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EVALUATION OF BENEFICIAL EFFECTS OF *MORINDA CITRIFOLIA* L. IN PRESENCE OF CISPLATIN ON EHRLICH'S ASCITES CARCINOMA BEARING MICE

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Keywords:

NJ, DNG, EAC cell, Anticancer, Anti-angiogenesis, antioxidant

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ABSTRACT: *Morinda citrifolia* L. (Rubeaceae) is a medicinal plant commonly called as Noni. Traditionally the entire plant is used for the treatment of cancer, inflammation, hypertension, diabetes, bacterial infections, and arthritis. The present study aims to explore the antineoplastic activity of Noni Juice (NJ) and Divine Noni Gold (DNG) concentrate on Ehrlich ascites carcinoma (EAC) bearing mice. Antineoplastic activity of NJ and DNG was evaluated in EAC bearing mice by administrating 0.35 ml/mouse p.o. respectively once daily for 14 days, before half an hour of NJ and DNG administration animal received single dose of cisplatin (CP) at the dose of 5.0 mg/kg b.w. i.p. on day 1 in respective cluster. Antitumor activity of NJ and DNG were measured by evaluating Mean Survival Time (MST), percentage Increase in Life Span (%ILS), body weight, tumor volume and viable cell count, additionally biochemical markers as well as hematological parameters were also evaluated. In the result, observed NJ and DNG respectively showed significant decrease tumor volume, viable cell count, body weight and raised MST and %ILS. Hematological parameters and serum biochemical markers were reverted and maintained closed to normal level in CP challenged mice. Results indicates that NJ and DNG possesses antineoplastic activity, this impact may be for the sake of their antioxidant and anti-angiogenic properties. In conclusion, NJ and DNG may be beneficial supplements in CP chemotherapy for enhancing the antitumor efficacy and decreasing the toxicity of CP.

INTRODUCTION: The crude products of numeral plants are using to treat various disorders in different systems of medicine *i.e.* Ayurveda, Siddha and Unani, and very less of them are scientifically proven. Herbal plants are affluent source of phytoconstituents *viz.* phenolic compounds, flavonoids, terpenes, alkaloids, anthraquinones [1 - 3], and many have received substantial attention in last few years for the sake of their cytotoxic and cancer chemopreventive impact [4].

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Several popular anticancer drugs like vincristine, vinblastine, taxol, etoposide already being using for the treatment of various malignancies which has been derived from plant origin. The most effective approaches in search for malignant tumorigenic remedies from herbs is that the choice of plants supported ethnomedical leads and challenging the designated herbs efficiency and wellbeing in the light of current science. Ancient therapeutic system have been explored at thoughtful ethnomedical use of NJ for the treatment of tumors in various parts of India.

Moreover, the plant of Noni is called as antineoplastic agent in ancient systems of medicine like Ayurveda [5]. *Morinda citrifolia* L. (Rubeaceae) plant commercially known as Noni. It is a small popular herbal plant mainly cultivate in South Asia with lengthened leaves, white tubular flower

bunches and greenish fruits turn to whitish-yellow when it becomes ripe. Traditionally Noni products are using since more than hundreds of years to treat numerous ailments including cancer globally.

A variety of phytoconstituents has been identified in Noni plant, contains more than 160 phytoconstituents among them more than 120 are nutraceuticals which are biologically and pharmacologically active [6, 7]. Noni fruit derives from an evergreen ligneous Noni plant grows extensively throughout the Pacific Ocean in forest regions. Noni was considered as a holy plant in the ancient healing system of Ayurveda, and is documented in ancient versions in the name of Ashyuka, that is Sanskrit for "longevity" [8]. In latest development, herbal remedies are using as a combination therapy with anticancer drugs due to their anticancer impact.

Several important phytoconstituents like alkaloids, flavonoids are present in Noni fruit showed the activity in contradiction of broad range of cancers [9]. Glycosides and iridoid glycoside isolated from Noni fruit that exhibited to have preventive impact on activator protein-1 (AP-1) transactivation and cell transformation in the mouse epidermal JB6 cell line [10 - 14].

NJ is one of the primary popular ancient medication documented to use as anticancer, anti-inflammatory, antiangiogenic, antibacterial, antihypertensive, pain relief and antioxidant activities [15]. Presently established that NJ inhibits 7, 12-dimethylbenz [a] anthracene (DMBA)-DNA adduct formation which suggested protective role in chemically induced cancers. NJ precipitates exhibits antitumor impact depending on macrophages, NK and T cells and prolonged their synergistic impacts with anticancer drugs [16, 17].DNG concentrate is one of the Noni formulation containing Noni fruit juice and extract of *Garcinia cambogia* fruit. DNG concentrate is available in the market people are consuming as nutraceutical and also for the treatment of cancer. Reported that *Garcinia cambogia* fruit contained phyto constituent like garcinol which exhibited as good antioxidant and anticarcinogenic activity [18, 19]. Therefore the hypothesis of the current study is to judge the antineoplastic impact of NJ and DNG in presence of CP on EAC bearing mice.

MATERIALS AND METHODS:

Animals: Inbred Swiss albino mice weighing 25–30 g has been obtained from central animal house facility, JSS Medical College, Mysuru, India, to use for the experiments. Before start the experiment we obtained permission from Institutional Animal Ethical Committee (IAEC) of JSS College of Pharmacy, JSS University, Mysuru, and followed CPCSEA guidelines for animal care and handling. The obtained IAEC number of the present study is 161/2016.

Chemicals and Drug: Sodium chloride, trypan blue, propylene glycol, methyl violate, methylene blue and various kits were used to perform this experiment and supplementary chemicals and reagents used were of highest analytical grade. Cisplatin hydrochloride injection 50 mg/50 ml vial were procured from JSS Hospital, Mysuru, India.

Noni Samples: The ripe Noni fruits and DNG concentrate were procured from Noni Biotech Pvt. Ltd. Tamil Nadu, India. Fresh NJ was prepared from fully ripped Noni fruit by hand squeezing method and both the samples were kept in freeze throughout the experiment.

Transplantation of Tumor: The EAC fluid derived from a spontaneous murine mammary adenocarcinoma were maintained in the ascetic form by consecutive passage in Swiss albino mice by means of weekly i.p. transplantations of $10x10^6$ tumor cells. From this stock suspension 0.1 ml of tumor cell suspension containing $2.5x10^6$ tumor cells were injected /mouse to obtain ascitic tumor on day 0 to all the prescribed groups of experimental animals [20, 21]. After 24hr of tumor inoculation, animals were treated as follows.

Treatment Schedule: Mice were divided into 6 clusters and each cluster contained 16 mice, subjected to various daily treatment regimens. After 14 days of treatment blood samples were collected from 6 mice for the estimation of hematological parameters and serum biomarkers from respective cluster and other 10 mice were kept for the assessment of tumor parameters i.e. MST, body weight, tumor volume and viable cell count.
Group-I represented as control which was untreated. Group-II received single dose of CP (5.0 mg/kg b.w. i.p.) [22] on day 1. Group-III received NJ

(0.35 ml/mouse p.o.) once daily for 14 days. Group-IV received DNG (0.35 ml/mouse p.o.) once daily for 14 days. Group-V received CP (5.0 mg/kg b.w. i.p.) on day 1, after half an hour received NJ (0.35 ml/mouse p.o.) once daily for 14 days. Group-VI received CP (5.0 mg/kg b.w. i.p.) on day 1, after half an hour received DNG (0.35 ml/mouse p.o.) once daily for 14 days.

The dose of NJ and DNG were calculated according to the following formula: Human adult dose * body surface area ratio convertible factor of mouse =133 ml * 0.0026 = 0.3458 ml [23].

Measurement of Antitumor Activity: Antitumor activity was evaluated with respect to the following parameters mentioned below.

Determination of MST and %ILS: At the end of the experiment, the effect of NJ and DNG on tumor growth was monitored by recording the mortality daily for five weeks. MST and %ILS were calculated by the following formula mentioned below [24].

$$MST^{*}_{==} = \frac{\text{Day of first death + Day of last death}}{2}$$

*Time denoted by days

$$\%ILS = \left[\frac{\text{MST of the treated group}}{\text{MST of the control group}} \text{ -- } 1 \right] \text{ X } 100$$

Measurement of Tumor Volume: The ascitic liquid was collected from the peritoneal cavity of mice by 1 ml disposable syringe. The volume of tumor liquid was measured in graduated centrifuge tube.

Measurement of Viable Cell Count: Viable cells were checked by trypan blue assay. The cells were stained trypan blue (0.4% in normal saline) dye. The cells which not received the stain were viable and those received the stain were non-viable. In this manuscript we have represented only viable cells count. The viable cells were counted by the following formula.

Viable cell count = (Number of cells x Dilution factor)/ (Area x Thickness of liquid film) [25].

Body Weight Analysis: Body weight were started to record from day 0 of the experiment and successively on every 3 day for 15 days. Average body weight and percentage decrease in body weight was calculated using the following formula [26].

$$\% \text{ change in body weight} = \left[\frac{\text{Animal weight on respective day}}{\text{Animal weight on day 0}} \text{ -- } 1 \right] \text{ X } 100$$

Estimation of Hematological Parameters and Biochemical Markers: After 14 day's of treatment, on day 15th blood was collected from carotid vein and heart puncture routes were used for the estimation of hematological parameters i.e. RBC estimated according to the D'Armour *et al.,*[27] method, WBC and Hb are estimated according to the Wintrobe *et al.,*[28] method. Biochemical markers i.e. aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were estimated according to the Reitman and Frankel method [29].

Statistical analysis: Statistical analysis was performed by using graph prism - 6 followed by one way and two way ANOVA. All the data were expressed as mean±S.E.M. Statistical significance was considered at $p<0.05$, $p<0.01$ and $p<0.001$.

RESULTS:

Effect of NJ and DNG on MST and % ILS: In EAC control group observed that MST and %ILS were simultaneously decreased which significantly augmented by co-administration of NJ and DNG as adjuvant therapy in CP challenged mice (**Fig. 1**).

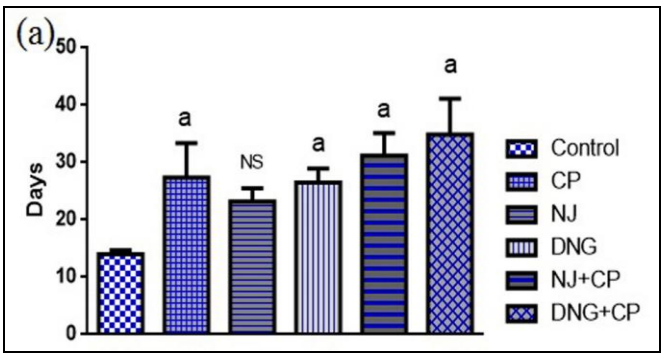


FIG. 1: MST (1a), ALL VALUES WERE CONSIDERED AS MEAN±S.E.M. OF TEN MICE, $p<0.05$ compared to control

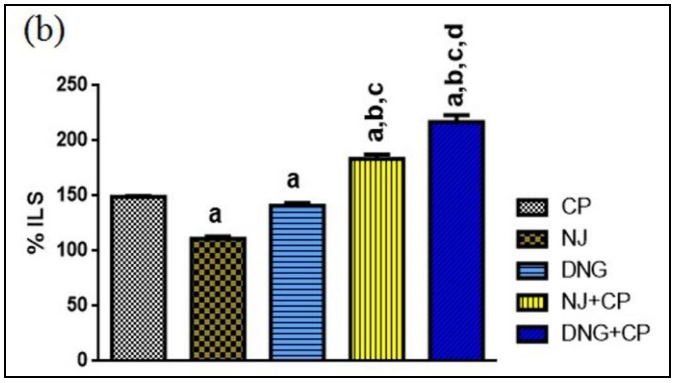


FIG. 1: %ILS (1b), ALL VALUES WERE CONSIDERED AS MEAN±S.E.M. OF TEN MICE [a]*p*<0.01 compared to CP, [b]*p*<0.01 compared to NJ, [c]*p*<0.01 compared to DNG, [d]*p*<0.01 compared to NJ+CP

Effects of NJ and DNG on Tumor Volume: Adjuvant therapy of NJ and DNG significantly (*p*<0.01) decreased tumor volume, viable cancer cell count, body weight in CP challenged mice in comparison to control (**Fig. 2**).

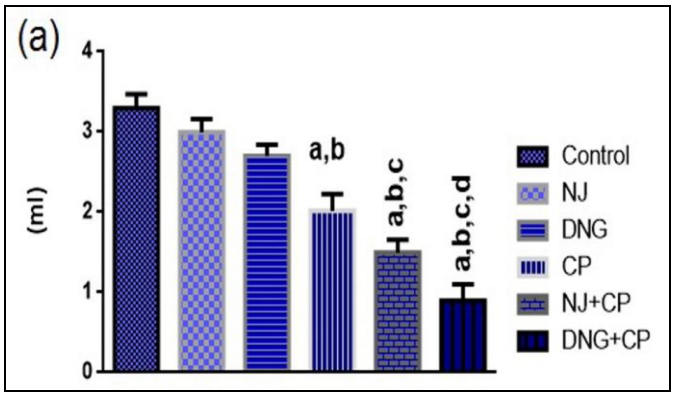


FIG. 2: TUMOR VOLUME (2a), ALL VALUES WERE CONSIDERED AS MEAN±S.E.M. OF TEN MICE, [a]*p* compared to control, [b]*p* compared to NJ, [c]*p* compared to DNG, [d]*p*<0.01 compared to CP, [e]*p*<0.01 compared to NJ+CP.

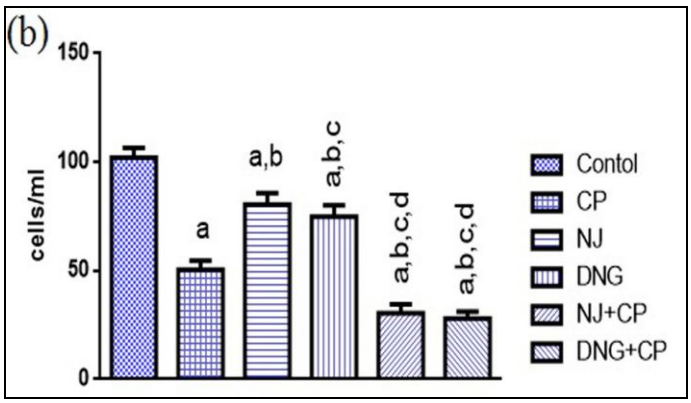


FIG. 2: VIABLE CELL COUNT (2b), ALL VALUES WERE CONSIDERED AS MEAN±S.E.M. OF TEN MICE, [a]*p*<0.01 compared to control, [b]*p*<0.01 compared to CP, [c]*p* compared to NJ, [d]*p*<0.01 compared to DNG, [e]*p*<0.01 compared to NJ+CP.

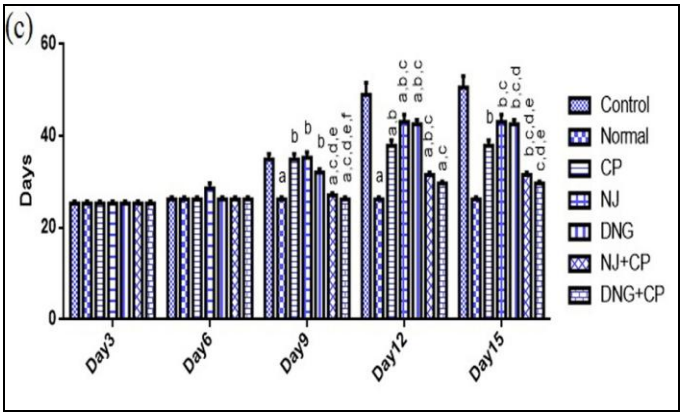
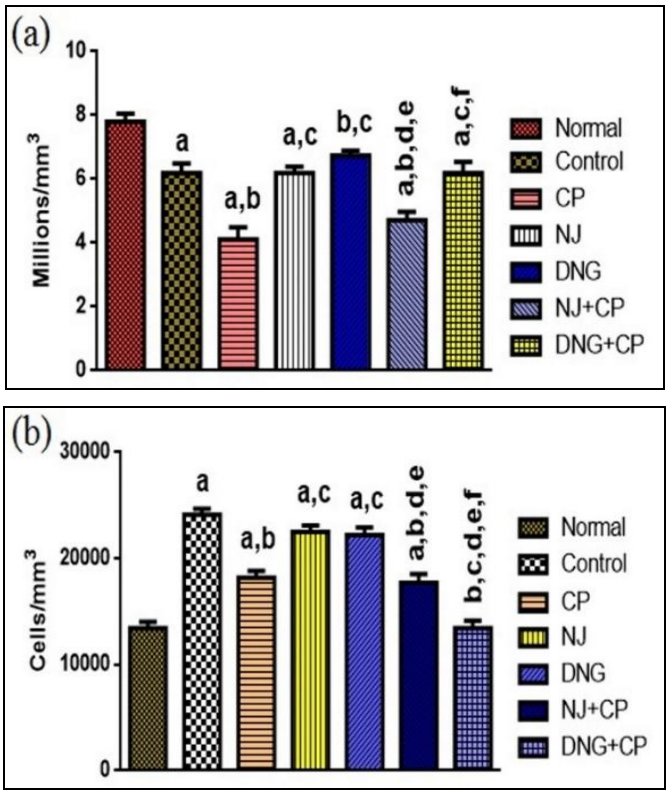


FIG. 2: BODY WEIGHT (2c), ALL VALUES WERE CONSIDERED AS MEAN±S.E.M., n=10, [a]*p*<0.01 compared to control, [b]*p*<0.01 compared to normal, [c]*p*<0.01compared to CP, [d]*p*<0.01 compared to NJ, [e]*p*<0.01 compared to DNG, [f]*p*<0.01 compared to NJ+CP.

Effect of NJ and DNG on Hematological Parameters: Fig. 3 shows RBC count and Hb content were significantly declined and simultaneously drastically augmented WBC count in the control when compared to normal group which is significantly reverted by adjuvant therapy of NJ and DNG in CP challenged mice. Moreover, NJ and DNG also showed myeloprotective effect (Group III and IV). Results indicates that NJ and DNG can be diminished myelotoxicity induced by EAC cell.



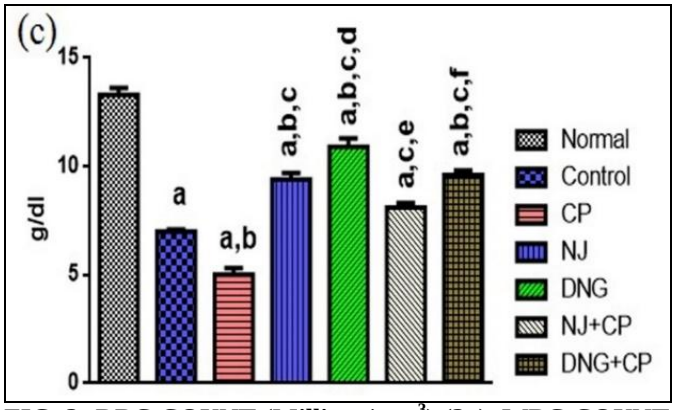
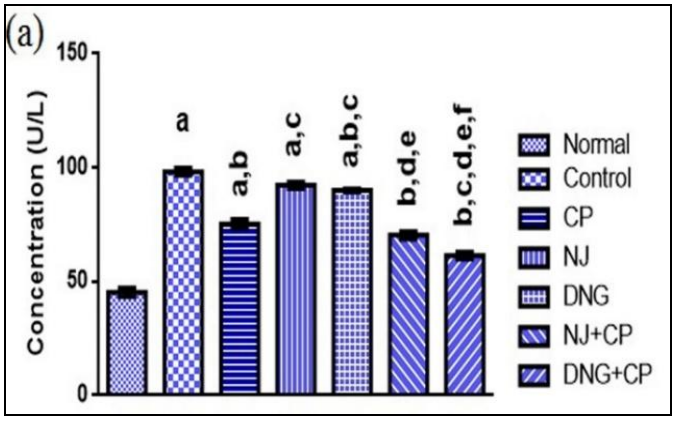
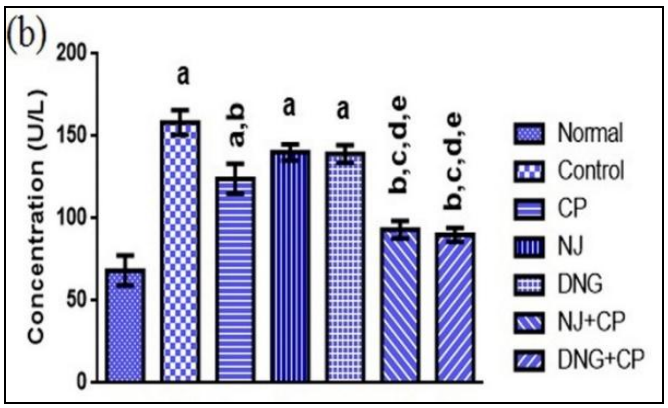


FIG. 3: RBC COUNT (Millions/mm^3) (3a), WBC COUNT (Cells/mm^3) (3b), Hb CONTENT (g/dl) (3c). All statistical values were considered as mean±S.E.M., n=6, $^a p<0.01$ compared to normal, $^b p<0.01$ compared to control, $^c p<0.01$ compared to CP, $^d p<0.01$ compared to NJ, $^e p<0.01$ compared to DNG, $^f p<0.01$ compared to NJ+CP.

Effect of NJ and DNG on Biochemical Markers: In control animals ALT, AST and ALP levels were significantly elevated in comparison to normal. However, treatment of NJ and DNG respectively revealed significant abridged their concentrations in CP challenged mice in comparison to control group indicates that NJ and DNG have hepatoprotective activity against EAC cells induced hepatotoxicity (**Fig. 4**).





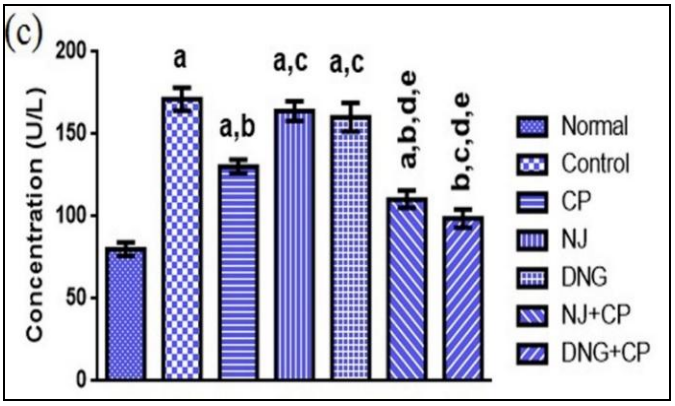


FIG. 4: ALT CONCENTRATION (U/L) (4a), AST CONCENTRATION (U/L) (4b), ALP CONCENTRATION (U/L) (4c). All statistical values were considered as mean± S.E.M., n=6, $^a p<0.001$ compared to normal, $^b p<0.001$ compared to control, $^c p<0.001$ compared to CP, $^d p<0.001$ compared to NJ, $^e p<0.001$ compared to DNG, $^f p<0.001$ compared to NJ+CP

DISCUSSION: Present *in-vivo* study exhibited that NJ as well as DNG significantly enhanced the life span in comparison to EAC control mice. Animals treated with DNG showed more MST and %ILS than NJ may be because of containing the extract of *Garcinia cambogia* fruit **(Fig. 1a)** and **(Fig. 1b)**. The reliable criteria for arbitrating the value of any antitumor drug extend life span in addition to decline WBC count [30]. Furthermore, the abridged volume of EAC and augmented survival time of mice suggests the deterring effect of NJ and DNG on cell proliferation.

This result support the recent study which suggested crude extract of *Morinda citrifolia* fruit exhibited antiproliferative activity against breast cancer (MCF-7) and neuroblastoma (LAN5) cell line at 29% and 36% respectively [31].

In the present study, adjuvant therapy of NJ and DNG significantly decreased the tumor volume **(Fig. 2a)**, viable cell count **(Fig. 2b)** and body weight **(Fig. 2c)** in EAC bearing mice suggests that they have antitumor impact in contradiction of EAC cells in mice. This outcome indicates that both preparations can kill the cancer cells indirectly through the stimulation of immune system involving macrophages, NK cells and T cells. Also reported that it had been conjointly prepared to induce earlier cell death in cancer cells and inhibit the formation of blood vessels over the tumor by anti-angiogenesis process [15].

Generally anemia is the main drawback in cancer chemotherapy owing to the reduction in RBC. The anemia encountered in EAC bearing mice is mainly due to reduction of RBC or Hb percentage and this may occur either due to iron deficiency or due to haemolytic or myelopathic conditions. Existing study indicates that NJ and DNG significantly improved RBC count **(Fig. 3a)** and Hb **(Fig. 3c)** content on the other hand attenuated WBC **(Fig. 3b)** level compared to EAC control. These indicates that NJ and DNG possesses protective effect on haematopoietic system against EAC cells induced myelotoxcity. Alteration of hematological parameters may be due to the over production of oxidative stress which leads to damage of macromolecules *i.e.* lipids that can induce lipid peroxidation *in-vivo.* Increased lipid peroxidation may cause degeneration of tissue in the body [32].

This myeloprotective effect may be due to antioxidant property of flavonoid compounds present in NJ and DNG which is correlated with the study of Allison *et al.,* [33] who demonstrated that oral intake of bioflavonoid antioxidant to be effective in averting oxidative stress which damage RBCs.

Researchers suggests that serum enzymes plays very important role as diagnostic markers in neoplasia as well as to apprehend the unwellness condition [34]. Several scientific reports has been revealed that tumor cell causes liver damage and disturbances in hepatic cell metabolism that leads to change in serum enzymes activity [35, 36]. Similar results exhibited in the current study that serum biochemical markers i.e. ALT **(Fig. 4a)**, AST **(Fig. 4b)** and ALP **(Fig. 4c)** levels were elevated in EAC control cluster which indicates that EAC cells induce hepatotoxicity. Reduction in the above biochemical markers levels by dint of NJ and DNG respectively in CP challenged mice indicates that NJ and DNG correspondingly possesses the protective effect against EAC cell induced hepatotoxicity this result is correlated with Wang *et al*.,[37] who were demonstrated that hepatoprotective activity of fermented NJ against CCl_4 induced liver injury. Exhibited above myeloprotective and hepatoprotective properties of NJ and DNG may be due to the antioxidant activity of their phenolic and flavonoids compounds.

Reported on various components present in NJ act on anticancer therapy where sulphated polysaccharides stops metastasis by destabilizing the interaction between glycosaminoglycan and certain proteins [38]. Whereas the most important anthraquinone *i.e.* damnacanthal impede the formation of tumors either by interfering with the expansion of ras gene activation [39], or by increasing apoptosis in human colorectal cancer cell lines [40].

Another important anthraquinone compound *i.e*. alizarin has an antiangiogenic impact through blocking blood circulation on malignant cells. Limonene inhibits mammary liver and lung cancers by stimulating thymus gland to secrete T cells which destroys the malignant cells. Ursolic acid inhibits the expansion of cancerous cells and induces apoptosis by modulating the body immune process [41]. Researchers stated that noni fruit contains flavonoids revealed to possess antimutagenic and antimalignant impact [42]. Furthermore, flavonoids and anthraquinones have a chemoprotective role in tumor through their impact on signal transduction in cell propagation and angiogenesis [43]. These information's suggests that anticancer activity of NJ and DNG most likely may be due to the presence of anthraquinone, polyphenol and flavonoid compounds.

CONCLUSION: Overall results indicates that DNG showed more protective effect than NJ. This effect may be due to containing the fruit extract of *Garcinia cambogia*. Moreover, NJ is having bad odour and unpleasant taste so patient may reluctant to consume it. Therefore, this fact concluded that DNG may be a useful supplement in CP chemotherapy for augmenting the antitumor efficacy and dropping the toxic effects of CP.

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CONFLICT OF INTEREST: The authors have declared that no conflict of interest.

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