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METABOLIC MYOPATHIES (MMS)

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Abstract:

Metabolic myopathies are a group of inherited illnesses affecting skeletal muscle metabolism due to enzymatic deficiencies in glycogen breakdown, fatty acid oxidation, or mitochondrial energy production. These disorders result in exercise intolerance, muscle weakness, & rhabdomyolysis (muscle breakdown resulting in the release of toxic cellular components into the bloodstream), which may progress to chronic muscle degeneration and functional impairment. Diagnosis relies on clinical symptoms, biochemical markers, genetic testing, and muscle biopsy. Common disorders include glycogen storage diseases like McArdle illness, which impairs glycogen breakdown, fatty a` oxidation disorders like carnitine palmitoyl transferase II deficiency that disrupts lipid metabolism, and mitochondrial myopathies, which affect cellular energy production. Management strategies focus on dietary modifications, including tailored carbohydrate or fat intake, controlled exercise programs to prevent muscle damage, and novel therapies like enzyme replacement treatment and gene therapy. Supportive treatments, including symptom management and physical therapy, also play a crucial role in improving mobility & overall well-being. Early diagnosis and individualized interventions are essential for optimizing patient outcomes, minimizing complications, and enhancing quality of life. Continued research into the molecular mechanisms of these disorders is vital for developing more effective therapies and improving long-term prognosis.

Keywords: Metabolic myopathies, Muscle weakness, Rhabdomyolysis, Gene therapy, Mitochondrial myopathies.

Introduction:

Metabolic myopathies, often known as MMs, are a heterogeneous group of metabolic illnesses that are marked by deficits in enzyme pathways that are associated with myocyte metabolism. These deficiencies are referred to as inborn errors of metabolism. Metabolic myopathies may exclusively impact skeletal muscle or involve both muscle and additional tissues or organs (metabolic myopathy plus (MM+), collateral myopathy). In metabolic

myopathy plus, myopathy can be the predominant characteristic or a non-dominant collateral characteristic among others. In metabolic myopathies, the muscles of limb are primarily impacted, although extraocular, facial, axial, & respiratory muscles can be included [1],[2].

Metabolic myopathies / metabolic myopathies + are heterogeneous hereditary illnesses arising from different illness mechanisms and complex pathophysiologies. Based on their causes, MMs can be categorized into four distinct classifications: 1) Metabolic malfunctions resulting from impaired glucose metabolism, 2) Metabolic malfunctions resulting from impaired lipid metabolism, 3) Metabolic malfunctions resulting from impaired energy metabolism, or metabolic malfunctions resulting from additional defective pathways. Mitochondrial myopathies, characterized by defective muscle cells, are the most affected types resulting in MM. This involves mitochondrial pathways, like respiratory chain (oxidative phosphorylation) as well as ß-oxidation, subsequent by cytoplasmic pathways, involving glycogen synthesis, glycolysis, and lysosomal pathways, like glycogen degradation (as Pompe Disease) and fat metabolism. Recently, several new faulty pathways were identified, that could phenotypically present as MM/MM+ [3] .

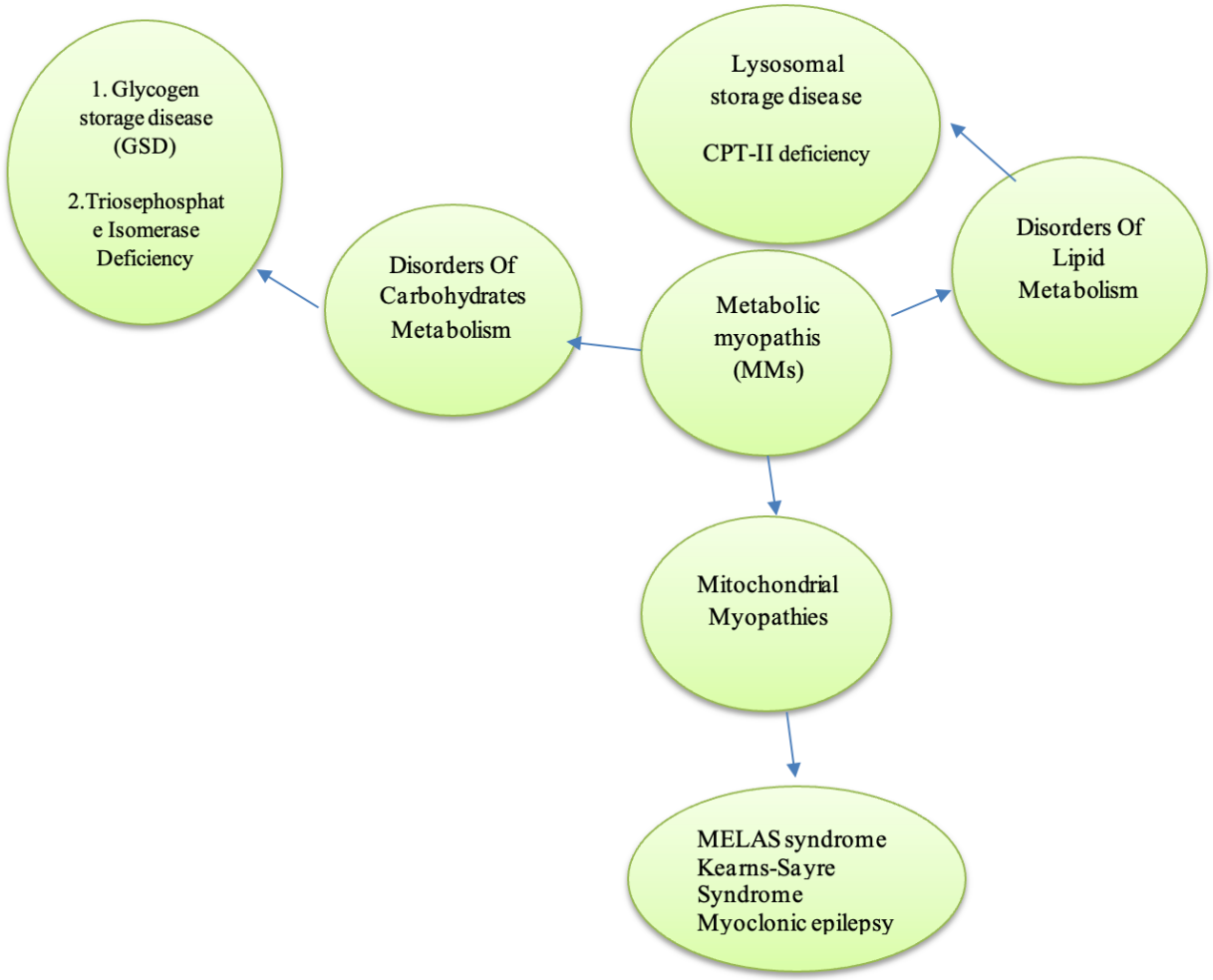

Fig 1: causes of Metabolic myopathies (MMs)

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1.Disorders Of Carbohydrates Metabolism

1. Glycogenosis

- **Glycogenosis Type II**: Glycogen storage disease (GSD) type II (deficiency of acid maltase) is an autosomal recessive disorder caused by a deficiency of lysosomal α-glucosidase. This enzyme cleaves 1,4 and 1,6 linkages in glycogen, and its deficiency results in glycogen accumulation. The threshold amount seems to vary depending on the organ, and the process by which skeletal muscle is eventually impaired is still not fully understood. Both atrophy and reduced performance by unit of muscle mass seem to have a role [4] .
- **Glycogenosis Type III**: Deficiency of debranching enzyme, additionally recognized as Cori disease or GSD-III, represents approximately 25% of all GSD. It is an autosomal recessive disorder due to a deficiency of amylo-1,6-glucosidase and 4-α-glucanotransferase enzymes, which degrade glycogen branches, releasing glucose in a two-step reaction catalyzed by its two distinct activities [5] .
- **Glycogenosis Type IV**: Glycogen storage disease-IV, additionally recognized as Andersen disease, is an autosomal recessive disorder caused by branching enzyme deficiency. This enzyme catalyzes the last step in glycogen biosynthesis by transferring short glucosyl chains in α,1-6 glycosidic links to naked peripheral chains of nascent glycogen [6] .
- **Glycogenosis Type V**: Glycogen storage disease-V, additionally recognized as McArdle disease, is the most common disorder of carbohydrate metabolism. It is an autosomal recessive disorder triggered by defects in the gene (*PYGM*) encoding for myophosphorylase enzyme. This enzyme is involved in the breakdown of glycogen to glucose for use in muscle. Myophosphorylase removes 1,4 glycosyl residues from outer branches of glycogen and adds inorganic phosphate to form glucose-1 phosphate [7].
- **Glycogenosis Type VII:** Glycogen storage disease-VII, additionally recognized as Tarui disease, is caused by deficiency of phosphofructokinase (PFK), the rate-limiting enzyme in the glycolytic pathway that catalyzes the adenosine triphosphatase–dependent phosphorylation of fructose-6 phosphate to fructose 1,6-biphosphate [8].
- **Glycogenosis Type VIII**: Glycogen storage disease -VIII is because of deficiency of the phosphorylase b kinase (PBK) enzyme that catalyzes the conversion of inactive phosphorylase to the active form. In addition, the enzyme converts glycogen synthetase to a less active form [9].
- **Glycogenosis Type IX**: Glycogen storage disease-IX outcomes from a deficiency of phosphoglycerate kinase (PGK), the enzyme that catalyzes the transfer of the acyl phosphate group of 1,3-diphosphoglycerate to adenosine phosphate (ADP) with formation of 3-phosphoglycerate and adenosine triphosphate (ATP) in the terminal stage of the glycolytic pathway [10].
- **Glycogenosis Type X**: deficiency of phosphoglycerate mutase (PGAM) is a muscle disease of glycogen storage which leads to a terminal block in glycogenolysis. The interconversion of 3-

phosphoglycerate & 2-phosphoglycerate is what PGAM is responsible for catalyzing. 2 subunits are existing: brain (PGAM-B) in addition to muscle (PGAM-M) [11].

- **Glycogenosis Type XI**: Lactate dehydrogenase facilitates the transformation between lactate & pyruvate, simultaneously interconverting Nicotinamide adenine dinucleotide & its oxidized form, nicotinamide adenine dinucleotide. [12].
- **Glycogenosis Type XII**: Glycogen storage disease -XII results from a lack of aldolase A. This enzyme facilitates the transformation of fructose 1,6-phosphate into dihydroxyacetone phosphate as well as glyceraldehyde 3-phosphate [13].
- **Glycogenosis Type XIII**: β-Enolase is a metalloenzyme that catalyzes the transformation of 2-phosphoglycerate to phosphoenolpyruvate, the 9th & penultimate stage in glycolysis [14].
- **Glycogenosis Type XIV**: Phosphoglucomutase 1 facilitates the transport of phosphate groups among the one & six positions of glucose [15].

2.1. Triosephosphate Isomerase Deficiency

The enzyme triosephosphate isomerase catalyzes the reversible transformation between the D-glyceraldehyde 3-phosphate & triose phosphate isomers dihydroxyacetone phosphate [16].

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2.Disorders Of Metabolism of Lipid

- **Carnitine Transporter deficit:** Carnitine transmitter deficit is the predominant disease of the metabolism of lipids. Carnitine deficiency may be primary, resulting from mutations in the gene encoding the sodium-dependent carnitine transporter, which facilitates carnitine transport across cell membranes, or 2^{ry} to systemic conditions like organic acidurias, chronic hemodialysis, defects of respiratory chain, malnutrition & renal Fanconi syndrome, as well as certain medications like zidovudine & valproate.
- **Carnitine Palmitoyl Transferase II Deficiency:** it's a peripheral inner protein of membrane off mitochondria that facilitates transesterification of palmitoylcarnitine into palmitoyl–coenzyme A (CoA), thereby providing an active substrate for ß -oxidation within matrix.
- **Medium-Chain Acyl–Coenzyme A Dehydrogenase (MCAD) Deficiency** is involved in the catabolism of fatty acyl- coenzyme A derivatives with acyl chains including 4 to 14 carbon atoms.
- **Long-Chain Acyl–Coenzyme A Dehydrogenase (LCAD) Deficiency** metabolizes fatty acyl-Coenzyme A derivatives with acyl residues exceeding twelve carbon atoms; hence, cases with LCAD deficiency exhibit an inability to metabolize long-chain fatty a`.
- **Very-Long-Chain Acyl–Coenzyme A Dehydrogenase (VLCAD) Deficiency** participates in the early phase of mitochondrial ß -oxidation & exhibits activity to Coenzyme A esters of extended-chain substrates: arachidoyl- coenzyme A, lignoceroyl- Coenzyme A, & behenoyl-Coenzyme A.
- **Deficiency of Short-Chain Acyl–Coenzyme A (SCAD) Dehydrogenase:** enzyme catalyzes reactions involving fatty acyl- Coenzyme A derivatives with acyl chains of 4 to 6 carbon atoms [23].

- **Multiple Acyl–Coenzyme A Dehydrogenase Deficiency (MADD):** The electron-transfer-flavoprotein α-polypeptide, also known as ETFA, plays a role in the process of enhancing the 1st phase of mitochondrial fatty a` ß-oxidation. This enzyme is responsible for the transportation of electrons between the membrane-associated electron transfer flavoprotein ubiquinone oxidoreductase & the 1ry flavoprotein dehydrogenases [24].

3.Mitochondrial Myopathies

MMs constitute a complex group of disorders associated with genetic, metabolic, or structural abnormalities in mitochondria. The predominant neuromuscular characteristic of mitochondrial disorder is myopathy, resulting in proximal weakness frequently associated with exercise intolerance that is disproportionate to the weakness. Ptosis & persistent developmental external ophthalmoplegia are prevalent symptoms, frequently correlated with dysphagia. Peripheral neuropathies are prevalent. [25], [26].

- **Myoclonic Epilepsy with Ragged Red Fibers** is a multisystem illness marked by ataxia, myoclonus, weakness, dementia, as well as generalized epilepsy.
- **Mitochondrial Encephalomyopathy, Lactic Acidosis, & Stroke-like Episodes Syndrome, which is recognized as (MELAS)** is a metabolic condition typically marked by seizures & stroke like episodes in the young population. This condition illustrates a mitochondrial abnormality, characterized by maternal inheritance & a fluctuating ratio of altered mitochondria throughout various organs throughout time (heteroplasmy). It impacts tissues with elevated metabolic needs (as the brain and muscle), & a specific tissue seems to necessitate a particular threshold of damaged mitochondria prior clinical symptoms manifest (threshold effect) [28].
- **Kearns-Sayre Syndrome** is diagnosed depending on 3 characteristic characteristics: pigmentary retinopathy, progressive external ophthalmoplegia, & cardiac block.
- **Mitochondrial Neurogastrointestinal Encephalopathy** is characterized by severe gastrointestinal dysmotility, leukoencephalopathy, sensorimotor polyneuropathy, external ophthalmoplegia, ptosis, & cachexia**.** [29].

Lines of Treatment of the most comment types of MMs

The treatment of MMs is predominantly symptomatic & infrequently causal. Treatment of symptoms could be either invasive or non-invasive. Non-invasive symptomatic management encompasses physiotherapy, dietary modifications, pharmacological interventions, non-invasive ventilation, & conservative orthopedic measures. Avoiding triggers for episodic manifestations of metabolic myopathies is additionally crucial. Invasive interventions encompass orthopedic operation & invasive mechanical ventilation. [2].

1. Treatment of Metabolic myopathies due to defect in Metabolism of Carbohydrate

Ample data has been gathered in currently indicating that exercise training in numerous forms of glycogen storage disease can enhance exercise tolerance & promote oxidation of fatty a`. Oral

galactose administration might positively influence certain clinical symptoms of PGM1-associated glycogen storage disease. Recent research indicates that normal dosages of 1–2.5 grams per kilograms body weight (BW) are inadequate for restoring deficient glycosylation in all cases. A high-protein nutrition was documented to enhance cardiomyopathy in GSD III. Recent studies indicate that albuterol may serve as an additional therapy for cases with EOPD, however its overall efficacy appears to be limited. [30].

2. Treatment of Metabolic myopathies because of Lipid Metabolism Defect

Disorders of fat metabolism must often be managed with carbohydrate-dense nutrition to prevent catabolic conditions. The substitution of long-chain fatty a` with medium-long chain fatty a` may be advantageous for very-long-chain acyl–coenzyme a dehydrogenase insufficiency. Carnitine is efficacious in the treatment of PCD & multiple acyl–coenzyme A dehydrogenase deficit. Riboflavin or carnitine is typically advantageous in multiple acyl–coenzyme A dehydrogenase deficit. Bezafibrate hasn't demonstrated efficacy in vivo. Triheptanoin & trioctanoin have demonstrated encouraging outcomes in some fatty acid oxidation disorders. [31].

3. Treatment of Metabolic myopathies (MMs) due to Mitochondrial Disorders Defect

The management of mitochondrial disorders defects depends on either non-invasive or invasive interventions. Non-invasive symptomatic interventions involve pharmaceuticals like antioxidants, electron acceptors, electron donors, co-factors, or alternative energy resources. Coenzyme Q is especially efficacious in addressing 1ry coenzyme Q insufficiency. A crucial treatment measure is the exclusion of mitochondrial-toxic agents. If muscles of respiration are affected, either non-invasive or invasive artificial ventilation is necessary. The management of phenomena, like stroke-like episodes, relies on the administration of anti-seizure medications or L-arginine. Deoxynucleoside treatment may be advantageous for TK2-associated myopathy. [32].

4. Lysosomal Storage Diseases

Glycogen storage disease II is the only metabolic disorder for which an efficacious treatment exists. This is an enzyme replacement treatment utilizing recombinant human alpha glucosidase administered intravenously at a dosage of twenty milligrams per kilograms biweekly. The earlier the ERT is commenced, the more efficacious it becomes. Several research utilizing recombinant human alpha glucosidase, either independently or in conjunction with chaperones, are presently ongoing. [33].

5.Ursolic acid (UA) therapy

Ursolic a` is extracted from the leaves of multiple plants (marjoram, organum, thyme, lavender, & rosemary), as well as from flowers, fruits (apple peel), & berries. Ursolic a` facilitates various pharmacological procedures & modulates multiple signaling pathways to inhibit the onset of chronic illnesses; it demonstrates antioxidant, anti-carcinogenic, anti-inflammatory, anti-obesity, hepatoprotective, cardioprotective, neuroprotective, anti-diabetic, anti-skeletal muscle atrophy, as well as thermogenic properties. The mechanisms through which UA provides these advantageous impacts may encompass the control of nuclear factor-kappa B (NF-kB) & apoptotic signaling in neoplastic cells, the expression of heart damage indicators in the heart, insulin signaling in adipose

tissue, inflammation as well as antioxidant levels in brain, metabolic signaling & oxidant con in the liver, as well as atrophy & metabolic signaling in skeletal muscles. [34].

- **Structure Of UA**

UA (3β-3-hydroxy-urs-12-ene-28-oic a`) is a pentacyclic triterpenoid with chemical formula C30H48O3 & a molecular weight of 456.71 grams per mole. Ursolic a` dissolves in heated glacial acetic a` & alcoholic sodium hydroxide. Biosynthesis mostly occurs from dammarenyl cation via the folding & cyclization of squalene, resulting in the development of the 5$^{th}$ ring of ursolic a` via ring extension & the creation of an additional ring. The molecule contains three atoms of oxygen that activate triple or double neutral ligands & facilitate the donation of electron pairs to the transition metal atom. [35].

- **Beneficial impacts of ursolic a`**
  - **Anti-inflammatory effects**

The close correlation among inflammation & numerous disorders, including osteoarthritis, Parkinson's disease, cancer, diabetic nephropathy, cardiovascular events, & influenza infection, is well established. Prior in in vivo & vitro investigations have demonstrated that ursolic a` decreases both endogenous & external inflammatory triggers, exhibiting beneficial anti-inflammatory properties. Ursolic a` (twenty-five milligrams per kilogram of body weight, orally administered) can inhibit the degeneration of dopaminergic neurons in mice produced with Parkinsonism via 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. [36], [37].

  - **Antioxidant activity**

Oxidative stress arises from the overproduction of ROS in cells & tissues, subsequently contributing to numerous inflammation-related disorders. The in vitro antioxidant efficacy of ursolic a` has been assessed by reducing 2,2-diphenyl-1-picrylhydroxyl at an inhibitory concentration (IC50) of 59.7±1.0 micrograms per milliliters. The administration of UA (twenty-five and fifty milligrams per kilogram of body weight per day, intragastrically) for six weeks reduced CCl4-induced nephrotoxicity, illustrating the antioxidant properties of ursolic a` & its capacity to suppress the phosphorylation of the Signal transducer as well as activator of transcription 3- nuclear factor kappa B pathway.[38]

In hamster V79 lung fibroblast cell line & the human lymphocytes, ursolic a` has been revealed to be a natural antioxidant that mitigates deoxyribonucleic a` damage induced by H2O2, resulting in a fifty percent decline in viability of cell at 224.85 mM. Moreover, ursolic a was proposed as a viable candidate for management & prevention of illnesses mediated by oxidative stress, encompassing neurodegenerative disorders in mouse models, diabetes & obesity in mice, cardiovascular illnesses in rats, skin carcinogenesis in epidermal cells of mouse, illness of liver in rats with CCl4-induced hepatic fibrosis, & osteoporosis in MG-63 cells. [39].

  - **Anticancer activity**

Regarding its anticancer efficacy, UA is mostly related to apoptosis & the demise of tumor cells. Mitochondria are crucial for cellular oxidative phosphorylation & respiration, & mitochondrial impairment results in apoptosis. It is through the stimulation of mitochondrial dependent signaling

pathways that Ursolic A is able to cause its anticancer action. For example, Ursolic acid enhances & stimulates the expression of the AMP-activated protein kinase (AMPK) & the cancer antigen p53 signaling pathway, while concurrently diminishing the expression of apoptosis regulator Bcl-2. [40].

- **Hepato-protective activity**

In C57BL/6 rats subjected to high-fat nutrition for fifteen weeks, oral administration of eighty milligrams per kilogram of UA significantly decreased total cholesterol & triglyceride concentration in both plasma & liver, efficiently alleviating liver steatosis & reducing number of fat cells in epidermis. In vitro tests showed that ursolic a` (20μM) significantly decreased total cholesterol (37.2%) & triglyceride (50.4%) levels in HepG2 cells whereas upregulating expression of P-AMPK protein [36]. Consequently, ursolic a` could reduce cellular lipid content & delay lipid production by triggering the AMP-activated protein kinase signaling system. Ursolic a` enhances the diversity of advantageous gut microbiota by inhibiting the NOX4/NLRP3 inflammasome pathway, hence mitigating hepatic fibrosis induced by CCl4. Ursolic a` can diminish the triggering of mitogen-activated protein kinases (ERK, JNK, p38 MAPK) & inactivate immunoregulatory transcription factor nuclear factor kappa B in the liver following CCl4 therapy, thereby alleviating CCl4-induced inflammation. [41].

- **Antibacterial activity**

In C57BL/6 mice subjected to nutrition rich in fat for fifteen weeks, oral administration of eighty milligrams per kilogram of UA significantly decreased triglyceride & total cholesterol concentrations in both plasma & liver, efficiently alleviating liver steatosis & reducing the number of fat cells in epidermis. In vitro tests showed that Ursolic acid (20μM) significantly decreased total cholesterol (37.2%) & triglyceride (50.4%) levels in HepG2 cells whereas upregulating expression of P-AMPK protein [36]. Consequently, Ursolic acid could reduce cellular lipid content & delay lipid production by stimulating the AMPK signaling system. Ursolic acid enhances the variety of advantageous gut microbiota by inhibiting the NOX4/NLRP3 inflammasome pathway, hence mitigating hepatic fibrosis induced by CCl4. Ursolic acid might diminish the triggering of mitogen-activated protein kinases (p38 MAPK, JNK, ERK) & inhibit immunoregulatory transcription factor nuclear factor kappa B in the liver following CCl4 therapy, thereby alleviating CCl4-induced inflammation. [42].

- **The side effects of ursolic a`**

It was observed that ursolic a` (five milligrams per kilogram body weight, administered intraperitoneally) may suppress spermatogenesis in three-month-old male Wistar strain albino rats. 50μM UA, isolated from loquat (Eriobotrya japonica), demonstrates cytotoxic effects on NTUB1 cells (human bladder cancer cell line) & A549 (lung cancer cell line). In the acute toxicity assessment, ursolic a` (21.5 gram per kilogram BW, administered orally) derived from Ledum palustre L. might impair the neurological & digestive systems of mice, with an LD50 of 9.26 grams per kilogram. [43].

6. Coenzyme Q10 (CoQ10) therapy

CoQ10, or ubiquinone, is a hydrophobic, vitamin-like compound inherently detected in all cellular membranes throughout the body. This enzyme is a common dietary component, though it is also produced endogenously. Despite CoQ10 not receiving permission from the United States FDA for the treatment of any medical illness, it is readily available as an over-the-counter dietary supplement & is frequently endorsed by primary care specialists & physicians. Conditions include diabetes, cardiac failure, fibromyalgia, tumor, &mitochondrial, neurodegenerative, & muscle illnesses are related to diminished circulating concentration of coenzyme Q10. Numerous investigations were undertaken to determine if elevating systemic CoQ10 levels will improve physiological function [44]. ff

Primary CoQ10 insufficiency is an uncommon autosomal recessive illness resulting from genetic mutations affecting CoQ production, characterized by clinical manifestations such as optic atrophy, steroid-resistant nephrotic syndrome, retinopathy, & encephalopathy. Coenzyme Q10 substitute treatment is required for this uncommon condition. [45].

- **Contraindications**

Cases undergoing chemotherapy should avoid using CoQ10 due to inadequate research regarding its interaction with these medications. Coenzyme Q10 reduces fasting blood glucose in certain cases; hence, it must be administered carefully to those with diabetes & those liable to hypoglycemia events. People who have a history of hypersensitivity to coenzyme Q10 or its excipients should not take coenzyme Q10 because it is not contraindicated for them. Certain supplements include SiO2, which can cause hypersensitivity reactions. [46].

- **Mechanism of Action**

Coenzyme Q10, or ubiquinone, is a lipophilic, vitamin-like compound naturally existing in all cellular membranes in the body & is a frequent component of our food, though it is additionally created endogenously. Coenzyme Q10 is essential for the effective transport of electrons in mitochondrial oxidative respiratory chain & the synthesis of ATP. Coenzyme Q10 may enhance the synthesis of essential antioxidants, including superoxide dismutase, an enzyme that efficiently diminishes vascular oxidative stress in hypertensive people. Furthermore, coenzyme Q10 reduces lipid peroxidation levels by decreasing pro-oxidative components. Additionally, coenzyme Q10 enhances blood circulation & protects blood vessels by maintaining NO levels.[47]

Supplements provide coenzyme Q10 in 2 forms: the diminished form (ubiquinol) & the oxidized form (ubiquinone). The bioavailability of a specific coenzyme Q10 supplement is contingent upon the lipid carrier in which it is suspended & any incorporated preservatives. [48].

- **Pharmacokinetics**
  - **Absorption:** Coenzyme Q10 is a hydrophobic (lipophilic) compound with a significant molecular weight; the absorption of dietary Coenzyme Q10 is gradual nonetheless is enhanced when consumed with fatty meals. Solubilized coenzyme Q10 formulations enhance bioavailability, with peak plasma level often occurring between 5.80 and 8.10 hours, contingent upon the particular formulation. Different formulations, including

liposomes, nanocapsules, & nanoemulsions, are being investigated to enhance bioavailability. A secondary plasma peak might additionally be detected because of enterohepatic recycling & redistribution from the liver to the bloodstream. [49].

- **Distribution:** Coenzyme Q10 is predominantly absorbed in small intestine, thereafter, integrated into chylomicrons, & redistributed through the bloodstream, primarily within HDL, LDL, & VLDL. Preclinical investigations demonstrate that high doses of CoQ10 are absorbed by all organs, involving the mitochondria of the heart & brain; thus, a positive impact is noted in neurodegenerative & cardiovascular disorders. The largest concentrations of coenzyme Q10 in tissues of human are found in the muscles, kidneys, heart, & liver, which have elevated energy demands. [50],[51].
- **Metabolism:** Coenzyme Q10 is metabolized in all organs, & the resultant metabolites are phosphorylated within the cells & transferred via the plasma. Coenzyme Q10 is converted to ubiquinol throughout or following absorption in small intestine, with the decreased form constituting about ninety five percent of circulating coenzyme Q10 in humans. [52].
- **Elimination:** The principal route of elimination is via the biliary system & feces. A minor portion is excreted in urine. [53].
- **Monitoring:** Several investigations have evaluated blood concentrations of coenzyme Q10 to determine the effectiveness of supplementation. The average plasma values are approximately 0.34 to 1.65 µg/mL. The hazardous threshold for blood CoQ10 remains undetermined, mostly due to the absence of toxicity even at maximal oral supplementation doses. Periodic urinalysis for proteinuria, assessments of kidney function, neurologic evaluations, ophthalmologic examinations, & audiometric testing are necessary for 1ry coenzyme Q10 deficiency. [54].
- **Toxicity:** Coenzyme Q10 is a safe dietary supplement. Toxicity is improbable with a daily dose of up to 1200 milligrams, while standard dosages range from one hundred to two hundred milligrams per day. In preclinical research, the No-Observed-Adverse-Effect Level (NOAEL) of ubiquinol ranges from three hundred to six hundred milligrams per kilogram in Sprague Dawley mice. [55].

The usual human supplementation dosage of CoQ10 ranges from one hundred to three hundred milligrams per day. Assuming a human dosage of three hundred milligrams per day (five milligrams per kilogram BW), the safety factor ranges from sixty to one hundred twenty folds. The research demonstrated that prolonged consumption of ubiquinol as a food supplement in people is safe. [55].

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