

# Effect of Silver nanoparticles and Omega-3 on some biomarkers on male mice induced by ovalbumin

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## Abstract :

**Background and Objectives** :-The study was done to investigate the level of biomarkers in male mice asthma models induced by Ovalbumin such as periostin and Galectin -3 and Interleukin -33 levels in serum as predictive indicators of the disease for detection, diagnosis and early treatment of disease .

**Materials and Methods** :-In the current study ninety one of male mice weighting (25-30 g) aged (15-17)weeks at the animal house faculty of science / university of Kufa during the period from January 2017 to September 2017. This study included some physiological criteria to evaluate the protective role of omega-3(2 and 3 mg/kg) and silver nanoparticles (5 and 10 mg/kg) against asthma that induced by ovalbumin .The animals experimental are divided into 16 groups (n=6 mice per each group) for duration of one and two months.

**Results** :-The result showed significant increase( $p<0.05$ ) in the serum level of periostin and Galectin -3 and Interleukin -33 in asthma group as compared with control group . The results of protective group(for 21 days ) also showed a significant decrease ( $p<0.05$ ) in leukocyte count in the group of omega-3 and silver nanoparticles for 21 days after treatment by ovalbumin induced in mice. The results indicated a significant increase ( $p<0.05$ ) in the serum level of Periostin , Galectin -3 and Interleukin -33 in asthma group as compared with control group ,while ,there was a significant decrease ( $p<0.05$ ) in the serum level of periostin and galectin-3 and interlukine -33 in the treated groups with omega-3 and silver nanoparticles as compared with asthma group.

**Conclusion**:-The present study concluded that omega-3 and silver nanoparticles had a protective and treated effect on asthma disease that induced by ovalbumin .

**Keywords:** Asthma disease, Mice ,Ovalbumin,Omega-3,Silver nanoparticles.

## INTRODUCTION:

Asthma is a chronic inflammatory disorder of the respiratory airway characterized by a multicellular process including eosinophil, neutrophil, mast cell ,T-lymphocyte and CD+4 also the most important features represented by infiltration of eosinophil {1}. Fatty acids Omega-3 are synthesized in the body and the body can be obtained from the diet such as naturally diet enriched in fatty fish like Salmon and tuna and fish oil supplements{2} There are many roles of the major components of omega-3 fish fatty acids docohehexanoic acid (DHA) and eicosapentanoic acid (EPA ) have been reported to have a protective function in coronary artery disease ,dyslipidemia and hypertension {3} . Nanoparticles (NPS ) a structures have a range of dimension from 1-100 nm .Silver is the main products among all nanoparticles and used widely in many applications because of its broad spectrum properties ,in addition to inflammatory activity the anti-microbial activity used against bacteria ,viruses and fungi{4}. Periostin is a useful biomarkers for bronchial asthma and it has been shown to down regulate of immune responses such as (IL-4) and (IL-13) and it can predict the hypo responsiveness to corticosteroid inhalation in asthma patients {5}. Galectin-3 are one of the most biomarkers which have functions in variety of biological processes such as allergic pathology and inflammation also, the Galectin-3 belong to the family of B-galactose side binding animal lectins{ 6}. IL-33 is a member of cytokines which mostly drive the Th-1 immune responses and have many names including (IL- IF11,NF-HEV)also nuclear factor from endothelial venues . and recently described as a member of IL-1 family {7}.

## MATERIALS AND METHODS

### Animals :

Ninety one male albino mice weighting (25-30 g) and aged between (15-17 week) were obtained from the faculty of science Thi/Qar university .The study started from Jan.2017 to Seb. 2017 .Animals were housed in the animal house of faculty of Science /University of Kufa under control condition ,light 12 and 12 dark hours and a temperature range from (20-24 C°).

### Induction of Asthma in mice

Mice were sensitized by three intraperitoneal injection of 0.5 mg/ml of ovalbumin and 20 mg/ml of alum on days 0,7 and 14 at the days 18,19 and 20 the mice will receive ovalbumin and alum by intranasal instillation by micropipette and drop in its nose ,mice were challenged at day 21.

### Biomarkers

The assessment of periostin ,Galectin -3 and Interlukine-33 mice Elisa Kits provided by (elabscience – china) Sandwich immunoassay technique , (enzyme-linked immuneosorbent assay – automated microtiter plate), Elisa reader (Biokit ELX 800 reader, ELX50 washer/USA).

### Statistical Analysis:

The data of present study were articulated as (Mean± Standard Error), the statistical analysis were calculated by using megastat and Graphpad prism, when P value <0.05 was statistically significant {8} .

## RESULTS:-

### Biomarkers

#### Periostin Level:-

#### Effect of two concentration of omega-3 and silver nanoparticles on periostin level

The figure( 1) showed significant increase ( $p<0.05$ ) in the periostin level in the asthma group (1.151±0.120) for 21 days compared with control ( 0.178±0.059) . also , the figure showed significant decrease in the periostin level in all treated group (T1,T2,T3,T4) (0.154±0.060), (0.189±0.050), (0.093±0.047), (0.154± 0.058)for both concentration of Omega-3 (2 and 3 mg/kg) both concentration of silver nanoparticles (5 and 10 mg/kg) compared with asthma . while ,showed no significant differences ( $p>0.05$ ) between all treated group (T1,T2,T3,T4) (0.154± 0.060) ,( 0.189±0.050) 0.093±0.047 ,(0.154±0.058) for both concentration to omega-3 and silver nanoparticles compared with control group (0.178± 0.059),there are no significant differences ( $p>0.05$ ) between all treated group.

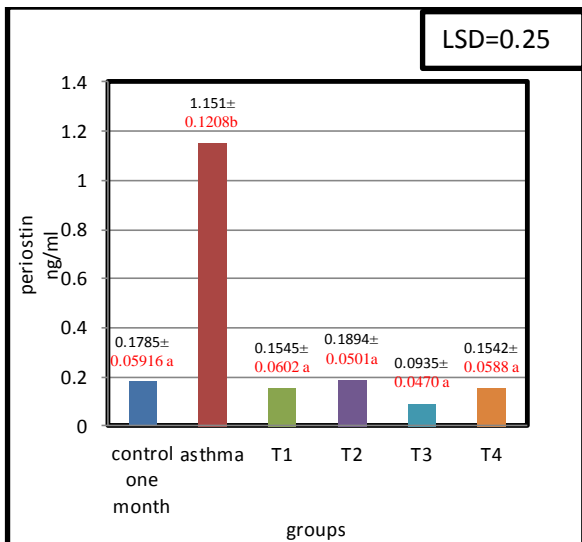
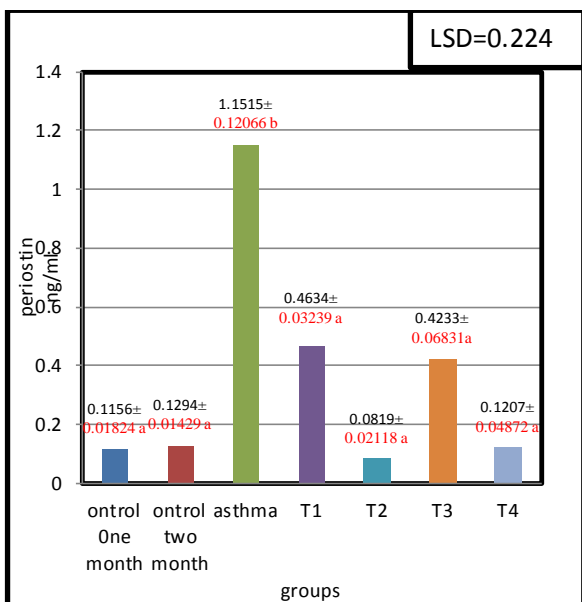


Figure ( 1 ) effect of two concentration of omega-3 and silver nanoparticles on periostin serum level in male rats treated with ovalbumin for 21 days .

**Effect of two period of omega-3 and silver nanoparticles on periostin level**

The figure( 2 ) showed significant increase ( $p < 0.05$ ) in the periostin level in the asthma group ( $1.151 \pm 0.1206$ ) for 21 days compared with control (  $0.115 \pm 0.0182$ ) for one month and control for two month ( $0.129 \pm 0.0142$ ) ,also the figure revealed significant decrease( $p < 0.05$ )in the treated group (T1,T2,T3,T4) for both period one and two month (  $0.463 \pm 0.0323$ ),(  $0.0819 \pm 0.02118$ ),(  $0.423 \pm 0.0683$ ) ,(  $0.1207 \pm 0.04872$ ) for omega-3 and silver nanoparticles compared with asthma ,while showed no significant differences ( $p > 0.05$ ) in all treated group as compared with control group .



Figure( 2 ) effect of two period of omega-3 and silver nanoparticles on periostin serum level in male rats treated with ovalbumin for 21 days .

**Effect of interaction between two concentration and period of omega-3 and silver nanoparticles on periostin level**

The figure (3) showed no significant differences(  $p < 0.05$ ) between all treated groups for omega-3 (T1,T2,T3,T4),(  $0.045 \pm 0.0089$ ),(  $0.127 \pm 0.06193$ ),(  $0.21367 \pm 0.0679$

),(  $0.09583 \pm 0.01976$ )and for silver nanoparticle (T5,T6,T7,T8),(  $0.178 \pm 0.10554$ ),(  $0.19567 \pm 0.0771$ ),(  $0.09750 \pm 0.01797$ ),(  $0.16017 \pm 0.09650$ ).

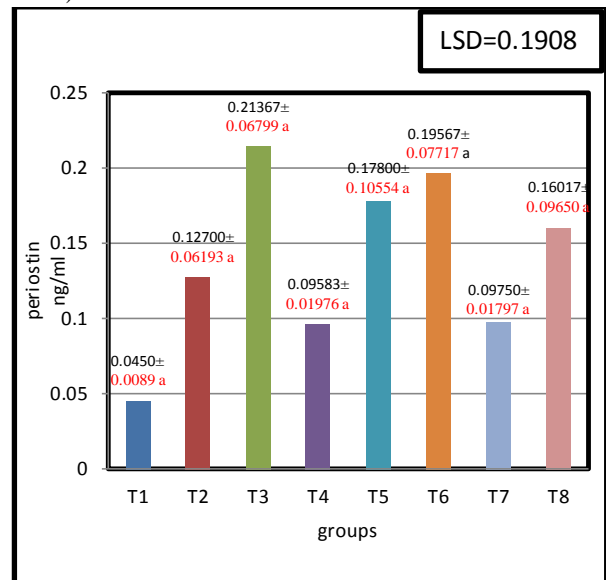
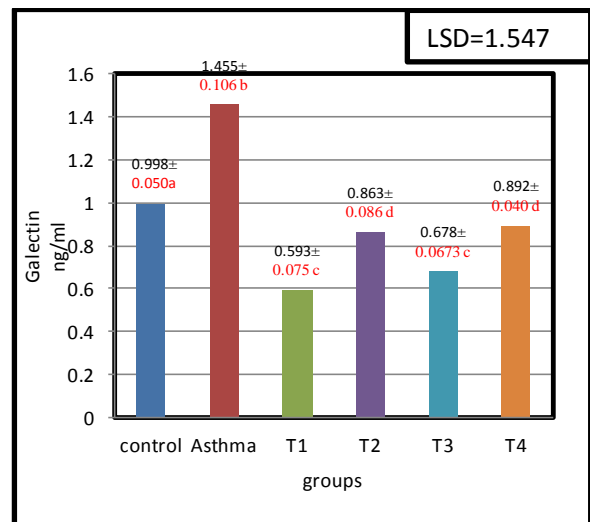


Figure (3) effect of interaction between two concentration of omega-3 and silver nanoparticles on periostin serum level in male rats treated with ovalbumin for 21days .

**Galectin-3**

**Effect of two concentration of omega-3 and silver nanoparticles on galectin level**

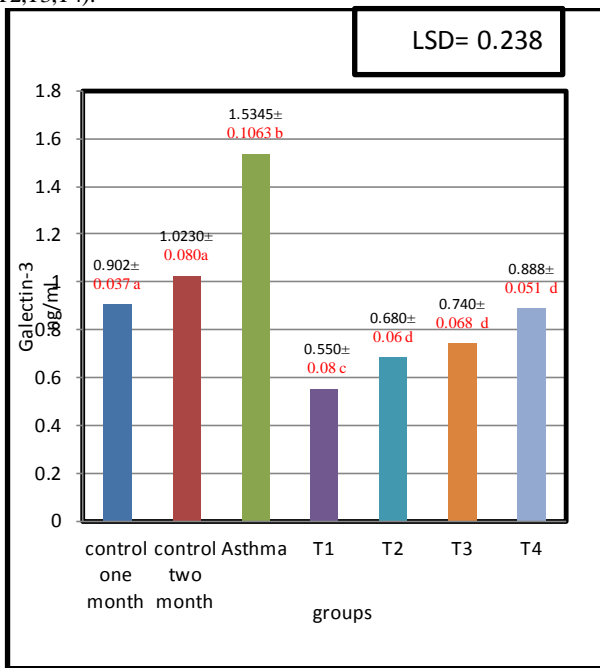
This figure( 4 ) found significant increase ( $p < 0.05$ ) in the galectin level in the asthma ( $1.455 \pm 0.106$ ) for 21 days compared with control ( $0.998 \pm 0.050$ ) , also showed significant decrease ( $p < 0.05$ ) in all treated group (T1,T2,T3,T4) of omega-3 and silver nanoparticles ( $0.593 \pm 0.075$ ) ,(  $0.863 \pm 0.086$ ),(  $0.678 \pm 0.0673$ ),(  $0.892 \pm 0.040$ ) compared with asthma. also, showed no significant differences ( $p > 0.05$ ) between treated group (T1) and (T3) .also, there are no significant differences ( $p > 0.05$ ) between treated groups(T2) and (T4) . The figure proved significant decrease ( $p < 0.05$ )in the galectin level in all treated group (T1,T2,T3,T4) for one month of omega-3 and silver nanoparticles ( $0.593 \pm 0.075$ ) , ( $0.863 \pm 0.086$ ) (  $0.678 \pm 0.067$ ),(  $0.892 \pm 0.04$ ) compared With control ( $1.768 \pm 0.050$ ) .



Figure( 4 ) effect of two concentration of omega-3 and silver nanoparticles on galectin serum level in male rats treated with ovalbumin for 21 days .

**Effect of two period of omega-3 and silver nanoparticles on galectin-3 level**

The figure (5) revealed significant increase ( $p < 0.05$ ) in the galectin level in the asthma (1.5345±0.106) for 21 days compared with control (0.902±0.037) for one month and control for two month (1.0230± 0.080) .while showed significant increase ( $p < 0.05$ ) in the galectin level in all treated group (T1,T2,T3,T4) for two month of omega-3 and one and two month of silver nanoparticles (0.55±0.08),(0.856±0.06),(0.740±( 0.068),( 0.888±0.051) compared with asthma ( 0.458±0.106) . also, showed significant decrease ( $p < 0.05$ ) in the galectin level in all treated group (T1,T2,T3,T4) for one month and two month of omega-3 and silver nanoparticles compared with control (1.840±0.037) for one month and control (1.672±0.080) for two month.no significant differences ( $p > 0.05$ ) between treated groups (T2,T3,T4).



Figure( 5) effect of two period of omega-3 and silver nanoparticles on galectin serum level in male rats treated with ovalbumin for 21 days .

**Effect of interaction of two concentrations of omega-3 and silver nanoparticles on galectin level**

The figure(6) showed significant decrease ( $p < 0.05$ ) in the galectin level in the treated group (T1) for one month of omega-3 (0.499±0.079) compared with other treated group (T2,T3,T4) for one and two month of omega-3 (0.903±0.149),(0.831±0.058), (0.906±0.078) .the figure showed significant decrease ( $p < 0.05$ ) in the treated group (T5) in the level of galectin (0.520 ±0.086) for one month of silver nanoparticles compared with other treated group (T6,T7,T8) for one and two month of silver nanoparticles (0.785±0.020),(0.808±0.115),(1.105±0.173) .The group T1 and T5 were significant decrease than other group .

**Interleukin-33**

**Effect of two concentration of omega-3 and silver nanoparticles on Interleukin 33 level**

The figure( 4-27) showed significant increase ( $p < 0.05$ ) in the interleukin level in the asthma group(1,551.54 ±158.0868) compared with control (485.99±62.567) ,also, the figure showed ,significant decrease ( $p < 0.05$ ) in the level of Interleukin 33 in the treated group (T1,T3,T4) for one and two month for both concentration of omega-3 and silver nanoparticles (673.136±122.93) ,( 608.041± 102.143), (757.51±161. 737) compared with

asthma (1,551.547±158.086) while, indicated significant increase ( $p < 0.05$ ) in the interleukin level in the treated group (T2) for two month for omega-3 (1,028.248) compared with other treated group .the figure indicated no significant differences ( $p > 0.05$ ) in the Interleukin level in the treated group ( T1,T3,T4) for both period one month and two month for omega-3 and silver nanoparticles( 673.136±122.931),(608.041±102. 143),(757.519±161.737) compared with control (485.99± 62.567) while showed significant increase ( $p < 0.05$ ) in the interleukine 33 in the treated group (T2) for two month for omega-3 compared with control (485.99± 62.567) .

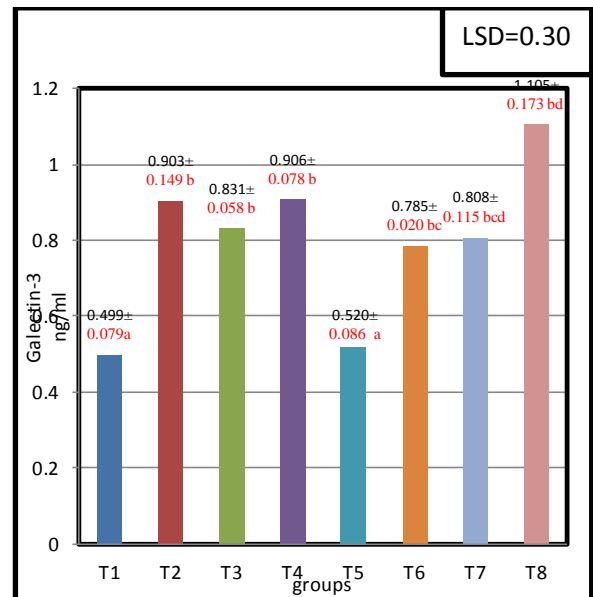
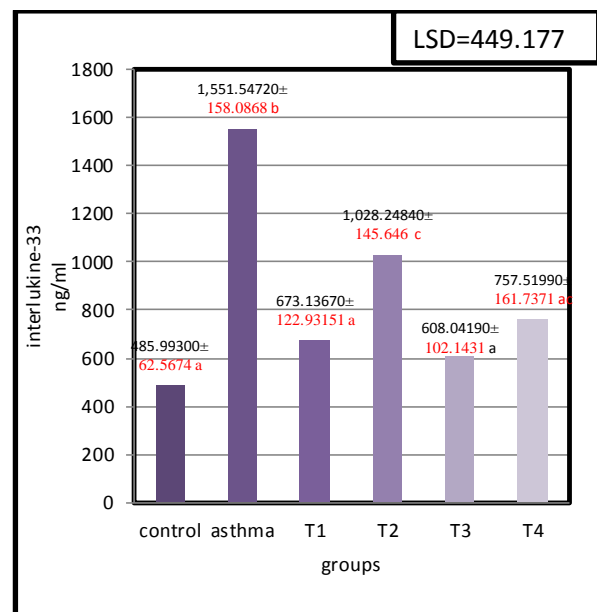


Figure (6) Effect of interaction between two concentration of omega-3 and silver nanoparticles on galectin serum level in male rats treated with ovalbumin for 21 days.



Effect of two concentration of omega-3 and silver nanoparticles ) Figure (7 on interleukine-33 serum level in male rats treated with ovalbumin for 21 days.

**Effect of two period of omega-3 and silver nanoparticles on interleukin level**

The figure (8) indicated significant increase ( $p < 0.05$ ) in the interleukin level in the asthma group ( $1,238.286 \pm 227.723$ ) compared with control ( $546.178 \pm 75.07$ ) for one month and control for two month ( $425.807 \pm 100.842$ ), also showed significant decrease ( $p < 0.05$ ) in the interleukin level in all treated group (T1,T2,T3,T4) for one and two month for omega-3 and silver nanoparticles ( $650.443 \pm 100.842$ ), ( $631.903 \pm 116.587$ ), ( $659 \pm 117.93$ ), ( $749.861 \pm 133.42$ ) compared with asthma ( $1,238.286 \pm 227.723$ ).

The figure showed no significant differences ( $p > 0.05$ ) in all treated group (T1,T2,T3,T4) for one and two month for omega-3 and silver nanoparticles ( $650.44 \pm 100.293$ ), ( $631.903 \pm 116.587$ ), ( $659.549 \pm 117.930$ ), ( $749.861 \pm 133.42$ ) and control group ( $546.178 \pm 75.07$ ).

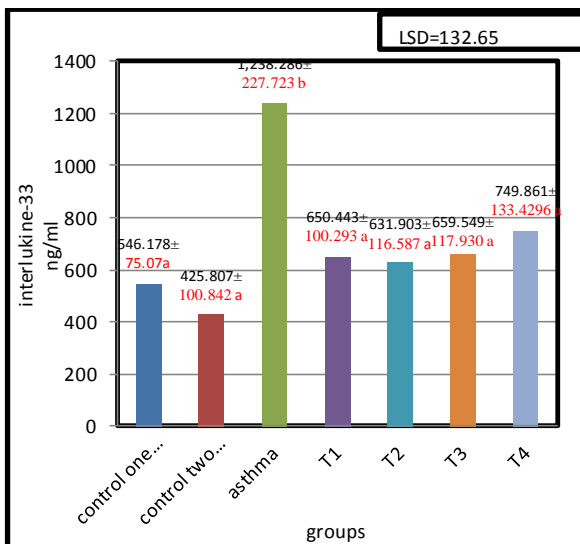


Figure (8) effect of two periods of omega-3 and silver nanoparticles on interleukin-33 serum level in male rats treated with ovalbumin for 21 days.

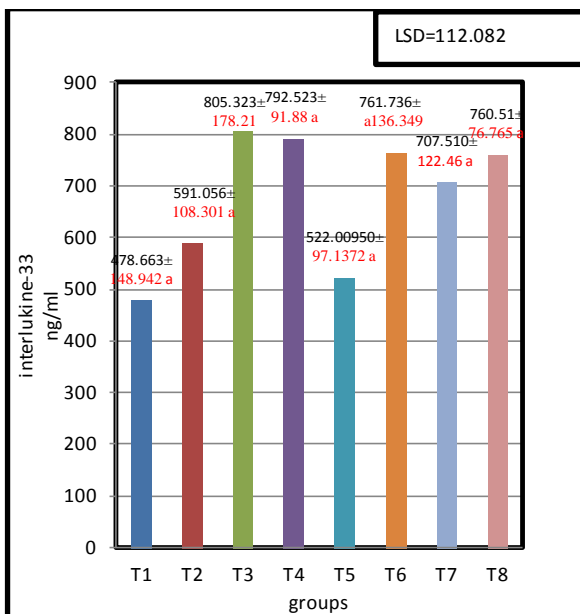


Figure (9) effect of interaction between two concentration of omega-3 and silver nanoparticles on periostin serum level in male rats treated with ovalbumin for 21 days.

**DISCUSSION**

**Effect of Asthma, Omega-3 and silver nanoparticles on Biochemical markers in serum.**

**Periostin level in serum**

The figure (1,2,3) revealed significant increase ( $p < 0.05$ ) in Periostin level in asthma group in compare with control group.

The present study agree with study of {9} that suggested the basal level of periostin is sufficient to acute response and with previous study that postulated that accumulation of periostin level have a major roles in the trafficking activation of cytokines release of leukocytes {10}.

Many number of studies have proved the relation between high plasma level of periostin and eosinophilic asthma {11}.

In mice experimental have Showed lower in eosinophil number periostin deficient mice {12}.

One of the most important hypothesis that explain why periostin level is high in asthma is eosinophil secrete periostin {10} and others suggested that eosinophilic asthma derives from production of periostin mainly in the airway epithelial cells and fibroblast {13}.

In a different studies on mice and human have showed a periostin lead to promote the TGF-B also enhance specific adhesion of blood eosinophil which are related with different cytokines such as IL-3 and granulocyte –macrophage colony stimulating factor (GM-CSF)

{14}. Another important explanation for increase a periostin is a periostin is a ligand for the integrins  $\alpha\beta$ ,  $\alpha\beta$  and  $\alpha\beta$ 2 (CD11b) and these were able to attract eosinophil and increase adhesion to fibronectin {15}.

In the presence of IL-5, eosinophil adhere to periostin and lend to form punctate structures that express filamentous actin, gelsolin and phosphotyrosin that considered as highly adhesive contact in air inflammation {16}. In a former study of {17} have indicated that  $\alpha$   $\mu$   $\beta$  2 (CD11b/CD18, MAC-1) was a periostin receptors which is expressed by cytokines stimulated eosinophil and serve as hypotactic stimulus to guide eosinophil to the inflammation of airway in asthma. Also, the Th2 immunity response lead to more deposition of periostin and function as guide for migration of eosinophil to the asthma air way. The study of {18} have postulated that IL-4, IL-13, IL-5, IL-9 and TGF- $\beta$  were a major trigger of periostin production.

In a study of {19} also, it has been suggested that macrophage produce periostin through autocrine stimulator of periostin and this may developed and contribute in asthma pathogenesis.

In a recent study {20} have proved that the activation of Th2 cell and differentiation occur by the interaction between dendritic cells (DCs) CD11b and periostin in mice.

Serum level of periostin may reflect the level of periostin in inflamed lesions that induced by Th2 type immune response. In a study on mice have found that postn +1+ mice had a higher airway responses the postn -1- {20}.

The current results of figure (1,2) indicated a significant decrease ( $p < 0.05$ ) in periostin level in treated and protective groups of omega-3 and silver nanoparticles in compare with asthma groups.

No previous studies deals with the effect of both omega-3 and silver nanoparticles on periostin level in asthma and other disease. The results may be discussed the decrement in periostin level by the relation between eosinophil and periostin. So the present study proved that after administration of both omega-3 and silver nanoparticles at different concentration and periods were led to significant decrease in eosinophil and these cells produce periostin therefore the decrement in eosinophil count may reflects the decline in periostin level in serum of treated and protective groups.

The anti-inflammatory effects of both EPA and PHA in omega-3 may lead to decrease in all reactant of eosinophil to the ligand present in periostin.

The inhibition in secretion of periostin may be by suppress the Th2 cytokines such as IL-4 and IL-13 that lead to decrease in the production of periostin by fibroblast .

The another explanation for periostin level reduction in treated and protective group is suppress receptors of periostin by inhibition of ligand interact with periostin such as  $\alpha v$  integrin .

The current study demonstrated that monocytes were decreased and these may give a reason for periostin decrement because monocytes (macrophage) is a source for periostin in production by Autocrine stimulation .

The Omega-3 and silver nanoparticles in this study may have a therapeutic value in all variety of concentration and periods because it is effected on development of disease and inflammatory status which is representing by suppression of eosinophil ,periostin that correlated with high inflammatory air way in asthma.

### Galectin -3 level

In the figure (4,5,6) showed a significant increase ( $p<0.05$ ) in the Galectin level in serum of asthma group in compare with control group .

The study accordance with various studies that evident o play role of Galectin -1,3and 9 in various inflammation also, that are expressed by eosinophil or others cells interfere with eosinophil recruitment in allergic asthma {21,22}.

In a study on wild type mice expired to acute allergen have been showed increase in Galectin -3 level also, expressed inflammatory cell such as (macrophage ,eosinophil ) the bronco alveolar lavage in wild type mice { 23} . In laboratory study have postulated that Galectin-3 expressed with high level on the eosinophil of allergic subject and exhibit .strong adhesion interaction on VCAM-1 {24} .

Former studies on leukocytes count in Gal-3 deficient mice have support the previous studies by the relation between Gal-3 level and decrease a total count of leukocytes from bone marrow {25} .

A recent study have showed in addition to bind of Galectin -3 with integrin receptors also, found to bind with CD66 $\beta$  which is considered as a single chain and highly glycosylated of Ig members on activated eosinophil lead to degranulation and induce of cell adhesion {26} .

The role of eosinophil in expressed Gal-3 in cell traffic king and activation has been proved by a study of {27}in cultured of bone marrow for mice of deficient Gal-3 and found a significant decrease in vascular cell, adhesion molecule -1 (VCAM) and was associated with intercellular adhesion molecules -1 (ICAM)-1 due to decrease in expression of integrins.

The extracellular G-3 have measured in BAL fluid of inflammation induced by OVA challenged mice and show a high level of Gal-3 in compare with control group {27}.

The regulation of Gal-3 have showed in response to IL-18 at the mRNA level also, in response to advanced glycation and product casein (AGE-Cas) { 28}.

Several studies has been detected the Gal-3 on the surface of eosinophil ,neutrophil and also, most cell, monocytes and lymphocytes and these cells are expressed high level of Gal-3 { 24}.

In previous study Gal-3 in vitro a activation lead to activate monocytes ,macrophage through the lectin function and lead promote uptake of apoptotic neutrophils and induce of infiltration and phagocytosis {29}.

In mice model treated with OVA,Gal-3 +mice were more developed in airway inflammation also, highly expression of Galectin in both airway and in the fluid lining the airway also ,elevation of eosinophil count also, elevation in airway inflammation compare with mice Gal-3 {27} .

According to overall studies the present study finding that activation or induction of Gal-3 in asthma mice lead to increase

leukocytes count infiltration ,especially eosinophil and representing that Gal-3 is a biomarker used for diagnosis of asthma.

The present study in figure (4,5) indicated a significant decrease ( $p<0.05$ ) in Galectin -3 level in treated and protected group in compare with asthma group.

The current study is the first study deals with the effects of omega-3 and silver nanoparticles on Gal-3 as biomarkers of asthma.

The explanation of our results depend on the fact proved by many researchers that showed elevation between the highly expression or level of Gal-3 related with increase the level of leukocytes (eosinophil ,monocytes and lymphocytes (therefor the different concentration of both omega-3 and silver nanoparticles may decrease the level of Gal-3 by different ways .the first way may be by suppress the expression of Gal-3 on eosinophil ,the second way by decrease the infiltration of eosinophil from bone marrow in which caused declining in Gal-3. Gal-3 may be interact with a different pathway lead to suppression of Gal-3 such as inhibition of CD66 in which the binding or adhesion with a cell surface become weakly or inhibit the integrin protein therefore the binding of Gal-3 with receptors are inhibited ,also adhesion molecules such as VACM-1,ICAM-1 may be lead to decrease the adhesion of Gal-3 .The suppression of cytokines by Th2 lead to decrease the Gal-3 production such as IL-4,IL-5,IL-13,IL-10,IL-9 and IL-1 $\beta$  .

### IL-33 Level

The figure (7,8,9) showed a significant decrease ( $p<0.05$ ) in the level of IL-33 in asthma groups in compare with control groups.

A recent study of {30} have postulated that IL-33 induce of allergic asthma because the Th2 inflammation was dependent on FCYRIII and IL-33 enhance a secondary response ligation FCYRIII on antigen presenting cells to develop Th2 – mediated response in the lung some other studies have documented that a signaling of IL-33 is required for eosinophil and production of IL-5 and IL-13 from innate lymphocytes (ILC25) .therefore it considered as an essential factors for severe asthma in mice{31}. Research of several studies have reported that IL-33 modulate a mast cell through a pathway signaling /and activated mast cell and basophil to enhance of maturation ,migration ,survival ,adhesion and production of several cytokines as pro inflammatory in air way of asthma {32} .previous study has demonstrated that IL-13 in eosinophil and invivo IL-33 have a crucial roles in eosinophil homeostasis and allergic inflammation {33} .

Many recent studies have proved that IL-33 stimulated an OVA allergin and protease ,the role of both allergen and protease can break down of barrier of epithelial cells and lead to rapid increase in the level of IL-33 and induced of airway inflammation by promote ILC2 {34}. Study of {35} have proved that endogenous IL-33 may be induce CD8+Tcell response to stimulate replicating of RNA and these events related with induction of immune response .

Several studies on a mouse model have proved that absence of IL-3 lead to reduce in airway hyper responsiveness and overexpression of IL-33 may lead to induction of air may inflammation and eosinophilia {36} .

Two recent analysis have supported the role of IL-33 in the pathogenesis of asthma in North American human patient and European and found that a genome associated with asthma and play role in susceptibility loci were identified in a specific region for ILIRLI (also known as ST2) and in IL-33 {37} .The IL-33 may lead to initiate a signal lead to activate the Th2 associated with inflammatory response during antigen exposer many different studies have showed that IL-33 rises activate the development of Th2 by several ways including Th2-

differentiation ,effect on CD, development of Th2 and ILC2 activation {38} .

The figure (7,8) showed a significant decrease ( $p<0.05$ ) in the level of IL-33 in the serum after treated with omega-3 and silver nanoparticles in compared with asthma group . As mentioned in a previous explanation ,the present study may explained the decrease of IL-33 to the role of the active compound present in omega-3 such as EPA and DHA also, a low concentration effects of silver nanoparticles as anti-inflammatory effect lead to decrease in Th2 responses and inflammatory response in protective and treated group .Another effect may be on the level of cytokines that imported in the activation of innate lymphocytes such as IL-5 and IL-13.

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