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Putative Role of *Moringa oleifera* in Prophylaxis of Chemotherapy Induced Neuropathic Pain in Mice

Srikanta Chandra[1]*, Avik Das[2], Tathagata Ray[3], Lucky Mukherjee[4], Jyotirmay Samanta[5]

[1] College of Technological Sciences, Department of Pharmacology, Asansol, West Bengal 713301

[2] Assistant Professor of Gupta College of Technological Sciences, Department of Pharmacology, Asansol, West Bengal, 713301

[3] Department of Pharmaceutical Technology, JIS University, Kolkata,

[4] Bengal College of Pharmaceutical Science & Research, Durgapur, West Bengal, 713212

[5] Genex College of Pharmaceutical Science & Technology , Assistant Professor , Department of Pharmacology , Chinsurah , West Bengal 712102

ABSTRACT

Cancer chemotherapy is associated with a plethora of morbidities among which neuropathic pain is a prevalent one. The pathology underpinning chemotherapy induced neuropathic pain can be multifarious, however, dearth of effective medication largely plagues the quality of life of such patients. A good rationale can be found behind focusing on herbal alternatives like extracts of *Moringa oleifera* for which anti-cancer potential has already been reported. Hence we have carried out a pilot study for evaluating the protective potential of the methanolic extract of the plant against paclitaxel induced neuropathic pain in mice. Our evaluation has been based on standard paradigms focusing on neuromotor, oxidative and histopathological assessments. We have found significant improvisation in groups treated with both pregabalin and extract, the amelioration being largely graded in nature. Hence our research has opened up the doors of a newer horizon of herbal alternatives available for chemotherapy induced neuropathic pain, however further look out into the domain is avidly awaited for.

Keywords: NP: Neuropathic Pain, CC: Cancer Chemotherapy, HA: Herbal Alternatives

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***Address for Correspondence:**

Srikanta Chandra, College of Technological Sciences, Department of Pharmacology, Asansol, West Bengal 713301

INTRODUCTION

As we know Neuropathic pain is an age old menace .According to International Association for Study of Pain is defined as pain initiated or caused by injury or dysfunction of the somato sensory pathway. The injury or dysfunction may involve peripheral or central nervous system structures characterized by pain, numbness tingling in the extremities and slow nerve conduction. The featured encountered in the clinical course of the disease are multiferrous spaning from pain, numbness weakness and loss of gait. Since, epidemiologically neuropathic pain has a greater prevalence in the global prospective. So we decided to zero in on neuropathic pain in our work ahead. As suggested in the literature the course of the neuropathic pain is often complicated due to the multifactorial etiology under pinning the condition which demands closer over view. The pivotal contours may be featured as pain signaling changes, ion channel alteration,and second order nociceptive neuronal alteration. Since, modern treatment strategy having some limitation. Gabapentin which is Gold Standard Medication for neuropathic pain that is associated with Sedation. On the other hand Pregabaline is associated with blurred vision (63%) and Dizziness (70%)[1]. So we decided to narrow down on a comparison between the prophylactic and curative option. Both of have pharmacological aspects and non-pharmacological aspects .In prophylactic group under non pharmacological approach life style changes like monitored dieting , exercise plays a pivotal role and Sleep retardation therapy also deployed to control the functional aspects of the disease . On the other hand Neutraceuticals are plays a crucial role as per as pharmacological aspects. In curative therapy under non pharmacological approach life style modification is plays a pivotal role on the other hand Pregabaline and Gabapentine are corner stone of the therapy as per as pharmacological aspects.[2] So in the modern treatment strategy chemotherapy induced peripheral neuropathic pain may occur in cancer patients in the course of chemotherapy or after repeated course .Hence ,we take the opportunity to present about *Moringa oleifera* which is

very common plant available in India , Pakistan and Bangladesh .

Aetiopathology:

Epidemiologically neuropathic pain has a greater prevalence in the global prospective. So we decided to zero in on neuropathic pain in our work ahead. The pivotal contours may be featured as pain signaling changes, ion channel alterations,and second order nociceptive neuronal alteration.

Pain signaling changes: Peripheral neuropathy alters the electrical properties of sensory nerves which lead to imbalance between central excitatory and inhibitory signaling such that inhibitory interneurones and descending control systems are impaired. In turn transmission of sensory signals and disinhibition or facilitation mechanisms are altered at the level of the spinal cord dorsal horn neurones.[3]

Ion Channel Alterations: Neuropathy cause alteration ion channel such as Na^+, K^+ $Ca2^+$ within the affected nerve which includes all types of afferent fibers thus affecting spinal and brain sensory signaling.

Second Ordered Nociceptive Neuronal Alterations: It steams from altered second order neuron culminating in thalamus which leads to altered sensory transmission in the tertiary fibers sending impulses to cortex.[4]

Mast cells: Mast cell plays a pivotal role to create allergic reaction and pivotal initiators of innate immunity .Since after partial ligation of the sciatic nerve, the resident population of mast cells in the peripheral nerve are activated and degranulated at the site of nerve damage. They release pro inflammatory mediators namely histamine, serotonin, cytokine andproteases.

Modern Treatment Strategy:

Coming to the option available for management they include both non pharmacological aspects and pharmacological aspects. Under non pharmacological aspects life style changes life monitored dieting, exercise plays a pivotal role in the treatment of peripheral neuropathic pain. On the other hand Pregabalin and Gabapentine are still consider as a corner stone of the therapy as per as pharmacological aspects. However, Pregabalin and Gabapetin both are bind with α2 and delta subunit resulting in decreased central sensitization and nociceptive transmission. Pregabalin is not effective because of starting dose of 150 mg/day, segregated either two or more times daily, that's why it's may be titrated up to 300 mg/day after one to two weeks. Since, in the modern era Pregabalin having some limitation. It's associated with Dizziness, Weakness Headache. On the other hand Gabapentin which is a Gold Standard Medication (GSM) started at a dose of 300 mg/day .[4] However , Gabapentin are associated with Sedation ,ataxia and fatigue .Tricyclic antidepressant namely Amitriptyline , Nortryptyline are plays a pivotal role in the treatment of peripheral neuropathic pain.[5] Tricyclic antidepressant are associated with cardiotoxicity . TCA should be started at low doses 10 mg to 25 mg /day at night and can be titrated up to 75 mg/day. Since serotonin norepinephrine reuptake inhibitors namely Duloxetine are plays a pivotal role in the treatment of peripheral neuropathic pain. Duloxetine block the presynaptic serotoninand norepinephrine transporters proteins. Duloxetine having some limitation it's associated with nausea, vomiting. Briefly, opioid like drugs that's not recommended as first line therapy in the treatment of peripheral neuropathic pain. Opioid associated overdose, morbidity and mortality.[6] Tramadol and Tapentadol are plays a crucial role in the treatment of peripheral neuropathic pain. Tapentadol is centrally acting opioid analgesic. Local anaesthetics having plays a putative role in the treatment of peripheral neuropathic pain namely Lidocaine, Pilocaine etc as per as pharmacological aspects.[5] They blocks voltage gated sodium channel. However, it's having some limitations. Its act on the vital organ of the tissue that's why increase the chance to damage the vital organ namely Heart, Liver, Lungs.[7]

***Moringa oleifera*: A lacunae Revisited**

So in the modern treatment strategy chemo therapy induced peripheral neuropathic pain may occur in cancer patients either early in the course of the chemotherapy or after repeated course of chemotherapy. Hence, we take the opportunity to present about *Moringa oleifera*which is very common plant available in India, Pakistan and Bangladesh. Local name of Moringa oleifera in Arabic its called rawag , Assames : Saijna , Sohjna in Bengali its called Sajina, Burmese its called daintha in English it's called ben tree or drumstick tree from hindi it's called mungna . Moringa belonging to family Moringaceae .Moringa oleifera is a small, fast growing evergreen or deciduous tree that usually grows up to 10 or 12 m in height .It has a spreading, open crown of drooping, fragile branches whitish bark. Since, the leaves are bipinnate or more commonly tripinnate , up to 45 cm long and are alternate and spirally arranged on the twigs. Leaflets are 1.2 to 2.0 cm long and 0.6 to 1.0 cm wide .The fragrant,bisexual, yellowish white flowers are borne onslender, hair stalks in spreading or drooping axillary cluster 10 to 25 cm long. The bark is whitish gray thick , soft , fissured and warty or corky , becoming rough .When wounded , the bark exudes a gum which is initially white in colour but changes to reddish brown or brownish black on exposure .Moringa oleifera contains hydrocarbons , fatty acids , alcohols , esters oleic acids 84 % , Ascorbic acids and methyl ester hexadecanoic acids 1.31%. [8]

METHODS

Fresh plant of M.oleifera were collected from Asansol , West Burdwan , in the month of 2nd January .Plants were identified and confirmed by Mr. Subhomoy Panda , Department of Life Science . The leaves were separated and air dried, which were then crushed and powdered .Methanolic extract was prepared by percolation method with 95 % Methanol followed by steam evaporation. Exactly 250 g of dry powder was percolated to get a net yield of 30.6 hm of concentrated extract .All the animals used in the study were taken care of under ethical consideration as per CPCSEA guidelines. The study was conducted after getting approval fromInstitutional Animal Ethics Committee, Gupta College of Technological Sciences, Asansol(Protocol no: GCTS/IAEC/ 18th December /03).So here is the blue print of the procedural aspects we have followed in our study it start with male mice of age 8 weeks are chosen. They are assigned into different groups negative control group provided with normal saline, positive control group provided with Paclitaxel, standard group provided with Paclitaxel and Pregabaline, on the other hand Test (1) group provided with extract of *Moringa oleifera* 200 mg/kg 15 days prior, Test (2) group provided with extract of *Moringa oleifera* 100 mg/kg 15 days prior and curative group provided with extract of *Moringa oleifera* 100 mg/kg 21 days prior. Thenwe check a plethora of parameters such as sensory assessment and oxidative damage assessment after post induction periods. So in our study we aim to carry out based on the aim the objectives may conjured up as establish oxidative stress as pivotal factor under pinning pathology of neuropathic pain , evaluating the damaging potential of oxidative stress in

chemotherapy induced peripheral neuropathic pain , determination of prophylactic potential of *Moringa oleifera* against chemotherapy induced neuropathic pain.

Neurosensory Assessment –Modified Von Frey Test:

The assay was performed based on the procedure described by J. Ferry et al. in the year of 2016 with slight modification .Animals were placed on wire mesh plateform and covered with a polypropylene confine so as to allow free movement on limb on each of 0,14, 22 days animals were subjected to three intermitant sessions of allodynic jalts separated by a span of two hours.

Fig: 1 Modified Von Frey Test

Foot Fault Test:

Fig :2 Foot Fault Test

The assay was performed based on the process described by Macbrid et a*l*. in the year of 2011 with slight modification .Animals were taken respectively bins and weights. They are assigned into two different groups respectively bin. Animals of all the groups dosed according to protocol. Then faulty step paradigm evaluated according to the standards.

Assessment of antioxidant status in peripheral tissue :

Oxidative stress is defined as the imbalance in the redox characteristics of some cellular environment which can be the result of either biochemical process leading to the production of reactive species ,exposure to damaging agents (i.e environmental pollutants and radiations) or limited capabilities of endogenous antioxidant systems .Reactive oxygen and nitrogen species (ROS/RNS) produced under oxidative stress are known to damage all cellular biomolecules (lipid , sugars , proteins and polynucleotides) .Thus several defense systems include nonenzymatic molecules (glutathione , vitamins A ,C , E and several antioxidants present in food) as well as enzymatic scavengers of ROS with superoxide dismutase (SOD) best known defence systems. Tissue was taken then its homogenized .To 1.0 mL of the suspension 10% TCA was added. Then centrifuged was done for 5 minutes at 5000 rpm .To 1.0 mL of supernatant , 1.0 mL of 0.67% TBA in 0.05% mol/L NaOH was added .Tubes were kept in boiling water bath for 20 min at temperature greater than 90^0 C and cooled. Then absorbance was measured at 532 nm spectrophotometrically .The concentration was measured with respect to blank & expressed as nmol/mg protein [9,10]

Statistical Analysis:

Results have been expressed as mean ± SEM. One way ANOVA have been employed for comparing majority of parameters such as SOD, reduced GSH. Post hoc tests were used for identification of groups having significant differences for one way ANOVA. Tukey's Multiple Range Test was used for comparisons. Whereas for two way ANOVA Bonferronies test was used for the post hoc analysis .The significant groups were identified on the figure by designated alphabets.

RESULTS:

Flinching threshold

Days	D0	D7	D14	D22
Negative control (Normal saline)	0	4	8	15
Positive control (Paclitaxel)	0	6	15	18
Standard (Paclitaxel & Pregabalin)	0	5	14	20
Test(1)(Extract of *M .oleifera* 200 mg/kg)	0	6	20	25
Test(2) (Extract of *M .oleifera* 100 mg/kg)	0	4	14	20
Curative(Extract of *M.oleifera* 100 mg/kg)	0	5	9	12

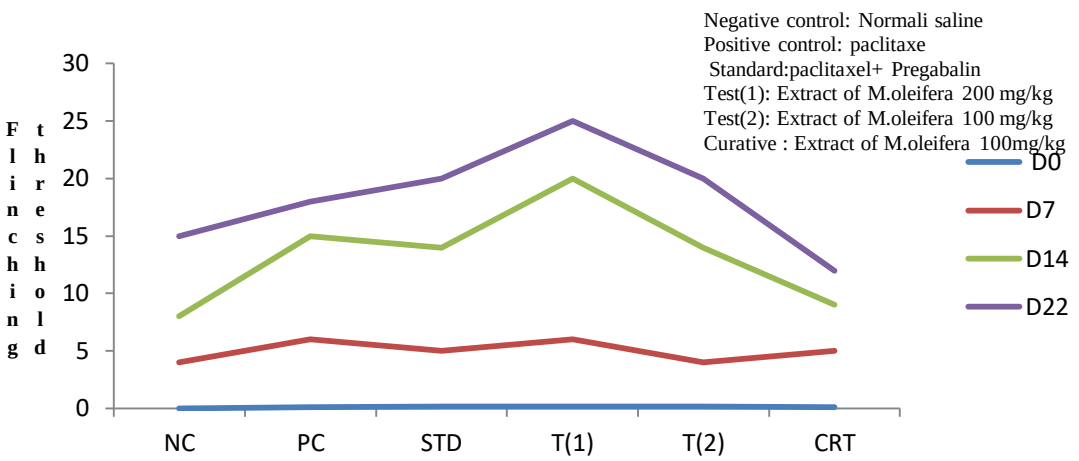


Fig 3: Flinching threshold

No. of Foot Fault

Days	D0	D7	D14	D22
Negative control	0	2	3	3
Positive control	0	5	8	10
Standard	0	4	6	7
Test(1)	0	2	4	3
Test(2)	0	3	5	6
Curative	0	4	10	14

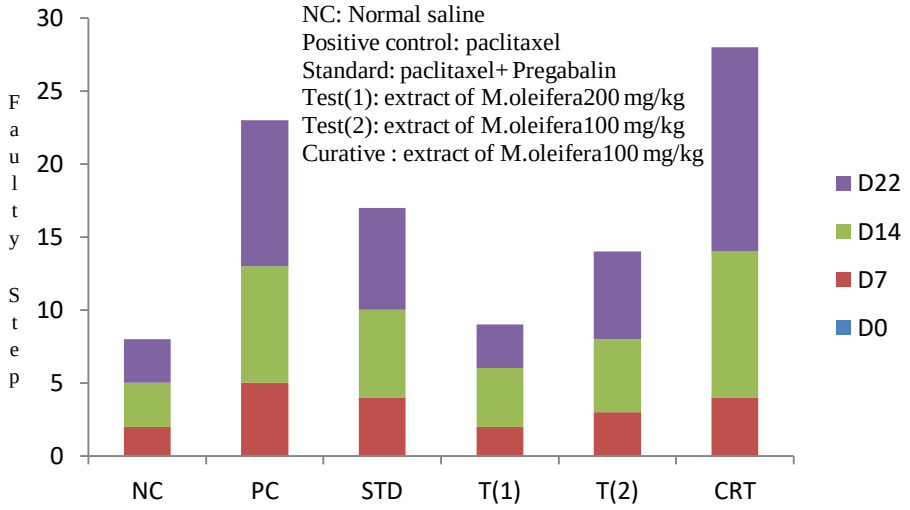
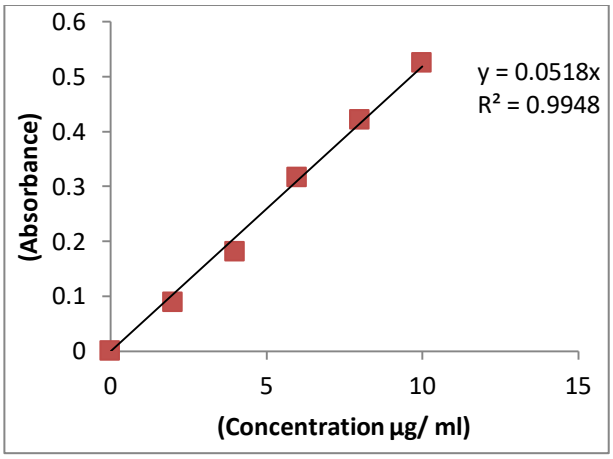


Fig 4: Faulty steps paradigms

Standard Curve of Malondialdehyde (MDA)



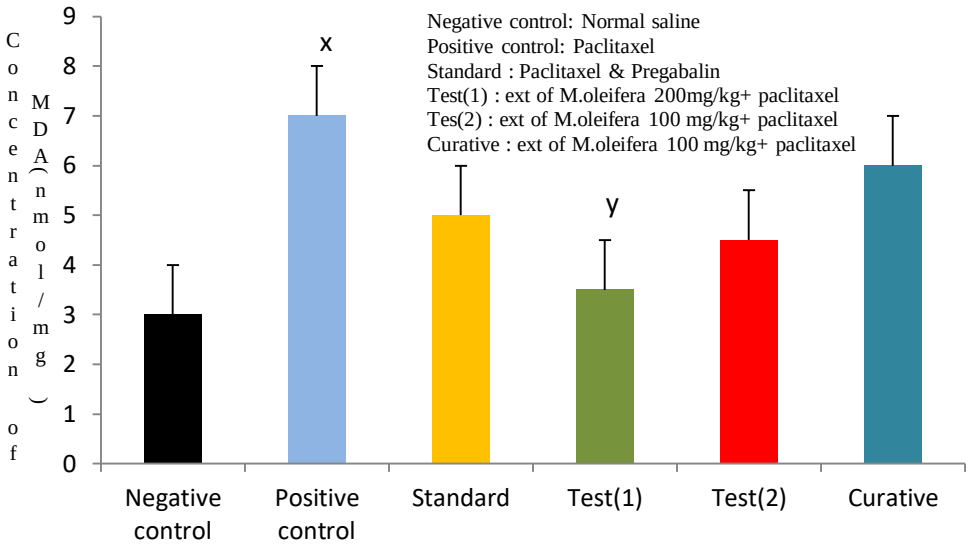
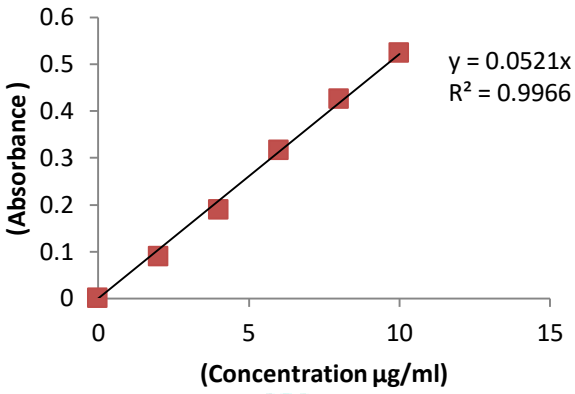


Fig 5: Variances in level of MDA in control and treated groups. Value presented as mean ± SEM x p< 0.001 in comparison between positive control and negative control group . y p < 0.001 in comparison between positive control and treated groups.

Positive control group treated with paclitaxel was found to have a significant hike in level of peripheral MDA a compare to negative control while the standard and test group showed and appreciable decrease .However , the Test(1) group treated with extract of *Moringa oleifera* 200 mg/kg showed the most significant decrease .

Standard Curve of Reduced Glutathione



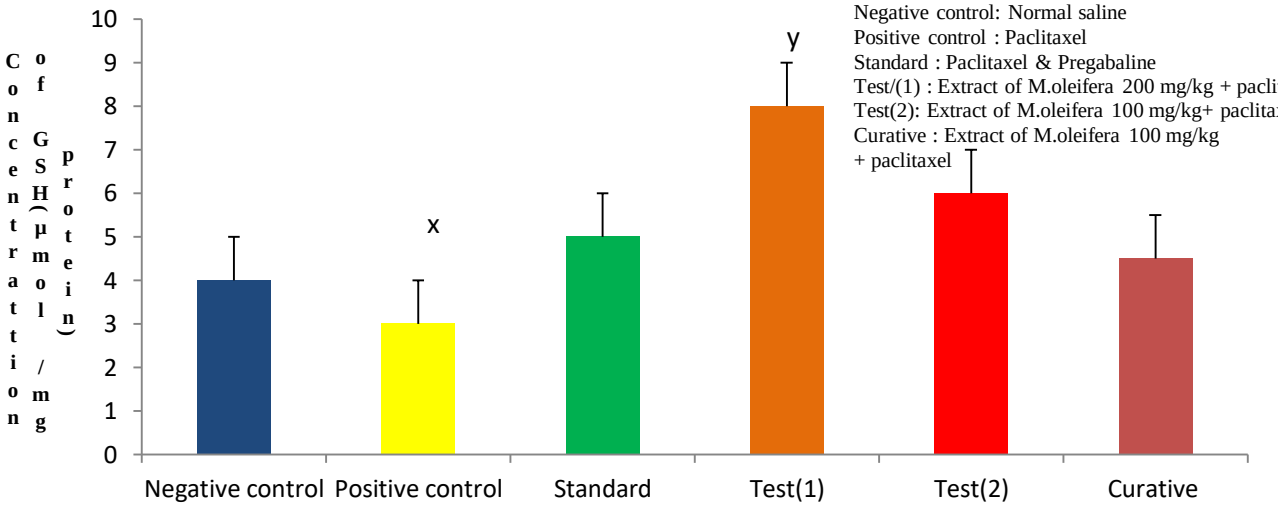


Fig 6: Variances in level of reduced GSH in control and treated groups. Value expressed as mean± SEM x p < 0.001 in comparison between positive control and negative control group. Y p <0.001 in comparison between positive control and treated groups.

Positive control group treated with Paclitaxel was found to have decrease in the level of peripheral GSH compare to negative control while the standard and test group showed and appreciable increase however test (1) group treated with extract of *Moringa oleifera* 200 mg/kg showed the most significant increase.

CONCLUSION

As we know neuropathic pain is an age old meance . So, here we concluded that *Moringa oleifera* 200 mg/kg have a prophylaxis role in the amelioration of paclitaxel induced peripheral neuropathic pain in Mice.

DISCUSSION

As we know neuropathic pain is an age old menace .According to International Association for Study of Pain is defined as pain initiated or caused by injury or dysfunction of the somatosensory pathway. The injury or dysfunction may involve peripheral or central nervous system structures characterized by pain, numbness tingling in the extremities and slow nerve conduction .Epidemiologically neuropathic pain has a greater prevalence in the global prospectives .Hence, we decided to narrowing down peripheral neuropathic pain in our work ahead. As suggested in the literature the course of neuropathic pain is often complicated due to the multifactorial etiology under pinning the condition which demands closer overview. The pivotal contours may be featured as pain signaling changes, , ion channel alteration and second ordered nociceptive neuronal alteration . [11]

Coming to the option available for management they include both non pharmacological aspects and pharmacological aspects. Under non pharmacological aspects life style changes like monitored dieting, exercise plays a pivotal role in the treatment of peripheral neuropathic pain. On the other hand Gabapentin and Pregabalin plays a crucial role as per as pharmacological aspects.

However, Gapbapentin and Pregabalin have some limitation. Gabapentin associated with sedation and Pregabaline associated with dizziness. Hence we found a good rationale behind probing for prophylaxis role in our pipeline that is *Moringa oleifera*[12]

So in our study we take male mice of age 8 weeks and they are divided into different groups such as Negative control treated with normal saline where as positive control treated with paclitaxel standard provided with paclitaxel and pregabaline on the other hand Test(1) provided with extract of *Moringa oleifera* 200 mg /kg and Test (2) provided with extract of *Moringa oleifera* 100 mg /kg , curative group provided with extract of *Moringa oleifera* 100 mg/kg as per protocol . [13]

The severity of peripheral pain in the disease was evaluated by measuring standard parameters namely neurosensory assessment, MDA, reduced GSH activity. In present study , we found that Test(1) increased the fletching threshold in the following treatment with extracts of *Moringa oleifera* 200 mg /kg significantly declined the scored compared to the positive control group .This is the line with the conclusion published by

Many studies have revealed that the increase of oxidative stress MDA and GSH has been notable feature of Peripheral Neuropathic Pain , which resulted in a pathological cascade of free radical reactions and further yielding more oxidative free radicals .Failure of the endogenous antioxidant defense mechanism promote formation of excessive free radicals and consequent tissue damage .Parameters such as MDA , GSH activity can be indicative of oxidative stress status of the disease .MDA level can be determining by TBARS .As observation in our study increase in the MDA levels in the periphery affected by the paclitaxel administration suggests enhanced lipid peroxidation that could be responsible for the tissue damage . This is the line with the conclusion published by In the present study animal group treated with paclitaxel suffered an increase in the oxidative stress indicated by higher MDA and GSH activity which are responsible for the tissue damage and amelioration of pain respectively bin. In our study we found that animals treated with extract of *Moringa oleifera*had reduced MDA expression and increased GSH activity which was significant in comparison to the positive control group thus suggesting its antioxidant property.

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REFERENCES

1. Guido Cavaletti , Paola Alberti , Barbara Frigeni , Marialusia Piatti , Emanuela Susani ; Chemotherapy Induced Neuropathic Pain ; Cuurent Treatment Options in Neurology (2011)13:180 -190
2. Hau Jung Park ; Chemotherapy induced peripheral neuropathic pain ; Korean Journal of Anesthesiol ,2014 July 67(1) :4-7
3. R Gupta , A Bhaskar ; Chemotherapy – induced peripheral neuropathic pain in mice ; BJA Education , Volume 16 , No :4 , April 2016
4. Nicolas Tsavaris , Petros Kopterides , Christos Kosmas , Athina Efthymiou , Hlias Skopelitis , Antonios Dimitrakopoulos , Eyterpi Pagouni , Dimitrios Pikazis , Panagiotis –Vasilis Zis , Christos Koufos ; Gabapentin Monotherapy for the treatment of chemotherapy induced neuropathic pain : A pilot study; American Academy of Pain Medicine , 2008 , Volume :9 , Number :8 , Page no : 1209-1216
5. Mark J. Lema , Kathleen M. Foley , Frederick H. Hausheer ; Types and Epidemiology of Cancer –Related Neuropathic Pain : The Intersection of Cancer Pain and Neuropathic Pain ; The Oncologist 2010;15 , Page no : 3-8
6. Shrikant Atreya ; Pregabalin in chemotherapy induced neuropathic pain ; Indian Journal of Palliative Care , 2016 , Volume :22 , No : 1 , Page no 101 – 103
7. M .T . Fallon ; Neuropathic pain in cancer ; British Journal of Anaesthesia 111 (1) : 105 -11 (2013)
8. V Loomba , H Kaveeshvar , A Upadhyay , N Sibai ; Neuropathic pain in cancer patients : A brief review ; Indian Journal of Cancer , 2015 , Volume : 52 , No : 3 , Page no : 425 -428
9. Renata Zajaczkowska , Magdalena Kocot Kepska , Wojciech Leppert , Anna Wrzosek , Joanna Mika , Jerzy Wordliczek ; Mechanisms of Chemotherapy - Induced Peripheral Neuropathy ; International Journal of Molecular Sciences. 2019 , 20(6) , 1451 -1459
10. Wang X , Shen X , Xu Y Xu S , Xia F , Zhu B , Liu Y , Wang W, Wu H , Wang F; The etiological changes of acetylation in peripheral nerve injury – induced neuropathic hypersensitivity ; Molecular Pain , Volume 14: 1-9
11. Brandolini Laura , Benedetti Elisabetta , Ruffini Pier Adelchi , Russo Roberto , Cristiano Loredana , Antonosante Andrea ,d' Angelo Michele , Castelli Vanessa , Giordano Antonio , Allegretti Marcello , Cimmi Annamaria ; CXCR1 /2 pathways in paclitaxel – induced neuropathic pain ; Oncotarget , 2017 , Vol .8 (No .14), PP: 23188 – 23201
12. Lisa A. Griffiths, Natalie A. Duggett , Ann L. Pitcher , Sarah J.L . Flatters; Evoked and Ongoing Pain – Like Behaviours in a Rat Model of Paclitaxel –Induced Peripheral Neuropathy; Pain Research and Management;2018, Volume 17.
13. Guilia Donvito , Jenny L. Wilkerson , M. Imad Damaj , Aron H. Lichtman ; Palmitoyethanolamide Reverses Paclitaxel – Induced Allodynia in Mice ; The Journal of Pharmacology and Experimental Therapeutics 359 : 310 -318 , November 2016