REVIEW ARTICLE

Black Tea: A Possible Multitherapeutic Combinatorics Aiding Neuroprotection in Alzheimer's Disease

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Abstract

This article aims at reviewing the effectiveness of compounds in black tea in combating neuroinflammation in Alzheimer's disease (AD). Detailed chemo profiling of black tea showed the presence of theaflavins, different catechins, and amino acids viz., L-theanine and methylxanthines. A literature search showed a multitude of pharmacological activities diversity of black tea. Structural and anti-inflammatory activity relationship studies showed the anti-inflammatory potentials of benzotropolone moiety containing compounds, flavonoids, flavones, phenolics and methylxanthines e.g. caffeine, theobromine, theophylline. Black tea is a good source of several multifunctional pharmacophores and thus can combat neuroinflammation in AD providing neuroprotection from multidimensional perspectives.

Keywords: Alzheimer's disease, Benzotropolone, Black tea, Neuroinflammation, Neuroprotective, Theaflavins.

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Introduction

Black tea, a popular beverage, owing to its astringency and being a rich source of polyphenols, have attracted research attention owing to multifaceted health benefits and antioxidant potentials.[1-4] Antioxidant potentials of green tea and its health potentials is widely studied.[5] In India, cut, tear, curl (CTC) black tea alone accounts for around 89% of the total tea production, and 78% mass consumer acceptance in comparison to other tea varieties amongst different sections of the society (Source: Tea Board of India, www.ibef.org).[6] Alzheimer's disease (AD), is a fatal neurodegenerative disorder with no treatment modalities that assures total curative outcomes or absolute halt of progression.[7] The paradigm of drug discovery now focuses to develop multi-targeting therapeutic entities not only by multi-component agents but also by single entity or pharmacophore.8 Multi potent therapeutic entities either of natural and synthetic origin are in vogue and natural pharmacologically active entities are gaining the equivalent limelight as the synthetic counterparts.[8] AD, being affected by multi pathogenic factors, designing therapeutic candidates for AD need to consider one or more of the properties such as inhibitors of acetylcholinesterase (AChE), antioxidant, anti-inflammatory, anti-apoptotic potentials, catechol-o-methyl transferase inhibitors, monoamine oxidase inhibitors, elevators of the level of neurotransmitters like norepinephrine, dopamine, serotonin, etc., to combat its devastating neurodegenerative disorder in multi-directional approach.[9] Accumulation of β-amyloid plaques, neurofibrillary tangles, inflammatory responses are key pathogenic factors in AD and the conditions get aggravated in case of oxidative and nitrosative stress. Anti-inflammatory effects of black tea have different protective functions in several diseases e.g., arthritis, and inflammatory bowel disease (IBD), and also reduce oxidative/nitrosative stress in lipopolysaccharide (LPS) induced by murine macrophages and exhibited immunomodulatory role in immunocompetent/immunodeficient mice.[10-14] This article reviews how the major black tea compounds and their structural activity relationship along with anti-inflammatory potentials aid neuroprotection in AD.

Neuroinflammation in alzheimer's disease and anti-inflammatory drugs

The inflammatory components related to neuroinflammation in AD include the astrocytes and microglia, cytokines and chemokines, the complement system.[15] Chronic inflammation of microglia leads to neuronal dysfunction.[16] Production of inflammatory mediators viz., chemokines, pro-inflammatory cytokines, monocyte chemoattractant proteins, prostaglandins, leukotrienes, thromboxanes also triggers neuroinflammation. Chemokine generation influences microglial migration and recruitment of astrocytes to the area of neuroinflammation.[16] Inflammation generates oxidative stress. Oxygen-free radicals contribute significantly to the pathogenesis of AD. Thus a therapeutic entity with antioxidant as well as anti-inflammatory potentials is a desirable option in AD. Different nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid steroids have been considered for the treatment of AD.[16] NSAIDs reduce inflammation in AD brains mostly by inhibition of cycloxygenase-2 (COX-2) and also affect Aβ production.[15] Basing on the pathophysiology, drug molecules treating neuroinflammation in AD can target on the inhibition of the formation of Aβ fibrils and oligomers. The antiaggregatory effects on amyloid β sheet conformation were witnessed with some NSAID drugs viz. indomethacin, naproxen, aspirin, ibuprofen, ketoprofen, celecoxib, rofecoxib, etc. Some NSAID drugs viz. naproxen, sulindac exert their actions through the activation of peroxisome proliferator activator receptor γ (PPARγ). However, several clinical trials have shown the ineffective of selective COX-2 inhibitors in patients affected with mild to moderate AD.[17- 19]

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Black tea: multiple therapeutic combinatorics to combat alzheimer's disease

Despite the availability of several NSAIDs, the associated complications of drowsiness, gastric irritation on chronic uses prompted researchers to seek anti-inflammatory agents from natural sources. Several medicinal plants have anti-inflammatory and antioxidant potentials and can be beneficial in treating AD. Some of the herbs like ginseng, turmeric, licorice, white willow bark, German chamomile with anti-inflammatory potentials were effective in treating neuroinflammation in AD.[20] Treatment options have undergone a radical change and dietary interventions either in the form of nutraceuticals or functional foods are playing a significant role in adjuvant therapy in several ailments. The multi-component therapeutic cocktail is utilized in complicated ailments.

Black tea has several multifunctional pharmacophores and is a complex mixture of about 2000 chemical compounds viz., polyphenols, benzotropolone compounds viz., theaflavins (3-6%), thearubigins (12–18%), small amounts of theaflagallins, methyl xanthenes like caffeine, theobromine, theophylline, flavonol glycosides viz., myricetin, kaempferol, quercetin, phenolic acids, amino acids viz., L-theanine; carbohydrates, proteins and minerals like Cr, Zn, Se, Mn and volatile compounds like octanal, linalool, geraniol, ionones, farnesene, nerolidol, etc.[1-3,6,21] These are mostly monoterpenes, sesquiterpenes, higher aldehydes, unsaturated aldehydes, ketones and some heterocyclic compounds like the furanoids etc. Presence of these also supported by research data on chemoprofiling of black tea by UV, FT-IR, MALDI-ToF, quantitative HPLC and GC-MS.[1-3, 6, 21] Black tea extracts with a high range of safety profile, improved cognitive performance in AD rat models studied in different cognitive assessment tests for animals and improved the levels of depleted neurotransmitters like acetylcholine, norepinephrine, dopamine, serotonin and endogenous antioxidant levels viz., superoxide dismutase, catalase or reduced glutathione.[22] Black tea extracts exhibited anti-inflammatory effect in animal models, where inflammation was induced by the actions of carrageenin, arachidonic acid, etc.[23] Black tea extracts interfered with the expressions of cycloxygenase and lipoxygenase and also reduced arachidonic induced edema.[23]

Regarding the chemistry of black tea compounds, a major source of dietary polyphenols, the simplest structure of polyphenols consists of more than one aromatic ring and more than two OH groups. Flavonoids are a group of phenolic compounds composed of two aromatic rings linked through an oxygen heterocycle. Based on the replacement of heterocycle and degree of hydrogenation, flavonoids can be further classified into flavonols, isoflavones, flavones, flavanols, flavanones, etc.[24] Flavonoids are three-ring structured (A, B, C) compounds with various substitutions. Subdivisions of flavonoids can be due to the presence of an oxo group at position 4, OH group at position 3 of the middle ring and double bonds between carbon atoms 2 and 3.[24]

The theaflavins and thearubigins in black tea retain the basic C6-C3-C6 structure and come under the group of flavonoids.[24] Theaflavins consists of two catechin molecules. Catechol is an active center to bind with metal ions and scavenge the reactive oxygen species (ROS) found to prevent the aggregation of Aβ and hence is effective as multifunctional pharmacophore and has effectivity as a multi-target therapeutic entity in AD.[22, 24]

Structural and anti-inflammatory activity relationship of black tea compounds

The study of the anti-inflammatory potentials of black tea compounds has been done based on chemical groups under phenolics, flavonoids, containing benzotropolone compounds and the methylxanthines. The structure of the phenolic compounds influences their anti-inflammatory actions and pro-inflammatory mediators. Some of the anti-inflammatory actions of different flavonoids include planar ring system of the flavonoid molecules, presence of OH groups at C5 and C7 of the A and B, the number and position of OH groups as catechol groups at ring B, double bond at C2 and C3 and unsaturations in ring C as ketonic carbonyl at C4. Anti-inflammatory activities of the flavones were found to be higher than the corresponding isoflavones, flavonols, flavanones; higher activities were noticed with flavones and flavonols with an OH group at 4′ position of the B ring; further methylations of the OH groups at 3, 4′ and 5 positions further improved the activity.[25]

Black tea compounds containing benzotropolone moiety include the four major black tea components such as theaflavins (theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate, theaflavin-3,3′-digallate) and other compounds containing benzotropolone viz., epitheaflavic acid, isotheaflavin, theaflavin A, theaflavin B, epitheaflavic acid-3′-O-gallate.[21]

Benzotropolone compounds can be either isolated from black tea or synthesized from precursor molecules with pyrogallol or catechol units.[26] Epicatechin (EC) and epi-gallocatechin (EGC) are the parent flavonols of simple theaflavin, epigallocatechingallate (EGCG) and EC of theaflavin-3-gallate, EGC and ECG of theaflavin-3′-gallate, ECG and EGCG of theaflavin-3, 3′-digallate, EC and gallic acid (GA) of epitheaflavic acid, ECG and gallic acid (GA) of epitheaflavic acid gallate. Compounds containing benzotropolone ring system exhibited anti-inflammatory properties[26] and theaflavins have been identified as potent anti-inflammatory compounds.[27, 28] Based on structural activity relationship (SAR) and the anti-inflammatory actions of the theaflavins, some researchers believe that increase in the number of phenolic OH groups and gallate groups attributed to the increase in anti-inflammatory potentials. Thirteen OH phenolic groups in TF3, 10 OH groups in TF2 and 7 OH groups in TF1 suggests the anti-inflammatory actions in the order of TF3>TF2>TF1. Increase in the number of gallate groups is also enhanced the anti-inflammatory potentials; TF3 has two gallate groups, TF2 has one gallate group and TF-1 contains no gallate group. However, the presence of gallate groups or increase in the number of phenolic OH groups enhances the anti-inflammatory effect is opposed by the fact that compounds that have no gallate group have an anti-inflammatory effect equivalent to theaflavin-mono gallates. Rather the presence of benzotropolone moiety is responsible for the anti-inflammatory properties.[26]

A relationship exists between phenolic structures and pro-inflammatory mediators. High inhibition of prostaglandin has been found by the presence of double bond at C2-C3, 4-oxo functional group of ring C; the NO inhibitory potentials of the flavonoids are due to C2-C3 double bond, OH groups at 7 and 4′ position; however

the presence of bulky substituents nullifies the inhibitory potentials of the compound.[25]

Black tea is reported to contain a number of monoterpenes and sesquiterpenes. Some researchers have reported the presence of flavonoids like quercetin, myricetin, kaempferol and flavonoid glycosides in black tea infusions.[29] Inhibitory effect of flavones against histamine, tryptase, interleukin 6 and interleukin 8 release was influenced by the hydroxylation patterns of the B ring. Hydroxyl groups at 3′,4′, and 5′ positions contribute to anti-inflammatory activity, but OH group at 2′ position almost eliminates the activity; oxo group at position 4 of the middle C ring and OH group at position 3 and 4 increases the activity. The catechol group (o-dihydroxy) in the B ring influences the inhibitory potentials of quercetin; better effect was observed with myricetin due to the effect of the pyrogallol group (trihydroxy) (Fig. 1).[30]

Another group of compounds in black tea with diversified pharmacology and having anti-inflammatory potentials are the methylxanthines.30,31 Xanthines are the precursor of uric acid and the final product of catabolism of the purines. Methylxanthines are heterocyclic organic compounds that are formed from coupled pyrimidinedione and imidazole rings. Most relevant methylated xanthines or methylxanthines in black tea are caffeine (1,3,7 trimethylxanthine), theobromine (3,7 dimethylxanthine) and theophylline (1,3 dimethylxanthine). Aminophylline, pentoxifylline are other substituted methylxanthines. Methylxanthines act as weak bases due to the presence of imino nitrogen at 9 position. Caffeine have electrophilic sites at 1, 3 and 7 positions, theophylline has electrophilic predisposition at 1 and 3 positions and Brønsted acid site at the 7th position. Theobromine lacks a methyl group at 1 position; this methyl group being present in caffeine confers to its versatile physicochemical properties.30 Available literature evidences showing the content of methylxanthines in mg/g dry weight basis include caffeine (41.6-71.2), theobromine (1.8-3.6) and theophylline (<1).30,32-34 The anti-inflammatory potentials of methylxanthines are due to phosphodiesterase inhibition or due to adenosine receptor antagonism.30,35,36 Structural modulations of xanthine molecule influence its specific physiologic effects. Substitution at 1 position is responsible for high affinity and selectivity for adenosine receptor sites, substitution at 3 position increases the bronchodilator effect, substitution at 7 position decreases both adenosine receptor antagonism and bronchodilator potency, substitution in 8 position increases adenosine antagonism and selectivity towards substitution in 9 position decreases adenosine receptor affinity. Presence of 1 methyl group is essential for the inhibitory effects of methylxanthines at adenosine receptor levels (Fig. 2).

Methyl xanthenes are nonselective competitive inhibitors of phosphodiesterases and phosphodiesterase 4 (PDE4) in particular.[30] PDE inhibitory activity contributes to both bronchodilatory and anti-inflammatory activities. Substitution of xanthine molecules at 1, 3 and 8 positions exhibited PDE inhibitory effects (Fig. 3).[30,35,36] GC-MS analyses of the black tea have shown the presence of several mono and sesquiterpenes; literatures have reported the anti-inflammatory potentials of these groups of compounds.[21,37] Thus the wide range of compounds present in black tea has shown to possess anti-inflammatory actions and has potentialities to combat neuroinflammation in AD.

Conclusion

AD is a progressive neurodegenerative disorder that lacks treatment modalities with total curative outcomes. However, if proper preventive approaches are adopted at early detection of the disease, further deterioration can be prevented. Such complex diseases can be combated either by multicomponent therapeutic strategy, where several active ingredients act within a single drug cocktail or any active therapeutic molecule that is capable to hit the multiple targets. Surprisingly, black tea is such a cocktail with

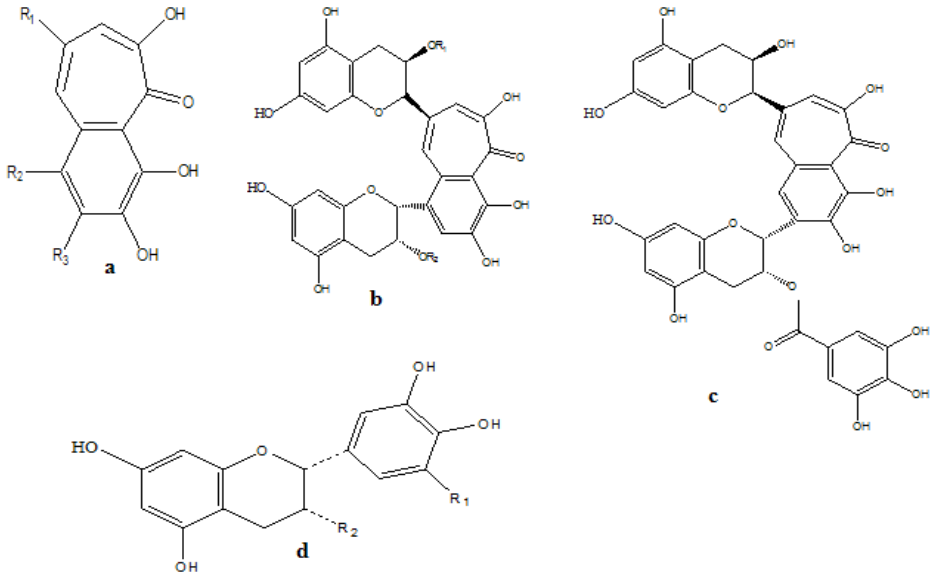

Fig. 1: Theaflavins and the catechins of BTE. (a) Benzotropolone ring structure (b) theaflavin (theaflavin: R1=R2=H; theaflavin-3-gallate: R1= galloyl, R2=H; theaflavin-3′-gallate: R1=H, R2= galloyl; theaflavin-3,3′-gallate: R1=R2=galloyl) (c) theaflavin-3′-O-gallate (d) catechins (EC: R1=R2=H; EGC: R1=OH, R2=H; ECG: R1=H, R2=gallate; EGCG: R1=OH, R2=gallate)

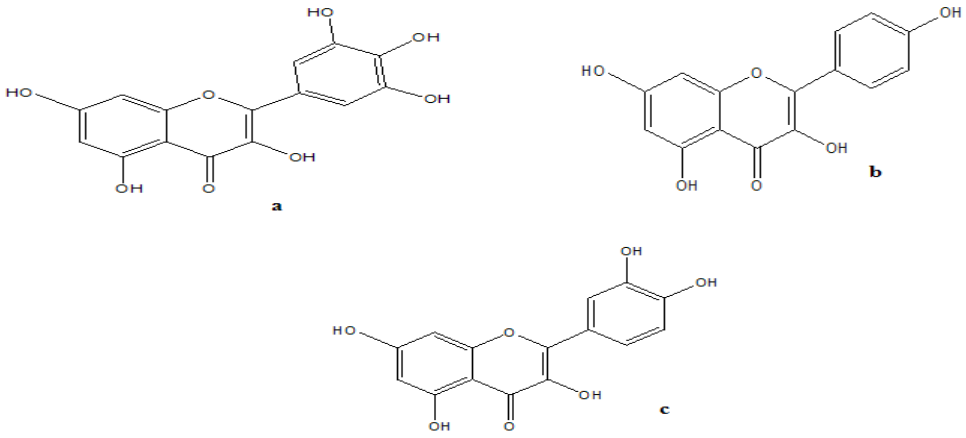

Fig. 2: Volatile compounds in black tea (a) myricetin (b) kaempferol (c) quercetin

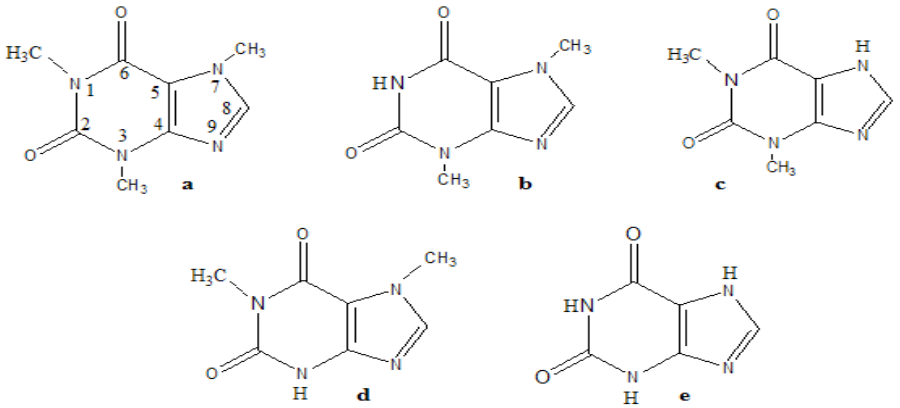

Fig. 3: Methylxanthines in BTE. (a) Caffeine (b) Theobromine (c) Theophylline (d) Paraxanthine (e) Xanthine

multifunctional pharmacophores that can exert neuroprotective and brain-boosting effect and is also effective in combating neuroinflammation.

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