Effect of Metformin in Rat Model of Vincristine Induced Peripheral Neuropathy

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A B S T R A C T

Chemotherapy has many side effects one of it is peripheral neuropathy. Aim of the study is to examine the effect of metformin either alone or in combination with pregabalin on chemotherapy induced peripheral neuropathy (CIPN). CIPN was induced in 40 spraguedawley rats; the study was hold on 5 equal groups; group I (normal control group), group II (diseased group), group III, (metformin treated group), group IV (pregabalin treated group), group V (metformin + pregabalin treated group). Tail immersion, acetone drop tests, serum malondaldehyde (MDA), serum tumor necrosis factor (TNFα), serum nerve growth factor (NGF) and tissue reduced glutathione (GSH), were assessed. Sciatic nerves were excised for histological examination and immunohistochemistery detection of caspase 3. Results: Combined administration of metformin and pregabalin significantly ameliorates neuropathy detected by attenuation of thermal hyperalgesia and allodynia along with restoration of oxidative stress markers (MDA & GSH), decrease of inflammatory mediators (TNFα), caspase 3 and increase of (NGF). Current results proved that Metformin has neuroprotective effect in addition to pregabalin that ameliorates vincristine induced peripheral neuropathy.

Introduction

Peripheral neuropathy is an important side effect induced by chemotherapeutic drugs (Zajaczkowska *et al.,* 2019). It can occur with vinca alkaloids as vincristine, vinblastine and vinorelbine, taxanes as docetaxel and paclitaxel, platinum derivatives as cisplatin, carboplatin and oxaliplatin, thalidomide and bortezomib (Simao *et al.,* 2015) ado-trastumab, emtasine, brentuximab and vedotin (Shah *et al.,* 2018). Vincristine is one of the vinca alkaloids extracted from the periwinkle plant, it has been used in the treatment of many tumors including Hodgkin's disease and leukemia (Ja'afer *et al.,* 2006). It inhibits microtubule formation by binding to β-tubulin which is an important component of nerve

axons that resulting in slowly progressive sensory-motor neuropathy (Mora *et al.,* 2016).Several studies discussed the role of oxidative stress, inflammation and release of cytokines as TNF α in the pathophysiology of vincristine and their role in the development of neuropathy (Starobova *et al.,* 2019). Pregablin is anticonvulsant drug that is used in treatment of diabetic and post herpetic neuropathic pain. It binds to presynaptic N type Ca^{+2} channel at the $\alpha_2\delta$ subunit leading to decrease the release of presynaptic transmitters as substance-P and glutamate (Bansal *et al.,* 2009; Kaur *et al.,* 2019).

Metformin is a common anti hyperglycemic drug used in treatment of diabetes. It has antioxidant effect as it decreases oxidative stress biomarkers. It is under investigations for its neuroprotective effect. It has been discovered to decrease neuropathic pain by activation of AMPK which inhibits TOR (El-Fatatry *et al.,* 2018). It also Decreased reduction of density of intra epidermal nerve fibers (IENFs) in mouse model (Mao-Ying *et al.,* 2014) diminished amyloid-beta induced reduction of human neural stem cells by reduction of apoptosis in an in vitro model of Alzheimer (Chiang *et al.,* 2016) and decreased degeneration of dopaminergic neurons of the substantianigra pars compacta in murine models of Parkinson's disease through inhibition of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and 3, 4-methylenedioxymethamphetamine (MDMA) (Bayliss *et al.,* 2016 and Francesca *et al.,* 2016). In addition to its anticancer effects through direct insulin independent and indirect insulin dependent action (Witters, 2001).

Materials and Methods

Drugs and chemicals

Metformin, vincristine sulfate, pregablin and all the other chemicals used obtained from Sigma (Sigma Chemicals Co., St. Louis, MO, USA.).

Experimental animals

Forty adult spraguedawley rat sweing (200-250 g) were used for this study divided into 5 equal groups (n=8 per group). All rats undergo acclimatization to the laboratory environment before starting experiments for one week. All the animals had free access to standard chew and water and maintained on a 12 hr light/dark cycle.

Peripheral neuropathy induction

Induction was done by injection of vincristine 0.1mg/kg intra-peritoneal for 10 days for 2 weeks with 2 days spare between 2durations (5 days per week from Saturday to Wednesday) (Park *et al.,* 2012).

Experimental groups

Group I (control group) received a vehicle of distilled water by oral gavage and by intra-peritoneal (I.P) injection for 28 day. Group II (diseased group) received vincristine 0.1 mg/kg as mentioned before. Group III (metformin treated group) received metformin (200 mg/kg/day by oral gavage) from the first day of induction of peripheral neuropathy till the 28th day (Oda, 2017). Group IV (pregabalin treated group) received pregabalin (10 mg/kg/day by oral gavage) from the first day of induction of peripheral neuropathy till the 28th day (Bhardwaj *et al.,* 2016). Group V (metformin + pregabalin treated group) from the first day of induction till the 28th day by oral gavage by the same previous doses. All drugs were dissolved in distilled water.

Behavioral tests

All rats were tested for various types of behavioral examinations on different time intervals of 1, 7, 14 and 28 days 2 hours

before any Drug administration (Bhardwaj *et al.,* 2016 and Choi *et al.,* 1994).

Tail thermalhyperalgesia (tail immersion test)

Terminal part of rat tail (1cm) was impeded in a hot water (55°C) with recording the time of withdrawal and the test was terminated at 15th second. Shortening of duration indicated hyperalgesia (Bansode *et al.,* 2014).

Paw cold allodynia (acetone drop test)

Rats were put on a wire mesh and acclimatized for 20 minutes then place 100 μL (0,1 ml) of acetone on the planter surface of hind paw. Licking, shaking or rubbing the paw was recorded as a positive result and the cut off time was one minute (Choi *et al.,* 1994 and Mangaiarkkarasi *et al.,* 2015 and Bhardwaj *et al.,* 2016).

Processing of samples

All rats were scarified under ether anesthesia at the end of the experiment then the blood was obtained by open cardiac puncture method, left to clot for 30 min at the temperature room then centrifuged at 4,000 rpm for 15 min at 4°C for serum separation then the serum was stored in -80°C until use.

Serum used for determination of malondialdehyde (MDA), tumor necrosis factor alpha (TNF α) and nerve growth factor (NGF). Both siatic nerves were excised, the right nerve was homogenized in 5 – 10 ml cold buffer (i.e., 50 mM potassium phosphate, pH7.5. 1mM EDTA) per gram tissue by the use of tissue homogenizer then centrifuged at 4,000 rpm for 15 minutes at 4°C and the supernatant used for determination of reduced glutathione (GSH) while the left one used for histopathological and immunohistochemical examination.

Estimation of serum of malondialdehyde (MDA)

Assessment of MDA was spectrophotometrically measured using commercial kits supplied by Biokit company. MDA was assayed in serum according to the methodology prescribed by Satoh 1978. In acidic medium thiobarbituric acid (TBA) reacted with MDA at temperature of 95°C for 30 min forming thiobarbituric acid reactive product then measurement of the absorbance of the resultant pink product by spectrophotometer at absorbance of 534 nm. The amount of MDA was expressed in nmol/ml.

Estimation of serum tumor necrosis factor (TNF-α)

TNF-α was analysed using ELIZA kits from Biokit company. The procedure was according to the instructions of the manufacturer. Recombinant anti-Rat TNF-alpha was used as a standard to build a standard curve. The optical density was measured at absorbance of 450. The results were calculated aspg/ml of TNF-α.

Estimation of serum nerve growth factor (NGF)

NGF was analyzed using ELIZA kit from Biokit company. The procedure was according to the instructions of the manufacturer. Recombinant anti-Rat NGF was used as a standard to build a standard curve. The optical density was measured at absorbance of 450. The results were calculated as pg/ml of NGF.

Estimation of tissue reduced glutathione (GSH)

Assessment of GSH was spectrophotometrically measured using

commercial kits supplied by Biokit company. Itwas assayed in tissue according to the method prescribed by Beutler *et al.,* 1963. The method depends on the reduction of 5,5` dithiobis (2 - nitrobenzoic acid) (DTNB) with glutathione (GSH) producing a yellow product measured spectrophotometrically at absorbance of 405 nm. The concentration of GSH was expressed in mg /g tissue.

Histopathological examination

The left sciatic nerves were immediately fixed in formaline 10% buffered solution. 5 microns of nerve specimens sections were stained with haematoxilin and eosin (H&E) then examined by light microscope.

Immunohistochemistery of caspase 3

Caspase 3 was assayed using kits supplied from Biokit company. Method was done According to Buchwalow and bocker, 2010. Percentage of apoptotic cells per section was scored according to the method described by (Bodey *et al.,* 2004)score 0 or -ve(less than 1%), score 1 or +1 (2-10%), score 2 or +2 (11-50%), score 3 or +3 (51-90%) and score 4 or +4 (more than 90%).

Statistical analysis

The present study used SPSS version 22 for statistical analysis. Continuous numerical data were tested by Shapiro wilk test for normality. Values expressed as mean $\pm$ SEM. An analysis of variance (ANOVA) test was used for comparison between the studied groups with post hoc Games-Howell test used to determine pairwise comparison between the studied groups. Kruskal-Wallis test was used for data that were not normally distributed for comparison between the studied groups followed by pairwise comparison using Dunn-Bonferroni test. $P < 0.05$ was considered statistically significant.

Results and Discussion

Effect on tail thermal hyperalgesia

The shortest duration was observed in group II however, best results were observed in co-treated groups (group V) (table 1).

Effect on paw cold allodynia

The shortest duration was recorded in group II however, best results were observed in co-treated groups (group V) (Table 2).

Effect on biomarkers of oxidant antioxidant status (MDA &GSH)

Group II showed a significant increase in MDA level ($p < 0.05$) while significant decrease in GSH level ($p < 0.05$) with comparison to groups III, IV and V. Moreover group V showed a significant decrease ($p < 0.05$) in MDA level with comparison to groups II, III & IV while GSH showed significant increase ($p < 0.05$) with comparison to group II (Table 3).

Effect on serum TNF-α

Groups III, IV & V showed significant decrease in the level of TNF-α in comparison to group II ($p < 0.05$) with the lowest result was for combination treated group V (table 3).

Effect on serum NGF

Groups III, IV&V showed significant increase in the level of NGF in comparison to group II ($p < 0.05$) with the highest result was for combination treated group V (Table 3).

Effect on apoptosis (caspase 3)

Significant increase observed in group II ($P < 0.05$) with comparison to group I with non significant difference ($P > 0.05$) between the treated groups (table 4).

Table.1 Tail immersion test (seconds) in different studied groups recorded on the 1st, 7th, 14th and 28th days

Tail immersion test	Group I	Group II	Group III	Group IV	Group V
Day 0	14.25 ±0.25	13.88 ± 0.3	14 ± 0.27	14.25± 0.25	14.25±0.25
Day 7	14 ± 0.27	10.13 ± 0.30 ^{a}	12 ± 0.60 ^{a,b}	11.50± 0.50 ^{a}	11.87±0.35 ^{a,b}
Day 14	14.25 ±0.25	7 ± 0.27 ^{a}	11.63± 0.50 ^{a,b}	11.38± 0.50 ^{a,b}	13± 0.27 ^{b,d}
Day 28	14.25 ±0.25	8.88 ± 0.30 ^{a}	12.75± 0.45 ^{b}	12.88± 0.40 ^{b}	13.88± 0.30 ^{b}

Data are expressed as mean ± standard error of mean by using one-way ANOVA with Games-Hawel post hoc test, SPSS computer program. $^{a–d}$ significant difference between groups at $p < 0.05$. $^{a)}$ significance from group I. $^{b)}$ significance from group II. $^{c)}$ significance from group III. $^{d)}$ significance from group IV.

Table.2 Acetone drop test (seconds) in different studied groups recorded on the 1st, 7th, 14th and 28th days

Acetone drop test	Group I	Group II	Group III	Group IV	Group V
Day 0	12.13± 0.64	11.75± 0.67	13.25± 0.82	12± 0.73	12.38± 0.62
Day 7	12±0.8	9.38± 0.56 ^{a}	11 ± 0.46	10.13± 0.64	10.50 ± 0.57
Day 14	13.25± 0.25	7± 0.27 ^{a}	11.63± 0.50 ^{a,b}	11.38± 0.50 ^{a,b}	11± 0.38 ^{b,d}
Day 28	12± 0.76	7.13 ± 0.52 ^{a}	10.75± 0.45 ^{b}	10± 0.57 ^{b}	11.75± 0.67 ^{b}

Data are expressed as mean ± standard error of mean by using one-way ANOVA with Games-Hawel post hoc test, SPSS computer program. $^{a–d}$ significant difference between groups at $p < 0.05$. $^{a)}$ significance from group I. $^{b)}$ significance from group II. $^{c)}$ significance from group III. $^{d)}$ significance from group IV.

Table.3 MDA, TNF-α, NGF and GSH biomarkers in all studied groups at the end of the experiment

	Group I	Group II	Group III	Group IV	Group V
MDA(nmol/ml)	10.41±0.21	101.34±0.82 ^{a}	29.59±0.72 ^{a,b}	30.66±0.73 ^{a,b}	17.69±0.48 ^{a,b,c,d}
TNF-α (pg/ml)	2.1±0.4	8±0.5 ^{a}	5.4± 0.3 ^{a,b}	.4±0.4a,b	2.6±0.2 ^{b,c,d}
NGF (pg/ml)	9±0.3	6.5±0.3 ^{a}	8.4±0.2 ^{b}	8.6±0.2 ^{b}	9.9+0.26 ^{b,c,d}
GSH (mg/g.tissue)	72.4±1.1	48.3±1.1 ^{a}	67.5±1.6 ^{b}	66.1±1.5 ^{a,b}	71.3±1.2 ^{b}

Table.4 Caspase 3 immunostaining in different studied groups

	Group I	Group II	Group III	Group IV	Group V
Caspase-3 immunostaining	0(0-1)	3(2-4)[a]	1(0-1)[a,b]	1(0-2)[a,b]	0(0-1)[a,d]

Fig.1 H&E staining: A Group I showed compressed nerve fibers with adhesive attachment of the perineural membrane[Magnification x200]. B Group II showed moderate degree of edema between nerve fibers and vaculations in the cytoplasm as well as inflammatory cellular infiltrate and apoptotic bodies in the perineural tissue [Magnification x200]. C Group III showed compact nerve fibers with mild edema and few inflammatory cellular infiltrates in the perineural tissue [Magnification x200]. D Group IV showed compact nerve fibers with mild edema [Magnification x100]. E Group V showed compact nerve fibers with focal mild edema in the perineural tissue [Magnification x200]
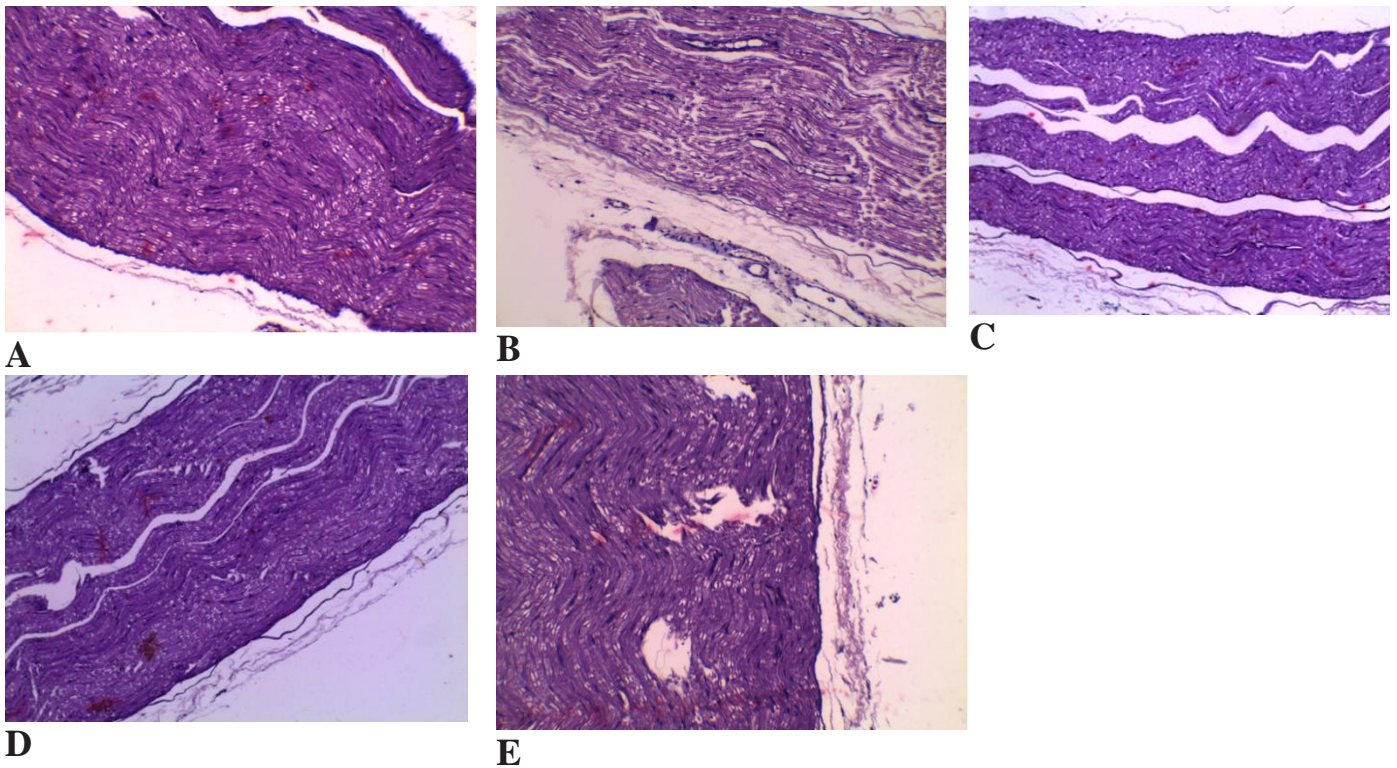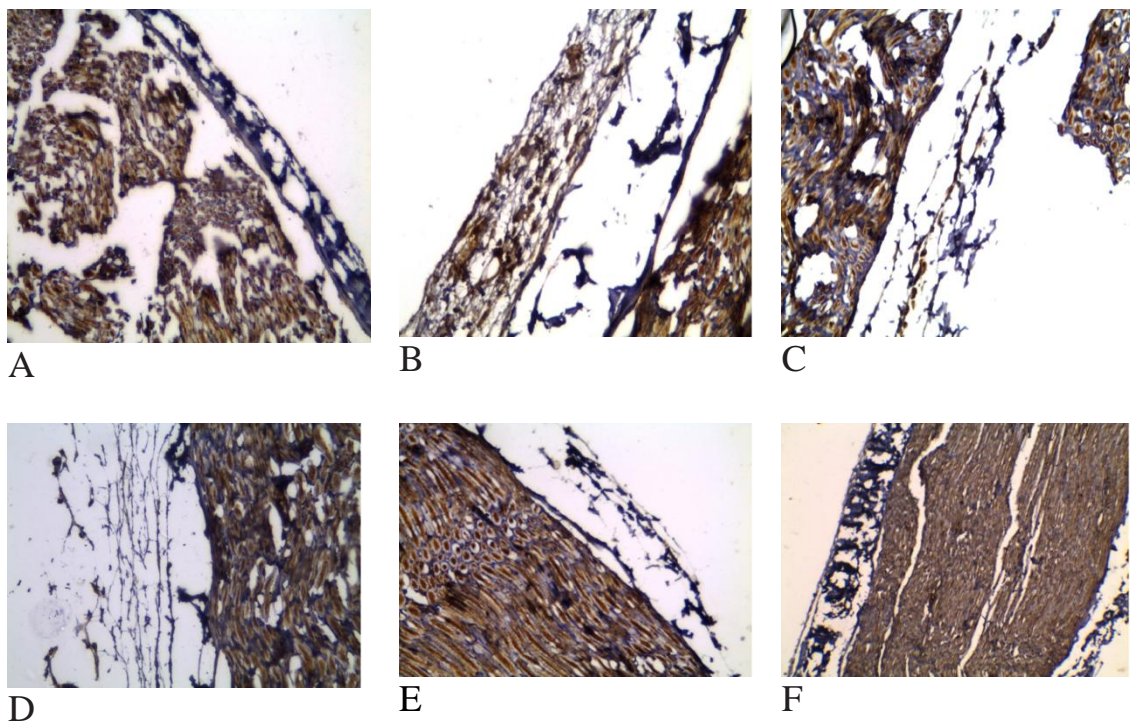
Fig.2 Immunohistochemical staining of sciatic nerve A Group I showed negative expression of caspase 3. B, C Group II showed +4 & +3 expression of caspase 3. D Group III showed +1 expression of caspase 3.E Group IV showed negative expression of caspase 3. F Group V showed negative expression of caspase 3 [Magnification x400]

Histopathological and immunohistochemistry examination. Histological examination of longitudinal sections of siatic nerve showed compact nerve fibers in the group I fig 1(A). In the group II there were edema between nerve fibers and inflammatory cellular infiltrate fig 1 (B). The fibers became compacted together with less edema and inflammatory infiltrate in groups III&IV fig1 (C, D). The pathological changes were reversed in group V fig1 (E). Immunohistohemical examination showed decreased expression of caspase 3 in group III fig 2 (D) with comparison to group I fig 2 (A) or group II fig 2 (B&C). In group V there were negative expression of caspase 3 and this confirms the better response was present with the use of both drugs.

Vincristine is a chemotherapeutic drug that is used in treatment of many types of tumors but its use is limited by peripheral neuropathy that occurs as a side effect (Babu *et al.,* 2015).Although there is no specific treatment of neuropathic pain, However many drugs are used to give symptomatic treatment of neuropathy as antiepileptic, opioid analgesics and antidepressants but they are used in a combination of two or more drugs to give a good response but this increase the incidence of side effects (Bhardwaj *et al.,* 2016). Many researches are needed to discover new drugs and new mechanisms to terminate the problem of neuropathy. This research tries to examine the effect of metformin alone and in combination with pregabalin as a standard drug in CIPN used in previous studies (Bhardwaj *et al.,* 2016).

The present study proves the neurotoxicity that occurs with vincristine determined by the presence of thermal hyperalgesia detected by

decrease of withdrawal latency of tail immersion and paw cold allodynia detected by acetone drop test, increasing oxidative stress detected by increasing of MDA and decreasing GSH, increasing inflammation detected by increasing TNF-α, decreasing NGF and increasing apoptosis detected by increasing of caspase-3.

Metformin is commonly prescribed as anti-hyperglycemic drug in treatment of diabetes (Gunton *et al.,* 2003). Also it has anticancer effect observed when the incidence of cancer with diabetic patients used metformin decreased (Franciosi *et al.,* 2013). It has antioxidant effect as it decreases oxidative stress biomarkers (El-Fatatry *et al.,* 2018), anti-inflammatory effect observed by reducing TNF-α (Hyun *et al.,* 2013) and anti-apoptotic effect detected by reducing caspase-3 (Weng *et al.,* 2017). It is under investigations for its neuroprotective effect. Recently it has been discovered to decrease neuropathic pain by activation of AMPK which inhibited mTOR (El-Fatatry *et al.,* 2018).

These results showing a novel insight into a therapeutic approach of metformin regarding to its neuroprotective effect by increasing of NGF.

Nerve growth factor is a neurotrophin which is important for the growth and survival of neurons. It was observed that its level was decreased in diabetic neuropathy models, cancer patients and administration of recombinant human NGF in cisplatin induced neuropathy in mice attenuated or delayed neuropath (Youk *et al.,* 2017). Also Sun *et al.,* (2018) has reported decreased level of NGF in diabetic neuropathy model and decreased expression of its receptors (neurotrophin receptor p75NTR and TrkA) and this was in accordance with our result. But this result was in controversy with Wild *et al.,* (2007); Aloe

et al., (2012) who discussed that level of NGF was high in patients of diabetic neuropathy and exogenous administration of recombinant human NGF can induce hyperalgesia and allodynia. Also it was reported that NGF level was high in models of chronic painful condition as pancreatitis, arthiritis, cancer pain and diabetic neuropathy and this means that it has a role in the pathogenesis of pain as it bind to TrkA receptor making a complex that increase expression of cell surface receptors responsible for nociception as bradykinin receptors, voltage-gated sodium channels, delayed rectifier potassium channels, voltage-gated calcium channels and pain mediators as calcitonin gene-related peptide (CGRP), substance P and brain derived neurotrophic factor which increase central sensitization to pain also NGF is released responding inflammatory mediators as interlukin-1 and TNF-α(Chang *et al.,* 2016). Additional mechanism of NGF is binding to TrkA receptor on the surface of mast cells increasing release of inflammatory mediators as (histamine, serotonin and NGF itself making a positive feedback mechanism) (Mantyh *et al.,* 2001; McKelvey *et al.,* 2013). Treatment with pregabalin and metformin increased the level of NGF with comparison to group II and this is a new mechanism in CIP also, showed antioxidant effect by decreasing of MDA and GSH as compared to group II, anti-inflammatory effect by decreasing TNF-α, anti-apoptotic effect by decreasing of caspase-3 and improvement of hyperalgesia and allodynia. All of these effects amilorate vincristine induced neurotoxicity as a model of CIPN.

In conclusion, this work summarized that the combination of metformin and pregabalin could expand the neuroprotective efficacy for treatment of neuropathy via pleiotropic effects including decreased oxidative stress, inflammation, apoptosis, hyperalgesia, allodynia and increased level of NGF.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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