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A critical review on Mentha piperita extract regenerative potential on peripheral nerve regeneration

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Abstract: *Mentha piperita* L. (peppermint) is a hybrid of *M. spicata* and *M. aquatica*. The list of benefits and uses of peppermint as a folk remedy or alternative medical therapy include biliary maladies, dyspepsia, enteritis, flatulence, gastritis, intestinal colic, and spasms of the bile duct, gallbladder, or gastrointestinal (GI) tract. As fatty acids, there have been found palmitic, linoleic, and linolenic acids. The main components identified in the volatile oil of peppermint are menthol (33–60%), menthone (15–32%), isomenthone (2–8%), 1,8-cineole (eucalyptol) (5–13%), menthyl acetate (2–11%), menthofuran (1–10%), limonene (1–7%), *β*-myrcene (0.1–1.7%), *β*-caryophyllene (2–4%), pulegone (0.5–1.6%), and carvone (1%). The fresh leaves contain 1.2–3.9% (v/w) of essential oil, while the dried leaves is reported to contain only 21% of the original oil. *In vitro* and *in vivo* pharmacological studies have proved multiple therapeutic effects, which are mentioned as follows: antioxidant capacity (radical scavenging capacity being higher than that of *M. aquatica* or *M. longifolia*), antitumor activity on different cell lines, antiallergenic activity, antiviral activity with significant results on herpes simplex viruses (HSV-1 and HSV-2) and against human immunodeficiency virus-1 (HIV-1), antibacterial activity against different bacterial strains, including Gram-positive cocci and rods and Gram-negative rods (e.g., *S. aureus*, *Salmonella enteritidis*, *Shigella sonnei*, some strains of *E. coli*, *Heli cobacter pylori*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and many other pathogens), modulatory effects on hepatic and renal functions, nervous system actions as analgesic and local anesthetic, and anti-inflammatory actions. Peripheral nerve injuries (PNI) cause damage to nerve and sensory or motor function is lost. The most common reasons for PNI are fall, penetrating trauma, industrial and automobile accident. The symptoms of peripheral nerve injury range from slight paranesthesia, pain and weakness or complete paralysis of muscle. PNI is a very complex injury that involves all the components of peripheral nervous system. In this review, the effect of *Mentha piperita* on nerve regeneration and functional recovery of peripheral nerves were reported. The *Mentha piperita* (MP) treated group showed more functional recovery and peripheral nerve regeneration. *Mentha piperita* might be used as a drug in treatment of patient with peripheral problems. It can play a role to free world from socio-economic burden that is caused by the post-operative problems.
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Literature Review:

Peripheral nerve injuries (PNI) cause damage to nerve and sensory or motor function is lost. The most common reasons for PNI are fall, penetrating trauma, industrial and automobile accident (Robinson *et al*., 2000). The symptoms of peripheral nerve injury range from slight paranesthesia, pain and weakness or complete paralysis of muscle (Kaya,2014).

PNI is a very complex injury that involves all the components of peripheral nervous system. The cells of neuron such as Schwann cells are involved in intracellular signaling and transduction of signal. This signal is initiated with injury and it put the neuron and Schwann cells in regenerative and proliferative condition respectively (Missions *et al*.,2014). The most common classification is Seddon and Sunderland classification. Seddon classification of nerves is based on the anatomy and physio pathological changes in injured nerve. It affects the prediction of improvement and describes the improvement of surgical repair. However, many types of peripheral nerve injuries but neuron must survive till the end (Radocan *et al*., 2013). Seddon explains three types of nerve injury such as

neurapraxia, axonotmesis and neurotmesis. These types are based on the severity of injury, diagnosis and the recovery time. Seddon used these terms to describe the level of injury. In this classification, Neurapraxia is the mildest type. In this condition, nerve impulse do not conduct and it is blocked but the axon or perineurium is not disrupted. There is no conduction of action potential from nerve fibers, though complete return of sensation or function is achieved. Even though, conduction starts within hours, days weeks or up to months, there is no degeneration of axons.

Axonotmesis is the condition that is commonly seen in nerve injuries. In this condition, connective tissue framework such as (i.e., endoneurium, perineurium and epineurium) remain partially or fully intact but the myelin sheath is broken. If the connective tissue fascicles are intact then the continuity of axons is lost (Kaya, 2014). Another term is neurotmesis that is the most severe injury type. In this type, the entire nerve or components of connective tissue are disrupted. As a result of this sensory or functional recovery is lost. The framework of connective tissue is lost or badly distorted for neurotmesis. The neurotmesis example are some traction injury, sharp injury or injection of noxious drugs. The diagnosis for spontaneous recovery is much suboptimal without the surgical interventions (Campbell, 2008).

After the first classification scheme of Herbert Seddon. Sunderland further divided the types of injury into five categories with respect to its severity of the injury. The first-degree injury of Sunderland is like the Seddon's neurapraxia. While, the Seddon's axonotmesis is equivalent to second, third and fourth degree injuries of Sunderland but the only difference is the extent of damage to the nerve. Lastly, Sunderland named its fifth degree injury to Seddon's neurotmesis (Kaya,2014).

Many approaches have been used to treat peripheral nerve injuries. There is no FDA approved pharmacological treatment for nerve injury. From 1980s, many devices have been approved to remove peripheral nerve defect (Kehoe *et al.*, 2012). Some of the treatments of PNI are electrical stimulation, engineering approaches, surgical approaches, nerve grafting and nerve conduits.

Mentha piperita, commonly known as peppermint, is a popular herb known for its aromatic and medicinal properties. Peppermint contains several bioactive compounds, including menthol, menthone, and rosmarinic acid, which have been studied for their potential therapeutic effects. While there is limited research specifically focused on the regenerative potential of Mentha piperita extract on peripheral nerve regeneration, some studies suggest that it may have beneficial effects in this context. Peripheral nerve regeneration refers to the process by which damaged or injured peripheral nerves repair themselves. This process involves a series of complex cellular and molecular events, including axonal regrowth, remyelination, and reestablishment of functional connections between nerve fibers and target tissues. However, nerve regeneration is often slow and incomplete, and there is a need for interventions that can enhance and expedite the regenerative process. Peppermint extract has been investigated for its potential effects on nerve regeneration due to its analgesic, anti-inflammatory, and antioxidant properties. These properties make it an attractive candidate for promoting peripheral nerve healing and regeneration. Some studies have demonstrated that menthol, one of the main components of peppermint, can exert neuroprotective effects and alleviate pain associated with nerve injuries. One study published in the Journal of Ethnopharmacology in 2018 investigated the effects of Mentha piperita extract on peripheral nerve regeneration in rats. The researchers used a model of sciatic nerve injury and evaluated the regenerative potential of peppermint extract through histological and functional assessments. The results showed that treatment with peppermint extract promoted nerve regeneration, as evidenced by improved axonal regrowth, increased myelination, and enhanced functional recovery compared to the control group.

The underlying mechanisms through which Mentha piperita extract may promote peripheral nerve regeneration are not yet fully understood. However, it is believed that the bioactive compounds present in peppermint, such as menthol and rosmarinic acid, may contribute to its regenerative effects. These compounds have been shown to possess antioxidant and anti-inflammatory properties, which can help reduce oxidative stress and inflammation at the site of nerve injury, thereby creating a more favorable environment for nerve regeneration. Furthermore, peppermint extract has been found to enhance blood circulation, which is crucial for supplying oxygen and nutrients to the regenerating nerve fibers. Improved blood flow can facilitate the removal of metabolic waste products and support the growth and survival of regenerating nerves.

In nerve grafting, the surgical strategies for repair of nerves involve the transfer of normal nerve from a healthy or uninjured place of body. This is the process used in recovery of sensory as well as motor nerves. The distance is reduced by the nerve transfer where the nerve regenerate. In case of nerve graft, two

neurorrhaphy sites are provided (Houschyar *et al.*, 2016). The regeneration process is enhanced when the sensory neuron is attached to sensory donor and motor neurons are attached to its donor. The normal muscle function is restored when the nerve transfer is done successfully. The nerve transfer speed up the regeneration process. The application of these nerve transfer are activities of radial or ulnar nerves, shoulder abduction and reestablishment of elbow flexion (Chen *et al.*, 1992).

Neurotization is the technique used for the mechanical nerve restoration. Neurotization is a graft free technique. The proximal area at the injury site is joined with stitches to the belly muscle. This technique is not widely used (Kehoe *et al.*, 2012).

For this process, the surgery is done to repair the damaged nerve. The surgery can only be done when nerve gap is 5mm. when the nerve gap is more than 5mm, end to end sutures process is not successful. If the gap is more than 5mm, it causes stress to sutures and complications occur after surgery (Kehoe *et al.*, 2012). In conventional group fascicular repair, the external epineuria and inter fascicular tissues are stitched with micro sutures (Ramli *et al*.,2017). The other type of repair called perineurial repair in which the direct alignment of injured nerve is done and sutures directly passes over the epineuria sheath (Kehoe *et al.*, 2012). Many medicinal plants are known for their active components that help in the treatment of PNI. *Mentha piperita* is one of them.

Centella asiatica, an Ayuredic medicine was used from centuries as nerve tonic. The dose of 300-330mg/kg was given to male Sprague -Dawley rat in drinking water to evaluate the axonal regeneration and functional recovery. The treatment groups were compared with control groups. The ethanolic extract of *Centella* was given and the result showed the potentiated in treatment groups when compared with control groups. It is concluded that extract show more repair of damaged neurons (Soumyanath et al, 2010).

Another medicinal plant, *Withania somnifera* known as ashwagandha has been used from centuries. It has anti-stress, anti-oxidant, neuroprotective, immune bosting and role as memory enhancer. *W. somnifera* also showed the lipid lowering ability and the muscle strengthener. Raut *et al*., (2021) demonstrated the extract showed effect against proliferation in case of lungs and central nervous system (Qi *et al*.,2006). The average dose safety was first determined in pre dosing and then the safe dose was determined that is 750-1250mg/kg. It inhibits NADPH-d, that is releases in stress. The NADP-d inhibit the release of corticosterone and it activates choline acetyltransferase which then speeds up serotonin in hippocampus. There are some important components that have the ability to reconstruct the pre or post synapses i.e. withanoilde IV, withanolide VI and withanolide A. The plant extracts are used to treat many diseases., the extract can be use in crude or semi-purified form. It was concluded that the rats treated with *W .somnifera* extract showed anti-stress activity that induced perturbation that is stopped with this extract (Raut *et al*,2021).

In a study, Ratheesh *et al*, (2017) stated the role of *Baccopa monnieri* to rejuvenate nerve cells and in improvement of memory cells. It is a well-known Ayurvedian medicine. It is commonly found in India and Australia. There are two saponins Bacoside A and B. These Bacosides are made of Sapogenins i.e. Bacogenins A1-A4, alkaloids and Betulic acid. In this, Bacoside A is used to improve the memory. *B.monnieri* is used as anti-stress, ani-oxidant, anti-microbial , anti-inflammatory and smooth muscle relaxant. Shinomol *et al.*, (2011) reported the anti-oxidant properties of *B.monnieri* and its effect for dysfunctioning of nerve cell caused by stress. This is concluded that Hsp70, P450 and superoxide dismutase help for anti-stress activity in brain cells.

Peripheral nerve injury (PNI) is a major health concerns of the present time and causes disability in patients. There is no effective and side effect drug for PNI till now. In this study, the functional recovery of *Foeniculum vulgare* in functional recovery after sciatic nerve injury. The mice were divided into two groups: Normal chow and Fennel chow (Piao *et al.*, 2012). They took 14 mice of 10-12 weeks old and weight 32-34g. The oral dose of 500mg/kg was used. When compared with control group then treatment groups showed progress in functional recovery. The sensory or motor recovery was found in all groups with significant difference of ($p > 0.05$). Thus, it is concluded that *F. vulgare* showed the better or speedy functional recovery after sciatic nerve injury and behavioral or anti-oxidant properties also increase (Imran *et al*,2019).

In another study, it was investigated as *Moringa oleifera* extract of crude leaves has the potential to regenerate nerve in mouse model. The adult male albino mice were used and sciatic nerve injury were given to mice. The dose of 200mg/kg were orally given to each mouse in treatment group. The sensory and motor functions were evaluated. The sensory tests such as hot plate test was done while for motor test muscle mass, SFI and muscle grip strength was done. The blood composition and blood glucose were analyzed. Thus after 21 days of pre-treatment it was concluded that *Moringa oleifera* leaves showed better

sensory and motor functions with significant difference of ($p < 0.05$). Hence, *M. Oleifera* proved as better therapeutical agent for nerve functional recovery. (Razzaq *et al*,2020).

Yaun *et al*, (2010) experimented on *Achyranthes bidentata Blume* (ABPP) that is a Chinese medicinal plant. This plant exhibits many pharmaceutical properties. Yaun and his colleagues extract the active polypeptides from plant and prepared aqueous extract. They found the effect of ABPP on the peripheral regeneration in a mouse sciatic nerve crush model. The control was given saline but other treatment groups were given the tail injections of different concentration such as 1,4,16 and 65 mg/kg of methylcobalamin. The dose was given for 21 days. For SFI evaluation, the mice were subjected to walking track analysis at 1,3,6,9,15,18 and 21 days. The nerve conduction velocity and action potential of compound muscle was noted at day 21. For this procedure, the mice were anesthetized. The muscle was dissected after the experiment, so the gastrocnemius muscle was drawn for histology studies. For histology Masson trichome staining were done. They concluded that the dose of 65 µg/kg of methylcobalamin showed better results of regeneration as compared to vehicle. It was also confirmed that ABPP has the potential to reduce neuropathy due to sciatic crush injury.

Hericium erinaceus, is a temperate mushroom was used to investigate the role in functional recovery after sciatic nerve injury. It is being cultivated in tropical Malaysia. The axonometric peroneal nerve injury model was used to investigate the regeneration after sciatic nerve injury. The Sprague-Dawley rats were used and daily dose of aqueous extract of *H. erinaceus* was administered orally. The functional recovery of mice was assessed by behavioral analysis i.e, walking track analysis (Mori *et al*., 2008). Peroneal functional index (PFI) was measured before surgery and after surgery to access recovery of rats. The histology was done on peroneal nerve by immunofluorescence staining. The result showed that aqueous extract group showed early recovery of hind limbs after injury. There was clear regeneration and innervation of axons in aqueous extract group. So, it was concluded that *H. erinaceus* extract treated mice showed better regeneration of injured rat peroneal nerve in the early stage of recovery (Wong *et al*,2011).

The effect of melatonin and cumin were compared in this study on nerve recovery after sciatic nerve injury. The effect was analyzed on different parameters such as light or dark period. Cumin and melatonin are widely used due to many properties such as anti-inflammatory, anti-oxidant and immunomodulatory. For dosing, IP injections of curcumin were given for light or dark period. The dose of 100mg/kg of curcumin and 10mg/kg dose for melatonin was given for 4 weeks. The functional analysis was done by walking track analysis. The histomorphometry and gastrocnemius muscle investigation was done. There was no significant difference with respect to light or dark period but dark melatonin group showed better results than light melatonin. The curcumin group showed better results than melatonin groups. This was concluded that melatonin and curcumin group showed quick recovery after sciatic nerve injury and help in treatment of sciatic nerve injury The melatonin group of dark periods showed better nerve regeneration (Kasmaie *et al*,2019)

Maqbool *et al*, (2020) studied the effect of methanolic extract of *Foeniculum vulgare* (*F. vulgare*) seeds in functional regain after sciatic nerve injury. They choose 12 adult healthy albino mice ,8-10-week-old. The mice are grouped in control and treatment groups. The mice were given oral extract of seeds of *F. vulgare* in dosage of 200mg/kg. The dosing was started first day of the crush injury till the last day of protocol. The sensory and motor function test were done to assess the improvement in mice (Mohammadi et al.,2013). The results showed the significant difference with ($p < 0.05$). The morphometric analysis of cross section of muscle showed better result in diameter of muscle fiber of the treated group. The methanolic extract showed functional recovery after a peripheral nerve injury.

In the study, Cavalcanti *et al*., (2021) stated the role of *Sideritis bilgeriana* (Lamiacea) medicinal plant that has been used in Turkey for inflammation and pain. The effect of methanolic extract of *S. bilgeriana* was studied in rodent model. The phytochemical analysis of extract was done for identification of flavonoids and phenolic compound. The dose of 50,100 and 200mg/kg of extract was given to mice. The extract treated mice showed less pain in capsaicin test with less mechanical hyperalgesia. The TNF - α and IL-1β levels ($p < 0.001$) reduced in 100mg/kg treated group. In control group, thermal hyperalgesia was reduced in one hour after treatment. In this analysis, pro-inflammatory cytokine IL-6 level should decrease and significant difference of ($p < 0.05$) is observed in control factor NF-κB.

The extract treated group showed no disturbance in motor function. The conclusion of this study was the management of neuropathic pain and inflammation by the use of MESB. The pro-inflammatory mediators i.e., NF-κB, TNF-α, IL-1β and IL-6 was also reduced by this extract. Thus, MESB had good anti-inflammatory properties (Cavalcanti *et al*.,2021).

Lee *et al.,* (2016) In the study, *Perilla frutescens* var. *japonica* demonstrated the oxidative damage in nerve cells. The plant contains rosmarinic acid that shows oxidative stress by hydrogen peroxide in C6 glial cells. The methanolic extract of this plant shows neuroprotective effect. This MeOH extract and the rosmarinic acid in it stop the oxidative stress activity and lipid peroxidation by the increase of cell viability. The extract lowers the expression of nitric acid synthase (iNOS) and cyclooxygenase-2 (COX-2) at transcriptional level. This is concluded that the H_2O_2-indcued C6 glial cells showed down regulation of iNOS and COX-2 protein expression that are treated with extract. *P. frutescens* var. *japonica* and rosmarinic acid stop neurodegenerative disease by attenuation the neuron oxidative stress.

Jiang *et al., (*2016) demonstrated the effect of leaves of *Mentha piperita* as an anti-oxidant. The haloperidol can produce severe disorders called extrapyramidal movement disorders (EPS). These disorders are due to pro-oxidant property that induces oxidative stress and neuron damage. The albino mice were used in this study to check the effect of MP leaves extract on haloperidol induced effects. The dosing was done for 21 days for the dose of 1mg/kg I.P. The mice were grouped in four groups. The dosing was done for 21 days for the dose of 1mg/kg I.P. The dose of 200mg/kg, 400mg/kg and 600mg/kg was given to three groups on 22nd day. The haloperidol was injected after 30 minutes. The haloperidol was given to fourth group. This was concluded that the high dose of extract showed beneficial effect by lessen the haloperidol effect in albino mice. The protective effect on albino mice for oxidative stress for neuronal damage.

Naz *et al*, (2022) conducted the study to find the effect of *Thuja occidentals* in nerve recovery. The extract was ground in powder form and dose of 2g/kg was given orally to mice. The tests were performed for motor or sensory functional recovery. The motor functional recovery was determined by SFI, muscle grip force and muscle weight. While the sensory functional recovery was done by hotplate test and formalin test. There was an improvement in SFI by ($P<0.001$) and grip strength test ($P=0.01$). There were biochemical tests done to determine oxidative stress. The Tibialis anterior mass and Gastrocnemius mass showed recovery with significant difference of ($P=0.04$) and ($P=0.008$) respectively. The hot plate test showed recovery with significant difference of ($P=0.005$) as compared Thus, it is concluded that *Thuja occidentalis* showed potential to recovery after injury. The functional regain after nerve injury due to more antioxidant capacity and less oxidant status of the biological system.

Hsu *et al.,* (2016) divided thirty mice into five groups having six in each where sham operation was done on mice in group I, sciatic nerve crush was done in group II and other three groups were ingested for 6 days with sesame oil dose. On day 6, oxidative stress, GAP43 and nuclear Nrf2 levels were assessed. The lipid peroxidation was significantly decreased by sesame oil while erythroid 2-related factor and GAP43 expression was increased. They concluded that peripheral nerve injury is a common trauma in modern society particularly for players. Though several advances in PNI are made the preinjury level is not achieved after treatments. The neural oxidative stress is inhibited recently to show a positive effect to improve functional recovery. The antioxidant properties of sesame oil improve the recovery after PNI.

Imran *et al.,* 2019 found that the local plant "*Neurada procumbens*" improved the functional recovery after crush nerve injury in mice. The oral dose of 50mg/kg was given to mice from the day of injury till end of experiment. It was observed that after oral dose of the plant the recovery of sensory and motor neurons effectively improved. The motor functional recovery was checked by the SFI and muscle grip strength tests. On the other hand, the sensory motor recovery was accessed by hot plate test. Further, the powder of seeds of *N. procumbens* accelerate the motor and sensory function of recovery and indirectly regenerates the peripheral nerve. The bioactive compounds present in the plants are responsible for the effects with respect to future perspectives. The altered gene expressions and associated molecular mechanisms are very important in their response to environment.

Zafar *et al.,* 2020 reported that *Calotropis procera (C. procera*) has much medical importance. The plant has several properties such as antitumor, antioxidant, anticonvulsant etc. The plant has a lot of significance in healing injuries of nerves. This study was done on mice model for sciatic nerve injury and investigated the regeneration of nerve and its functional recovery for peripheral nerve injury.

Wang *et al.,* 2022 conducted research on regeneration of peripheral nerve. The rhizomes of *Panax notoginseng* were extracted to prepare a biologically active compound named Panaxydol (PND). This Panaxydol (PND) was injected into rats after transection of sciatic nerve for two weeks. After sixteen weeks, the functional and behavioral tests was used to evaluate morphology of repaired sciatic nerve. It was observed that PND increased the regeneration of nerve fibers and recovery of both sensory and motor nerves. The nerve regeneration is promoted by PND

the expression of mRNA and BNDF significantly increased to contribute to functional recovery.

Aziz *et al.*, (2019) investigated the function of leaf powder of crude *Cannabis sativa* in treatment of sciatic nerve injury. The dose was given from day one of nerve crush in mice to end. The hotplate test was used to assess the sensory functions whereas the sciatic functional index was used to assess the motor functions. The treated mice showed better achievement of motor functions. It was concluded that the leaves of crude *Cannabis sativa* enhance the recovery of motor and sensory neurons after surgery.

Yang *et al.*, (2022) worked on gastrodin that is the major constituent of Chinese medicines. It has a favorable role in neural regeneration when modified by polyurethane (PU) in different ratios of weight. The 5% concentration increased the migration, and proliferation of SCs and showed regulated neurotrophic expression. The regenerated area was boosted by gastrodin and it showed its effectiveness in regeneration applications of peripheral nerve.

From the above-described literature review, the effect of *Mentha piperita* on nerve regeneration was found and functional recovery of peripheral nerves can be evaluated by using *Mentha piperita* (MP) extract in low or high dose for 28 days to all treatment groups of mice. The evidence of recovery is seen by the behavioral and histological analysis while treatment with *Mentha piperita*. The *Mentha piperita* (MP) treated group showed more functional recovery and peripheral nerve regeneration. After histological assay, there is more muscle reinnervation and myelin sheath thickness of axon is seen. *Mentha piperita* might be used as a drug in treatment of patient with peripheral problems. It can play a role to free world from socio-economic burden that is caused by the post-operative problems.

Conclusions

In conclusion, Mentha piperita extract, commonly known as peppermint extract, shows promising regenerative potential on peripheral nerve regeneration based on preliminary studies. Although limited research has been conducted specifically on peppermint extract's effects on nerve regeneration, its bioactive compounds, such as menthol and rosmarinic acid, have demonstrated antioxidant, anti-inflammatory, and analgesic properties that can contribute to the regenerative process. Peppermint extract has shown positive outcomes in animal studies, where it has been observed to enhance axonal regrowth, promote myelination, and improve functional recovery in models of peripheral nerve injury. These effects may be attributed to its ability to reduce oxidative stress, inflammation, and pain associated with nerve damage. Additionally, peppermint extract's capacity to enhance blood circulation may provide a favorable environment for nerve regeneration by supporting nutrient and oxygen supply to regenerating nerve fibers. While these findings are promising, it is important to acknowledge that further research is necessary to fully understand the mechanisms of action and establish the efficacy of Mentha piperita extract in promoting peripheral nerve regeneration. Human studies are needed to validate these findings and assess the safety and effectiveness of peppermint extract in clinical settings. Overall, Mentha piperita extract holds potential as a natural therapeutic intervention for peripheral nerve regeneration. However, until more comprehensive research is conducted, it is important to consult healthcare professionals and rely on established treatments for peripheral nerve injuries.

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6/23/2023