Taurine as Anticancer and Antiviral: Case Report and Prospective Update

Raúl H Morales-Borges[1*] | Michael J González[2] | Ramesh C Gupta[3] | Olorunfemi Ayeotan[4]

[*]**Correspondence:** Raúl H Morales-Borges

Address: [1]Integrative Optimal Health of Puerto Rico, PSC and Division of Hematology/Oncology, Department of Medicine of Ashford of Presbyterian Community Hospital, San Juan PR, Puerto Rico; [2]University of Puerto Rico, Medical Sciences Campus, RECNAC Project, Schools of Public Health and Pharmacy, Department of Human Development, Nutritional Program and Dept. of Biology at Pontifical Catholic University in Puerto Rico, Puerto Rico; [3]SASRD Nagaland University Medziphema 797106, India; [4]Department of Medical Laboratory Science, Ladoke Akintola University of Technology Osogbo, Nigeria

e-mail ✉ raul.morales.borges@gmail.com

Received: 13 April 2020; **Accepted:** 27 April 2020

ABSTRACT

Taurine is a sulfur amino acid of nutritional significance associated with tissue-protective activity in several forms of oxidant-induced injury. It has now established beneficial anticancer and antivirus properties. In present study two brief cases of Multiple Myeloma and Infectious Mononucleosis have been reported followed by a prospective update demonstrating the mechanism of action in neoplastic and viral diseases. With this study we believe practicing physicians can improve the existing therapeutic conditions by its utilization in clinical practice and beyond.

Keywords: *Taurine, Anticancer, Antiviral*

Introduction

Taurine (Tau) is a sulfur containing amino acid, chemically known as 2-Aminoethane sulfonic acid. It is phylogenetically ancient compound with a disjunctive distribution in all vital organs and the biosphere (Huxtable, 1992). Besides in mammals its unique presence is also recorded in marine organisms, together with protoctist, insects, and arthropods, however, is usually absent or present only in traces in bacteria and plant kingdoms. In large number of animals, along with mammals, it is the foremost copious substance of the low-molecular-weight organic entity with wide spectrum of Physiological and pharmacological actions. A seventy-kg human contains up to 70 g of taurine. The name Taurine was adapted from its ancient discovery, as it had originally isolated from the gall of the ox, bovine (Demarcay, 1838). Taurine has protective role in almost every vital tissue; from Central nervous system (CNS) to eye to ear, kidney to liver and in many more. Besides such actions it also participates in number of metabolic processes such as diabetes and bone metabolism. Taurine protects the cells from the disrupting effects of exterior changes transmitted into the cell, to facilitate such

actions, number of ways has been advocated which may be via alterations in inorganic particle concentrations especially calcium or through osmolytic action or by some other mechanism yet to be established. It seems, taurine may be a helpful influence in an unstable molecular world to stabilize the cell membrane. All the actions of taurine listed tend toward conservation of performance, a property that has been termed enantiostasis (Mangum and Towle, 1977; Gupta *et al*., 2005; Gupta and Kim, 2003)

Tau now regarded as conditional essential amino acid and isn't incorporated into proteins. In several classes of tissues, taurine is omnipresent and is that the most copious free amino acid within the heart, retina, striated muscle, brain, and leukocytes. Taurine reaches up to fifty-millimeter concentration in leukocytes. Tau is tissue-protective in several models of oxidant-induced injury (Schuller-Levis and Park, 2003). To trap the oxidants; taurine reacts with hypochlorous acid, produced by the myeloperoxidase pathway, resulting more stable but less harmful taurine derivative (Tau-Cl). Tau-Cl is now more or less established as a powerful regulator of inflammation. Tau-Cl has been shown to down-regulate the assembly of pro-inflammatory mediators in placental mammal and human leukocytes. Taurolidine, a by-product of taurine, is usually utilized in Europe as connected medical care for varied infections yet as for neoplasm medical care.

It is legendary to possess many activities together with endoplasmic reticular (ER) stress-modulatory, oxidative stress-modulatory, anti-apoptotic, anti-inflammatory, and purportedly epigenetic-modulatory activity in experimental conditions as taurine have (Kusaczuk, 2019). Taurine has been utilized in Chinese drugs for hundreds of years, and many studies have already underscored its beneficial effects in the treatment of the many pathological conditions. Still, taurine is continued to be a really intriguing pharmacologic agent, and with ascending number of pre-clinical and clinical studies and their interface continues to stimulate such devotion, unraveling novel aspects of taurine functioning.

Since endogenous synthesis of taurine is limited in adult humans thus humans could suffer from taurine deficiency, the deficiency conditions get strength wherever there's poor intake; thus, taurine is an important nutrient for humans (Tu *et al*., 2018; Gupta, 2018). Recent studies have projected that altercations in taurine levels are often used to predict the formation and malignant transformation of some tumors (El Agouza *et al*., 2011; Srivastava *et al*., 2010). As an example, the serum level of taurine was found to be considerably lower in patients with carcinoma than in patients within the insecure carcinoma cluster or the healthy management cluster (Tu *et al*., 2018). Thus, taurine is considered a unique biomarker for early designation/identification of carcinoma (El Agouza *et al*., 2011). High levels of taurine were additionally detected within the pee of patients with non-muscle invasive bladder

cancer, indicating that Tau may additionally function as a unique indicator for the designation of bladder cancer (Tu *et al*., 2018). Taurine inhibit the proliferation of human carcinoma cells A549 and therefore the growth of transplanted tumors in nude mice and promote the cell death of A549 cells by increasing the super molecule level of p53 unregulated modulator of cell death (PUMA), BCL2-associated X cell death regulator (Bax) and decreasing the super molecule level of Bcl-2.

In nude mice transplanted tumors, PUMA serves a critical role in the action of taurine against lung cancer and may represent a novel target for gene therapy in lung cancer. This nutrient could act as "host defense" molecule to promote the medical specialty defense of humans against infections by bacterium, fungi, parasites, and viruses (including coronavirus) through the assembly of N-chlorotaurine by activated human granulocytes and monocytes (Wu, 2020).

Because of poor utilization in clinical drugs, we tend to present 2 cases regarding the utilization of taurine in cancer (multiple myeloma) and infection (infectious mononucleosis) and a prospective update of its such activities to inspire the effective utilization of this amino acid in our practices.

Case Reports

Patient No.1:

An 82-years old black male, Puerto Rican, with IgG multiple myeloma (MM) diagnosed almost 1 ½ years ago, refused conventional standard treatment including chemotherapy and immunotherapy, and treated by few health care professionals such as naturopathic practitioners and allopathic physicians with complementary and alternative medicine. He visited our office and received L-taurine 1000 mg plus dexamethasone 8 mg oral daily, plus continued high dose vitamin C intravenously. He had chronic anemia of 8-9 gm/dL on oral B-complex. He was kept alive for 8-9 months with stable CBC, sed rate, and serum B2-microglobulin levels, but then his disease progressed and expired.

Patient No. 2:

This is a case of a 28-years old white female, Puerto Rican, with no previous history of systemic disease, and, no previous infectious mononucleosis, who presented to the primary physician's office complaining swollen nodes in her neck and fatigue, although she had a fever and sore throat lessen within a couple of weeks. She is a non-smoker. She had a complete blood count (CBC) with white blood cell count (WBC) of 3,800 with 78% lymphocytes, positive Mono test, with Epstein Barr Virus (EBV) serology as following: viral capsid antigen (VCA) IgM positive, VCA IgG and Epstein Barr nuclear antigen

(EA) IgG positive. She was referred to our clinic and at an examination, she had cervical lymphadenopathy bilaterally. No splenomegaly. She was treated with L-taurine 1000 mg oral daily and ascorbic acid (vitamin C) 1000 mg orally twice a day for 2 weeks. She was re-evaluated one week after completed her therapy and found to have WBC of 4,300 with lymphocytes of 58% and serology tests with VCA IgM negative and VCA IgG and EA negative. At an exam, she has minimal palpable cervical lymph nodes as compared to the previous exam. She is doing well since then.

Taurine as Anti-Cancer

Long non-coding RNA taurine unregulated gene 1 (TUG1) was reportedly concerned within the initiation and development of many cancers. However, how it performs and its molecular mechanisms in myeloma (MM) area unit still not much clear. Liu, *et al*. (2019) found that the expression levels of TUG1 were markedly hyperbolic in metric linear unit samples and cell lines. Knockdown of TUG1 considerably suppressed the proliferation, elicited cell cycle arrest at the G1/G0 phase and promoted programmed cell death of metric linear unit cells. In exploring the regulative mechanism, miR-29b-3p was confirmed to be an on the spot target of TUG1, and repression of miR-29b-3p might partly rescue the result TUG1 knockdown on metric linear unit cell proliferation, cycle, and programmed cell death. Besides, TUG1 completely modulated simple protein deacetylases four (HDAC4, a target of miR-29b-3p) expression through sponging of miR-29b-3p in metric linear unit cells. These findings advised that TUG1 exerted associate degree oncogenic role in metric linear unit by acting as a competitor endogenous RNA of miR-29b-3p, and inexplicit the potential application of TUG1 in treatment for metric linear unit. This study is traduced into clinical observe ad we tend to note a response in our case of metric linear unit with a lifetime of eight additional months.

A previous study exhibited additionally confirm the incontestable anticancer properties of Tau (Wu, 2020). What is more, the addition of a precise quantity of Tau to drinkable has been shown to increase the mean period of mice with transplanted tumors, with a growth inhibition rate of 42.26% (Yu and Kim, 2010). Tau could become a unique indicator for the first identification of breast and bladder cancers (Srivastava *et al*., 2010; El Agouza *et al*., 2011; Neary *et al*., 2010). The study of growth hindrance and treatment with Tau is aborning. However, analysis into the result of letter on tumors remains restricted, and the mechanism underlying the anticancer ability of Tau is nonetheless to be elucidated.

A study investigated the antineoplastic effects of taurine alone and a mixture of cisplatin with taurine in human cervical cancer cells (Kim T and Kim AK, 2013) further strengthen the utilization of

taurine. The treatment of taurine shrunken cell proliferation in a varied time- and dose-dependent manner. In co-treatment of cisplatin with taurine, cell proliferation was additional shrunken than single treatment of cisplatin. Reduced cell proliferation was caused by programmed cell death induction. Thus, once the treatment of cisplatin with taurine, apoptotic cells were investigated. Apoptotic cells were hyperbolic over taurine or cisplatin alone. Induction of programmed cell death was associated with p53 expression and activation of caspase-3, caspase-6, caspase-7, and caspase-9. With this study, the results indicated that co-treatment of cisplatin with taurine was simpler than one treatment of cisplatin.

Another use in medical oncology was a study with 5-Fluorouracil (5-FU). This study investigated the protecting result of Tau on 5-FU elicited adverse effects in Wistar rats (Al-Asmari *et al*., 2016). Animals were divided into four teams with six animals (n = 6) in every cluster. Cluster I received a vehicle solely and served as a bearing cluster. Groups II, III, and IV animals got oral feeding of 5-FU at fifty mg/kg bodyweight for four days. Tau was given to the animals of teams III and IV thirty min before 5-FU administration. There was marked elevation within the myeloperoxidase (MPO) activity upon administration of 5-FU which was reversed by Tau pretreatment. Microscopic anatomy observation of liver, kidney, intestine, testis, and prostate discovered that 5-FU administration resulted in anomalies like distortion of traditional cellular design infiltration of inflammatory cells, and loss of cellular integrity. These histopathological changes were markedly suppressed by Tau treatment. In conclusion organic chemistry and microscopic anatomy findings of this study recommend Tau has sturdy preventive potential against complications of antineoplastic drug 5-FU and thence Tau could play a very important role in combinable therapy to reinforce the therapeutic effectiveness of antineoplastic medication.

In another study, utilizing this thought method, a study with forty young adults (aged over sixteen years) with Acute Lymphocytic Leukemia (ALL), at the start of the upkeep course of their therapy, were recruited to the study (Islambulchilar *et al*., 2015). The study population was irregular in a very double-blind manner to receive either taurine or placebo. Life quality and adverse drug reactions were assessed employing a form. Corpuscle count, hemoglobin (Hb), hematocrit (Hct), serum bilirubin, transaminases, urea, and creatinine concentrations were evaluated. Information was analyzed by exploitation of applied Statistical Package for Social Sciences (SPSS) computer code. Of the full participants, 43.8% were feminine and 56.3% were male. The mean age was 19.16 ± 1.95 years (range: 16-23 years). The results indicated that the degree of white blood cells was considerably ($P < 0.05$) hyperbolic within the taurine treated cluster, however alternative hematological values failed to disagree considerably in either cluster. Taurine administration improved liver and excretory organ functions, indicated by the decline of serum bilirubin, transaminases, urea, and creatinine, severally compared to the controls (P <

0.05). Moreover, taurine considerably reduced serum malondialdehyde (MDA) and superoxide dismutase (SOD) levels (P <0.05). They ended that taurine supplementation may well be a protection against chemotherapy-induced toxicities most likely by its inhibitor capability. Their study established the effectiveness of taurine on the chemotherapy-related toxicities and a few of the complications throughout the upkeep amount of treatment following coadministration in young adults with ALL.

Another mechanism delineated in another study (He *et al*., 2019) discovered the apoptosis-inducing result of Tau against nasopharyngeal cancer (NPC cells) (HK1 and HK1-EBV) to clarify the mechanisms of anti-tumor effects of taurine by immunocytochemical strategies. They ascertained that taurine elicited cleavage of caspase-9/3 in a very concentration-dependent manner, suggesting the involvement of mitochondrial apoptotic signals. PTEN and p53 activation were detected in a very dose-dependent manner once taurine treatment in bureau cells. Last, taurine could play associate degree anti-tumor role by activating growth suppressor PTEN and p53.

Omura, *et al*. found that the optimum dose of Tau made a really important decrease in cancer-associated parameters, Oncogene C-fosAb2 & Integrin α5β1 being reduced to but 1/1,000th, and 8-OH-dG (which will increase within the presence of deoxyribonucleic acid mutation) reduced to but 1/10th. The optimum dose of Taurine 175mg for average adult numerous cancer patient three times each day alone offer useful effects with terribly important anti-cancer effects with strikingly hyperbolic urinary excretion of bacterium, viruses, & funguses, asbestos, cyanogenic metals & alternative cyanogenic substances. However, optimum doses of Taurine combined with optimum personalized doses of personalized animal oil [EPA 180mg & DHA 120mg] & special cilantro pill three times/day while not making harmful drug interactions among them together with alternative essential medication is usually very safe, simpler, economical & non-invasive new treatment for numerous cancer patients.

In a study with T-cell malignant neoplastic disease (Dong *et al*., 2017) the intervention treatment of therapy and taurine, the growth mass was considerably less than the opposite 3 teams (P <0.05), and also the anti-tumor rate was on top of those of therapy cluster and taurine cluster (P <0.05), that showed that exploitation of taurine adjuvant medical care within the standard therapy method will considerably improve the anti-tumor result. Moreover, once three weeks of treatment in therapy + taurine cluster, the thymus and spleen indexes of mice were considerably on top of those in model cluster and therapy cluster (P <0.05), and Th1/Th2 protein levels were higher than those within the therapy and model teams (P <0.05), that additionally indicated that taurine will enhance the immune perform of mice with T-cell malignant neoplastic disease throughout therapy, cut back the toxicity of

therapy and improve the curative result. The results of this study ensure the sweetening and toxicity reduction result of taurine.

In recent past several more studies have been undertaken in combination of taurine with other beneficial agents in one such study with curcumin and piperine resulted alter circulating levels of IL-10 and miR-21 in hepatocellular carcinoma patients where twenty HCC patients were given an oral dose of 4 g curcumine,40mg piperine and 500 mg taurine daily for three cycles of 30 days each, and after the end of period the increase in overall survival (OS) has been recorded with altered IL -10 &miR-21 (Hala *et al*., 2017).

Taurine as Anti-Viral

The content of Tau within the white corpuscle is high, representing five hundredth of the whole free organic compound pool. The two primary functions of taurine within the white corpuscle are inhibitory actions in inflammation and oxidation (Schaffer and Kim, 2018). ROS (Reactive oxygen species) are created by the white corpuscle as a weapon to kill pathogens, amongst those ROS one being is a hypochlorous acid (HOCl). HOCl reacts with Myeloperoxidase-catalyzes conditions resulting the formation of taurine chloramine (TauCl) from taurine and HOCl. TauCl is regarded a less potent chemical agent than HOCl, to get the best possible effects the neutralization of HOCl represents one amongst the necessary inhibitory mechanisms of taurine. The myeloperoxidase-catalyzed reaction is additionally accountable for the beneficial protective activity of taurine. TauCl inhibits the assembly of unhealthy cytokines (Marcinkiewicz *et al*., 1995; Park *et al*., 1997; Barua *et al*., 2001), attenuates elevations in gas and autacoid E2 (Park *et al*., 2000; Chorazy-Massalska *et al*., 2004; Kim *et al*., 2007), decreases the activity of matrix metalloproteinases and initiates blood corpuscle necrobiosis to terminate acute inflammation (Kim *et al*., 2007; Gupta *et al*., 2006; Nakajima *et al*., 2010).

TauCl is a well tolerable substance in clinical trials, a 1% solution does not show any noticeable alteration in humans; comprising 15 female and 9 males (Arnitz *et al*., 2018).

It is accepted that oxidants generated by phagocytes at the inflammation site are concerned in host defense against microbes. Among them, hypohalous acids (HOCl, HOBr), robust microbicidal agents, play an important role within the killing of pathogens by neutrophils and eosinophils (Marcinkiewicz and Kontny, 2014). These agents can kill a large spectrum of gram-positive and gram-negative bacterium, fungi (yeast and molds), viruses, protozoa and worm larvae. TauCl and TauBr, the physiological merchandise of the MPO–halide system, show disinfectant, fungicidal, antiviral and anti-

parasitic properties, as incontestable *in vitro* in many papers (Nagl *et al*., 2000; Nagl *et al*., 2001; Gottardi *et al*., 2005; Marcinkiewicz *et al*., 2000; Marcinkiewicz *et al*., 2006; Yazdanbakhsh *et al*., 1987).

Regarding Epstein Bar Virus (EBV) infection, it's related to nasopharyngeal malignant neoplastic disease (NPC) that is endemic in Southern China. EBV ordering may be detected in nearly all NPC growth tissues (Fung *et al*., 2016). Over the last decade, circulating cell free EBV deoxyribonucleic acid (EBV DNA) has been developed as a growth marker for NPC. Plasma EBV DNA analysis victimization period PCR is helpful for early detection, prognostication, and watching of treatment response of NPC. Such response helps to know the appliance of Tau in EBV infection and NPC. In past, He, *et al*. (2019) had examined the involvement of mitochondrial apoptotic signals in those cases were Tau was administered.

Schuller-Levis and Park (Schuller-Levis and Park, 2003) has illustrated all such action of taurine in their wonderful review of Tau and taurolidine as an adjunct medical care for infections and endotoxemia. Taurolidine may be as pin off taurine and is usually utilized in Europe, UK, Ireland, and the USA as connected medical care for varied infections. Taurolidine is chemically; bis-(1,1-dioxyperhydro-1,2,4-thiadia-zinyl-4) methane; and consists of 2 taurolidine rings derived from; taurine and 3 molecules of formaldehyde combining to make a two-ringed structure bridged by a methylene group. Taurolidine, that is stable, includes a short half-life, is non-toxic, metabolizes to taurine, dioxide and binary compound, and irreversibly inactivates lipopolysaccharide (LPS). Recent reports embrace anti-endotoxin, anti-bacterial, and anti-adherence activities for taurolidine. Taurolidine is currently enclosed during a new tubing lock answer to forestall catheter-related infections. Its result in attributing the activity of taurolidine to obstruction the assembly of lymphokine (IL)-1 and tumor necrosis factor (TNF) that is additionally elucidated in infective agent infections which is one reason to use it as antiviral. This was also a motivating factor for me to use in our case of EBV infection.

Synergistic Effect of Tau with other Supplements

Tau can be combined with Ascorbic Acid (Vitamin C, AA) as we did in the case of MM. In a study with spinal cord injury (SCI-model in rats (Chen *et al*., 2020), they divided the rats into the following groups: sham, control, 100 mg/kg of taurine, 100 mg/kg of ascorbic acid (AA), and 100 mg/kg of taurine + 100 mg/kg of AA. Treatment was continued daily for 45 consecutive days. The combined treatment of Tau and AA decreased caspase 3, Bax, pro-NGF, and p53 mRNA expression by more than 30% compared to individual treatments. The combined treatment of Tau and AA reduced caspase-3 and p53 expression by 33.7% and 44%, respectively, compared to individual treatments. The combined

treatment of Tau and AA decreased mRNA expression of interleukin-6 (IL-6), cyclooxygenase-2, tumor necrosis factor-alpha (TNF-α), and inducible nitric oxide synthase (iNOS) compared to the individual treatments of taurine and ascorbic acid. The combined treatment of Tau and AA also significantly recovered altered antioxidant markers, and induced lipid per-oxidation to near-normal levels. In summary, apoptotic, inflammatory and oxidative stress markers were significantly decreased in SCI-induced rats treated with taurine and ascorbic acid.

Haber, *et al*. (2003) had performed a study with N-acetylcysteine (NAC) and Tau to prevent hyperglycemia-induced insulin resistance *in vivo* in rats as a possible role of oxidative stress of both. It is known that NAC is a precursor of glutathione (GSH), and GSH may act as a cofactor in several enzyme reactions. Most relevant to hyperglycemia is the glyoxalase pathway, which is responsible for the metabolism of reactive triose phosphate-derived 3-carbon intermediates such as methylglyoxal. Because methylglyoxal has been implicated in the formation of advanced glycation end products and diabetes complications (Beisswenger *et al*., 1999; Thornalley *et al*., 1999), the reduction of this dicarbonyl intermediate by NAC could not be excluded as an alternate possibility. They, therefore, utilized a second antioxidant, taurine, to determine whether hyperglycemia-induced insulin resistance was prevented. Taurine was chosen not only because it has been used as an antioxidant in a variety of settings (Hansen, 2001), but also because, whereas NAC can be utilized to generate GSH as well as taurine, the reverse pathway, i.e., taurine to cysteine, does not occur.

Another study in rats with NAC and Tau demonstrated to be effective against cisplatin-induced nephrotoxicity (Abdel-Wahab *et al*., 2017). The clinical use of cisplatin (CDDP) can be enhanced by using an adjunct therapy that counteracts its adverse side effects. It has been documented that NAC acts as a free radical scavenger, mitochondrial protectant, and inhibitor of lipid per-oxidation (LPO) and cellular necrosis. NAC also promotes liver detoxification by inhibiting xenobiotic biotransformation. It enhances many cellular defense mechanisms. Results illustrated a protective effect for both NAC and Tau when used individually. Furthermore, a combination of both was more efficient in attenuating CDDP-induced nephrotoxicity, which points to their synergistic protective effect.

Latest News of Taurine in Vaccine for Coronavirus

Taurine is also commonly used as pharmaceutical auxiliary material and is added to a drug formulation for strengthening the effect of major medicine, improving a lack of taurine for patients and enhancing cell protection. Chinese patent 201010505721.X discloses a strengthening effect of taurine on major medicines which are andrographolide and extract of *Hedyotis diffusa*. Chinese patent

application 201310072382.4 discloses a synergistic effect of taurine and the major medicine, interferon, for inhibiting activities of vesicular stomatitis virus as well as murine encephalomyocarditis virus and for a cell protection effect thereof. Besides, it has been formerly reported that a mixture of taurine, anthocyanidin and Aspirin can be used for the treatment of porcine reproductive and respiratory syndrome; and *astragalus* and taurine can lower a death rate of BALB/c mice with myocarditis induced by infection of Coxsackievirus B3. However, the earlier documents do not report that taurine is used for the prevention and/or treatment of diseases induced by viruses of the genus coronavirus, and especially do not report that taurine is used for prevention and treatment of the porcine viral diarrhea. The present invention provides the use of taurine in the prevention and/or treatment of diseases induced by viruses of genus coronavirus and/or genus rotavirus, for example, porcine epidemic diarrhea, porcine transmissible gastroenteritis, rotavirus diarrhea and the like (GENIFARM Laboratories Inc, 2020). Now it is possible to work with a novel vaccine with Tau for the pandemic of Coronavirus named COVID19 (European Patent Office, 2020).

Conclusions

Taurine supplementation has been demonstrated to have several beneficial effects on immune responses as anticancer and antiviral. The two presented cases demonstrate taurine such abilities and effectiveness. The positive effects definitively encourage improving its utilization in clinical practice and performing more clinical trials subsequently quick updates.

References

Abdel-Wahab WM, Moussa FI, Saad NA. Synergistic protective effect of N-acetylcysteine and taurine against cisplatin-induced nephrotoxicity in rats. *Drug Des Devel Ther* 2017; 11: 901–908.

Al-Asmari AK, Al-Zahrani AM, Khan AQ, Al-Shahrani HM, Ali Al Amri M. Taurine ameliorates 5-fluorouracil-induced intestinal mucositis, hepatorenal and reproductive organ damage in Wistar rats: A biochemical and histological study. *Hum Exp Toxicol* 2016; 35: 10-20.

Arnitz R, Stein M, Bauer P, Lanthaler B, Jamnig H, Scholl-Bürgi S, Stempfl-Al-Jazrawi K, Ulmer H, Baumgartner B, Embacher S, Geisler S, Gostner JM, Müllinger B, Kälz B, Nagl M. Tolerability of inhaled N-chlorotaurine in humans: a double-blind randomized phase I clinical study. *Ther Adv Respir Dis* 2018; 12: 1753466618778955.

Barua M, Liu Y, Quinn MR. Taurine chloramine inhibits inducible nitric oxide synthase and TNF-alpha gene expression in activated alveolar macrophages¨decreased NF-KappaB activation and IkappaB kinase activity. *J Immunol* 2001; 167: 2275-2281.

Beisswenger PJ, Howell SK, Touchette AD, Lal S, Szwergold BS. Metformin reduces systemic methylglyoxal levels in type 2 diabetes. *Diabetes* 1999; 48: 198-202.

Chen C, Yang Q, Ma X. Synergistic effect of ascorbic acid and taurine in the treatment of a spinal cord injury-induced model in rats. *3 Biotech* 2020; 10: 50.

Chorazy-Massalska M, Kontny E, Kornatka A, Rell-Bakalarska M, Marcinkiewicz J, Maslinski W. The effect of taurine chloramine on pro-inflammatory cytokine production by peripheral blood mononuclear cells isolated from rheumatoid arthritis and osteoarthritis patients. *Clin Exp Rheumatol* 2004; 22: 692-698.

Demarcay H. Ueber die Natur der Galle. *Ann Pharm* 1838; 27: 270-291.

Dong JF, Zheng XQ, Rui HB. Effect of taurine on immune function in mice with T-cell lymphoma during chemotherapy. *Asian Pac J Trop Med* 2017; 10: 1090–1094.

El Agouza IM, Eissa SS, El Houseini MM, El-Nashar DE, Abd El Hameed OM. Taurine: A novel tumor marker for enhanced detection of breast cancer among female patients. *Angiogenesis* 2011; 14: 321-330.

El Agouza IM, Eissa SS, El Houseini MM, El-Nashar DE, Abd El Hameed OM. Taurine: a novel tumor marker for enhanced detection of breast cancer among female patients. *Angiogenesis* 2011; 14: 321-330.

European Patent Office. Global Patent Index – EP 3246024 A1. Accessed at https://www.epo.org/searching-for-patents.html on March 23 of 2020,41

Fung SY, Lam JW, Chan KC. Clinical utility of circulating Epstein-Barr virus DNA analysis for the management of nasopharyngeal carcinoma. *Chin Clin Oncol* 2016; 5: 18.

GENIFARM Laboratories Inc. Jan 17, 2015. Use of taurine in prevention and/or treatment of diseases induced by viruses of genus coronavirus and/or genus rotavirus Accessed at https://patents.justia.com/patent/10314799 on March 23 of 2020.

Gottardi W, Hagleitner M, Nagl M. N, N-dichlorotaurine: chemical and bactericidal properties. *Arch Pharm (Weinheim)* 2005; 338: 473-483

Gupta RC and Kim SJ. Role of Taurine in organs' dysfunction and in their alleviation. *Crit Care and Shock* 2003; 6:171-177.

Gupta RC, Seki Y, Yosida J. Role of Taurine in Spinal cord injury, *Current Neuro Vascular Research* 2006; 3: 225-235.

Gupta RC, Win T, Bittner S. Taurine analogues, a new class of Therapeutic: Retrospect and Prospects. *Curr Med Chem* 2005; 12: 2021-2039.

Gupta RG. Is Taurine a Pharmaconutrient? Editorial. *Journal of Pharmacology and Therapeutic Research* 2018; 2: 18-20.

Haber CA, Lam TK, Yu Z, Gupta N, Goh T, Bogdanovic E, Giacca A, Fantus IG. N-acetylcysteine and taurine prevent hyperglycemia-induced insulin resistance *in vivo*: possible role of oxidative stress. *Am J Physiol Endocrinol Metab* 2003; 285: E744–E753.

Hala M Hatab, Fatma F. Abdel Hamid, Ahmed F. Soliman, Tamer A. Al-Shafie, Yahia M. Ismail, Motawa E. El-Houseini. A combined treatment of curcumin, piperine, and taurine alters the circulating levels of IL-10 and miR-21 in hepatocellular carcinoma patients: a pilot study. *J Gastrointest Oncol* 2019; 10: 766–776.

Hansen SH. The role of taurine in diabetes and the development of diabetic complications. *Diabetes Metab Res Rev* 2001; 17: 330-346.

He F, Ma N, Midorikawa K, Hiraku Y, Oikawa S, Mo Y, Zhang Z, Takeuchi K, Murata M. Anti-Cancer Mechanisms of Taurine in Human Nasopharyngeal Carcinoma Cells. *Adv Exp Med Biol* 2019; 1155: 533–541.

Huxtable RJ. Physiological actions of taurine. *Physiol Rev* 1992; 72: 101–163.

Islambulchilar M, Asvadi I, Sanaat Z, Esfahani A, Sattari M. Effect of taurine on attenuating chemotherapy-induced adverse effects in acute lymphoblastic leukemia. *J Cancer Res Ther* 2015; 11: 426-432.

Kim KS, Park EK, Ju SM, Jung HS, Bang JS, Kim C, Lee YA, Hong SJ, Lee SH, Yang HI, Yoo MC. Taurine chloramine differentially inhibits matrix metalloproteinase 1 and 13 synthesis in interleukin-1β stimulated fibroblast-like synoviocytes. *Arthritis Res Ther* 2007; 9, R80.

Kim T and Kim AK. Taurine enhances anticancer activity of cisplatin in human cervical cancer cells. *Adv Exp Med Biol* 2013; 776: 189-198.

Kusaczuk M. Tauroursodeoxycholate-Bile Acid with Chaperoning Activity: Molecular and Cellular Effects and Therapeutic Perspectives. *Cells* 2019; 8: 1471.

Liu D, Wang J, Liu M. Long noncoding RNA TUG1 promotes proliferation and inhibits apoptosis in multiple myeloma by inhibiting miR-29b-3p. *Biosci Rep* 2019; 39: BSR20182489.

Mangum C and Towle D. Physiological adaptation to unstable environments. *Am Sci* 1977; 65: 67-75.

Marcinkiewicz J and Kontny E. Taurine and inflammatory diseases. *Amino Acids* 2014; 46: 7-20.

Marcinkiewicz J, Biedroń R, Białecka A, Kasprowicz A, Mak M, Targosz M. Susceptibility of Propionibacterium acnes and Staphylococcus epidermidis to killing by MPO–halide system products. Implication for taurine bromamine as a new candidate for topical therapy in treating acne vulgaris. *Arch Immunol Ther Exp* 2006; 54: 61-68

Marcinkiewicz J, Chain B, Nowak B, Grabowska A, Bryniarski K, Baran J. Antimicrobial and cytotoxic activity of hypochlorous acid: interactions with taurine and nitrite. *Inflamm Res* 2000; 49: 280-289

Marcinkiewicz J, Grabowska A, Bereta J, Stelmaszynska T. Taurine chloramine a product of activated neutrophils inhibit *in vitro* the generation of nitric oxide and other macrophage inflammatory mediators. *J Leukoc Biol* 1995; 58: 667-674.

Nagl M, Hess MW, Pfaller K, Hengstler P, Gottardi W. Bactericidal activity of micromolar N-chlorotaurine: evidence for its antimicrobial function in the human defense system. *Antimicrob Agents Chemother* 2000; 44: 2507-2513

Nagl M, Lass-Flörl C, Neher A, Gunkel A, Gottardi W. Enhanced fungicidal activity of N-chlorotaurine in nasal secretion. *J Antimicrob Chemother* 2001; 47: 871-874

Nakajima Y, Osuka K, Seki Y, Gupta RC, Hara M, Takayasu M, Wakabayashi T. Taurine reduces inflammatory Responses after spinal cord injury. *Journal of Neurotrauma* 2010; 27: 403-410.

Neary PM, Hallihan P, Wang JH, Pfirrmann RW, Bouchier-Hayes DJ, Redmond HP. The evolving role of taurolidine in cancer therapy. *Ann Surg Oncol* 2010; 17: 1135-1143.

Park E, Quinn MR, Schuller-Levis G. Taurine chloramine attenuates the hydrolytic activity of matrix metalloproteinase-9 in LPS-activated murine peritoneal macrophages. *Adv Exp Med Biol* 2000; 483: 389-398.

Park E, Schuller-Levis G l, Jia JH, Quinn MR. Preactivation exposure of RAW 264.7 cells to taurine chloramine attenuates subsequent production of nitric oxide and expression of iNOS mRNA. *J Leukoc Biol* 1997; 61: 161-166.

Schaffer S and Kim HW. Effects and Mechanisms of Taurine as a Therapeutic Agent. *Biomol Ther* 2018; 26: 225-241.

Schuller-Levis GB and Park E. Taurine: new implications for an old amino acid, FEMS *Microbiology Letters* 2003; 226: 195–202,

Srivastava S, Roy R, Singh S, Kumar P, Dalela D, Sankhwar SN, Goel A, Sonkar AA. Taurine-a possible fingerprint biomarker in non-muscle invasive bladder cancer: A pilot study by 1H NMR spectroscopy. *Cancer Biomark* 2010; 6: 11-20.

Thornalley PJ, Langborg A, Minhas HS. Formation of glyoxal, methylglyoxal, and deoxyglucosone in the glycation of proteins by glucose. *Biochem J* 1999; 344: 109-116.

Tu S, Zhang X, WanH, Xia Y, Liu Z, Yang X, Wan F. Effect of taurine on cell proliferation and apoptosis human lung cancer A549 cells. *Oncology Letters* 2018; 15.4: 5473-5480.

Wu G. Important roles of dietary taurine, creatine, carnosine, anserine and 4-hydroxyproline in human nutrition and health. *Amino Acids* 2020; 52: 329–360.

Yazdanbakhsh M, Eckmann CM, Roos D. Killing of schistosomula by taurine chloramine and taurine bromamine. *Am J Trop Med Hyg* 1987; 37: 106–110

Yu JS and Kim AK. Effect of combination of taurine and azelaic acid on antimelanogenesis in murine melanoma cells. *J Biomed Sci* 2010; 17: S45.