

**MODULATORY EFFECT OF CURCUMIN AGAINST
GENOTOXICITY AND OXIDATIVE STRESS INDUCED BY
CERTAIN ANTICANCER DRUGS**

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By

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APPROVAL SHEET

:Title of Ph.D. Thesis

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Summary and Conclusion

The use of chemotherapeutic drugs in the treatment of cancer has opened new possibilities in the improvement of the quality of life of cancer patients and even in the cure of the disease. Despite their success against many forms of human cancers, the majority of these drugs is extremely cytotoxic and has been shown to induce undesirable physiological side effects. Most of these drugs are not target specific and have genotoxic effects on normal cells, particularly the proliferative ones. The result is the occurrence of secondary malignancies in cancer patients who survive for a longer period after chemotherapy.

Cisplatin and methotrexate are two widely used anticancer drugs; the genotoxic and carcinogenic potential of these agents were reported in many studies.

Recently, many authors focused their attention on the study of anticarcinogenic and antimutagenic effects of polyphenols to ameliorate the toxic side effects of anticancer agents. Among these polyphenols, curcumin, a yellow pigment obtained from rhizomes of *Curcuma longa*, a major component of turmeric is a commonly used spice, which has been shown to possess many medicinal properties including immunomodulatory, antioxidant, antimutagenic and anticarcinogenic effects.

The aim of the present study is to evaluate the possible protective effect of CMN against the genotoxic effects and oxidative stress induced by two widely used anticancer drugs (CIS and MTX) *in vivo*.

Male CD-1 mice were used as the experimental animals. The two used anticancer drugs CIS and MTX were injected as a single i.p. injection at dose levels of 6.5 and 10 mg/kg body weight, respectively and animals were sacrificed 24 hours after treatment. Another groups of animals received CMN orally at three dose levels, namely; 60, 90 and 120 mg/kg for three consecutive days before anticancer drugs administration. Control groups either received distilled water (negative control) or CMN alone.

In the present study, genotoxicity was evaluated via two different assays. The first assay was micronucleus assay to measure clastogenic/aneugenic effects in bone marrow cells. The second was comet assay (in bone marrow and kidney tissues) which measures DNA strand breaks. Measurement of PCE ratio was used as indicator of cytotoxicity in bone marrow cells. In addition, oxidative stress markers were used to assess oxidative damage induced by the two tested anticancer drugs. These include measurement of malondialdehyde level (MDA) and reduced glutathione (GSH) level in kidney homogenates.

Our results showed that the frequencies of micronuclei and DNA damage in the group of animals treated with the highest tested dose of CMN were not significantly different from those of the negative control group. The non-cytotoxic effect of CMN was also indicated by the non significant changes in the percentage of polychromatic erythrocytes (%PCEs) compared to the negative control group.

Treatment with the two anticancer drugs (CIS and MTX) used in the present study resulted in DNA damage in bone marrow cells and kidney tissues of mice as reflected by the significant increase in the tested parameters of comet assay (Tail length, % of DNA in tail and tail moment) as well as in the number of micronucleated polychromatic erythrocytes (MNPCEs) compared to the negative control group.

Moreover, induction of oxidative stress and reactive oxygen species generation by CIS and MTX were confirmed in this study by observed significant elevation in MDA level, an indicator of lipid peroxidation, and significant decreases in GSH level in groups treated with the two anticancer drugs alone.

Administration of CMN (60, 90 and 120 mg/kg b.w) prior to CIS and MTX administration was found to be effective in reducing the DNA damage induced by the two anticancer drugs as indicated by the significant decrease in the tail length, % of DNA in tail and tail moment as well as in the number of micronucleated polychromatic erythrocytes

(MNPCEs) compared to CIS and MTX treated groups, but still significantly higher than the negative control value. Moreover, MDA level was significantly decreased while GSH level was significantly increased in CMN pretreated groups compared with CIS and MTX treated groups. This protective effect of CMN could be attributed mainly to the antioxidant activity by scavenging reactive oxygen species.

Treatment with CMN before CIS and MTX caused a significant enhancement in bone marrow mitotic activity as reflected by increase in the %PCEs compared to CIS and MTX treated group.

In conclusions, in the light of genotoxicity tests and biochemical results the present study showed that supplementation of curcumin may be a plausible way to reduce genotoxicity and cytotoxicity mediated by CIS and MTX due to its direct ROS scavenging activity. Administration of curcumin prior to cisplatin was recommended to reduce its genotoxic and cytotoxic effects without affecting its chemotherapeutic activity. However, further investigations were needed to elucidate the effect of curcumin on the antitumor activity of methotrexate.