"Molecular Pathophysiology and Pharmacotherapy of Wilson Disease: Revisiting Trientine as a Safer Chelating Agent"

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ABSTRACT

Wilson disease (WD) is a rare autosomal recessive disorder of copper metabolism first described by Dr. Samuel Alexander Kinnier Wilson in 1912. It is caused by harmful mutations in the ATP7B gene on chromosome 13, which codes for an ATPase that transports copper and is in charge of biliary copper excretion and ceruloplasmin incorporation. Hepatic, neurological, and psychiatric symptoms result from systemic copper accumulation caused by the faulty ATP7B protein, which mostly occurs in the liver, brain, and cornea. Toxic copper buildup and oxidative tissue damage are caused by mutations in ATP7B that hinder copper integration into ceruloplasmin and its biliary excretion. Wilson illness affects about 1 in 30,000 people worldwide, and it is more common in countries with higher levels of consanguinity. Preventing irreversible hepatic and neurological damage requires early diagnosis and continuous treatment. For both first-line and second-line treatment of WD, trientine tetrahydrochloride (triethylenetetramine) has proven to be a safe and efficient copper-chelating agent. It works by limiting intestinal copper absorption and binding free copper ions to generate stable, water-soluble complexes that are mainly eliminated through urine. Trientine exhibits a better safety profile, more long-term tolerance, and less hypersensitivity events than D-penicillamine. WD was once a deadly genetic ailment, but because to developments in molecular diagnoses and pharmaceutical treatment, it is now a chronic illness that can be controlled. Because of its effectiveness, safety, and capacity to restore copper balance and stop progressive organ damage, trientine tetrahydrochloride continues to be a key component of treatment.

KEYWORDS: Wilson disease; ATP7B gene; chromosome 13; pathogenic mutation; autosomal recessive disorder; ATPase enzyme; hepatic copper accumulation.

INTRODUCTION

Dr. Samuel Alexander Kinnier Wilson initially identified Wilson disease (WD), a rare autosomal recessive condition of copper metabolism, in 1912. [1] It is caused by pathogenic mutations in the ATP7B gene on chromosome 13, which codes for an ATPase that transports copper and is involved in biliary excretion and ceruloplasmin. [3] Toxic copper buildup in the liver, brain, and other tissues results from the faulty ATP7B protein's impairment of hepatic copper removal and incorporation into ceruloplasmin. [4–6]

The systemic toxicity of excess copper is reflected in the clinical manifestations of WD, which include hepatic, neurological, and mental disorders. Hepatocellular necrosis, cirrhosis, and steatosis are examples of histopathological alterations in the liver. At the molecular level, the damaged ATP7B enzyme causes reduced ceruloplasmin synthesis and poor biliary excretion of copper, which raises free copper levels and causes cellular damage due to oxidative stress. [7]

Clinically, WD manifests with hepatic, neurological, and psychiatric symptoms, reflecting the systemic toxicity of excess copper. Histopathological changes in the liver include steatosis, hepatocellular necrosis, and cirrhosis.[7] At the molecular level, the defective ATP7B enzyme leads to decreased ceruloplasmin synthesis and impaired biliary excretion of copper, resulting in elevated free copper levels and oxidative stress-mediated cellular injury.[8–12]

Approximately 1 in 30,000 people worldwide have WD, with geographical differences linked to consanguinity and genetic heterogeneity. Despite being regarded as uncommon, the actual prevalence can be underestimated because of its inconsistent clinical presentation and restricted access to diagnostics in some areas. To avoid irreparable hepatic and cerebral damage, early identification and lifetime copper-chelation therapy are crucial.[13,14]

For both first-line and second-line treatment of WD, trientine (triethylenetetramine) has become a well-tolerated and efficient copper chelator. It works by limiting intestinal copper absorption, increasing urine output, and creating stable, water-soluble complexes with free copper. Trientine is a safer long-term substitute for D-penicillamine in the treatment of WD since it has better tolerance and fewer side effects.[15-19]

ETIOLOGY OF WILSON DISEASE

- Wilson disease is caused by mutations in the ATP7B gene, which is located on chromosome 13. This gene codes for a copper-transporting ATPase enzyme that is crucial for the proper regulation and excretion of copper in the body.[20]
- The enzyme ATP7B is involved in the incorporation of copper into ceruloplasmin, a copper-carrying protein in the bloodstream, and in the excretion of excess copper into bile. When the ATP7B protein is defective due to genetic mutations, (Figure 1**)** copper is not properly incorporated into ceruloplasmin or excreted in the bile

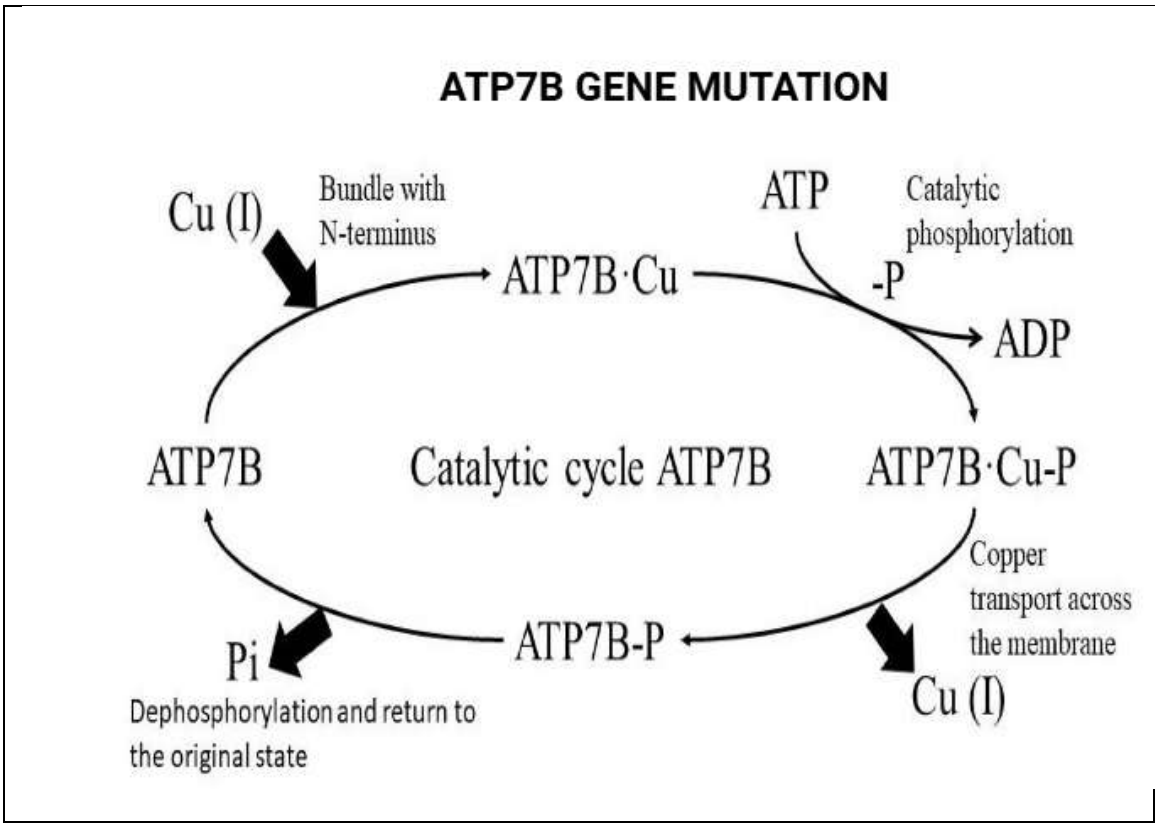


Figure 1 : ATP7B gene mutations

This leads to:

- Copper accumulation in the liver: Copper builds up within the liver cells (hepatocytes),

leading to liver damage, cirrhosis, and, if untreated, liver failure.[21-23]

- Copper deposition in the brain: Especially in the basal ganglia, which is involved in motor control, leading to neurological symptoms such as tremors, dystonia, and dysarthria.(Figure 2**)**

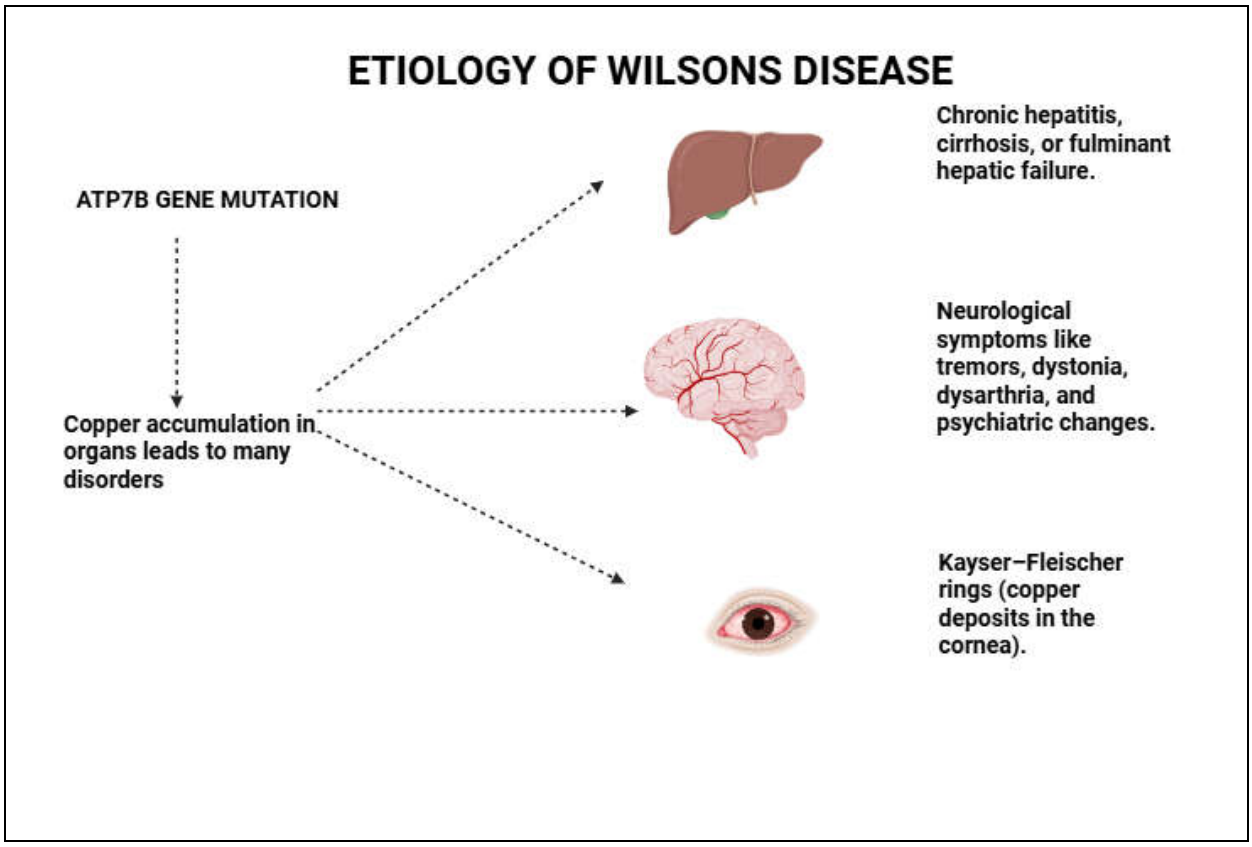


Figure 2 : Etiology of Wilson Disease

PATHOGENESIS

- Cytochrome c oxidase is an enzyme that contains copper as a cofactor and functions in the final stage of the electron transport chain. Copper is essential for its enzymatic activity. In early stages of Wilson's disease (WD), copper accumulation is associated with several histopathological changes, including macro vesicular steatosis and glycogenated hepatocytes.[24] A genetic defect in WD leads to two major disruptions at the cellular level: first, the impaired incorporation of copper into apoceruloplasmin results in decreased levels of ceruloplasmin a key copper-transport protein in the blood, thereby increasing free copper

availability in peripheral tissues. **(**Figure 3)

- Second, copper excretion into bile is hindered due to defective transport into bile canaliculi, limiting its elimination from the body.[8]
- Because of mutations in the ATP7B gene, apoceruloplasmin (the copper-free form) fails to bind copper and is rapidly degraded, further lowering blood ceruloplasmin levels. This reduction leads to copper accumulation in various tissues due to the inability to properly excrete it.[25]
- The mutation affects ATP7B, a P-type ATPase gene comprising 21 exons and spanning over 80 kb of DNA. This enzyme, also known as "Wilson ATPase," contains six copper-binding domains in its N-terminal region and is primarily expressed in the liver.[26-27] Mutations that impair ATP7B synthesis, stability, copper transport within the trans-Golgi network, or copper binding to ceruloplasmin result in intracellular copper overload.
- This buildup leads to toxic accumulation in hepatocytes and cellular damage. Excess free copper can also cross the blood-brain barrier, contributing to neurodegeneration and systemic toxicity.[28]The most common ATP7B mutation in individuals of European descent is the substitution of histidine with glutamine at position 1069 (H1069Q). Additionally, COMMD1 (COMM domain-containing protein plays a role in biliary copper excretion and is linked to copper toxicosis.[13]Some mutations prevent the production of any functional ATPase protein, while others result in misfolded or partially functional forms.[29,30]
- Copper is primarily excreted through bile; hence, impaired biliary excretion leads to hepatic copper buildup and eventual release into the bloodstream, affecting other organs. Free copper promotes oxidative stress by generating reactive oxygen species (ROS) through Fenton chemistry, resulting in cellular damage and clinical manifestations. Chronic exposure to high copper levels can cause demyelination and neuronal damage, particularly in regions such as the basal ganglia, thalamus, mesencephalon, and cerebellum.[31] High circulating levels of unbound copper can also induce non-immune hemolysis. A hallmark feature of Wilson's disease is the presence of Kayser-Fleischer rings golden-brown rings in the cornea caused by copper deposition.[32]
- Prolonged hepatic damage may progress to chronic liver disease and portal hypertension.[33]

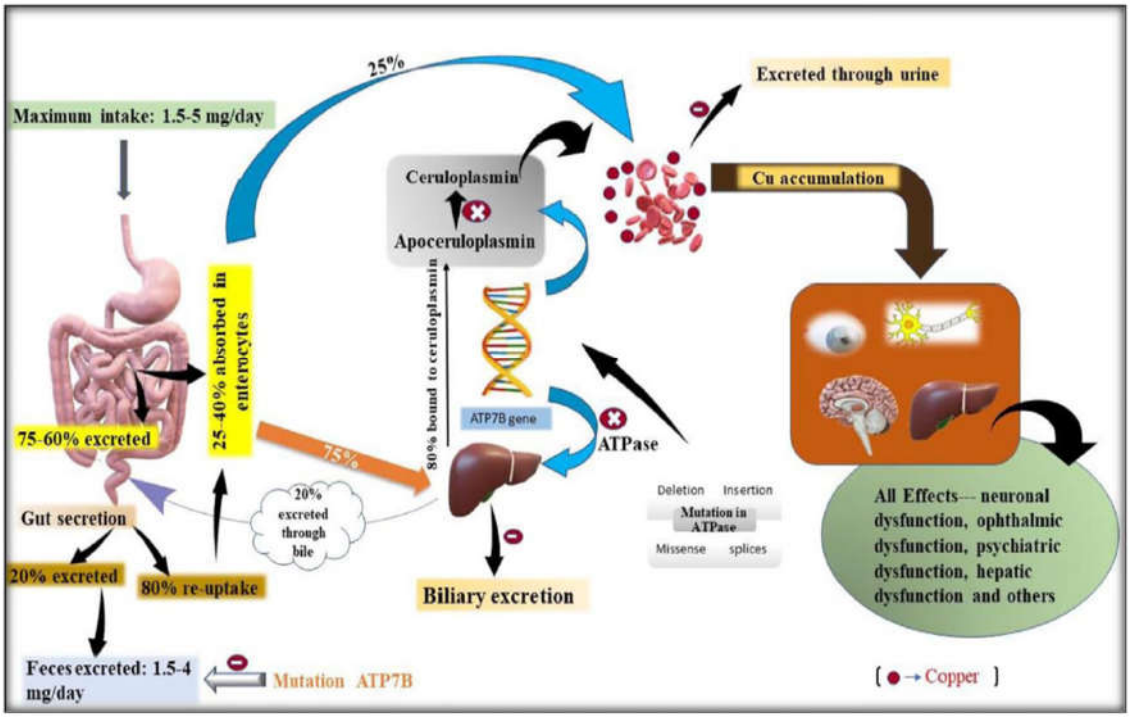


Figure 3 :Pathogenesis Of Wilson Disease

EPIDEMIOLOGY

In the 1970s, epidemiological studies reported a prevalence of Wilson disease (WD) at 29 cases per 1,000,000 individuals in Germany and 33 cases per 1,000,000 in Japan.[33,34]By 1984, the global prevalence of WD in non-isolated populations was estimated to be 1 case per 30,000 individuals, with a carrier frequency (individuals with one disease-associated allele) of 1 in 90 representing nearly 1% of the general population.[35] These estimates remain widely referenced today. The prevalence of WD is notably higher in China (58.7 cases per 1,000,000 individuals) and other Asian countries compared to Western regions. Studies from genetically isolated communities have reported even higher rates of WD, largely due to consanguinity. For instance, the Canary Islands reported a prevalence of 1 case per 2,600 individuals, while Sardinia reported 1 case per 7,000 individuals.[36]

In a molecular study from the UK, it was estimated that approximately 1 in 7,000 individuals may carry two pathogenic ATP7B alleles, with heterozygous mutations potentially present in up to 2.5%

of the general population.[37] However, the actual prevalence of WD may be underestimated due to its variable clinical presentation, which can lead to under diagnosis or misdiagnosis. Additional contributing factors include the limited sensitivity of certain copper metabolism tests and the unclear age-related clinical penetrance of ATP7B mutations. With increased awareness among healthcare professionals and improved access to genetic testing, more individuals are being diagnosed with WD. Though comprehensive ATP7B gene sequencing remains costly and is not universally available, it is valuable for refining prevalence estimates when accessible. Mortality rates in pre symptomatic WD patients who adhere to treatment are comparable to those of the general population.[38] (Figure 4)

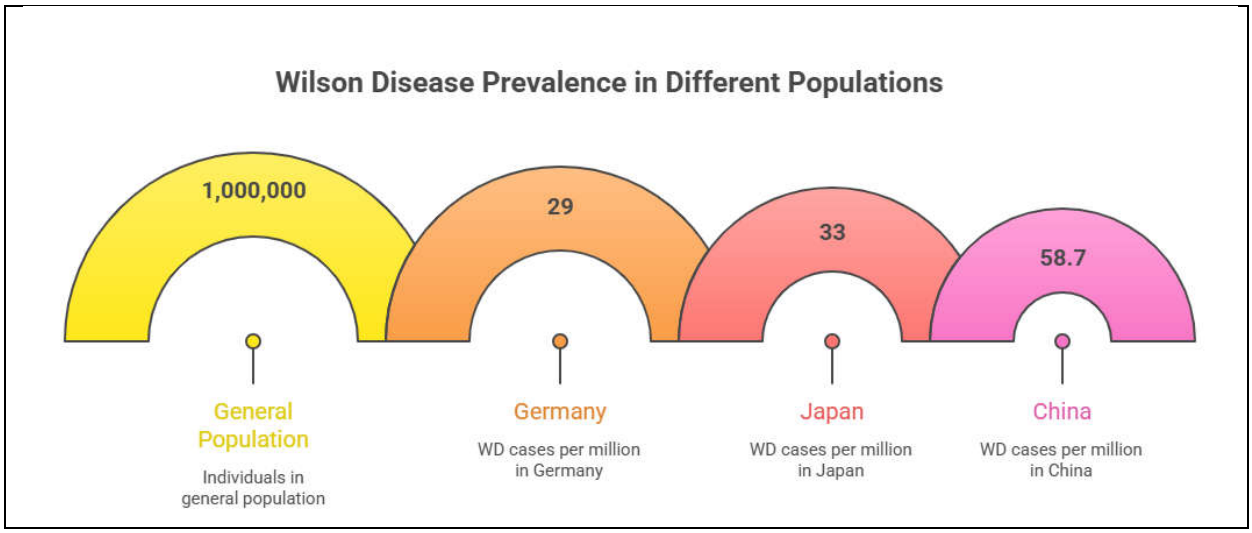


Figure 4 : Distridisbution of Wilson disease in different population

However, when considering all WD patients regardless of clinical symptoms, disease progression at diagnosis, or treatment adherence studies have shown that mortality is 5–6.1% higher than in the general population[39-41]. Survival outcomes are significantly influenced by the presence of advanced hepatic or neurological disease and by adherence to prescribed treatment regimens. (Table 1**)**

Table 1 : Prevalence of Wilson disease in different population

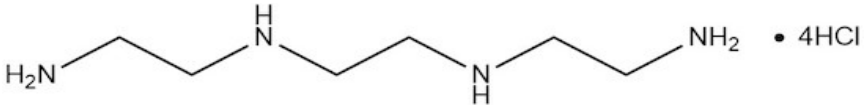
Parameter	Prevalence	Contributing Factors
Global prevalence (historical estimate)	~1 in 30,000 individuals	Widely cited estimate since 1984; applies mainly to non-isolated populations
Early epidemiological data (1970s)	Germany: 29 per 1,000,000Japan: 33 per 1,000,000	Based on clinical diagnosis; likely underestimates true prevalence
Carrier frequency (heterozygotes)	~1 in 90 (~1%)	Carriers usually asymptomatic but important for genetic counseling
Prevalence in China	58.7 per 1,000,000	Higher prevalence compared to Western countries
Prevalence in other Asian countries	Higher than Western regions	Possibly due to genetic background and better case identification
Genetically isolated populations	Canary Islands: 1 in 2,600Sardinia: 1 in 7,000	High consanguinity increases autosomal recessive disorders
UK molecular genetic estimate	~1 in 7,000 with two pathogenic ATP7B alleles	Suggests many undiagnosed or pre-symptomatic cases
ATP7B heterozygous mutations	Up to 2.5% of general population	Indicates WD may be more common than clinically recognized
Age of onset	Typically childhood to early adulthood	Symptoms may appear from 3–40 years; wide variability
Reasons for underestimation	Variable clinical presentationLimited sensitivity of copper testsUnclear age-related penetrance	Leads to underdiagnosis and misdiagnosis
Impact of genetic testing	Improves detection and prevalence estimates	Comprehensive ATP7B sequencing costly and not universally available
Mortality (treated, presymptomatic patients)	Comparable to general population	Early diagnosis and adherence to therapy are key
Overall mortality (all WD patients)	5–6.1% higher than general population	Includes advanced disease and non-adherent patients
Factors affecting survival	Advanced hepatic diseaseNeurological involvementPoor treatment adherence	Strong predictors of worse outcomes

MODERN TREATMENT STRATEGIES

Trientine Tetrahydrochloride

Trientine, also known as triethylenetetramine (TETA), trien, or 2,2,2-tetramine, is a copper-selective chelator used in the treatment of Wilson disease (WD). Its chemical structure contains four nitrogen atoms and lacks sulfhydryl groups, forming a stable complex with copper through a planar ring structure, which distinguishes it from penicillamine.[42]Trientine has gained importance both as a primary treatment and as a second-line therapy, particularly due to its lower risk of adverse effects compared to d-penicillamine (d-PCA). Although it mobilizes less cellular copper than d-PCA, this is associated with fewer side effects.[43]Therapeutic doses typically range from 750 to 1500 mg per day, divided into 2 to 4 doses. Increases in urinary trientine levels correlate with increased copper excretion in the urine, indicating its effectiveness in copper removal.[31,32]Intestinal absorption of trientine is regulated by polyamine carrier proteins, which may compete with dietary polyamines and limit absorption efficiency.[44-45] It is recommended that trientine be taken before meals, as its absorption window spans 1–3 hours post-ingestion.[46]

Structureof Trientine Tetrahydrochloride



Trientine exhibits a broad distribution throughout the body, maintaining a stable apparent volume of distribution.[47] Historically, penicillamine was the first-line treatment for WD. However, due to its extensive side effect profile including worsening of neurological symptoms trientine was initially used as a backup therapy. Today, it is often favored as the first-line therapy, supported by studies comparing adverse effect profiles between the two drugs.[48]

Although trientine is generally well tolerated, it can occasionally lead to mild liver damage, sideroblastic anemia, and allergic dermatitis, none of which typically have a major clinical impact.[49-51] Trientine has also been associated with delayed hypersensitivity reactions, including drug-induced lupus and nephritis, which are similar to those reported with penicillamine use. In such cases, corticosteroids may be employed, and switching to an alternative therapy is advised if severe

reactions occur.[52-54]One notable benefit of trientine is its ability to prevent rapid deterioration seen in some patients after d-penicillamine discontinuation, making it a suitable alternative in such circumstances.[44]Long-term use of trientine can cause a reduction in serum iron levels, though these typically normalize quickly with oral iron supplementation.[55,56]

MECHANISM OF ACTION

Trientine (triethylenetetramine) is a polyamine copper-chelating agent that exerts its therapeutic effect by binding free and loosely bound copper ions to form stable, water-soluble complexes that are primarily eliminated through urinary excretion.[57] The drug acts as a potent alternative pathway for copper elimination, facilitating the mobilization of copper from hepatic stores and extracellular binding sites, thereby reducing total body copper burden.[58] In addition to systemic chelation, trientine exhibits local chelating activity in the gastrointestinal tract, where it binds dietary copper and decreases its intestinal absorption, further preventing copper accumulation in circulation.[59]This dual mechanism enhancing renal excretion and minimizing gastrointestinal absorption leads to a progressive reduction in copper overload, which is essential for halting hepatic and neurological damage in Wilson disease.[60] (Figure 5)

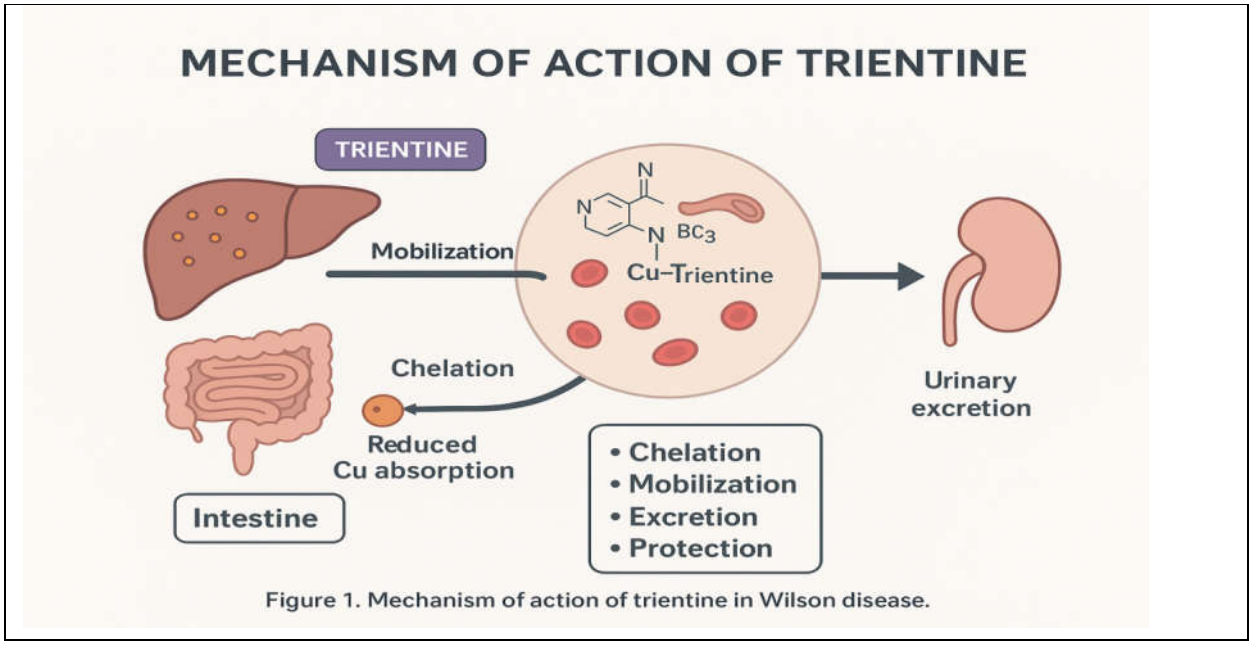
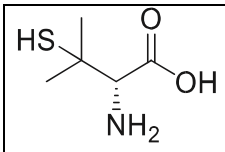


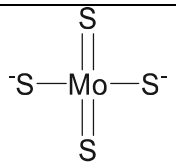
Figure 5 : Mechanism Of Actio

Structure of the existing drugs.

Chelating agent



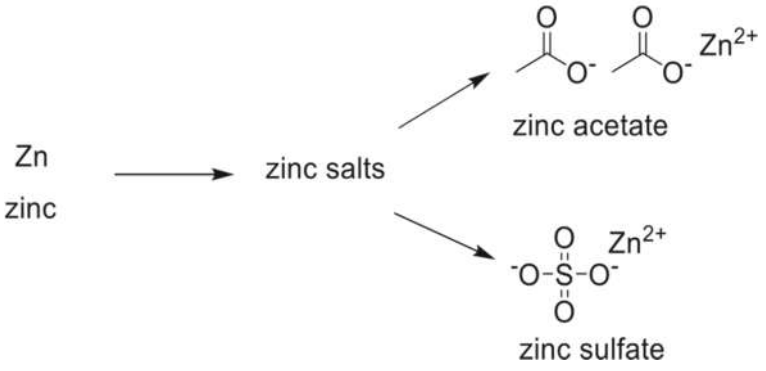
d penicillamine



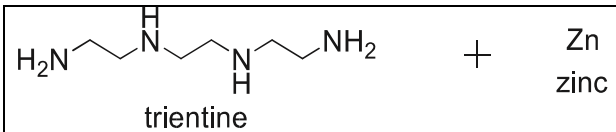
tetrathiomolybdate

Caution: A net charge appears to be present

Inhibit intestinal absorption



Combination drug



Unlike D-penicillamine, trientine lacks sulfhydryl groups and therefore exhibits lower potential for hypersensitivity, nephrotoxicity, and dermatologic reactions, making it particularly suitable

for patients intolerant to penicillamine therapy.[61] Trientine's metabolites, including monoacetyl- and diacetyl-trientine, possess reduced chelating affinity but contribute to sustained copper excretion through urinary pathways.[62] Overall, the pharmacodynamic profile of trientine ensures effective copper removal with improved safety and tolerability, supporting its long-term use in the management of Wilson disease.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products.

PHARMACOKINETIC PROPERTIES

Absorption

Patients with Wilson disease had inconsistent and limited absorption of trientine after oral treatment. In healthy male and female volunteers, the pharmacokinetic profile of trientine tetra hydrochloride was assessed following a single oral administration of 450, 600, and 750 mg of trientine. Trientine's plasma levels increased quickly after treatment, reaching the median peak level in 1.25 to 2 hours. After that, the trientine plasma concentration decreased in a multiphasic fashion, first quickly and then more slowly throughout the elimination phase. Males had higher amounts of trientine, but overall pharmacokinetic profiles were similar to those of females.[63]

Distribution

The distribution of trientine in organs and tissues is poorly understood.

Metabolism

N(1)-acetyltriethylenetetramine (MAT) and N(1),N(10)-diacetyltriethylenetetramine (DAT) are the two main metabolites of acetylated trientine. MAT may possibly contribute to Cuprior's overall clinical activity, however it is yet unknown how much MAT contributes to Cuprior's overall impact on copper levels.

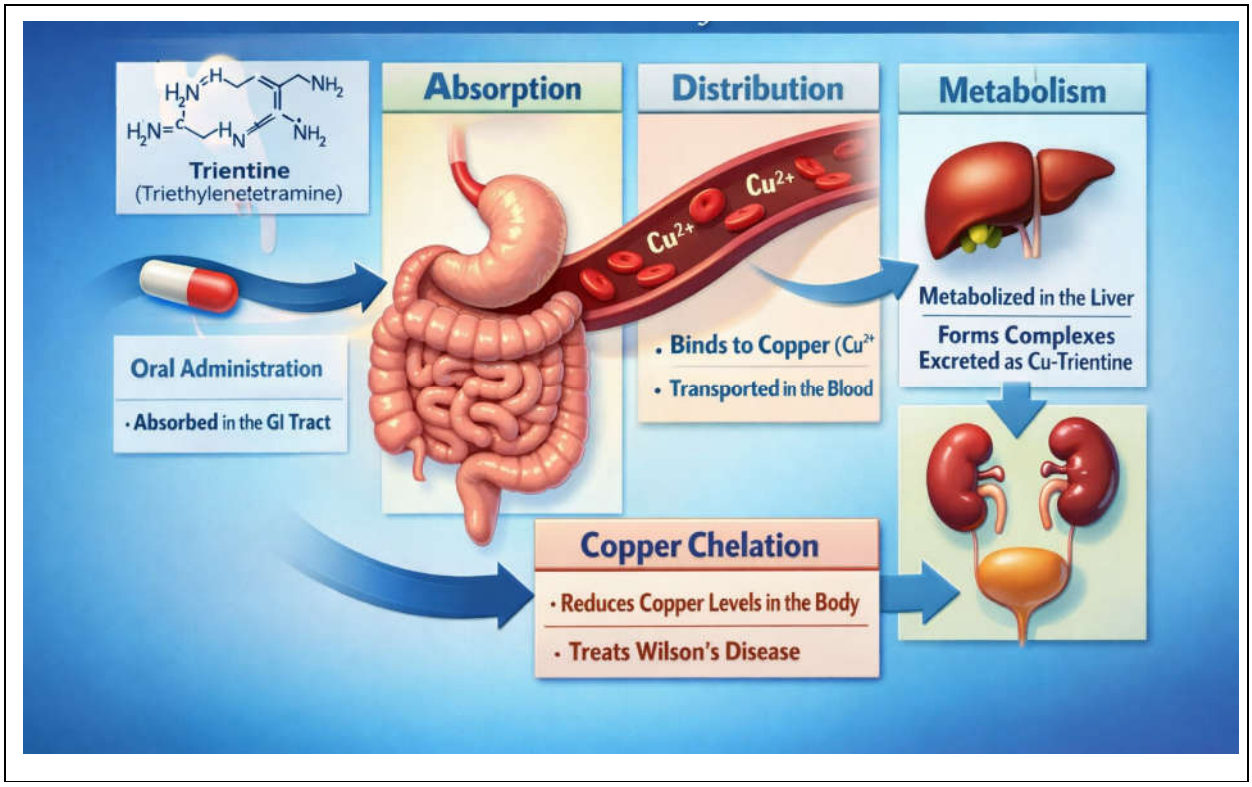


Figure 6: PHARMACOKINETIC PROPERTIES of trientine

Elimination

Although minor amounts of trientine might still be found in the plasma after 20 hours, trientine and its metabolites are quickly eliminated in the urine. Trientine that has not been absorbed is expelled through the feces.[64,65]

CONCLUSION

Wilson disease is a prime example of a hereditary condition where serious hepatic and neurological consequences can be avoided with early diagnosis and adequate pharmacologic treatments. Copper homeostasis is upset by mutations in the ATP7B gene, which causes toxic buildup in essential organs and progressive tissue damage. While continuing research continues to improve therapy approaches, advances in molecular diagnostics have improved disease identification.

Because of its superior safety profile over D-penicillamine and its effectiveness in removing copper, trientine tetrahydrochloride, a powerful polyamine copper-chelating agent, has emerged

as a key component of WD treatment. It successfully restores copper balance and stops the progression of illness through its dual action of increasing urine copper excretion and decreasing intestine absorption. For the best long-term results, medication adherence and metabolic markers must be regularly monitored.

In conclusion, Wilson disease has changed from a deadly genetic disorder to a controllable and mostly avoidable condition with prompt diagnosis and ongoing chelation therapy, highlighting the significance of early genetic and biochemical screening in at-risk groups.

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