SUMMARY

In the present study, the short term sub-chronic toxicity of two drugs: paracetamol and indomethacin given alone or in combination with α-tocopherol, ß-carotene, melatonin, nigella seeds and carrot, were investigated. The studies were carried out on 200 adult male albino rats divided into 20 equal groups each comprising 10 rats. These groups received paracetamol (900 mg/kg), indomethacin (5 mg/kg) orally daily for 2 weeks given alone, or along with α-tocopherol (9 mg/kg), ß-carotene (12,800 IU/kg), melatonin (0.3 mg/kg), nigella seeds or carrot ad libitum. At the end of the experiment, the following biochemical parameters were carried out: (1) total proteins, (2) albumin, (3) globulin, (4) A/G ratio, (5) SGPT, (6) SGOT, (7) Alkaline phosphatase (ALP), (8) Serum glucose, (9) Bilirubin, (10) Serum thiols, (11) Creatinine and (12) Uric acid. Moreover, hepatic reduced glutathione and lipid peroxides were measured.

In addition, some histochemical parameters were carried out in liver slices such as: (1) Alkaline phosphatase, (2) Acid phosphatase, (3) Succinic dehydrogenase, (4) Carbohydrates, (5) Total proteins, (6) Neutral lipids.

A. General Toxicological Findings:

The obtained results indicated that the administration of α-tocopherol, melatonin, nigella seeds or carrot markedly

reduced the mortalities induced by paracetamol. The administration of α-tocopherol protected completely against indomethacin induced mortalities. ß-carotene reduced the toxicity of indomethacin to a marked extent. On the other hand, unexpectedly the number of mortalities were markedly increased in response to the combination of indomethacin with nigella seeds or carrot.

The reduction of body gain in response to paracetamol was potentiated by the concomitant administration of melatonin. The concurrent administration of either α-tocopherol or ß-carotene slightly antagonized the side effect of paracetamol, while carrot completely abolished this effect. Nigella seeds antagonized the effect of paracetamol and further more elevated the growth rate over control values. Indomethacin reduced the weekly body gain, this effect was potentiated by the concomitant administration of both nigella seeds and carrot. The concurrent administration of α-tocopherol, ß-carotene or melatonin did not antagonize this effect.

B. Serum Biochemical Findings:

The administration of paracetamol along with nigella seeds resulted in a slight increase in serum total proteins, albumin and a more marked increase in A/G ratio. On the other hand, its combination with α-tocopherol, ß-carotene and melatonin did not induce any significant change in the levels of serum total proteins, albumin, and A/G ratio.

While its combination with carrot induced slight elevation in albumin, significant decrease in globulin and marked increase in A/G ratio. This increase in serum total proteins was related to dehydration of decreased water intake or possible nutritional effects. The administration of indomethacin along with both α-tocopherol and carrot induced a slight decrease in serum total proteins. Its combination with both nigella seeds and carrot induced decrease in serum globulins.

The administration of paracetamol resulted in significant increase in serum transaminases GPT and GOT. Its combination with α-tocopherol was able to abolish this effect. The administration of paracetamol along with both ß-carotene or melatonin caused an elevation in SGPT and SGOT. The administration of paracetamol along with nigella seeds or carrot elevated serum GPT.

This elevation was related to the destruction of some liver parenchymal cells, or to an enhancement of the enzyme activity itself to counter balance the damaging effect of free radicals resulted from paracetamol.

The administration of paracetamol along with α-tocopherol induced marked decrease in alkaline phosphatase, while its combination with nigella seeds caused an elevation in alkaline phosphatase.

The administration of indomethacin in combination with melatonin or nigella seeds elevated SGPT. On the contrary, the administration of indomethacin along with carrot induced marked decrease in SGPT.

The administration of paracetamol alone or along with α-tocopherol, ß-carotene, melatonin or carrot slightly decreased serum bilirubin. Paracetamol induced a slight decrease in serum glucose. Its combination with α-tocopherol, ß-carotene, nigella seeds or carrot were able to antagonize this effect. On the contrary, its combination with melatonin caused slight increase in serum glucose. The effect of paracetamol on serum glucose was related to its metabolic effects.

Paracetamol given alone or along with either ß-carotene or melatonin caused marked elevation in serum triglycerides. This elevation was related to partial impairment of certain aspects of hepatic function. Its combination with α-tocopherol, nigella seeds or carrot abolished this effect.

Indomethacin given along with either nigella seeds or carrot induced a decrease in serum bilirubin, however, the changes did not reflect any pathological effects.

Paracetamol given along with carrot caused slight decrease in serum uric acid, but it was still within the normal ranges.

The administration of indomethacin caused a slight increase in serum creatinine, but was still within the normal ranges.

Paracetamol did not affect serum thiols, when it was given along with α-tocopherol, ß-carotene, it caused a diminution in serum thiols, but its combination with melatonin induced much greater reduction. On the other hand, paracetamol combined with carrot induced marked elevation in serum thiols, while a slight increase was observed when it given along with nigella seeds. Indomethacin given alone or in combination with ß-carotene caused marked elevation in serum thiols. On the other hand, indomethacin given along with either nigella seeds or carrot caused a decrease in serum thiols.

C. Liver Homogenate Biochemical Findings:

The administration of paracetamol alone or in combination with α-tocopherol, ß-carotene or carrot decreased hepatic reduced glutathione (GSH). Both melatonin and nigella seeds were able to completely antagonize this decrease. Indomethacin given along with both nigella seeds and carrot induced marked decrease in reduced glutathione. This decrease may be due to the unsaturated fatty acid contents of nigella seeds acting as a source of free radical. While in case of indomethacin /

carrot combination it may origin from a probable metabolic interaction between nutrients or the non ß-carotene components of carrot and the metabolic biotransformation byproducts of indomethacin.

Paracetamol given alone induced marked increase in lipid peroxides. Its combination with α-tocopherol, ß-carotene, melatonin or carrot were effective to a great extent in antagonizing this elevating effect. While nigella seeds was not effective in this concern. Indomethacin given alone induced marked elevation in lipid peroxides. This effect was completely abolished by both α-tocopherol and melatonin, but was partially antagonized by ß-carotene. Neither nigella seeds nor carrot were able to antagonize the elevating effect of indomethacin on lipid peroxides. this finding was related to the high unsaturated fatty acids content of nigella seeds.

D. Liver Histochemical Findings:

Paracetamol given alone decreased the glycogen content of the liver. Nigella seeds was able to antagonize this effect. While, this diminution was not modified by the concurrent administration of any of α-tocopherol, ß-carotene, melatonin or carrot. Indomethacin given alone caused a marked loss in glycogen contents. This loss was antagonized by α-tocopherol, ß-carotene, melatonin and nigella seeds. This depletion of glycogen indicates that both paracetamol and indomethacin caused liver injury.

Paracetamol given alone or combined with α-tocopherol, ß-carotene or melatonin showed mild loss in total proteins. Its combination with nigella seeds was able to make an enhancement in protein picture to a great extent, while its combination with carrot failed in this concern.

The administration of indomethacin caused marked loss of protein contents in the hepatocytes. Its combination with α-tocopherol, ß-carotene, or melatonin was able to correct this loss completely. While, its combination with nigella seeds was able to enhance this picture to a great extent. On the other hand, its combination with carrot was not influential. The decrease in hepatic proteins may indicate the excessive catabolism of proteins for energy production or decreased protein synthesis, which is an early indicator of hepatic damage.

The administration of paracetamol revealed the appearance of some fat droplets in the hepatocytes cytoplasm and blood sinusoids. The concurrent administration of α-tocopherol and ß-carotene was able to abolish this effect. On the other hand, melatonin, nigella seeds and carrot failed to correct this effect.

Indomethacin given alone induced marked fat droplets deposition within the cytoplasm of the hepatocytes. Alpha-tocopherol, ß-carotene, melatonin, nigella seeds and carrot notably improved this picture. The appearance of fat

droplets in the hepatocytes indicates the presence of hepatic malfunction due to a defective assimilation of lipids.

The administration of both paracetamol and indomethacin induced generalized decrease in alkaline phosphatase activity and a notable induction of the enzyme inside the hepatocytes. The combination of either of them with each of the tested antioxidants did not change this picture, but the induction of the enzyme inside the hepatocytes was markedly diminished.

Both paracetamol and indomethacin given alone induced high acid phosphatase activity in hepatocytes. Their combination with each of the tested antioxidants were able to enhance this elevation of enzymatic activity to a notable extent. The increase in acid phosphatase activity may indicate a disturbance in synthesis or degradation of proteins by the liver.

Both paracetamol and indomethacin given alone induced diminution in hepatocytic succinic dehydrogenase activity. Their combination with the antioxidant agents, notably masked this response.