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Tryptophan in banana peel (*Musa paradisiaca*) as an anti-dementia alternative treatment: A narrative review

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Article Review

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ABSTRACT

As the prevalence of dementia increases from year to year, the discovery and invention of preventive measures are growing increasingly urgent. Banana peels contain tryptophan, an amino acid that plays a substantial role in the mechanism of dementia prevention, yet under-utilized for this purpose. Tryptophan acts as a precursor to serotonin and kynurenine. The serotonin metabolite, 5-hydroxyindoleacetate or 5-hydroxyindoleacetic acid (5-HIAA), can degrade amyloid-β (Aβ) oligomers, a peptide group of 36–43 amino acids derived from amyloid precursor protein found in people with Alzheimer's disease. The degradation of brain cells through the increase of neprilysin (NEP) and melatonin inhibits glycogen synthase kinase-3β (GSK3β) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) by reducing the decrease in peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1). Meanwhile, in the kynurenine pathway, kynurenic acid (KYNA) also induces the NEP gene, thus preventing Aβ aggregation.

Prevalensi demensia meningkat dari tahun ke tahun. Oleh karena itu perlu upaya untuk pencegahannya. Kulit pisang mengandung asam amino triptofan yang berperan dalam mekanisme pencegahan demensia, namun pemanfaatan untuk ini belum optimal. Triptofan berperan sebagai prekusor serotonin dan kinurenin. Metabolit serotonin yaitu asam 5-hidroksiindolasetat atau 5-hydroxyindoleacetic acid *(5-HIAA) mampu mendegradasi oligomer amiloid (Aβ), yaitu suatu gugus peptida yang terdiri dari 36-43 asam amino dari amiloid precursor protein yang ada pada penderita demensia Alzheimer. Proses degradasi melalui peningkatan nefrilisin (NEP) dan melatonin menghambat glikogen sintase kinase-3β (GSK3β) dan* nuclear factor kappa-light-chain enhancer of activated B cells *(NF-κβ) dengan mengurangi penurunan* peptidyl-prolyl cis-trans isomerase NIMA-interacting *(Pin1). Sedangkan pada jalur kinurenin, asam kinurenat atau* kynurenic acid *(KYNA) juga menginduksi gen NEP sehingga agregasi Aβ dapat dicegah.*

INTRODUCTION

Dementia is a chronic or progressive syndrome in which cognitive functions, decline more substantially than normal brain aging. This condition affects thinking, memory, comprehension, orientation, calculation, language, learning capacity, and judgment but not consciousness. Also, dementia is sometimes preceded by deterioration in motivation or enthusiasm for life and emotional control and social behavior disorders.[1] In 2010, 35.6 million people worldwide had dementia. This prevalence is predicted to increase until 2050 and projected to nearly double every 20 years.[2]

According to Alzheimer's Disease International, 60% of people with dementia live in low and middle-income countries.[3] Dementia is more common in women than men and 25 times more common among >90 years old than 60-69.[4] In Indonesia, people with dementia was estimated to be around 1.2 million in 2016 and is predicted to increase to 4 million by 2050.[5]

The pathophysiology of dementia remains indistinct, although various molecular processes are thought to cause loss of synaptic connections, brain cell death and dysfunction, gliosis, and inflammation. All types of dementia share molecular mechanisms linked to nerve inflammation, neurodegeneration, hypoxia, oxidative stress, mitochondrial bioenergy, and impaired blood-brain barrier permeability. Dementia is divided into several types: Alzheimer's dementia, Lewy body dementia (LBD), frontotemporal dementia, vascular dementia, and mixed dementia.[6] In dementia attributed to Alzheimer's disease, the defining neuropathologic substrates are tau neurofibrillary tangles (NFTs) and Aβ plaques.[7] Based on the amyloid cascade hypothesis, amyloid precursor protein (APP) is broken down by the α-secretase enzyme and not properly processed by β-secretase and γ-secretase, creating an imbalance between the production and clearance of Aβ peptides. Aβ peptides accumulate into soluble oligomers, aggregate to form fibrils that are insoluble in the beta-sheet conformation, and are finally stored in plaques.[8] These Aβ plaques will trigger hyperphosphorylation of the tau protein, nerve cell apoptosis, loss of synapses, brain vascular damage, and microglia activation. They are formed primarily in the hippocampus area of the brain, which regulates memory functions, and the other cerebral cortex, which modulates thinking and decision-making functions.[9]

Pharmacological therapies used for dementia are cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists (memantine), serotonergic agents, dopamine receptor blocking agents, and benzodiazepines.[10] These synthetic drugs are, however, not without side effects. The use of cholinesterase inhibitors still sparks controversy in all types of dementia, except for dementia attributed to Alzheimer's disease, vascular dementia, mixed dementia, LBD), and Parkinson's dementia. Also, donepezil is the most selected cholinesterase inhibitor because galantamine, rivastigmine, and tacrine have more side effects.[11] Memantine can improve memory by altering Aβ oligomers dissolution and reducing the formation of fibrils and plaques. However, it has to be administered together with other drugs because it exhibits no distinctive positive effects in clinical studies.[12] Therefore, it is imperative that concerted efforts to look actively for drug alternatives persist.

Banana is a frequently consumed fruit, and the wide variety of its cause an increasing number in the by-products, i.e., peels. The peels constitute a relatively large proportion of total banana weight, namely 40%.[13] Instead of going to waste, they are proposed for better utilization, including for dementia prevention. Banana peels are rich in compounds like carotenoids, polyphenol compounds like delphinidin and resveratrol, amine compounds like tryptophan.[14,15] Through immunoblot analysis, high doses of delphinidin can reduce acetylcholinesterase (AChE), APP, and Aβ contents in the mouse models of Alzheimer's disease (AD).[16] Resveratrol can significantly improve spatial learning and memory in rats with vascular dementia.[17] Furthermore, dried and ground banana peels contain tryptophan at 0.46–1.32 g/100 g of protein which is substantially large compared to other amino acids found in banana peels.[18] These studies have revealed that tryptophan has a mechanism related to the pathology of dementia. The tryptophan metabolites, namely 5-HIAA and KYNA, can induce NEP expression to prevent Aβ neurotoxicity.[19] Another tryptophan metabolite, melatonin, can improve memory, relieve anxiety, and repair hippocampal cell damage in Aβ-injected animals.[20] Therefore, the purpose of this narrative review is to investigate the mechanism by which tryptophan in banana

peels potentially functions as an anti-dementia agent.

Tryptophan content of banana peels and its correlation with dementia

Banana peels possess several essential elements for the human body, including carbohydrates, magnesium, protein, calcium, phosphorus, iron, sodium, and flavonoids.[21] Banana peels contain significant amounts of starch, crude protein, crude fat, total fiber, di-unsaturated fatty acids (especially linoleic and α-linolenic acids), pectin, and essential amino acids (leucine, valine, phenylalanine, threonine, and tryptophan).[22] They also contain neurotransmitters, such as norepinephrine, serotonin, and dopamine.[23] Containing carbohydrates, banana peels can increase the plasma tryptophan ratio, allow tryptophan to enter the brain straightforwardly, and at the same time, be used as the main component in the formation of serotonin along with other bioactive ingredients in banana peels, namely vitamins B6, B12, and magnesium.[22,2]4

Tryptophan has neuroprotective properties. tryptophan exhibits a neuroprotective effect on oxidative damage in rats due to lipopolysaccharide (LPS)-induced endotoxic shocks.[25] Intake of tryptophan-tyrosine (WY)-related peptides can suppress microglial activation and prevent memory impairment in old mice, mice injected with LPS, and the mouse models of AD.[26] A diet high in tryptophan has been shown to improve learning and memory in these test animals because it prevents the decreased synthesis of 5-hydroxytryptamine (5-HT) or serotonin and 5-HIAA.[27,28]

Tryptophan in banana peels can be obtained by extraction, i.e., the maceration method. In Safitrah et al. banana peels were dried in an oven at 70°C for 9 hours and then grounded into fine powders, which were macerated using 96% ethanol.[29] The maceration result is filtered, and the macerate is evaporated until a thick extract is obtained.

Tryptophan metabolism on the serotonin pathway and its effect on dementia

Tryptophan plays a crucial part as a precursor to serotonin and kynurenine metabolisms associated with dementia in Alzheimer's disease. In the serotonin pathway, the tryptophan hydroxylase (TPH) enzyme hydroxylates tryptophan to 5-hydroxytryptophan (5-HTP). Then, 5-HTP is decarboxylated to 5-HT or serotonin by aromatic L-amino acid decarboxylase (AAAD).[30] Serotonin can produce two metabolites that can break down Aβ aggregation. Its metabolism uses monoamine oxidase (MAO) to form 5-hydroxyindole acetaldehyde, which is immediately converted to 5-HIAA by aldehyde dehydrogenase.[31] 5-HTP and 5-HIAA treatments increase NEP activity of rat brains through MAP-kinase/ERKpathway.[19,32] NEP is a zinc-dependent metalloendopeptidase, which is mainly located at presynaptic neuron terminals, especially in hippocampal and neocortical neurons.[33] NEP plays a vital role in the degradation of Aβ in the brain.[34] NEP regulates the concentration of Aβ as it serves as an Aβ-degrading enzyme so that communication in the brain cells runs normally.[35] This makes NEP a target for AD therapy. NEP activation can accelerate Aβ degradation.[36] NEP plasma can reduce approximately 30% of Aβ levels in the brain.[37] Neprilysin not only degrades amyloid monomers but also Aβ1–40 and Aβ1–42 oligomers.[38] Neprilysin cleaves Aβ peptides by forming internal disulfide bonds, thus reducing aggregation and neurotoxicity of amyloid peptide fragments.[39]

Serotonin also plays a role in the formation of N-acetyl-serotonin with arylalkylamine N-acetyltransferase (AANAT). Then, N-acetyl-serotonin uses hydroxyindole-O-methyltransferase (HIOMT) to generate N-acetyl-5-methoxytryptamine (melatonin) as the final product.[40] Melatonin treatment can increase hippocampal SIRT1 and TFAM expression.[20] Preclinical research proves that melatonin can improve memory, relieve anxiety,

and repair hippocampal cell damage in animals injected with Aβ.[20] In line with them, melatonin can also prevent the reduction of peptidyl-prolyl cis/trans isomerase NIMA-interacting (PPlase Pin1).[41] PPlase Pin1 is an enzyme that can hamper activities of GSK3β during the phosphorylation of tau and NF-κβ in inducing neuroinflammation. Tau and NF-κβ are some elements that can increase Aβ production.[41] Through this mechanism, melatonin can prevent amyloidogenic and inhibit the pathology of AD.

Tryptophan metabolism on the kynurenine pathway and its effect on dementia

In the kynurenine pathway, indolamine 2,3-deoxygenase or tryptophan dioxygenase and formamidase metabolize tryptophan to kynurenine (KYN). Afterward, KYN is converted into KYNA with the help of kynurenine aminotransferase. Kynurenine is also metabolized to anthranilic acid (AA, by kynureninase) and 3-hydroxykynurenine (3-HK, by kynurenine-3-monooxygenase). Anthranilic acid and 3-HK are metabolized to 3-hydroxyanthranilic acid (3-HAA), which is converted to 2-amino-3-carboxymuconate-semialdehyde that spontaneously transforms to quinolinic acid—i.e., a neurotoxin serving as a substrate for the redox agent NAD+. On the other hand, 3-HAA produces picolinic acid, which is the second step of enzymatic production with the help of 2-amino-3-carboxymuconate-semialdehyde decarboxylase.[42,43]

The kynurenine pathway metabolites produce neuroprotective and neurotoxic metabolites. Kynurenic acid acts as a neuroprotective molecule because it is a neurotoxicity antagonist induced by glutamate receptors.[43] Meanwhile, a neurotoxic effect is derived from the increase of 3-HK and quinolinic acid (QUIN) metabolites.[44] However, the 3-HK formation can be inhibited by kynurenine-3-monooxygenase (KMO), which helps alleviate synaptic loss and memory deficit in the mouse models of AD.[45] Such inhibition can support the synthesis of KYNA as a proven NEP inducer.[44,46]

The neuroprotective properties of KYNA are generally attributed to its antagonistic effects on the NMDA receptor. Through cellular, biochemical, molecular, and pharmacological approaches, low micromolar concentrations of KYNA have been proven to induce NEP gene expression strongly, protein levels, and enzyme activity increase in SH-SY5Y neuroblastoma cells in humans. Kynurenic acid protects SH-SY5Y cells by increasing their survival through a mechanism that is dependent on NMDA receptors. Therefore, part of the neuroprotective KYNA relies on its ability to induce the expression/activity of NEP—an amyloid-degrading enzyme—in nerve cells.[46] Besides, 3-HAA can interact with many residual amino acids in EVHHQK-amyloid. There are three preferred binding orientations, namely His13–His14, Glu11–His14, and His13–Lys16. Through such interaction or binding prevent(s) amyloid aggregration.[47]

Also, patients with dementia attributed to AD have low plasma levels in KYN, HAA, xanthurenic acid (XA), KYNA, and tryptophan.[48] Increased tryptophan degradation and elevated levels of kynurenine that is simultaneously altered are also found in plasma of these patients. It proves that the activation of the peripheral kynurenine pathway is present in this type of dementia (attributed to AD). Changes in the two metabolites of KYN (i.e., KYNA and QUIN) are associated with impaired cognitive functions in AD patients. Thus, there is a new therapeutic opportunity, in which a novel compound is developed as a promising brain-neuroprotective agent.[49] Based on these advantages and mechanisms, tryptophan in banana peels can be used to prevent dementia.

CONCLUSION

Tryptophan links to the pathophysiology of dementia because this essential amino acid is metabolized in two pathways, namely serotonin and kynurenine. KYNA and 5-HIAA degrade Aβ oligomers by increasing NEP, while melatonin inhibits GSK3β and NF-κβ by reducing the decrease in Pin1.

CONFLICT OF INTEREST

No conflict of interest.

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