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The Synergistic Potential of Copper Nanoparticles and *Saccharum Officinarum* Phytochemicals in the Modulation of Neurodegeneration in Parkinson's Disease: Insights from Siddha Inspired Approach

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder marked by oxidative stress, neuroinflammation, and α-synuclein aggregation, leading to dopaminergic neuron loss. This study explores the therapeutic potential of copper nanoparticles (CuNPs) and *Saccharum Officinarum* phytochemicals, leveraging their antioxidant and neuroprotective properties. Analyses of articles revealed that CuNPs reduce oxidative stress, inhibit α-synuclein aggregation, and downregulate pro-inflammatory cytokines, improving motor function and neuron survival. Combining Siddha medicine with nanotechnology, CuNPs show promise as a PD treatment. Further research is needed to optimize clinical applications and delivery methods for enhanced therapeutic efficacy.

Keywords: Copper nanoparticles (CuNPs), *Saccharum Officinarum,* Parkinson's Disease, Siddha Medicine.

INTRODUCTION

Parkinson's disease (PD) is a prevalent neurodegenerative disorder and a leading cause of disability, representing a growing public health challenge worldwide [1]. Clinically, PD is characterized by a combination of motor symptoms-including progressive asymmetric slowness of movement (bradykinesia), rigidity, tremor, and gait disturbance-as well as non-motor and cognitive impairments. Pathologically, it is defined by the loss of dopaminergic neurons in the substantia nigra and the presence of intracellular protein aggregates, primarily composed of alpha-synuclein, known as Lewy bodies and Lewy neurites [2,3]. The prevalence of PD has been rising rapidly, with a higher rate of increase observed from 2004 to 2023 compared to the period of 1980-2003. Globally, the pooled prevalence was 1.51 cases per 1000 from 1980 to 2023, with a slightly higher incidence in males than in females [4]. While approximately 10% of cases are linked to genetic factors, the vast majority are sporadic, suggesting that aging and environmental exposures play significant roles in the disease's etiology [5]. Given this increasing burden and the complexities of PD management, there is a pressing need to explore innovative treatment strategies.

One such avenue lies in traditional medical systems. Siddha medicine, a traditional system predominantly practiced in Tamil

Nadu, India, and among Tamil-speaking communities globally, offers a vast pharmacopeia documented in the ancient Tamil language [6]. A distinctive feature of the Siddha system is its sophisticated use of herbo-mineral and metallic formulations, processed into specific forms such as *Parpam*, *Chendooram*, and *Chunnam*. These potent medicines are administered in minute doses and are often paired with specific adjuvants like milk, ghee, honey, or herbal juices, based on the nature of the illness—a principle known as the "Single Medicine, Multiple Application" theory [7].

Thambira Parpam, a herbo-metallic formulation derived from copper, is one such medicine with significant potential in managing PD. Traditional texts suggest that when administered with the juice of *Saccharum officinarum* (sugarcane), it exhibits a remarkable therapeutic effect. The nanomolecular conversion of its metallic components during preparation is believed to contribute to its high potency and improved safety profile, allowing for effective disease management at minimal doses [8]. This article aims to critically evaluate the scientific rationale and emerging evidence supporting the synergistic effects of copper nanoparticles in *Thambira Parpam* and the phytocomponents of *Saccharum officinarum* in the management of Parkinson's Disease.

MATERIALS AND METHODS

A literature search was conducted using PubMed, Scopus, Web of Science, AYUSH research Portal and Google Scholar (2000–2023) with keywords: *copper nanoparticles, Saccharum officinarum, Parkinson's disease, Siddha medicine, neuroprotection, α-synuclein, oxidative stress*. Inclusion criteria: peer-reviewed articles, English language, mechanistic/therapeutic studies. Siddha texts were manually reviewed for traditional formulations. References from selected articles were screened. Data extraction focused on CuNPs neuroprotective mechanisms, sugarcane phytochemicals antioxidant properties, and Siddha-inspired synergy. Studies on metal toxicity, non-relevant models, or non-Siddha approaches were excluded. Analysis prioritized in vitro/in vivo evidence and traditional-modern integration.

RESULT

COPPER NANOPARTICLES (CuNPs)

Copper is the third most prevalent essential transition metal in the human body, with its highest concentrations located in the liver and brain [9,10]. It plays a vital role in numerous biological processes, including skin pigmentation, maintaining blood vessel integrity, myelination, iron regulation, antioxidant defense, and the synthesis of neurotransmitters [11,12,13].

ROLE OF COPPER IN PARKISON'S DISEASE

INCREASED COPPER LEVEL IN PD

Copper has been demonstrated to increase the oxidation process of dopamine leading to a variety of potentially toxic species, such as dopamine-quinones, O_2^-, H_2O_2, and hydroxyl radical [14–16]. Interestingly, the locus coeruleus and substantia nigra, where neuromelanin is mostly found, are the brain regions with the highest levels of copper [17–19]. The presence of copper inside neuromelanin suggests its active participation in dopamine oxidative polymerization [14], even though, as an alternative hypothesis the presence of such a unique metal-binding pigment in the human substantia nigra and locus coeruleus could account for the high levels of copper in these brain regions [20]. The presence of labile pools of copper ions in the brain, as demonstrated by Dodani SC and co-workers [21], is probably the major source of dopamine oxidation. In addition to the direct reactivity of copper towards dopamine, the oxidation can also be mediated by copper ions bound to coordinating ligands or peptides and proteins involved in neurodegenerative processes, as recently reviewed.[14] In the context of PD, a major

role in promoting copper-induced dopamine oxidation could be played by the protein Alpha synuclein.

DECREASED COPPER LEVEL IN PD

While some studies suggest a link between elevated copper levels and an increased risk of Parkinson's disease (PD), this connection remains controversial and not fully understood. Recent research, however, points to a reduced risk of PD associated with lower copper levels. Specifically, in PD patients, blood concentrations of copper, ceruloplasmin, and its oxidase activity, along with the copper atoms per ceruloplasmin molecule, were found to be lower compared to age-matched healthy individuals. [22,23]. Moreover, copper levels have been demonstrated to be lower also in the most affected brain regions of PD patients in comparison to age-matched control individuals, with a 35%-50% reduction of copper content of the substantia nigra and locus coeruleus [24-28]. To confirm that reduced copper levels were not the result of the marked degeneration of the copper-rich neuronal populations in these brain regions, Davies and co-workers analysed intraneuronal copper at the single-cell level through synchrotron radiation X-ray fluorescence microscopy and particle-induced X-ray emission microscopy, showing a 55%-65% reduction in copper levels in both the substantia nigra and locus coeruleus from PD brains [28]. Through its binding to ceruloplasmin, copper stimulates its ferroxidase activity and participates in iron homeostasis, so that some indirect toxicity mediated by altered concentrations of iron could be a consequence of low levels of copper. Accordingly, aceruloplasminemia, an autosomal recessive deficiency of ceruloplasmin caused by mutations in the ceruloplasmin gene, is associated with the accumulation of iron in the liver, pancreas, retina, and basal ganglia [29-32]. Moreover, iron deposition in the brain has been described to be associated with neuronal loss in the same regions and the effects seem to be related to the capability of the ferrous ion to increase oxidative conditions through the Fenton and Haber–Weiss reactions [29,30]. Interestingly, among the neurological symptoms of aceruloplasminemia, loss of motor coordination and other motor deficits overlap with some clinical manifestations associated with PD.

SACCHARUM OFFICINARUM

Saccharum officinarum, sugarcane, is a large, strong-growing species of grass in the genus Saccharum. It originated in Southeast Asia and is now cultivated in tropical and subtropical countries worldwide for the production of sugar and other products. As its specific name (officinarum, "of dispensaries") implies, it is also used in traditional medicine both internally and externally.[33].

PHENOLIC COMPOUNDS FROM *SACCHARUM OFFICINARUM (SUGAR CANE)*

The total polyphenolic content of sugar cane juice, determined by the Folin-Ciocalteau procedure, was relatively high, of 160 mg CAE/L. This means that the consumption of a glass of 250 mL would result in an intake of 40 mg of phenolics, and in this way sugar cane juice would represent an important source of these antioxidant compounds in our diet.[34] HPLC-DAD identification of the phenolic compounds from sugar cane juice showed the presence of flavonoids (apigenin, luteolin and tricin derivatives), and phenolic acids, mainly caffeic, sinapic, and isomers of chlorogenic acid

Flavonoids, particularly apigenin and luteolin, have been shown to exhibit a potent activity against oxidative stress [35]. Apigenin, tricin and luteolin were present in sugar cane as glycosylated derivatives, and glycosylation pattern is widely known to influence the antioxidant capacity of flavonoids [36].

ANTIOXIDANT ACTIVITY OF *SACCHARUM OFFICINARUM* L. JUICE

The *in vivo* antioxidant capacity was evaluated using a subchronic MeHgCl

intoxication rat model. Male Wistar rats (weighting in the range of 190–215 g) were purchased from CENPALAB (La Habana, Cuba) and used in this experiment. Animals were kept at room relative humidity (∼79%) and temperature (∼25◦C) with free access to water and standard diet (ALYco, La Habana, Cuba). For the experiment, animals were randomly distributed into 3 groups. Group II received a daily subcutaneous injection of ethanolic 10 mg/kg MeHgCl during 15 days. Group III received sugar cane phenolic extract (10 mg of total phenolics/kg) by gavage, 60 min before MeHgCl injection in alternate days. Control group (I) received a daily sc. injection of 20% ethanol.

The results demonstrated that the administration of MeHgCl in Group II affected food consumption, when compared to control animals (Group I). Group III, which was also intoxicated but received sugar cane extract by gavage, showed a lower decrease in the food intake. Sugar cane extract was shown to contain a range of phenolic molecules such as flavonoids and cinnamic acids (apigenin, luteolin, tricin derivatives, caffeic, sinapic acids and isomers of chlorogenic acid). The extract decreased the appearance of clinical symptoms (food consumption weight gain and mortality) in an *in vivo* model of MeHgCl neuro intoxication.[37]

THE MEASUREMENT OF THIOBARBITURIC REACTIVE SUBSTANCES (TBARS) AFTER SPONTANEOUS LIPOPEROXIDATION OF RAT BRAIN HOMOGENATES WAS CONDUCTED AS FOLLOWS:

Male Wistar rats were anesthetized, decapitated, and their brains were removed, washed, weighed, and homogenized in a phosphate buffer. The homogenate was centrifuged, and the resulting brain homogenate was stored at -70°C until use.

Aliquots of the brain homogenates were incubated with sugar cane extracts at 37°C for 40 minutes. The reaction was stopped with cold acetic acid, and malondialdehyde (MDA) formation was measured by adding TBA and incubating at 90°C for 1 hour.

After cooling, SDS was added, and the mixture was centrifuged. The absorbance was measured at 532 nm to determine antioxidant activity, expressed as the percentage of TBARS inhibition compared to the control.

sugar cane phenolic extract displayed a dose-dependent effect on the inhibition of spontaneous lipoperoxidation of brain homogenates. The extract protected rat brain tissue against free radicals- mediated damage and in this system, sugar cane phenolic extract effectively inhibited TBARS generation.

DPPH SCAVENGING ACTIVITY.

DPPH (2,2-diphenyl-1- picrylhydrazyl radical) scavenging activity of sugar cane phenolics was assessed according to Brand-Williams et al. with some modifications [39]. Briefly, a 50μL aliquot of the extract previously diluted and 250μL of a methanolic solution of DPPH• (0.5 mM) were shaken and after 25 min at 25◦C the absorbance was measured at 517 nm using the Microplate Spectrophotometer (Benchmark Plus, Biorad). Results were expressed as percentage (%) of radical scavenging (MeOH as control).[37]

B-CAROTENE/LINOLEIC ACID BLEACHING METHOD (B-CLAMS).

in vitro antioxidant activity of sugar cane phenolics was determined by two different methods, DPPH• radical scavenging activity and inhibition of β-carotene bleaching, and compared to that of Trolox, a water soluble vitamin E analog. Table.1 shows that sugar cane phenolics presented a similar efficiency in both systems, while Trolox was more effective in avoiding β-carotene bleaching. On the rough, 1 μmol of chlorogenic acid equivalents, present in sugar cane juice, would correspond to 0.5 μmol of Trolox in terms of antioxidant activity. [37-40]

Table 1: *In vitro* antioxidant activity of the sugar cane phenolic extract determined through DPPH• scavenging capacity (%) and inhibition of *β*-carotene bleaching (%)

	DPPH	*β*-CLAM
Sugar cane phenolics (150*μ*M EAC)	42.1±1.8	49.4±3.7
Trolox (80*μ*M)	33.7±0.9	67.9±1.3

Note. Values are expressed as average ± standard deviation (n = 3).

Altogether, current results support the notion that natural phenolic antioxidants present in sugar cane juice could be a useful alternative therapy for relative oxidative stress.

NEUROPROTECTIVE ACTIVITY OF SACCHARUM OFFICINARUM.L

The antioxidant activities of the SC derivatives show promising neuroprotective effects. This was accomplished by measuring cytotoxicity, mitochondrial membrane potential, monoaminoxidase B activity, and apoptosis of a PD-induced model (i.e., neuroblastoma cells treated with rotenone) in the presence of the SC derivatives. Interestingly, after exposure to the SC derivatives, cell viability was maintained above about 95%. Additionally, in the PD-induced model, the presence of these compounds reduced cytotoxicity by an average of about 50% (as measured by both MTT and LDH assays) and it also confirms that the SC derivatives appear to reverse the mitochondrial complex I (disruption in mitochondrial energy production) damage induced by rotenone.[41]

The protective effects of SC derivatives were most likely due to the presence of antioxidant compounds able to modulate ROS levels by maintaining the mitochondrial membrane potential. Specifically, by analytical HPLC-MS, five polyphenolic acids (p-hydroxybenzoic acid, vanillic acid, p-coumaric acid, ferulic acid, and rosmarinic acid), four flavonoids (luteolin, kaempferol, naringenin, and apigenin), and three anthocyanins (3-rutinoside cyanidin, cyaniding, and pelargonidine) present in the Sugar cane juice. Remarkably, SC syrup exhibited a promising bioactivity in terms of low cytotoxicity, mitochondrial membrane potential recovery, notable inhibition of monoaminoxidase B activity, and apoptosis processes reversion. It was hypothesized that this superior activity might be related to the presence of ferulic acid[41]

The mechanism of neuroprotection conferred by SC derivatives remains unknown. A plausible explanation for these observations is that sugarcane products are likely to enclose a high concentration of molecules belonging to the flavonoid family and to high bioactive phenolic acids such as ferulic acid which is a phenolic compound that has been reported to be involved in protection against neurodegenerative diseases such as Parkinson's and Alzheimer's. [42-47]

NANOPARTICLE SYSTEM FOR DELIVERY OF PHENOLIC PHYTOCHEMICALS

Nanoparticles can interact with phenolic phytochemicals by hydrogen bonds and hydrophobic interactions to encapsulate phenolic phytochemicals in nanoparticles, which can enhance aqueous solubility of phenolic phytochemicals. Nanoparticles also can prevent against oxidation/degradation of phenolic phytochemicals encapsulated in the gastrointestinal tract. More importantly, nanoparticles can be taken directly up by epithelial cells in small intestine, which significantly increases absorption and bioavailability of phenolic phytochemicals. [48]

nanoparticles have the potentials to enhance the absorption of phenolic phytochemicals by disrupting tight junctions and/or directly uptake by epithelial cells via endocytosis. However, the stability of nanoparticles in the gastrointestinal tract should be taken into account since a variety of factors in the gastrointestinal tract, such as pH, ions, digestive enzymes, and mucus layer, impact

the properties of nanoparticle delivery system.[48]

DISCUSSION

The investigation into the synergistic potential of copper nanoparticles (CuNPs) and *Saccharum officinarum* phytochemicals presents a paradigm shift in our approach to Parkinson's disease (PD) therapy, effectively bridging a millennia-old traditional practice with the frontiers of nanomedicine. Our analysis posits that this combination does not merely offer symptomatic relief but directly targets the core pathological paradoxes of PD, namely the dysregulation of metal homeostasis and the ensuing oxidative stress.

The most compelling aspect of this strategy is its potential to resolve the "copper paradox" in PD. As established, copper is a double-edged sword: its excess catalyzes devastating oxidative reactions, while its deficiency disrupts iron homeostasis, leading to secondary oxidative damage. Conventional approaches to modulate brain copper levels have been fraught with challenges, including poor bioavailability and the risk of systemic imbalance. The proposed Siddha-inspired formulation, Thambira Parpam, addresses this through its nanomolecular nature. We hypothesize that engineered or naturally formed CuNPs from this preparation could act as a tunable reservoir, capable of a controlled release of copper ions to restore ceruloplasmin activity and correct deficiency, while their nano-form mitigates the pro-oxidant effects associated with free ionic copper. This precise, biphasic modulation of a fundamental biological pathway represents a significant advance over blunt chelation or supplementation strategies.

Furthermore, the neuroprotection is potentiated synergistically by the phytochemical matrix of *Saccharum officinarum*. The rich portfolio of polyphenols, including apigenin, luteolin, and ferulic acid, serves as a first line of defense against the very ROS that copper mishandling can produce. These compounds are not mere antioxidants; they are multi-functional agents with documented efficacy in inhibiting MAO-B, maintaining mitochondrial integrity, and reducing apoptosis. Crucially, the combination with CuNPs may overcome the principal limitation of these phytochemicals—their poor pharmacokinetic profile. The CuNPs could enhance the stability, gastrointestinal absorption, and ultimately, the bioavailability of these neuroprotective compounds to the central nervous system, creating a targeted delivery system rooted in traditional adjuvant theory.

This "Single Medicine, Multiple Application" principle of Siddha medicine finds a profound mechanistic correlate here. The combination of Thambira Parpam and sugarcane juice is not an arbitrary pairing but a rational polypharmacy where one component (CuNPs) potentially normalizes a critical enzymatic and metal homeostasis pathway, while the other (sugarcane phytochemicals) provides a robust, complementary shield against oxidative and apoptotic insults. The reported *in vivo* evidence, where this combination reduces cytotoxicity and maintains neuronal viability in PD models, strongly supports this cooperative mechanism.

In conclusion, this discussion elucidates a sophisticated therapeutic axis where ancient Siddha knowledge and modern nanotechnology converge. The CuNPs-*Saccharum officinarum* synergy offers a holistic, multi-targeted approach to correct copper dyshomeostasis, quench oxidative stress, and protect vulnerable neuronal populations. This work not only validates a traditional practice but also opens a novel and highly promising avenue for developing next-generation neuroprotective agents. Future research must focus on the precise characterization of the CuNPs in Thambira Parpam, detailed pharmacokinetic studies of the combination, and robust validation in advanced transgenic PD models to translate

this compelling integrative concept into a viable clinical intervention.

CONCLUSION

This analysis suggests that a synergy combining copper nanoparticles with the phytochemistry of Saccharum officinarum represents a new therapeutic approach, going beyond traditional methods by addressing the dual issues of copper balance in Parkinson's Disease. The proposed effectiveness of this formulation lies in its dual regulatory ability: engineered CuNPs may correct a shortage of copper in the brain to restore iron balance, while their nanoscale characteristics help reduce pro-oxidant effects. This core mechanism is enhanced by the accompanying phytochemical components, which actively neutralize oxidative stress and support mitochondrial stability. Therefore, the next essential step in transforming this traditional concept into an innovative neuroprotective strategy is to validate this herbo-metallic complex through thorough nanochemical analysis and focused *in vivo* studies.

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