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PHARMACOLOGICAL ACTIVITY OF COMBINATION OF CURCUMIN AND VITAMIN C AGAINST OXIDATIVE STRESS INDUCED BY NAPROXEN IN MALE RATS

NAWRAS NOORI BASHBOOSH [a*]

[a] Department of Biology, Faculty of Science, University of Kufa, Iraq.

AUTHOR'S CONTRIBUTION

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

The Aim: The goal of this study was to see if curcumin and vitamin C might protect male rats' blood from oxidative stress caused by naproxen using hematological criteria and antioxidant measures.
Study Design: The rats were aged 2.5-3 months and contemplated (200-250) gm. The purpose of this study was to see if Cur and Vitamin C might protect male rats against oxidative damage caused by NP, as well as hematological.
Place and Duration of Study: From April to October 2019, the experiment was conducted out on 48 male rats weighing between (200-250) gm and aged 2.5-3 months at the animal house of the faculty of science/university of Kufa.
Methodology: The 48 male Wister albino rats were separated into six groups at random; Group (1) NP was administered orally to rats at a dose of 40 mg/kg (as positive control). Group (2) cur at a dose of 150 mg/kg was given orally to the rats as a treatment. Group (3) During a 14-day period, rats were given 150 mg/kg of vitamin C by oral administration. Group (4) cur (150 mg/kg) and Vitamin C (150 mg/kg) were given orally to the rats as a treatment. Group (5) The oral administration of NP (40 mg/kg) plus Cur (150 mg/kg) plus Vit C (150 mg/kg) was performed on rats. Group (6) normal saline solution was given to the rats orally during the experiment (as negative control).
Results: Finishing the experiments, the findings displayed a considerable decrease ($p<0.05$) in the average of body weight, hemoglobin concentration (HB) and haematocrit (HCT) while considerable increase ($p<0.05$) in the white blood cells(WBC) counts in the animals treated with NP compared to the control and other treated groups , while the results offered considerable increase ($p <0.05$) in the average of body contemplate , HB, HCT and a considerable decrease ($p<0.05$) in WBC rate in the animals treated with Cur, VitC, Cur+Vit C, Cur +Vit C+ Np compared the control group .

**Corresponding author;*

Conclusion: In conclusion, whereas naproxen has a harmful impact on the body by increasing oxidative stress, curcumin and vitamin C operate as powerful antioxidant supplements that reduce malonal di aldehyde (MDA) and boost overall antioxidant capacity by increasing superoxide dismutase (SOD) in the body.

Keywords: Curcumin; naproxen; oxidative stress; antioxidant.

1. INTRODUCTION

Oxidative stress is fairly common in humans. In typical settings, physiologically relevant amounts of reactive oxygen species (ROS) include superoxide radical (O2•-) and hydroxyl radical (HO•), as well as non-radical molecules like hydrogen peroxide (H2O2). Stress increases the concentration of these ROS, providing a major health danger [1]. Polyunsaturated fatty acids are a preferred oxidation target for reactive oxygen species (ROS). Oxygen-free radicals, superoxide anion radicals (O2•−) in particular, hydroxyl radicals (HO•−), and alkyl peroxyl radicals (RCOO•−), are potent initiators of lipid peroxidation, and their role in the pathophysiology of a wide variety of diseases is well established. Antioxidants protect the body's cells and organ systems against ROS. Antioxidant enzymatic molecules such as malondialdehyde, MDA, SOD, GPX, and no enzymatic molecules that are normally dispersed between the cytoplasm and other cell organelles (e.g., GSH, vitamins E, C, and trace metals like selenium) also operate as immediate ROS scavengers [2]. Curcuma Longa is a natural food dye, fragrance, antioxidant, and a component in a variety of medical preparations [3]. C. Longa's therapeutic benefits are related to the presence of curcumin (Cur), fundamental oils, and phenolic [4]. Turmeric's vivid yellow hue is mostly due to fat-soluble, polyphenolic pigments known as curcuminoids [5]. Curcumin has several biological functions, including" "anti-inflammatory, antioxidant, ant carcinogenic, ant mutagenic, anticoagulant, antifertility, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, ant fibrotic, ant venom, antiulcer, hypotensive, and hypocholesteremic properties" [6]. Cortisone and phenylbutazone have been demonstrated to be equally efficient in the treatment of acute inflammation, but Cur has been found to be less effective in the treatment of chronic inflammation when given orally. In arthritis-infected rats, curcuma longa therapy reduced inflammatory edema relative to controls [7]. Because vitamin C (ascorbic acid) is water soluble and cannot be manufactured by humans, it is critical to have it in our diet [8]. Vitamin C has been linked to a lower risk of cancer, blood pressure, immunity, drug metabolism, and tissue regeneration in humans.. An enzyme cofactor for the production of a number of important biochemical, vitamin C is a potent antioxidant. Enzymes involved in protein, carbohydrate, and lipid metabolism are activated by this supplement as well. SOD (Mn and Cu-Zn), GSH and GSH-Px, catalase, vitamin C and E, and other antioxidant enzymes are capable of quenching the ROS generated in the body under normal physiological circumstances. Due to its molecular nature, vitamin C works as a cofactor and lowers some enzymes by giving electrons [9]. In the medical world, naproxen (NP) is an anti-inflammatory and analgesic non-steroidal anti-inflammatory drug (NSAID) that is widely prescribed. It works by inhibiting cyclooxygenase, resulting in a reduction in prostaglandin levels in numerous fluids and tissues.

2. MATERIALS AND METHODS

1.2 Materials

Sigma Chemicals provided the curcumin and naproxen (USA). Rats weighing between (200-250) gm, received 150 mg/kg of curcumin dissolved in saline and naproxen (40 mg/kg body mass) dissolved in normal saline via oral gavage in a volume of 5 ml/kg using an adequate feeding needle. The drugstore sells vitamin C (*ascorbic acid*) in a dosage of 150 mg/kg.

2.2 Experimental Animals

For the current study, 48 male rats pondering between (200 and 250) grams (Rattus norvegicus) were used. Under typical settings (temperature 25-28°C and a 12-hour light-dark cycle), the animals were housed at the animal home of the University of Kufa's Faculty of Science, where they were provided with a regular laboratory meal and access to water on a daily basis.

2.3 Experimental Design

The rats were housed in an animal housing for two weeks before being used in the experiment to allow them to become acclimated to the laboratory environment. They were divided into (6) groups, with each group containing eight (8) rats, and the treated materials were given to them by mouth, in the following sequence:

Group (1) Rats were fed NP at a dose of 40 mg/kg orally (as positive control). **Group (2)** rats were given Cur at a dosage of 150 mg/kg orally. **Group (3)** Vit C was controlled orally to rats at a level of 150 mg/kg. **Group (4)** Cur (150 mg/kg) and Vitamin C

(150 mg/kg) were given orally to the rats as a treatment. **Group (5)** oral administration of NP (40 mg/kg) plus Cur (150 mg/kg) plus Vit C (150 mg/kg) was performed in rats. **Group (6)** normal saline (as a negative control) was administered orally to the rats for three weeks, following which the animals in each group were slaughtered and their hematological parameters and serum antioxidant enzymes were measured.

2.4 Blood Collection

Each animal was anesthetized with a combination of 0.1 mL xylazine and 0.5 mL ketamine and scarified at the end of the studies [10]. 2-5 ml of blood was gently and carefully taken from the heart with a disposable syringe. Results were recorded for each half of a blood sample . First, a little amount of the first component (about 5 ml) was placed in a tube that contained anticoagulant EDTA (22 mg/ml) and thoroughly mixed before being used for hematological analysis by an automated analyzer.

2.5 Hematological Analysis

Ruby was used to analyze EDTA blood for hematological characteristics (Abbott, United States of America). Red blood corpuscles, white blood cells, hemoglobin (HB), and Hematocrit (HCT) are all measured by Ruby, a hematology analyzer [11].

2.6 Determination of Antioxidant Parameters

ELISA Kit (Elabscience, USA) (www.elabscience.com, 2018) was used to measure blood superoxide dismutase level (SOD) activity, malondialdehyde activity (MDA), and glutathione peroxidase activity (GPX).

2.7 Statistical Analysis

Statistical analysis was performed using the ANOVA test, followed by the least significant difference analysis at 0.05% probability levels for the means and standard deviations (means S.E.) (L.S.D.). Use of a personal computer with the SPSS application [12].

3. RESULTS

3.1 Body Weight and Body Organ Weight

As the results in table (1) display no considerable difference ($p<0.05$) in the average of body weight, liver weight ,kidney and spleen weight in the group of rats treated with NP in compare with control group , while considerable decrease ($p<0.05$) in the average of body weight in the group of rats treated with NP in compare with before treated. Also, the results in the same table show considerable increase ($p<0.05$) in the average of body weight in the group of rats treated with only Cur in compare with two groups of rats treated with Vit C and Cur + Vit C and in the groups of rats treated with Cur, VitC, Cur + VitC and Cur + VitC + NP in compare with before treated .As this results a considerable decrease ($p<0.05$) in the average of body weight in the groups of rats with Cur + VitC compare with other treated groups. The results also were shown a considerable increase ($p<0.05$) in the average of body weight in the group of rats treated with Cur + VitC + NP in compare with the groups of rats treated with Cur, VitC and Cur + VitC and no considerable difference between the treated groups and control.

Table 1. Effect of the doses in the regular of body mass, liver weight , kidney weight and spleen weight in the treated rats by NP, Cur, VitC, Cur + VitC and Cur + VitC + NP

Dose (mg/kgBW)	"Initial body weight" (gm)	"Final body weight" (gm)	"Liver weight" (%)	"Kidney weight" (%)	"Spleen weight" (%)
NP	372 ± 10.64	343± 9.94a	12.16 ± 0.41	1.36 ± 0.05	1.39 ± 0.09
Cur	200 ± 21.51	297 ±5.43 ab	7.91 ± 0.45	0.79 ± 0.05	1.07 ± 0.12
VitC	205 ± 6.31	260 ± 7.55a	12.22 ± 0.38	1.17 ± 0.13	0.86 ± 0.009
Cur + VitC	195 ± 25.17	211 ± 22.5a	8.46 ± 0.97	1.002 ± 0.05	1.20 ± 0.10
Cur+VitC+NP	210 ± 22.2	328 ± 4.53 ab	12.44 ± 0.78	1.18 ± 0.05	1.05 ± 0.009
Control	252 ± 19.84	324 ± 9.07	12.83 ± 0.13	1.28 ± 0.02	1.84 ± 0.28

Values are mean ±Standard Error NP: Naproxen / Cur: Curcumin / Vit.C: vitamin C (a) considerable differences between before and after treated groups at p-value <0.05. (b) considerable differences between treated groups at p-value <0.05

3.2 Hematological Parameters

The findings in table (2) show no considerable difference ($p<0.05$) in the average of RBCs in groups with each one another and in compare with control group . When the findings in the same table show considerable increase ($p<0.05$) in the average of WBCs in the groups of rats treated with NP and Cur + Vit C compare with Cur , VitC and control groups .As well as, the findings in the same table appear considerable increase ($p<0.05$) in the average of HCT in the groups of rats treated with VitC, Cur + VitC and Cur + VitC + NP in compare with NP and Cur groups , while the findings also display considerable decrease ($p<0.05$) in the average of HCT in the group of rats treated with NP in compare with the other treated groups and control group. As well as, the results in the same table show significant decrease ($p<0.05$) in the average of HB in the group of rats treated with NP in compare with the other treated groups and control group.

Table 2. "Effect of the doses in the hematological parameters in the treated" rats by NP, Cur, VitC, Cur + VitC and Cur + VitC + NP

Dose (mg/kgBW)	WBC (10^6/mm^3)	RBC 10^6/mm^3)	HB (mg/dl)	HCT (%)
NP	10.40 ± 2.29 ab	5.04 ± 0.23	8.52 ± 0.34 ab	29.42 ± 0.69 ab
Cur	5.22 ± 0.53	6.70 ± 0.16	11.35 ± 0.58	38.54 ± 2.38
VitC	4.90 ± 0.36	6.78 ± 0.09	13.21 ± 0.58	43.91 ± 0.04 b
Cur+VitC	12.96 ± 1.28 ab	7.53 ± 0.24	13.98 ± 0.50	47.84 ± 1.62 b
Cur+VitC+Np	9.19 ± 1.58	6.91 ± 0.09	13.25 ± 0.16	44.24 ± 1.11 b
Control	5.50 ± 0.51	7.17 ± 0.02	12.88 ± 0.10	45.10 ± 0.84

Values are mean ±Standard Error NP: Naproxen / Cur: Curcumin / Vit.C: vitamin C.
(a) At a p-value of <0.05, the treatment and control groups showed significant differences. b) a p-value less than <0.05 indicates statistically significant differences between the treatment group

Table 3. "Effect of the doses in the Antioxidant Oxidative stress parameters" in the treated rats by NP, Cur, VitC, Cur + VitC and Cur + VitC + NP

Dose (mg/kgBW)	SOD	GPX (10^6/mm^3)	MDA (%)
NP	5.07± 0.206	389.10 ± 30.170	613.71 ± 19.676 ab
Cur	6.38 ± 0.111	389.10 ± 1.616	706.29 ± 16.150
VitC	5.36 ± 0.146	391.23 ± 5.656	742.04 ± 6.017 b
Cur+VitC	4.98 ± 0.487 ab	389.10 ± 11.255	560.65 ± 55.047 b
Cur+VitC+NP	2.27 ± 0.111	376.27 ± 30.706	270.34 ± 20.266 b
Control	4.75 ± 0.303	321.22 ± 11.181	587.46 ± 45.584

Values are mean ±Standard Error NP: Naproxen / Cur: Curcumin / Vit.C: vitamin C.
At a p-value of <0.05, the treatment and control groups showed significant differences. (b) A p-value of <0.05 or less indicates that there are significant differences among the different treatment groups.

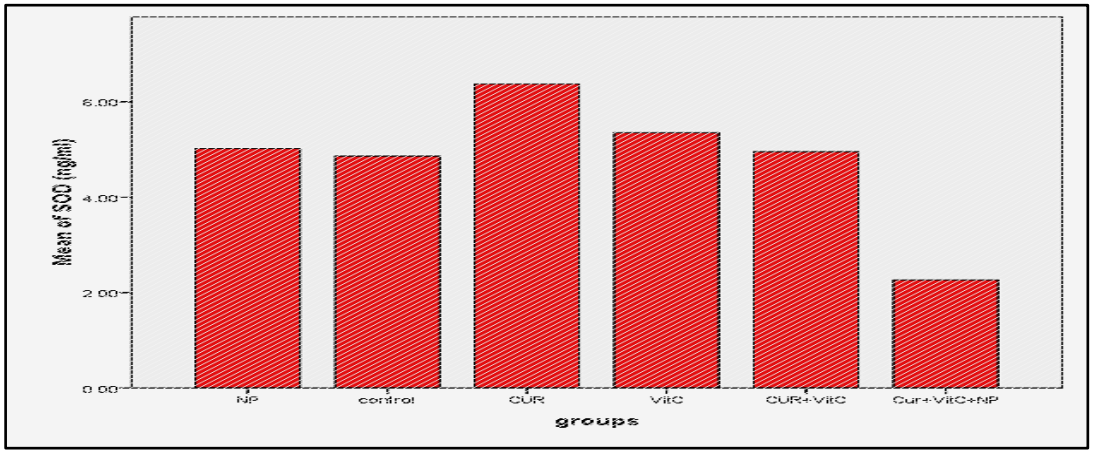

Fig. 1. Show the effect of NP,Cur, VitC and there combination on Superoxide Dismutase (SOD) serum level in male rats

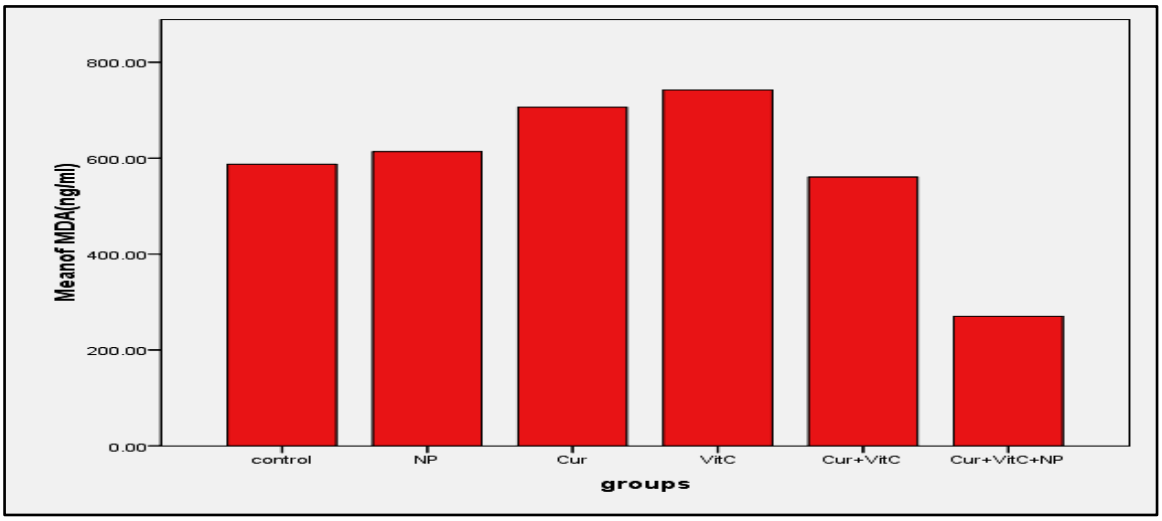

Fig. 2. Effect of NP,Cur, VitC and there combination on Malondialdehyde (MDA) serum level in male rats

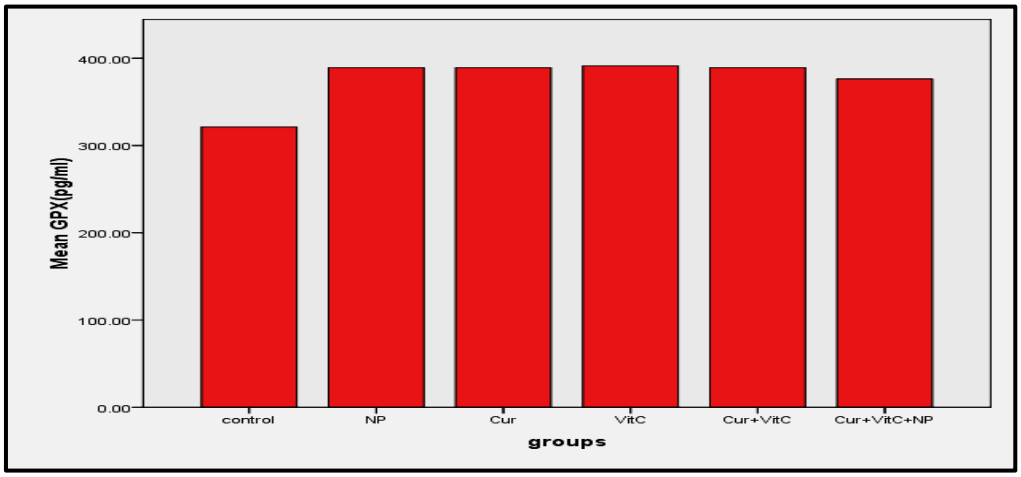

Fig. 3. Effect of NP,Cur, VitC and there combination on Glutathione peroxidase (GPX) serum level in male rats

3.3 Antioxidant Oxidative Stress Parameters

In fig.(1) the compassion between the effects of NP,Cur and VitC with their combination on superoxide dismutase (SOD) serum level in male rats. The results revealed the level SOD in groups treated with NP alone and with the combination with Cur and VitC were lower than groups treated with Cur , Cur +VitC and VitC while the highest level of SOD was in group Cur alone comparing to other treated groups and control, then the groups VitC and Cur+VitC have high level of SOD in compare with NP, Cur+VitC+NP and control.

In Fig. (2), (3) the compassion between the effects of NP,Cur, VitC and there combination on malondialdehyde (MDA) serum level and glutathione peroxidase (GPX) respectively in male rats. The results revealed the level MDA in groups treated with NP is higher than Cur + VitC + Np , Cur + VitC groups and control, while the level MDA in Cur and VitC were higher than other groups as the results , moreover, the results demonstrate that the level of MDA in the Cur + VitC + NP was the most lower than all groups, while there is no differences between all groups.

4. DISCUSSION

4.1 Body Weight and Body Organ Weight

According to the findings of this study, the ultimate body mass of rats given naproxen (NP) is considerably lower than that of healthy normal rats,

and the unfavorable effect of NP on body weight gain increases as exposure duration increases. Reactive oxygen species (ROS) is hypothesized as the source of renal side-effects of certain antibiotic medication; lipid peroxidation induced by oxygen-free radicals is also regarded to be a key cause of cell membrane breakdown and damage.

Also, the result of the current investigation was displayed a considerable increase ($p<0.05$) in the average of body weight in the groups of rats after treated with Cur, VitC, Cur + VitC and Cur + VitC + NP in compare with before treated and in only Cur group in compare with two other groups of rats treated with Vit C and Cur + Vit C. Foldesiova et al. [13] evaluated the effect of adding Cur dry powder to the full feed combination on average weekly and total average weight growth (g) of rabbit does, whereas Cur + VitC groups showed a significant reduction ($p<0.05$) in comparison to other treatment groups. The greater quantity of Curcuma longa in the feed combination may have caused inadequate absorption from the colon, as stated by Habeebad and EL-Tarabany [14] research. Al-Sultan [15] found that birds fed a food containing Curcuma longa at a concentration of 0.5 percent gained more weight than birds fed 0.25%, 1%, or control diets. Durrani et al. [16] also found a statistically significant favorable effect of Cur at 0.5% on avian weight increase. Adding curcumin to children's diets throughout the hot summer months enhanced their ultimate live body weight and average daily body gain compared to the control group. Similarly to our results, Mehala and Moorthy [17] reported no significant impact of adding curcuma powder in broiler rabbits (Basavaraj et al., 2010) and broiler chicks fed a mixture. Vitamin C activates enzymes involved in protein, carbohydrate, and fat metabolism; nevertheless, these enzymes can degrade macromolecules including lipids, proteins, and DNA. Vit C helps to prevent DNA damage by reducing oxygen species generated during lipid peroxidation, reducing radical inhibitors in protein oxidation, and preventing nitrosamine production [18]. Vit C has a strongly regulators to act directly by scavenging ROS in neutrophil, this vitamin used in tissues repairing and protection from lipid peroxidation.

4.2 Blood Parameters

The results in the table (2) of the current study is agreed with AL-Mayah and ALAhmed [19], study which explains that used of antibiotics resulted in a considerabke decrease ($p<0.05$) in haematological values and Burek and Cunha [40-43], study who stated that previous antibiotics exerts effects on different elements of blood, some agents produce anemia or leukopenia. The loss of store iron in the liver tissues is also due to oxidative damage induced by ROS, which is hazardous to cells, particularly cell membranes, where free radicals interact with lipid bilayers to form lipid peroxides, which causes hemoglobin concentration to drop significantly. The concentration of red blood cells in the blood affects haematocrit [21]. The large drop in HB may be ascribed to the loss of store iron in the liver tissues due to oxidative damage from antibiotics [2]. Curcuminoids, which have a strong antioxidant activity, can reduce the generation of ROS, which causes haemolysis, as shown in the current study [23,24]. Curcumin's capacity to react with reactive oxygen and nitrogen species (ROS and RNS) explains its potential to protect erythrocytes from oxidative stress [25].

Curuminoids are treat inflammation in the joints and tendons due to the antioxidant feature of it as a result curuminoids had returned the leukocytes count and erythrocyte sedimentation rate into normal values in the blood so, these results were agreement with Calabrese *et al.*, [26] , Barzegar and moosavi-movahedi [25]. However, as the study result considerable increase ($p<0.05$) in the average of WBCs in the groups of rats treated with Cur + Vit C compare with Cur , VitC and control groups may be according to inflammatory response to treat . Furthermore, Verma et al. [27] said that leukocytosis in rats implies immune system activation. Vitamin C has the ability to digest reactive oxygen species directly. One of the key effects of oxidative stress that might be reduced by vitamin C is pathogenic tissue malfunction due to cell death via apoptosis [28].

4.3 Antioxidant Parameters

The current study's findings suggested that NP treatment decreased SOD levels and increased MDA levels in the experimental rats when compared to the other treated groups and control. Mir et al. [29] found that NP therapy reduced tissue sulfhydryl (GSH) levels, reducing the action of tissue antioxidants including SOD and CAT, and increasing oxidative stress. Lipid peroxidation caused by oxidative stress can cause DNA damage and mutation. Curcumin is capable to remove superoxide anion ($O_2^{\bullet-}$) [30], hydroxyl radicals ($HO^{\bullet}$) [25], single oxygen ($O^{\bullet}$), nitric oxide [31-35], peroxynitrite and peroxyl radicals ($ROO^{\bullet}$) [36-39]. Schwartz *et al.* (2008) demonstrated a favorable correlation between oxidative stress molecules, MDA, total oxidative state, and central sensitization in mice with hyperalgesia. Under normal physiological conditions, antioxidant defense mechanisms such as enzymatic and non-enzymatic scavengers protect biological

systems from oxidative damage induced by ROS. Several free radical scavenging enzymes, including SOD, CAT, and GPX, are commonly employed as biomarkers of oxidative stress because they constitute the first line of cellular defense against the damaging effects of reactive oxygen species (ROS) [44-47]. Furthermore, the antioxidants Cur and VitC enhanced SOD levels and lowered MDA levels in the rats treated with Cur, VitC, and Cur+VitC. These findings support Khedr and Khedr [48-51] findings that Cur's antioxidant activity plays a major role in its therapeutic effect in nonalcoholic fatty liver disease and may prevent fibrosis. Khe According to Jeong et al. (2016), cur can also prevent naproxen-induced stomach antral ulcers by reducing lipid peroxidation and activating radical scavenging enzymes such as SOD (2016). Farther more [52-57] concluded the treatment with the solution containing Vit C, Vit E have synergism effect in the reduction of oxidation process and shown the best antioxidant effective in the animals treated with vancomycin . Vitamin C has been demonstrated to prevent cisplatin-induced liver damage by altering the antioxidant defense system or allocating electrons to free radicals, therefore lowering oxidative damage [58-63].

5. CONCLUSION

Naproxen having the toxic effect by increase the oxidative stress in the body , curcumin and vitamin C act as the strong antioxidant supplement which are decreases malondialdehyde (MDA) and improves total antioxidant capacity like increase superoxide dismutase (SOD) in the human and animal body.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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