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Ameliorative Effects of Ethanolic Leaf Extract of *Palisota hirsuta* K. Schum (Commelinaceae) on Vincristine-Induced Neuropathic Pain in rats

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ABSTRACT

Vincristine-induced neuropathy is a major dose-limiting side effect of cancer chemotherapy and thus effective therapeutic strategy is required. The present study utilized a rodent model of neuropathy to determine whether an ethanolic leaf extract of *Palisota hirsuta* (PHE), a plant widely used in West African traditional medicine for pain management and CNS disorders, could attenuate vincristine-induced neuropathic pain. Neuropathic pain was induced by injecting rats intraperitoneallywith vincristine (0.1 mg kg^{-1} day^{-1} in two 5-day cycles with a two-day break). Randall-Selitto Paw Pressure, Hargreaves, cold water (4-5˚C) and Von Frey Filaments tests were performed. These tests were used to assess the degree of mechanical hyperalgesia, thermal hyperalgesia and cold and tactile allodynia respectively as an index of peripheral and central pain sensation.Oral administrations of PHE (30-300 mg kg^{-1}) significantly and dose-dependently ameliorated vincristine-induced pain-related behaviors. It significantly reduced both mechanical and thermal hyperalgesia and completely reversed vincristine-induced tactile allodynia at 100 and 300 mg kg^{-1} after 24 h. It however showed little effect on cold allodynia. These effects were similar to that of the gabapentin-treated group. In conclusion, oral administration of an ethanolic leaf extract of *Palisota hirsuta* attenuates pain-related behavior in vincristine-induced neuropathic pain model

INTRODUCTION

Pain is one of the most common and stressful symptoms experienced by both human and veterinary oncology patients which makes cancer-related pain a significant clinical problem. Beside the cancer-induced pain, about 30 % of adult cancer patients who have undergone treatments that include radiation, chemotherapy, or surgery also have experienced pain resulting from these therapeutic procedures (Grond *et al.*, 1996; Vecht, 2000). Neuropathic pain is caused by a lesion or dysfunction of the peripheral and/or central nervous system (Merskey *et al.*, 1994). It is often severely debilitating and is among the most challenging to treat, being largely resistant to traditional pain therapies (Finnerup *et al.*, 2005; Attal *et al.*, 2006). Large range of etiologies of neuropathic pain has been established (Caraceni *et al.*, 1999; Siddall *et al.*, 2003; Jung *et al.*, 2004; Davies *et al.*, 2006). Of these identified causes of neuropathic pain is cancer chemotherapy that accounts for about 80 % of current cancer treatment regimes. Although the efficacy and usefulness of gabapentin, the 5 % lidocaine patch, opioid analgesics and tricyclic antidepressants (TCAs) has been consistently demonstrated in multiple randomized controlled trials, these drugs still present with untoward side effects limiting their clinical usefulness (Devers *et al.*, 2000; Serpell, 2002; Sindrup *et al.*, 2003). *Palisota hirsute* (Commelinaceae) is a robust West African herb. The whole plant and various parts are used extensively in Ghana and other West African countries for the treatment of various conditions. Heated leaves are applied over the lumbar region for kidney pains or smoked for toothache (Burkill, 1985). The stem sap is also applied for fractures, adenitis and arthritic pains as well as an ointment of the whole plant is used for gunshot wounds and swellings by the Igbos in Nigeria (Burkill, 1985).

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Scientifically, leaf extracts of *P. hirsuta* has been shown to possess significant anti-nociceptive (Woode *et al.*, 2009), anxiolytic and antidepressant (Woode *et al.*, 2010) as well as anti-inflammatory and anti-oxidant effects (Boakye-Gyasi *et al.*, 2011).

Based on its scientifically proven pharmacological effects including its anti-nociceptive and antidepressant effects as well as its use in the management of pain traditionally, this current study seeks to find the effects of *P. hirsute* leaf extract on vincristine-induced neuropathic pain in rats.

MATERIALS AND METHODS

Preparation of Extract

Leaves of *Palisota hirsuta* were collected from uncultivated fields on the campus of Kwame Nkrumah University of Science and Technology, Kumasi, Ghana in October, 2012. The leaves were authenticated by comparing to the voucher specimen (NO FP 10081) at the Department of Herbal Medicine herbarium, KNUST, Kumasi.

The leaves were shade-dried then pulverized with a hammer mill. One kilogram (1 Kg) of the resultant powder was cold macerated in eight litres (8 L) of 70 % (v/v) ethanol for 4 days. The hydroalcoholic extract obtained was evaporated under reduced pressure to a syrupy mass using a rotary evaporator at 60 ^{o}C to yield a dark green semi-solid mass (14.11 % w/w) of *Palisota hirsuta*extract (PHE).

Animals

Male Sprague Dawley rats (190-205 g) were obtained from the Noguchi Memorial Institute for Medical Research, Ghana and housed in the vivarium of Department of Pharmacology, Kwame Nkrumah University of Science and Technology, KNUST. They were housed in stainless steel cages (34 x 47 x 15 cm^3) in groups of six-seven (6-7) animals per cage with soft wood shavings as bedding.

They were fed with normal commercial pellet diet (GAFCO, Tema, Ghana), given water *ad libitum* and maintained under laboratory conditions (temperature 24-25 °C, relative humidity 60-70 %, and 12 h light-dark cycle). All procedures and techniques used in these studies were in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals (NIH Publication No. 85 -23, 1985, revised 1996). All protocols used were approved by the Departmental Ethics Committee.

Drugs and chemicals

Vincristine was obtained from Biochem Pharmaceutical Industries Limited, Mumbai, India and gabapentin from Pfizer, Inc., New York, USA. Vincristine was administered intraperitoneally to the rats and was prepared with normal saline while gabapentin and *P. hirsuta* extract were administered as oral suspensions in 2 % tragacanth.

Induction of neuropathic pain and drug treatment

After habituating the animals to the behavioural testing environment, baseline measurements of pain sensitivity were measured and rats injected intraperitoneally (i.p.)with vincristine 0.1 mg kg^{-1} day^{-1} in two 5-day cycles with a two-day break (days 0-4 and 7-11). This dose produces hyperalgesia with no significant motor deficit. Responses were measured in the Randall-Sellito test, Hargreaves test, Von Frey test (4 g, 8 g and 15 g) and cold allodynia (cold water at 4-5 ° C). Pain sensitivity measurements were taken again on day 11 to establish the presences of hyperalgesia before starting drug treatments. The animals were later put into seven groups (n=6-7) and treated with PHE (30-300 mg kg^{-1} *p.o.*), gabapentin (10-100 mg kg^{-1} *p.o.*) or saline (10 ml kg^{-1}). Post-drug treatment responses were taken at 1, 4, 7, 24, 48 and 72 h.

Evaluation of Neuropathic Pain

Tactile Allodynia and Hyperalgesia using von Frey Filaments

Tactile allodynia and hyperalgesia was assessed using three von Frey filaments (IITC Life Science Inc. Model 2888, Woodland Hills, CA, USA) with bending forces of 4 g (tactile allodynia), 8 g (intermediate hyperalgesia) and 15 g (hyperalgesia). Animals were placed on an elevated wire mesh floor and confined. In ascending order of force, each filament was applied to the mid-plantar area of each hind paw five times, with each application held for 5 s. Withdrawal responses to the von Frey filaments from both hind paws were counted and then expressed as an overall percentage response.

Assessment of Mechanical Hyperalgesia

Mechanical hyperalgesia was measured in the rat paw pressure test (Randall *et al.*, 1957; Stohr *et al.*, 2006) using an analgesimeter (Model No. 15776, Ugo Basile, Comerio, Varese, Italy). The analgesimeter was used to apply a linearly-increasing pressure to the dorsal region of the right hind paw until withdrawal or vocalization. Paw withdrawal thresholds (PWTs) were recorded as the weight (g) required to elicit paw withdrawal or vocalization with 250 g used as cut-off.

Assessment of Thermal Hyperalgesia

Thermal nociception was assessed in the rat hind paw as described by (Hargreaves *et al.*, 1988) to assess thermal nociception. The rats were individually placed into plastic cubicles on top of a glass surface. A thermal stimulus from radiant heat emitted from a focused projector bulb was applied to the tail and triplicate paw withdrawal latency recorded 30 s apart with maximum time exposure set at 25s to limit possible tissue damage.

Assessment of Cold Allodynia

Cold allodynia was assessed by immersing the tail of a rat into a water bath containing cold water (4-5° C), and the latency to tail withdrawal was measured using a digital timer (Na *et al.*, 1994). The maximum cut-off time was limited to 20 s. For

each animal, two recordings were made and data represents the mean of both values.

DATA ANALYSIS

All data are presented as mean ± S.E.M (n=6-7). GraphPad Prism for Windows version 6.0 (GraphPad Software, San Diego, CA, USA) was used for all statistical analyses and ED_{50}determinations. $P< 0.05$ was considered statistically significant. Time-course curves were subjected to two-way (dose × time) repeated measures analysis of variance (ANOVA) with Sidak's *post hoc* test. Total anti allodynic or anti-hyperalgesic effect for each treatment was calculated in arbitrary unit as the area under the curve (AUC).

Differences in total anti allodynic or anti-hyperalgesic effect were analyzed using one-way ANOVA with drug treatment as a between subject factor. When differences are significant further comparisons between vehicle- and drug-treated groups were performed using the Holm-Sidak's*post hoc*test. Dose-response relationships were generated by iterative curve fitting using computer least squares method, with the following nonlinear regression (three parameter logistic) equation

$$Y = \frac{a + (b - a)}{\left(1 + 10^{(LogED_{50} - X)}\right)}$$

Where *X* is the logarithm of dose and *Y* is the response. *Y* starts at *a* (the bottom) and goes to *b* (the top) with a sigmoid shape. The fitted midpoints (ED_{50}s) of the curves were compared statistically using *F* test.

RESULTS

Tactile Allodynia/Hyperalgesia

Intraperitoneal injection of vincristine for ten (10) days produced a marked, prolonged dynamic tactile allodynia in rats as exhibited by normal saline treated rats (fig. 1a, c and e). Oral administration of PHE (30-300 mg kg^{-1} *p.o.*) caused significant ($F_{5,102}$ =50.33, p<0.001) reduction in tactile allodynic response at all doses 1 h post treatment with a complete reversal of allodynic effect occurring at 72 h (Fig 1a). PHE (300 mg kg^{-1}), caused the highest ($F_{3,17}$ =58.72, p<0.001) reduction in tactile allodynic response by 72.863 % (fig. 1b). PHE also completely and significantly ($F_{5,101}$ =33.07, p<0.001) reversed intermediate hyperalgesia (8 g von Frey filament) (Fig 1c) with the highest dose used causing a reduction of 67.792 % ($F_{3,16}$ =41.06, p<0.001) (Fig 1d).

PHE also showed a significant effect ($F_{5,101}$ =55.65, p<0.001) in mechanical hyperalgesia (15 g von Frey filament) induced by vincristine administration (Fig 1e) with the 30 mg kg^{-1} given the highest inhibition of 33.682 % ($F_{3,16}$ =13.06, p=0.001) (Fig 1e). Gabapentin also produced a significant reversal of tactile allodynia ($F_{5,78}$ =47.48, p<0.001), intermediate hyperalgesia ($F_{5,78}$ =45.94, p<0.001)and mechanical hyperalgesia ($F_{5,78}$ =34.17, p<0.001) dose dependently (Fig 1b, d and f). PHE was more potent than gabapentin in ameliorating tactile allodynia but both drugs showed similar efficacies (Table 1and fig. 5).

Table 1: ED50s and Emax values for PHE and gabapentin in the various models used.

Test	*Palisota hirsuta*Extract		Gabapentin	
	ED_{50}	E_{max}	ED_{50}	E_{max}
Tactile allodynia (Von Frey)	1.51 ±0.675	66.97±2.795	0.70 ±0.725	69.9±4.389
Thermal Hyperpalgesia (Hargreaves)	34.63±0.348	60.73±12.21	9.34±0.289	64.86±10.56
Mechanical Hyperalgesia (RandallSellito)	8.35±0.411	44.39±4.787	23.61±0.246	46.22±9.876

Mechanical Hyperalgesia with Randall Selitto

Vincristine administration produced marked reduction in paw withdrawal latency in the Randall-Selitto paw pressure test which persisted over the 72 h study period (fig. 2a and c).

PHE (30-300 mg kg^{-1} *p.o.*) increased significantly and dose dependently paw withdrawal latencies in vincristine-treated animals ($F_{4,85}$ =151.7, p<0.001) (Fig 2a) with the highest dose of 300 mg kg^{-1} producing the maximum anti-hyperalgesic effect of 45.402 % ($F_{3,17}$ =13.490, p<0.001) (Fig 2c).

The administration of gabapentin (10–100 mg kg^{-1}) significantly ($F_{4,60}$= 305.20, *P*<0.001) attenuated mechanical hyperalgesia (Fig.2c) with the highest dose used causing a significant ($F_{3,12}$ =9.497, p=0.002) increase in paw withdrawal latencies (Fig 2d). PHE was more potent than gabapentin in reducing mechanical hyperalgesia but both drugs showed similar efficacies (Table 1 and fig.5).

Thermal Hyperalgesia using the Hargreaves test

Responses to thermal radiation in the Hargreaves test reduced after 10 days of vincristine administration as shown in figures.3a and c. PHE (30-300 mg kg^{-1} *p.o.*), however exhibited significant ($F_{4,85}$ =110.6, p<0.001) anti-hyperalgesic effect after 24 h post treatment (fig. 3a).

The 100 and 300 mg kg^{-1} of PHE caused 51.189 % increase in total anti-hyperalgesic effect compared to control ($F_{3,17}$ =6.670, p=0.003) (fig. 3c). Gabapentin also produced a significant and dose related ($F_{4,60}$ =98.62, p<0.001) (Fig 3 b) increase in anti-hyperalgesic effect with the highest dose of 100 mg kg^{-1} producing a significant ($F_{3,14}$ =4.603, p<0.091) increase of 49.243 % (fig. 3d). PHE was less potent than gabapentin in reducing thermal hyperalgesia (Table 1 and fig 5).

Cold Allodynia

Although vincristine produced a marked cold allodynic effect in all treated rats, both PHE($F_{3,17}$ =2.410, p=0.103) and gabapentin($F_{3,17}$ =1.023, p=0.417) at all doses tested could not ameliorate this allodynic effect (fig. 4a and b).

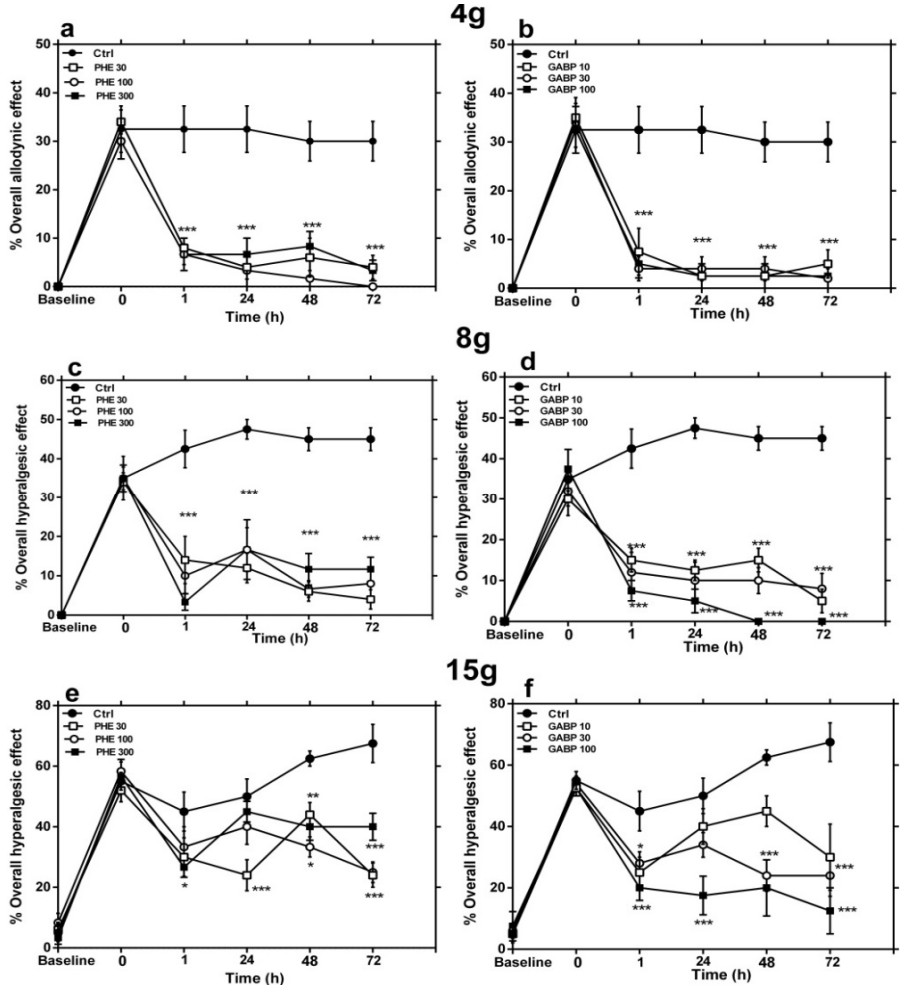

Fig. 1: Effect of PHE (30 -300 mg kg^{-1}) and gabapentin (10-100 mg kg^{-1}) on tactile allodynia (a and b), intermediate hyperalgesia (c and d) and hyperalgesia (e and f) on vincristine–induced neuropathic pain using von Frey filaments 4, 8 and 15 g. Data points are group means (±SEM). Significantly different from control: *P<0.01,**P<0.01, ***P<0.001, by two –way ANOVA followed by Holm-Sidak post hoc test.

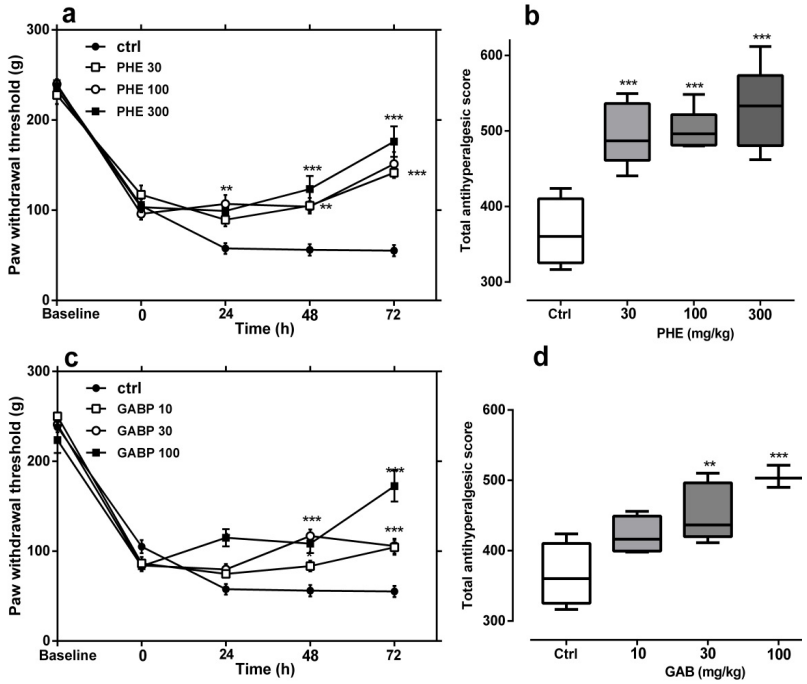

Fig. 2: Effect of PHE (30 -300 mg kg^{-1}) and gabapentin (10-100 mg kg^{-1}) on paw withdrawal threshold (a and c) and total antinociceptive effect (b and d) in the Randall Sellito test for mechanical hyperalgesia **P<0.01, ***P<0.001, by one –way ANOVA followed by Sidak's post hoc test. Box and whisker plot (median with 5-95th percentile) represents total antinociception in 72 h.

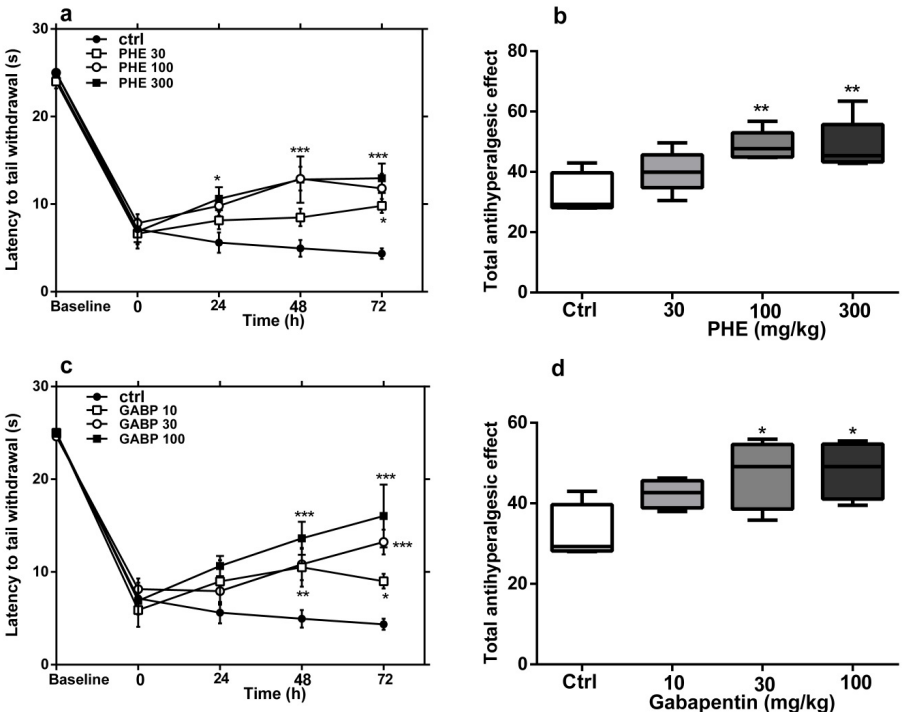

Fig. 3: Effects PHE (30 -300 mg kg-1) and gabapentin (10-100 mg kg-1) on paw withdrawal threshold (a and c) and total antinociceptive effect (b and d) in the Hargreaves test for thermal hyperalgesia **P<0.01, ***P<0.001. One –way ANOVA followed by Sidak's post hoc test. Box and whisker plot (median with 5-95th percentile) represents total antinociception in 72 h.

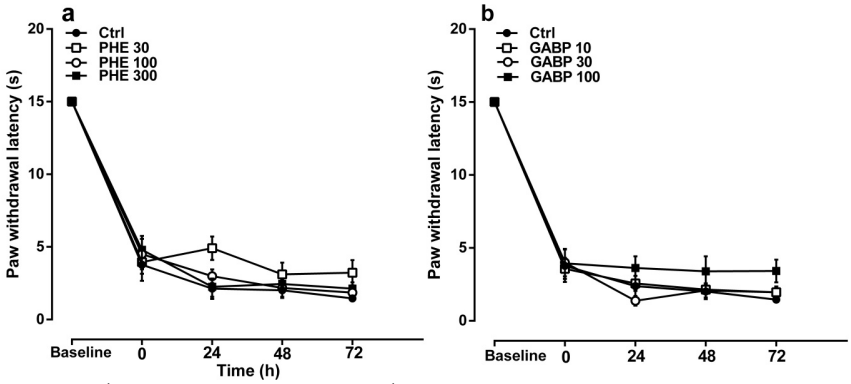

Fig. 4: Effect of PHE (30 -300 mg kg^{-1}) and gabapentin (10-100 mg kg^{-1}) on vincristine–induced cold allodynia. Data points are group means (±SEM). Significantly different from control: *P<0.01,**P<0.01, ***P<0.001, by two –way ANOVA followed by Holm-Sidak post hoc test.

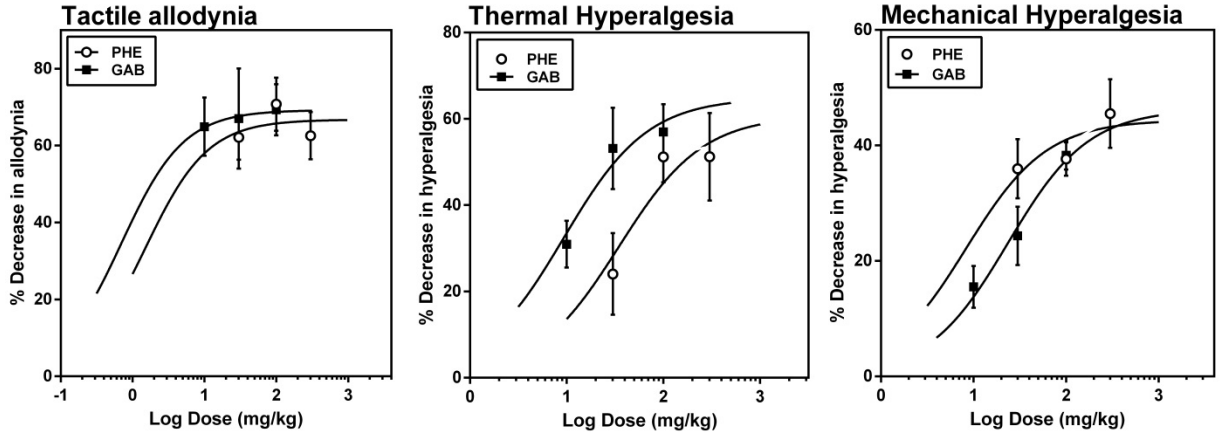

Fig. 5: Dose-response effects of PHE 30-300 mg kg^{-1} and gabapentin 10-100 mg kg^{-1} on vincristine-induced neuropathic pain assessed in different models. Data points represents mean ± SEM of n=6-7 rats.

DISCUSSION

This study has been able to show that oral administration of *P. hirsuta* extract (PHE) has significant anti-hyperalgesic and anti-allodynic effects in neuropathic rats.

The rodent chemotherapy-induced neuropathic pain model has consistently proven valid and useful in investigating agents for the pharmacological attenuation of neuropathic pain (Seltzer, 1995). In consistency with literature, *rats* treated with vincristine 0.1 mg kg^{-1} $day^{-1}$for 10 days developed a reliable thermal and mechanical hyperalgesia and allodynia. (Siau *et al.*, 2006; Muthuraman *et al.*, 2008; Kaur *et al.*, 2010). PHE had significant effects on tactile allodynia, mechanical hyperalgesia and thermal hyperalgesia with less significant effects on cold allodynia.

Both neuroinflammatory and non-inflammatory mechanisms have been identified in the pathogenesis of vincristine-induced neuropathy. Activation of JAK-STAT 3 pathway due to the release of inflammatory cytokines recruited from destruction of Schwann cells and the neurons of the dorsal root ganglion by vincristine has been implicated in the neuroinflammatory pathway. The role of proinflammatory cytokines like TNF-α has been well documented in peripheral as well as central sensitization in neuropathic pain (Leung *et al.*, 2010).

The up-regulation of TNF-α has been detected at the injury site mainly in macrophages and Schwann cells (Wagner *et al.*, 1996; Sommer *et al.*, 1998). Suggested noninflammatory mechanisms involved in vincristine-induced neuropathic pain include alterations in cellular calcium and free radicals levels and drugs modulating calcium and oxidative stress, for example gabapentin, have been shown to attenuate pain related behaviors in vincristine treated *rats* and rats (Muthuraman *et al.*, 2008; Kumar *et al.*, 2010).

In the present study, oral administration of *P. hirsuta* extract (30-300 mg/kg) significantly attenuated vincristine-induced peripheral and central behavioral alterations including tactile allodynia and hyperalgesia as well as mechanical and thermal hyperalgesia. It however showed very little effect in cold allodynia. PHE has been shown to exhibit significant anti-inflammatory and anti- arthritic effects in animal models which was attributed partly to its anti-oxidant effects (Woode *et al.*, 2009; Boakye-Gyasi *et al.*, 2011). Moreover, PHE has also demonstrated significant anti-nociceptive effect which was suggested to be through the activation of the nitric oxide-cyclic GMP-ATP-sensitive potassium channel pathway (Woode *et al.*, 2009). This is however the first report suggesting the ameliorative potential of PHE in vincristine-induced neuropathic pain.

Therefore, PHE mediated neuroprotective effect in neuropathic pain may be attributed to its inhibition effects on cascade of inflammatory and nociceptive reactions in peripheral nerve region. Furthermore, the inhibition of inflammatory and spinal nociceptive processes in dorsal root ganglia and dorsal horn neurons of the spinal cord, set off after peripheral nerve injury, may also be responsible for the observed effects of oral administration of PHE on pain behavior.

Central effects of PHE including its antidepressant and anxiolytic effects (Woode *et al.*, 2010) could also account for its beneficial effects in neuropathic pain since vincristine exposure results in a central sensitization of spinal cord neurons (Weng *et al.*, 2003). In addition several antidepressants including tricyclic antidepressants have been used in the treatment of neuropathic pain (Uhm *et al.*, 1999).

In this study, both PHE and gabapentin did not show any significant activity against cold allodynia. This effect of gabapentin actually confirms what is already in literature that gabapentin is less sensitive to cold allodynia even in relatively high doses (Back *et al.*, 2004). Thus PHE might also be modulating cellular calcium levels just like gabapentin.

CONCLUSIONS

Oral administration of an ethanolic leaf extract of *Palisota hirsuta* attenuates pain-related behavior in vincristine-induced neuropathic pain model.

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