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(CASE REPORT)

AMELIORATION OF GABAPENTIN-RESISTANT NECK RADICULOPATHY PAIN WITH *S. AROMATICUM* & *A. COMOSUS* WATER DECOCTIONS – A CASE REPORT AND MINI LITERATURE REVIEW

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ABSTRACT

Background: Gabapentin is listed as a first liner for neuropathic pain. However, the drug is subject to frequent discontinuation on account of therapeutic ineffectiveness and/or severe/intolerable adverse drug reactions. This study is a report on a 50-plus years postmenopausal woman with acute-on-chronic cervical radiculopathy pain.

Methodology: Oral and written narrations obtained from the client were captured into this report. Internet literature search was undertaken using relevant search terms related to gabapentin, gabapentinoids, neuropathy, analgesia, phytotherapy, etc. Abstracts of peer-reviewed manuscripts were perused and those found relevant were included in the final writeup.

Results: A full case report was obtained and transcribed largely unedited. 127 peer-reviewed journal articles were selected from over 2000 publications initially included in our search. Abstracts of these were read through, their conclusions extracted and included in the final writeup.

Discussion/Conclusion: Gabapentin was discontinued in this client due to its failure to relieve the pain and its severity of adverse drug reactions. Evidence indicates discontinuation is frequent with gabapentin. Administration of combined water decoctions of *Sizygium aromaticum* (*S. aromaticum*) flower and *Ananas comosus* (*A. comosus*) peel/crown extracts ameliorated the cervical pain and restored client's function within days. Healing has been sustained for months now, without significant adverse effects so far – despite use of the herbal decoctions once in while. The observed analgesic/anti-inflammatory efficacy of the herbal decoctions may be due to their multi-target therapeutic properties compared to gabapentin's single-target action. There is a need to investigate the cost-effectiveness of continued use of gabapentin as analgesic agent, and to further research/develop *S. aromaticum* & *A. comosus* extracts for wider analgesic usage.

Keywords: Discontinuation Syndrome, Clove Flower Bud, Pineapple Peel/Crown, Spondylosis

1 INTRODUCTION

Gabapentin is a non-proteinogenic (synthetic) structural analogue of gamma-aminobutyric acid (GABA)(1). It belongs to the gabapentinoid class of drugs – along with pregabalin, mirogabalin, crisugabalin (HSK16149), phenibut (β-phenyl-γ-aminobutyric acid) and gabapentin enacarbil (gabapentin prodrug). This class of drugs attains clinical anxiolysis, analgesia and anti-epileptogenesis not through their interactions with the GABA receptors, despite their structural similarities, but through a different protein, the alpha-2-delta-1 ($\alpha_2\delta$-1) subunit of the central nervous system (CNS) voltage-gated calcium channels(2–4). This attenuative modulatory action of gabapentinoids on these channels is said to lead to reduced presynaptic nerve terminal calcium influx, which in turn results in diminished excitatory (noradrenaline, glutamate and substance P) neurotransmission(5,6).

Although gabapentin was developed in 1993 and recommended as a specific adjunctive anticonvulsant in the treatment of partial seizures in adults, the scope of its and its derivatives' uses was subsequently expanded to include the following regulatory agencies-approved and 'off-label' clinical indications(7). These include adjunctive role in the treatment of partial onset simple or complex seizures whether in ≥ year-old children or adults, first-line treatment of restless leg syndrome (particularly, gabapentin enacarbil), uremic pruritus, benzodiazepines-alternative treatments in the management of mild-to-moderate alcohol withdrawal and dependence symptoms. Additional clinical uses include being reserve/alternative medications for generalized (GAD) and social (SAD) anxiety disorder patients that are either resistant/unresponsive to or intolerant of selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenalin reuptake inhibitors (SNRIs) (8–13). Yet, other current clinical uses of gabapentin and derivatives are as first-line analgesics for post-herpetic and diabetic peripheral neuropathies, mild-to-moderate effective therapies in brain/spinal cord injury-linked spastic neuropathy, fibromyalgia, low back pain, sciatica and postoperative pain(2,3,14,15).

The unique efficacy of gabapentin and other gabapentinoids in CNS/spinal cord injuries-related neuralgia/neuropathies, which have been hitherto a therapeutic challenge to the usual first-line analgesics such as non-steroidal anti-inflammatory (NSAIDs) and opioid drugs, is viewed to derive from their unique analgesic mechanism of being potent inhibitors of presynaptic nerve terminal calcium channels alpha-2 delta-1 ($\alpha_2\delta$-1) subunits (16–18). These subunits which are essential excitatory mediators of nerve pain have been shown to be upregulated in the spinal cord dorsal horn in the earlier mentioned pathologic conditions, and their inhibition by gabapentin and related compounds result in attenuated presynaptic nerve terminal calcium influx and pain signalling (2–4).

Despite their usefulness in these indications, public concerns have always been raised over multi-systemic potentially serious adverse drug reactions associated with the use of the gabapentinoids, particularly gabapentin (19–21). Adversities/toxicities arising from this class of drugs, expectedly are viewed to be due to both their mechanism(s) of drug action and peculiar pharmacokinetic property (22,23). The mechanistic inhibition of the presynaptic calcium channel $\alpha_2\delta$-1subunits and the attendant suppression of the CNS excitatory neurotransmission are thought to increase the risk of emesis dysregulation – leading to nausea/vomiting, and CNS perturbations – resulting in gait disturbances, altered consciousness and perception, respiratory depression, cognitive and visual defects, etc, on one hand (24–26). On the other hand, the saturable nature of the L-amino acid transporter-based gastrointestinal gabapentin absorption makes its absorption limited. This results in decreasing proportion of administered gabapentin absorbed, thereby raising gastrointestinal toxicity risk as drug doses are increased (23,27). Additionally, the presence of the L-amino acid transporter-based active blood-brain barrier gabapentin transfer, the absence of protein binding and of hepatic metabolism of gabapentin indicates administered gabapentin is 100% biologically active and exclusively (i.e., 100%) excreted unchanged via the kidneys. The former pharmacokinetic factors raise its systemic toxicity risk (25,27) while the latter factor raises a concern when there is impaired patient's renal function (28).

It is the sheer severity and multiplicity of gabapentin's adverse effects in this client, serious enough for her to discontinue the drug in the face of little or nil analgesic relief, that has prompted this report. It is hoped that this case report will serve as a pharmacovigilance report on gabapentin commercial brands available in our environment (Abuja, Federal Capital Territory, Nigeria) where randomised controlled trials on such medications are hard to come by. This report may also trigger appropriate conversation on the cost-effectiveness of gabapentin as a neuropathy analgesic on one hand and on the timeliness of greater role for phytotherapy in pain management.

2 METHODOLOGY

For the case report component of this study, oral narration on the client's personal, clinical and treatment history was recorded verbatim. Full client consent obtained following her assurance of confidentiality/anonymity. The literature review component of the study was executed by searching Google, Google scholars, PubMed, and Scopus search engines for peer-reviewed publications on topics relevant to gabapentin/gabapentinoids, their clinical uses, dosages and formulations, mechanism(s) of action vis-a-vis their therapeutic efficacy, scope and adverse drug reactions, their discovery and evolution, etc. The different combinations of key words used in surfing the internet include but not

limited to phrases like 'gabapentin chemical clarification', 'the gabapentinoid definition', 'gabapentin/gabapentinoid clinical uses,' gabapentin/gabapentinoid mechanism(s) of analgesic action,' 'gabapentin/gabapentnoid adverse drug reactions.' Specific prompts such as 'what chemical class is gabapentin', 'historical perspectives of gabapentin', 'how did gabapentin become an analgesic drug', 'what are the clinical indications of gabapentin/gabapentinoids', what are the intrinsic factors of gabapentin/gabapentinoids responsible for its/their efficacy in neuralgias/neuropathies', 'what are the reported adverse drug reactions/effects of gabapentin/gabapentinoids', 'studies on gabapentin/gabapentinoid therapy discontinuation' were used to pull relevant information from the internet. About 2300 publications originally obtained from the internet search were filtered to 127 peer-reviewed journal articles. Abstracts of these were read and conclusions extracted and included in this writeup.

3 CASE REPORT

This client is a 53-year old Nigerian woman with an insidious onset of recurrent neck pain. The pain was said to be mild to moderate and limited to the back of neck for the first 3 weeks of pain onset and was fairly well managed by the client herself with on-the-counter acetaminophen brands and a non-steroidal anti-inflammatory drug (NSAID) diclofenac for the first 3 weeks. But, towards the end of the third week, the neck pain aggravated, became continuous and started radiating down both arms. About this time the mild analgesics were perceived to no longer provide adequate respite. At this point, proper medical consultation was sought and a clinical diagnosis of cervical spondylosis with radiculopathy was made. Significantly, client denied any history of significant trauma to her neck, back or upper body; denied any personal or family diabetics mellitus or chronic arthritis history; nor was there any known drug allergy history prior to onset of neck pain. However, she has had medications-controlled mild-to-moderate fluctuating blood pressure (130-150/80-95 mm Hg) for some years now and a surgical ovariectomy a few years previously. She further narrated her menopausal symptoms started shortly following her surgery-induced hypogonadism.

Her main complaints were pains which started at the posterior aspect of her neck and upper chest. The pains which were mild to moderate in severity and intermittent in nature at the onset later became severe and excruciating in nature. They radiated only to the arms initially but later spread downwards to involve the whole lengths of both forearms, including the wrists and fingers. At her first medical consultation, she was placed on oral gabapentin 150 mg thrice a day for the first one week. Shortly after the commencement of this treatment, client claimed she started experiencing nausea, gastrointestinal upset, blurring of vision, dizziness and lightheadedness. Treatment was however continued with the anticipation that the adverse drug reactions would wane out with time. Despite these adverse effects and due to worsening pains, gabapentin dose was increased to 300 mg thrice daily for another 2 weeks. Yet the pains did not abate but instead worsened and were now associated with emergence of bizarre multiple dreams, somnolence, extreme fatigue and weakness of upper limb muscles. This was in addition to worsening of the existing adverse drug reactions. At this stage, due to these adversities, the client submitted that she could hardly perform her routine domestic and official duties as attempts to move about were often met with aggravation of her general body aches, malaise, dizziness and extreme fatigue.

Perhaps to mitigate gabapentin adversities and enhance efficacy, the pain medication was changed to a combination drug Biopentin tablet, consisting of 400 mg gabapentin and 10 mg nortriptyline to be taken thrice daily. Following ten (10) days of treatment with this gabapentin combination, the client observed pains still did improve but rather the existing adverse drug reactions were aggravated and additionally, new side effects comprising palpitations and irregular heartbeats emerged. Subsequently, neurotrophic supplements made up of Nucleo CMP (2 tablets daily), Renerve plus (2 tablets daily), and Sirdalud (2 mg nocte daily), were serially added to the gabapentin-based regimes. The addition of these drugs, however, neither ameliorated the neck pains nor the gabapentin-induced adverse side effects.

This therapeutic scenario led to the consideration of an urgent cervical spinal surgical intervention. However, the client said she declined this advice, but instead decided to discontinue the gabapentin medications, opting for herbal treatment options. She further said the alternative herbal treatment consisted of repeated oral administrations of hygienically prepared water decoctions of clove (*S.aromaticum*) flower and pineapple (*A. comosus*) peel and crown. Clove decoction was prepared by macerting a teaspoonful of its fine powder in 2.0 – 2.5 L of drinking water that was allowed to undergo gradual decoction at room temperature overnight. The resulting decoction was taken orally over the next 24 hours while a fresh one to be ready at the end of the same period was being prepared. The pineapple parts decoction was prepared by boiling briefly washed crown and peels of an average sized fruit, blended and boiled together in about 2 litres of water for about 15-20 minutes. The cooled pineapple mixture was sieved, the resulting decoction was refrigerated at -4 degrees Celsius, and a glass cupful (250-300 ml) was taken orally three times daily. This way the clove-pineapple parts water decoctions were orally used by the client religiously for about three weeks following the commencement of their use and sparingly thereafter. Our client asserted she started feeling relieved of the neck pain within hours, felt almost both pain and gabapentin-linked adversities free, and resumed her routine shores within 2-3

days of commencing the use of this herbal combination therapy. So far, our client claimed she has been largely pains and adverse effects free for about 7-8 months following the commencement of the herbal treatment.

4 DISCUSSION

This study is yet another report highlighting not just the unimpressive gabapentin's toxicity and efficacy profile but also the often rescuing role of phytotherapy in difficult-to-treat or chronic clinical diagnoses. It also draws attention to the need for greater scrutiny of the risk-benefit profile of gabapentin (or any gabapentinoid, for that matter) on one hand and the adoption of unbiased/equal openness/readiness to appropriately deploy orthodox or alternative therapies in the management of clinical diagnoses. As clearly demonstrated in this report, this approach is likely to be beneficial to all stakeholders: it may reduce patients' sufferings, spending and toxicity risk exposure, may shorten treatment time spent on clients by caregivers, and overall, may save health care delivery systems unnecessary funding.

Discontinuation of gabapentin use on account of intolerable or severe adverse drug reactions is common in clinical occurrence (29,30). Previously, in more than 10% of gabapentinoid, including gabapentin, prescriptions for general clinical uses(23); up to nearly 19% oral gabapentin prescriptions for postherpetic neuralgia(31), and up to 85% of gabapentin – particularly - or pregabalin, prescribed for chronic pain had to be discontinued on account of one or more intolerable adverse effects. It is to be noted that in the latter case, the study also indicated the observed lack of proven efficacy of gabapentin or the other gabapentinoid significantly contributed to drug discontinuance by usersClick or tap here to enter text.. For instance, previously gabapentin use has been reported discontinued due to repeated emergence of severe myoclonus with its use (33).

Studies indicate somnolence, fatigue, gait disorders (ataxia) and dizziness are among the most frequent adverse effects of gabapentin administration for both acute or chronic on-/off-label indications and the most frequent causes of its discontinuation in most instances (34–36). As hinted earlier, these and other gabapentin/gabapentinoid adversities are viewed to be due to CNS excitatory neurotransmitters downregulation and attendant CNS depression resulting from the binding interaction of its/their molecules with the alpha-2 delta-1(α2δ-1) auxiliary subunit of voltage-gated calcium channels (24–26,37).

That these same sets of gabapentin-induced adversities were manifested early during its use, even at moderately low 450 – 900 mg divided daily doses by the client of this report, despite attempts to ameliorate them by adding some supplements and other drugs to the gabapentin regimes only goes to highlight the low CNS tolerability of gabapentin. Biopentin NT nocte – a combination of 400 mg of gabapentin with 10 mg of nortriptyline – was the first of the adjunctive drugs administered her to improve efficacy and/or to help her cope with gabapentin toxicity. However, her clinical status worsened, with drowsiness, somnolence, fatigue, blurring of vision and dreaminess being the most impacted adversities. This largely agrees with a previous report in which weight gain, blurring of vision, gait imbalance, dizziness, somnolence and pedal oedema were found with gabapentin use (23). Nortriptyline is a tricyclic antidepressant (TCA) indicated for neuropathic pains – often as an adjunct (38). Nortriptyline toxicities include somnolence, drowsiness, tinnitus, dizziness, etc., weight gain, blurred vision and cardiovascular toxicity arising from its cardiac sodium and potassium ions-blocking, chronotropic and vascular alpha-1 blocking actions (31,35,39). The summation of effect potentially from combining nortriptyline with gabapentin may explain the worsened CNS depressant effects as reported by/in this client. The consciousness of this possibility and the potential adverse cardiac events that could result from nortriptyline in a radiculopathy pain-induced insomniac should be/have been a disincentive to prescribing this combination medicine in this case.

Nucleo CMP Forte is a nucleotide-based medication made up mainly of cytidine-5'-monophosphate (CMP) plus uridine-5'-triphosphate (UTP), uridine-5'-diphosphate (UDP), and uridine-5'-monophosphate (UMP) (40). This regulated drug has been shown effective in diabetic neuropathy, alcoholic neuropathy, carpal tunnel syndrome, lumbosacral sciatica, trigeminal neuralgia and potentially in glutamate-induced traumatic brain cell injuries (40–42). Its efficacy in these peripheral neurological disorders is linked to its capacity to generate endogenous cytidine and uridine phosphate required for the synthesis of neuronal as sphingomyelin, phosphatidylcholine and phosphatidylethanolamine – and neuronal sheath regeneration (40,43). However, this client's radiculopathy pains were not ameliorated even with the addition of nucleo CMP Forte to her analgesic medications. Rather, previous reports indicate its concurrent use with gabapentin is associated with increased hyperglycaemia risk (42).

Renerve plus is an oral nutritional supplement composed of folic Acid (1.5 mg) (44), methylcobalamin (i.e., the active, bioavailable form of Vitamin B12) (1500 mcg) (45), alpha lipoic Acid (200 mg) (46) and inositol (100 mg) (47). It also contains zinc monomethionine (25 mg) (48), selenomethionine (55 mcg) (49), and chromium polynicotinate (200 mcg) (50,51). Renerve plus adjunctive therapeutic role in diabetic neuropathy and peripheral neuropathy is viewed to derive from the antioxidant and nerve-regenerative activity of these vitamins and minerals (44,45,47,48,52,53). However, in

this case there was no remarkable relief from the sharp pains even upon adding this otherwise highly effective composite supplement to the gabapentin-based analgesic regime.

Sirdalud, a brand of tizanidine, is a centrally acting alpha (α)-2 adrenergic agonist that is primarily prescribed to alleviate muscular spasticity but now increasingly used for off-label neuropathic pain treatment (54,55). It is thought to mitigate hyperalgesia and neuroinflammation in neuropathies by its overall inhibitory effect on the excitatory neurotransmission, and on the glutamate/aspartate and pro-inflammatory cytokine (i.e., IL-1β, IL-6, and TNF-α) turnover in the spinal cord dorsal horn. Research shows these effects are mediated via tizanidine downregulation of the toll-like receptor 4 (TLR4) and nuclear factor-κB (NF-κB) signalling (56).

The anticipated analgesia of tablet sirdalud (2 mg nocte) for its indication in the case under review was not met and must have been offset by the emergence of mouth dryness, daytime sedation/drowsiness, light-headedness, severe hypotension and dizzy spells. These effects, which have been shown to be amongst the most frequent adversities associated with tizanidine use and most of which are shared with gabapentin (57–60), must have additively worsened her clinical course, thereby leading to her decision to discontinue gabapentin and opting for herbal therapy instead.

Phytotherapy (herbal therapy), the use of medicinal plants and plant parts for the treatments of diseases and disorders, has come a long way in human evolution. The plant kingdom has been a veritable source of several clinically relevant therapeutic agents such as paclitaxel, vincristine (anticancer), digoxin (cardiovascular), aspirin (analgesic/anti-inflammatory/cardiovascular), atropine (anticholinergic autonomic), morphine (analgesic), capsaicin (analgesic/cardiovascular), artemisinin (antimalarial) and berberine (antimicrobial) (61–67).

Herbal medicines or plant-based natural products are generally perceived more effective than synthetic medicines for the prevention/management of chronic diseases because of the following factors (68,69). They are believed to be less toxic than their synthetic counterparts because their molecules having accumulated within living cells overtime have come to possess structures similar to those of biomolecules of human cells – making them to be better positioned to support, stimulate and to holistically restore deranged human physiologic systems compared to the synthetic drugs designed to act only on single/specific biologic systems (70–72). Additionally, by their possession of rich bioactive constituents (e.g., flavonoids, terpenoids, polyphenols, alkaloids, etc.) which act synergistically together to produce superior efficacy even at lower functional doses of their individual phytochemical constituents compared to synthetics that typically possess only one active pharmaceutical ingredient designed for a specific pharmacological/biological target that may result in suboptimal efficacy (72–74). Arising from the foregoing, the single-molecule-single-target design and pharmacodynamics of synthetic drugs make them not well-suited for the treatment of complex, multi-receptor/facetted disorders, e.g., dementias, which require multi-prong, multisystemic therapeutic approach afforded by the multi-target nature of herbal medicines due to their possession of multiple macromolecules (73,74).

These positive efficacy and safety profiles of plant-based natural products were demonstrated by the water decoctions of *S. aromaticum* (clove) and *A. comosus* (pineapple) fruit crown/peel of this report. Their analgesic/inflammatory ameliorative effects were noticeable within 48 hours by the client – with almost full functional recovery and disappearance of symptoms of body parts observed within one week of their administration. Meanwhile, according to the client, there has not been any remarkable adverse effects associated with these combination herbal decoctions since commence of use up till the writing of this report.

The first of the two medicinal plants under review, *S. aromaticum* (clove), (synonyms: *C. aromaticus* L., *E. aromatica* (L.) Baill., *E. caryophyllata* Thunb., *E. caryophyllus* (Spreng.) Bullock & S.G.Harrison and *J. caryophyllus* (Thunb.) Nied.), of the Myrtaceae family, is an aromatic, tropical 5-21 meters tall evergreen tree. This plant that is native to Indonesia is identified by its reddish-brown flower buds that are widely used as a spice and by clove-smelling shining leaves (75,76).

Extracts and decoctions of *S. aromaticum* have been traditionally deployed in many world's cultures as a carminative agent effective for the treatment of flatulence, emesis, and gastrointestinal infections (75,77). Its products have also been indigenously used as food preservatives, cough expectorant and as topical ointments to relieve joint, musculoskeletal and burns pains, as well as oral/dental analgesic, anaesthetic, and local antimicrobial remedies in several parts of Southeast Asia, the Middle East, and the Americas (75,78,79).

Important biological/pharmacological activities Numerous pharmacological activities of *S. aromaticum* extracts include antihyperlipidemic, antioxidant, antimicrobial, anti-hyperglycaemic, anticancer, cytotoxic, neuroprotective, anti-inflammatory, anaesthetic, antinociceptive and analgesic effects (77,79–85). Clove extracts are believed to be generally safe when used in small doses as in this client, even following her clove water decoction use for months. However, administration of moderate to large doses different extract of clove may be associated with hepatoxicity, skin/mouth irritation, seizures, blood dyscrasias, acute hypoglycaemia and respiratory distress (86–90).

Since it is *S. aromaticum*'s analgesic/antinociceptive and anti-inflammatory properties that are relevant to the subject of this report, even though this spicy medicinal plant part has been shown to possess rich presence of phytochemical molecules and metabolites within its essential oil reported for diverse pharmacological activities, this discourse will be restricted to only those chemical constituents responsible for analgesic and anti-inflammatory actions and their mechanism(s) underlying such (78).

The first, and most abundant clove's phytoconstituent, eugenol, or 4-Allyl-2-methoxyphenol, is a volatile bioactive phenylpropanoid, constituting 70-90% of clove's essential oil. Eugenol's phytotherapeutic application has gained significant traction due to its multi-target mechanisms. One, eugenol exerts a direct analgesic/antinociceptive/anaesthetics-like action that is largely mediated via the inhibition of voltage-gated sodium channels and the modulation of transient receptor potential vanilloid 1 (TRPV1) channels. Two, it also attains analgesia indirectly via its potent anti-inflammatory actions by inhibiting the cyclooxygenase-2 and lipoxygenase enzymatic pathways, thus inhibiting synthesis of pro-inflammatory prostaglandins and leukotrienes. Additional indirect analgesic mechanism of eugenol is via downregulating the production of pro-inflammatory cytokines such as tumour necrosis factor (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) (82,91–95).

The second most abundant bioactive factor in *Sizygium aromaticum*, β-Caryophyllene, is a bicyclic sesquiterpene constituting about 5–20% of the essential oil (91,92).

Anti-inflammatory, antioxidant and peripheral analgesic effects of β-Caryophyllene have been shown to be due to its selective full agonist action on and activation of the peripheral cannabinoid type 2 (CB2) receptors. Notably, these effects are achieved with no attendant psychoactive effects from this phytochemical (96–98).

The next most abundant clove's compound is eugenyl acetate (acetyl eugenol) which may constitute up to 10% of the essential oil. This compound is viewed to contribute to the overall anti-inflammatory, spasmolytic and analgesic effects obtainable from clove by its synergistic action with eugenol, its main essential oil (97,98).

Alpha (α)-humulene (α-caryophyllene) is a monocyclic sesquiterpene that has also been identified in smaller quantities in clove. Its indirect analgesia is attributable to its strong anti-inflammatory effects via prevention of the systemic production of pro-inflammatory cytokines as well as inhibition of the activation of the nuclear factor kappa B (NF-κB) intracellular signalling (82,99,100).

In addition to the volatile phytochemicals, some secondary non-volatile constituents, mainly phenolics and flavonoids, identified in *S.aromaticum* have also been shown to contribute to the clove's overall anti-inflammatory and analgesic effects (101).

Some key mechanisms by which clove flavonoids e.g., quercetin, kaempferol and rhamnetin exert anti-inflammation are by facilitating reduction in the expression of proinflammatory cytokines like TNF-α, interleukin-6 (IL-6) and interleukin-1β (IL-1β), exerting potent antioxidant action via reactive oxygen species (ROS) scavenging and preventing intracellular superoxide, peroxyl, and hydroxyl radicals (ROS) accumulation that can trigger inflammatory cascades and their cellular consequences, including the activation of nuclear factor kappa B (NF-κB) and cellular membrane lipid peroxidation (102–104).

Some aspects of anti-inflammatory activity of Kaempferol and quercetin have been shown to be due to inhibition of cyclooxygenase (COX) and lipoxygenase (LOX), responsible for producing inflammatory mediators (prostaglandins, leukotrienes, histamine, etc.) (104–106).

- Additional minor anti-inflammatory mechanisms of clove-derived flavonoid quercetin,
- Kaempferol and/or rhamnetin include inhibition of chronic inflammation-induced
- fibrosis by limiting extracellular matrix protein deposition; chelation of free metals like
- iron and free thereby limiting free radical generation; and blockade of the NF-κB
- pathway – a factor regulating inflammation via the expression of pro-inflammatory
- cytokines, inducible nitric oxide synthetase and vascular adhesive molecule (103,107,108)

Research indicates clove-derived phenols in much smaller quantities compared to eugenol, mainly phenolic acids (caffeic acid, gallic acid, ellagic acid, ferulic acid, & salicylic acid derivatives) also exhibit both direct and indirect contribution to the overall analgesic/inflammatory effects from this spicy medicinal plant. The direct analgesic/anti-inflammatory/antipyretic effects are attributable to the structural and pharmacodynamic similarities between clove-derived salicylic acid derivatives and the acetylsalicylic acid (aspirin) of the non-steroidal anti-inflammatory drugs, leading to anti-inflammation. Their indirect anti-inflammatory/analgesic activity is achieved via a couple of biologic pathways. These include reduction/blockade of expression of pro-inflammatory genes and their potent cellular free-

radical scavenging and antioxidant effect through intrinsic ability of phenolic acids to readily donate hydrogen atoms from their hydroxyl groups to neutralize reactive oxygen and nitrogen species and inhibiting membrane lipid peroxidation (77,91,99).

The various direct and indirect analgesic/anti-inflammatory properties of Syzigium aromaticum may well explain its ameliorative effectiveness in the radiculopathy pains being reported in this study as well as in neuropathic pains generally.

The other component of the two-part herbal decoction remedy of this report is *Ananas comosus* (pineapple) peel and crown. *Ananas comosus* L. Merr., commonly called pineapple, is a fruity, edible herbaceous perennial monocot in the Bromeliaceae family, cultivated in in most tropical regions of the world (109).

Almost every part of the pineapple fruit is known to serve one or more nutritional, industrial and/or medicinal purposes. For ages the peel and crown of this highly fleshy have been anecdotally credited with efficacy across several disease spectra. Extracts and decoctions from these pineapple parts have been effective in traditional treatment of hypercholesterolaemia, hypertension, parasitic infections – including malaria and salmonellosis, arthritis, wounds and skin ulcer and indigestion (109–111).

Among their reported pharmacological activities are anti-diarrheal, pro-digestive, immunomodulatory, hepatoprotective, antidiabetic, wound-healing, antimalarial, anticancer, neuroprotective, antioxidant, antihypertensive, antilipidaemic, antimicrobial, anti-nociceptive and anti-inflammatory (111–114).

These biologic activities are viewed to be due to presence of vitamins, minerals, bromelain – a complex mix of therapeutic enzymes (thiol (cysteine) proteases) and potent secondary metabolites such as flavonoids, saponins, alkaloids, cardiac glycoside, phenolic compounds including ferulic, gallic, and rosmarinic acids- which together exert additive antioxidant effects on biologic systems. The vitamins contained in pineapple include Vit. C (ascorbic acid) and citric acid. Minerals include as calcium, potassium, and magnesium (112,113,115). Again, A. Comosus fruit peel/crown extracts are regarded as generally safe, however, intake of extra large amounts of extracts of this nutritional/medicinal plant parts may be associated with skin allergies/rashes, gastrointestinal upset, mouth irritation and bleeding disorders (115).

Analgesia from *A. comosus* peel and crown extracts have been shown to be due to direct and indirect bromelain-related biologic activities. Reports indicate bromelain's direct analgesic effect are derived from its kinin-kallikrein system-linked modulation on peripheral as opposed to central nociception by its enzymatic breakdown of pro-hyperalgesia substrates, kininogens. kininogens that are normally mobilised to sites of injuries are lysed by bromelain proteases, thus with kininogens depleted, bradykinin, a potent peptide that is a direct stimulator and sensitiser of primary afferent A-delta (A-δ) and C nociceptive fibres cannot be generated - ultimately resulting in a direct halting/dampening of centrally directed peripheral pain neurotransmission (116–118).

Indirect analgesic mechanisms of pineapple bromelain are viewed to result from nerve compression mechanical relief caused by bromelain's fibrinolytic and anti-oedematous properties. The proteases in bromelain and the increased plasminogen to plasmin conversion by bromelain lead to increased fibrin degradation, increased tissue permeability, increased fluid reabsorption into the systemic circulation and decreased extracellular fluid retention/accumulation, leading to reduced compression/pressure on peripheral nociceptors (118–121).

Studies indicate the anti-inflammatory properties of bromelain from pineapple crown/peel extracts are mediated via one or more of the underlisted mechanisms. Bromelain attains reduced inflammation by lowering pro-inflammatory cytokines such as PE2 and PGF, and thromboxane A2 by inhibiting cyclooxygenase-2 (COX-2). Reduced PGE2 , as well as cause downregulation of the expression of pro-inflammatory TNF-α, IL-1β, IL-6, and IL-8 cytokines. These factors are known to play key role in vascular permeability, pyrexia and hyperalgesia associated with cellular/tissue inflammation at injury sites (117,121,122).

Bromelain also attains anti-inflammation by causing reduced pro-inflammatory intracellular signal transduction via inhibition of the Mitogen-Activated Protein Kinase (MAPK) and Activator Protein 1 (AP-1) pathways. Furthermore, bromelain has been shown to supress inducible nitric oxide synthase (iNOS) expression. This suppression results in reduced generation of nitric oxide and reactive nitrogen species that are associated tissue injury and inflammation (123,124).

Additional anti-inflammatory mechanism of bromelain involves its inhibitory modulatory effect on cell surface CD44 – an adhesion molecule involved in cell adhesion, migration and chemotaxis of leucocytes during inflammatory processes. Bromelain has intrinsic ability to cleave/lyse this molecule. This cleavage markedly reduces CD44 ability to serve as

adhesion molecule for leucocytes and other pro-inflammatory immune to migrate to within the vasculature into the inflamed tissue (125,126).

Antioxidant synergy amongst the abundant plethora of flavonoids and phenolic acids in pineapple peel/crown extracts is yet another of their anti-inflammatory mechanism. These bioactive compounds prevent cellular oxidative stress and membrane lipid peroxidation and thus chronic inflammation by scavenging and neutralising reactive oxygen species (127).

5 CONCLUSION

This case report shows oral gabapentin was discontinued in a cervical radiculopathy pain following over 2-week use due to nil analgesic response and severe adverse effects. However, co-administration of *S. aromaticum* flower bud and *A. comosus* peel/crown water decoctions provided a prompt analgesic/anti-inflammatory relief therapeutic response that has been sustained for months now. The observed efficacy of the herbal combination may be due to the already highlighted multi-target therapeutic properties of bioactive factors contained in the decoctions of these plant parts.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

No competing interest(s) exist among the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

AUTHORS' CONTRIBUTIONS

Umarudeen A. M. & Maduagwuna C. A. conducted the oral and written interviews, did the internet literature search, collated, extracted and interpreted revevant literature, and prepared the manuscript. Ephraim-Oluwanuga O. T. did the proof-reading. All authors agreed and approved the final manuscript.

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