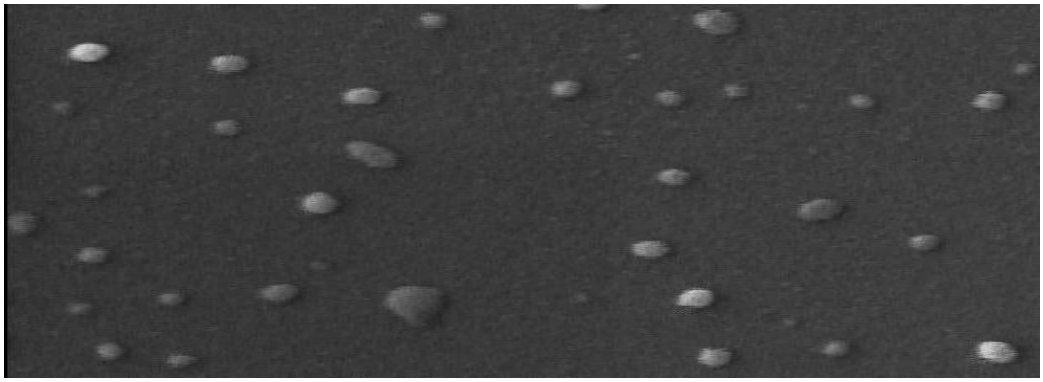


Fig. 2. Appearance of LNPs-PL under scanning electron microscopy (SEM image of LNPs-PL at 50,000× magnification. Scale bar: 200 nm)

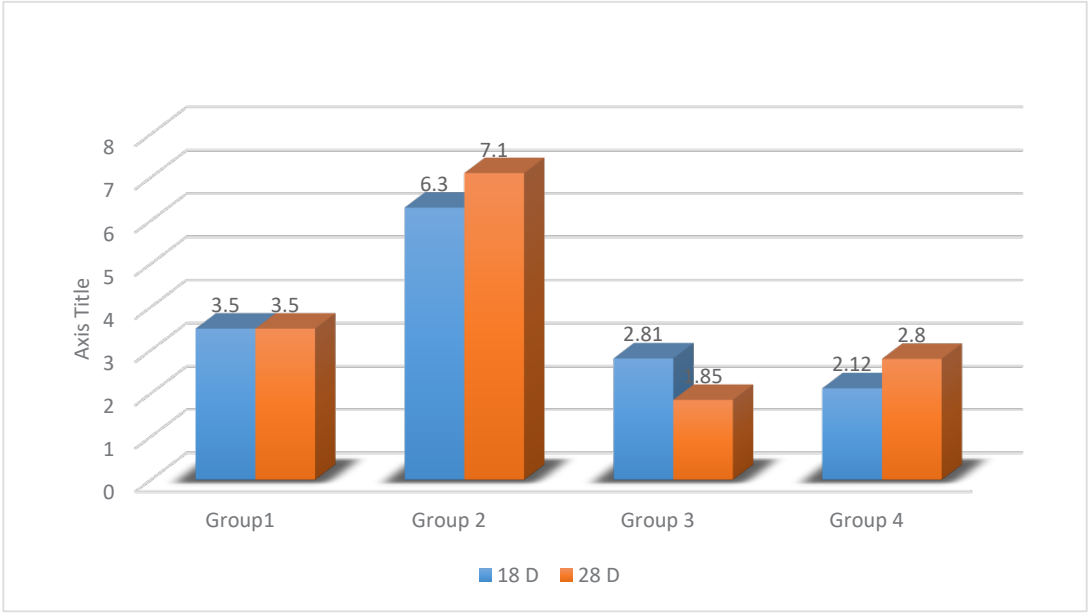


Fig. 3. The role of LNPs-PL on alanine aminotransferase (ALT), LSD = for period=0.152, for groups = 0.231. Group 1: Control group, drenched with distilled water for 28 days. Group 2: Drenched with PL (20 mg\kg\days) for14, 28,days. Group 3: Drenched with LNPs (20 mg\kg\days) for14, 28, days. Group 4: Drenched with LNPs-PL (20 mg\kg\days) for14, 28, days.

5-Glyceraldehyde-3-phosphate dehydrogenase (Gapdh), mRNA, Rattus norvegicus NM_017008.4 is the NCBI reference sequence.

Statistical Analysis

The data were analyzed using the Chi-square test and SPSS Preogram (version 18) software (2010). A P value of $p \leq 0.05$ was deemed to indicate statistical significance [9].

RESULT AND DISCUSSION

X-Ray diffraction of LNPs-PL

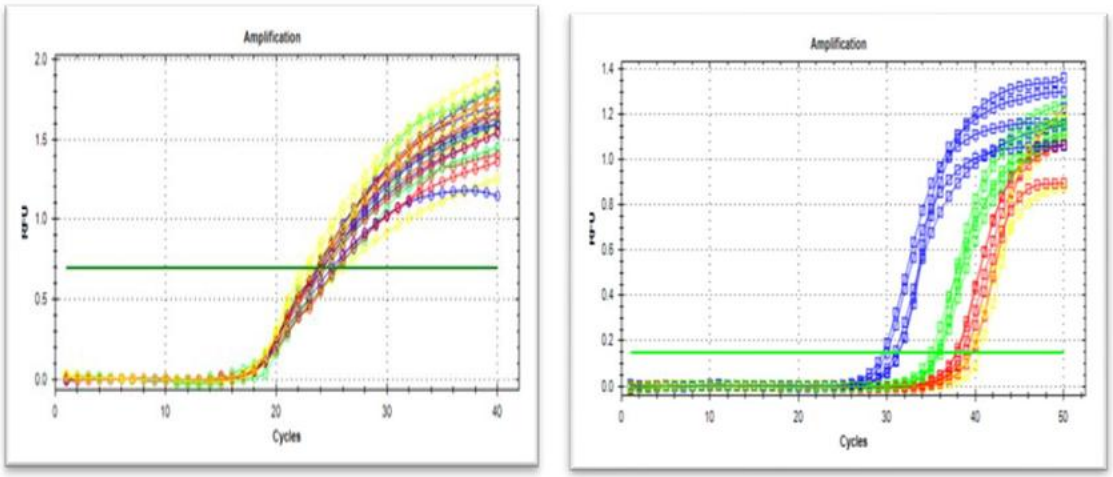
X-Ray diffraction (XRD) The x-ray patterns of LNPs have been captured distinctive peaks that are crisp and strong are readily identifiable in both LNPs and LNPs-PL as shown in Fig. 1. On the other hand, compared to pure PL, the LNPs major peak at 28.56° in the diffract to gram has moved to a lower 2θ value. The high overlap occurring in the peaks indicates that the two oxides are superimposed together, and the width of the band indicates its small crystalline size. The average crystallite size of the synthesized LNPs-PL was calculated by using the Debye-Scherrer equation. The average crystal size of LNPs nanoparticles was 89 nm [10].

Field emission scanning electron microscopy (FE-SEM)

The SEM image of LNPs-PL is displayed in Fig. 2. The SEM scan revealed that the prepared LNPs had a spherical shape. Particle size distribution was similar to DLS. After loading, the nanocapsules had a spherical form, high dispersion, and a limited size distribution [11].

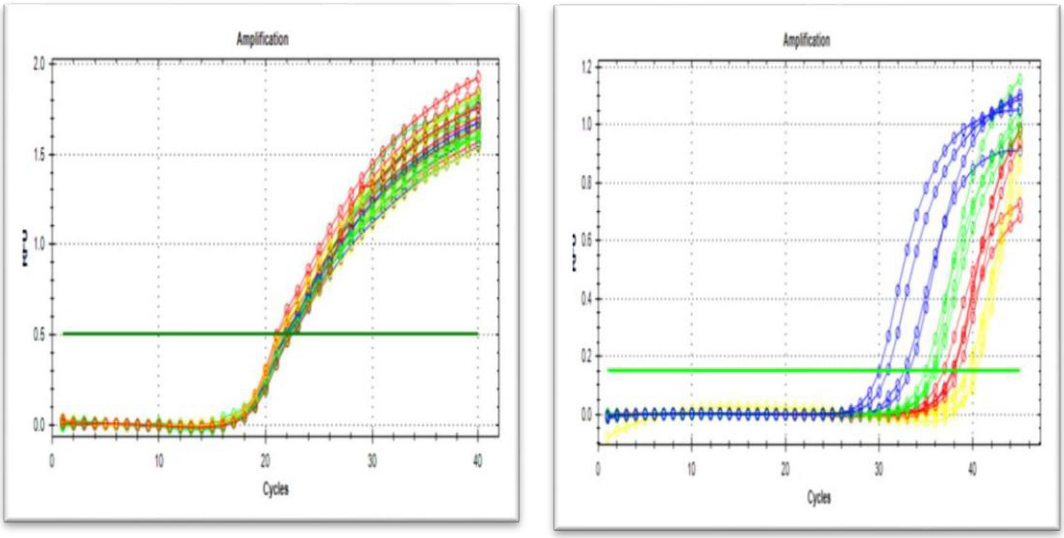
Polydispersity Index (PDI)

The PDI values provide critical insights into the size distribution and homogeneity of the nanoparticle populations. A PDI of 0.418 for the free LNPs. suggests a moderately broad size distribution, indicating some variability in particle size. Conversely, a PDI of 0.265 for the LNPs-PL. indicates a more homogeneous and uniform size distribution compared to the free LNPs. This suggests that the incorporation of propolis extract has contributed to a more uniform population of nanoparticles. Generally, PDI values below 0.3 are considered acceptable for pharmaceutical applications, indicating a relatively homogeneous population. The figure elicits a very clear size increase after loading of propolis. The LNPs-PL peak is shifted to the right and is bigger than that of the free LNPs. The decreased width of the peak in LNPs-PL corresponds to lower PDI value indicating more homogenous size distribution. Noticeably, the LNPs-PL sample has the small peak at the larger size range, which implies that a small portion of the nanoparticles becomes



A B

Fig. 4. (A) Plasmas of the ALT genes in RT-PCR of the treatment and control groups after 14 days. (B) The RT-PCR plots of the housekeeping GAPDH gene were undertaken at 14 days in experimental rats that are treated and untreated.



A. B.

Fig. 5. (A) The ALT gene plot abundance using RT-PCR in the treatment and control group with 28 days of incubation. (B) RT-PCR plots of house keeping gene GAPDH in experimental rats, which were treated and untreated after 28 days.

aggregated. overall, the data indicate that the addition of the propolis extract to the lipid nanoparticles has caused to increase in size and uniformity of the size distribution of the particles. The comparison of the PDI of LNPs-PL in the lower value underlines the idea of a better homogeneity which is beneficial in the pharmaceutical context. The intensity graph, along with size distribution data substantiates these results. The SLNs can play a good role in controlled release and protection of essential oil that is encapsulated because it is spherical. It is explained by the fact that compared to other types of nanoparticles, the spherical form has the longest path of access of essential oil filling nanoparticles and the minimum contact area with the aqueous phase of the dispersed phase [12].

Zeta Potential

When loaded with propolis extract the zeta potential of the lipid nanoparticles further decreases in magnitude to -48.7 mV compared to -33.7 mV. This variation to negative surface charge reveals a considerable change in surface characteristics of the nanoparticles. The propolis extract probably introduces negative values to the surface of the nanoparticles thereby increasing the entire negative charge. A very important parameter in the determination of the stability of the colloidal dispersions is the zeta potential. Generally, zeta potential of more than +30 mV or less than -30 mV may be suggestive of good colloidal stability with the electrostatic repulsion between the particles overcoming the aggregation. The zeta potential range of the free LNPs and LNPs-PL has a range that indicates good stability within the range. It is important to note that a greater level of stability, will be even even greater than that of the free LNPs as indicated by the more negative zeta potential of the LNPs-PL (-50.7 mV). This added stabilization can be explain by the extra number of negatively charged component that the propolis extract has added thereby adding more electrostatic repulsion between the particles and thereby stopping aggregation [13].

Zeta potential distribution shows the number of zeta potential values spread amongst samples. The LNPs-PL have a narrower and homogenous distribution of the zeta potential distribution in comparison to the free LNPs indicating a more evenly distributed surface charge after loading of propolis. The dependence of the peak shift to the more negative values of LNPs-PL supports the fact that more negative surface charging increases, and the incorporation of propolis extract and effect on its surface properties of nanoparticles were noticed to be positive. Finally, the zeta potential of the propolis extract and the lipid nanoparticles shows that a more negative zeta

potential, therefore, greater colloidal stability is achieved due to the addition of propolis extract to the lipid nanoparticles. Further, the zeta potential distribution in LNPs-PL has been found to be more corresponding, which further confirms the homogenous surface charge which is good in terms of stability and performance of the nanoparticle formulation in pharmaceutical formulations. The data depicts an in-depth perception on the surface charge change and the stability induced by the propolis extract [14].

Liver enzymes

Gene expression of alanine aminotransferase (ALT)

The results of the present study demonstrated that there is statistically significant (P 0.5) elevation of the expression of the alanine aminotransferase (ALT) gene of the G2 group. However, after both 14 days and 28 days, a significant reduction (P 0.05) was seen in G3 group and G4 group when

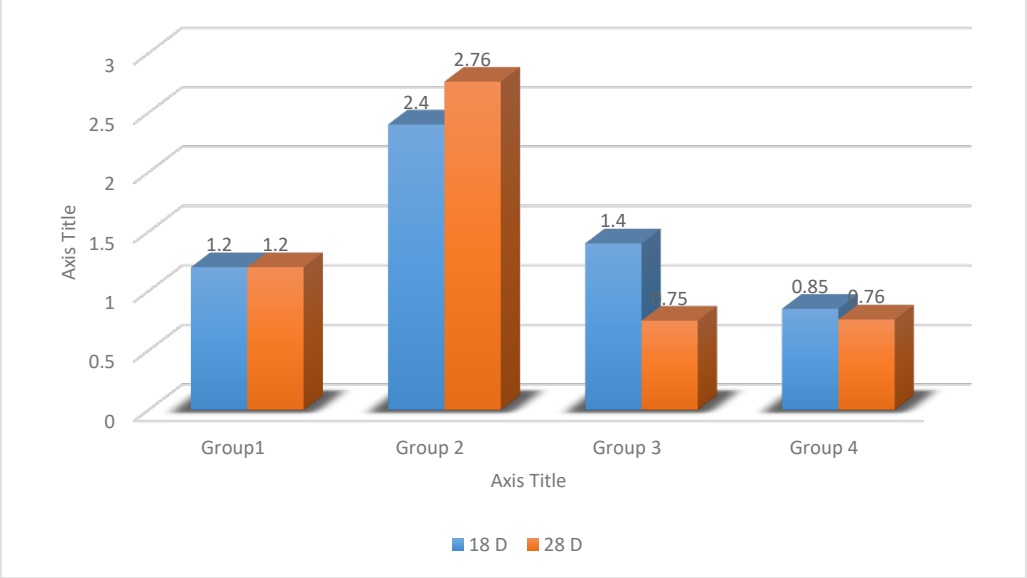


Fig. 6. the result of the LNPs-PL on the alanine aminotransferase (ALT). LSD = for period=0.092, for groups = 0.121. Group 1: Control group, drenched with distilled water for 28 days. Group 2: Drenched with PL (20 mg\kg\days) for14, 28, days. Group 3: Drenched with LNPs (20 mg\kg\days) for14, 28, days. Group 4: Drenched with LNPs-PL (20 mg\kg\days) for14, 28, days.

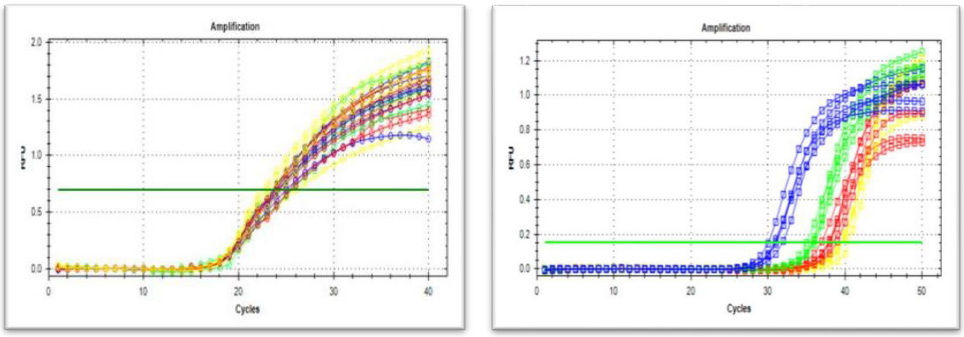


Fig. 7. (A) ADAGN and graph of AST gene in RT-PCR in treatment and control groups after 14 days. (B) RT-PCR graphs of the housekeeping gene GAPDH on the experimental rats of housekeeping gene after 14 days of treatment and untreated.

compared to the control group. Moreover, G2 group had particularly a significant increase (P 0.05) in the expression of ALT at 28 days than it was at 14 days and on the other hand the G3 and G4 groups denatured particularly a significant decrease (P 0.05) at the 28 days relative to the corresponding level of the 14 days (Figs. 3, 4 and 5).

Expression of Aspartate aminotransferase (AST)

It can be concluded that the gene expression of Aspartate Aminotransferase (AST) increased significantly in the G2 group of the current study (P 0.05). Comparatively, there was a drastic decline (P <=0.05) in G3 and G4 groups in comparison to control group on the 14th and 28th day. Also, with G2, there was a significant increase (P 60.05) in AST gene expression after 28 days compared to 14 days of post-IR injury, whereas the expression of AST among the G3 and G4 groups significantly reduced (P 60.05) after 28 days compared to respective groups which were 14 days after IR injury. The findings can be represented as in Figs. 6, 7 and 8.

Expression of Alkaline phosphatase (ALP) genes

The results of the present research showed a statistically significant alteration (P < 0.05) in the gene expression of the Alkaline Phosphatase (ALP) in the G 2 group. Conversely, a considerable reduction (P <0.05) was found in the animals of G3 and G4 groups compared to the control group at the end of 14 and 28 days. Appreciable increase (P 0.05) was found between G2 and G4 group after 28 days and their individual level after 14 days whereas, G3 studied showed significant reduction (P 0.05) at 28 days and its level at 14 days. The described findings are represented in Figs. 9, 10, and 11.

The results of this study are consistent with findings reported in (15), which demonstrated that Propolis reduced levels of liver enzymes ALT and AST. Additionally, clinical laboratory trials have shown that curcumin can reduce liver damage [16]. These findings Propolis those of [17], who reported a study involving 35 participants in each group. The intervention group received Propolis at a dosage of 1 g twice daily for 12 weeks, after which biochemical analysis revealed a slight reduction in serum levels, along with a significant decrease in ALT, AST, and fatty liver grading.In experimental studies involving male rats treated with Propolis -Loaded Lipid Nanoparticles (PLNs), there was a significant increase in the gene expression levels of ALT, AST, and ALP after 14 and 28 days, compared to the control group. This increase was attributed to elevated oxidative stress in liver tissue [18]. Regarding antioxidant status, Propolis enhances the activity of antioxidant enzymes across various tissues and helps reduce oxidative stress. Free radicals can damage key macromolecules, leading to cellular injury and disturbance of homeostasis.

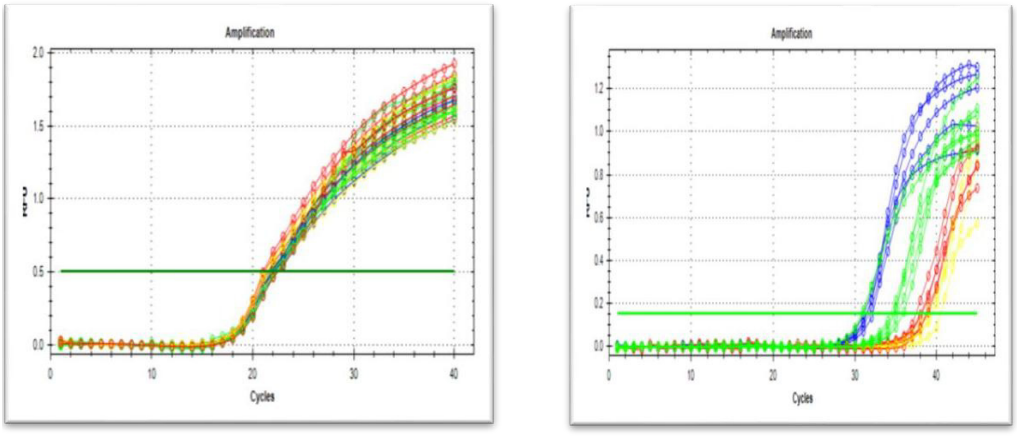


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Fig. 8. (A) AST gene plots in RT-PCR at the end of 28 days in the treatment group and the control group. There were plots of the housekeeping GAPDH gene by RT-PCR at 28 days in experimental rats with or without treatment.

All biomolecules in the body are susceptible to free radical attack, with proteins, nucleic acids, and lipids being the primary targets [19].

Gene expression of antioxidants
Super Oxide Dismutase (SOD1)

The results of the current study demonstrated a significant decrease (P<0.05) in gene expression in the G2 group. In contrast, a significant increase (P<0.05) was observed in the G3 and G4 groups compared to the control group after 14 and 28 days. Furthermore, gene expression significantly increased (P≤0.05) in the G2 and G4 groups at 28 days compared to their respective levels at 14 days. Conversely, the G3 group showed a significant decrease (P≤0.05) at 28 days relative to its expression at 14 days. These findings are illustrated in Figs. 12, 13, and 14.

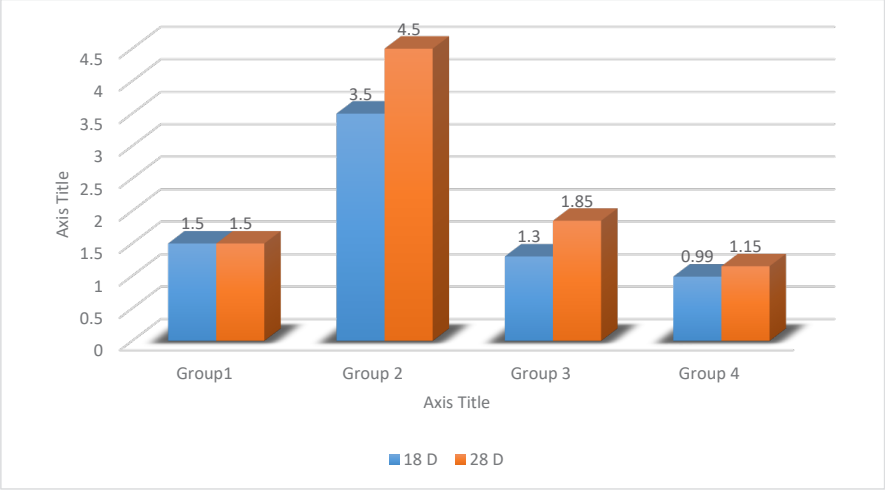

Fig. 9. the effects of LNPs-PL on an Alanine aminotransferase (ALP). LSD = for period=0.092 , for groups = 0.121 Group 1 : Control group ,drenched with distilled water for 28 days. Group 2 : Drenched with PL (20 mg\kg\days) for14, 28, days. Group 3: Drenched with LNPs (20 mg\kg\days) for14, 28, days. Group 4 : Drenched with LNPs-PL (20 mg\kg\days) for14, 28, days.

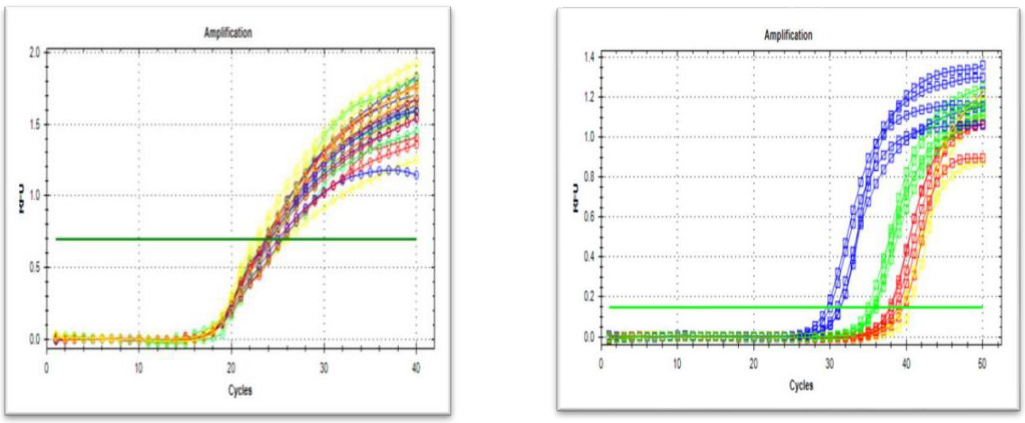

Fig. 10. (A) Treatment and control 14 days after planting cell plots of the ALP gene in RT-PCR. (B) RT-PCR graphs of house keeping GAPDH genes after 14 days in experimental rats treated and untreated.

These findings highlight the protective and antioxidant roles of LNPs-PL, as they led to significantly faster Changes in gene expression levels. Cells are protected from oxidative damage by a complex network of antioxidant enzymes [20]. Antioxidants in living cells are broadly categorized into enzymatic and non-enzymatic types. Enzymatic antioxidants act through various mechanisms such as metal ion chelation, hydrogen or electron donation, peroxide decomposition, singlet oxygen quenching, enzyme inhibition, and free radical scavenging. Both enzymatic and non-enzymatic antioxidants, present in intracellular and extracellular environments, play vital roles in neutralizing reactive oxygen species (ROS).

Antioxidants function primarily through two mechanisms. The first involves donating an electron to free radicals, thereby interrupting

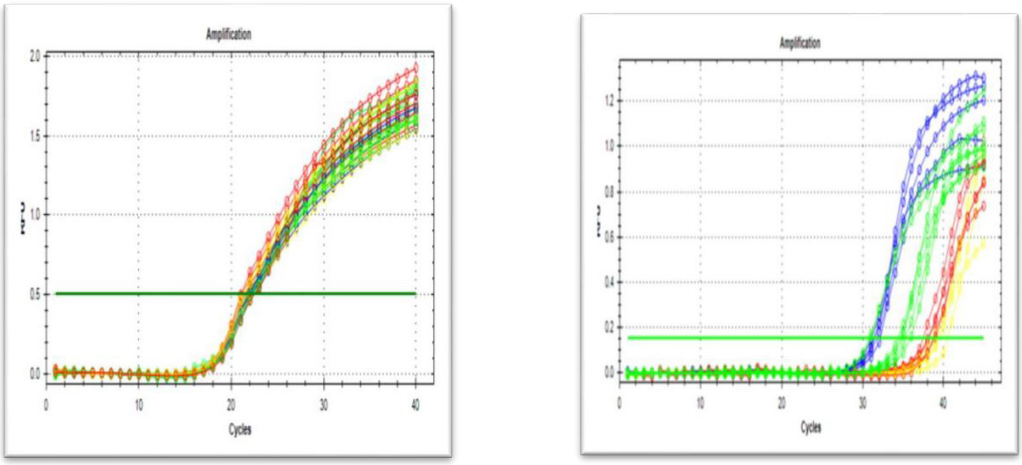

Fig. 11. (A) Plots of the ALP gene in RT-PCR after 28 days in the treatment and control groups. (B) RT-PCR plots of the housekeeping GAPDH gene after 28 days in experimental rats treated and untreated.

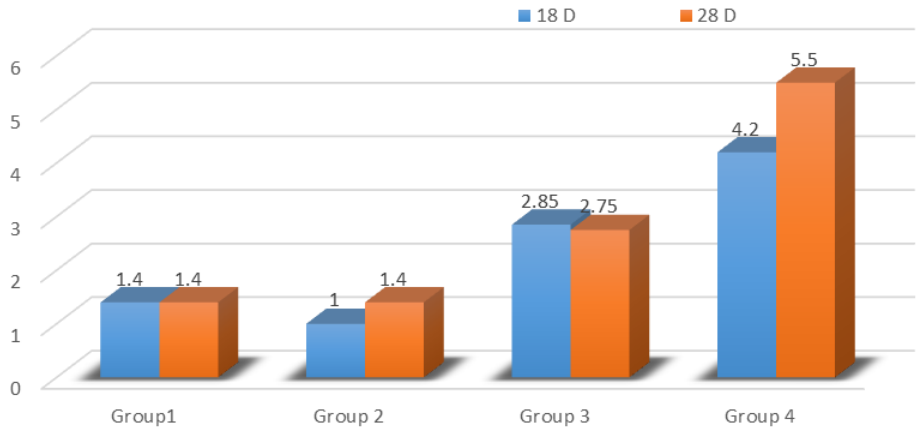

Fig. 12. The effect of LNPs-PL on Super Oxide Dismutase. LSD = for period=0.118, for groups = 0.159. Group 1: Control group, drenched with distilled water for 28 days. Group 2: Drenched with PL (20 mg\kg\days) for14, 28, days. Group 3: Drenched with LNPs (20 mg\kg\days) for14, 28, days. Group 4: Drenched with LNPs-PL (20 mg\kg\days) for14, 28, days.

radical chain reactions—a process known as chain-breaking. The second mechanism, associated with secondary antioxidants, works by deactivating ROS and their initiators, effectively halting oxidative chain reactions. Antioxidants influence biological systems in several ways, including acting as co-antioxidants, donating electrons, chelating metal ions, and regulating gene expression. As referenced in [21], glutathione was utilized in biochemical assays to assess the activity of antioxidant enzymes in tissues. Environmental stressors can lead to the generation of intracellular ROS, causing oxidative stress. This condition is marked by a reduction in antioxidant enzyme activity [21].

CONCLUSION

Propolis is a drug with low bioavailability and poor water solubility. The solubility and

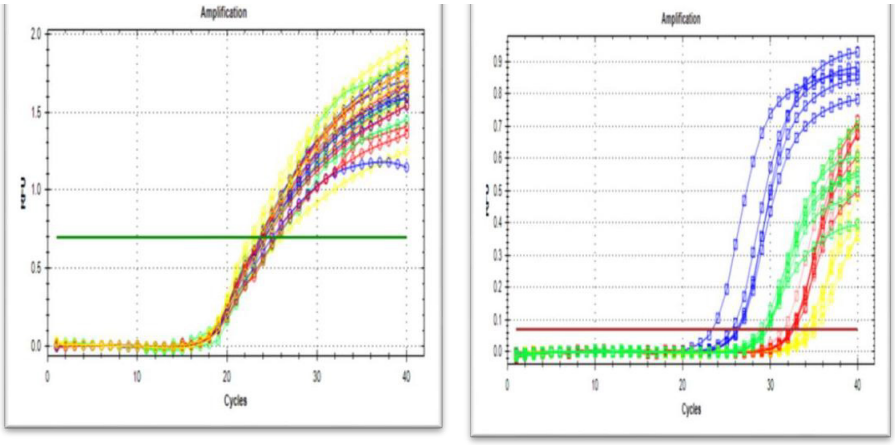

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Fig. 13. (A) Plots of the (GSS) gene in RT-PCR after 14 days in the treatment and control groups. (B) RT-PCR plots of the housekeeping GAPDH gene after 14 days in experimental rats treated and untreated.

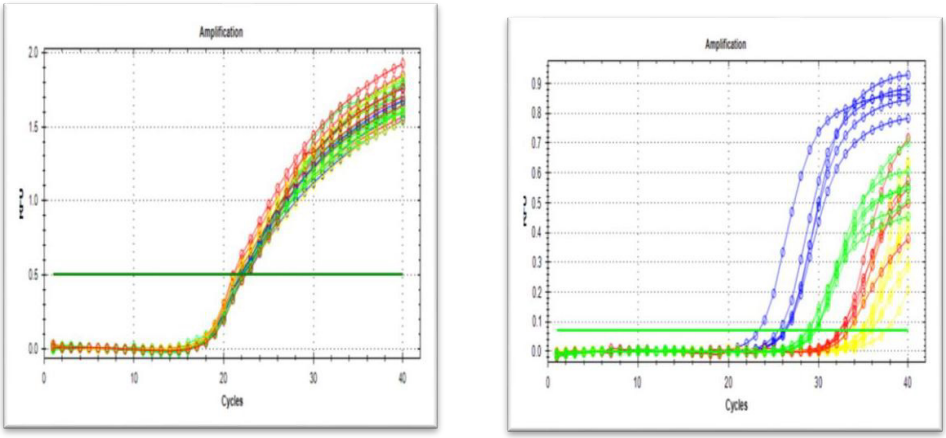

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Fig. 14. (A) Plots of the (GSS) gene in RT-PCR after 28 days in the treatment and control groups. (B) RT-PCR plots of the housekeeping GAPDH gene after 28 days in experimental rats treated and untreated.

bioavailability of medications that are poorly soluble are increased when lipid systems are used in lipophilic compounds. Rat liver enzyme antioxidant levels are positively impacted by Propolis Loaded Lipid Nanoparticles (PLNs), which also boost anti-oxidative enzymes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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