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Review Article

Potentiality of Coffee (*Coffea robusta*) and its Bioactive Compounds in Memory Function: A Review

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ABSTRACT

Memory dysfunction is a neurodegenerative disorder in which a person loses his memory, where AD (Alzheimer's disease) is appraised as the major trigger of it. Today, everyday consumption of coffee has become a modern lifestyle, and this culture has gained more attention to the researchers. In this study, the potentiality of *Coffea robusta* and its bioactive compounds in memory function are presented. The latest articles (2018 to 2023) from databases (Scopus, Google Scholar and PubMed) were screened and 120 references were selected for this review. The major keywords for searching were "Coffee", "*Coffea robusta"*, "bioactive compounds", "memory dysfunction" and "Alzheimer's disease". For the improvement of memory function, *C. robusta* and its bioactive compounds, such as caffeine acts as antioxidant and its major targets are adenosine receptors while chlorogenic acid reduces amyloid *β* (A*β*) deposition, neo and crypto-chlorogenic acid scavenge reactive oxygen species (ROS) in neuronal cells, moreover, trigonelline prevents neuronal injury by bringing down astrocyte activity, and antioxidant activity of melanoidins (especially interfering redox-sensitive transcription factors) contribute to their beneficial effects in AD and impart neuroprotection as well as increase memory function.

Keywords: coffee, caffeine, chlorogenic acid, Alzheimer, neuroprotective

Introduction

Memory dysfunction is a neurodegenerative disease in which memory of an individual is affected.[1] Majorly, memory dysfunction is developed by AD (Alzheimer's disease) which was demonstrated by Alois Alzheimer over a century ago,[2] the most persistent cause of dementia aged ≥65 years[3] and leads to a progressive memory dysfunction.[4] AD pathological process chiefly includes the aggregation of Aβ (amyloid β) peptides extracellularly and NFT (neurofibrillary tangles) of Tau protein intracellularly,[5] which are triggered by oxidative stress, modulation of cholinergic as well as glutamatergic systems and ion channels (for instance, Ca^{2+}).[6] Global burden,[7] incidence, prevalence and mortality are increasing by leaps and bounds as a consequence of lack of proper diagnosis of AD.[3] In 2020, worldwide fifty five million population were believed to be living with dementia. Some strategies reported, with the increase in the population, this figure is estimated to raise to 78 and 139 million people in 2030 and 2050, respectively.[8] In recent decades, scientists and researchers are focusing on the bioactive compounds to improve memory function in AD patients.

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Coffee is the most predominant beverage,[9–11] commercially traded and cultivated commodity globally. Over the last ten years, interest in coffee consumption has been increased continuously and the utilization is aggrandized 1-2% by each year in the world.[12] ICO (International Coffee Organization) stated, the global coffee exports in trade statistics-July 2022 counted as to 10.12 million bags[13]. On the other hand, in 2020-2021, *Coffea robusta* (*C. robusta*) has 73.72 million 60 kg bags production and is forecasted to increase in size to over 77 million 60 kg bags.[14] The yearly sale of coffee is approximately $200 billion USD, and it is anticipated that upcoming demand of coffee will keep rising.[12] Historically, *Coffea* species are originated from Africa, specifically Ethiopia, cultivated annually and once or twice a year cherries are collected to get beans.[10] Indonesia, Uganda and India are considered the main coffee producing countries[12] while Indonesia, Brazil, Philippines, Ethiopia, Mexico, India, Vietnam, Venezuela, Thailand and Colombia are reported as coffee consuming top 10 countries, where the highest consumption of coffee has been reported in Brazil.[9]

Genus *Coffea*, family Rubiaceae, has 124 distinct known species,[12,15] among them, *C. robusta* and *Coffea Arabica* (*C. arabica*) are the most famous worldwide.[16] Vietnam and Brazil are the world's the biggest producer of *C. robusta*,[9,15,17] also known as *Coffea canephora*.[12] *C. robusta*, due to many good characteristics, has been superseded over *C. arabica*, as it is cheaper[18] and has higher quantities of caffeine and chlorogenic acid than *C. Arabica*.[10] Also, *C. robusta* is more stable to biotic and abiotic stresses than *C. arabica*.[19] *C. robusta* is one of the natural product which is beneficial in promoting human health,[9–11,20] including antipsychotic,[16] hepatoprotective, antidiabetic (especially in Type 2 diabetes), antiobesity, anticancer,[20] antiamyloidogenic[21], anti-inflammatory,[20,22] antioxidant[20] and antiglycation activities due to its bioactive compounds. But its antioxidative activity is broader as compared to black and green tea extracts.[23] Moreover, increased values of caffeine and chlorogenic acid in *C. robusta*[10] make it

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possible beneficial candidate for different neurodegenerative diseases, specifically AD, Parkinson Disease (PD), dementia and memory dysfunction,[16,24] Currently, there is no medication for AD that completely reverse it, however there are many scientific evidences on the consumption of coffee as well as AD development, and their focal point is that coffee consumption has an inverse link with the progression of AD,[25] thereby enhancing memory.

This is the first review that collected information from the most recent literatures about the effect of *C. robusta* on memory function. The aim of this review was to summarize the data on *C. robusta* and its bioactive components that have a potential effect on memory function.

Methodology

Authors explored the core collections of Scopus, Google Scholar, and Pubmed databases for the data related to *C. robusta* and its bioactive compounds in memory function using major keywords: "Coffee", "*Coffea robusta"*, "bioactive compounds", "memory dysfunction" and "Alzheimer's disease". More than 210 papers (from 2018 to October 2023) were reviewed, among them 120 references were found suitable for this review. All the chemical structures were drawn using ChemDraw Ultra 12.0.2.

Pathology behind memory dysfunction

Aβ deposition, Tau accumulation and oxidative stress are the major causes of AD which leads memory dysfunction.

Amyloid β deposition causes oxidative stress resulting in memory dysfunction

The sequential cleavage of APP (amyloid precursor protein) undergoes nonamyloidogenic processing by γ-secretase and β-secretase, and generates Aβ peptides.[26] In accordance with the "amyloid hypothesis",[27] the neurotoxic deposition of Aβ in neuron cells in the cerebral cortex and hippocampus areas triggers AD development[26,28] which leads to serious impairment of synaptic capacity, neuronal function and cognitive decline as well.[29] By contrast, the physiological role of APP except AD pathogenesis has not been fully explored.[27] Further, many metal ions have negative effect on Aβ peptides, as Zinc ion (Zn^{2+}) has affinity to bind with Aβ by interfering with the residues at the N-terminal region, and consequently is proactively involved in the formation of Aβ fibrils and induce cytotoxicity due to Aβ plaques.[30] Aβ accumulation activates ROS (reactive oxygen species) synthesis which results in oxidative stress, and thus damages neuron cells in AD[26] that resulting in memory dysfunction.

Tau accumulation causes oxidative stress leading memory dysfunction

From bio-medical point of view, the curiosity in Tau protein emerged abruptly when Tau had gained importance as an integral part of NFT, a pathological hallmark of AD. Tau, a highly soluble intrinsically disordered protein, was identified by Weingarten and colleagues[31] to search microtubule-associated protein that promotes microtubule self-assembly. This microtubule-associated protein Tau increases the stability of axonal microtubules in the CNS, and also, regulated axonal outgrowth and transport. Tau binds with microtubules and is governed by post-translational modifications, mainly phosphorylation, which also regulate a number of other minor functions of Tau.[32] Notwithstanding, if one time Tau becomes hyperphosphorylated, it abides a conformational change and no longer available for microtubules. The unbound Tau accumulates, known as Tau oligomers which aggregate and form NFT. Tau oligomers explicated more neurotoxicity than NFT that consists of highly phosphorylated Tau, Aβ and senile plaques[33] which causes severe memory impairment, neuronal function and synaptic capacity disabilities in brain.[29] NFT of hyperphosphorylated Tau proteins exhibit mitochondrial damage that induces oxidative stress by ROS and neuron cells injury in AD[34], thereby leading memory dysfunction.

Unfortunately, the mechanism responsible for AD development and memory dysfunction is not yet clear. However, oxidative stress is considered to be the initial event in AD pathogenesis as well as in memory dysfunction.[35]

Association of oxidative stress and memory dysfunction

Oxidative stress, a redox steady-state imbalance,[36] arises from ROS which is released by defective mitochondria. There are many factors that trigger oxidative stress and give rise to AD, including hypoxia, aging, traumatic brain injury, autophagy and synaptic disability.[37] Notably, AD is followed by oxidative stress, loss of synapses and cortical neurons, mitochondrial functional and structural deformities, neuroinflammation, micro-ribonucleic acid (RNA) deregulation, deposition of Aβ, hyperphosphorylation of Tau protein, neuronal loss,[38] cholinergic dysfunction and ROS generation.[39,40] The vital element of mitochondrial ETC (electron transport chain) is the production of ROS, a physiological by-product of ETC[41] synthesized under multiple enzymatic reactions.[40] Bearing in mind that mitochondria are susceptible to oxidative stress provoked by rampant ROS production,[42] which eventually interferes with the function of neurons and hastened neurodegeneration[39] and neuroinflammation during AD.[40] It is clear that oxidative stress is the main reason of neuronal cell death in AD that effects memory (Figure 1).

On the other hand, several subcellular organelles, such as nitric oxide synthase (NOS), xanthine oxidase (XO), NAD(P)H oxidase (NOX), and cyclooxygenase (COX) as a specific enzymes they produce intracellular ROS. The cellular molecules, including NF-κB (nuclear factor-kappa B), MAPK (mitogen-activated protein kinase), and mTOR (mammalian target of rapamycin) pathways trigger ROS generation, e.g., hydroxyl radical (OH^-), hydrogen peroxide (H_2O_2), and superoxide anion (O_2^-), and they exert neurotoxicity. In addition to this, inadequate antioxidant status worsens the pathology of AD.[40] Neurotoxicity induced by Aβ peptides and hyperphosphorylated Tau proteins are reinforced by oxidative stress in AD in which kinky levels of oxidized proteins, modifications of nuclear and mitochondrial deoxyribonucleic acid (DNA), lipid peroxidation and advanced glycation end (AGE) products come across as the driving force in AD-linked cellular structural changes. Consequently, this causes permanent cellular damage and neuronal death.[43]

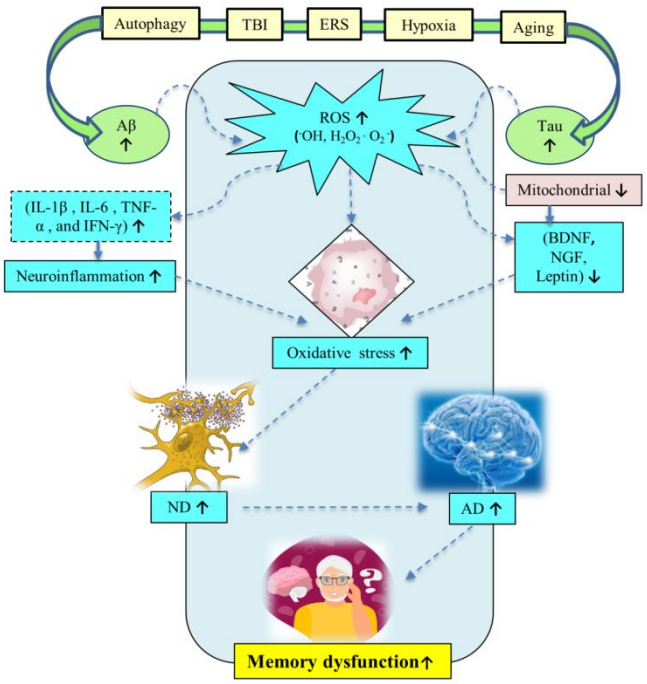

Figure 1: Schematic diagram of memory dysfunction caused by oxidative stress and its inducing factors.[36-70]

Abberivations: TBI: Traumatic brain injury; ERS: Endoplasmic reticulum stress; Aβ: Amyloid beta; ROS: Reactive oxygen species; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; IFN-γ: Interferon gamma; OH−: Hydroxyl radical; H2O2: Hydrogen peroxide; O2−:superoxide anion; BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor; ND: Neurodegeneration; AD: Alzheimer's Disease.

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Furthermore, oxidative stress activates proinflammatory cytokines which are key mediators in the development of AD.[44] However, the endogenous antioxidant defense system such as mitochondrial glutathione (GSH) can execute a potential activity in cell survival under both pathological and physiological situations.[42] Reduction in ROS production by GSH and similar enzymes increases the life span of neurons and subsequent prevention in AD and related memory dysfunction.

Endogenous antioxidant defense system and memory function

Oxidation reactions can create free radicals when chain reaction occurs in a cell and this reaction can cause injury or death to a neuron cell. Antioxidants are molecules that halt free radical generation and their reactions, thereby inhibiting neuronal cell damage.[45] The natural antioxidant system protects neurons from injuries, for instance, Nrf2 (nuclear factor erythroid 2-related factor 2), a redox-sensitive transcription factor, keeps redox homeostasis by governing ARE (antioxidant-response element)-dependent transcription as well as the expression of antioxidant defense enzymes. Considering that Nrf2 triggers the antioxidant system in retaliation to oxidative stress. Nrf2, one of the primary pathway, counterbalances mitochondrial ROS synthesis. Nrf2-dependent antioxidant enzymes include GSH and thioredoxin (TRX).[42] Likewise, mitochondrial transcription factor A (TFAM), peroxisome proliferator-activated receptor-gamma (PPARγ), nuclear factor erythroid 2-related factor 1 (Nrf1), Nrf2, and peroxisome proliferator-activated receptor-γ coactivator-1 alpha (PGC-1α) in the nucleus and mitochondria are among the transcriptional factors that regulate the process of synthesis in new mitochondria in neurons.[35] Lucon-Xiccato *et al.*[46] suggested that BDNF (brain-derived neurotrophic factor) is another transcription factor and largely expressed in brain, where it regulates vital signaling pathways for neuron differentiation, growth, survival, synaptic plasticity, and neurotransmitters release, hence they protect from neurodegeneration and increase neuroplasticity and memory function. Moreover, microglial cells have a considerable role in neuronal recovery and normal brain development, however microglia over activation causes neuronal death linked with neurodegenerative diseases such as AD[47] and memory dysfunction.

Natural antioxidants are quite safer than synthetic antioxidants (potentially dangerous for human health).[48] Owing to high natural antioxidant activity,[20] coffee has been a widespread research concern against AD.[49]

Molecular targets of C. robusta and memory function

There are many targets [such as Nrf2, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), Aβ peptides, Tau protein, N-Methyl-D-aspartic acid receptor (NMDAR), interleukin-6 (IL-6), interlukin-1β (IL-1β), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), glial fibrillary acidic protein (GFAP), cAMP (cyclic adenosine monophosphate)-dependent PKA (protein kinase A), CREB (cAMP response element binding protein), JNK (c-Jun N-terminal kinase), BDNF and tropomyosin receptor kinase B (TrkB)] in neuron cells in which *C. robusta* has successfully counteracted AD and masked its associated symptoms. These targets regulate ROS, such as OH^-, H_2O_2, and O_2^- that damage neuron cells by inducing oxidative stress, thereby leading to multiple serious health issues like neurodegenerative diseases, e.g., AD, memory dysfunction and ageing.[50]

C. robusta has reduced the generation of ROS in a radiation-induced DNA damage and apoptosis by activating Nrf2 factor[51] and prevented from AD development due to oxidative stress[52] Roasted coffee extract has been proven the best tyrosinase,[50] an enzyme that acts as an important role in adaptive immune responses and neuroinflammation,[53] inhibitory activity.[50] Coffee and its bioactive compounds deliver antioxidant and anti-inflammatory activities, which help to reduce cognitive decline.[54] The antioxidative effect of *C. robusta* is chiefly linked with its polyphenols because they have scavenging free radicals capability in the biological system.[55] Marucci *et al.*[56] have investigated, acetylcholine (ACh), a muscarinic agonist, is hydrolytically broken down by two cholinesterases, AChE and BChE, in the brain (cerebral cortex and hippocampus regions). An impaired cholinergic signaling is required in the pathology of learning and memory impairments in AD. Furthermore, the *in-silico* studies investigated, the role of sumptuously rich caffeine and chlorogenic acid in AChE inhibition in AD.[55] The inhibition of AChE and BChE, the ACh catabolic enzymes, can participate to rise Ach (an important regulator of memory) levels in brain.[56] However, ethanol and water extracts of coffee exhibited predominant AChE and BChE inhibition activity in AD and normalized memory function.[50]

Zidan *et al.*[57] described, coffee is an effective therapeutic intervention against AD, protects from memory decline and lowers serum levels of Aβ peptides, the fundamental contributor to AD pathogenesis. Interestingly, coffee appears to provide prominent protection against AD as proofed by the higher abatement in Aβ serum levels. Large quantity of coffee consumption efficiently improves cognitive function by delaying cerebral Aβ aggregation, and thus mitigating the accompanying Aβ-mediated inflammatory processes neurotoxicity and oxidative stress. [58] Furthermore, Paz-Graniel *et al.*[59] have evaluated, certain *in-vivo* and *in-vitro* animal models implied that phytochemicals present in coffee show neuroprotective action that halt Aβ synthesis, thereby preventing neuronal damage, cognitive deficit and synaptotoxicity in Aβ-challenged rat. Albeit, the identification of coffee bioactive compounds in blood is extremely crucial since a different technique to lower Aβ in the brain is attributed to decline Aβ levels in periphery. As Aβ peptides are in balance in the brain and periphery, however the elimination of Aβ from the peripheral organs with subsequent its passive diffusion down a concentration gradient, would result in reduction Aβ in the brain. Hence, *C. robusta* and its bioactive constituents have capability to lower Aβ both centrally and periphery, this feature of coffee can restore memory function.

Likewise, hyperphosphorylated Tau protein, a highly neurotoxic protein, promotes neurodegeneration in AD.[60] Consumption of brewed *C. robusta* can provoke neuroprotection by inhibiting tau accumulation in AD.[61] Geoffroy *et al.*[62] illustrated that NMDAR hyper or hypo function contributes to produce neurological and psychiatric problems largely, such as intellectual disability, schizophrenia and age-related cognitive dysfunction in AD. Coffee interferes with NMDAR[2] and its inhibition probably a useful neuroprotective therapeutic strategy.[63] In line with this, neuroinflammation is another problem in neurodegenerative pathologies that is linked to AD progression. Mainly astrocytes and microglia produce eccentric pro-inflammatory mediators, including IL-6, interferon-γ (IFN-γ), TNF-α, and IL-1β, and increase ROS and NOS,[64] where they induce neuronal cells death. These cytokines escalate the synthesis of glutamate in neurons and intensify neuronal dysfunction and death, also called excitotoxicity, via the activation of NMDAR.[65] *C. robusta* relieves from IL-6, IFN-γ, TNF-α, and IL-1β expression, inflammatory cytokines[22] participate in neuroinflammation.[65] The alterations and breakdown of active substances of BBB (blood-brain-barrier) can happen spontaneously with aging, even without the underlying conditions that initiate dementia and memory dysfunction.[66] Coffee raises the tier of occludin, a BBB-tight junction protein, and reduces astrocyte activation marker GFAP levels in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced mice, thereby protecting from neuronal damage and restore memory function.[67]

In addition, coffee modulates signal transduction including protein kinase, cAMP-dependent PKA, CREB, JNK, BDNF and TrkB pathways and exhibits neuroprotection in neurodegenerative diseases.[2] This property of coffee have been densely associated with its caffeine-rich substances, but it has been complicated to explain solo caffeinated beverages have confounding effect of other components.[49] Natural polyphenols are absorbed from the gastrointestinal tract after oral intake and next spread to other compartments via blood as well as tissues and cross the BBB, imparting their neuroprotective role there.[68] Many studies have proved that daily intake of a moderate amount of coffee from 3 to 5 cups per day is linked with low risk of memory dysfunction function especially in AD progression[69] and dementia.[70] Therefore, the probable connection between consumption of *C. robusta* and cognition is of considerable topic of interest.[59]

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Chemical composition of C. robusta

Primary metabolites

Primary metabolites are known as chemical substances which are required for plant growth, reproduction, and development.[71] *C. robusta* (unroasted) seeds contain primary metabolites, such as lipids (11.7 to 14 g/100 g),[12] proteins (18.5 g/100 g), amino acids (4 mg/g),[20] large quantities of soluble dietary fiber (0.47–0.75 g/100 ml), minerals (3–5% w/w), free amino acids (9–12% w/w),[18] and vitamins.[59] Waxes and Oils are also considered important substances that holds to be for 8 to 18% together with proteins (dry basis). On the other hand, *C. robusta* (roasted) is consisted of protein (10%), lipids (11–17%), carbohydrates (38–42% dry basis), minerals (4.5–4.7%), aliphatic acids (2.4–2.5%),[18] fats,[16] and organic acids.[72] However, these metabolites not only are beneficial for growth of plants but also provide energy to human and promote human health as well, for example, brain needs energy to work efficiently, thus dietary sources can fulfill that demand.

Secondary metabolites

Secondary metabolites are chemical compounds synthesized by plants to contribute defensive activities and control defense signaling pathways in order to protect plants from herbivores.[73,74] *C. robusta* consists of major two secondary metabolites, i.e., chlorogenic acid and caffeine,[11, 20] however crypto-chlorogenic acid, neo-chlorogenic acid,[23] trigonelline,[16] and melanoidins[75] are recently identified new compounds.[23] Undoubtedly, fermentation process influences coffee's quality,[15] however chlorogenic acid and trigonelline face some roasting processes, they decrease in quantities significantly during roasting, but caffeine remains unaffected.[16] Many investigations are available for caffeine, chlorogenic acid and trigenolline indicating their this type of behavior (during roasting process caffeine, chlorogenic acid and trigenolline quantities decrease), but no study has been found in literature yet which has investigated melanoidins, crypto-chlorogenic acid and neo-chlorogenic acid‘s behavior in unroasted and *C. robusta* (roasted). Bioactive compounds and their concentrations in unroasted and roasted *C. robusta* have been mentioned in Table 1.

Correlation between bioactive compounds (C. robusta) and memory function

There are six compounds (including caffeine, chlorogenic acid, cryptochlorogenic acid, neochlorogenic acid, trigonelline and mellanoidins) in *C. robusta* that participate in improving memory function by different targets.

Caffeine

Caffeine (Figure 2) (1,3,7-trimethylxanthine), a purine alkaloid, is synthesized from xanthosine[10] and present in >60 plants, including *C. robusta* seeds with the highest quantities.[24] Caffeine is known as a stimulant,[10,18] possesses nitrogen in its ring[72] and contributes to *C. robusta* bitterness.[10,18] Caffeine imparts health beneficial effects as its chemical structure akins with adenosine which can be a factor for relaxation and sleep.[24] It augments alertness, concentration[20] and imparts ergogenic effects.[75] Caffeine acts as antioxidant and brings down harmful free radicals, thereby increasing immunity against many diseases,[22] including AD and PD.[24] Low doses of caffeine have improved exercise and cognitive performances.[78] In contrary, clinical studies illustrated, caffeine is a cognitive normalizer and not a memory enhancer. Additionally, caffeine increases cAMP levels, where cAMP augments the release of norepinephrine, glutamate and dopamine, thus enhancing neural activity.[79] Carman *et al.*[80] documented, caffeine, being a short-acting neurostimulator, has ability to inhibit phosphodiesterase, intracellular calcium, antagonize adenosine receptors, and regulate γ-Aminobutyric acid (GABA) receptor action. Studies on AD models of rodents revealed, caffeine can block Aβ generation and can boost memory. Caffeine pulls water in and encourages the removal of Aβ plaques by membrane. It inhibits AChE in *in-vitro* and *in-silico* studies, reduces cognitive impairment which is arisen by elevated oxidative stress and increases BNDF in mice AD model. Hence, it promotes neuroprotection and increases memory function.

Moreover, caffeine has a direct neuroprotective action and its intake dwindle Tau hyperphosphorylation.[81] Chaturvedi *et al.* and Adeoluwa *et al.*[82,83] proposed, co-administration of caffeine with piracetam has exhibited memory boosting effect in scopolamine-induced memory loss in rats. The recent discoveries pointed, caffeine interferes with age-related neurodegenerative diseases, including AD, PD, dementia and cognitive decline. Caffeine enhances short-term memory and cognition, few studies have also investigated, long-term consumption may protect from cognitive decline or dementia.[80] Furthermore, caffeine interferes with dopamine and glutamate signaling, competitively inhibits cyclic nucleotide phosphodiesterase, non-competitively inhibits AChE, competes with other substrates on cytochrome P450 and blocks nicotinic acetylcholine receptors,[84] thereby promoting cognitive function. Caffeine has good bioavailability with 99% after absorption from gastrointestinal tract within 45 min.[49] Moreover, metabolism of caffeine takes place in liver into theobromine, theophylline and paraxanthine, also known as dimethylxanthines, each dimethylxanthine has its own physiologic effects in the body,[80] therefore, these effects of caffeine are important to enhance memory function.

In this review, we also reported, the mystery of caffeine's ability to improve memory in relation to adenosine and its interaction with adenosine receptors. Adenosine manifests neuromodulatory and neuroprotective effects in brain, consequently controls motor and cognitive function upon binding at adenosine receptors.[85] Moreover, Martins *et al.*[86] suggested, adenosine affects NMDAR function at the pyramidal *cornu ammonis*-1 neurons in hippocampus. They also explained, NMDAR, an ionotropic glutamate receptor, helps not only in synaptic plasticity but also in excitotoxicity because of its Ca^{2+}-permeability properties.

The major targets of caffeine, which is a non-selective of adenosine A1 receptor (A1R) and adenosine A2A receptor (A2AR) antagonist in brain,[85] are adenosine receptors (G-protein coupled receptors), such as A1R-inhibitory and A2AR-facilitatory receptors. According to Martins *et al.*[86] the A1R is present in pre- and post-synaptic sites with its chief expression on hippocampus, cerebellum and cortex. They also observed, the A2AR is often present in the basal ganglia but it is also expressed in hippocampus and cortex with its pre- and post-synaptic signaling. The A1R antagonism is responsible for the excitatory effect of caffeine upon synaptic transmission, while A2AR antagonism mediates the inhibitory action of caffeine upon synaptic plasticity. As adenosine is a homeostatic regulator of neuronal function, the inhibition of its receptors by caffeine exerts several positive effects on brain function. In truth, A2AR encourages excitotoxicity, however various investigations have glimpsed neuroprotective properties of caffeine or related compounds in neurodegenerative disorders, inclusive of memory dysfunction which has been seen in AD or aging. In addition, caffeine enhances memory function by inhibiting dorsal hippocampal A2A receptors. Cornelis *et al.*[87] suggested, caffeine consumption interferes with A2A receptors and depresses toxicity of alpha-synuclein (α-Syn)-aberrant protein aggregates, and in α-Syn mouse models, improves synaptic and cognitive decline. The protective effect of caffeine in neurodegeneration in *in-vivo* models of neuropsychiatric disorders, e.g., AD and memory dysfunction, has been related with its ability to make normal synaptic plasticity through A2A receptors.[69]

Chlorogenic acid

Coffee is a unique and rich source of chlorogenic acid (Figure 2) in the diet.[87] Chlorogenic acid (5-O-caffeoylquinic acid), a thermos-labile[25] and soluble polyphenol,[20] is an ester of trans-cinnamic acid and quinic acid which gives an astringent taste to coffee.[10] Chlorogenic acid is widely used as food additives in food industries due to its medicinal values, cosmeceutical values[88] and low molecular weight properties.[89] Chlorogenic acid is a good bioactive compound with low toxicities,[90] however it is broken down during roasting.[12] *C. robusta* beans have higher quantities of chlorogenic acid as compared to *C. Arabica* beans.[10,20,91] Chlorogenic acid has an antioxidant activity, thereby having capability to scavenge free radicals and improving immunity.[22] Only cinnamates, metabolites of chlorogenic acid, are readily absorbed by small intestine. After hydrolysis by either digestive or microbial

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enzymes and reaches to its target site for action.[87] Further, chlorogenic acid has potential to protect BBB from destruction and improve differentiation of neuronal cells in mice.[49] Authors claimed, chlorogenic acid promotes human brain health such as neuroprotection in neurodegenerative diseases[20,49] by which improves memory function. Farah and Lima have found, a reduction in Aβ is supposed to be due to anti-inflammatory activity of chlorogenic acid. Besides, an emerging evidence indicates that chlorogenic acid inhibits AChE and BChE in the CNS and due to high antioxidant activity prevents from neurodegeneration caused by oxidative stress.[25] Albeit, chlorogenic acid improved memory function by protecting neurons from oxidative stress.

Additionally, in rat brain cerebellum, an intraperitoneal injection of chlorogenic acid minimized oxidative damage induced by methotrexate, an anticancer drug. Pre-treatment with chlorogenic acid has been displayed neuroprotective effect by decreasing pro-inflammatory cytokines including IL-1β and TNF-α synthesis in substantia nigra, a midbrain dopaminergic nucleus that modulates reward functions and motor movements. Caffeic and ferulic acids are two metabolites of chlorogenic acid, when they were assessed in rat cerebellum, it was seen that caffeic acid had broader range of neuroprotection than its parent agent chlorogenic acid or ferulic acid. Moreover, in brain, chlorogenic acid has shown antianxiety activity by binding with GABAA-benzodiazepine receptors.[25] Chlorogenic acid undergoes microbial degradation, where the microflora degrades chlorogenic acid into different aromatic acids e.g., phenyl propionic acid, coumaric acid and benzoic acid derivatives, ferulic acid, caffeic acid, hydroxyphenyl acids, isoferulic acid, hippuric acid, hydroxyhipuric acid and hydroxybenzoic acid.[10] Chlorogenic acid's metabolite dihydrocaffeic acid increased nitric oxide production and decreased free radicals in cultured human endothelial cells.[80] Subsequently, these products impart different actions as this section has already dealt with neuroprtective and memory enhancing effects of chlorogenic acid.

Crypto-chlorogenic acid

Crypto-chlorogenic acid (Figure 2) (4-O-caffeoylquinic acid) is a positional isomer of chlorogenic acid present in *C. robusta*[14,92,93] and even can be obtained from the esterification of caffeic acid with 4-hydroxyl of quinic acids.[93] Being chlorogenic acid isomer, crypto-chlorogenic acid has capability to attenuate of oxidative stress[48,91] by eliminating superoxide radicals in neuronal cells. A decrease in radicals surge protects neurons from oxidative damage in brain.[94] This property of crypto-chlorogenic acid can augment memory improving property of *C. robusta*. Notwithstanding, there is no evidence in the literature that crypto-chlorogenic acid has positive effect on memory function.

Neo-chlorogenic acid

Neo-chlorogenic acid (Figure 2) (3-O-caffeoylquinic acid) is also a positional isomer of chlorogenic acid and can be obtained from the esterification of caffeic acid with 3-hydroxyl of quinic acids as well.[93] Neo-chlorogenic acid is predominant in green *C. robusta*[14] bean extracts[48] and has potential health promoting effects,[95] such as antioxidant activity.[48,91] In hippocampus, this activity may elevate endogenous oxidative stress markers, namely GSH, lipid peroxidation (LPO), and superoxide dismutase (SOD).[96] In return, these markers act as neuroprotective matrices by scavenging ROS,[97] thereby imparting neuroprotection and increasing memory function.[98] This effect of neo-chlorogenic acid can escalate cognitive enhancing effect of *C. robusta*, further studies are required. However, there is unavailability of data related to neo-chlorogenic acid that has beneficial effect on memory function.

Table 1: The comparison of bioactive compounds composition in roasted and unroasted *C. robusta*

Compound name	Unroasted Coffee	Roasted Coffee	Reference
Caffeine	-	1.5 - 2.5 %	10
	4.32 – 7.95 mg/100 g	-	11
	1.45% - 2.38%	-	20
	0.85 - 1.03 g/100 g	0.88 - 1.53 g/100 g	16
	1 to 4%	1.3 – 2.4%	18
	-	22.38 mg/g	14
Chlorogenic acid	-	6.1 - 11.3 %	10
	3.20 – 5.75 mg/100 g	-	11
	5.17% - 14.4%	-	20
	2.80 - 5.42 g/100 g	1.30 - 3.54 g/100 g	16
	11.3%	-	76
	12%	2.7 – 3.1%	18
	-	0.7 ± 0.0 mg/mL	23
	-	4.65 mg/g	14
Cryptochlorogenic acid	-	0.2 ± 0.0 mg/mL	23
	-	8.23 mg/g	14
Neochlorogenic acid	-	0.3 ± 0.0 mg/mL	23
		14.09 mg/g	14
Trigonelline	0.80 - 1.08 g/100 g	0.72 - 1.03 g/100 g	16
Melanoidin	-	250 - 810 mg/ 100mL	77
	-	23%	18

mg=milligram, g=gram, %=percent, mL= milliliter

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Trigonelline

Trigonelline (Figure 2) (N-methylnicotinic acid),[99] a plant alkaloid,[16] also known as phytoestrogen, is found in green *C. robusta*. Same like caffeine, it contains nitrogen in its ring too.[72] At higher roasting temperature (230°C), 85% of trigonelline is converted into nicotinic acid. Trigonelline has neuroprotective effects[20,49] and ability to stimulate brain activity.[59] Moreover, recently trigonelline has received considerable attention owing to its memory improving effects in patients with AD.[100] Although trigonelline preserved mitochondrial integrity, it prevents neuronal injury by bringing down astrocyte activity, oxidative stress and neuroinflammation,[49] thereby imparting improving memory function. From the current review, we noticed two controversies that indicating trigonelline's memory improving and dysfunctioning properties.

By describing positive side, trigonelline administration has significantly improved cognitive function, mitigated oxidative stress, AGE products and AChE in d-galactose induced amnesia in mice.[101] Also, trigonelline protected from oxidative stress, proinflammatory mediators such as TNF-α and IL-6, decreased AChE and overhauled BDNF levels in lipopolysaccharide (LPS)-induced memory dysfunction in adult mice.[102] Besides, in a dose-dependent manner, trigonelline in LPS-challenged rats exhibited an enhancement in spatial recognition memory by lowering AChE, malondialdehyde (MDA), improving SOD, catalase, GSH activities, and also, abating nuclear factor kappa B (NF-κB), TNF-α and toll-like receptor-4 in hippocampus, hence, protecting from oxidative stress and neuroinflammation.[103] Moreover, trigonelline displayed an *in-vitro* inhibition of AChE and positive effect on memory function.[99] Additionally, trigonelline pretreatment in Aβ-model of AD modified hippocampal neuronal injury through preservation of mitochondrial integrity and blocking inflammation, oxidative stress and astrocyte activity.[104] These data indicated, trigonelline can be used to enhance memory function.

In contrast, there are some investigations reporting opposite memory function effects of trigonelline, an inhibitor of Nrf2/antioxidant response element (ARE) pathway. Trigonelline treatment accelerated the streptozotocin (STZ)-induced GFAP expression in AD mouse model and decreased the memory improving effect of plumbagin.[105] Also, trigonelline abrogated the neuroprotective effects of quercetin in STZ-induced behavioral, biochemical and molecular changes in the AD-like animal.[39] Furthermore, trigonelline hindered the dose dependent improvement in neurobehavioral functions of protocatechuic acid and attenuated Nrf2 pathway in ischemia-reperfusion mice model.[106] According to Varshney and Garabadu,[107] trigonelline facilitated memory impairment in STZ-induced animals, disclosing the fact that trigonelline could be used as a chemical entity that can estimate the Nrf2-mediated activity of any medicinal agent. Adding that, trigonelline abolished angiotensin from 1 to 7-induced increased learning, memory and working memory, cholinergic activity, diminished Aβ aggregation, increased mitochondrial function, integrity and bioenergetics in Aβ-infused animals, curtailed apoptosis and increased HO-1 expression in brain regions. This part of study restricted the use of trigonelline for the purpose of improving memory. However, based on the negative features of trigonelline, it can be applied to assess the Nrf2-mediated activity of another drug candidate.

Melanoidin

Coffee is the second most ample source of melanoidins (Figure 2) after bread.[108] Melanoidin is a class of polymer-like bioactive substance[109,110] present in *C. robusta* and formed in the last stage of the Maillard reaction,[109,110] where sugars and amino acids coalesce at low water activity and high temperature.[111] Melanoidins are brown-colored compounds[112] that can be measured at 420 nm[113] and have high molecular weight heterogeneous nitrogenous polymers[111] with carbohydrate-phenol structure.[114] They have a significant impact on sensory properties of coffee and also grant many health benefits,[110,115] especially by stimulating brain activity.[69] As per Hu *et al.*[115] report, the recent investigations on animal models exhibited antioxidant activities in brain. Moreover, antiaging and neurobiological activities were reported in *in-vitro* assays against AChE. Melanoids inhibited tyrosinase activity[108] and negatively regulated the transcription factor NF-κB,[80] after LPS-stimulation of RAW 264.7 cells, subsequently decreased nitric oxide (NO) release and interleukin 8 (IL-8) production and provided memory enhancing effect by neuroprotection.[108]

Supporting the belief that melanoidins represent antioxidant activity in roasted coffee. They have capability to trap positively charged electrophilic species, reduce oxygen free radicals, and/or execute metal chelation to develop inactive complexes,[80,114,115] which may abate lipid oxidation during digestion.[80]

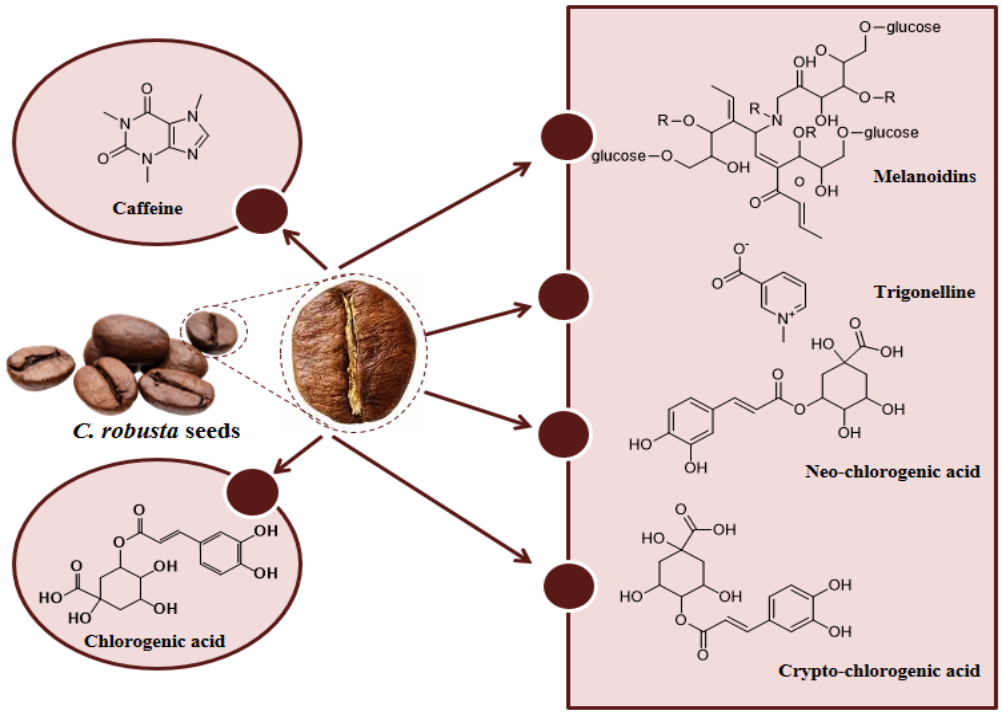

Figure 2: *C. robusta* seeds and the structures of their major bioactive compounds.

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Melanoidins have counteractive effects on oxidative stress-induced diseases by inducing Nrf2-regulated signaling pathways in multiple cells.[115] which are beneficial for memory function. Antioxidant activity of melanoidins contribute to its beneficial effects in AD by interfering redox-sensitive transcription factors like NF-κB and Nrf2.[116] Furthermore, melanoidins protected and rescued IMR32 cells, neuroblast cells isolated from brain tissue with neuroblastoma, significantly from the oxidative damage induced by hydrogen peroxide and displayed neuroprotective effects, particularly in AD.[89] Melanoidins can also prevent from neurotoxicity that is triggered by inflammation in the body via decreasing the synthesis of inflammatory mediators,[115] and hence can increase memory function.

In addition, melanoidins blocked Aβ deposition (neurotoxicity) and cytotoxicity in SH-SY5Y cell line, a human neuroblastoma cell, triggered by oxidative stresses, thereby improving memory. Besides this, melanoidins induced a number of autophagic pathways that expand the view of beneficial biological activities associated with AD, observed in coffee.[21] According to Hu *et al.*[115] observation, though coffee melanoidins have a variety of bioactivities in humans, the complex structure largely restricts the investigation of their biological activities. Hence, melanoidins demand great attention to conduct more and more systematic researches in future and distinguish between chemically identified melanoidins' beneficial and harmful health effects.[117]

Recommended daily allowance (RDA)

Caffeine in a single cup of coffee is found as high as 95-330 mg.[118] *C. Robusta* beans contain 22.38 mg of caffeine/g.[14] In healthy adults, RDA of caffeine (up to 400 mg/day) is not linked with adverse effects.[20,118] The average regular intake of caffeine is in the range of 210 to 238 mg per person per day for Canada and US.[2] RDA for children (6-12 years old) is 2.5 mg/kg. In addition, Food and Drug Administration endorsed intake of caffeine at <400 mg/day in pregnancy. According to WHO statement, moderate drinking of coffee, caffeine up to 300 mg/day, during pregnancy is considered safe.[79] On the flip side, chlorogenic acid can be found in coffee as maximum as 70 to 350 mg each cup.[118] RDA of chlorogenic acid for the modest coffee consumers is 100-300 mg /day.[25]

Drawbacks of C. Robusta consumption

C. Robusta has bitter taste, not much sweetness and acidity than *C. Arabica*, therefore it often blends with *C. Arabica* or made ready to drink coffee.[14] Caffeine in large doses produces certain side effects, such as anxiety,[119] restlessness, nervousness, psychomotor agitation, and long term usage of caffeine causes irregular heartbeat,[18,20] Additionally, it causes insomnia, nausea, upset stomach, exhaustion, headaches, faster breathing and diarrhea. Specifically, nursing or pregnant mothers must avoid taking green coffee extract, possibly it can lose calcium from the body through the urine, thereby causing hypocalcemia that can result in serious illnesses, in particular osteoporosis.[20] Moreover, it causes DNA damage and oxidative stress in brain of offspring.[79] Some people such as pregnant women and hypertensive individuals who are sensitive to caffeine, they should consume decaffeinated beverages instead of caffeinated ones.[72,120] *C. robusta* consumption is quite safe and beneficial to improve memory function if it is taken under RDA limits.

Data gap

During this review, some study gaps have been found which demand further research. While short-term improvements in memory, alertness and attention have been observed in caffeine and caffeinated coffee, their action on age-associated memory loss is still unclear.[80] Cornelis *et al.*[87] have suggested that the use of specific biomarkers involved in pathology of AD should be evaluated between caffeine and dementia. The exact activity of caffeine in neuroprotection during AD is recommended.[49] More research is still required to investigate the consumption of coffee could be considered as a modifiable lifestyle factor aimed at slowing AD onset.[58] Worldwide regulatory policies should be fabricated against coffee intake in pregnancy. Whether coffee (especially caffeine) has teratogenic effect in humans, current literature is lacking this evidence.[79] Vats has mentioned that the Harvard School of Public Health stated that attention should be paid on adverse effects accompanying long term coffee consumption in pregnant women, children, and youth.[20] The chemical transformations happen in chlorogenic acid in roasted coffee is still not clear.[18] In a clinical study caffeine has been seen as a cognitive normalizer and not a cognitive enhancer, there is need to strengthen this statement.[49]

Conclusion

C. robusta has many potential health benefits owing to secondary metabolites present in it. Usually, *C. robusta* has been found rich in caffeine and chlorogenic acid that have been investigated by many studies, however there are some other compounds crypto- and neo-chlorogenic acids, trigenolline and melanoidin that have been reported quite recently. All these compounds enhance the value of *C. robusta* in neurodegenerative diseases, including AD, PD, dementia, and memory dysfunction by interfering with many cellular targets. The most of these phytochemical substances scavenge ROS and protect neuron injuries from ROS, decrease deposition of Aβ, Tau accumulation, inflammatory cytokines that damage neurons, thus promoting neuroprotection and restore memory dysfunction initiated in AD. Regular consumption of *C. robusta* and its bioactive compounds is beneficial for brain health to increase attention and normalize memory function if it is taken in moderate doses. In future, research needs to be done on melanoidins, cypto- and neo-chlorogenic acids.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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