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A pilot study on the efficacy of an *Antiaris toxicaria* subsp. *africana* (Engl.) C.C. Berg based Ghanaian herbal product in the management of peripheral neuropathy

[Estudio piloto sobre la eficacia de un producto herbal de Ghana a base de *Antiaris toxicaria* subsp. *africana* (Engl.) C.C. Berg en el tratamiento de la neuropatía periférica]

Ronald Yeboah[1*], Kwesi P. Thomford[2], Rudolph Mensah[1], Alfred A. Appiah[1], Ama K. Thomford[3], Augustine Ocloo[1]

[1]Centre for Plant Medicine Research, Mampong-Akuapem, Ghana.
[2]Department of Herbal Medicine, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana.
[3]Department of Biomedical Sciences, University of Cape Coast, Cape Coast, Ghana.
*E-mail: royebus@yahoo.com

Abstract

Context: Peripheral neuropathy is a common neurologic disease that accounts for a lot of physician visits.

Aims: To evaluate the efficacy of a Ghanaian herbal product prepared from the stem bark of *Antiaris toxicaria* subsp. *africana* (known as Mist Antiaris) in the management of neurological disorders in patients clinically diagnosed with peripheral neuropathy.

Methods: A prospective open label non-comparative study was undertaken involving 24 patients seen at the clinic of the Centre for Plant Medicine Research, Mampong-Akuapem. A modified Neuropathic Symptoms Score (NSS) and a visual analogue scale (VAS) using the standardized Wong-Baker faces rating scale (WBFRS) were used to grade each participant on the first day of visit. The VAS was subsequently used to grade and monitor improvements in the symptom characteristics of peripheral neuropathy at the fourth week and on the eighth week.

Results: Mean age of participants involved in the study was 46.08 ± 2.77 years with the most significant comorbidity associated with participants being hypertension and type II diabetes, which accounted for 10 (41.66%) of the cases recorded. Baseline NSS indicated that 20 (83.0%) of the participants had severe symptoms and 4 (17.0%) reporting with moderate symptoms of neuropathy. Treatment resulted in an improvement of symptoms with a decline in mean VAS from a baseline of 6.04 ± 0.41 to 3.79 ± 0.74 on day 28 and 2.13 ± 0.93 by day 56.

Conclusions: The results gathered from this pilot study indicates that the product Mist Antiaris has good prospects as an anti-neuropathic medication.

Keywords: *Antiaris africana;* efficacy studies; herbal medicines; neuropathy.

Resumen

Contexto: La neuropatía periférica es una enfermedad neurológica común que representa muchas visitas al médico.

Objetivos: Evaluar la eficacia de un producto herbal de Ghana preparado a partir de la corteza del tallo de *Antiaris toxicaria* subsp. *africana* (conocida como Mist Antiaris) en el tratamiento de trastornos neurológicos en pacientes con diagnóstico clínico de neuropatía periférica.

Métodos: Se realizó un estudio prospectivo, abierto, no comparativo, en el que participaron 24 pacientes atendidos en la clínica del Centro de Investigación de Medicina Vegetal, Mampong-Akuapem. El primer día de la visita se utilizó una puntuación de síntomas neuropáticos modificados (NSS) y una escala analógica visual (VAS) utilizando la escala de calificación de caras de Wong-Baker (WBFRS) estandarizada. Posteriormente, se utilizó el VAS para calificar y monitorear las mejoras en las características de los síntomas de la neuropatía periférica en la cuarta semana y en la octava semana.

Resultados: La edad promedio de los participantes involucrados en el estudio fue de 46,08 ± 2,77 años, con la comorbilidad más significativa asociada con los participantes que fueron hipertensión y diabetes tipo II, que representaron 10 (41,66%) de los casos registrados. El NSS de referencia indicó que 20 (83,0%) de los participantes tenían síntomas graves y 4 (17%) síntomas moderados de neuropatía. El tratamiento resultó en una mejoría de los síntomas con una disminución en el VAS promedio desde un valor inicial de 6,04 ± 0,41 a 3,79 ± 0,74 en el día 28 y 2,13 ± 0,93 en el día 56.

Conclusiones: Los resultados obtenidos de este estudio piloto indican que el producto Mist Antiaris tiene buenas perspectivas como medicamento antineuropático.

Palabras Clave: *Antiaris africana*; estudios de eficacia; hierbas medicinales; neuropatía.

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INTRODUCTION

Peripheral neuropathy is a common neurological problem with a highly variable clinical presentation. This term is generally used to describe any disorder of the peripheral nervous system. The overall prevalence of the condition is about 2400 per 100 000 population (2.4%) in Italy but in people older than 55 years, the prevalence rises to about 8000 per 100 000 (8%) (Martyn and Hughes, 1997).

Peripheral neuropathy is a complication of several different medical conditions with three types of nerves normally involved being the autonomic, motor and sensory nerves (Meijer et al., 2002). Classification of the condition can be based on the number of nerves implicated: mononeuropathies involve only one nerve trunk, multiple mononeuropathies have successive involvement of several nerve trunks and distal polyneuropathies include diffuse, symmetrical involvement of all four limbs. The duration of the symptoms may also be used as with most medical conditions: acute (up to one month), subacute (months), and chronic (years) (Kraychete and Sakata, 2011).

Presenting features of the disease encompass varying combinations of altered sensation (numbness, tingling and burning sensation), pain, muscle weakness or atrophy and autonomic symptoms involving involuntary body functions such as breathing, intestinal function and regulation of blood pressure. Sensory neuropathy involving small fibers can affect patients with diabetes mellitus, leprosy, HIV infection, sarcoidosis, amyloidosis, Tangier disease and Fabry disease. Sensory and autonomic changes are also caused by diseases such as: diabetes mellitus, amyloidosis, paraneoplastic syndrome, Sjögren syndrome, porphyria, HIV infection and demyelinating inflammation (Willison and Winer, 2003). Globally, type II diabetes, alcohol abuse, HIV, chemotherapy and aging account for a substantial number of most clinical cases. The usual sites of affliction are the hands and feet, although peripheral neuropathy can affect other areas of the body (Martyn and Hughes, 1997; Huges, 2002).

There are varied forms of assessing these altered sensations and neuropathic pain. The modified neuropathy symptom score (NSS) and a visual analogue scale (VAS) are two assessment tools widely used. The NSS has been validated clinically for diagnoses of peripheral neuropathy by evaluating the score assigned to a categorized group of symptoms experienced in peripheral neuropathy and the total score noted (Meijer et al., 2002; Edward et al., 2005; Ambreen et al., 2010; Chawla et al., 2013). VAS serves as a measure of a characteristic perception of pain or discomfort believed to range across a continuum of values that cannot easily be measured. This is due to perspective of patients that their discomfort experienced in such condition do not fit into the more traditional categorization of none, mild, moderate and severe. A more patient available type of the VAS known as the Wong-Baker faces rating scale (WBFRS) was developed by Wong and Baker (1988) and similar in the aim of measuring pain/discomfort just like VAS. The scale shows a series of faces ranging from a happy face at 0, "No hurt" to a crying face at 10, "Hurts worst". The patient must choose the face that best describes how they are feeling.

The debilitating and crippling nature of neuropathies call for effective preventative and treatment strategies (Ambreen et al., 2010). The socioeconomic effects of complications such as amputation, the high cost of treatment and low productivity can be a burden to the patient, their families and the society (Brian and Kenneth, 2004). Although there are several conventional treatments available for this condition, questions still exist about their efficacy and safety. The recommended first line treatments: Duloxetine, Gabapentin, Pregabalin and the tricyclic antidepressants, have been reported to be efficacious but with some debilitating side effects (Finnerup et al., 2015). Patients taking Duloxetine for instance will experience at least one side effect, which can include dizziness, headaches, a sense of illness and headaches (Lunn et al., 2014). Other like the tricyclic antidepressants are associated with sedation and an increased risk of falling. The second line (capsaicin, lidocaine and tramadol) and third line (botu-

linum toxin and the opioids) of treatments are also known to cause degeneration of epidermal nerve fibres on long-term use, cognitive impairment, endocrine changes and an increased risk of addiction (Finnerup et al., 2015).

The illustrated challenges with the available conventional treatments bring to fore the pressing need to explore and develop effective forms of treatments for neuropathies. Alternative medicines present great prospects in this regard: vitamin E, glutathione, folate, pyridoxine, biotin, myo-inositol, omega-3 and -6, fatty acids, L-arginine, L-glutamine, taurine, N-acetylcysteine, zinc, magnesium, chromium, St. John's Wort, acupuncture, magnetic therapy and yoga constitute just a few of the options available (Head, 2006). The antioxidant properties of these treatments imply that most offer some neuroprotection against the effect of free radicals, which are key in the development of neuropathy (Bordet and Pruss, 2009; Chi-zi et al., 2013). This property also provides the anti-inflammatory and analgesic effects needed during the prevention and treatment of neuropathy.

Antiaris toxicaria subsp. *africana* is a tree in the mulberry and fig family (Moraceae) that grows to about 15-20 m high and, in some instances, as high as 40 m. The plant is referred to in the local Akan language of Ghana as Kyenkyen. Traditionally, the plant is used for diverse ailments examples of which include syphilis, chest pains, seizures, chronic tremors and mental diseases. Extracts from the stem bark have also been shown to have antioxidant and anticancer properties supporting some of its traditional uses. Other authors have indicated the anti-inflammatory activity of the plant. The relevance of the plant in the management of neurological diseases has also been reported by Mante et al. (2013). This group indicated that *A. toxicaria* increased the latency to seizures as well as reduction in duration and frequency of seizures in rodents indicating an anticonvulsant activity. These biological activities provide a basis for the traditional use of the plant as a neuroprotective agent (Kuete et al., 2009; Moronkola and Faruq, 2013).

The stem bark of *A. toxicaria* has been used for decades at the Centre for Plant Medicine Research (CPMR), Mampong-Akuapem, Ghana for the management of neurological diseases. A decoction of the plant is prepared according to a standardized recipe and dispensed in 330 mL bottles. This product is sold under the tradename Mist Antiaris. Currently, there is no scientific evidence to back the use of the product in the management of peripheral neuropathy and its benefits for patients or otherwise. This pilot study was therefore aimed at assessing the potential clinical benefits of using the herbal product Mist Antiaris in the management of patients diagnosed with peripheral neuropathy.

MATERIAL AND METHODS

Study design

A prospective open label non-comparative study was undertaken involving 24 patients seen at the clinic of the CPMR.

Ethical considerations

The study was approved by the Independent Ethics Committee for Human Research of the Centre for Plant Medicine, Mampong-Akuapem, Ghana (CPM/A.127/7/2016). The protocol used for the study, the consent form and the patient information sheet were reviewed and approved prior to study initiation. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice (WHO, 2001). Written informed consent from every study subject was obtained prior to the trial-related activities after an explanation of the risk and benefits of the study.

Inclusion and exclusion criteria

Inclusion criteria comprised male and female patients between the ages of 20 - 70 years who were be able to complete the informed consent process. Participants were also required to present with any or all the symptoms of peripheral neuropathy such as numbness, tingling, burning sensation, pain, cramps and weakness in the periphery with a total NSS > 3.0. These symptoms should

have been present for at least 12 weeks prior to reporting at the clinic. Exclusion criteria included patients on any orthodox treatments such as the tricyclic antidepressants, benzodiazepines, analgesics, vitamins and other herbal supplements. Individuals with any acute condition, pregnancy and lactating mothers, chronic liver or kidney diseases were also not recruited.

Diagnosis and assessment of peripheral neuropathy

A modified NSS (Meijer et al., 2002; Ambreen et al., 2010) and the VAS using the standardized WBFRS were used to grade each participant on the first day of visit (day 0). The WBFRS was subsequently used to grade and monitor improvements in the characteristic symptoms such as burning sensation, numbness, tingling, fatigue, cramping and aching feelings in the lower extremities at the fourth week (day 28) and at the eighth week (day 56). Demographical data for the participants were also gathered for analysis. The validity, sensitivity, and diagnostic efficacy of the NSS and WBFRS have each been proven and extensively used in clinical practice to assess symptoms of neuropathies and painful neuropathies (Wong and Baker, 1988; Meijer et al., 2002; Ambreen et al., 2010).

Primary end point and definition of clinical effectiveness

Clinical effectiveness of the product was categorized into 3 levels: No Effect, Partially Effective and Clinically Effective. No effect was defined as a WBFRS of > 5.0; Partially Effective when, WBFRS was between 5.0 - 1.0 and Clinically Effective when participants recorded a WBFRS of 0.0 at the end of the study.

Intervention

Participants were assigned to receive 60 mL of Mist Antiaris three times a day during the study period.

Monitoring adverse effects

Surveillance of harms associated with the use of the product was routinely undertaken and it employed the World Health Organization's adverse reaction questionnaire as a guide.

Statistical analysis

Results are presented as mean ± standard deviation (SD) and in percentages where necessary. Inferential statistical analysis was done using a paired *t*-test (GraphPad Prism 5.0 Software, San Diego California USA.). Differences between compared data were considered significant at $p < 0.05$.

RESULTS

Participant demographics

A total of 24 participants were recruited for the study as reported in Table 1. Participants comprised 14 females and 10 males with a mean age of 46.08 ± 2.77 years. Comorbidities related to peripheral neuropathy identified with the participants for the study included hypertension and type II diabetes and were seen in 10 (41.66%) of the participants.

Table 1. Demographical data of participants in the study.

Age [mean (± SD)]	46.08 (± 2.77)
Sex	
Male [n (%)]	10 (42)
Females [n (%)]	14 (58)

Clinical effectiveness of Mist Antiaris

The baseline NSS indicated that 20 (83.0 %) of participants had severe symptoms of neuropathy and 4 (17.0 %) moderate symptoms of neuropathy. The mean of the VAS at the baseline was 6.04 ± 0.41.

A total of 14 participants were seen during the first follow up (day 28). A repetition of the VAS using the WBFRS showed a reduction in the mean

VAS from 6.04 ± 0.41 to 3.79 ± 0.74. The last and final follow up (day 56) had 8 of the participants reporting back. An analysis of their feedback using WBFRS showed a reduction in their mean VAS from 3.79 ± 0.74 to 2.13 ± 0.93. The clinical effect of the product during the study period is summarized in Fig. 1 and Table 2. At the end of the study, only 1 (12.5%) participant reported that he had no change in the final VAS compared to their baseline, while 4 (50%) reported with improvements that could be classified as partial efficacy of the product. Again, 3 (37.5%) participants achieved the primary outcome of clinical effectiveness when their baseline VAS was compared to the final. The percentage of participants falling in the various definition of clinical effectiveness is illustrated in Fig 2.

Table 2. Neuropathic symptom score (NSS) and visual analogue score (VAS) for participants during the study period.

	Baseline	Day 28	Day 56
NSS	7.38 ± 0.97	-	-
VAS	6.04 ± 2.01	3.79 ± 2.78*	2.13 ± 2.64**

Data presented as mean ± SD. *p<0.05 and **p<0.01 compared to the baseline

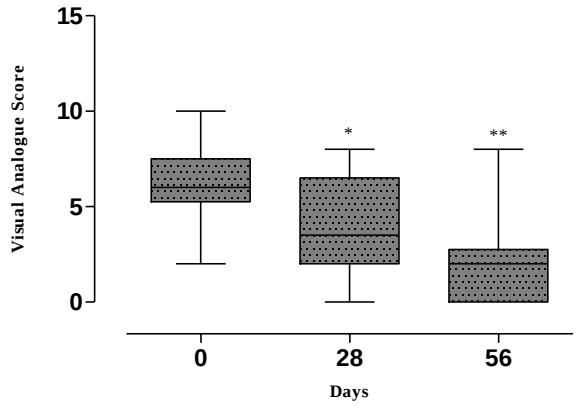

Figure 1. The clinical effect of the herbal medicinal product (Mist Antiaris) using the visual analogue scale (VAS) during the study.

A paired *t*-test indicated a statistical difference between the VAS on day 28 and day 56 compared to the baseline (day 0). *p<0.05 and **p<0.01.

DISCUSSION

The reduction in the quality of life of individuals suffering from neuropathy is of concern. This impact has resulted in numerous individuals resorting to the use of multiple treatments. The choice of treatment comes with some economic burden and a risk to the general health of the individual in cases where treatments are not proven. Although a lot of herbal medicines in Ghana are touted to have some anti-neuropathic actions, most of them remain unverified. As highlighted earlier, the absence of any form of evidence puts the patient at risk. This pilot study was untaken to verify the claim that *Antiaris toxicaria* subsp. *africana* (Engl.) C.C. Berg and a proprietary product prepared from it is clinically useful in the treatment of peripheral neuropathy.

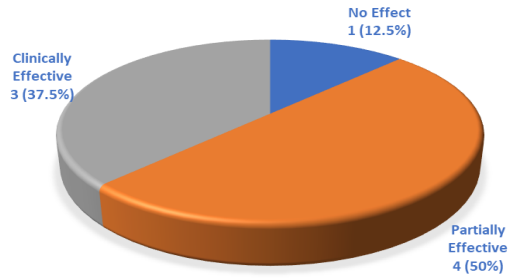

Figure 2. Classification of the effectiveness of *Antiaris toxicaria* subsp. *africana* and its herbal medicinal product (Mist Antiaris) for participants seen at the end of the study (day 56).

The study showed a reversal of neuropathic symptoms in the population treated with the product Mist Antiaris. The mechanism underlying this biological action may be multifactorial just like the processes leading to the development of peripheral neuropathy. One of these mechanisms could be the antioxidant action of *A. toxicaria*. Oxidative stress is considered as one of the pathways in the pathogenesis of the peripheral neuropathy. Here, the enhanced production of reactive oxygen species (ROS) as well as a defect in their clearance is fundamental in the development of the disease. The activity of ROS yield advanced glycosylated end products (AGEs), accumulation of polyol, decreased nitric oxide/impaired endothelial function, impaired Na^+/K^+-ATPase activity and homo-

cysteinemia. The antioxidant effect of *A. toxicaria* has been documented by Kuete and colleagues in an assay of a methanol fraction of the plant and some of its chemical isolates (Kuete et al., 2009; Moronkola and Faruq, 2013).

Apart from the actions of ROS, vascular changes that occur with age is also implicated in the development of peripheral neuropathy. Here, changes in the endothelium of the blood vessels result in diminished blood flow to the peripheral nerves and a resultant decrease in neuronal nitric oxide (NO) synthase and Na^+/K^+-ATPase activity (Gupta et al., 2002). *A. toxicaria* has been indicated as upregulating the actions of (Na^+/K^+)-ATPase in a report that explored the neuroprotective action of the plant in strokes using an *in vivo* model. The plant significantly restored the redox status in strokes and ischemic pathologies evident by improvements in biochemical markers such as: malondialdehyde, reduced glutathione, xanthine oxidase, superoxide dismutase, catalase and glutathione peroxidase, which are implicated in oxidative stress associated with strokes (Ilesanmi et al., 2017). Further confirmation of the neuroprotective actions of *A. toxicaria,* is also provided by Adewunmi and colleagues using an *in vitro* KCN-induced neurotoxicity model (Adewunmi et al., 2018).

A. toxicaria is again reported to ameliorate imbalances in the markers that cause neurochemical disturbances and excitotoxicity. The medicinal plant decreased the actions of myeloperoxidase and glutamine synthase while increasing the activity of Na^+/K^+-ATPase, acetylcholinesterase and tyrosine hydroxylase (Ilesanmi et al., 2017). These biological actions also add on to the evidence for the use of the plant in neurological disorders and in neuroprotection specifically.

Despite the high attrition rate of 16 (66.67 %) participants by the second follow up (day 56), the outcomes recorded at on day 28 indicated the product as having some effect on the decline of the neuropathic symptoms reported by these patients. At day 28 when 14 participants were reviewed, 8 (71.43%) reported a decline in symptoms, 3 (21.43 %) reported there was no change and 1 (7.14 %) participant reported of an increase in symptoms. On day 56, a total of 8 participants reported for the follow up with 3 (37.5 %) indicating some decline in neuropathic symptoms and 5 (62.5 %) reporting there was no change compared to day 28. The participant who had an increase at day 28 reported of a decline when followed up at day 56. The pattern of recovery seen in the study also gives an indication that the product used in this study may require at least two months of treatment for measurable clinical effects to be observed.

In terms of safety, the herbal product Mist Antiaris was well tolerated as none of the participants reported of any adverse effects. This product can thus be suggested as an alternative or a complement to current conventional treatments since patients continue to raise concerns about their cost and potential side effects.

CONCLUSIONS

This pilot study highlights the beneficial role *Antiaris toxicaria* subsp. *africana* can play in the management of peripheral neuropathy. The added advantage of cost and the safety given how well the participants tolerated the product goes to emphasize this point. However, an expanded and a more rigorous study will be need if the product is to be adopted for widespread use. The Ghanaian herbal product Mist Antiaris may therefore hold some good prospects for use as a neuroprotective agent.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION:

Contribution	Yeboah R	Thomford KP	Mensah R	Appiah AA	Thomford AK	Ocloo A
Concepts or ideas	x	x			x	
Design	x	x			x	
Definition of intellectual content	x	x	x	x	x	x
Literature search	x	x	x			
Clinical studies	x	x	x		x	
Data acquisition	x		x			
Data analysis	x	x			x	
Statistical analysis	x	x			x	
Manuscript preparation	x	x		x	x	
Manuscript editing	x	x		x	x	x
Manuscript review	x	x	x	x	x	x

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