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Review Article

Role of Taurine and its Analogs Against Various Disorders and its Beneficial Effects: A Review Article

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Abstract

Taurine (Tau), a sulphur containing amino acid, chemically known as 2 aminoethane sulphonic acid, it's a non-proteinogenic β-amino acid, often referred to as semi essential amino acid as new born mammals have very limited ability to synthesize taurine and they have to depend on dietary sources, it is not incorporated into proteins as no aminoacyl tRNA synthetase has yet been identified and is not oxidized in mammalian cells, it attains an important place because of the antioxidant defence network. It has multiple function in the CNS, it serves as an osmoregulator, antioxidant, inhibitory neuromodulator, and regulator of intracellular Ca2flux.First time when it was discovered from ox bile by the German professors Friedrich Tiedemann and Leopold Gmelin they named it GallenAsparagin, later it was known as taurus, in latin Bos taurus means Ox, but it attains its current name (Taurine) in 1838 by von H. Demarcay. Because of presence of sulphonic acid instead of carboxylic acid it is not metabolized and not involved in gluconeogenesis and thus not envolve in direct energy sources. Taurine is produced by liver and kidney including retina, brain, heart and placenta. Taurine plays extensive role against different disorders of the body and in deadly diseases like cancer, liver cirrhosis etc. Human body contains about 0.1% of body weight as taurine. It has a number of physiological and pharmacological actions. In case of spinal cord injury elevated level of taurine has been seen, In methyl prednisolone (MP), treatment in case of SCI, elevation in level of taurine is observed, this elevated level seems to be involved in protection and regeneration of tissues following injury. In this review we try to cover every possible role of taurine which may provide enough information for future research.

Keywords: SCI; Tau; ZEN; Hcy; PSA; AMK; SCI; ASIA Scale; Osteoporosis

Introduction

Taurine, chemically known as 2 aminoethane sulphonic acid, was discovered more than 200 years ago, isolated from animal sources from ox bile in the year 1827, that time it was labelled as non-essential, biologically inert, end product of sulfur metabolism, and that it was got its common name Bos taurus [1,2]. By the publication of an excellent review on this wonderful molecule throw light again and paved the way for re examination, evaluation and extensive research on taurine and its derivatives [3]. Presence of taurine in living beings were first discovered by two great scientist Tiedemann and Gmelin. It is true to say taurine an ancient molecule because it is found in algae in high concentration especially in red algae but almost absent in viruses and bacteria, although taurine is described as source of carbon, nitrogen and sulfur in Bacillus subtilis [4]. Whereas it is found in trace amount in plants and fungi [5]. High concentration of taurine is found in animal kingdom from insects to mammals, in which

it is most abundant amino acid related molecule [5]. We can say this molecule as ancient amino acid, though it is not incorporated into protein sequences. It is considered as non essential amino acid though most of the taurine is obtained from the diet source because it is endogeneously synthesized in the liver of mammals, although this synthesis is insufficient as in cats. In mammals Total taurine pool exist in their body is balance between (i) synthesis from methionine/cysteine, or absorption from food in the intestine or reabsorption from the urine in the kidney, excretion as bile salt (taurocholate) and unconjugated taurine in urine via the kidney. New born babies are unable to synthesize taurine so they are depend on dietry supply, whereas human colostrum is richest source of taurine. It is a semi essential amino acid. In comparison to rodents or rabbit taurine content is appear to be lower in primates [6]. Plasma taurine concentration ranges from 80 mM to 770 mM, as a function of species. One of the recent study by Rosolen., *et al*. [7] on 69 pet dogs, they obtain mean plasma taurine concentration of 162 mM [7]. Skeletal muscles in adult human tissues are the largest pool of taurine [5]. Whereas, all vital organs including CNS, kidney, heart, liver have also high content of taurine [8], ranges between 5-30 mmol/g tissue [9]. Studies have shown that its concentration is very high in eyes, but its physiological role still remains unclear. Inspite that in ocular tissues of eyes such as the cornea, iris, lens and ciliary bodies this amino acid is present in abundant quantity [6]. In ciliary bodies concentration of taurine is about 10 mmol/g dry tissue [10], Concentration of taurine is also highest in ocular fluids such as vitreous humor of rat [10], methionine and cysteine i.e. precursors of taurine is also present in the structure of eyes, concentration of methionine ranges between 0.09 and 0.37 mmol/g dry tissue in the eye, whereas except retina cysteine is present in a trace amount [10]. During aging, plasma taurine concentration and tissue contents gradually declines in all organs such as liver, spleen, kidney, heart, skeletal muscles, brain and eyes [11], so it is clear that aging may be associated with taurine deficiency. In case of retinitis pigmentosa (RP), a heritable retinal dystrophy, it has been seen that subjects with RP have lower levels of taurine uptake into platelets [12], and lower taurine concentration in blood in comparison to controls [12], But in case of RP taurine concentration is not considered as reliable biomarker [13], Nevertheless, for preservation of photoreceptors in RP taurine supplementation is proposed as a treatment [14]. One of the recent study by Pasantes-Morales., *et al*. 2002 it was shown that taurine supplementation in combination to diltiazem and vitamin E helps in slowing the progression of vision deficits in RP subjects [15]. Taurine has immense role in broad spectrum in case of nervous system disorders, showing its protective activity against toxicity in different neurodegenerative disease models for Parkinson's, Alzheimer's and Huntington's diseases [16]. At molecular level it has been investigated that it may be a neuroprotectant against stroke [17]. In case of both cats and rodents smaller birth weights have been seen in them when they are taurine deficient [18]. Cats fed on taurine free diet exhibit profound developmental abnormalities such as smaller brain and body weight, degeneration of retina and visual cortex as well as abnormal development of hind legs development [18]. Mice deficient in taurine transporter TauT shows smaller overall size, as well as development of heart and skeletal muscle has found, most likely due to mitochondrial effects, whereas no information regarding birth weight is available [19]. In comparison to other neuroactive amino acids taurine displays exclusive physical properties due to the presence of sulphonic acid rather than carboxylic acid in its structure which creates difficulty for it in crossing blood brain barrier (BBB). Due to its monobasic property its solubility is very low in water (10.48 g/100 mL at room temperature). In comparison to aspartic acid, glycine, β-alanine and γ-aminobutyric acid (GABA), taurine is more acidic because its pKa value is 1.5, whereas the pKb value is 8.82, that is less basic than GABA, glycine and β-alanine. Due to cyclic conformation structure with an intramolecular hydrogen bonding, it displays low passive diffusion [20].

Taurine sources

Two German scientists Friedrich Tiedemann and Leopold Gmelin were first to discover this wonderful molecule in 1827 from ox bile [21], chemically it is known as Tau (2-aminoethanesulfonic acid), having molar mass and molecular formula 125.15 g/mol, C2H7NO3S respectively [21]. It does not contain a carboxyl group and its amino group is present at the β-position, though its commonly called an amino acid, tau is not shown to be incorporated into proteins but found in abundance in animal tissues [21]. Taurine is obtained from the dietry source or endogeneous sources by human, animals, farm animals and poultry. Main natural dietry sources of taurine are Food/feed ingredients of animal origin, including fish, dairy products and human milk (colostrum) [21]. Terrestrial plants are mostly taurine free (major feed ingredients for farm animals/poultry) [22], whereas *in vivo* synthesis of taurine is species specific, rodents have high capacity of taurine synthesis,

cats lack the ability to synthesize Tau because of limited activity of enzyme cysteine sulfinate decarboxylase whereas humans are characterised by an intermediate capacity to synthesise Tau [23]. In rats about 80% of the cysteine pool is converted into taurine whereas in cats only 20% conversion occurs [6], whereas in animals taurine synthesis occurs in liver cysteine catalysed by cysteine dioxygenase and cysteine sulfinate decarboxylase, and in other tissues also like brain, lungs, skeletal muscle and adipose tissue [24], Biosynthesis of taurine in humans and birds still did not meet their daily requirements, and dietary Tau intake is absolutely essential for Tau homeostasis [21]. In humans tissues can be divided into three groups depending on taurine turnover rate, the liver, kidney and pancreas, tissues with a fast Tau turnover rate is included in first group, group second includes The lung, spleen, intestine, testes, and bone marrow are characterised by a medium rate of Tau turnover (2-3 days), tissues with the slowest rate of Tau turnover (the brain, heart and skeletal muscles) (3-7 days) were included in group 3 [21].

Metabolism of taurine in humans

Taurine undergoes limited catabolism in animal cells, through taurine: pyruvate transaminase or taurine:α-ketoglutarate transaminase, which catalyzes the transamination of taurine with pyruvate or α-ketoglutarate to form 2-oxoethanesulfonate, 2-hydroxyethanesulfonate, or isethionate (2-sulfoacetaldehyde) and l-alanine or l-glutamate [25]. Very similar reactions also takes place in aerobic and anaerobic bacteria [26]. In case of aerobic bacteria in the presence of cytochrome C as the physiological electron acceptor, taurine is converted into ammonia plus 2-sulfoacetaldehyde by taurine dehydrogenase (its an oxidation reaction) [27], Further taurine is oxygenated by α-ketoglutarate-dependent taurine dioxygenase to generate sulfate and 2-aminoacetaldehyde in microorganisms (including *E. coli*) [28]. Through Transamination, oxidation, or oxygenation, taurine catabolism is initiated in a species and cell specific manner. Bile salts are secreted from gall bladder via the common bile duct into the duodenum, during feeding. Absorption and digestion of dietry lipids are facilitated by duodenum. Due to the lack of their apical transporters and bile salts are resistant to deamidation by pancreatic and mucosal enzymes (including peptidases) they are not absorbed by the proximal small intestine (duodenum, jejunum and proximal ileum). Instead, bile salts enter the distal ileum where microbial bile salt hydrolases hydrolyzed them to form bile acids and taurine after the absorption of dietry lipids [29]. After that through specific transporters present into the enterocyte of the distal ileum remaining large portion of bile salts, taurine and bile acids are efficiently absorbed.

Taurine content in adult human tissues, plasma, and urine

Taurine is predominantly intracellular in human body, its plasma concentration being comparatively minute. In human body plasma taurine concentration is approximately 0.07 mM (in the range of 0.025 to 0.150 mM) Though human skeletal muscle has taurine concentration ranges 15.4 mM [30]. Whereas taurine concentration is constant in the plasma of arterial, portal venous, hepatic venous and renal venous [31]. Acute taurine supplementation elevated plasma taurine concentration but within 8 hours it returns to baseline levels. Within 1.5 hours after administration of 4 gm taurine by healthy volunteers, elevated plasma taurine concentration was seen from 40 μM to 690 μM [32]. Studies have shown that consumption of 6.0 g/day (2 g three times a day) taurine for 2 weeks elevates plasma taurine concentration [33]. Taurine starts accumulating in subjects with kidney failure if they are consuming it [34]. In healthy subjects it was observed that in case of seven days period of starvation there is slight decrease in plasma taurine level in comparison to baseline [35]. According to taurine availability in human body, kidney adjust urinary taurine excretion means if there is scarcity of taurine in the body, excretion declines and it elevates when dietry consumption of taurine is abundant [36]. 140 to 2, 650 μmol/day is the normal range of daily urinary taurine excretion. One of the multicentre study in which 16 countries were participants it was concluded that Japanese population have shown highest urinary taurine excretion while lowest urinary taurine excretion was shown in Canadian and Russian population, this data reflects that Japanese prefer taurine rich diets in comparison to Canadian and Russian [37].

Mahdavi AM., *et al.* [38] demonstrated in one of his metanalysis that researches have shown Taurine directly or its analogs via Tau derivatives such as Tau-chloramine, Tau-bromamine, taurochenodeoxycholic acid, and taurolidine) can help in Controlling Rheumatoid arthritis an autoimmune joint disorder through different mechanism like suppressing oxidative stress, reducing inflammation and inducing apoptosis. After anaesthesia induction taurine plasma concentration increases [39]. Due to high concentration of taurine in neutrophil granulocyte it is clear

that it plays important role in immune function may be associated with inflammation caused by oxidative stress [40]. Subjects with immunological dysregulation and suffering from septic shock has taurine content almost depleted [41]. Administration of taurine to healthy subjects causes a large increase in the rate of urinary excretion. After administration of labeled taurine to healthy subjects, radioactivity in urine is retrieved predominantly as taurine, most of the remainder being present as sulfate, With less than 5% is the deamination product of taurine i.e. isethionate. There is no difference in the fraction of excreted sulfate of labelled taurine from that of normal taurine which is obtained from diet, suggesting that taurine conversion to sulfate does not augment with taurine supplementation [42]. In healthy subjects during starvation urinary taurine excretion decreases, compared to baseline [43].

Taurine has very important role in neonatal development, therefore mothers are encouraged to feed their babies as colostrum is the best source of taurine, or should feed their babies with taurine-supplemented formulas and taurine-supplemented total parenteral nutrition [44]. Taurine synthesizing enzymes are lower in concentration in cats, dogs and foxes, therefore they are primarily depend on taurine supplemented diets [44]. These animals develop different pathologies like cardiomyopathy and myocardial dysfunction [45], retinal and tapetal degeneration that leads to blindness [46], neurological abnormalities [47], weakened immune response [48], gastrointestinal problems [49], pregnancy followed by foetal complications [50], when fed with taurine deficient diet.

These animals were protected against these pathologies when fed with taurine supplemented diet as well as improved reproductive performance and neurological development [44], seizure [51], retinopathy [52] and cardiomyopathy [45]. Energy drinks such as Red Bull, Monster, Tab Energy and Rockstar are rich in taurine [44]. It was estimated that on average, an 8 oz can of energy drink there is 750 mg of taurine [44].

Role in neurodevelopmental disorders

Many studies have shown the clinical role of taurine in neurodevelopmental disorders [53]. These studies have shown the clinical potential of acamprosate, a synthetic analog of taurine that is already proved by the United States Food and Drug Administration (FDA) for the treatment of alcohol dependent subjects [56]. In the first study on acamprosate was performed on three adults with fragile X Syndrome, when they were supplemented with acamprosate for 21 weeks (1 g/day), a significant improvement in communication was seen [54]. In another study in 12 young children with Fragile-X syndrome and comorbid autism spectrum disorders, when they were given oral supplementation of acamprosate for 10 weeks (1 g/day), a significant improvement in social skills and inattention/hyperactivity were observed [55]. One of the other study has shown that an oral supplementation of 1 g/day for 20 weeks in young children having autism spectrum disorders have shown significant improvement in social deficits [53]. Wide multi-center, cross-sectional World Health Organization investigation known as the CARDIAC study, Studies have demonstrated inverse relationship between dietry taurine supplementation and cardiovascular mortality, by monitoring through urinary taurine levels [37]. An opposite action is exerted by taurine on different events that influence atherosclerosis, hypercholesterolemia, inflammation and oxidative stress [56]. Platelets function is also regulated by taurine, their talent to undergo aggregation is significantly elevated due to deficiency of taurine [57], these results or finding supports the beneficial role of taurine in reducing risk of stroke and myocardial infarction, an idea that needs further study. Peculiar characteristic of Huntington's disease is occurrence of mutation in huntingtin gene, that cause the formation of polyglutamine repeats that prevent the degradation of huntingtin protein by the ubiquitin-proteasome system. At present though there are no ongoing clinical trials that examines the effect of taurine treatment on this disease, but taurine diminished mitochondrial oxidative stress and elevates striatal GABA levels, these effects may be important in reducing locomotor hypoactivity in an animal model of Huntington's disease. It also inhibits endoplasmic reticular stress, thus promotes in reducing toxicity of the polyglutamate repeats [58]. Research has shown that greater risk of incident dementia is more common in comparison to AD if there is lower plasma taurine level [59]. This insensitive variation of plasma taurine level corresponding to AD suggest the this variation of plama taurine level is not a significant prediction of Occurrence of AD. In comparison to controls, it was found in post mortem studies of AD subjects that there is significant decrease in taurine level in special regions of brain like temporal cortex [60]. Inspite of that post -mortem, Brain samples of Down's syndrome with early genetic mental retardation similar to AD, there was no difference

in taurine concentration of both cases and controls (R. Seidl., *et al*. 2001), Bidirectional variation in taurine concentration was found in different phases of biopsies of AD subjects. Studies by Alom J., *et al*. demonstrated that in the CSF of AD subjects endogeneous taurine content were significantly lower suggesting that there is a pathological shift of balance occurring in neuronal environment. Another study has demonstrated that in more advanced symptoms of AD, taurine level decreased in CSF [61]. One of the clinical finding on 14 AD subjects and 17 age matched controls, showed that in case of early AD subjects ratio of plasma taurine and the plasma levels of methionine and serine was significantly increased, whereas no difference in plasma taurine levels were found in AD subjects in comparison to healthy controls, suggesting that early AD only exhibits imbalance in the metabolism of sulfur amino acid though the variation is not significant correlation with behavioral symptomatology. Recently in one of the survey on 202 AD subjects, Negative, corelation was found between levels of taurine in CSF, and with depression and behavioral disturbances [62]. One of the research on animal model has shown that taurine concentration was found to be elevated in regions of brain such as hippocampus, rhinal cortex, midbrain, and cerebellum within six month of age in transgenic mice expressing mutant human amyloid precursor protein (APP_{SL})—serving as a model of neuropathological changes in AD, compared to healthy mice [63], whereas it was found that some metabolites/neurotransmitters decreased at 1 month age (including glutamate and N-acetyl aspartate (NAA) whereas glutamate, NAA, myo-inositol, creatine, phosphocholine, GABA decrease at the age of 3 month. These result suggest that more possibly cognitive impairments of transgenic AD mice is because of taurine disorder because the decline of cognitive function occurred usually in six month age, in transgenic AD mice (D. Giuliani., *et al*. 2016). Whereas one of the latest research on mouse model of AD, 8 weeks old were when injected with Aβ 25-35 solution into bilateral hippocampus had impaired spatial learning function, whereas together with formation of amyloid beta, and tau phosphorylation, taurine level also decreases. So by these data we can say that taurine may be a selective marker in investigation of pathology of Alzheimer disease using various animal models and would possibly be helpful for accessing the accuracy of AD models (Y. Liu., *et al*. 2018).Whereas recent clinical trials have used taurine as adjunctive therapy in AD subjects, in which administration of taurine (0.175 g, three times per day), could help in reducing β-amyloid (Aβ) (1-42) content and helps in improving cognitive function based on Borrelia Burgdorferi, which was almost of no effect alone thus clinical intervention of taurine may be valuable and safest mode for AD prevention in future (Omura, Y., *et al*. 2016).

Abdulkadir TS., *et al*. [64] has investigated the role of taurine in combination with camel milk in aluminium chloride model of 35 female Wistar Alzheimer's disease (AD) rats, they divided them in seven groups as follows: Normal saline (0.2 mL/kg body weight); AlC_{l3} (100 mg/kg) (AD); CM (33 mL/kg); Taurine (50 mg/kg); $AlCl_3$ (100 mg/kg) + CM (33 mL/kg); $AlCl_3$ (100 mg/kg) + Taurine (50 mg/kg); and $AlCl_3$ (100 mg/kg) + CM (33 mL/kg) + Taurine (50 mg/kg), for eight weeks through oral gavage these administration was given, and they found significant increase in the duration of motor endurance in AD + CM rats, in comparison to AD rats, whereas forced swimming duration time was lowest in ($p < 0.0001$) in $AlCl_3$ + Taurine rats, compared to that of AD rats, AD rats treated with CM and/or combination have reduced Concentration of Aβ peptide ($p < 0.05$), superoxide dismutase activity was significantly ($p < 0.05$) higher in taurine-treated rats in comparison to AD rats, where as acetylcholinesterase activity was increased in taurine + CM treated group in comparison to controls. Thus their study concluded that taurine in combination to camel milk, by decreasing Aβ peptide concentration and increasing superoxide dismutase and acetylcholinesterase activities enhances cognition and sensorimotor activity in AD rats.

Bhattacharjee A., *et al*. [65], states the beneficial role of taurine supplementation in post-traumatic stress disorder (PTSD) characterized by hyperarousal, heightened reactivity, cognitive, affective and behavioral disturbances, this disease is limited only to few antidepressants, in PTSD mitochondrial dysfunction along with altered potassium homeostasis is observed, Nutritional supplementation of taurine helps in improving ionic homeostasis thus contributing in reducing PTSD-like symptoms, in rats they administer taurine orally (100, 200, and 300 mg/kg) and paroxetine (PAX) (10 mg/kg) an antidepressant daily from day 8 to 32 followed by restress, thereafter on Day-32. The plasma concentration of taurine, corticosterone, and potassium was measured along with mitochondrial function in discrete brain regions and it was found that high and medium doses of taurine significantly suppress PTSD-like symptoms such as hyperarousal, anxiety, and improved spatial recognition memory, in addition every doses of taurine restored the plasma concentration of corticosterone and potassium.

Bhupinder P.S. Vohra has demonstrated earlier that taurine extracted from Pegasus laternarius Cuvier helps in protecting mice model from memory impairement caused due to consumption of four pharmaceuticals i.e. alcohol, pentobarbital, cycloheximide, and sodium nitrite at three doses of 0.01g, 0.02, 0.04g per kg BW either for 10 or 30 days [66].

According to one of the latest article it was concluded that cognitive impairments in ethanol fed mice have suppressed taurine concentration in the thalmus [67]. Another study on mice model has shown that taurine supplementation to mothers consuming alcohol can help in protecting learning and memory impairments in offspring [68]. However the effect of taurine does not exist when given after birth, this indicates that timely supplementation of taurine only exerts protective role in neural development. Anaesthetic isoflurane that have high toxic effect of cognitive defects at elderly stage, one of the study has demonstrated that in aged rats spatial memory impairment can be prevented if they were administered by taurine before exposure to isoflurane. Taurine pretreatment also helps in suppressing Endoplasmic reticulum (ER) stress and apoptosis that were the potential factors in contributing in cognitive deficits [69].

He W., *et al*. 2021 demonstrated that taurine can promote axonal sprouting and brain plasticity and helps in restoring motor function in ischemic rats, they detected motor function by Rota-Rod test on D7, D14, and D28 after stroke, using immunocytochemistry with biotinylated dextran amine (BDA), they detected axonal sprouting, taurine also promotes mtDNA content, increased the levels of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PCG-1a) and Transcription factor A of mitochondria (TFAM), So their study concluded that taurine promotes influence on axonal sprouting in cerebral ischemic stroke by mitochondrial improvement.

Taurine deficiency is common in subjects with heart failure., so we can say it may be a therapeutic agent for cardiovascular diseases [70]. Taurine supplementation helps in improving contractile function and helps in restoring levels of taurine in these subjects. In the cytosol of mitochondria it acts as an osmoregulator and a modulator of protein phosphorylation (Thurston., *et al*. 1981; Schaffer., *et al*. 2002; Ramila., *et al*. 2015), phospholamban and the sarcoplasmic reticular Ca^{2+} ATPase (SERCA2), are two proteins that play central roles in excitation-contraction coupling, both of these are regulated by cytosolic taurine (Ramila., *et al*. 2015), Whereas normal respiratory chain function in the mitochondria is maintained by taurine (Jong., *et al*. 2012), Cardiomyocyte respiration is reduced by taurine deficiency as well as its deficiency promotes generation of reactive oxygen species by the mitochondria. TaşS., *et al*. 2006 demonstrated in his study the beneficial role of taurine supplementation against experimental hypothyroidism and the antioxidant effect. They randomly divided 40 male Sprague Dawley rats into four groups, group one is control, group 2, control + taurine; group 3, propylthiouracil (PTU); group 4, PTU + taurine), along with drinking water taurine is supplemented at a concentration of 1% for 5 weeks, It was found that in PTU group malondialdehyde levels were increased in Plasma ($p < 0.05$), red blood cell ($p < 0.01$), liver ($p < 0.001$) and kidney tissue ($p > 0.05$) in comparison of control rats, and the levels were also decreased in the PTU + taurine group compared with the PTU alone group, whereas in level of glutathione in liver as well as kidney tissue no significant changes were observed but the elevated level was noticed in taurine supplemented group, although decreased activity of Paraoxonase and arylesterase were found in PTU group while taurine supplementation caused no significant changes in paraoxonase and arylesterase activities, these results suggest that taurine supplementation may play a protective role against the increased oxidative stress resulting from hypothyroidism.

Kalender S., *et al*. 2019 demonstrated in his study the combined beneficial effect of taurine and curcumin against Bisphenol A (BPA) chemically known as (2, 2- (4, 4-dihydroxydiphenol) propane, its an endocrine disrupting chemical widely used in the world. In mouse model 130 mg/kg bw, 100 mg/kg bw and 100 mg/kg bw, respectively oral administration of BPA, curcumin and taurine were given for 4 weeks, when Pathology and oxidative damages were investigated it was found that in comparison to control group, BPA elevates the level of malondialdehyde (MDA) whereas decreased the activity of antioxidant enzyme such as (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST)) in testes of rats. In contrast reduce level of MDA and increased GPx, GST, CAT, SOD activities compared to BPA group were seen in groups that were Co-treated with curcumin or taurine with BPA. In the testis of BPA treated group some pathological findings were also observed whereas less histopathological findings were observed in group treated with BPA plus curcumin and/or taurine so these findings revealed that

curcumin and taurine significantly protect testicular damage in rat by BPA/xenoestrogen compound.

Sinha M., *et al*. 2008 demonstrated the beneficial effect of this amino acid against the potent neurotoxin cadmium (Cd)-induced oxidative impairment in mice brain, it was found that oral taurine administration (at a dose of 100 mg kg^{-1} body weight for 5 days) found effective against Cd-induced oxidative impairment in the brain tissue of experimental mice, as well helps in preventing the reduction in the *in vivo* antioxidant power linearly up to a dose of 100 mg kg^{-1} body weight.

Lobo MV., *et al*. 2000 demonstrated the location of taurine in various compartments of male rat reproductive organs by immunohistochemical methods, abundance of taurine was found in smooth muscle cells of tissues and skeletal fibers of cremaster muscles, in the testis, Leydig cells, vascular endothelial cells, and other interstitial cells are rich in taurine, In the male reproductive system, it is found as free amino acid in sperm cells (van der Horst and Grooten 1966; Hernvann., *et al*. 1986; Holmes., *et al*. 1992 a, b). It acts as antioxidants in preventing sperm lipid peroxidation (Alvarez and Storey 1983), as a capacitating agent (Meizel., *et al*. 1980; Meizel 1985), and as a sperm motility factor (Fraser 1986; Boatman., *et al*. 1990). It also modifies the activity of sperm phospholipid methyltransferase (LLanos and Ronco 1994).

OwumiSE., *et al*. 2021observed in his study the beneficial effect of taurine (TAU) against Benzo-a-pyrene (BaP) exposure which is toxic to reproductive system, when rats were co-treated with BaP (10 mg/kg) and TAU at doses of 100 and 200 mg/kg for 28 successive days, it was seen co-treatment with taurine helps in diminishing BaP-induced decrease in sperm quality, reproductive hormones, oxidative stress and inflammatory biomarkers. epididymal and testicular injuries in rats is also lessened by TAU supplementation. Toxic responses in the epididymis and testes of rats that is caused by BaP is mitigated due to TAU supplementation, as taurine diminished oxidative and inflammatory responses, thus improved sperm quality and enhanced reproductive hormone levels.

Aglan HS., *et al*. 2021 in his study demonstrate the possible role of taurine against the adverse effect of toxic substance lead on pregnant Sprague-Dawley rats and their fetuses after maternal exposure, on gestational days (GD), 7-16, Pregnant rats were divided into Group 1 (control) was given distilled water; Group 2 was exposed to Pb (250 ppm) in drinking water (GD 7-16), whereas Group 3 received TA (50 mg/kg/day) by oral gavage (GD 1-20); Group 4 was exposed to Pb (GD 7-16), whereas pretreated with TA from GD 1 till the end of the gestation period, at the end of the GD it was assessed that Pb toxicity results reduction in the maternal body weight, weight gain, uterine and placental weight, in addition to a high incidence of abortion and fetal resorption, Whereas decrease foetus weight and length, whereas chances of external and skeletal abnormalities with a high rate of mortality is seen. Severe hematological and biochemical alterations have been seen in both mother and foetus due to Pb toxicity, The toxicity of Pb was further emphasized by placental histopathological examination and hepatic DNA fragmentation, whereas group which received pretreatment of taurine has much less impact of Lead on both mother and foetus, as it soothed greatly incidence caused by Pb like chances of placental damage and hepatic DNA fragmentation.

Sevin G., *et al*. 2021 describes the beneficial effect of taurine against cataract an age related eye disorder which is caused due to loss of glutathione in the centre of lens, they investigated their findings in rabbits by applying l-Buthionine - (S, R)-sulfoximine (BSO)- a glutathione inhibitor, and found that taurine supplementation reversed the effects of BSO by increasing concentration of GSH and total GSH levels and GSH/GSSG ratio. In addition Malondialdehyde levels were also normalized by taurine which was enhanced by BSO.

Taurine transporters

Taurine that we get from food is absorbed by small intestine, presence of active transport in the brush border membrane helps taurine to enter in the enterocytes, which directs it to portal veins [71], then it is imported to liver cells where taurine start to exerts its action, regulating hepatic metabolism, with the final step being the transport of taurine to circulatory cells. TauT transporter or PAT1 transporter, are two types of transporters, that helps in delivering taurine from hepatic tissue to different sites. Major taurine transporter or most investigated transporter is TauT transporter, or Solute carrier family 6 membrane 6 (SLC6A6), having a special ratio of sodium ion/chloride ion/taurine (2:1:1) [60], which is characterized by its dependence on sodium or

chloride ions, the high affinity and the low capacity against its substrates, in various organs of body like placenta and skeletal muscle, thyroid, heart, lung, brain, liver, kidney, gut, osteoblast this transporter is distributed [60].

Another taurine transporter is PAT1 transporter (SLC36A1) or proton-coupled/pH-dependent transporter/proton-dependent carrier, has ability to transport substrate like betaine, glycine, GABA, proline (I. Thondorf., *et al*. 2011). This transport has high capacity and low affinity for substrates. Gut, heart, skeletal muscle, liver, kidney, placenta, lung, brain, stomach, spleen and testis are the different organs where PAT1 transporter is identified. Besides these two transporters there are some other carriers involved in taurine transport.one of them is GABA transporters found in kidney can also accept taurine as the substance for transporting [60], but still the process and mechanism of transport is still unclear. Some of other transporters are P-glycoprotein (M. Uhr., *et al*. 2004) and cytochrome P450 (CYP) 2D6 (C. Nordin., *et al*. 2003), these transporters are associated with the elimination of brain taurine, regulates taurine flow into and out of brain, however their mechanism of action needs further studies. Taurine transporters are located in nucleus and other intracellular sites. Presence of taurine transporters in nuclear contributes in its swelling/ shrinking elicited by taurine [71]. β-alanine is responsible for time dependent elimination of taurine content, but taurine content in mitochondria is almost uneffected by this inhibitor despite the total observed low taurine content [71], this suggested that presence of taurine transporter in mitochondria (UbukaT., *et al*. 2008), It is investigated that for import of taurine in mitochondria atleast one taurine transporter is present in it (Suzuki T., *et al*. 2002). Whereas thePAT1 transporter has been found localized on endosomal and lysosomal membranes (Ögmundsdóttir MH., *et al*. 2012). 12 hydrophobic transmembrane (TM) domains has been present in TauT transporter, with the N and Cterminal being exposed to the cytosolic compartment, for taurine transport sodium (Na+) and chloride (Cl-) ions are required, and to the first Nterminal, extracellular loop, both the ions (Na+ and Cl-) binds (Takeuchi K., *et al*. 2000), this suggest that taurine transporter is strongly depends on ions.one to three Na+ ions are required to elicit taurine transport (Mollerup J., *et al*. 1998).

Important features of taurine transporters are as follows

The renal adaptive regulation of TauT depends on taurine availability and controls the body pool of Tau, ionic environment, electrochemical charge and pH mostly affected Tau accumulation in renal tissues. TauT guides transfer of taurine across cell membrane and controlled by PKC phosphorylation post-translationally; TauT expression is suppressed by p53, protective effects on renal cells has been exerted by over -expression of TauT against oxidative stress-induced nephrotoxicity [21].

Liver, kidney, brain, retinas and placenta of mammals have high expression of taurine transporter [21]. Various methodologies including reporter gene assay, DNA binding, Western blot analysis, and immunohisto-chemistry has demonstrated that p53 and c-Jun regulates expression of TauT [21], p53 was detected to down-regulate TauT whereas up-regulated by c-Jun. Increased TauT promoter activity is associated with inhibition in activity of c-Jun N-terminal kinase (JNK). Studies on TauT transgenic mouse model has shown that TauT, exerts protective effect against cisplatin-induced kidney damage [21], Both the transporters i.e. PAT1 - and TauT-mediated transport of taurine, in the brush-border membrane of human intestinal cells, so when there is less taurine concentration under physiological conditions, then major taurine uptake or absorb is mediated by taurine transporter (TauT), whereas when concentration of taurine is high in human intestinal cells then uptake or absorption is mediated by taurine transporter PAT1 [21]. Highest concentration of taurine is found in heart, ranging from mM in cows to 40 mM in mice [21]. Taurine is mostly excreted through urine predominantly (95%) as unmetabolised Tau (70%) and as a sulphate (about 25%), probably reflecting possible bacterial degradation of Tau in the intestine (Sturman, J.A., *et al*. 1975).

Relationship between the taurine level and taurine transporters

In physiological state taurine balance is affected by dietary intake, cellular synthesis and the regulation of taurine transporters. Relationship between taurine levels in the body is determined by these factors i.e. dietary intake, cellular synthesis and the regulation of taurine transporters, and the status of taurine transporters (especially TauT), is more important for normal taurine function [60]. The major function of taurine transporters is to control the relative balances of taurine contents in different body fluids, As from plasma into brain at blood brain barrier the net flux of taurine is controlled by TauT [60]. Therefore, In brain TauT can maintain lower taurine concentration primarily inside brain cells [60], than

those in plasma [60]. Suppressed taurine level in different body parts as well as interrupted normal function in various organs occurs if TauT is knockout as due to impaired taurine transport and taurine depletion in a systemic summary (U. Warskulat., *et al.* 2007). By applying TauT inhibitor, Taurine depletion can be induced, according to one of the recent report (W. Hadj-Said., *et al*. 2016). Thus to get rid from above abnormal physiological functions and to rectify them again, taurine administration is needed [60]. Studies have shown that TauT knockout mice, when supplemented with taurine can correct the activity of striatal network which is associated with restored GABA effects [60], Another study by Ito *et al*2008 has managed to remove exons 2-4 of TauT transporter, they found that in cardiac and skeletal muscle there is suppressed level of taurine by 100 and 96%.Study by Heller-Stilb., *et al.* 2002 by generating knockout TauT mice, and by eliminating exon 2 from taurine transporter, it was demonstrated that those mice have suppressed taurine levels in cardiac muscle at a rate of 98%, In one of the study they developed a mouse model with a disrupted gene encoding the taurine transporter (TauT-/-) and found a heavy loss of taurine in heart and skeletal muscles (95% decrease), following lower concentration of taurine in plasma, kidney, liver, and the eye (74% decrease), in addition vision loss along with retinal degeneration [71]. From above discussion it is clear that decline in the level of taurine gives rise to abnormalities in tissues and organs. In addition phenotypic appearance of TauT KO mice were: lower body weight, exercise intolerance and muscle atrophy (Warskulat U., *et al*. 2004, Ito T., *et al*. 2008), loss of retinal photoreceptor function, reduced responsiveness to nociceptive stimulation (LötschJ., *et al*. 2014) inner ear degeneration, alteration of renal development and function, unspecific hepatitis/liver fibrosis and cardiomyopathy (Ito T., *et al*. 2010, Han X., *et al*. 2013), reduced memory generation by T-cell (Kaesler S., *et al*. 2012), including blunted apoptosis in erythrocytes following changes in the balance of blood cells (Lang PA., *et al*. 2003). Whereas the research team of Häussinger provide evidence that in taurinetransporter deficient tissues, there is presence of apoptotic cells, in case of Tau T deficient mice it was found emergence of Apoptosis in photoreceptor cells, leading to blindness at an early age, given that the differentiation of cells was not closely dependent on taurine transporter, whereas the olfactory receptor neurons of TauT KO mice, also followed the same apoptotic trend displaying signs of immaturity (Warskulat U., *et al*. 2007).

Zhang H., *et al*. 2021 demonstrated in their study the beneficial effect of taurine against Doxorubicin (DOX) an effective anticancer anthracycline drug; but due to strong affinity for myocardium cells it gets accumulated in heart thus causing cardiomyopathy and congestive heart failure, so exogeneous supplementation of taurine (DOX-induced chronic cardiotoxicity in mice), prevents the loss of weight caused by DOX, activity of myocardial enzymes i.e. creatine kinase (CK) and lactate dehydrogenase (LDH) has been accelerated by taurine supplementation, in addition activity of superoxide dismutase (SOD), glutathione (GSH) content, glutathione peroxidase 4 (Gpx4) expression was accelerated by taurine supplementation, whereas action of malondialdehyde (MDA) content was suppressed by taurine, and taurine also helps in preventing myocardial myofibrillar disruption and mitochondrial edema, and also inhibits apoptosis by suppressing the expressions of cleaved caspase-3 and Bax/Bcl2. Thus the study conclude that taurine helps in enhancing antioxidant capacity and reducing oxidative damage and apoptosis against the myocardial damage caused by doxorubicin.

Faruqui AA., *et al*. 2021 describes the beneficial effect of taurine against anaemia, taurine along with iron supplementation enhances four parameters, i.e. Enhances red blood cells (RBC) membrane stabilization, osmoregulation, and detoxification, Anti-oxidant and anti-inflammatory effect helps ion reduction of gastrointestinal side effects, by building up energy gives symptomatic relief from lethargy and weakness, by increasing the activity of light chain ferritin isoform (FTL) involved in cellular iron storage.

Samadi M., *et al*. 2021 Demonstrated in their latest study the beneficial role of taurine against Aluminum phosphide (AlP) which is cardiotoxic, in the study. AlP-induced animals were divided into seven groups, including the control group, i.e. taurine group (500 mg/kg), AlP with LD50 dose, AlP + taurine 20, 50, 100, and 200 mg/kg group. Wistar rats, 60 min after AlP gavage, received taurine intraperitoneally.Upto180 min Cardiac hemodynamic parameters were evaluated, and for biochemical investigation, the animals were sacrificed24 h after AlP treatment, it was observed that abnormalities in ECG, BP, and HR cause due to AlP poisoning were improved after taurine treatment. In addition taurine treatment helps in improving AlP induced biochemical alterations including complexes I and IV activities, the ADP/ATP ratio, mitochondrial membrane potential, cytochrome C release,

and oxidative stress biomarkers, improved apoptosis, decreased CK-MB and troponin I level whereas no changes were seen in taurine 500 mg/kg and the control group in tests.

Why analogous and what?

Gastrointestinal tract has poor capacity to absorbed amino acid and the ratio between doses administered orally and the corresponding levels attained in the CNS are very unfavourable, this is because of limited supply of absorbed amino acid in the GIT into the CNS by mechanism of active transport that has finite capacity. Due to their polar character and highly ionised state, Passive diffusion of amino acids is negligible. Poor absorption is accompanied by high loss through metabolic degradation, which occurs in both the gut and the liver. These losses, constitute the well-known 'first pass effects'. As taurine is also an amino acid so possess all these characteristics, apart from these taurine has some extra peculiar problems as unfavourable pharmacokinetics, very strong hydrophilic nature, lipophobic character and fast rate of extraction through urine. As in case of animal epilepsy model taurine acts as a potent anticonvulsive agent, it has different effect through their mode of action as it prevents seizures in animals effectively when administered intra-cerebroventricularly, but effect to show such effect when administered orally or peritoneally, and to achieve any clinical efficacy very high dose much greater than 3 g/day is needed (Gupta RC., *et al*. 2006, 2005). Thus, taurine analogs helps to overcome these situations by modifying some changes in taurine structure with increased lipophilic character that may quickly diffuse through membrane, then undergo transformation to the target molecule; taurine at the site of action. Nowadays analogs of taurine are used as an anti-convulsant, antialcohol, anti-cancer and cardio-tonic (Gupta., *et al*. 2005).

Walczewska M., *et al*. 2019 states that due to strong antiseptic and anti-inflammatory properties, Taurine haloamines (N-chlorotaurine, N-bromotaurine) are good candidates for topical application in treatment of skin inflammatory/infectious disorders, other more stable analog of N-bromotaurine which has strong microbicidal and anti-inflammatory properties at concentrations well tolerated by human cells and tissue has been identified and named as N-dibromo-dimethyl taurine, N-monobromo-dimethyl taurine) and bromamineT, their demonstrated in their study the combined immunomodulatory effects of bromamines and ibuprofen on J774.A1 macrophages cell lines, it was shown that in combination with bromamines, the activity of ibuprofen got increased in inhibiting the production of prostaglandin E2 (PGE2) that contributes in suppressing the function of T cell with aging, which increases the susceptibility to infections, another contribution of bromaminesis that it all inhibits the production of inflammatory cytokines (TNF-α, IL-6) whose production is stimulated by ibuprofen/ one of the side effect of it.so the result suggest that along with administration of NSAIDs, ibuprofen in treatment of inflammatory/infectious skin diseases, topical application of bromine should also be supported as an adjunctive therapy.

Role in cancer

By modulating multiple signalling cascades, taurine exerts its anticancer effect (Zhang X., *et al*. 2014, Zhang X., *et al*. 2015, Choi EJ., *et al*. 2015, Yousef HN., *et al*. 2017, Vanitha MK., *et al*. 2015 Tu S., *et al*. 2015), through its anti-oxidant capacity (Sadzuka Y*et al* 2015, DaigelerA., *et al*. 2008 Jacobi CA., *et al*. 2005, RodakR., *et al*. 2005, RefaiNS., *et al*. 2019).By neutralizing insults derived from strong oxidant and cytotoxic agents it protects cells from oxidant-induced injury (MatésJM., *et al*. 2012).Taurine acts as an antioxidant, as it hampers accumulation of Reactive oxygen species in tumour cells, thereby compromising cancer progression (MatésJM., *et al*. 2012). In addition taurine enhance the activity of chemotherapeutic drugs, though minimizing their toxicity (Okamoto K., *et al*. 1996, Abd-Allah AR., *et al*. 2005). Studies have shown that taurine oral supplementation, helps in reducing chemotherapy-induced complications, because of its antioxidant property (IslambulchilarM., *et al*. 2015, Desai TK., *et al*. 1992, Tabassum H., *et al*. 2007, Parvez S., *et al*. 2008, Tabassum H., *et al*. 2018, Han X, *et al*2009). Because of its strong potential, taurine helps in attenuating the side effects of classic chemotherapeutic drugs such as doxorubicin (DOX), 5-fluorouracil (5-FU), cisplatin, tamoxifen (TAM), though strongly promotes their therapeutic efficacy (Al-Asmari., *et al*. 2018, Das J., *et al*. 2012, Das J., *et al*. 2011, Parvez S., *et al*. 2008, Sadzuka Y*et al* 2009). By enhancing immune surveillance taurine also plays role in immune rejection of cancer cells (Song XD., *et al*. 2003). By inducing apoptosis taurine exerts its preventive action on cancer cells [72]. Whereas in different cancer like colon cancer [72], breast cancer [73], and hepatocarcinoma (Tu S), taurine attenuates apopoptosis and exerts its preventive role. By up-regulating the expression of the p53 transcription factor, while

down-regulating the expression of anti-apoptotic proteins such as B-cell lymphoma 2 (BCL-2) [72], taurine exerts apoptotic effect on cancer cells. Similarly by inducing apoptotic effect in neoplastic cells taurine exerts its anti-neoplastic activity (He F., *et al*. 2018). The mechanism underlying the apoptotic effect of taurine is based on stimulating endoplasmic reticulum stress and inactivating the protein kinase B (Akt) signaling pathway (He F*et al* 2018). Invasiveness of cancer cells from primary site through bloodstream to other sites, in response to ionizing radiation is also prevented by taurine, as this amino acid prove effective in downregulating matrix metalloproteinase 2 (MMP2), and upregulate the activity of N-acetylgalactosaminyltransferase (Neary PM., *et al*. 2010), Epidemological studies on breast cancer have demonstrated that antioxidant rich diet may be helpful in reducing the emergence of breast cancer [71]. In biological samples of breast cancer. By using high-resolution magic angle spinning magnetic resonance spectroscopy (HR-MAS MRS) coupled with the relative principal component analysis technique researchers have evaluated that in subjects suffering with breast cancer have very small taurine content with metastasis compared to healthy subjects [71].

Hou X., *et al*. 2021 in their study analyzed the metabolites of resected tissues through gas chromatography-mass spectrometry (GC-MS), and observed that taurine concentration in Colorectal cancer tissues (CRC), one of the most common malignant tumors diminished whereas concentration of hypotaurine, ananalog of taurine got increased in tissues, their result invitro showed that taurine significantly reduced cellular proliferation, metastasis, and colony formation whereas it induced apoptosis in CRC cells, also regulates the expression of epithelial mesenchymal transition (EMT)-associated genes in a dose-dependent manner, helps in suppressing hypotaurine-induced CRC progression, which was linked to the inhibition of the ERK/RSK-signaling pathway and decaying in intracellular hypotaurine.it also weakened hypotaurine-induced tumor growth and metastasis *in vivo*, CRC subjects have lower serum taurine level that might be a promising biomarker reflecting a poor prognosis in CRC.

Study by El Agouza., *et al*. 2011 on female Egyptian subjects breast cancer, they recruited them in four groups as follows i) 50 diagnosed subjects with breast cancer subjected to surgery; ii) 10 female subjects with benign breast cancer signs; iii) 5 females equipped with high predisposition to breast cancer, due to their family history; and iv) 20 healthy women who were used as control evaluate the diagnostic importance of taurine in them and found reduced level of taurine in serum of subjects with a high risk of breast cancer, so taurine can be establish as a biomarker which can provide a clue for predisposition of women to breast cancer or the early diagnosis of females with early malignant lesions due to taurine detection. One of the interesting fact is that taurine level ranging from 40 to 57 µmol/l and from 18 to 31 µmol/l, respectively in females with positive family history of breast cancer and women with benign breast lesions [71] whereas taurine content in healthy women ranges from 46 to 70 µmol/l, women who are highly susceptibility to breast cancer have lower taurine values, proposing that minimal taurine value of high-risk group did not exceed the lower limit recorded in control healthy group [71].

Vanitha MK., *et al*. [74] demonstrated that 7, 12-dimethyl benz [a]anthracene (DMBA) induced breast cancer in Sprague-Dawley rats, when administered with taurine (100 mg/kg body weight) have suppressed liver mitochondrial LPO whereas levels/activities of enzymic and non enzymic antioxidants, tricarboxylic acid cycle enzymes and ETC complexes ((superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-S-transferase (GST)), non-enzymic antioxidants (reduced glutathione (GSH), vitamin C, and vitamin E), in citric acid cycle enzymes (isocitrate dehydrogenase (ICDH), alpha ketoglutarate dehydrogenase (alpha KDH), succinate dehydrogenase (SDH) and malate dehydrogenase (MDH) were seen elevated after taurine treatment.

A study by Tang Y., *et al*. [75] has demonstrated the role of taurine against prostrate cancer in Korean population, Prostate-specific antigen (PSA) is a marker for prostate cancer, They treated prostrate cancer cell lines with taurine for 24 h and then harvested and found that taurine exerts anti prostate cancer metastasis effect and help in suppressing prostate specific antigen and several metastasis related genes in human prostate cancer cells, LNCaP and PC-3, and also prevent migration of these cell lines.

Samadi M., *et al*. [76] in one of their non clinical study on side effects of chemotherapy in inducing cardiotoxicity suggest that body and heart weight decreases by chemotherapy and mortality rate increases so taurine administration along with chemotherapy, biochemical and histological changes compared to the control group, returned near to average level, based on clinical studies, taurine improves chemotherapy-induced cardiotoxicity, but its

interaction with the efficacy of anticancer medicines that mostly act through induction of oxidants still needs investigation in future, so well design studies need to be planned in future to assess the effectiveness and safety of combined treatment of taurine plus anticancer medicines simultaneously.

Srivastava S., *et al*. 2010 in his pilot study on Urinary bladder cancer in 103 subjects through non-invasive 1H NMR spectroscopy evaluated probing the metabolic perturbations occurring in BC, The non-overlapping resonances of citrate, dimethylamine, phenylalanine, taurine and hippurate were first identified and then quantitated by 1H NMR spectra, with respect to an external reference sodium-3-trimethylsilylpropionate (TSP), in comparison to control a significant ($p < 0.05$) variations in concentration of hippurate and citrate levels were seen in cancer subjects, whereas elevation in taurine level of cancer subjects was observed, which was below the sensitivity limit of 400MHz in control cases.

Role in reproductive system

AdedaraI A., *et al*. 2017 in their study describe the beneficial role of taurine on sodium fluoride (NaF)-induced functional changes along the brain pituitary-gonadal axis in male rats.

Taurine has shown its protective effect against Zearalenone (ZEN), a non -steroidal estrogenic mycotoxin produced by the *Fusarium* species (Bertero., *et al*. 2018), having xeno-estrogenic structure and therefore it acts as an endocrine disrupter (Turcotte., *et al*. 2005). Study conducted by Güner A., *et al*. 2021 has shown that taurine suppressed the action of ZEN in human lymphocyte when it is exposed to it and neutralize cytotoxic, genotoxic, and oxidative effects of it as well as its irritating effect in vascular formations. In simple terms we can say that taurine blocked the toxic potential effect of ZEN through the reductions in oxidative stress levels and maintaining membrane stability.

Taurine exerts its protective effect in development of reproductive system, study by Manna P., *et al*. 2008 investigate its role taurine against cadmium induced testicular pathophysiology, when cadmium chloride was administered in wistar rats at a dose of 4 mg/kg body weight for 6 days significantly, reduction in plama testosterone level along with decreased testicular 5-3-HSD and 17-HSD activities were observed. Testicular sperm count and sperm motility was also decreased due to Cd-intoxication. Intracellular concentration of reactive oxygen species and testicular Cd accumulation was increased as well increased levels of lipid peroxidation, protein carbonylation, glutathione disulfide and DNA fragmentation as well as decreased levels of the activities of the antioxidant enzymes, total thiols and reduced glutathione by cadmium toxicity. Where as pre treatment with taurine at a dose of 100 mg/kg body weight for 5 days could prevent all above parameters. Taurine treatment, in addition also increased the *in vivo* ferric reducing antioxidant power linearly up to a dose of 100 mg/kg body weight.

Yahyavy S., *et al*. 2021 shows beneficial effect of taurine on male reproductive system by reducing the negative impacts of di (2-ethylhexyl)phthalate (DEHP), because of its antioxidant properties taurine exerts beneficial impacts on reproductive system.in their study they used DEHP-induced Leydig TM3 cell, they exposed the cell for 24 hrs to DEHP (0.8 µmol) or TAU (100 mg/ml), due to effect of DEHP Cell viability (MTT assay) percentage, oxidative stress and testosterone level were reduced whereas increase apoptosis, elevate Bax/ Bcl-2 ratio and enhance caspase-3 and -9 activity in the TM3 cells were seen, malondialdehyde contents and reactive oxygen species levels were also elevated due to DEHP effect. Elevated activity of superoxide dismutase and catalase were seen in the Leydig cells. Co-treatment of DEHP with TAU reverse above function like cell viability and testosterone level, whereas reduced apoptosis and oxidative stress, reduced activity of Bax/Bcl-2 ratio and caspase-3 and -9 activity.

Protective effects of tau in stress conditions of poultry production

Due to its antioxidant property, its protective effect has been reviewed under various stress conditions in poultry production, Tau plays important role in fighting against heat stress, immunological challenges or homeostasis disturbances associated with the increased stocking density of poultry [21]. Taurine supplementation (2.50, 5.00, and 7.50 g/kg of the diet) in commercial broiler birds has shown to improve growth performance, antioxidant capacity, and lipid metabolism (Han, H.L., *et al*. 2020), By regulating perk signalling and preventing oxidative stress taurine supplementation helps in suppressing muscle loss in chronic heat stressed broilers (Ma, B., *et al*. 2021). In chicken gut, Taurine acts as protective shield by regulating mucosal barrier function and mitigating Lipopolysaccharides (LPS) -induced duodenal inflammation in chickens (Xiao, M., *et al*. 2018).

Taurine and osteoporosis

Osteoporotic subjects possess lower serum taurine level in comparison to healthy subjects (Pontes TA., *et al*. 2019), lower taurine level in urine is a marker of post-menopause and osteoporosis where taurine levels in urine were decreased 1.9 fold in post-menopausal women with osteoporosis compared total pre-menopausal women with normal BMD (Yu L., *et al*. 2019). Taurine levels can be elevated by using drug bisphosphonates in osteoporotic subjects. One of the study on ovariectomized mice has shown that treatment with alendronate sodium, a bisphosphonate elevates taurine levels from 467.6 ± 116.0 uM to 669.2 ± 127.6 uM (Chen SY., *et al*. 2014). Elevated level of taurine uptake in retinal capillary endothelial cells [(3)H] significantly by pretreatment with alendronate and pamidronate (Lee NY., *et al*. 2013). *In vitro*, a bisphosphonate named alendronate, that acts like taurine helps in inhibition of bacteria-stimulated osteoclast formation (Kum KY., *et al*. 2003). Rabbits that were fed on atherogenic diet, when supplemented with taurine normalized level of hyper homocysteinemia were found (Zulli A*et al* 2009). Increased in activities of enzymes of cystathionine beta-synthase and cystathionine gamma-lyase was seen in human who receives taurine supplementation, as both the enzymes are involved in the transsulfuration pathway, and could help in lowering homocysteine (Hcy) levels, thus shows indirect effect of taurine in preventing osteoporosis and significant decreased in plasmahomocysteine (Hcy) level (Ahn CS., *et al*. 2009, Sun Q., *et al.* 2016), Taurine regulates Intracellular calcium homeostasis (Chen WQ., *et al*. 2001, El Idrissi A., *et al.* 1999, 2003, Foos TM., *et al*. 2002). Intracellular calcium homeostasis can be dysregulated if there is taurine deficiency, though there are near normal calcium serum levels or normal calcium serum levels. Due to taurine deficiency, dysregulation of intracellular calcium occurs in osteoblasts and osteoclasts leading to decreased bone growth and increased bone resorption, High level of taurine is found in bones [79], Taurine helps in bone formation and prevents bone resorption [79]. In bone forming cells i.e. osteoblaststaurine transporters are found which play role in bone homeostasis [79], osteoblast formation is stimulated by taurine [79]. Taurine supplementation stimulates extracellular signal-regulated kinase (ERK) pathway, thus contributes in increase activity of osteoblasts cells [79]. Taurine promotes the activity of Alkaline phosphatase, a marker of bone formation, and bone mineralization in a concentration-dependent manner, taurine also induces the expression of osteogenic growth factors [79]. Osteoclastic activity, bone resorption is prevented by taurine [79]. Taurine could increase bone formation by inhibiting the reverse mode of the Naþ/Ca2þ exchanger (NCX), as NCX exports calcium from cells while importing Na; however, in reverse mode the Naþ/Ca2þ exchanger imports Ca2þ and exports Naþ so reverse mode of NCX is prevented by taurine [79]. NCX is located on the mineralizing side of osteoblasts, So Osteoblasts express NCX (Sosnoski DM., *et al*. 2008, Stains JP., *et al*. 1998, 2002). Berry TM., *et al*. [79] in his latest article proposed that in case of osteoporosis increase in BMD could be found by combined supplementation of three nutraceuticals i.e. taurine, calcium, vitamin D and vitamin K, thus helps in reducing disability and death due to fractures of fragile bones in subjects with osteoporosis. Supplements that can be used to treat osteoporosis.

Supplement	Rationale	Safety
Taurine	Involved in intracellular calcium homeostasis and assists with absorption of vitamin D and vitamin K	3000 mg a day (Shao A., *et al*. 2008)
Calcium	assists with bone formation	600 mg of calcium twice a day in form of calcium carbonate. Recommended dose of calcium for women 51 and older by The National Osteoporosis Foundation holds adequate calcium intake is 1200 mg/day (Cosman F., *et al*. 2014)
Vitamin D3	promotes absorption of calcium	Once a day recommended dose of vitamin D3is 2000 IUs. According to The Institute of Medicine (US) the recommended dose of vitamin D intake for adults is set 4000 IUs as adequate and tolerable (Institute of Medicine (US) 2011)

Vitamin K MK-7	needed for bone to bind calcium	No toxicity has been observed with vitamin K MK-7 supplementation which is better absorbed than other kinds of vitamin K. Approximately 2 mg of MK-7 would be taken a day (Marles RJ., *et al*. 2017).

Table a

Study	Study population	Dosage and Study design	Duration	Key observation
Durelli., *et al*. (1983)	18 myotonic dystrophy patients	100-150 mg/kg bw Tau/d (equivalent to 7-10 g/d in an adult); randomized, controlled, crossover	6 months (180 d)	Approximate doubling of serum Tau levels; increased urinary Tau observed; no other outcome measures related to safety reported
Jeejeebhoy., *et al*. 2002	Congestive heart failure (CHF).	3 g/day	for 30 to 45 days	Decreased left ventricular end-diastolic volume
Azuma., *et al*. 1982	Congestive heart failure (CHF).	6 g/day	for 4 weeks	Cardiac function was improved, no side effects
Zhang., *et al*. 2004	Overweight	3 g/day	for 7 weeks	Decreased TG and body weight
Mizushima., *et al*.1996	High lipid diet	6 g/day	for 3 weeks	Decreased serum cholesterol and LDL, increased VLDL and TG
Hayes., *et al*. 1989	Healthy volunteer	0.4 g/day	for 2 weeks	Decreased platelet aggregation and platelet release
Franconi., *et al*.1995	Diabetes	1.5 g/day	for 90 days	Decreased platelet aggregation
Militante and Lombardini2002	Hypertension	6 g/day	for 1 week	Decreased blood pressure
ChupelMU., *et al*. 2018	Older Women	1.5g per daynaturalistic, prospective, controlled trial	For 14 weeks	Exercise, along with taurine treatment, produced an anti-inflammatory effect and maintained the integrity of BBB.
VidotH., *et al*. 2018	Chronic liver disease	2g/day, Randomised clinical trial	For 4 weeks	No adverse side effect reported, reduction in the frequency, duration, and intensity of muscle cramps in patients with chronic liver disease

Pearl PL., *et al*. 2014	SADH deficiency, rare autosomal genetic disease	50 mg/kg/d to a target 200 mg/kg/d, open-label study	weekly	Serious adverse event reported(hypersomnia) No effect on adaptive behavior after taurine therapy, Pre- and posttherapy adaptive scores also demonstrated no statistically significant difference
Brons., *et al*. 2004	Overweight men	1.5 g/day for	8 weeks	No significant difference in insulin secretion
Li., *et al*.	Sensory neuron cells from STZ-diabetic rats	2% in diet	for 6-12 weeks	Improved Ca2+ homeostasis
Azuma., *et al*. 1985	14 congestive heart failure patients	6g Tau/d; randomized, controlled, crossover	4 weeks (28 d	No adverse effects observed; no change in heart rate or blood pressure.
Azuma., *et al*. 1983	58 congestive heart failure patients	6g Tau/d; randomized, controlled, crossover	4 weeks (28 d	No adverse effects reported, but no specific safety parameters were assessed
Mizushima., *et al*. 1996	11 healthy adult males	6g Tau/d in presence of high fat (40% kcal), high cholesterol (1000 mg/d) diet; randomized, controlled	3 weeks (21 d)	Significant increase in VLDL and triglycerides; significant decrease in urinary norepinephrine; no change in blood pressure; no adverse effects observed.
Jeejeebhoy*et al* 2002	18 congestive heart failure patients	3g Tau/d (plus coenzyme Q10, carnitine, creatine) randomized, controlled	Up to 45 d	Significant increase in myocardial Tau levels; no effect on blood biochemistry; 4 patients complained of GI disturbances.
Chauncey., *et al*. 2003	22 type II diabetes patients	3g Tau/d; randomized, controlled	4 months (120 d)	Significant 33% increase in serum Tau; no effect on HBA1C or fasting glucose; no other relevant safety parameters assessed.
Zhang., *et al*. 2004a	13 healthy adults	3g Tau/d; randomized, controlled	12 d	Significant 8-fold increase in urinary Tau; no other safety parameters assessed.
Zhang., *et al*. 2004b	15 healthy overweight adults	3g Tau/d; randomized, controlled	7 weeks (49 d)	Significant decrease in serum triglycerides; no change in HDL-C or fasting glucose; no adverse effects reported; no other relevant safety parameters assessed
Colombo., *et al*. 1996	12 teenage cystic fibrosis patients w/ liver disease	500-1500 mg Tau/d; randomized, controlled	1 yr (365 d)	No clinically relevant changes in biochemical measurements, including liver enzymes, bilirubin, albumin, urea, etc ..No adverse effects observed.

Brons., *et al*. (2004) and Spohr., *et al*. (2005)	18 healthy men	1.5g Tau/d; randomized, controlled	8 weeks (56 d)	No clinically relevant changes in biochemical measurements; no adverse effects observed
Sirdah., *et al*. (2002)	26 anemic women	1.0g Tau/d (+325 mg/d ferrous sulfate); randomized, controlled	20 weeks (140 d)	No adverse effects observed; no other relevant safety parameters assessed

Table b

Published safety observations* for human taurine (Tau) supplementation.

Miscallenous roles

Taurine synthesis is well recorded in brain and spinal cord in high amount, it is mostly present in glia and synaptosomes (Gupta RC., *et al*. 2006). However studies have proved taurine synthesis in brain but its synthesis in spinal cord is not documented, whereas presence of cysteine, one of the precursor of taurine is found to be present in cat's spinal cord (Gaitode, 1970, Gupta RC., *et al*. 2006), and presence of Cystein sulfinate has been documented in rats spinal cord (Baba., *et al*. 1980, Gupta RC., *et al*. 2006). So presence of taurine precursor in spinal cord provides some clue that may taurine synthesis occurs in spinal cord, yet a detailed study behind this is needed. Taurine concentration is highest in dorsal horn and lowest in ventral horn (Palkovits., *et al*. 1901).

According to Waliullah S., *et al*. 2021 in SCI subjects vitamin D deficiency is widely common at admission to the trauma centre, in their study they observed lower level of vitamin D deficiency below 30 ng/m in almost seventy six percent of subject, at the time of admission Routine measurement of 25 (OH) vitamin D3 levels is recommended early diagnosis of vitamin D deficiency, so to get rid of it early nutritional supplementation is very boonful as there is limited research on role of taurine in knee OA in humans but its anti-inflammatory role is explained by one of the study by Bian Y., *et al*. [78], that taurine treatment helps in exhibiting anti -OA effect by alleviating H_2O_2 induced ER stress and subsequently inhibiting chondrocyte apoptosis. According to Waliullah S., *et al*. 2014 osteoporosis is mainly characterized by decreased in bone mineral density of mostly mineralized bone which make it fragile and Indian females are at high risk of post menopausal osteoporosis so its necessary to create awareness among them and to get rid from it or to reduce it nutritional supplementation is easy to administer and cost effective, studies have shown that this wonderful molecule helps in stimulating the secretion of reproductive hormones in female animal model as female reproduction can be achieved by regulating the activities of hypothalamic-pituitary-ovarian axis-related hormones (Mu T., *et al*. 2015).

Exposure to pesticides at prenatal or early postnatal stage may lead to functional deficits in the developing brain.one of the study on rat model by Liu F., *et al*. 2020 has shown potential effect of taurine against it, They administered rats with paraquat (PQ) and maneb (MB) intragastrically for 12 continuous weeks, while for 24 weeks continuously rats were fed with taurine dissolved in water, In the behavioral tests, the rats' trajectories became complex, and the reaction latencies and mistake frequencies increased, whereas groups with paraquat (PQ) and maneb (MB) have significant changes in the hippocampal neurons whereas no such changes were seen in tau group, cAMP was activated in PQ□+□MB group that reduces the production of protein kinase A (PKA) as well inhibited the activation of other elements, such as brain-derived neurotrophic factor (BDNF), cAMP response element binding protein (CREB), phospho-CREB (p-CREB), immediate-early genes (IEGs) Arc, and c-Fos, whereas expression of above mentioned protein and level of cAMP was regulated in taurine treated group. Thus their study proves that taurine exerts neuroprotective effect, Guizoni DM., *et al*. [77] states in his study that taurine plays major role in protecting endothelial dysfunction in the lieno-pancreatic artery (LPA) by upregulating the CBS-H2S pathway, for endocrine islet activity, pancreatic vasculature plays important role, thus we can say taurine is an important therapy in case of vascular and metabolic dysfunction associated with malnutrition and comorbidities.

BianY., *et al*. [78] explores the role of taurine in Osteoarthritis, one of the complex disease using rat model by establishing anterior cruciate ligament transection (ACLT) plus medial meniscus

resection (MMx) surgery on the right knees, After surgery they were given taurine injection in a dose dependent and time dependent manner, and it was observed that there is decrease in secondary mechanical allodynia, in hind limb weight-bearing alterations, and inhibited knee swelling, In addition In a dose-dependent manner matrix loss and cartilage degeneration is prevented by taurine, as well expression of matrix metalloproteinase-3 (MMP-3) and CHOP were also suppressed by Taurine administration. Desforges M., *et al*. 2013 states that taurine plays major role in maintaining trophoblast turnover and cytoprotection, In comparison to normal pregnancies taurine concentration was found lower in Foetal growth restriction (FGR) due to reduced activity of taurine transporters (Surai., *et al*. 2015).

Madbouly N., *et al*. 2021 has shown in his recent study that taurine has effective role against drug induced nephrotoxicity, In there study they showed the effect of taurine in preventing the action of Amikacin (AMK) an effective aminoglycoside antibiotics, when taurine is co-administered along with AMK it proved effective against renal toxicity by downregulating HSP25, Toll like receptor-4, Caspase-3, IL-18 with up-regulation of IL-10 levels, into mouse model which they divided rats into 4 groups: Group 1: rats received saline (normal control), group 2: normal rats received 50 mg kg^{-1} TAU intraperitoneally (i.p.). Groups 3 and 4: received AMK (25 or 50 mg kg^{-1}; i.p.). Groups 5 and 6: received TAU (50 mg kg^{-1}; i.p.) concurrently with AMK (25 or 50 mg kg^{-1}; i.p.) for 3 weeks. One of the randomized double-blind clinical study, has proved effective role of taurine against first-episode psychosis, when these subjects were given taurine for 12 weeks (4g per day), as an adjunctive therapy of antipsychotic medication, it was demonstrated that after taurine treatment symptoms of schizophrenia were significantly diminished, where no increment is shown in composite cognitive scores.

Conclusion

In this review we try to describe all the best possible roles of taurine, its sources origin and its interaction with life processes and evidences for its ability to modify activities in bone, brain, heart, liver and other organs, It is true to say taurine a wonderful molecule due to its unique physico-chemical character derived from being a b-amino-sulfonic acid, In cancers taurine has been established as biomarker, studies have proved that its deficiency in body leads to different abnormalities, but more research needed to be conducted on human model as most of the studies till date is performed on animals. The absorption of taurine is very low in the gastrointestinal tract. Due to the low passive diffusion through the membranes, therefore it's a fascinating and interesting area of research in future to develop or identify new lipophilic derivatives of taurine that can cross the BBB in disease circumstances and/or increase binding receptors, as we know taurine is lipophobic in nature so its therapy requires very high dose long duration. As nutritional supplementation is easiest and safest mode so nowadays researchers focussed more on supplementation and disease like OA is very common worldwide so in these nutritional supplementation is best therapy as proved in one of his study by Srivastava RN., *et al*. 2015 in his study on KOA has proved that a possible risk factor for KOA is low intake of vitamin D and vitamin C diets, so above mentioned data also proved beneficial effects of taurine in case of OA but most of them were performed on animal studies so research need to be conducted on human beings to establish the role of taurine in OA as we know taurine is an antioxidant. Similarly as we know SCI is an extremely complex disease with high morbidity (Kaur and Sharma, 2018, Srivastava RN., *et al*. 2020), and cost effective, one of the study by Srivastava RN., *et al*. 2019 demonstrated in his study on stem cell in 193 subjects with complete paraplegia and they allocated 3 groups i.e. conventional with stem cell augmentation (Group-1), conventional (Group-2), and conservative (Group-3), after 1 year ASIA, sensory and motor scores were evaluated and found much better result in group 1 in comparison to group 2 and group 3, but stem cell therapy and all is cost effective so if nutritional supplementation is given in SCI cases so its easy mode and subjects can easily afford so as studies have proved beneficial effects of taurine because of its antioxidative properties so still human trials are needed in taurine supplementation in case of SCI, although research is performed on animal model in case of SCI, as this is still a hot topic of debate. Perfection is the end of search, thus this field of research is not perfect yet and we hope that this review will provide enough inputs to ignite the minds.

Conflict of Interest

The authors have no potential conflict of interest. The disclosure of potential conflict of interest in the prescribed format has been obtained from all the authors.

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