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# The Therapeutic Effects of Stem Cell Enhancer on Changes of Some Physiological Parameters in Male Albino Rats Treated With Mixture of Food Additives (Food Preservative, Food Coloring Agent, and Flavor Enhancer)

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## ABSTRACT

**Background:** food additives are substances intentionally added to food to change its characteristics, to maintain and improve safety, to improve or maintain the nutrient value and to improve taste, texture, and appearance. Sodium nitrite is an inorganic salt with widespread applications in the food industry as a food preservative in meat and fish. However, Annatto is used as a dyeing agent in the food industry in coloring butter, cheese, and ice-cream whereas Monosodium Glutamate (MSG) is one of the most used flavorenhancers which is ingested as part of commercially processed foods. Stem cell enhancer is a natural stem cell mobilizer that can trigger the release of millions of adult stem cells from bone marrow into the circulation, and its considerable safety allows for a sustained oral daily intake over long periods of time.

**Aim of the work:** this study was aimed to determine the therapeutic effects of Stem Cell Enhancer (SCE) against the hazardous effects of sodium nitrite, annatto and monosodium glutamate on some physiological parameters in male albino rats. **Materials and methods:** this study had been done on thirty male albino rats with an average body weight 120-140 g. The animals were divided into three groups; **Group 1:** control (untreated group), **Group 2:**rats treated with food additives mixture (sodium nitrite, annatto, and monosodium glutamate); **Group 3:** rats treated with food additives mixture, in addition to Stem Cell Enhancer. Blood samples were collected, and the separated sera were used for estimation of some biochemical parameters (liver enzymes, kidney functions, glucose, protein profile and lipid profile) and hormonal levels [testosterone,triiodothyronine (T3) and thyroxine(T4**)**].

**Results:** the biochemical results showed an increase in the activities of liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], and the levels of glucose, kidney functions (urea, and creatinine), lipid profile [total cholesterol, triglycerides, low-density lipoprotein(LDL-c), high-density lipoprotein(HDL-c)and risk factors 1& 2] and thyroid hormones [T3 and T4]in the mixture accompanied by a significant decrease in protein profile (total protein, albumin and globulin), HDL-and testosterone hormone levels as compared to the control rats. On the other hand, these results turned back to nearly to the normal values after receiving the Stem cell Enhancer.

**Conclusion:** the present study clearly revealed thetherapeutic capability of SCE to fight the grievous effects of food additives mixture on major physiological parameters.

**Keywords**: food additives, sodium nitrite, annatto, monosodium glutamate, Stem Cell Enhancer.

## INTRODUCTION

Humans are continuously exposed to different kinds of chemicals such as food additives. Many of these additives have been increasingly recognized as potentially hazardous to human health. Sodium nitrite is a food additive that is used as a color fixative and preservative for meats and fish [(1)] as a result of itswell-known role in inhibitingthe growth of *Clostridium botulinum*spores in refrigeratedmeats [(2)].While sodium nitrite will prevent the growthof bacteria, in large amounts it can be toxic to animals, including humans. The cytotoxicity and detrimental effects of nitrite can be attributed to its oxidative properties [(3)].

Annatto is a shrub native to the South American tropics, the natural reddish-yellow color is obtained from the outer coating of its seeds. The pigments contain carotenoids, including a large amount of cis-bixin and



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other minor constituents, such as trans-bixin, cis-norbixin, and trans-norbixin[4].
Monosodium Glutamate (MSG) is one of the world's most extensively used food additives which is ingested as part of commercially processed foods[5].
Stem cell enhancer (StemEnhance®) is a novel mobilizer of bone marrow adult stem cells that was shown to increase the number of circulating stem cells. One gram of StemEnhance has shown to support an increased release in the number of circulating stem cells in the body by 25% to 30% that greatly increased the potential of the body's active repair and renewal system [6]. StemEnhance® is a blend of 4 compounds: *Aphanizomenonflos- aquae* (AFA) that extracted from blue-green algae, *Undaria pinnatifid, Polygonum multiform, and Cordyceps sinensis*. They may have an individual physiological effect or synergistic effects with one another, such as serving as both a releasing agent and migration agent [7].
Stem cell therapeutic strategies are being evaluated as an attractive promising approach for liver repair. Several studies have reported the ability of various types of stem cells to improve the pathological outcome of liver cirrhosis and to attenuate the clinical symptom of the disease [8].

The aim of the present study was to explore the therapeutic effects of Stem Cell Enhancer (SCE) against the hazardous effects of sodium nitrite, annatto and monosodium glutamate on some physiological parameters in male albino rats.

## MATERIALS AND METHODS

Thirty male albino rats (weighing 120-140 g) were used in this study. Animals were housed in stainless steel cages, fed on rat chew and offered water *ad libidum*. Theanimals were divided into three equal groups (10 rats/each) as follows: **the first group:** the control untreated group, **the second group:** rats were orally administered with a mixture of food additives: sodium nitrite(0.1 mg/kg b.wt./ day), annatto(0.065 mg/kg b.wt./day) and monosodium glutamate(15 mg/kg b.wt./day)and **the third group:** rats were orally administrated with the previous mixture of food additives in addition to a dose of Stem Cell Enhancer (7.85 mg/kg b.wt./day). Body weights were recorded every week. After30 days oftreatment, animals were weighed and then decapitatedafterthey were anesthetizedwith inhALTion anesthesia using alcohol, chloroform, and ether in a ratio of 1:2:3 [9].
Blood samples were collected and centrifuged for 10 minutes at 5000 rpm and sera were separated for analysis of biochemical parameters without storage or delay.

### *Biochemical investigations*

Inthe present study, total protein (TP) and albuminconcentration were estimated, then serum globulin concentrations were calculated according to the formula:
**Globulin (g/dl) = total protein (g/dl) – albumin (g/dl)**
Aspartate aminotransferase (AST), alanine aminotransferase (ALT) activities, creatinine, urea, fasting blood glucose concentrationsas well as lipid profile that including total cholesterol, triglycerides LDL-C and HDL-C were also determined. Concentrations of testosterone and thyroid hormones (T3 and T4) were measured. All parameters were estimated using **BioMerieux SA kits, France.**
The both ratios of serum albumin/ globulin and albumin/creatinine were determined. However, ratios of TC/HDL (risk factor 1) and LDL/HDL (risk factor 2) were also calculated after calculation of serum LDL-C (low-density lipoprotein cholesterol) and VLDL (very low-density lipoprotein cholesterol) using the **Friedwald's[10]** and **Norbert [11]**formulas, respectively as following:

**Friedewald's[10] equation**: **LDL (mg/dl) = TC- {HDL + [TG/5]}.**
**Norbert [11] equation: VLDL = TG/5**

### *Statistical analysis*

The results were expressed as Mean ± SEM of the mean. Data were analyzed by one-way analysis of variance (ANOVA) and were performed using the Statistical Packagefor Social Sciences (SPSS) program, version 20. The Bonferroni test was used as a method to compare significance between groups. The significance level was accepted at p-value $<0.05$.

## RESULTS

**Body weight:** no significant change was noticed in the percentage of body weight change in bothtreated groups **(Table 1).**

**Glucose level:** there was a highly significant increase ($p<0.001$) glucose level in the mixture group in comparison to control rats. While in the group of (mixture + SCE) there was a significant increase ($p<0.05$) as compared to control rats. Percentage of change of mixture treated rats was 51% and using SCEreducedthepercentageto5%**(Table 1).**

**Protein profile:** the present study showed thattherewasa highly significant decrease in total protein, albumin and globulin in the mixture treated rats ($p<0.001$), on the other hand, albumin/globulin ratiorecordeda highly significant increase ($p<0.001$) when compared to control group, while SCE caused no significant change in total protein, but there was a significant increase ($p<0.05$) in albumin, significant decrease ($p<0.05$) in globulin and highly significant increase ($p<0.001$) in albumin/globulin ratio in comparison to control rats. Percentages of change in mixture treated rats of total protein, albumin, globulin and albumin/globulin are(-59%, -50%, -73%, 104%) respectively, and after using SCE theses ratios were(4%, 19%, -22%, 52%) respectively**(Table 2).**

**Liver functions:**therewas a highly significant increase ($p<0.001$)in ALT and AST activities in mixture treated animals and SCE treated group recorded a lower significant increase ($p<0.05$) in liverenzymesactivities as compared tocontrolgroup. Percentages of change in mixture treated animals of ALT and AST were(156% and 125%) respectively, but when using SCE there was a reduction in these percentages to (17% and 8%) respectively**(Table 3).**

**Lipid profile:**theanimals that received a mixture of food additives (group 2) have a highly significant increase in all the parameters of lipid profile ($p<0.001$), except HDL-C level that showed ahighly significant decrease ($p<0.001$) in comparison with control group. On the other hand, SCE treated rats showed no significant change in all the parameters of lipid profile, except total cholesterol and LDL-C where there was a significant increase ($p<0.05$) as compared to control rats. Percentages of change in lipid profile (TC, TG, HDL-C, LDL-C, VLDL, LDL/HDL, TC/HDL) of mixture treated rats were: (85%, 151%, -90%, 931%, 153%, 995.2%, 117.7%) these percentages were decreased to (7%, 7%, -5%, 73%, 8%, 76%, 15%) after giving rats SCE**(Table 4)**.

**Kidney functions:**there was an obvious increase in the levels of creatinine and urea in rats of the second group which treated with the mixture of food additives ($p<0.001$) while using SCE caused no significant change in the previous levels as compared to control rats **(Table 5).**

**Hormones:**T3 and T4 levels revealed a highly significant increase ($p<0.001$) in the mixture treated group with regard to the control rats, while there was no significant change in these parameters when the rats received SCE in the third group. Meanwhile, there was a highly significant decline ($p<0.001$) in testosterone level in the group received food additives, while there was less significant decrease ($p<0.05$) in group 3 that has been taken SCE in comparison to the control animals. Percentages of change in T3, T4 and testosterone hormone of mixture treated rats were: (50%, 133%, -36%) and using SCE recorded a reduction in T3 and T4and an increase in testosterone level as follows:( 0.7%, 6% and -5%) **(Table 6).**

**Table (1): Percentage of body weight change and glucose level in control, Mixture (consists of sodium nitrite+ annatto+ monosodium glutamate) and mixture+ Stem cell enhancer treated animals.**

| Parameter | Control (mean ±SE) | Mixture (mean ±SE) | Mixture and Stem cell Enhancer(mean ±SE) |
|---|---|---|---|
| **% of body weight change** | **35.34 ± 0.3** | **32.8 ± 3.6** | **34.4 ± 1.7** |
| **Glucose(mg/dl)** | **66.6 ± 1.3** | **100.5 ± 1.4**** | **69.7 ± 0.9*** |
| **% of change** | | **51%** | **5%** |

Values represent mean ±SE (standard error). (P*<0.05, P**<0.001 as compared to control group).

**Table (2): Serum total protein (g/dl), albumin (g/dl), globulin, albumin/globulin ratio and albumin/creatinine ratio in control, Mixture (consists of sodium nitrite+ annatto+ monosodium glutamate) and mixture+ Stem cell enhancer treated animals.**

| Groups | Control (mean ±SE) | Mixture (mean ±SE) | Mixture +Stem cell Enhancer(mean ±SE) |
|---|---|---|---|
| **Total Protein(g/dl)** | 6.28 ± 0.4 | 2.6 ± 0.2** | 6.5 ± 0.4 |
| **% of change** | | -59% | 4% |
| **Albumin(g/dl)** | 3.86 ±0.29 | 1.94 ± 0.17** | 4.6 ± 0.2* |
| **% of change** | | -50% | 19% |
| **Globulin (g/dl)** | 2.43 ± 0.1 | 0.65 ± 0.1** | 1.9 ± 0.2* |
| **% of change** | | -73% | -22% |
| **Albumin/Globulin** | 1.58 ± 0.08 | 3.23 ± 0.7** | 2.4 ± 0.2** |
| **% of change** | | 104% | 52% |

Values represent mean ±SE (standard error). (P*<0.05, P**<0.001 as compared to control group).

**Table (3): ALT and AST activities in control, Mixture (consists of sodium nitrite+ annatto+ monosodium glutamate) and mixture+ Stem cell enhancer treated animals.**

| Groups | Control (mean ±SE) | Mixture (mean ±SE) | Mixture +Stem cell Enhancer (mean ±SE) |
|---|---|---|---|
| **ALT (U/l)** | **20 ± 0.88** | **51.1 ± 1.4**** | **23.4 ± 1.6*** |
| **% of change** | | **156%** | **17%** |
| **AST (U/l)** | **50 ± 1.06** | **112.4 ± 1.4**** | **54.2 ± 1.4*** |
| **% of change** | | **125%** | **8%** |

Values represent mean ±SE (standard error). (P*<0.05, P**<0.001 as compared to control group).

**Table (4): Changes in total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, VLDL-C, LDL/HDL ratio and TC/HDL ratio in control, Mixture, and mixture+ Stem cell enhancer treated animals.**

| Groups | Control (mean ±SE) | Mixture (mean ±SE) | Mixture +Stem cell Enhancer (mean ±SE) |
|---|---|---|---|
| **Total Cholesterol(mg/dl)** | **55.02 ±1.2** | **101.88 ± 1.8**** | **58.84 ± 1.1*** |
| **% of change** | | **85%** | **7%** |
| **Triglycerides (mg/dl)** | **49.6 ± 0.8** | **124.41 ± 1.5**** | **52.91 ± 1.4** |
| **% of change** | | **151%** | **7%** |
| **HDL-C (mg/dl)** | **36.976 ± 1.2** | **3.79 ± 0.9**** | **35.17 ± 1.2** |
| **% of change** | | **-90%** | **-5%** |
| **LDL-C (mg/dl)** | **7 ± 1.5** | **72.2 ± 1.9**** | **12.1 ± 2.8*** |
| **% of change** | | **931%** | **73%** |
| **VLDL (mg/dl)** | **9.84 ±0.37** | **24.88 ± 0.5**** | **10.58 ± 0.3** |
| **% of change** | | **153%** | **8%** |
| **LDL/HDL** | **0.19 ±0.02** | **19.1 ± 3.5**** | **0.3 ± 0.1** |
| **% of change** | | **995.2%** | **76%** |
| **TC/HDL** | **1.48 ± 0.02** | **26.9 ± 4.7**** | **1.7 ± 0.1** |
| **% of change** | | **171.7%** | **15%** |

Values represent mean ±SE (standard error). (P*<0.05, P**<0.001 as compared to control group).

**Table (5): Serum creatinine and urea levels in control, Mixture (consists of sodium nitrite+ annatto+ monosodium glutamate) and mixture+ Stem cell enhancer treated animals.**

| Groups | Control (mean ±SE) | Mixture (mean ±SE) | Mixture +Stem cell Enhancer (mean ±SE) |
|---|---|---|---|
| **Creatinine(mg/l)** | **0.51 ± 0.04** | **1.1 ± 0.1**** | **0.56 ± 0.04** |
| **Urea(mg/dl)** | **34.44 ± 0.6** | **58.3 ± 1.3**** | **34.5 ± 1.7** |

Values represent mean ±SE (standard error). (P*<0.05, P**<0.001 as compared to control group).

**Table (6): Serum Testosterone, T3 and T4 levels in control, Mixture (consists of sodium nitrite+ annatto+ monosodium glutamate) and mixture+ Stem cell enhancer treated animals.**

| Groups | Control (mean ±SE) | Mixture (mean ±SE) | Mixture +Stem cell Enhancer (mean ±SE) |
|---|---|---|---|
| **Testosterone(ng/dl)** | **60.6 ± 1** | **38.6 ± 0.6**** | **57.42 ± 1.4*** |
| **% of change** | | **-36%** | **-5%** |
| **T3(ng/dl)** | **115.41 ±1.1** | **172.63 ± 1.3**** | **116.25 ± 1.1** |
| **% of change** | | **50%** | **0.7%** |
| **T4(µg/dl)** | **5.578 ± 0.19** | **13.02 ± 1.9**** | **5.91 ± 0.2** |
| **% of change** | | **133%** | **6%** |

Values represent mean ±SE (standard error). (P*<0.05, P**<0.001 as compared to control group).

## DISCUSSION

Food additives are substances that are part of a food product when added (intentionally or unintentionally) during the processing or production of food. They include using salt to preserve meats, adding herbs or spices to foods, or pickling foods in vinegar solutions. However, concerns about food additives most often relate to artificial ingredients added to food [(12)].As it is illustrated in the results, there was a slightly decrease in the body weight in the treated animals with mixture of food additives (sodium nitrite, monosodium glutamate, and annatto) in contrast to control rats, this decrease may be due to the effect of sodium nitrite which considered by some authors to be a good reliable sensitive toxicity indicator [(13)].Also, there may be an interaction occur between sodium nitrite (which reduced the body weight) and MSG (which cause obesity) to balance the both effects of the two food additives to be close to the body weight value of control rats.

There is a highly significant increase in glucose level of the rats that have been taken food additives as compared to the control group,that might be attributed to the ingested glutamate which is rapidly removed from the blood to the liver where it enters the mitochondria, then it is converted to α – ketoglutarate and othertricarboxylic acid cycles components namely, mALTe and oxaloacetate[(14)].mALTe diffuses into the cytoplasm then it is converted to phosphoenolpyruvate, then to glucose or due to the inhibiting effect of MSG on growth hormone, thereby decreasing glycogenesis in liver [(14)]. Meanwhile, after treating with Stem Cell Enhancer reduction in glucose concentration occurs, this perhaps is resulting from the high fiber content of blue-green algae that interferes with the glucose absorption or probable action of producing polypeptides after digestion of blue-green algae [(15)].Sanaei *et al*.[(16)] and Anwer*et al*.[(17)]recommend the use of StemEnhance as a functional food in the management of diabetes, and this is in accordance with the results of this study. They reported that the antihyperglycemic effects of StemEnhance may be attributed to the increased insulin secretion from β-cells of the pancreatic islet or due to the enhancement of transport of blood glucose to the peripheral tissue.

We can notice that there is a highly significant decrease in total protein, albumin, and globulin while there was a highly significant increase in albumin/globulin ratio as compared to control rats, in this mixture groupthese reductions may be due to oxidative stress which affects liver (the main site for protein synthesis in the body) thus the synthetic function of liver was altered by MSG and / or NaNO2, which indicated liver damage, arising from the uptake of the chemical compound. This may be an indication of diminished synthetic function of the liver which may consequently lead to enhanced retention of fluid in the tissues spaces [(18)]. Also, NaNO2 and/or MSG reflect stimulation of thyroid and adrenal glands by NaNO2 and MSG which lead to a blocked protein synthesis, fast breakdown increased and decreased protein turnover [(19)].

Our study demonstrated that liver activities (AST and ALT) showed a highly significant increase in food additives treated rats in comparison with a control group that may be resulted from hepatotoxicity and liver damage, as the more severe the liver damages the higher the release of the liver enzymes [(20)]. Since these additives cause damage of liver cells and cellular degeneration or destruction in the liver as the hepatic cell membrane is damaged, varieties of enzymes normally located in the

cytosol are released into the bloodstream[21].When the animals treated with SCE, ASTandALT elevation reduced to a value close to the normal, this may be due to the antioxidant activity of some StemEnhance constituents that exhibited a hepatoprotective effect against liver damage caused by these food additives[22].

In the present work, treatment of rats with a mixture of food additives resulted in obvious changes in the lipid profile causing a highly significant increase in total cholesterol, triglycerides, LDL-C, VLDL-C, TC/HDL and LDL/HDL while HDL-C representing a highly significant decrease in contrast to control rats. Several studies have shown that sodium nitrite and MSG exposure induces alterations in serum lipid profiles [23].The elevation in total cholesterol may be due to the mobilization of free fatty acids from the adipose tissue to the bloodstream and increase the level of acetyl CoA, that lead to anincrease in the synthesis of cholesterol or due to peroxidation of cell membrane lipids [24].Similarly, the high cholesterol level in plasma may be due to increased uptake of exogenous cholesterol and subsequent deposition and decreased cholesterol catabolism as evidenced by a reduction in bile acid production and turnover of bile acids [25]. Lowering levels of high-density lipoprotein was a contrary effect because high HDL-C levels have been shown to bear an inverse correlation with risks for atherosclerosis [26]. Increase in LDL, VLDL levels increase the risk of cardiovascular diseases [27]. Oxidative stress, specifically the oxidation of low-density lipoprotein, has long been suspected of having a critical role in the development of atherosclerosis, in consequence of which antioxidants have been expected to have potential asantiatherogenic agents. Such agents would be able to inhibit the oxidative modification of LDL that leads to the accumulation of cholesterol in atherosclerotic lesions [28].

Results of the present study which have shown that co-administration of SCE with sodium nitrite,annatto, and MSG to male albino rats induced a significant reduction in serum cholesterol, triglycerides, LDL-c and VLDL-c concentrations and elevation in serum HDL-cholesterol. Sanaei*et al.*[16] stated that blue-green algae inhibit intestinal cholesterol absorption, decreases the hepatic lipids and leads to attenuation of plasma total cholesterol and triglycerides concentrations. Additionally, *Polygonum multiflorum* (PM) was found to possess an anti-atherosclerotic and hypolipidemicactivity[29].The decrease in the TC/ HDL cholesterol level in the stem cell-treated group may be related to cellular protection effect of *Polygonum multiform* (constituent in StemEnhance) which reduce lipid peroxidation by up-regulating of cellular antioxidants and decrease MDA concentration[29].

In the present study, the concentration of creatinine and urea in serum samples of food additives treated group showed a highly significant increase in comparison with control rats. The significant increase in creatinine content of the serum following the administration of food additives ($NaNO_2$+ annatto+ MSG) may be attributed to MSG which have either interfered with creatinine metabolism leading to increased synthesis or the tissues might have compromised all or part of its functional capacity of tubular excretion [30].Also, Sodium nitrite may react with amines of the foods in the stomach and produce nitrosamines and free radicals which may increase lipid peroxidation leading to oxidative stress and can be harmful to different organs including kidney [31].However, treatment with StemEnhance has significantly improved creatinine and urea levels. This may be due to its antioxidant properties that improved renal functions via attenuating an oxidative stress-mediated decline in GFR and renal hemodynamics[32].

As it is explained in the previous results, there is a highly significant decrease in the mixture ($NaNO_2$+annatto+MSG) treated animals in testosterone level. Food additives work to reduce androgens which indirectly affect the axis connecting the pituitary gland. This has negative effects on social behavior and the relative weight of members of the sex - producing a hormone[33].MSG cause reduction on testosterone hormone as it obstruction the hypothalamic-pituitary-testes regulatory axis that controls testosterone production by testicular Leydig cells[34]**.**Deficiencies of the testosterone hormone might cause social behavioral changes because of its importance in the regulation of aggression in mammals [35].Meanwhile, SCE recorded a significant improvement in the value of testosterone hormone and elevated its level as compared to the mixture treated animals.

The current investigation demonstrates that the daily intake of NaNO2, annatto, and monosodium glutamate exhibited an increase in thyroid hormones T3 and T4. These changes in thyroid hormones might result from alteration in the pituitary – thyroid axis and this might play a role in children hyperactivity probably through affecting higher centers in the brain [(36)] or may be due to the stimulation of the thyroid and the adrenal glands by NaNO2 which can lead to a blockade of protein synthesis, fast breakdown, increased rate of free amino acids, and decreased protein turnover[(19)].On the other hand, in SCE treated group we can notice that there is an excellent reduction occurs in the levels of T3 and T4 in contrast to the mixture of food additives treated rats.

Finally, it was concluded that food additives have extreme destructive effects on most physiological parameters like liver and kidney enzymes, thyroid and testosterone hormones, lipid and protein profiles, so we should minimize their use in most foods especially for kids. Also, we recommended the use of SCE as it achieved excellent therapeutic effects against the abnormal analyses that occurred to animals due to food additives administration, and returning these analyses to around the normal control values.

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