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EFFECT OF 3 MONTHS-FEEDING OF A POWDER DIET FORTIFIED WITH CHILLI (GUNTUR, BIRD'S EYE, AND NAGA KING) ON SUPEROXIDE DISMUTASE LEVELS IN SD RAT

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ABSTRACT

Purpose: *Chilli has been considered a culprit and saviour in various non-communicable disorders in the scientific world. We hypothesise that varying proportions of active principles in different chilli affect its therapeutic potential significantly, and it could be a game-changer in the area of drug discovery.*

Design/methodology/approach*: In this regard, nutritional analysis was performed for three chillies, followed by the animal study on SD rats fed a standard rodent powder diet (20% protein) fortified with 0.005% of capsaicin (CAP) equivalent chilli powder for three months to measure superoxide dismutase (SOD) in five visceral organs/tissues.*

Finding: *The NKC and BEC groups have shown opposite results to the GC and capsaicin equivalent groups (CEG) regarding animal body weight and SOD levels in various tissues. However, there is no change in feed intake.*

Research limitations/implications: *In parallel, serum SOD should have been tested. Other methods for SOD analysis would fetch confirmatory results. Using a mild or moderate stress rodent model would prove its therapeutic efficacy. CAP alone might affect anti-obesity and SOD levels; however, the DHC content of chilli plays an essential role in providing synergistic or antagonistic effects on anti-obesity or activating the antioxidant system depending on the threshold level. It means it could have biphasic properties similar to capsaicin.*

Originality/value: *The present paper generates evidence that capsaicinoid relative proportion in chilli plays an essential role in its therapeutic or negative impact on health.*

KEYWORDS: *Naga King Chilli, Guntur Chilli, Bird's Eye Chilli, Capsaicin, Wistar rat Paper type: Original article*

1. INTRODUCTION

The active component of chilli is Capsaicin (CAP) which is a type of chemical (alkamide) causing a burning sensation on exposure; however, it is also used as a therapeutic agent in case of neuralgia [1, 2], anti-inflammatory [3, 4], gastroprotective, muscle sprains/strains [5, 6], anti-obesity [7-12], antipruritic [13, 14], anti-apoptotic [15, 16], anti-oxidant [17], anti-cancer [18, 19], neuroprotective functions, cardio-vascular-related diseases, metabolic disorders, and gastric mucosal protection. On the contrary, few studies suggest increasing apoptosis and oxidative stress [15, 20]. Dietary CAP may be fighting obesity by activating TRPV1 channels and affecting the browning of white adipose tissue [21]. It activates metabolic genes and UCP1 expression on brown adipocytes, causing glycerol recycling and triglyceride synthesis [8]. The superoxide dismutase (SOD) enzyme is present in mammals in three forms where the cytoplasm of cells has SOD1, mitochondria will have SOD2, and SOD3 will be present in the extracellular fluid of cells. The primary function of the SOD enzyme is to catalyse the superoxide radical into H2O2 and O2. Many fruits, algae, and cantaloupes are used to extract SOD to provide exogenous SOD for boosting immunity or fighting stress [22] through SOD supplements. Similarly, studies suggest that chilli also has endogenous SOD [23]. In one of the earlier studies (unpublished data) from our group on acute toxicity, the SOD levels were quantified in various tissues and organs of rats undergoing ethanol insult followed by oral chilli dosing. However, chronic dosing was tested in this study by comparing control groups like regular standard diet, capsaicin control, and low dose chronic ethanol oral dosing group to find the impact on superoxide dismutase activity. Regarding chilli consumption, similar ambiguous information is available in the literature. However, it is believed that it could be true to a particular population, specific types of chillies, or environmental changes. Therefore, in this study, the levels of

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SOD enzyme, which is a part of antioxidant defence present in all living cells, were studied in five tissues of SD male rats.

2. OBJECTIVES

To quantify and compare the change in tissues SOD levels upon 90 days of chilli-feeding trial in a rodent model

3. METHODOLOGY

3.1. Sample collection and processing: The red chillies (fresh) were collected from Kohima in Nagaland (Naga King chilli), Shillong in Meghalaya (Bird's-Eye chilli), and Guntur in Andhra Pradesh (Guntur chillies) for this study for two months. Our earlier publication [24] describes CAP's extraction process of chillies, along with the capsaicinoids, amino acid, and fatty acid profiles of Naga King Chilli. The CAP content for all three chillies used during this study was analysed. It was found that Naga King chilli has 7.1 times higher CAP than Guntur chilli, 3.5 times higher than Bird's Eye chilli, and 31.5 times higher than average chilli [25]. All groups received the same amount of CAP, which is 0.005%, irrespective of groups except the standard normal control (SNC) group (Graph1).

3.2. Animal Study: The animal study was performed after local institutional animal ethics committee (NIN-IAEC) approval (No: P-5F/IAEC/2014/1/RA/SD rats). Animals were housed in the ICMR-NIN animal facility, which follows CPCSEA guidelines for housing lab animals (e.g., temperature maintained between 22+/-2°C, humidity at 40-60%, noise below 80dB, light intensity in the room at around 300 lux). These animals were provided adequate water and feed during the experimental phase. The study design (Image-1) for the chronic study includes the 90-day housing of the Sprague Dawley rat strain to evaluate the impact of chilli fortified standard powder diet (containing 20% protein) on SOD levels in various tissues and visceral organs. The ethanol-induced ulcer model was used as a negative control, whereas the capsaicin-fed group was the positive control for the study. The other three test groups had chilli (Guntur, Bird's eye, and Naga King) fortified diet with varying amounts of chilli powder (Graph-1) depending on the CAP percentage in chillies (Graph-2) to reach the final CAP concentration of 0.005% in the diet (Graph-1). The feed was prepared using trained personnel in the ICMR-National Institute of Nutrition diet section (in-house). The Ulcer control group received 1mL of 80% ethanol through oral gavage just 30 minutes before offering a standard powder diet for three months. Our earlier pilot study revealed that 80% ethanol produces a better ulcer model in SD male rats than 40% or 60% of Ethanol groups (unpublished data). The body weight of animals was measured every 3rd day, whereas feed intake was measured every day.

3.3. The analysis of Superoxide Dismutase (SOD) activity in the animal model: The SOD activity in the animal model was determined by using a rapid and straightforward method of pyrogallol autooxidation using standard protocol. The pyrogallol solution (0.2 mM) for SOD analysis was prepared by dissolving 0.25 grams of pyrogallol in a solution of 0.6 mL of concentrated hydrochloric acid (HCl), diluted in one litre of distilled water (DW). Similarly, the Tris- EDTA buffer was prepared by dissolving 2.85 grams of the tris salts and 1.11 grams of EDTA-Na2 in one litre of distilled water while pH of solution was adjusted to alkaline (8.2). The 25uL homogenate from each sample was used for further analysis. After three months of chilli/CAP fortified diet feeding, all animals were euthanised using CO2 asphyxiation. The visceral organs were collected as fresh frozen samples for further analysis. The 0.1 gram of visceral organs/tissues (Liver, Stomach, Spleen, Pancreas and Colon) were individually triturated using a cold mortar and pestle. Homogenates of tissues were further analysed for SOD estimation using the pyrogallol method (colourimetry). A spectrophotometer was adjusted to read zero using the Tris-EDTA buffer. The absorption wavelength was read at 420 nm against Tris-EDTA buffer at zero time and after one minute of the addition of pyrogallol. The calculation of SOD was performed using the following formula.

$$\% \text{ Inhibition of pyrogallol autoxidation} = \frac{\Delta A_{\text{test}}}{\Delta A_{\text{control}}} \times 100\%$$

$$\text{(Cu-Zn) SOD Activity (U/ml)} = \frac{\% \text{ inhibition of pyrogallol autoxidation}}{50\%}$$

4. RESULTS

There is no significant change in feed intake in all groups (Graph 3). The average food intake of all groups ranged between 14.64 - 15.64 grams/day. All animals were found active, alert, and healthy during the study. However, animals from the NKC group (208 grams) and the BEC group (211 grams) showed a decrease in body weight gain compared to the SNC group (256 grams). This decrease in body weight gain (Graph 4) could be due to the anti-obesity effect of CAP content. However, the NKC group and BEG also showed decreased body weight gain than the capsaicin-equivalent group (CEG) group, which could be due to synergistic effects

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from DHC. However, the GC group showed slightly decreased body weight gain but was higher than the CEG group because DHC might have a biphasic effect similar to CAP. As per our earlier study, the Guntur chilli has 32.22 times higher DHC content than Naga King chilli and 3.68 times higher than Bird's eye chilli [24]. Similarly, a study of CAP concentration on SD male rats related to thermal preference test revealed that the CAP has a biphasic nature which changes its property as per concentrations [26].

4.1. The SOD levels in the Liver (Graph 5): It has been observed that liver tissues show depletion of SOD levels in the case of carcinogenesis with viral liver diseases [27], increased in liver tissue while infested with helminths [28]. The animals used in this study were procured from a CPCSEA registered animal facility which performs biannual health monitoring. During necropsy, we didn't find any lesions or signs of helminths. In this study, we found that liver tissue of the test group had increased levels of tissue SOD, which could be an advantage to animals. The study suggests that more SOD in the liver is beneficial for organ transplantation [29, 30]. It is also stated that SOD levels are dependent on the melanin content of the animal [31]; however, in this study, we have used SD rats (albino) for all groups, and a comparison was made among these groups. The general SOD quantification can be done using enzyme immunoassay of SOD in urine and serum samples [32]; however, in our study, we have used tissue homogenate using the pyrogallol method to see tissue-specific changes in the level of SOD. It is also suggested that it could have an anti-ageing effect [33] and tissue-specific SOD levels [34] in specific knockout animals; however, we have used outbred rats in our study. Old rats will also have greater SOD levels than young ones [35]; however, adult rats aged eight weeks old were used irrespective of the group in this study. SOD levels are also affected by the presence of tumour cells [36]; however, in this study, during necropsy, no such lesions or mass was found on liver tissue of animals from any group. Certain chemicals can also affect Mn-SOD in adult rats [37], like cocaine; however, in this study, no such drug was added to feed or used through the oral/parenteral route; instead, it was fed as a fortified diet. It has been observed in other studies that SOD levels increase in the serum of rats with liver and kidney intoxication [38]; however, during an acute study (published in NIN annual report 2014-15), no such lesion was found on the liver or kidney. According to the literature, the SOD levels in the liver could increase in partial hepatectomy or liver regeneration [39]; however, in this study, no such surgical procedure was performed. In this study, we found that SOD levels were high in BEC and NKC groups compared to the SNC group, which has a role in anti-inflammatory activity in liver fibrosis [40]. The SOD level had increased to normal in all groups, including CEG and Ethanol groups, except Guntur chilli. SOD levels increase in the liver when there is inflammatory or regeneration of the liver. NKC and BEC showed the highest increase in the level of SOD in the liver, which is a 1.83 and a 2.5-fold increase compared to control. This could be due to DHC levels which are high in Guntur chilli. Similarly, SOD levels in the liver in Guntur chilli decreased to 0.6 times that of the CEG group and to 0.33 times decrease in the SNC group, suggesting the antioxidant system is compromised. However, NKC and BEC are 0.5 times more than the CEG group, which suggests that they assist in activating antioxidant systems active in the body.

4.2. The SOD levels in the Stomach (Graph 6): SOD levels in stomach tissue of BEC increased 3.5-fold compared to the SNC group, whereas the ethanol group and NKC group have shown a two-fold increase in SOD levels of stomach tissue. However, the GC group reduced SOD levels of stomach tissue to 50% of the SNC group. Similarly, there is an increase in SOD levels found in the BEC (2.8-fold), NKC (1.65-fold), and Ethanol (1.60-fold) in SOD levels of stomach tissue, whereas the GC group (0.5-fold) has shown a decrease in SOD levels compared to the CEG group. CAP's slow, sustained release has been correlated with anti-cancer activity [18], a preventive role in gastric cancer [19]. Interestingly, a toxicokinetic study showed that CAP dosed per oral route doesn't reach circulation; however, it prevents gastric damage and works like NSAID [41], which may become a suitable candidate for therapeutic use. It was also observed in an exploratory study on human subjects that ingestion of red chilli strongly affects gastric accommodation, which could be helpful in gastroesophageal reflux disease patients [42]. CAP has anti-metastatic activity in gastric carcinoma [43] through modulating TGF-β signalling, which might be through an increase in SOD activity; however, in the current study, it was found to be a very minimal increase (1.25-fold) compared to the SNC group.

4.3. The SOD levels in the Spleen (Graph 7): In the current study, three groups showed an increase in SOD levels of spleen tissue which are the NKC group (2.75), followed by Ethanol group (2.58-fold), and the BEC group (2.25-fold), compared to the SNC group. In contrast, the other two groups (GC and CEG) had very minimal variations (0.92 and 1.17, respectively). Similarly, elevation in SOD of spleen compared to CEG group was seen in NKC (2.36-fold), followed by Ethanol group (2.21-fold) and BEC group (1.93-fold). A toxicity study causing apoptosis of splenic cells due to weeds [44] and high-fluorine diets [45] showed a decrease in SOD levels. However, when challenged with certain bacteria like E. coli, it enhances SOD levels [46].

4.4. The SOD levels in the Pancreas (Graph 8): Pancreatic cancer is a hot topic in the current research themes because the percentage of a pancreatic cancer population increases with little hope of reverting conditions. As a preventive measure, scientists found that endogenous and exogenous SOD can be a probable solution [47]. In this study, the BEC group had increased SOD levels (2.65-fold) in the pancreas compared to the SNC group, whereas other groups hardly changed. On the contrary, CEG reduced the SOD level of the pancreas to half (0.44-fold) of the SNC group.

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Superoxide dismutase promotes the epithelial-mesenchymal transition (EMT) in pancreatic tissue cancer [48] and predicts the early stage of acute pancreatitis [49]. It also plays a role in the growth of pancreatic adenocarcinoma [50], and its expression is negatively associated with pancreatic ductal adenocarcinoma [51]. However, in vitro study showed that overexpression of SOD can inhibit pancreatic carcinoma cells [52].

4.5. The SOD levels in the Colon (Graph 9): In this study, the SOD levels of the colon increased in all groups compared to the SNC group. The three groups (Ethanol, BEC, NKC) scored very high (5.74, 5.57, 4.83-fold increase, respectively), whereas CEG and GC groups also showed an increase (2.30, 1.91-fold, respectively) in SOD levels of the colon. Similarly, in comparison with CEG, the Ethanol, BEC, and NKC groups showed an increase (2.49, 2.42, 2.09-fold, respectively) in SOD levels of the colon. SOD also plays a role in the local prevention of oxidative stress in the Intestinal Epithelium [53] or tumour infiltrating lymphocytes, affecting cancer's relapse rate [54]. Lactic acid-producing bacteria also help us by producing SOD and improving colitis [55]. The diet also plays a role in increasing or decreasing SOD levels [56-58]. SOD levels also help to predict the survival rate [59] or staging and grading of colo-rectal cancer [60] in patients. Ironically, colon cancer in Nagaland [61] is very high (ranks 1st in India), which is supposed to be the largest producer and place of origin of Naga King Chilli and received Geographical Indices. This could be the result of the biphasic nature of capsaicin and dihydrocapsaicin. Although, colo-rectal cancer is first (males) and third (females) in the Saudi Arabia [62] whereas, world cancer burden is also similar [63]. In Thailand, people use chilli a lot, and coincidentally, the colorectal percentage is low compared to other countries [64]. However, the top five cancer in Thailand includes colorectal cancer, which is correlated with a high percentage of red meat consumption [65].

4.12. Organ-wise comparison of SOD (Graph 10-14): Upon comparison of SOD levels with five tissues, it was found that colon tissue gets affected significantly (4-to-6-fold increase). Similarly, a lower dose of ethanol also shows encouraging results in affecting the SOD level. Among chillies, NKC and BEC top in increasing SOD levels compared top standard normal control group. However, Guntur chilli has shown the opposite effect, whereas capsaicin alone has minimal effect on the SOD change.

5.0. SUGGESTIONS

An animal study using active ingredients of chilli like CAP and DHC will provide confirmatory evidence to the results of this study.

6.0. CONCLUSIONS

The change in SOD levels of the organs/tissues could result from the DHC percentage available in respective chillies. The DHC has a powerful but synergistic role in activating antioxidative systems in rodents; however, due to its biphasic nature, results change after reaching a threshold value. Further study on DHC is warranted. Upon analysis of five different tissues, it was evident that the colon has the highest fold increase of SOD levels compared to the standard normal control (SNC) group. However, among different groups, Naga King chilli, Bird's eye chilli, and the ethanol (80% @ 1mL/animal) have shown the highest fold increase compared to other groups. The conclusion of the study is capsaicin alone can't be credited for antioxidant property or stress induction but the relative ratio of DHC in chilli plays important role.

7.0. FIGURES, TABLES AND REFERENCES

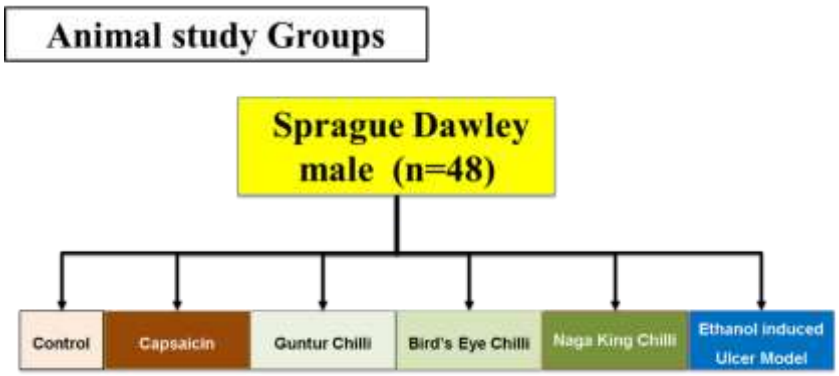

Image 1: Animal Study Design - Chronic Study

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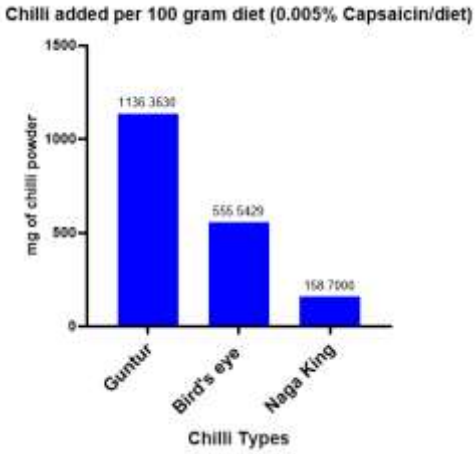
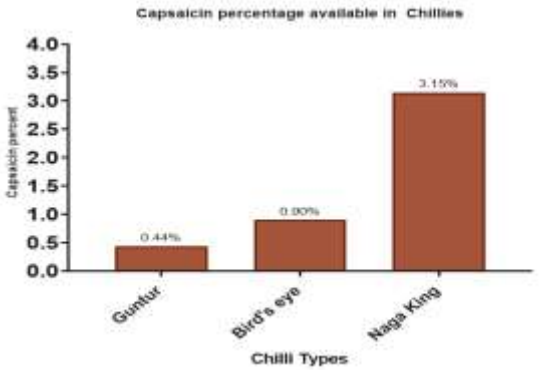
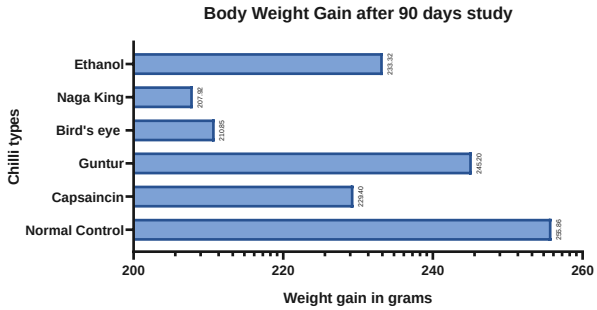


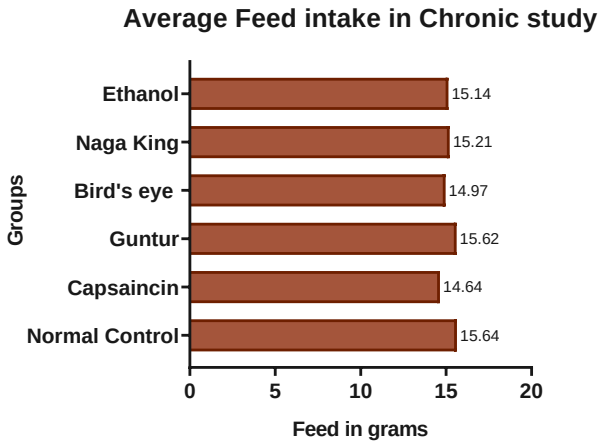
Graph 1:Chilli added in mg per 100 grams of diet to reach the 0.005% CAP concentration



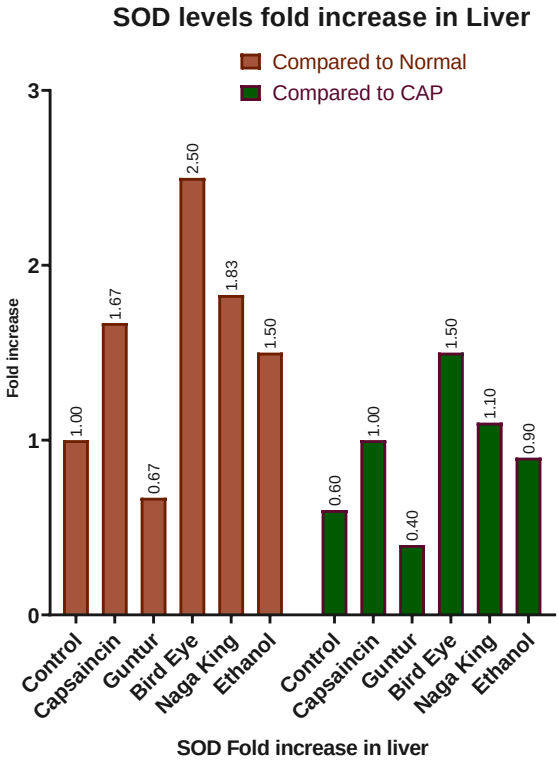
Graph 2: Capsaicin percentage available in chillies



Graph 3:Average Feed intake in a chronic study



Graph 4: Body weight gain after 90 days of feeding trial



Graph 5: Change in SOD levels of Liver tissue after 90 days of feeding trial (fold increase)

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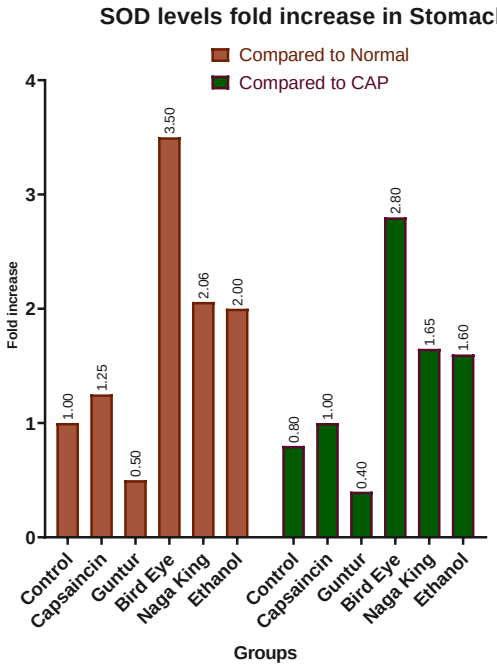
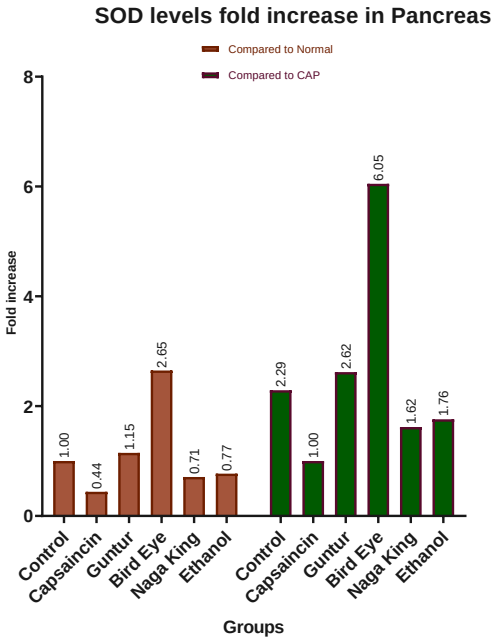
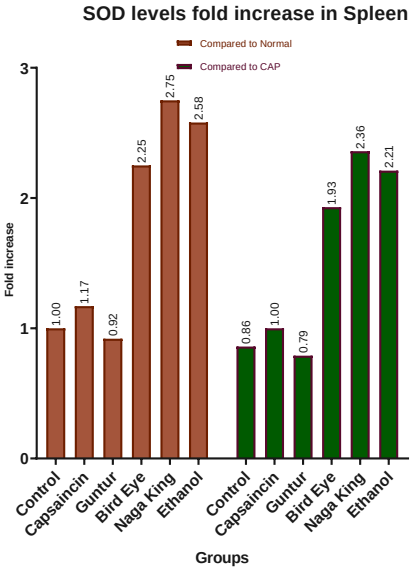


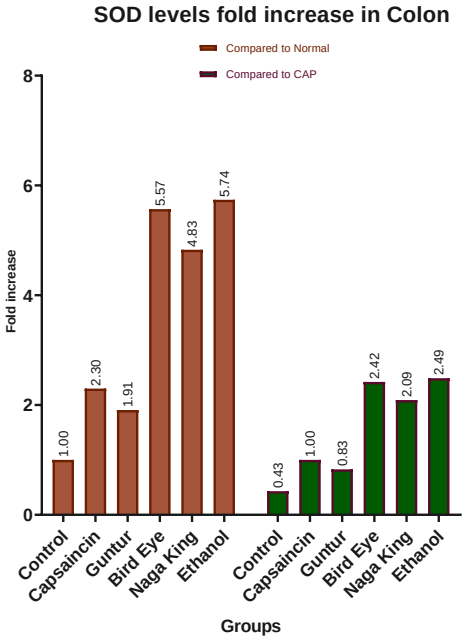
Graph 6: Change in SOD levels of Stomach tissue after 90 days of feeding trial (fold increase)



Graph 8: Change in SOD levels of Pancreas tissue after 90 days of feeding trial (fold increase)



Graph 7: Change in SOD levels of Spleen tissue after 90 days of feeding trial (fold increase)



Graph 9: Change in SOD levels of Colon tissue after 90 days of feeding trial (fold increase)

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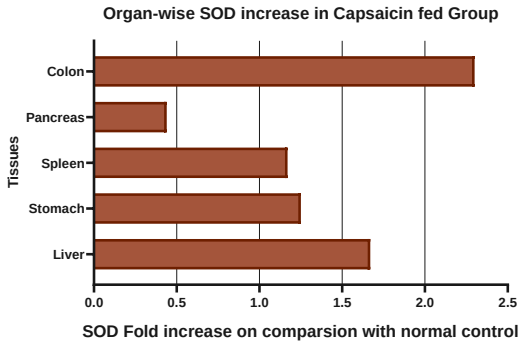
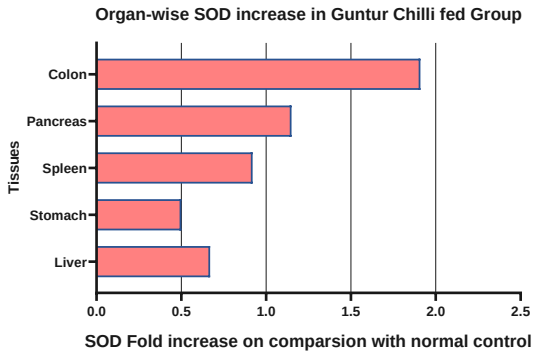
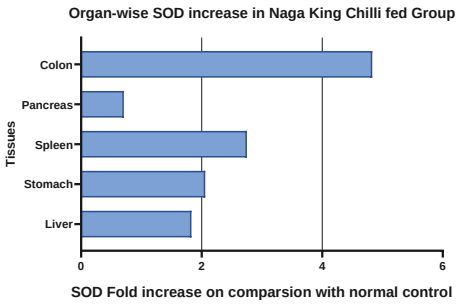


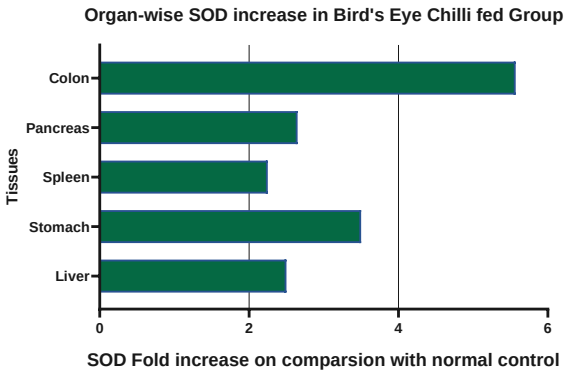
Graph 10: Organ-wise change in SOD levels in various tissues upon feeding of Capsaicin



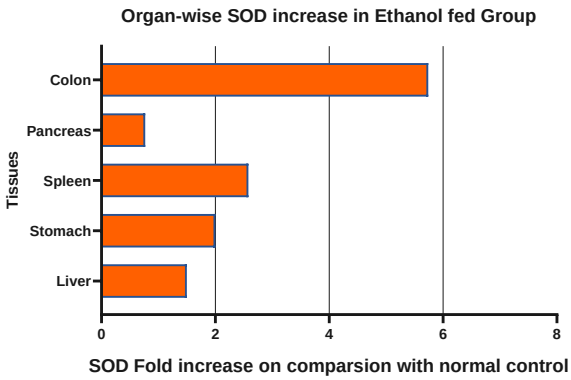
Graph 11: Organ-wise change in SOD levels in various tissues upon feeding of Guntur Chilli



Graph 12: Organ-wise change in SOD levels in various tissues upon feeding of NKC



Graph 13: Organ-wise change in SOD levels in various tissues upon feeding of BEC



Graph 14: Organ-wise change in SOD levels in various tissues upon feeding of Ethanol (80%)

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