Cross Current International Journal of Medical and Biosciences
Abbreviated Key Title: Cross Current Int J Med Biosci
ISSN: 2663-2446 (Print) & Open Access
DOI: https://doi.org/10.36344/ccijmb.2024.v06i06.001

Volume-6 | Issue-6 | Nov-Dec, 2024 |

Review Article

Enzyme Thiaminase: A Known Anti-nutritional Enzyme with Unknown Therapeutic Potentials in Cancer Treatment

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| **Received:** 01.11.2024 | **Accepted:** 06.12.2024 | **Published:** 20.12.2024 |

Abstract: Thiaminase (EC 2.5.1.2) is an enzyme that cleaves thiamine into its pyrimidine and thiazole moieties resulting in thiamine deficiency in various organisms. It is classified into two main types: Thiaminase I and Thiaminase II defined by the nucleophile used in the mechanism by which the cleavage is accomplished. Thiaminase I employs a variety of nucleophiles including, amines and sulfhydryl compounds while thiaminase II exclusively uses water for hydrolysis of thiamine. The crystal structure of thiaminase I reveals a deep cleft that accommodates thiamine and highlighting important residues that assists in its breakdown. This process disrupts thiamine's biological function leading to metabolic disturbances. Physiochemically, thiaminase exhibits specific properties that influence its activity, such as optimal pH of 4-8 and temperature ranges from 40-60◦c. Thiaminase is naturally found in various organisms including certain plants, bacteria and marine animals where it can act as an antinutrient. Consequently, thiaminase activity elicits life threatening conditions such as beriberi and Wernicke-korsakoff syndrome due to thiamine depletion. Furthermore, this can lead to significant neurological conditions, including ataxia and peripheral neuropathy. Interestingly, studies have suggested that native thiaminase and Polyethylene glycol-modified (PEGylated) thiaminase I enzyme may have potential applications in cancer therapy by impairing mitochrondrial respiration in cancer cells. This suggests that thiaminase may likely be a potential source of novel cancer chemotherapeutic agent via the impairment of DNA synthesis and energy metabolism in cancerous cells.

Keywords: Thiaminase, Enzyme, Vitamin B1, Antinutrient, Cleavage, Hydrolysis, Metabolism.

INTRODUCTION

Thiaminase is an enzyme that when ingested catalyzes the cleavage of Thiamine (Vitamin B1) into its pyrimidine and thiazole moieties (Cheryl *et al*., 2013) effectively destroying its vitamin properties and reducing its availability in the body. Thiaminase has been classified into two types: Thiaminase I and Thiaminase II respectively. Thiaminase I enzyme is present in plants such as nardoo and bracken Fern and in marine animals such as salmon, silver carp, anchovy, freshwater prawn in certain bacteria and one eukaryote; Naegleria gruberi (Tillit *et al*., 2005, Catherine *et al*., 2023, Katie *et al*., 2023). Thiaminase II enzyme is present in specific bacteria and yeasts (Kiku, 1982). A major cause of thiamine deficiency is an overreliance on diet items containing the enzyme thiaminase leading in deadly deficiency symptoms (Freya *et al*., 2023). Vitamin B1 is a vitamin necessary for proper cell function. It is important for energy production in the mitochrondria, protein synthesis and plays a special role as coenzyme necessary for the metabolism of carbohydrates, fats and proteins. It is also needed to ensure the proper functioning of the central and peripheral nervous system thus, its deficiency leads to mitochrondrial dysfunction, lactate and pyruvate accumulation, and consequently in neurodegenerative diseases including Alzheimer's disease which may manifest as Wernicke's encephalopathy or Wernicke-korsakoff syndrome. Its deficiency can also lead in neuropathy leading to ataxia, paralysis and confusion (Malgorzata *et al*., 2023). Once thiamine molecule is cleaved, the body is unable to restore it therefore, when significant amounts of thiaminases are ingested, thiamine deficiency may develop even when the concentration of dietary thiamine are adequate (Craig *et al*., 2024). Consumption of fish containing thiaminase has led to elevated mortality and inadequacy in farmed animals and wild salmonine populations around the world (Catherine *et al*., 2023). Thiaminase was first described as the cause of high mortal ataxic neuropathy in fur producing foxes eating

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Citation: Adeoye Bayo Olufunso, Nwachukwu Ijeoma Doris, Olanrewaju Okikiola Olamide, Omobude- Aisagbonhi Elizabeth (2024). Enzyme Thiaminase: A Known Anti-nutritional Enzyme with Unknown Therapeutic Potentials in Cancer Treatment. *Cross Current Int J Med Biosci*, *6*(6), 114-119.

the raw internal organs of river fish like carp. It is also known as the cause of cerebrocortical necrosis of cattle that feed on thiaminase containing plants (Okonji *et al*., 2012). When grazing animals such as sheep consume ferns, they develop thiamine deficiency which results in brain lesions and in the bending of the neck and in a phenomenon known as Stargazing where the animal falls to the ground with its feet in the air. In raising fisheries, there has been lot of economical losses as a result of thiaminase activity, example in yellowtail fed raw anchovy as the sole feed for a certain period, as well as in sea bream and rainbow trout (Okonji *et al*., 2012). Studies have also shown that native thiaminase I and Polyethylene glycol-modified (PEGylated) thiaminase I enzyme can be targeted to cancer inhibition by acutely down regulating cellular respiration making thiaminase an enzyme of dual importance (Daily *et al*., 2011, Liu *et al*., 2012).

Classification of Thiaminase

Thiaminases are generally classified into two types defined by the nucleophile used in the mechanism by which cleavage is accomplished. They include: Thiaminase I and Thiaminase II respectively. Thiaminase I (EC 2.5.1.2): This thiaminase is produced by certain bacteria such as Clostridium thiaminolyticum and Bacillus thiaminolyticus (Derrick, 2018). Thiaminase I is also produced by certain plants such as Ferns and Fishes such as Carp, Mackerel (Tillitt *et al*., 2005, Catherine *et al*., 2023, Katie *et al*., 2023).

Thiaminase II (EC 3.5.99.2): This thiaminase is produced by bacteria and yeasts. (Kiku,1982).

Mechanism of Action of Thiaminase

Thiaminase I catalyzes the breakdown of thiamine into pyrimidine and thiazole components. It uses various nucleophiles including aromatic and heterocyclic amines (such as aniline) and sulfhydryl compounds (such as Cysteine) in nucleophilic displacement reactions that target the methylene group of the pyrimidine moiety (Cheryl *et al*., 2013). Meanwhile, thiaminase II simply accelerates the hydrolysis of thiamine. It uses water as the nucleophile to cleave thiamine into 2-methyl-4-amino-5-hydroxymethypyrimidine (HMP) and 4-methyl-5-(2-hydroxyethyl) thiazole (Cheryl *et al*., 2013, Katie *et al*., 2023).

Natural Occurrence of Thiaminase

Thiaminase I is found in specific specie of microorganisms such as Bacillus thiaminolyticus, Clostridium botulinum and Clostridium sporogenes (Katie *et al*., 2023) as well as multicellular organisms including ferns like nardoo fern, in marine animals such as zebrafish, goldfish, alewife, anchioves, carp, salmon, mackerel and freshwater prawn (Barry & Bruce 1977, Tillitt *et al*., 2005, Catherine *et al*., 2023, Katie *et al*., 2023). It can also found in plant tubers (Ehigie *et al*., 2013a) and gut of grasshoppers (Ehigie *et al*., 2013b) as well as in moths (Okonji *et al*., 2012). Thiaminase II on the otherhand is found in bacteria such as Bacillus subtilis and in yeasts such as Trichosporon, Candida and Oospora (Kiku, 1982).

Table 1: Natural occurrence of Thiaminase I & II

Enzyme Classification	Source	References
Thiaminase I	Bacteria: Bacillus thiaminolyticus, clostridium botulinum, clostridium sporogenes Eukaryote: Naegleria gruberi	Katie *et al*., 2023 Cheryl *et al*., 2013
	Marine animals: E.g Zebrafish, goldfish, alewife, anchioves, carp, salmon, mackerel, freshwater prawn etc	Catherine *et al*., 2023, Tillitt *et al*., 2005, Katie *et al*., 2023
	Plants: Nardoo fern	Barry & Bruce 1977
	Plant Tubers Gut of grasshopper	Ehigie *et al*., 2013a Ehigie *et al*., 2013b
Thiaminase II	Predominantly bacteria: Bacillus subtilis, Candida albican, Trichosporon	Kiku,1982

Physiochemical Properties of Thiaminase

Physiochemically, thiaminase exhibits specific properties that influence its activity such as its optimum pH, its optimum temperature, its molecular weight, its activators and inhibitors respectively. Because thiaminase I and thiaminase II are produced from different organisms, its optimum pH, optimum temperature as well as molecular weight varies. In Anaphae venata (a specie of moth), thiaminase I was found to have an optimum pH of 6.0 at an optimum temperature of 60◦c. In Nardoo fern, thiaminase I was found to have an optimum pH of 8 to 9 at an optimum temperature of 55◦c. In Bacillus thiaminolyticus, thiaminase I was found to have an optimum pH range of 5.8 to 6.8 at an optimum temperature of 37◦c (Okonji *et al*., 2012). Bacteria thiaminase II was found to have an optimum pH of 5.0 at an optimum temperature of 30◦c (Akiji *et al*., 1951). The molecular weight of bacterial thiaminase I was found with ranges from 42,000 to 44,000 dalton,an estimated molecular weight range of 93,000 to 115,000 dalton was reported for nardoo fern and a molecular weight of 106,000 dalton for seawater fish. Bacterial thiaminase II (Bacillus subtilis) as well as thiaminase I of plant and shellfish was found with molecular weight range of 100,000 to 115,000 dalton respectively (Okonji *et al*., 2012). As for the activators

and inhibitors of both thiaminases; manganese(ii)ions, iron(iii)ions, pyridoxine(as co-substrate), cysteine accelerated the activity of thiaminase I while copper(ii)ions; an irreversible inhibitor of thiaminase I, application of heat, ascorbic acid, 4-amino-6-chloro-2-5-dimethyl pyrimidine (4 ACDP);a suicide inhibitor of thiaminase I inhibited the activity of thiaminase I (Megan *et al*., 2013,Katie *et al*., 2023, Patricia *et al*., 2023). For thiamnase II, bacterial thiaminase was found to be very active in the presence of nicotinic acid and nicotinamide. Application of heat and presence of copper (ii) ions inhibited activity of bacterial thiaminase II (Akiji *et al*., 1951, Katie *et al*., 2023).

Table 2: Physiochemical properties of Thiaminase

S/N	Thiaminase TYPE	Optimum pH	Optimum temp (℃)	Inhibitors	Activators	References
1	Thiaminase I	5.0-9.0	30-60	Copper (ii)ions, heat, ascorbic acid, 4-amino-6-chloro-2-5-dimethyl pyrimidine (4 ACDP)	Pyridoxine, cysteine, manganese (ii) ions, iron (iii) ions	Okonji *et al*.,2012, Megan *et al*.,2013, Katie *et al*.,2023, Patricia *et al*.,2023
2	Thiaminase II	5.0	30	Heat, copper (ii)ions	Nicotinic acid, nicotinamide	Akiji *et al*.,1951, Katie *et al*.,2023

Biochemical Target of Thiaminase

Thiamine or vitamin B1 is a water-soluble vitamin that is readily degraded by thiaminase. Thiamine is essential for carbohydrate metabolism, fatty acid metabolism and energy production and also serves as a cofactor for a number of enzymes involved in energy production. Thiaminase activity reduces thiamine availability making it unavailable for conversion to its biologically active form; Thiamine pyrophosphate (TPP). As a result, thiamine-dependent enzymes involved in carbohydrate, fatty acid metabolism as well as energy production are affected (Shibani *et al.*, 2019).

Impacts of Thiaminase Activity on the Pentose Phosphate Pathway

The pentose phosphate pathway is one of the pathways that is crucially affected in times of thiamine deficiency due to thiaminase activity. In the cytosol, the coenzyme form of Thiamine; Thiamine pyrophosphate (TPP) acts as a cofactor for Transketolase which is a key enzyme of the non-oxidative branch of the pentose phosphate pathway. This metabolic pathway generates Nicotinamide Adenine Dinucleotide Phosphate (NADPH) and Ribose-5-phosphate (R5P). NADPH is a key reducing agent in biosynthetic reactions and is a co-substrate of biosynthetic enzymes (fatty acid synthesis) and antioxidant enzymes such as the glutathione peroxidase-reductase system and thioredoxin peroxidases among others. R5P is crucially involved in the biosynthesis of DNA and RNA highlighting its role in high proliferating tissues. Therefore, a deficiency of thiamine due to thiaminase activity will reduce transketolase activity leading in impairment of the pentose phosphate pathway. This impairment leads in reduced NADPH and R5P production from the Pentose phosphate pathway (Shibani *et al*., 2019).

Effects of Thiaminase Activity on the Glycolytic Pathway

In the mitochrondria, thiamine pyrophosphate (TPP) is a cofactor for pyruvate dehydrogenase activity that is responsible for the decarboxylation of pyruvate to generate Acetyl-COA, which then enters the TCA cycle. Low TPP due to thiaminase activity inhibits pyruvate dehydrogenase activity thereby locking the system into the oxidation of glucose to pyruvate preventing its final conversion into Acetyl-COA. As a result, there is increase in lactate production and decrease in cellular ATP production from glucose metabolism (Shibani *et al*., 2019)

Effects of Thiaminase Activity on the Tricarboxylic Cycle

∝-ketoglutarate dehydrogenase in the TCA cycle is TPP (Thiamine pyrophosphate) dependent to catalyze the formation of Succinyl-COA from ∝-ketoglutarate in the TCA cycle and the consequent production of reduced Nicotinamide Adenine Dinucleotide (NADH). Low levels of TPP notably decrease ∝-ketoglutarate dehydrogenase activity, causing accumulation of ∝-ketoglutarate thereby decreasing energy production (ATP) and causing the accumulation of glutamate, hampering oxidative metabolism (Shibani *et al*., 2019).

Effects of Thiaminase Activity and Amino Acid Metabolism

Branched chain ∝-keto dehydrogenase (BCKDH) is an enzyme that requires Thiamine pyrophosphate (TPP) as cofactor for the catabolism of essential branched chain amino acids: Leucine, Valine, Isoleucine as well as in the decarboxylation of branched chain ∝-keto acids derived from these amino acids into acyl-coA derivatives that enter the TCA cycle for energy production. These amino acids are required for protein synthesis, their carbon skeletons (except Leucine) can be used as precursors for gluconeogenesis (Sperringer *et al*., 2017). Thus, low TPP due to thiaminase activity will lead in reduced Branched chain ∝-keto dehydrogenase activity which will consequently result in buildup of branched chain ∝-keto acids in the bloodstream. Since branched chain amino acids are important for energy production especially during fasting or intense exercise, impaired BCKDH activity will hinder utilization of these

amino acids for energy leading in reduced energy availability for tissues especially the muscle and brain.

Implications of thiaminase Activity in Neurological Disorders

The hippocampus which is the region of the brain that is crucial for the formation and retrieval of memory undergoes significant growth and neural proliferation during development. Considering that cell proliferation requires a large amount of ribose-5-phosphate for biosynthesis of nucleotides, a decrease of transketolase activity due to deficiency of thiamine influenced by thiaminase activity impairs the PPP leading in decrease in metabolism of ribose-5-phosphate and NADPH, thereby inhibiting hippocampal neurogenesis (Yanling *et al*., 2014) ultimately resulting in memory impairment such as in Alzheimer's disease (Zhao *et al*., 2009).

Reduced transketolase activity due to thiaminase activity impairs the PPP leading in reduced NADPH production, since NADPH is vital for resistance of oxidative stress, this decrease results in increased oxidative stress (excessive ROS levels) as well decreased fatty acid synthesis (including myelin). Reduced formation of R5P due to this impairment will limit biosynthesis of DNA and RNA which is crucial for cell proliferation as well as development of new neurons (Shibani *et al*., 2019). Excessive ROS levels can induce cytotoxicity and promote DNA damage and apotosis. Reduced R5P will also hinder development and proliferation of new neurons consequently leading in neuronal damage (Xin *et al*., 2024).

Thiamine-deficiency mediated inhibition of PDH complex will lock the system into oxidation of glucose to pyruvate, leading in increase in lactate and decrease in cellular ATP production (Shibani *et al*., 2019). In severe cases, metabolic deficits present as fatal lactic acidosis, Leigh encephalopathy, to later onset of neurological disease such as intermittent ataxia or dystonia. Females tend to have a more uniform presentation resembling nonprogressive cerebral palsy. Neuroradiological abnormalities such as corpus callosum agenesis are seen more frequently in girls, basal ganglia and midbrain disturbances in boys (Linda, 2013).

Accumulation of ∝ -ketoglutarate due to reduced ∝ -ketoglutarate dehydrogenase activity as a result of thiaminase activity will result in elevated levels of glutamate. Since glutamate is the main excitatory neurotransmitter in the central nervous system, excessive levels of glutamate can lead to excitotoxicity in the nervous system which can disrupt normal neurotransmission and contribute to neuronal injury or death (Fahimeh *et al*., 2023). Glutamate-mediated excitotoxicity also leads to neurodegeneration and its diseases such as Alzheimer's disease and Huntington's disease (Jan & Pamela, 2015), neuroinflammation, blood brain barrier permeability and cerebral vasodilation (Fahimeh *et al*., 2023). High levels of glutamate will also lead in sensitization of N-methyl-D-aspartic acid (NMDA) receptors, since NMDA receptors have high calcium conductivity, sensitization leads in increased influx of extracellular calcium ions (Jan & Pamela, 2015). Calcium once in the cell communicates with a number of systems and pathways including reactive oxygen species (ROS). Therefore, increased levels of calcium ions activate ROS-generating enzymes and formation of free radicals consequently leading mitochrondrial dysfunction (Agnes *et al*., 2015)

Buildup of branched chain ∝ keto acids due to impaired branched-chain ∝ -keto acid dehydrogenase (BCKADH) activity as a result of thaiminase activity results in a disorder known as maple syrup urine disease (MSUD) (Sperringer *et al*., 2017)

Maple syrup urine disease a rare, inherited metabolic disorder caused by defects in branched-chain ∝-keto acid dehydrogenase (BCKADH) activity which results in elevations of branched-chain amino acids (BCAAs) in plasma and ∝ keto acids in urine. Presentation occurs in neonatal period with developmental delay, maple syrup odor in the cerumen and urine, and can lead to irreversible neurological complications, including stereotypical movements, metabolic decompensation, and death if left untreated (Patrick *et al.*, 2017).

Thiamine deficiency due to thiaminase activity will also result in beriberi. Wet beriberi is accompanied by edema, resulting in an abnormal cardiovascular system, circulatory failure and heart attack. Dry beriberi is associated with abnormal functioning of the nervous system and the development of polyneuropathy and Wernicke's encephalopathy (Malgorzata *et al*., 2023).

Therapeutic Potentials of Thiaminase in Cancer Treatment

Studies have shown that native thiaminase I from Bacillus thiaminolyticus and linear chain Polyethylene glycol-modified (PEGylated) thiaminase I enzyme exhibits cytotoxicity activity in lymphoid leukemia cell lines (Daily *et al.*, 2011). In RS4 leukemia cells, native thiaminase and 5k-PEGylated thiaminase I showed significant anticancer cytotoxicity by acutely down regulating cellular respiration (Liu *et al*., 2012). Tumor cells require significant energy and substrates for indefinite proliferation, and the pentose phosphate pathway (PPP) particularly the thiamine-dependent enzyme Transketolase (TKT) is crucial for this process (Xin *et al*., 2024). TKT uses thiamine pyrophosphate (TPP) as a cofactor to produce ribose-5-phosphate (R5P); a precursor for nucleotide synthesis that supports cancer cell proliferation and DNA repair (Anna *et al*., 2015). Additionally, TKT mediates reversible reactions in the PPP, helping to replenish NADPH and mitigate oxidative stress (Sylwester *et al*., 2022). However, thiaminase activity reduces TKT activity, impairing the

PPP and decreasing R5P production, which suppresses DNA and RNA synthesis and lowers cancer cell proliferation (Seung *et al*., 2015, Shibani *et al*., 2019). Furthermore, decreased TKT activity leads to increased reactive oxygen species (ROS), which can induce cancer cell death (Seung *et al*., 2015).

CONCLUSION

In conclusion, thiaminase is a significant enzyme that plays a dual role in both health and disease. Its capacity to degrade thiamine disrupts vital metabolic pathways, leading to a range of neurological conditions and metabolic disorders. Understanding the biochemical properties and natural occurrences of thiaminase can enhance our knowledge of its impact on human health, particularly in relation to thiamine deficiency, which has been linked to cognitive impairments and various metabolic disorders.

REFERENCES

- Blackburn, P. R., Gass, J. M., Vairo, F. P. E., Farnham, K. M., Atwal, H. K., Macklin, S., ... & Atwal, P. S. (2017). Maple syrup urine disease: mechanisms and management. *The application of clinical genetics*, 57-66.
- Daily, A., Liu, S., Bae, Y., Bhatnagar, S., & Moscow, J. A. (2011). Linear chain PEGylated recombinant Bacillus thiaminolyticus thiaminase I enzyme has growth inhibitory activity against lymphoid leukemia cell lines. *Molecular Cancer Therapeutics*, *10*(9), 1563-1570.
- De Meirleir, L. (2013). Disorders of pyruvate metabolism. *Handbook of Clinical Neurology*, *113*, 1667-1673.
- Dhir, S., Tarasenko, M., Napoli, E., & Giulivi, C. (2019). Neurological, psychiatric, and biochemical aspects of thiamine deficiency in children and adults. *Frontiers in psychiatry*, *10*, 447129.
- Edwards, K., Randall, E., Wolfe, P., Angert, E., & Kraft, C. (2023). Dietary factors potentially impacting thiaminase I-mediated thiamine deficiency. *Article from Scientific reports*, 13,7008 https://doi.org/10.1038/s41598-023-34063-5
- Emuebie, O., Samuel, B., & Olusola, B. (2012). Biochemical properties of Thiaminase from Anaphe venata Burtler. *African Journal of Biotechnology*, *11*(20), 4543-4550 https://doi.org/10.5897/AJB11.3456
- Fujita, A., Nose, Y., Kozuka, S., Tashiro, T., Ueda, K., & Sakamoto, S. (1951). Activation of Thiamine breakdown by Organic bases. *Journal of Biological Chemistry*, *196*(1), 289-295 https://doi.org/10.1016/S0021-9258(18)55732-X
- Jackson, C., Furnes, M., Rod-Eriksen, L., Yap, K. N., Davey, M., Fossoy, F., Flagstad, O., Eide, N. E., Mjoen, T., & Ulvund, K., (2024). Subclinical thiamine deficiency results in failed reproduction in arctic foxes. *Veterinary medicine and science*, *10*(2) https://doi.org/10.1002/vms3.1358
- Joint center for Structural Genomics. (2014). Crystal Structure of putative thiaminase II from Staphylococcus epidermidis. Research Collaboratory for Structural Bioinformatics PDB https://doi.org/10.2210/pdb3NO6/pdb
- Jung, S. N., Shin, D. S., Kim, H. N., Jeon, Y. J., Yun, J., Lee, Y. J., ... & Kwon, B. M. (2015). Sugiol inhibits STAT3 activity via regulation of transketolase and ROS-mediated ERK activation in DU145 prostate carcinoma cells. *Biochemical pharmacology*, *97*(1), 38-50.
- Kloska, S. M., Pałczyński, K., Marciniak, T., Talaśka, T., Miller, M., Wysocki, B. J., ... & Wysocki, T. A. (2022). Queueing theory model of pentose phosphate pathway. *Scientific reports*, *12*(1), 4601.
- Kreinbring, C., Remillard, S., Hubbard, P., Brodkin, H., Leeper, F., Hawksley, D., Lai, E., Fulton, C., Petsko, G., & Ringe, D. (2013). Structure of a eukaryotic thiaminase I. *Proc Natl Academy Science U.S.A*, *111*(1), 137-142. https://doi.org/10.1073/pnas.1315882110
- Lewerenz, J., & Maher, P. (2015). Chronic Glutamate Toxicity in Neurodegenerative Diseases-What is the Evidence? *Frontiers in neuroscience*, *9*, 469, 10.3389/fnins.2015.00469
- Liu, S., Bae, Y., Leggas, M., Daily, A., Bhatnagar, S., Miriyala, S., ... & Moscow, J. A. (2012). Pharmacologic properties of polyethylene glycol-modified Bacillus thiaminolyticus thiaminase I enzyme. *Journal of Pharmacology and Experimental Therapeutics*, *341*(3), 775-783.
- Lonsdale, D. (2018). Thiamin. *Advances in food and nutrition research*, *83*, 1-56.
- Martami, F., & Holton, K. F. (2023). Targeting glutamate neurotoxicity through dietary manipulation: Potential treatment for migraine. *Nutrients*, *15*(18), 3952.
- McCleary, B. V., & Chick, B. F. (1977). The purification and properties of a thiaminase I enzyme from Nardoo (Marsilea drummondii). *Phytochemistry*, *16*(2), 207-213.
- Mrowicka, M., Mrowicki, J., Dragan, G., & Majsterek, I. (2023). The importance of thiamine (vitamin B1) in humans. *Bioscience Reports*, *43*(10), BSR20230374.
- Murata, K. (1982). Actions of two types of Thiaminase on thiamin and it's analogues. *Annuals of the New York Academy of Series*, *378*(1), 146-156 https://doi.org/10.1111/j.1749-6632.1982.tb31193.x
- Ritcher, C., Evans, A., Heppell, S., Zajicek, J., & Tilitt, D. (2023). Genetic basis of thiaminase I activity in vertebrate, Zebrafish Danio rerio. *Scientific reports*, *13*(1), 698 https://doi.org/10.1038/s41598-023-27612-5
- Rowland, F. E., Richter, C. A., Tillitt, D. E., & Walters, D. M. (2023). Evolutionary and ecological

correlates of thiaminase in fishes. *Scientific Reports*, *13*(1), 18147.

- Sikowitz, M. D., Shome, B., Zhang, Y., Begley, T. P., & Ealick, S. E. (2013). Structure of a Clostridium botulinum C143S thiaminase I/thiamin complex reveals active site architecture. *Biochemistry*, *52*(44), 7830-7839.
- Sperringer, J. E., Addington, A., & Hutson, S. M. (2017). Branched-chain amino acids and brain metabolism. *Neurochemical research*, *42*, 1697-1709.
- Tetsuka, S., & Hashimoto, R. (2021). Alcohol-Related Central nervous System Disorders Associated with Vitamin B deficiency. Article from *SN Comprehensive Clinical medicine*, *3*(12) http://dx.doi.org/10.1007/s42399-021-00741-6
- Tillit, D., Zajicek, J., Brown, S., Brown, L., Fitzsimons, J., Honeyfield, D., Holey, M., & Wright G. (2005). Thiamine and Thiaminase Status in Forage fish of salmonines from Lake Michigan. *Journal of Aquatic Animal Health*, *17*, 13-25 https://doi.org/10.1577/H03-081.1
- Wittliff, J. L., & Airth, R. L. (1970). [42] Thiaminase II (thiamine hydrolase, EC 3.5. 99.2). In *Methods in enzymology* (Vol. 18, pp. 234-238). Academic Press.
- Wolfe, P. C., Tuske, A. M., Tillitt, D. E., Allen, F., & Edwards, K. A. (2023). Understanding and mitigating thiaminase activity in silver carp. *Current Research in Food Science*, *6*, 100502.
- Zhao, Y., Pan, X., Zhao, J., Wang, Y., Peng, Y., & Zhong, C. (2009). Decreased transketolase activity contributes to impaired hippocampal neurogenesis induced by thiamine deficiency. *Journal of neurochemistry*, *111*(2), 537-546 doi 10.1111/j.1471-4159.2009.06341.x
- Zhao, Y., Wu, Y., Hu, H., Cai, J., Ning, M., Ni, X., & Zhong, C. (2014) Downregulation of Transketolase Activity Is Related to Inhibition of Hippocampal Progenitor Cell Proliferation Induced by Thiamine deficiency. *Biomedical research international*, *1*, 572915 https://doi.org/10.1155/2014/572915
- Zhen, X., Zhang, M., Hao, S., & Sun, J. (2024). Glucose-6-phosphate dehydrogenase and transketolase: Key factors in breast cancer progression and therapy. *Biomedicine & Pharmacotherapy*, *176*, 116935.