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PROTECTIVE ROLE OF HONEY AND ROYAL JELLY ON CISPLATIN INDUCED OXIDATIVE STRESS IN LIVER OF RAT

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ABSTRACT: Background: Cisplatin is active cytotoxic agents in the treatment of cancer and has many adverse side effects, including hepatotoxicity. Honey and royal jelly are natural products and having antioxidants properties. **Aim of the study:** To investigate the protective role of combined administration of honey and royal jelly against cisplatin-induced changes in biomarkers of oxidative stress in rat liver. **Materials and methods:** Male Wistar albino rats of approximately the same age and weight were randomly divided into four groups. Group I: rats were controlled and were given 0.9% saline. Group II; rats were injected cisplatin (7 mg/kg/day) intraperitoneally for 15 days. Group III; rats were fed orally honey (500 mg/kg/day) with royal jelly (100 mg/kg/day) for 15 days. Group IV; rats have injected cisplatin (7 mg/kg/day) intraperitoneally and fed orally honey (500 mg/kg/day) with royal jelly (100 mg/kg/day) daily for 15 days. At the end of experimental animals were deprived of food overnight and sacrificed by cervical decapitation for estimation of antioxidant enzyme in liver tissue. **Results:** Administration of cisplatin to rats (G, II), leads to a significant increase in the levels of malondialdehyde (MDA) in liver tissue of experimental rats as compared with control. While, the levels of glutathione (GSH) and activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were significantly decreased. Oral supplementation of royal jelly and honey to rat (G, III) showed comparable levels of malondialdehyde (MDA), glutathione (GSH) and activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) to control. In the rat group that was administered honey and royal jelly in the association of cisplatin (G, IV) improvement was observed in liver biomarkers of oxidative stress. **Conclusion:** Combined administration of bee honey and royal jelly attenuated the cisplatin-induced alterations in the liver biomarker of oxidative stress.

INTRODUCTION: Cisplatin is anticancer chemotherapy drug used against several human cancers [1]. Despite the fact of its effective anti-cancer action, it exerts many unwanted adverse effects, including hepatotoxicity, ototoxicity, nephrotoxicity, spermiotoxicity myelosuppression, and emetogenesis [2].

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There is increasing evidence that cisplatin-induced oxidative stress plays a critical role in liver diseases [3]. Cisplatin causes the generation of reactive oxygen species (ROS), such as superoxide anion and hydroxyl radical, which depletes glutathione levels and inhibit the activity of antioxidant enzymes in liver tissue.

ROS may produce cellular injury and necrosis *via* several mechanisms, including peroxidation of membrane lipids, protein denaturation, and DNA damage [4]. Some reports show that cisplatin induces ROS formation *in-vivo*, which is responsible for the severe side effects of cisplatin therapy, including hepatotoxicity and nephrotoxicity, which in turn,

are reduced by the addition of antioxidants. Some studies have reported the importance of oxidative stress in cisplatin-induced toxicity, including liver [5]. Studies have suggested that oxidative stress might be generated in the pathogenesis of cisplatin-induced toxicity [6]. The free radicals, especially oxygen species (OS) have been suggested as a causative agent for the death of the cell in many different pathological phases and different models of toxic liver failure, including cisplatin [7]. So, searching for a method to prevent cisplatin-induced hepatotoxicity constitutes an active area of investigation. Therefore, it is reasonable to suppose that the use of the antioxidant defense of liver tissue by exogenous antioxidants having additional properties such as anti-inflammatory and cytoprotective effects should be a strategy to protect the liver from the oxidative damage [9].

Through the past few years, the science of nutrition has been advanced significantly based on the greater understanding of physiological and genetic mechanisms by which diet and individual food components influence health and disease. Scientific evidence is supporting the view that diet controls and modulate human body physiology and appropriately partake in the maintenance of good health or homeostasis necessary to reduce the risk of many chronic diseases. Natural antioxidants have been studied to reduce severe side effects as well as enhance anticancer activities of antitumor drugs [9]. Although various experimental studies indicated that diet with honey and royal jelly have profound beneficial health effects against various pathologies [10].

Royal jelly and honey are a highly efficient antioxidant and has the free radical scavenging capacity against hepatotoxicity induced by cisplatin [7]. Royal jelly and honey contain many important compounds with biological activity [11]. Honey is a rich source of energy and providing energy for cellular activity. This resultant effect could abate the energy depletion and the consequent cytotoxic action of cisplatin, which has been largely attributed to elevated production of reactive oxygen species (ROS), [12] which disrupt mitochondrial membrane potential (MMP) and damage the respiratory chain, [13] resulting in the compromised supply of energy for cellular functions. Therefore the aim of the present study was to investigate the protective effect of combined administration of honey and royal jelly against cisplatin-induced changes in biomarkers of oxidative stress in rat liver.

MATERIALS AND METHODS:

Animals: Healthy male Wister albino rats weighing 200-250 gm (10-12 wake age) were obtained from the animal house of R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, India. All the experimental procedures were carried out by the guidelines of CPCSEA and the experimental protocol approved by the Institutional Animal Ethics Committee (IAEC) of RCPIPER, Shirpur (Reg No-651/PO/ReBi/S/02/CPCSEA).

Housing Conditions: The rats were housed in standard plastic cages. The bedding material of the cages was changed every day. Maximum of 3 rats were housed per polypropylene cage having a size of 32 × 11 cm with stainless steel grill top mesh having facility for holding food palate and a water bottle. The rats were allowed free access to diet and water throughout the experimental period. All animals were housed in an air-conditioned room at a temperature range between 22-25 °C, relative humidity in between 30%-60% and with a 12 h light-dark cycle.

Acclimatization: Selected rats were randomly divided into four groups containing 6 rats in each group and were allowed to acclimatize to laboratory conditions for 7 days before experimentation.

Water: Water processed by reverse osmosis and UV light was supplied *ad libitum* to the rats.

Chemicals: Cisplatin was purchased from Cipla Ltd Company-Goa-India. Bee honey and royal jelly were collected directly from the *Apis mellifera* colonies located in the University campus, Dr. B.A.M.U, Aurangabad, Maharashtra, India. Food pallets were purchased from Nutrivet Life Sciences, Pune, Maharashtra, India. All other chemicals used in the estimations were of analytical grade.

Preparation of Royal Jelly and Honey: 500 mg of honey and 100 mg of royal jelly were dissolved in distilled water and administered through an

intragastric tube through the mouth. The doses were weighed on digital scales where each dose relies on the relevant animal's weight, in which every single gram of the experimental rat should receive 0.5 mg of honey and 0.1 mg of royal jelly.

Experimental Design: For the study, 24 adult male Wistar albino rats of 10-12 wake age and with 200-250g weight randomly divided into 4 groups; each group consisting of 6 rats (n=6) and were treated for 15 days as below:

Group I (Control): 0.9% (10 ml/kg/day) saline solution was administered for 15 days.

Group II (Cisplatin): Cisplatin (7 mg/kg/day) injected intraperitoneally for 15 days [14].

Group III (Honey + Royal Jelly): Honey (500 mg/kg/day) + Royal jelly (100 mg/kg/day) orally administered for 15 days [15].

Group IV (Cisplatin + Honey + Royal Jelly): 7 mg/kg/day of cisplatin injected intraperitoneally while honey (500 mg/kg/day) and royal jelly (100 mg/kg/day) were orally fed through an intragastric tube for 15 days.

Estimation of Antioxidant Enzyme Levels: At the end of 15 days, the animals were deprived of food overnight and sacrificed by cervical decapitation for estimation of antioxidant enzyme in liver tissue.

Preparation of Liver Homogenate: The liver was carefully removed, weighed and excised, rinsed in ice-cold normal saline, followed by rinsing with 0.15 M Tris-HCl (pH 7.4) to remove the blood. The liver was sliced into pieces and homogeny to make a 10% w/v homogenate with buffer containing 0.25 M sucrose and 0.1M Tris HCl buffer (pH 7.4).

The homogenate was centrifuged at 3000 × g for 20 m at 0 °C in cold centrifuge. The supernatant was separated and used for the analysis of various antioxidant enzymes.

Assay of Antioxidant Enzyme: The levels of lipid peroxidation (LPO) in tissues were estimated by the method of Okhawa *et al.*, (1979) [16]. Superoxide dismutase (SOD) was assayed by the method of Kono, (1978) [17]. The activity of catalase (CAT) was determined by the method of Armstrong, (2006) [18]. Glutathione peroxidase (GPx) was estimated by the method of Rotruck *et al.* (1973) [19]. Reduced glutathione (GSH) was estimated by the method of Sharma *et al.*, 2006 [20].

Statistical Analysis: All data were expressed as mean ± S.E.M. and statistically analyzed using GraphPad Prism 7 for Windows (Prism Inc, Chicago, IL, USA). Statistical significance of differences among different study groups was evaluated by one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons test as a post hoc test. P value of 0.05 or less was taken as a criterion for a statistically significant difference.

RESULTS:

Results of Oxidative Stress in Liver: The effect of administration of cisplatin (G, II), oral supplementation of honey and royal jelly (G, III), and administration of cisplatin with honey and royal jelly (G, IV) on biomarkers of oxidative stress in male Wistar albino rats were evaluated and compared with control (G, I) and obtained results were summarized in **Table 1**.

The results demonstrate that cisplatin administered rats (G, II), exhibited a significant increase in the level of malondialdehyde (MDA) in liver tissue of experimental rats compare with control. The percentage increase was 286.6%. While, the levels of glutathione (GSH) and activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were significantly decreased by 51.02%, 57.14%, 38.4%, 74.28% respectively compared to the control.

It was observed that after oral supplementation of honey and royal jelly (G, III), the level of malondialdehyde (MDA) in liver tissue of experimental rat was non-significantly decreased. The percentage decreased was 2.6% compared to control. In contrast, the level of glutathione (GSH) and activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were non significantly increased by 2.0%, 3.5%, 3.8%, and 9.5% respectively, compared to control.

Administration of cisplatin with oral supplementation of honey and royal jelly to rat (G, IV), leads to a significant decrease in the level of malondialdehyde (MDA) compare to cisplatin

administrated rats (G, II), and the percent decrease was 59.82%. While, the level of glutathione (GSH), the activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were significantly increased by 83.33%, 104.16%, 31.25%, and 214.81%, respectively.

TABLE 1: EFFECT OF ROYAL JELLY AND HONEY ON CISPLATIN INDUCED CHANGES IN BIOMARKERS OF OXIDATIVE STRESS IN LIVER OF MALE WISTAR ALBINO RAT

Biochemical parameter	(G, I) Control	(G, II) Cisplatin	(G, III) Honey and Royal jelly	(G, IV) Cisplatin with Honey and Royal jelly
MDA (µg/mg of protein)	150 ± 15	580 ± 96***a # (286.6%)	1465.73NSa # (-2.6%)	233 ± 11**b w (-59.82%)
GSH (µg/mg of protein)	49 ± 5.71	24 ± 4.0**a # (-51.02%)	50 ± 4.4 NSa # (+2.0%)	44 ± 2.3*b w (+83.33%)
Catalase (U/mg of protein)	56 ± 2.6	24 ± 4.4****a # (-57.14%)	58 ± 0.69NSa # (+3.5%)	49 ± 3.0***b w (+104.16%)
SOD (U/mg of protein)	26 ± 0.4	16 ± 0.49***a # (-38.4%)	27 ± 0.17NSa # (+3.8%)	21 ± 0.23***b w (+31.25%)
GpX (µg/mg of protein)	21 ± 1.4	5.4 ± 0.91****a # (-74.28%)	23 ± 1.0NSa # (+9.5%)	17 ± 0.75***b w (+214.81%)

1. ± indicate S.D. of three observations. 2. # (+) or (-) indicate percent variation over respective control **(**G, I) rats. 3. w (+) or (-) indicate percent variation over cisplatin injected (G, II) rats. 4. Values are significant at **P*<0.001, ***P*<0.01, ****P*<0.05, NS -Non-significant. 5. a = *P*<0.001, ***P*<0.01, ****P*<0.05 values compared with respective control rats. 6. b = *P*<0.001, ***P*<0.01, ****P*<0.05 values compared with respective cisplatin

DISCUSSION: The obtained results show that administration of cisplatin to rat caused a marked increase in the level of malondialdehyde (MDA) of liver tissue. The increase in the level of MDA in the liver in cisplatin administrated rats was attributed to a cisplatin-induced increase in free radical generation and a decrease in lipid peroxidation protecting enzymes. Cisplatin can cause the generation of oxygen free radicals such as hydrogen peroxide, superoxide anions, and hydroxyl radicals. The hydroxyl radical is capable of abstracting a hydrogen atom from polyunsaturated fatty acids in membrane lipids to initiate lipid peroxidation. These radicals can evoke extensive tissue damage, reacting with macromolecules, such as membrane lipids, proteins and nucleic acids [21]. Moreover, continuous exposure to reactive oxygen species (ROS) or free radicals causes lipid peroxidation in cells and cell membranes enriched with polyunsaturated fatty acids (PUPA) decompose to yield highly reactive free radicals such as peroxides, hydroxyl radicals, H, O, and malondialdehyde (MDA) [22, 23].

Administration of cisplatin to rats leads to a decrease in the level of glutathione (GSH) in liver tissue. This was attributed by cisplatin, which may bind with a thesulfhydryl group of GSH and may substantially decrease the availability of GSH to scavenge free reactive oxygen metabolites. The cisplatin complex may also disrupt lipid peroxidation and mitochondrial damage. Several studies demonstrated that cisplatin-induced acute hepatotoxicity is mediated by depletion of GSH and by impaired activity of GPx as well as an increase in lipid peroxidation [24]. Nakano and Gemba, (1989) [25] reported that administration of cisplatin to rat resulted in depletion of glutathione and subsequent potential of lipid peroxidation in liver cortical slices. The reduced glutathione was reported to protect cells from cytotoxic damage by many toxic compounds [26,] and it is generally known as a potent factor in the control of lipid peroxidation [27]. The role of GSH depletion with the consequent lipid peroxidation in cisplatin-induced hepatotoxicity is confirmed by the data presented by Anderson *et al.,* (1989) [28]. Moreover, depletion of glutathione, a potent free radical scavenger, may contribute to cisplatin-induced lipid peroxidation [29].

The results demonstrate that cisplatin administered to rat showed a marked decrease in the level of glutathione (GSH) and activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the liver of the experimental rat compare to control. The results recorded in the present study are in harmony with the results of previous investigators [22, 23]. The decrease in the activities of the enzymes was attributed to the generation of ROS, and the inhibition of thioredoxin reductase (TrxR) occurred in response to treatment with cisplatin. The thioredoxin system plays an important role in the regulation of antioxidant defense and redox status of the cells [30].

TrxR is a critical component of the mammalian thioredoxin system and is over-expressed in many cancer cells. Cisplatin inhibits this system and hence may raise the OxS status due to an imbalance of antioxidant/oxidant molecules [31]. Furthermore, it has been shown that high NO level exerts toxicological effects by reacting with superoxide anions (O_2´) to generate short-lived but hyperactive peroxynitrite radicals (ONOO´) with subsequent nitration of protein tyrosine residues [32]. Also, NO output depletes intracellular GSH, which increases susceptibility to OxS and aggravates renal tissue damage, especially in glomerular diseases [33].

The decrease in the activities of the antioxidants enzymes was attributed to oxidative stress injury by cisplatin. Oxidative stress injury is actively involved in the pathogenesis of cisplatin-induced acute liver injury. Reactive oxygen species (ROS) directly act on cell components, including lipids, proteins, and DNA, and destroy their structure. In the presence of cisplatin, ROS are produced through all these pathways and are implicated in the pathogenesis of acute cisplatin-induced renal injury. Cisplatin induces glucose-6-phosphate dehydrogenase and hexokinase activity and stimulates ROS production by damaged mitochondria, which increase free radical production and decrease antioxidant production [34].

Earlier reports revealed that CP exerts their toxic effects by inducing the generation of reactive oxygen species (ROS) [35]. A major cellular defense against ROS is provided by SOD and catalase, which together convert superoxide radicals first to H_2O_2 and then to molecular oxygen and water. Other enzyme, *e.g.* GSH-Px, use thiol-reducing power of glutathione to reduce oxidized lipids and protein targets of ROS. However, oxidative stress can occur as a result of either increased ROS generation and decrease in antioxidant enzyme system. These antioxidant enzymes protect the cell against cytotoxic ROS. In agreement with the previous studies, present results show that cisplatin enhanced lipid peroxidation (LPO), an indicator of tissue injury and deplete protein thiols [36]. Cisplatin administration to control rats caused severe damage to liver tissue most likely by ROS generation as apparent by perturbation in the antioxidant enzymes (SOD, Catalase, and GPx-SH) that lead to increased lipid peroxidation.

That is why; cisplatin treatment causes an increase in lipid peroxide levels and a decrease in the activities of antioxidant enzymes that protect against lipid peroxidation in the tissues such as liver [37]. Honey and royal jelly administrated rats group (G, III), showed comparable results to the control regarding the oxidative stress indicator parameters like malondialdehyde (MDA) glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx). However, these observations may be attributed to the antioxidant properties of honey and royal jelly which protect liver tissues in the normal range.

In combined administration of cisplatin with honey and royal jelly rats group (G, IV), leads to a significant decrease in the level of malondialdehyde (MDA) in liver tissue compare to animal treated with cisplatin (G, II). While, the levels of glutathione (GSH) and activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were significantly increased compared to animal treated with cisplatin (G, II). However, the elevated GSH level, activities of GSH-Px, CAT, GST, and SOD enzymes in the cisplatin plus RJ and honey group implied a decrease in the number of free radicals after cisplatin administration and reflected that these enzymes played important roles in scavenging of free radical.

Royal jelly and honey may be used as functional foods because of their naturally high antioxidant potential. It contains many important compounds with biological activity such as free amino acids, amino acids such as aspartic acid, cysteine, cystine, tyrosine, glycine, lysine, leucine, valine, and isoleucine. As indicated by previous researchers, the antioxidant effect of RJ may be related to its free amino acid content [38]. Honey is a natural antioxidant, which may contain flavonoids, ascorbic acid, tocopherols, catalase, and phenolic compounds all of which work together to provide a synergistic antioxidant effect, scavenging and eliminating free radicals [39]. Exogenously administered l-arginine may decrease the oxidative stress in the liver and kidney [40]. Cystine and cysteine take part in the synthesis of GSH, an effective cellular antioxidant. GSH breaks down reactive oxygen species and detoxifies carcinogens,

both directly and by antioxidant enzymes with which it reacts [41].

In this study, royal jelly and honey application following that of cisplatin were found to prevent rapidly formed liver. Royal jelly was determined to include 57-kDa glycoprotein stimulating hepatocyte growth and executing liver regeneration [42]. The royal jelly and honey significantly restore the changes of malondialdehyde (MDA), glutathione (GSH) and activity of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) caused by cisplatin injection towards the normal control values due to its antioxidant effect and its ability to act as a free radical scavenger, thereby protecting membrane permeability [14].

This study indicates that honey and royal jelly administration prevented oxidative stress by could be related to the fact that it contains hepatocyte-stimulating substance and glutathione precursor cystine and cysteine having an important role in the liver detoxication system as well as free amino acids such as glycine, aspartic acid [58]. Many investigators reported that royal jelly and honey has a protective role against many drugs on a liver biomarker of oxidative stress [7, 15, 43-44].

CONCLUSION: In conclusion, the current study demonstrated that cisplatin treatment induced oxidative stress which leads to impairment of the antioxidant defense system and induced lipid peroxidation in liver, whereas treatment with honey and royal jelly provided a protective effect for biomarkers of oxidative stress caused by cisplatin. This effect was evidenced by the ability of honey and royal jelly to return the reduced activities of intracellular antioxidants and lowering the free radicals in the liver.

However, the protective effect of honey and royal jelly is attributed to its anti-oxidant properties because it acts as lipid peroxidation inhibitor and free radical scavenger. Our results suggest that honey and royal jelly can be used as therapeutic agents to prevent liver damage caused by oxidative stress induced by cisplatin treatment.

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