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Anti- inflammatory and Anti- Arthritic Activity of Nanocurcumin in Albino Rats against Freund's Complete Adjuvant Induced- Arthritis

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ABSTRACT

Goal: The inquiry intended to examine the potency of nanocurcumin (NC) at inhibiting FCA- persuaded osteoarthritis.

Methods: Rats selected randomly dispersed within three cohorts: (n = 6/group): healthy key group, osteoarthritis group (Urged with a single intradermal 0.1 ml FCA injection) and arthritis group received daily uttered gavage of 100 mg/kg of nanocurcumin for one month. haematological parameters as haemoglobin (Hb) scale, red blood cell count (RBC), white blood cell count (WBC), the erythrocyte sedimentation rate (ESR), C-reactive protein scale (CRP) and interleukin-10(IL-10) level were measured. Bone marrow smear was done to count bone marrow differential cells.

Results: The result of this study revealed that the changed haematological parameters and IL-10 in the arthritic rats were returned back generally to akin standard by the Nanocurcumin therapy at a dose 100mg/kg. Arthritis group treated with Nanocurcumin improve process of haematopoiesis in bone marrow.

Conclusion: In conclusion, based on the current study results, we suggest therapeutic effect of Nanocurcumin against FCA- caused osteoarthritis in albino rats. Nanocurcumin alleviates rheumatoid arthritis-induced inflammation.

Key words: arthritis, Nanocurcumin, Hematology, Bone marrow cells, interleukin 10.

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INTRODUCTION

Rheumatoid arthropathy (RA) is an inflammatory disturbance and chronic autoimmune leading to damage of articular bones and cartilage and joint malformation. A disproportion amid pro- and anti-inflammatory cytokines causes autoimmunity and chronic inflammation, triggering joint damage to the RA (McInnes and Schett,2007). Of these, pro-inflammatory interleukin -10 (IL-10) and tumor necrosis factor-alpha (TNF) are oftentimes targeted in RA strategy outlines (Zhuang et al.,2013). It is characterized by marked infiltration into the synovial membrane by a large number of inflammatory cells, excessive hyperplasia and vasculogenesis (Feldmann et al.,1996 and Bax et al.,2011). This turbulence additionally influences the tissues around the joints, such as the blood vessels, muscles, and skin (Asolkar et al.,1992). Bone degradation is mediated by hematopoietic-derived osteoclasts, multinucleated giant cells. Rats with adjuvant-motivate arthritis (AA rats) is an animal model widely used and is similar to human RA (Chen et al.,2008).

Though different drugs were used to control RA, these drugs have serious side effects linked to clinical RA care that restrict their chronic use (Stanford, 1984). Cytokine remedies, inclusive anti-tumor necrosis factor (TNF) antibodies, solvable TNF receptor, anti-interleukin (IL-)-6 receptor antibody, and IL-1 receptor antagonist, are broadly utilized in the remedy of RA, additionally, to anti-inflammatory and disease-modifying anti-rheumatic remedies (DMARDs), such as methotrexate, Nonetheless, there are some issues with these treatments, as it can modify the progression of the disease(Goldring and Marcu,2009 and Smolen et al.,2010). Therefore, there is tend to use more effective and safer therapy which acts on root cause of RA and alleviate the adverse effects.

Curcumin (diferuloyl methane) is the hydrophobic bioactive component isolated from Curcuma longa turmeric plant and its derivatives, known as curcuminoids. curcuminoids well known for their widespread range of biological and pharmacological activities against numerous human disorders, including metabolic and infective diseases, atherosclerosis, psoriasis, rheumatoid arthritis, Parkinson's and Alzheimer's diseases, and diabetes, cancer (Wilken et al., 2011). Sharma et al. (2005) stated that oral consumption of curcumin shows less bioavailability regarding simultaneous its feeble aqueous solubility and it undergoes intestinal metabolism. Recently, nanoparticle-based transportation operations are reasonable to be proper for profoundly hydrophobic factors earlier mentioned as curcumin that can remove these barriers of curcumin by synthesizing curcumin nanoparticles that can be used for longer circulation, permeability and improved metabolic resistance (Ravichandran, 2013). Nanocurcumin has been suggested to represent a potential therapeutic improvement over native curcumin (Flora et al.,2013). The special intention of this inquiry implied to appraise distinct effectiveness and mechanism of the unfolding of Nanocurcumin in trial rats' contra Freund 's Complete Adjuvant induced arthritis.

MATERIAL AND METHODS

Animals

18 adult male albino rats were utilized in the existing work. They were acquired from the pet residence of Biology Department, College of Education, University of Sallahaddin. Their weight ranged between 200-250g representing 8-9 weeks of age. Animals were permitted to acclimatize for 7 days' pre- examination, so as to prevent any problems during the trial (Alkubaisy et al., 2019). They were kept in metabolic cages and received *ad-libitum* water and food with fresh supplies on a daily basis.

Chemicals

Freund's complete adjuvant and Nanocurcumin were procured from Sigma-Aldrich.

Freund's complete adjuvant induced arthritis

Freund's complete adjuvant (FCA) was equipped by suspension in wet paraffin. A sole intradermal injection of 0.1 ml of FCA into the left hind metatarsal footpad rats caused arthritis. (Kadhem et al.,2016). Then, animals were distributed into three cohorts (n = 6/group): normal control cohort, arthritis cohort without treatment and arthritis cohort received daily oral gavage of 100 mg/kg of Nanocurcumin for one month (Rahmi et al.,2018).

At the end of the seek, blood samples were withdrawn aloof by cardiac puncture from all animals and the blood samples were then placed in two different tubes, the first one contains EDTA anticoagulant for haematological parameters as haemoglobin (Hb) level, white blood cell count (WBC), red blood cell count (RBC), erythrocyte sedimentation rate (ESR) and C-reactive protein levels (CRP) (Kadhem et al.,2016). While the second part of the collected blood was tubeled without EDTA, it centrifuged for 15 minutes at 5000 rpm to obtain serum for biochemical parameters like interleukin-10(IL-10) level was measured using commercially available ELISA kits for IL-10 (ab100765) according to Hassan *et al.* (2018).

Bone Marrow

Neutrophils are created in the bone marrow by a process known as leukopoiesis (Wood et al.,2004). Neutrophil ancestors are distinguished from hematopoietic stem cells that are driven toward the myeloid lineage, and further into mature neutrophils (van Lochem et al.,2004). The bone marrow is a compound tissue where numerous hematopoietic lineages coexist in several maturational stages. Knowing the expression levels of neutrophil specific markers and other lineage-specific markers during normal hematopoietic development gives us a standard by which to recognize abnormal patterns of differentiation (van Lochem et al.,2004). During granulocytic differentiation, myeloblasts, the most immature neutrophil precursor, cannot be distinguished from monoblasts, the most immature form of the monocytic lineage, since both participate in a well-known parental stem cell (Granulocyte-Macrophage colony forming unit –GM-CFU). The maturation process is regulated by growth factors, such as GM-CSF, M-CSF and G-CSF, as well as by cytokines and chemokines. The relative size of the cells, together with expression levels of specific markers such as CD34, CD117, CD45 (membrane-associated tyrosine phosphatase), CD13 (aminopeptidase N), CD33, CD16, and CD11b, can be used study granulocytic differentiation. The markers that have been used to identify neutrophils during different stages of hematopoiesis are summarized in Table 1.

Table 1: The markers that have been used to identify neutrophils precursors during different stages of hematopoiesis.

Stage of PMN maturation	Surface Expression	Size	Characteristics
myelo/monoblasts	CD16– CD13– CD45 ^{int}CD11b–	12-20 μm	Nucleus: round /ovoid Ratio: 6:1
promyelocytes	CD117 CD13^{high} CD33^{high} CD15, CD34, MHCII	15-21 μm	Nucleus: round /ovoid Ratio: 4:1
Myelocytes	CD13dim CD33dim CD34, CD15, CD11b	12-18 μm	Nucleus: round /ovoid/flattened on one side Ratio: 2:1
Metamyelocytes	CD13 CD33dim CD34- CD15, CD11b, CD16	10-18 μm	Nucleus: indented / kidney shaped Ratio: 1.5:1
Neutrophils	CD13high CD33 CD15, CD11bhigh CD16high	9-16 μm	Nucleus: segmented Ratio: 1: 3

To identify purified populations of neutrophils and its precursors, some studies have utilized cellular size, granularity, and expression profile of the CD13, CD15, CD11b, and CD16 surface markers, after excluding CD3, CD19, CD14, glycophorin-A, CD56, and CD61 positive cells. CD13 shows dynamic changes in expression during granulocytic differentiation. In combination with CD11b and CD16, these changes define the sequential stages of granulopoiesis. CD13 expression is up-regulated on myeloblasts (MB) and promyelocytes (PM), and then down-regulated on myelocytes (MC). CD13 expression is gradually up-regulated again as neutrophils reach their final stages of differentiation and develop into segmented neutrophils. On the other hand, CD11b and CD16, which are originally manifested at faint scale, show progressively increased effect throughout the developmental process, especially in the latest two steps of neutrophil differentiation. CD16 comprises the low affinity Fc receptors, FcγRIIIa (CD16a) and FcγRIIIb (CD16b). These receptors link to the Fc part of Immunoglobulin G (IgG) antibodies, which later spurs the (NK) cell for Antibody-Dependent Cell-mediated Cytotoxicity (ADCC). lack of

CD16 in a given population of neutrophils might show prematurity, as could be prompted by a left-shift (the exaggerated quotient of immature to mature leukocytes) debit to neutrophilic leukocytosis initiated by tissue necrosis or bacterial contagion (Lakschevitz 2015).

Statistical Analysis

The input earned from the analyses were represented as mean ±SD, the outcomes were statistically scrutinized exercising (ANOVA) SPSS programming version 25. The P-values at P < 0.05 were estimated significant. (Chan,2003).

RESULTS

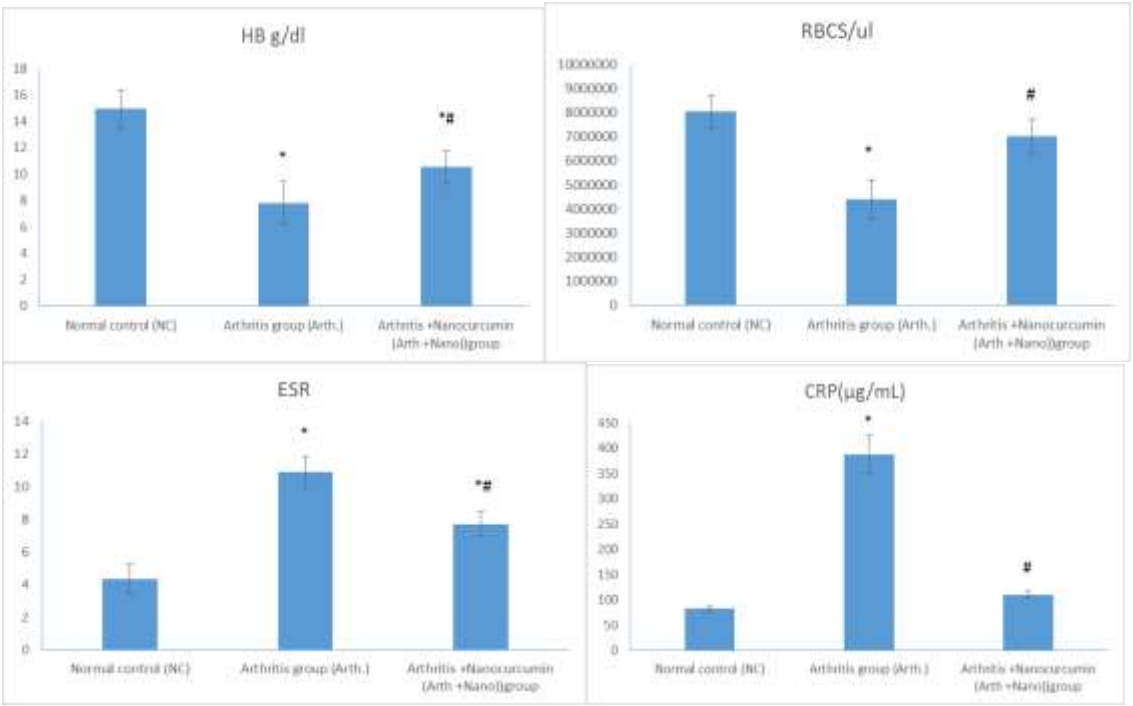
Effect of Nanocurcumin on haematological parameters:

The results obtained from the table (1) & fig (1) showed a significant reduction in the RBC and Hb scale with increases in the WBC scale, ESR, detected CRP arthritis cohort when vied to a standard cohort. Arthritic rats treated with Nanocurcumin exhibit significantly improve in RBC and Hb at the same time diminishes the WBC, ESR and CRP with P<0.05 when vied with arthritis group.

Table 1: Effect of Nanocurcumin on haematological parameters:

Parameters	Normal control	Arthritis group	Arthritis+Nanocurcumin
RBC(S/ul)	8045000±680962.55	4410000±807217.44 *	7020000±721914.12 #
WBC(S/ul)	8006.67±628.23	16903.33±420.79 *	10341.67±1310.12 *#
Hb (gm/dL)	14.95±1.44	7.82±1.6 *	10.53±1.24 *#
ESR(mm/hr.)	4.35±0.91	10.89±0.95 *	7.72±0.73 *#
CRP(µg/mL)	82.87±4.69	387.98±39 *	110.6±7.2 #

Values are presented as mean ±SD *: statistically significant compared to the corresponding control group value (P<0.05), #: statistically significant compared to the corresponding Arthritis group value (P<0.05).



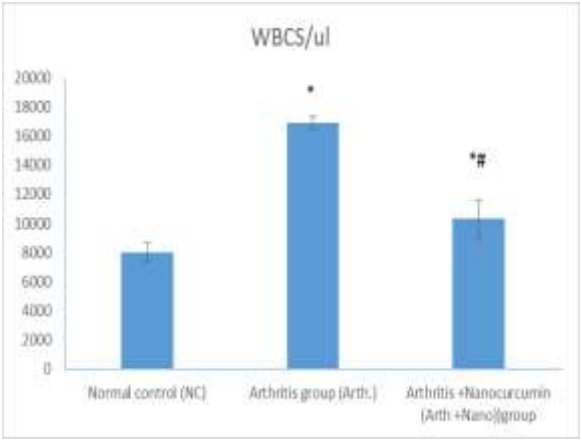


Figure 1: Effect of Nanocurcumin on hematological counts

Effect of Nanocurcumin on interleukin-10(IL-10) level

IL-10 in the serum of arthritis rats decreased (P<0.05) vied with the healthy animals. Treatment by Nanocurcumin induces increase in the scale of IL-10 when vied with arthritis cohort. Table (2) and fig. (2).

Table 2: Effect of Nanocurcumin on interleukin-10 (IL-10) level

Groups	Interleukin-10 (IL-10)
Normal control group	188.27±40
Arthritis group	78.57±5.92 *
Arthritis +Nanocurcumin group	170.32±6.43 *#

Values are presented as mean ±SD *: statistically significant compared to the corresponding control group value (P<0.05), #: statistically significant compared to the corresponding Arthritis group value (P<0.05).

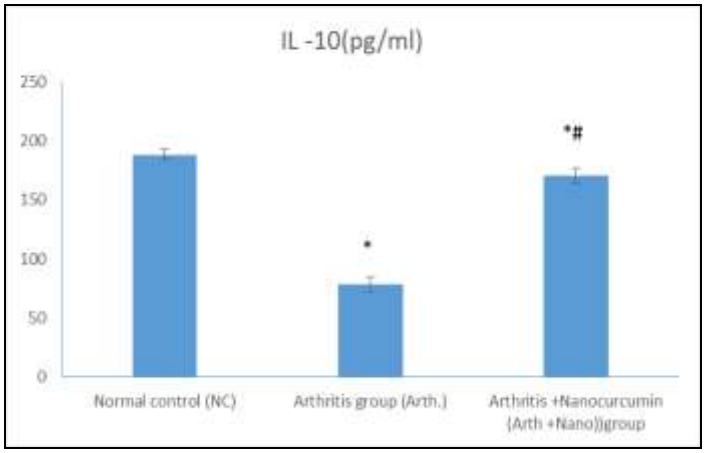


Figure 2: Effect of Nanocurcumin on interleukin-10(IL-10) level

Effect of Nanocurcumin on bone marrow differential count

Bone marrow smears showed noticeable hyper-cellularity in the arthritis cohort during vied with the normal cohort rats. Table 3 presents differential counts of bone marrow nucleated cells of standard rats and rats injected by FA. In the arthritis group there are more metamylocyte neutrophils with an arrest of maturation of N. myeloblast, N. Promyelocyte and N. myelocyte stages as shown in fig. (3). The lower proportion of eosinphils was mostly due to the decrease of mature forms Promyelocyte eosinphils, Myelocyte eosinphils and Metamyelocyte eosinophils fig. (4). There are also more erythroblasts- polychromatophils with an arrest of maturation at the Pro-erythroblasts and Erythroblasts basophils cells fig. (5). The percentage of Megakaryocytes was slightly increase. Treatment with Nanocurcumin improve cellularity of hematopoietic bone marrow.

Table 3: Mean Bone Marrow Differential Count

Parameters	Normal control (NC)	Arthritis group	Arthritis +Nanocurcumin group
Myeloblast neutrophils	1.74±0.46	0.94±0.11 *	1.31±0.3
Promyelocyte neutrophils	3.43±1.04	0.96±0.36 *	2.13±0.54 *#
Myelocyte neutrophils	13±1.8	9.95±1.07 *	13.66±2.14 #
Metamyelocytes neutrophils	10.03±1.42	21.31±2.23 *	15.3±1.49 *#
Promyelocyte eosinophils	3.43±0.7	1.07±0.45 *	2.75±0.44 #
Myelocyte eosinophils	2.03±0.37	0.09±0.21 *	1.06±0.16 *#
Metamyelocytes eosinophils	1.42±0.45	0.32±0.49 *	0.6±0.33 *
Pro-erythroblasts	0.57±0.49	0.33±0.26	0.75±0.42
Erythroblasts basophils	2.85±0.79	1.07±0.8 *	2.4±0.57 #
Erythroblasts-polychromatophils	11.21±1.87	17.02±5.08 *	11.47±1.54 #
Megakaryocytes	0.29±0.14	0.48±0.21	0.26±0.05

Values are presented as mean ±SD *: statistically significant compared to the corresponding control group value (P<0.05), #: statistically significant compared to the corresponding Arthritis group value (P<0.05).

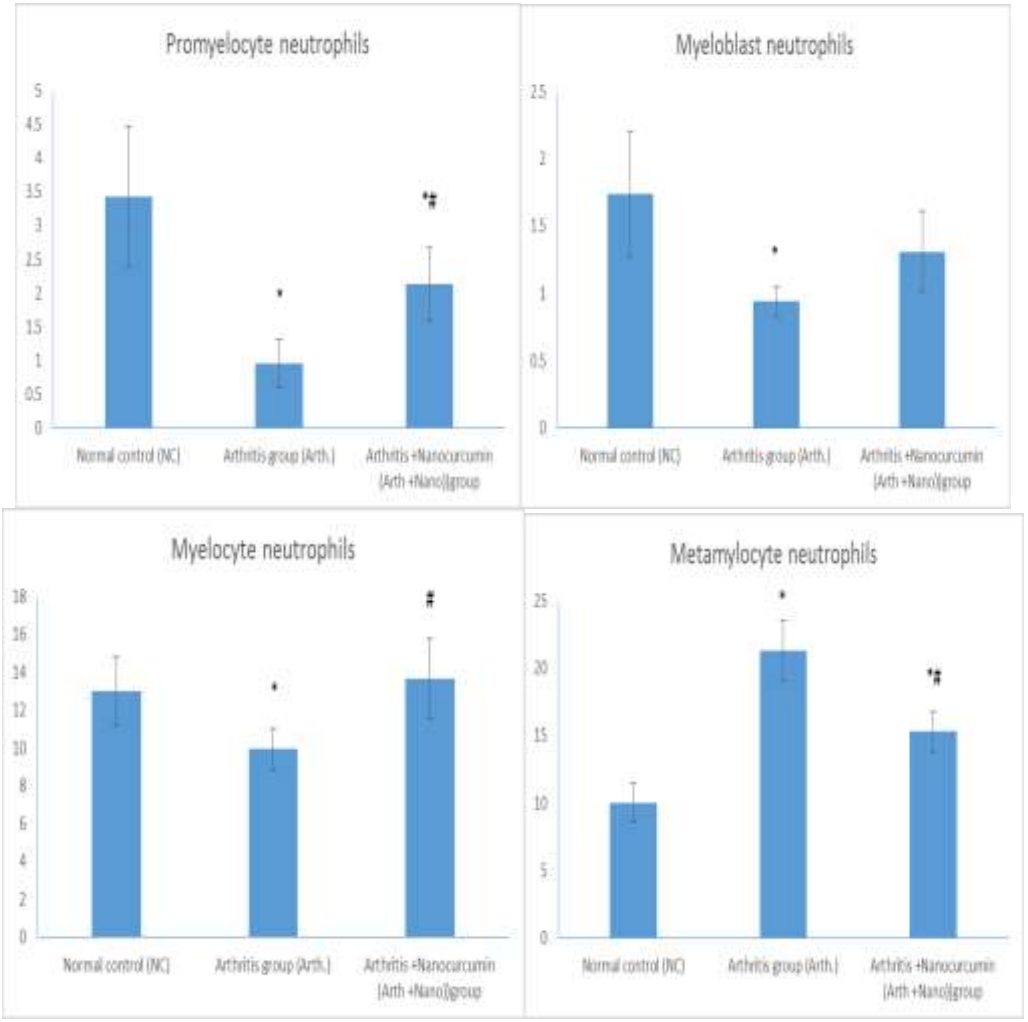


Figure 3: Effect of Nanocurcumin on neutrophils maturation

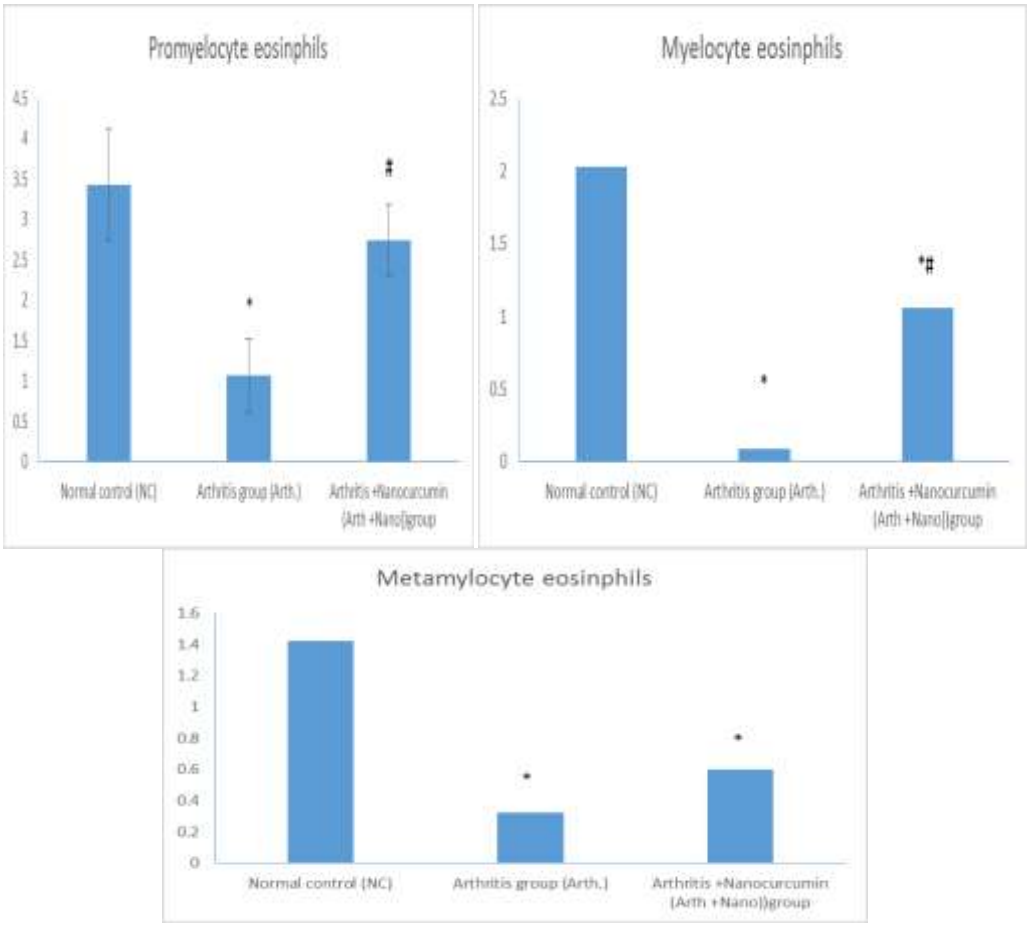


Figure 4: Effect of Nanocurcumin on eosinphils development

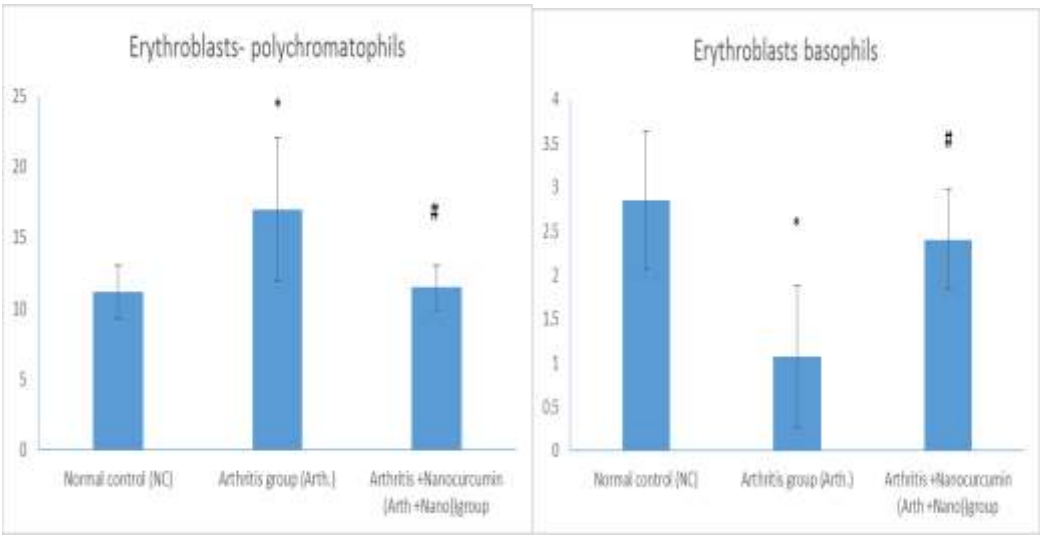


Figure 5: Effect of Nanocurcumin on Erythroblasts basophils and Erythroblasts- polychromatophils cells.

DISCUSSION

RA is a condition that triggers joint inflammation affecting approximately 1% of adults worldwide, where the causative agent persists vague (Karmakar et al.,2010 and Bax et al.,2011). In the present investigation, complete Freud adjuvant-induced arthritis was considered as an animal model of RA. CFA excited forms is practiced generally for evaluating the anti-arthritic effectiveness and anti-inflammatory of medications utilized for the remedy of RA (Lin et al.,2017). CFA-induced rat arthritis model has many similarities to RA-induced rats in humans, making it more suitable for the study model (Tag et al.,2014). In our study, the reduction in RBC count and hemoglobin scale in arthritic rats (group II) depicts the anemic disease which occurs from the unnatural accommodation of iron in the reticuloendothelial system and the disqualification of bone marrow to counter to anemias (Mowat et al.,1971). The significant increase in WBCs number in arthropathy rats

might be upon to the incentive of the immune system versus the attacking antigens. ESR is the usual ordinarily employed lab index of an inflammatory performance. Hu (2005) assured that ESR count significantly amplified in the arthritic key group may be as a consequence to the quickened configuration of endogenous protein such as fibrinogen and α, β globulin, and flow in the ESR intimates a powerful but complicated disease manner.

The C-reactive protein applies to the category of acute phase reactants, its scale spread within inflammatory progressions (McConkey,1973). Predominant CRP check is followed as an excellent lab technique for scrutinising RA and other inflammatory diseases arising from inflammation. It is an effective indicator of tissue damage, and the concentration of CRP in serum is correlated with disease activity. The higher level of CRP found in the arthritis group indicated joint pathology, and as a result of the activated fibroblasts and macrophages in the sore joints synovium, the production of CRP may have increased.

In addition to, CRP development is also mediated by inflammatory joint mediators like IL (interleukin)-1 and IL-6, hence the reverse in CRP levels after supplementation suggests a substantial decrease in synovial macrophage activation and fibroblast activation (Jones et al.,2011).

additionally, the treatment of Nanocurcumin at dosage 100 mg/ kg b.wt. to arthritic rat, pointed to a notable boost in RBC estimate and haemoglobin level, but caused decrease in WBCs, ESR and CRP counts. Several authors recorded that curcumin inhibits the signaling pathway of the nuclear factor-κB (NF-κB) which may control the production of cytokines and provoke the immune rebuttal. Curcumin reins some genes expression, notably cytokines genes. Adhesion molecules (ICAM, VCAM), IL-1, IL-8, IL-6, TNF α and C-reactive protein may be down-regulated by curcumin. These results are in harmony with those obtained by Rahimi et al. (2014); Rahimi et al. (2015).

IL-10 can minimize autoimmune pathologic inflammation by preventing various sides of the immune activity (Schulze-Koops and Kalden, 2001). It defeats the origination of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-12, IL-8 and interferon-γ (IFN-γ) through the macrophage. IL-10 likewise minimizes the reproduction of prostaglandin E2 (PGE2) and nitric oxide (NO) in macrophages. It is accordingly admitted to being an influential powerful anti-inflammatory cytokine (Fiorentino et al., 1991; Kang et al., 2009; Lin et al., 2014). Under treatment by (100 mg/kg Nanocurcumin for one month) after induction of RA, treated groups showed increase in IL-10 level as curcumin may prompt the expression and production of IL-10 to lower inflammatory conditions.

Neutrophils are phagocytic granulocytes which are a vital constituent of accelerated "non-specific" immune justifications. Likewise, other leukocytes, they are realized from pluripotent stem cell ancestors in the bone marrow. Superimposed stimulation via colony-stimulating factors, including stem cell factor, granulocyte-monocyte colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), phagocyte ancestors propagate and proceed into satisfied segmented neutrophils in the bone marrow. The initial three phases of neutrophil ripening—myeloblast, promyelocyte, and myelocyte incorporate young actively apportioning cells. The cells lack their aptitude to divide for scheme metamyelocytes, band cells, and lastly segmented polymorphonuclear neutrophils, subsequent the myelocyte acclivity. In the present study, arthritic group treated with Nanocurcumin showed increased in myeloblast, promyelocyte, and myelocyte cells but decreased in metamyelocytes cells. Curcumin has a potent immunomodulatory on the inflammatory response and can check the activation of T lymphocytes, B-lymphocytes, macrophages, neutrophils, and dendritic cells. Several reports suggested that these results seem to support curcumin's potential for treating arthritis in human analytical and empirical patterns of dawned arthropathy (Lantz et al.,2005, Mun et al.,2009 and Moon et al.,2010).

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