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REVIEW ARTICLE

Multimodal Neuroprotective Perspectives of Black Tea in Early Onset of Alzheimer- A New Paradigm

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with far reaching consequences. Therapeutic options assuring total recovery is not available till yet. Adjuvant therapy has attracted the research limelight and now equal importance is being given to dietary and lifestyle interventions parallel with western classical medicine. Therapeutic entities are being developed with multimodal and translational perspectives. Adjuvant therapy has gained prominence as it can treat most naturally without altering the normal lifestyle. This review aims to highlight the putative neuroprotective, neurostimulatory and antioxidant effects of potent black tea compounds like theaflavins, catechins, L-theanine, caffeine where a multimodal therapeutic remedy can be achieved with L-theanine that can successfully cross the blood brain barrier coupled with free radical scavenging capacity of theaflavins and the synergistic improvement in cognitive performance with L-theanine-caffeine combination. Development of black tea formulations to combat bioavailability issues also fulfills the translational purposes.

Key words: Alzheimer's disease, neurodegenerative, black tea compounds, neuroprotective, Adjuvant therapy, theaflavins, L-theanine

INTRODUCTION

The neuroepidemiology of India shows the prevalence of a wide range of neurological disorders viz. Alzheimer's disease (AD), Parkinson disease (PD), Huntington's disease (HD), stroke, epilepsy, seizures; the incidence and prevalence rate being highly variable. Available survey reports mentions about 30 million Indians to suffer from neurological disorders excluding the incidences of traumatic injuries or neuro infections. [1] Such disorders lead to a variable degree of disability with a loss of productive life. AD, a progressive neurodegenerative disorder with worrisome consequences is a growing public health problem amongst the elderly population mostly in those countries where the elderly population is rapidly increasing. This disease causes progressive cognitive erosion and commonly diagnosed amongst older adults mostly between the ages of 75 to 84, while an additional 45% are over age 85.[2] Age is a significant risk factor for the disease. With the progress of medical science and technology there has been a progressive increase in the life expectancy among older adults worldwide. Thus, simultaneously the number of people diagnosed with Alzheimer's disease will also continue to grow. In fact, by the year 2050, a person will develop Alzheimer's disease every 33 seconds. [2] In most cases symptoms of AD first appear in their mid-60s. Although treatment can help manage symptoms for a limited period of time in some people, no intervention is currently available to slow or prevent the underlying disease process. AD has great financial and social implications and demands a high level of trained care giving which often reports a immense level of physical and emotional burden on the caregivers. The summarized state of art in the field of Alzheimer's research urgently calls for the development of new conceptual models of the disease in order to broaden the range of therapeutic targets and increase the pipeline of potential treatments. Alzheimer's research requires a unifying theory to integrate all current hypotheses and clinical observations to develop an effective therapeutic regimen. Drug discovery and development is extremely expensive and time-consuming; takes 10 to 15 years with an average expenditure of about $1.8 billion to proceed from a molecule to a

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marketed drug. [3] Keeping in mind the facts of disease complexities, it is necessary to encompass a multidisciplinary research approach for faster transition of finished products from lab bench to patient bedside and overcome the challenges of translational research. Premier research institutes of the world funds a broad array of translational research, where scientists from multiple disciplines aims to link the research findings obtained from the knowledge of basic science and translate them into quantifiable outputs and medical technologies for proper implementation in clinical practice.[4-6] The fact holds true for both pharmacological as well as non pharmacological interventions. U.S. Food and Drug Administration approved drugs for treating AD viz. donepezil, galantamine, memantine, rivastigmine, recommended for different stages of AD provide symptomatic relief and may slow symptoms of cognitive decline but a total halt or reversal of disease progression is not yet achieved. The current research scenario on drug development pipeline focuses on developing multimodal pharmacological targets so as to counteract with the multiple etiologies of the disease. The strong correlations between diet and human disease have gained the limelight of research. Dietary supplements are highly recommended and suggested as a strategy against several diseases, together with other nutritional programs. "Nutraceutical" can be defined as any food or a part of a food such as a dietary supplement that produces a medical or health benefit including the prevention and treatment of a disease. [7, 8] Nutraceutical are administered in dosages that exceed those that could be obtained from normal foods in the forms of pills, beverages, capsules and differs from functional food that are mainly whole vegetable, fruit or natural product examined for their physiological benefits and for their ability to reduce risk factors in chronic diseases.[9,10] Nutraceuticals can serve the purpose of adjuvant therapy and enhance the effectivity of primary therapy. Research survey reports have shown that the global market for nutraceuticals generated an estimated $49 billion in 2011 and have reached $67 billion in 2016, with an annual growth rate of 6.4%.[7,8] Thus if nutraceuticals or dietary supplements either in the form of beverage or pills or capsules be considered as an adjuvant therapy along with parallel western classical drugs are expected to provide a better therapeutic outcome keeping intact the issues of patient compliance and also open new vistas of research domains highlighting the health potentialities of our common food and beverages.

Statistics of neurodegenerative disorders in world and Indian scenario

The far reaching impacts of AD with its associated social and financial implications are a matter of great concern. Out of every eight Americans, one individual has been diagnosed with Alzheimer's disease. [10] According to the Center for Disease Control (2010), Alzheimer's disease is among the ten leading causes of American deaths. It is the fifth most documented reason for deaths among individuals above age 65. [11] An insight into the Indian scenario shows a wide variation in the incidence and prevalence rates of AD. [12] The findings of Das *et al*. 2013 have been summarized and presented in **Table 1**. [13]

Table 1: Prevalence of AD and dementia in different regions of India

Region	Age/Sex	Prevalence rates (%)		literature
		All dementia	AD	
South India	≥60	3.39	1.31	Shaji et al. 1996[15]
	Male	2.8	0.73	
	Female	3.54	1.81	
	≥60	3.5		Rajkumar etal.1997[16]
	>65	3.36		Shaji et al. 2004[17]
North India	≥55	0.84		Chandra et al. 1998[18]
	≥65	1.36		
	Male	1.8	0.77	
	Female	1.25	0.46	
	>60	1.83		Raina et al. 2010[19]
West India	>60	0.43	0.25	Vas et al. 2001[20]
	≥65	2.44	1.5	
	Male		0.2	
	Female		0.3	
	>65	4.1		Saldanha et al.2010[21]
East India	60	0.8	0.38	Das et al. 2008[22]
	≥50	.62	0.34	Banerjee et al.2008[23]
	≥60	0.128		

Etiopathologies of Alzheimer's disease

AD is of multiple etiologies and influenced by a number of pathogenic along with the involvement of different cell signaling pathways.

Amyloidogenic pathway

The two major biochemical features related to the neuro pathogenesis of AD are the neurofibrillary tangles containing phosphorylated 'tau' protein in soluble intermediate form leading to synaptic toxicity and senile plaques containing amyloid-β-protein (Aβ) which is a soluble intermediate and inherently deleterious to synapses. According to the "amyloid hypothesis", the neuritic plaques and neurofibrillary tangles consisting of hyperphosphorylated protein 'tau' is the major neuropathologic hallmark of AD. AD is also known as 'taupathy'. [24] β-amyloid peptides (Aβ) which are 40-42 amino acid peptides are released

from Amyloid Precursor Protein (APP) by the action of β and γ secretases. During AD, there is increased formation of Aβ peptide which hastens the process of neuronal loss and thus can be hypothesized that components of apoptotic machinery has a direct or indirect contribution to the complex proteolytic processing. [25-28] Research evidences has shown that apart from Aβ; APP, presenilins, α2 macroglobulin, apolipoprotein E are other significant pathogenic factors in AD. The different signaling and metabolic pathways contributing to synaptoxicity, neuro degeneration in AD include the Wnt signaling pathway, 5'-adenosine monophosphate activated protein kinase (AMPK), c-Jun-N-terminal kinases, a subfamily of mitogen activated protein kinases (MAPK), mammalian target of rapamycin (mTOR), Sirtuin 1 (Sirt1, silent mating type information regulator 2 homolog 1) and peroxisome proliferator-activated receptor gamma co-activator 1-α(PGC-1α).

Oxidative stress and AD

Neurones and astrocytes are the two main brain cells that need massive O_2 consumption, about 20% of the total O_2 consumption is required by the brain. Though O_2 is essential for survival of all living tissues, however alterations in the electronic configuration of oxygen lead to production of toxic moieties. When the two outer orbital electrons are in an identical spin state, oxygen is kinetically stable. Once these spin states re scrambled by an external agent, oxygen becomes partially reduced and then this free radical is in a hyperactive state which always tends to donate or accept electrons. These are the reactive oxygen species or ROS; brain cells and neurons are highly prone to oxidative damages by ROS. [29,30]

Neurotransmitter depletion in AD

Acetylcholine (ACh) is an important neurotransmitter related to memory. Pre synaptic nicotinic receptors influence the release of neurotransmitters (ACh, glutamate, serotonin, nor epinephrine) important for memory and mood. Glutamatergic neuro transmissions are involved in learning, memory, neuronal architecture (plasticity). In AD, along with the loss of cholinergic neurons pathological changes are observed in glutamatergic, serotonergic and noradrenergic transmitter systems in AD. Norepinephrine (NE) released from locus ceruleus influences memory processes and attention which being depleted by colchicines affects the cognitive performance of the experimental animals. Dopaminergic neurons that arise from corpus striatum and project towards the mesocortical and mesolimbic regions of the brain forms the behavioral pathway and dopaminergic activity influences the motivational behavior, memory, learning habits, response selection etc. [31] Serotonin (5-HT) is present in the thalamus, hypothalamus, midbrain and raphe nuclei of lower brain stem; it regulates memory and emotional behavior in experimental animals. Serotonin deficits are responsible for emotional and behavioral symptoms; somatostatin defects correlated to the reduced cerebral metabolism and thus might be a central phenomenon. The glutamate defect has been suggested to represent the neurochemical correlate to clinical dementia, because the activity in the hippocampal glutamatergic synapses is normally increased during learning. Thus, the multiple transmitter defects cumulatively influence AD symptoms. [32]

Western classical medicines and adjuvant therapy- A synergistic approach?

Current therapeutic strategies give equal importance to both pharmacological and non-pharmacological interventions parallely to combat the chronic ailments and neurodegenerative disorders. Adoption of adjuvant therapy, dietary and lifestyle interventions have come into limelight and are well practiced simultaneously with western classical medicine so as to achieve synergistic therapeutic outcomes. Though many synthetic drugs are available for the treatment of AD, adoption of an adjuvant therapy can result in potentiating therapeutic effect to achieve better improvement in cognitive performance. Along with the development of several drug molecules, latest therapeutic strategies have also focused on the effects of nutritional supplements and modifiable lifestyle factors for treatment of AD. Lifestyle factors viz. dietary composition and physical activity has a positive effect and also helps to prevent AD. Moreover these approaches are inexpensive with expected fewer incidences of adverse side effects. [33] Some of the dietary interventions include minimization in the intake of saturated and Trans fats and thus avoid or maximally reduce the intake of coconut or palm oil and avoid French fries or fast food items with labeling "partially hydrogenated oils." Long-chain omega-3 fatty acids may play a role in prevention of AD. Docosahexaenoic acid (DHA) is a principal omega-3 fatty acid component of neuronal membranes. [34] DHA is especially abundant in the cerebral cortex, synaptosomes and

mitochondria. Neurons do not possess the enzymes necessary for *de novo* synthesis of DHA, so it must either be obtained directly from the diet or synthesized endogenously from its precursors α-linolenic acid and eicosapentaenoic acid or EPA.[35] OS and AD being strongly correlated, intake of functional foods enriched in natural antioxidants as well as vitamins C and E are highly recommended for the prevention of AD. Some of the dietary interventions recommended for AD patients include: Minimized intake of saturated or trans fats and increased intake of polyunsaturated fatty acids, vegetables, legumes, whole grains, fruits in place of meat or dairy products. Intake of banana, nuts, sweet potatoes, broccoli, spinach, beans, peas, citrus fruits are recommended along with plant based foods enriched in Vitamin B6 and folate and the B-vitamins. Recommended Daily Allowance (RDA) for vitamin B6 is 1.5 mg for women and 1.7 mg for men, for vitamin E it is 15mg per day and vitamin B12 it is 2.4 µg per day. As excessive iron and copper intake are found to cause cognitive problems, while choosing multi vitamins they are to be selected without iron or copper.[35] Though the role of Aluminum in AD is a matter of further investigation, still to minimize exposure AD patients can avoid the use of cookware, antacids, baking powder, or other products that contain aluminum. Inclusion of aerobic exercises in routine, brisk walking, 7-8 hrs routine sleep, involvement in mental activities that promotes new learning, for example 30 minutes per day, 4–5 times per week are some of the recommended lifestyle interventions.

Black tea Pharmacology –A breakthrough into our popular beverage

Black tea is enriched in benzotropolone compounds viz. theaflavins (3-6%), thearubigins (12-18%), small amounts of theaflagallins, flavonol glycosides viz. quercetin, myricetin, kaempferol, phenolic acids, methyl xanthenes like caffeine and amino acids viz. L-theanine; carbohydrates, proteins and minerals like Cr, Zn, Se, Mn etc are reported to be present in black tea [36-39]. A summarized detail on the diverse pharmacology of black tea components have been presented below in **Table 2**.

Table 2: Information on Black Tea components

Bio actives of tea	Chemistry	Pharmacological actions
Theaflavins	Group of poly phenol pigments formed by oxidation of flavanols by poly phenol oxidase during fermentation of black tea manufacturing; possess a benzotropolone chromophore; formed by co- oxidation of appropriate pairs of catechins, one with a *vic* tri hydroxy moiety and other with a ortho di hydroxy structure	• Strong antioxidant actions • Exerts neuro protection by combating OS • reduces total and LDL cholesterol of blood • *in vitro* lab findings have shown potent anti HIV-1 activity • found to regulate cancer cell growth, survival and metastasis • anti inflammatory actions
Catechins	Mostly (-)-epicatechin (EC), (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC) and (-)-epigallocatechin gallate (EGCG)	• Strong antioxidants • Hypoglycemic • Hypolipidemic • Anti hypertensive
Thearubigins	Polymeric poly phenols formed during enzymatic oxidation and condensation of epigallocatechin and epigallocatechin gallate with the participation of poly phenol oxidases	• Antioxidant • Astringency
L-theanine	Also known as γ-glutamyl ethyl amine is an amino acid analog of proteinogenic amino acids L-glutamate and l-glutamine	• enhances tranquility • exerts relaxation • positive role on alertness & calmness • neuroprotective & cognition enhancer • reduces oxidative protein and lipid damage • increases serotonin, GABA, dopamine and glycine in different regions of the brain
Methyl xanthine alkaloid	Mostly caffeine, theophylline; caffeine is a white crystalline, purine, a methyl xanthine alkaloid and chemically related to the adenine and guanine bases of DNA and RNA, can be extracted from natural sources or synthesized from uric acid	• Cardiac stimulants, • diuretics, • smooth muscle relaxants • caffeine increases wakefulness, decreases fatigue and brain booster • theophylline has vasodilatory, bronchodilatory and

	Theophylline is a methyl xanthine derivative from tea	inotropic actions

A strong correlation exists between oxidative stress and AD. Both catechins and theaflavins in black tea had stronger antioxidant effect than typical antioxidants viz. glutathione, ascorbic acid or Vitamin E.[40] Black tea components with proven antioxidant potentials can be arranged sequentially as epigallocatechin~ epigallocatechin gallate >> epicatechin gallate = epicatechin > catechin.[36,41-44] The theaflavins are dimeric catechins with a characteristic seven-member benzotropolone ring structure which is formed by the oxidation of the B ring of either (-)-epigallocatechin or (-)-epigallocatechin gallate, loss of CO_2 and simultaneous fusion with the B ring of a (-)-epicatechin or (-)-epicatechin gallate molecule.[45] Four theaflavins are formed in these transformations: theaflavin (TF_1), theaflavin 3-gallate (TF_2A), theaflavin 3´-gallate (TF_2B) and theaflavin 3, 3´-gallate (TF_3). Anti oxidative properties of catechins are attributed to their abilities to terminate chain reaction and inhibit free radical generation by inhibiting activity of existing enzymes participating in their generation in particular, xanthine oxidase [46] or by increasing the activity of enzymes with anti oxidative properties probably on the way of induction of protein molecule biosynthesis.[47] Based on the standard one-electron reduction potential ($E^{0´}$) values catechins scavenge free radicals and chelate with transition metal ions like Fe and Cu that catalyze free radical reactions.[36,40,43,47-49] Theaflavins TF_3, in black tea being catechin dimers have more hydroxyl (OH) groups which supports greater radical scavenging activity and possess higher anti oxidative properties than EGCG, the strongest antioxidant among all catechins.[50,51] Position of hydroxyl groups in theaflavins influences the antioxidant properties in the manner: TF_3> TF_2> TF_1>EGCG.[51] Again the theaflavin gallates demonstrate stronger anti oxidative properties compared with free theaflavins as gallic acid residues influences the increase in anti oxidative properties. [52] Tea catechins and theaflavins have $E^{0´}$values comparable to that of vitamin E value but higher than vitamin C, which is a superior hydrogen donor (antioxidant) to tea poly phenols. [49,53] Increase in concentration of endogenous antioxidants; prevention of changes of natural micro viscosity of cell membrane which are remarkably increased under oxidative stress, protection of membrane phospholipids against oxidation are other antioxidant potentialities of black tea. [54-56]

Black tea- synergistic neuroprotective outcomes in Alzheimer

Adjuvant therapy, nutraceuticals, functional foods or value added additives have attracted the research attention in developing effective therapeutic regimen not only to adopt preventive measures but also to delay the onset of devastating neurodegenerative disorders long before it reaches the stage of complications. Oxidative stress is an important pathogenic factor in AD. Theaflavins of black tea accounts for its significant antioxidant potentiality and are more potent antioxidants than EGCG and comparatively equipotent to vitamin E. L-theanine (γ-glutamylethylamide) present in black tea is structurally similar to glutamate, a neuro transmitter related to memory and can successfully cross the Blood Brain Barrier in 30 min thus providing neuroprotection. A standard 200 mL cup of black tea was found to contain about 24.2± 5.7 mg of l-theanine.[57] Thus intake of black tea is suggested to provide a dual protection by the neuro-boosting effect of L-theanine and antioxidant potentialities of theaflavins; moreover caffeine in black tea along with the L-theanine can also provide a refreshing cum neuro-boosting effect simultaneously. [58-62]

Glutamate (Glu), an important neurotransmitter plays a vital role in synaptic transmission of electric impulse to the synapse via an axon. Ca^{2+} ions act as second messengers; now during excitement there is excess release of glutamate that increases the efflux of Ca^{2+} ions in the post synaptic region. Increased flow of Ca^{2+} ions into neurons activates several enzymes and triggers ROS generation. Excitatory neuronal toxicity participates in neurodegenerative diseases such as AD.[59] L-theanine, is a structural analog of glutamate, binds with the Glu receptor in post synaptic membrane and attempts to control the excessive release of Ca^{2+} ions and tries to compensate with the excitotoxicity. This is one of the mechanism by which L-theanine exerts its neuroprotective effects. Glu is carried via the Glu transporters and engulfed via the adjacent glial cells. Glu is converted to Glutamine (Gln) by glutamine synthetase and is carried to the pre synaptic membrane by Gln transporter. Further Gln is converted to Glu by glutaminase thus initiating the next cycle. L-theanine binds with the

Gln transporter and prevents it entry into the pre synaptic membrane, a more stronger binding in comparison than with the Glu receptor.[59] Hence black tea has a multi modal and multi dimensional potentiality to serve as an effective adjuvant therapeutic remedy in AD.

Bioavailability problems of black tea poly phenols and remedies

Thus from the discussions so far it can be inferred that black tea has a neuroprotective effect with antioxidant potentials and can be used as an adjuvant to at least delay or as a protective in early stages of AD. Apart from that the diversified pharmacology of black tea compounds need not be retold. Despite immense potentialities, black tea poly phenols suffers from low bioavailability due to relatively high molecular weight, poor absorption, high rate of metabolisms and rapid inactivation of metabolized products leading to low internal activity.[39] Phenolic OH groups of tea poly phenols tend to form large hydration shells further affecting their bioavailability.[63] Some authors have opined the prolonged colonic metabolism of black tea poly phenols, theaflavins and thearubigins.[64] Black tea theaflavins and thearubigins strongly inhibited human recombinant sulfotransferase SULT1A1 and SULT1A3 isoforms representing liver and intestinal enzymatic activity and thus the mechanisms influencing their absorption is also affected. [65]

One of the important challenges of Drug delivery system is to combat the bioavailability challenges and develop the relevant dosage form or select the particular route of drug administration so that an optimum amount of the concerned drug is administered to the patient in such a way that it reaches exactly the 'site of action' and starts working then and there. To achieve maximum therapeutic outcomes modern medicine aims at targeting the affected zone of the patient's body exactly and delivers the therapeutic molecule at the desired site. The limitations of the traditional drug delivery systems can be overcome by applying Novel drug delivery systems (NDDS). Pharmacologically active compounds obtained either from plants or functional foods or beverages can't be applied in its crude form and for better applicability and patient compliance nutraceutical formulations can be developed. Nutraceutical formulations developed with the aid of NDDS helps to increase the efficacy and reduce the side effects of the crude components, ready to use products are highly suitable to fit into today's first lifestyle, long term stability and protection against contaminations can be achieved and associated bioavailability problems if any can be combated to some extent. [66]

Black tea a master therapeutic target- Translational perspectives

Black tea being a source of several pharmacologically active molecules can be considered as a master target in treating several ailments and is found to be an effective neuroprotective corroborated by the research works of Bhandari et al. 2015 which showed the antioxidant and AChE inhibitory potentials of aqueous extract of CTC black tea (BTE)[67] and its significant ameliorative effect in recovering the depleted neurotransmitter and endogenous antioxidant levels in colchicines induced Alzheimer rat models [68] and exhibited adjuvant potentiality with drug donepezil. Administration of six cups of black tea per day (2g of black tea in 100 ml of water, without milk or sugar) helped to improve the cognitive performance of diagnosed patients with early onset of AD evaluated by psychometric studies and further corroborated its adjuvant potentialities with drug donepezil.[69] However BTE can't satisfy consumer acceptance in its original form and keeping in mind the translational perspectives, BTE has been formulated into conventional and sustained release tablets for better applicability of the same. Black tea tablets have been developed with a dosage equivalent to 3 cups of black tea per tablet which serves as a good alternative rather than taking 6 cups of black tea per day.[70] Thus development of CTC black tea tablets helped in the fulfillment of the translational objectives to proceed with the development of a product at lab bench and it applicability at patient bedside.

CONCLUSION

AD is such a progressive neurodegenerative disorder that not only puts into great financial implications but virtually there are no well established treatment modalities that can assure a total recovery. In such cases an effective way is to stress on the preventive strategies with the aid of functional foods and beverages that we are accustomed to use in our daily lives and development of nutraceuticals with translational perspectives. Black tea is a popular beverage whose diverse pharmacology and wide range of pharmacologically active molecules especially the powerful antioxidants and neuro boosters can

serve as a multi modal therapeutic aid in AD. Further development of black tea formulations can open new research domains and promote the tie ups between pharmaceutical industries and tea industries.

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