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EFFECT OF ARTESUNATE, ESOMEPRAZOLE AND COFFEE INTAKE ON PRODROMAL PARKINSON'S DISEASE FEATURES IN ADULT MEN

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ABSTRACT

The convergent molecular mechanisms of aging, type 2 diabetes mellitus, Alzheimer's disease, Parkinson's disease and Huntington's disease offer druggable targets. Present drugs for treatment of Parkinson's disease (PD) often fail to maintain steady efficacy and are often associated with undesirable side- effects There is now a paradigm shift in this age-related neurodegenerative disorder to agents that co-operatively target immune activation, the noxious agents-induced ATP-P2X7 cell death receptor-NLRP3inflammasome-adenosine $A2_A$ receptor-HMGBI signalling, upregulate the anti-oxidant Nrf-2/ARE axis, insulin signalling, and enhance mitochondrial function to attenuate the hallmarks of this intriguing disease. Animal experimentations demonstrated that artesunate (30 mg/kg) has a significant additive effect ($P < 0.05$) with caffeine (6 mg/kg) in lowering glucose and uric acid levels in *ad libitum* high-lipid + low-dose streptozotocin-induced type 2 diabetic male mice compared to controls. In the clinical work, the effect of low-dose artesunate (12.5 mg daily) and low-dose esomeprazole (10 mg daily) use in conjunction with coffee intake was investigated in 5 elderly patients with prodromal Parkinson's disease who had non-motor symptoms and the motor symptoms of bradykinesia, tremors, rigidity and postural imbalance. 3 weeks institution of the combined therapy significantly ($P < 0.05$) abrogated the postural imbalance, tremors and rigidity; and improved the bradykinesia, rapid eye movement sleep behavioural disorder and memory decline. The implication of the present study is that the combined

remedies deserve more attention in the prevention of the progression and treatment not only of Parkinson's disease but also of other age-related neurodegenerative disorders.

KEYWORDS: Parkinson's disease; Prodromal Stage; Coffee; Esomeprazole; Artesunate; Abrogation; Hallmarks.

INTRODUCTION

Parkinson's disease is the second most common age-related neurodegenerative disease after Alzheimer's disease.[1] It is at present an incurable movement disorder which affects I% of the population above 60 years, rising to 1 to 3 percent among persons 80 years of age and older.[2] The diagnosis is made clinically, although other disorders with prominent symptoms and signs of parkinsonism, such as postencephalitic, drug-induced and arteriosclerotic parkinsonism, may be confused with Parkinson's disease (PD) until the diagnosis is confirmed at autopsy. There may be a lower incidence in sub-saharan Africa (SSA) due to a relative youthfulness of the SSA population.[3] Mutations and downregulation in the parkin cluster genes park I (alpha-synuclein), park 2 (parkin), park 5 (UCH-I), park 6 (PINK I), park 7 (DJ-I), park 8 (LRRK2), park 9 (ATPI3A2), ataxin 3 (ATXN 3) are known to cause early-onset familial PD.[4] Most of the PD cases, however, are sporadic resulting from a complex interplay between genetics and environmental factors.[5]

The multi-system neurodegenerative process targets select neuronal groups throughout the neuraxis, including the retina and autonomic ganglia, to account for the non-motor and motor symptoms. The prototypical pathological features which explain the motor features include the accumulation of aggregated alpha synuclein (SNCA) in intraneuronal cytoplasmic eosinophilic inclusions known as *Lewy bodies* and the progressive loss of dopaminergic neurons in the ventral substantia nigra pars compacta.[6] These striking neuronal losses are not only in this region, but in other aminergic nuclei in cortical and limbic structures and in cholinergic nuclei in basal forebrain and subcortical areas.[7] Early cholinergic denervation in PD without dementia may be important in the clinical phenotype such as the dopamine non-responsive gait, balance impairments and falls.

Aging, mitochondrial function, oxidative stress, NAD(P)H: Quinone oxidoreductase I (NQOI), aldehyde dehydrogenase I (ALDHIAI, the homeobox gene Pitx3, L-type CavI.3, dopamine D2 receptor, selective activation of the K-ATP potassium channel which enhances striatal iron uptake and the lower calbindin to buffer calcium in the ventral substantia nigra

pars compacta (SNpc) are some of the major determining factors in the selective vulnerability of SNpc dopaminergic neurons relative to the dopaminergic neurons in the ventral tegmental area.[8][9][10] NurrI, upregulated by the anti-malarials chloroquine and amodiaquine, is unlikely to play a role in selective dopaminergic neuron vulnerability.

Unfolding evidence suggests that the major neurodegenerative diseases of type 2 diabetes mellitus, Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) share convergent aetiopathogenic molecular mechanisms with aging. Aging, type 2 diabetes and neurodegenerative disorders share several dysregulated pathways.[5][11][12] These include immune inflammatory dysregulation,[13][14][15][16][17][18] disturbed proteastasis and autophagy leading to protein misfolding, aggregation and toxicity,[19][20][21][22] increased dopamine oxidation,[23][24][25][26] mitochondrial dysfunction which may also be induced by environmental toxins,[1][8][18][27] metal ion dyshomeostasis,[28][29][30] astrogliosis, microgliosis and increased ROS production from mitochondrial dysfunction, NAD(P)H oxidase, lysosomes and peroxisomes.[31][32][33]

The macroautophagy-lysosomal pathway is essential for maintaining protein and energy homeostasis.[34] The chatterbox (always spiking) phenotype of SNpc neurons impose heavy burden on mitochondria and its dysfunction is a pivotal step in PD pathogenesis.[35] Increased ROS- and RNS- induced nitrosative stress, (for example, due to excessive uric acid and AGEs),[36][37] lead to S-nitrosylation of chaperone proteins, mitochondrial and ubiquitin-proteasome system (UPS) dysfunction and this may be the early event leading to protein misfolding in aging, type 2 diabetes and age-related neurodegenerative diseases.[38][39] Although lewy body formation with alpha-synuclein accumulation is a critical pathological feature of PD and other lewy body diseases such as multi-system atrophy and lewy body dementia, interaction and reciprocal induction between alpha-synuclein and amyloid-beta and between them and tau protein complicates the clinicopathological picture.[22][40][41]

Critical regulatory pathways in Parkinson's disease

i) Activation of AMPK stimulates Na^+-K^+-ATPase which is downregulated in PD,[42] and prevents intracellular Na^+/Ca^{2+}-induced excititoxicity in SNpc.

ii) In PD, there is reduction in GABAergic synapses with increased function/neurotransmission of remaining dopaminergic neurons. This increased inhibitory basal ganglia inputs eventually induce excitatory motor signals in the thalamus. In a low

dopamine state, thalamic neurons with rebound firing increases leading to the PD motor symptoms.[4][43]

iii) Redox reactions induced by nitrosative stress mediate protein misfolding and mitochondrial dysfunction in neurodegenerative diseases.[38] Several PD-associated genes such as LRRK2 interface with mitochondrial dynamics regulating the structure and function of the mitochondrial network. Endogenous responses to upregulate Nrf2 and mitochondrial biogenesis in PD may be insufficient to prevent the progression of neurodegeneration. Thus, further activation of the Nrf2/ARE system using exogenous inducers may be a plausible therapeutic approach.[2] Reduction of oxidative-nitrosative stress decreases ATP release via pannexin-I channels, thus attenuating NAD(P)H oxidase levels. Additionally, inhibition of S-nitrosylation suppresses iron trafficking while antioxidants mediate both iron homeostasis and decrease oxidative stress.[44][45]

iv) Insulin resistance increases dopamine turn-over in brain, alters monoamine oxidase levels and enhances nigrostriatal neurodegeneration.[24][46] This and stress, drug addiction, iron, L-dopa treatment increase dopamine metabolism which favour prion protein accumulation and affect autophagic flux.[19]

v) Aging leads to upregulation of angiotensin II ATI subtype receptor which increases NAD(P)H oxidase levels and increases the vulnerability of the dopaminergic system to oxidative stress.[25][26]

vi) ATP-P2X7 cell death receptor-NLRP3 inflammasome activation- adenosine $A2_A$ receptor –Caspase I-HMGBI signalling pathway is critical for PD aetiopathogenesis. Extracellular ATP induces intracellular alpha-synuclein accumulation.[47] *Uric acid is an indicator of purinergic turn-over.*[48] Amyloid-beta, alpha-synuclein, huntingtin proteins, infections, stressors, glucose, uric acid and haemozoin induce ATP release.[49][50][51][52][53][54][55] Adenosine is required for sustained infammasome activation while the initial priming is by TLR/NF-kappa B.[56][57]

vii) The KEAPI-Nrf2 pathway is a promising therapeutic target to counteract ROS-mediated damage in cancers and neurodegenerative diseases.[18][58][59][60][61] The transcription factor nuclear factor erythroid 2-p-450 related factor 2 (Nrf2) is an emerging target to counteract mitochondrial dysfunction and its consequences in PD. AMPK activators and calorie restriction-mimetics such as sulforaphane and metformin activate Nrf2. Above all, Nrf2 mitigates LRRK2- and alpha-synuclein-induced neurodegeneration by modulating proteastasis.[62][63][64][65][66]

Aim of the study

The aim of the study of the study was i) to investigate the effect of artesunate and caffeine on uric acid levels in streptozotocin-induced diabetic mice; ii) to study the effect of artesunate, esomeprazole and coffee intake in male volunteers with prodromal or early onset parkinsonian features.

Methods

The first arm of the study was done in the Dept. of Pharmacology and Clinical Chemisty laboratory in University of Benin Teaching Hospital, Benin-City. Test mice were administered high fat diet (ground-nut feeding for a week) before the administration of streptozotocin (40 mg/kg ip) in buffered citrate solution at pH 4.5 daily for 5 days to induce type2 diabetes mellitus.[67] Control mice received citrate buffer ip. 8 mice in another control group received caffeine (6 mg/kg ip) while the test group received caffeine and artesunate (200 mg/kg ip). Uric acid levels were determined at 4 weeks, 6 weeks and 8 weeks by spectrophotometric analysis using only *clear plasma*.

Concurrently, glucose levels were determined by automatic analysers (ACCUCHECK). The test mice on caffeine and artesunate were pre-treated with these drugs for two weeks when the switch from hyperglycaemia to hypoglycaemia occurred.

Preparation of citrate buffer for dissolving streptozotocin

Streptozotocin was obtained from Sigma-Aldrich. Weight of citric acid: 2.01 gm; Weigt of sodium citrate: 2.94 gm. Citric acid was dissolved in 100 ml distilled water. Trisodium citrate was dissolved in the same volume of distilled water. A buffered solution of pH 4.5 was made after titrating the trisodium citrate (pH 7) against the citric acid (pH 4). A stock solution of streptozotocin was then prepared fresh each time.

For administration: weight of animal in KG multiplied by dose (40 mg/kg). This is divided by stock solution of 20 mg/ml to give 0.05 ml. 1 ml syringes are used for mice with 25 gauge needls for ip administration.

Technique of blood collection from mice: This was done as terminal procedure employing 80 mg/kg of ketamine ip as anaesthetic agent. 1 ml to 2 ml of blood is taken through cardiac puncture using the sub-xyphoid route.

In the second arm of the study at Oseghale Oriaifo Medical Centre, Ekpoma,5 volunteers 68-80 years with early-onset (prodromal) parkinsonian features participated. Two of these volunteers have had treatment –resistant essential tremor at least 4 years and the 3 other volunteers have had increasing anxiety/loss of interest in some areas of life. These were combined with sleep disorders for 2 years plus increasing poverty of movements, occasional memory loss, freezing and falls. There was unilateral asymmetry of facial expression and occasional fine tremors of one side of the body. One noticed loss of sense of smell. None was yet on treatment for Parkinson's disease before institution of present test treatment which lasted for 12 weeks.

Coffee intake was one cup to not more than 2 cups a day in order to prevent the possible neurotoxic effects of high coffee intake. Artesunate and esomeprazole daily doses were 12.5 mg and 10 mg tablets. Esomeprazole intake was for a two-weekly period in a month after the first 4 weeks in order to forestall its adverse effects such as pneumonia because of lessened stomach acidity.[68]

Table 1: Effect of Caffeine and Artesunate on Glucose and Uric Acid Levels in Streptozotocin + High Fat – Induced Diabetic Mice.

	Baseline		1 week		4 weeks		6 weeks		8 weeks	
	Glucose mg/dl	Uric mg/dl	Glucose mg/dl	Uric mg/dl	Glucose mg/dl	Uric mg/dl	Glucose mg/dl	Uric mg/dl	Glucose mg/dl	Uric mg/dl
Straptozotain (40mg/kg) + Groundnut Induction	126.20 ±2.20	2.81 ±0.70	144.8 ±3.80	3.04 ±0.27	345.0 ±7.30	7.30± 7.30	377.5 ±5.50	9.30 ±5.10	350.2 ±5.60	9.10 ±3.20
Caffeine (6mg/kg)	126.50 ±2.10	2.90 ±0.60	140.8 ±4.20	2.96 ±0.31	115.6 ±2.50	2.71± 7.10	108.6 ±4.40	2.50 ±6.30	107.3 ±6.30	2.50 ±1.80
Artesunate + Caffeine	125.80 ±2.00	2.88 ±0.50	141.20 ±4.40	2.74 ±0.28	103.1 ±4.20	2.24± 2.24	96.90 ±7.20	2.11 ±2.90	95.80 ±3.40	2.11 ±1.40

Table1: Artesunate + Caffeine administration significantly ($P<0.05$) reduced glucose and uric acid levels more than caffeine alone 4^{th} – 8^{th} weeks. Statistical analysis was done by Student's (unpaired) t-test.

Table 2: Clinical profile of participants.

Clinical characteristic	At presentation	After treatment for 4 weeks
Age at onset of PD in men, years	69-80	
Interval from onset to diagnosis, months	6-9	
Hoehn &Yahr scale	1.45 ± 0.5-1.9	0.5 ± 0.00-0.9
UPDRS Total score	26.24 ± 9.30	5.20 ± 7.20
UPDRS Motor score	12.62 ± 5.32	2.80 ± 0.60
UPDRS ADL score	3.12 ± 3.08	0.05 ± 2.64
Average glucose level (mg/dl)	115.36 ± 3.42	84.55 ± 7.28
Average uric acid levels (mg/dl)	9.21 ± 2.11	2.87± 1.68

Table 2: Drug treatment with coffee, artesunate and esomeprazole significantly (P < 0.05) abrogated the progress of Hoehn and Yahr Stage I parkinsonian features.

Fig. 1: Possible non-motor and motor features in Parkinson's disease.

Part I: Evaluation of mental activity, behaviour and mood: Intellectual impairment Thought disorder Motivation / initiative Depression Sleep Pain Bladder and bowel problems Fatigue	**Part II: Self-evaluation of activities of daily living:** Speech Salivation Swallowing Handwriting Cutting food Dressing Hygiene Turning in bed Falling Freezing Walking Tremor Sensory difficulties
Part III: Evaluation of motor function: Speech Facial expression Tremor at rest Action tremor Rigidity Finger taps Hand movements Rotation of hands and forearms so palms facedownward Rotation of hands and forearms so palms faceupward Toe taps Leg agility Rising from chair Posture Gait Postural stabilityBradykinesia	

Figure I: Non-motor and motor symptoms in Parkinson;s disease (Source: European Parkinson's Disease Association). In our series, bradykinesia was the most prominent motor symptom; while loss of memory was the most prominent non-motor symptom

Clinical diagnosis of Parkinson's disease

Patients had noticed sleep disorders, constipation and increasing olfactory loss (hposmia or anosmia) for at least 24 months before presentation. 3 of the patients had sleep disorders with acting out of dreams which were vivid. 1 of the patients noticed changes in sense of smell.

These were combined with later development of subtle bradykinesia/hypokinesia (slowness of movement and decrease in amplitude or speed as movements are continued), reduced arm swing, occasional rest tremor and rigidity. The mild rigidity was of the lead-pipe variety. These non-motor symptoms and unclear motor signs are diagnostic of the prodromal stage of Parkinson's disease, equivalent to Braak stage 2/3 or Hoehn and Yahr Stage I. Although the sample size is small, these features fulfil Movement Disorder Society (MDS) Clinical Diagnostic Criteria for early-onset Parkinson's disease. They also concord with results of the Tuebinger Evaluation of Risk Factors for Early Detection of Neurodegeneration (TREND) study. Sleep disorders especially rapid eye movement sleep behavioural disorders are common in the alpha-synucleinopathies.

2 of the patients were agricultural workers continuously exposed to pesticides and herbicides. One was a type 2 diabetic and the other 2 had family history of essential tremor. These had raised the index of suspicion. Also, 3 of the patients were on medications for essential hypertension which included losartan and we questioned whether this could have influenced disease progression.

Neuroimaging investigations such as SPECT, PET, MRI and DAT-SPECT were not done as facilities are not yet available.

Differential diagnosis of early-onset Parkinson's disease

- Essential (postural/kinetic) tremor
- Secondary parkinsonism due to drugs such as anti-psychotics, metoclopramide, MPTP, zinc, paraquat.
- Atypical Parkinson's disease. Examples are lewy body disease, multiple system aotrphy, progressive supranuclear palsy, corticobasal degeneration. There may be no tremors.
- Alzheimer's disease
- Huntington's disease
- Friedreich's ataxia
- Cardioembolic stroke
- Lacunar syndrome
- Normal pressure hydrocephalus
- Striatonigral degeneration
- Frontotemporal dementia

RESULTS

Streptozotocin-induced type 2 diabetes was pronounced between the 4th week and 8th weeks (Table 1) and then started to tail off. The experiments show that caffeine and artesunate combination was significantly ($P < 0.05$) more effective than caffeine alone in lowering elevated glucose and uric acid levels occasioned by streptozotocin-induced type 2 diabetes mellitus.

In the clinical arm of the results, bradykinesia was the most prominent motor symptom; while loss of memory was the most prominent non-motor symptom. Results showed that low-dose coffee consumption, low-dose artesunate and low-dose intermittent esomeprazole given sunchronically significantly abrogated the progression of bradykinesia, rest tremors, rigidity and postural imbalance due to subtle early-onset Parkinson's disease (Table 2). Non-motor symptoms such as depression, cognitive and memory decline were also reversed. The drug combination also decreased glucose and uric levels more than coffee alone (Table 2).

DISCUSSION

Present demographic pattern in sub-saharan Africa,[3] which may be presently skewed in favour of a high younger age distribution compared to Europeans may indicate the need for greater surveillance for prodromal Parkinson's disease features. The features may remain elusive unless the physician's index of suspicion is high.

Investigators have noted the beneficial effects of coffee consumption in early and advanced Parkinson's disease (PD) motor and non-motor symptoms,[69][70][71][72][73] and it is a known adjuvant drug for PD.[74] Helicobacter pylori infection may be associated with PD and its eradication with PPIs has been known to improve levodopa action, clinical symptoms and quality of life.[75][76]

Present report highlights the significant additive effect of artesunate and caffeine (present in coffee) in reversing streptozotocin-induced increases in blood glucose and uric acid levels mice. Artesunate, esomeprazole and coffee intake also significantly decreased elevated glucose and uric acid levels in human volunteers. High-glucose-induced advanced glycation end-products and uric acid, a major endogenous danger molecule, may increase nitrosative stress via NAD(P)H oxidase followed by endoplasmic reticulum stress-induced mitochondrial dysfunction.[77][78] They also activate NLRP3 receptor signalling.[79][80] AMPK activators such as low-dose artesunate, esomeprazole and coffee are associated with reducing

glucose and uric acid levels in human diabetics. Investigators have reported that uric acid causes hippocampal gliosis and cognitive decline via TLR4-NF-kappaB pathway.[81] There is the caveat, though, that uric acid may indirectly enhance adaptive immunity via antigen presenting cells. Also, the clinical study showed that the drug combination of artesunate, esomeprazole and low-dose coffee consumption abrogated the progression of parkinsonian features in prodromal or early-onset PD and treatment-resistant essential tremor.[82][83][84]

PPIs may directly enhance vesicular monoamine transporter 2 (VMAT2).[85] They also inhibit tyrosinase,[86] and of the absorption of iron and zinc (divalent metals). These effects may result in the induction of VMAT2 and enhancement of vesicular import of dopamine and implies that PPIs may induce attenuation of dopamine oxidation and prevent toxic effects of dopamine metabolism in PD.[87][88][89][90][91] Increased non-oxidative dopamine thus generated display protective anti-ferroptotic activity.[92] Ferrous ion is known to induce alpha-synuclein aggregation and neurotoxicity by inhibiting NRF2-HOI pathway.[18] The reduction of iron absorption in aging may be protective against neurodegenerative disorders. Esomeprazole and caffeine also inhibit monoamine oxidase to decrease the aberrant MAO oxidase activity associated with insulin resistance in aging, type 2 DM and neurodegenerative disorders.[93] Both agents may also induce acetylcholine release in basal fore-brain which is beneficial in early parkinson's dopamine non-responsive gait disturbance. Importantly, the low GABAergic neurotransmission in SNpc in PD responsible for the rebound firing and motor features may be rescued by the GABA-A receptor-enhancing properties of artesunate and regular low-dose coffee consumption.

Caffeine, artesunate and esomeprazole increase pancreatic beta-cell mass, increase beta-cell neogenesis via GABA-A receptors and via gastrin respectively.[94][95][96][97][98] Enhancing insulin signalling by hypoglycaemic drugs offsets the deleterious effect of alpha-synuclein/K-ATP channel interaction which attenuates pancreatic insulin secretion. This favourably impacts antioxidant aldehyde dehydrogenase I activity, mitochondrial function, decreases dopamine oxidation and decreases nigrostriatal neurodegeneration, and is a new target in PD pharmacotherapy.[24][46][99] The activation of AMPK by the three agents increase NA-K-ATPase activity which attenuate hyperplolarisation-mediated excitotoxicity. It also suppresses age-related increases in glucose and uric acid levels, oxidative stress, prion protein accumulation and iron trafficking.

Of a very significant import is the attenuation of the ATP-P2X7 cell death receptor-NLRP3inflammasome-adenosin$A2_A$ receptor-caspase-I signalling axis as an indispensable prognostic factor in the treatment of age-related tye 2 diabetes and neurodegenerative disorders.[47][100][101][102][103][104] Artesunate, esomeprazole and caffeine inhibit excessive ATP release associated with these disorders and attenuate this signalling pathway to confer benefits in aging, PD and other age-related neurodegenerative disorders.[105][106][107][108][109] Epidemiological evidence indicates that regular human consumption of caffeine, a non-selective $A2_2$ receptor antagonist, is associated with reduced cognitive decline in aging, AD, PD and HD.[110][111] The implication of the present work is that caffeine in coffee, which blocks adenosine $A2_a$ receptors and the NLRC4 inflammasome, by its modulatory effects on factors of the same signalling pathway with artesunate and esomeprazole, possesses a possible synergistic effect with these agents in the extenuation of the progression of PD. Coffee also inhibits the P2YI metabotropic receptor but needs combination with other agents such as artesunate that antagonise P2X7 ionotropic receptor signalling.[74][112][113]

The Nrf2-ARE signalling pathway negatively regulates ROS-induced NLRP3 inflammasome activity.[58] Artesunate, esomeprazole and coffee activate the NRF2-ARE signalling pathway by direct molecular interaction/modification of KEAP-I to inhibit NF-kappaB- and caspase-I-induced apoptotic pathways.[114][115][116][117] The agents also induce phase II detoxification enzymes such as NAD(P)H: Quinone oxidoreductase I and aldehyde dehydrogenase I via this mechanism mediated by this upregulation of the antioxidant Nrf2-ARE system which enhances mitochondrial function and insulin signalling pathway.[118][119][120] Induction of Nrf2 mitigates alpha-synuclein-induced neurodegeneration by modulating proteastasis.[63] The anti-aging agent, calorie restriction-mimetic and AMPK activator, rapamycin activates Nrf2 and inhibits NLRP3 inflammasome activation in an autophagy-dependent manner;[121] effects also exhibited by artesunate, esomeprazole and coffee.

PD has been hypothesized to be a Th_{17}-dominant auto-immune disorder against accumulated alpha-synuclein. An interaction between IL-17 and angiotensin II ATI subtype receptor may have a role in inflammatory tissue injury, autoimmunity, oxidative stress and aging.[15][122][123] Modulating the immune system for therapeutic gain in PD is being explored such as using Tregs to mediate immune suppression and attenuate Th_{17} cell-mediated nigrostriatal dopaminergic neurodegeneration.[124] A vaccine against alpha-synuclein increases Tregs,[125] an effect that may also be achieved by low dose artesunate.[126]

In conclusion, present evidence is that coffee intake, low-dose artesunate and esomeprazole may reverse early presentations in PD. The drug combination also significantly enhances glucose homeostasis and decrease uric acid levels, both which may be markers of oxidative stress and proteinopathy in aging, type 2 diabetes and neurodegenerative diseases.

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