CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/10680444

https://www.iajps.com/volumes/volume11-january-2024/63-issue-01-january-24/

Available online at: http://www.iajps.com *Review Article*

A REVIEW ARTICLE ON TRIAMTERENE DRUG – DIURETIC

M.Varalakshmi*[1], R.Jona Methusala[2]

[1]Student – Dr.K.V. Subbareddy Institute Of Pharmacy

[2]Associate Professor, Department Of Pharmacology, Dr.K.V. Subbareddy Institute Of Pharmacy

Abstract:

Triamterene is a potassium-sparing diuretic that has been in use since 1964. Triamterene is used by physicians who treat patients with fluid retention states secondary to conditions such as congestive heart failure, nephrotic kidney disease, liver cirrhosis, secondary hyperaldosteronism, or even merely idiopathic edema; all of which are FDA approved indications. When giving Triamterene in the combination dosage form with hydrochlorothiazide, other FDA-approved indications of use include the management of hypertension or the treatment of edema in patients who develop hypokalemia secondary to hydrochlorothiazide monotherapy. Of note, the use of Triamterene can also be indicated for overcoming diuretic resistance in patients on only one full dose of a diuretic; by combining two types of diuretics such as Triamterene with a loop diuretic, a diuretic synergism would successfully overcome the resistance and achieve the desired reduction in edema.

Triamterene (TA) is a mild 'potassium-sparing' diuretic usually employed in combination with other more potent diuretics in the treatment of hypertension. TA pharmacokinetics and pharmacodynamics in normal volunteers, elderly subjects and in patients with renal and hepatic dysfunction are reviewed. A variety of adverse renal effects, such as abnormalities in urinary sediment, nephrolithiasis, interstitial nephritis and acute renal failure, has been reported to occur and is also reviewed. Of particular concern with the increased availability of 'over-the-counter' nonsteroidal anti-inflammatory medications (NSAID) is the adverse interaction between TA and NSAID which may culminate in acute renal failure. Although a rare occurrence, the clinician should be aware of potential adverse reactions associated with the use of TA.

Corresponding author:

M.Varalakshmi,

Student,

Dr.K.V. Subbareddy Institute Of Pharmacy

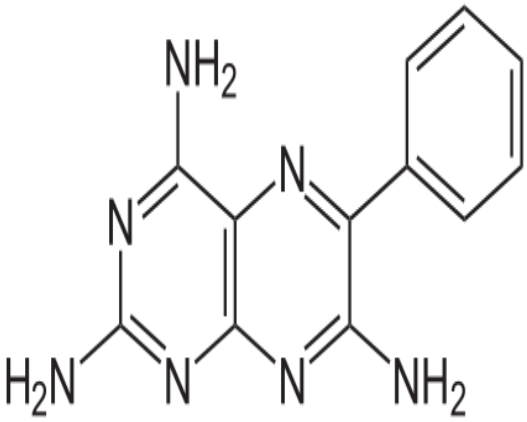
QR code

*Please cite this article in press M.Varalakshmi et al., **A Review Article On Triamterene Drug – Diuretic**, Indo Am. J. P. Sci, 2024; 11 (01).*

INTRODUCTION:

Triamterene (trade name Dyrenium among others) is a potassium-sparing diuretic often used in combination with thiazide diuretics for the treatment of high blood pressure or swelling. The combination with hydrochlorothiazide is known as hydrochlorothiazide/triamterene.

Triamterene



MECHANISM OF ACTION:

Triamterene
↓
Inhibit the sodium (Na) channel in the luminal membrane of the collecting Tubule and collecting duct
↓
Inhibit k secretion and facilitates H^+ ion secretion

HISTORY:

The Triamterene ring system is found in many naturally occurring compounds, such as folic acid and riboflavin. The observation that the naturally occurring compound xanthopterin had renal affects led scientists at **Smith Kline and French** Laboratories in Philadelphia to begin a medicinal chemistry campaign to discover potential drugs, as part of a program to discover potassium-sparing diuretics. The first clinical studies were published in 1961 and the first trials combining it with hydrochlorothiazide were published the next year.

Smith Kline & French launched it as a single agent under the brand Dyrenium in 1964-83 The combination drug with hydrochlorothiazide, Dyazide, was first approved in the US in 1965 and the first generic, brought by Bolar Pharmaceutical Co., was approved in 1987. In 1986 Dyazide was the most prescribed drug in the US and had $325 million in sales, making it SmithKline Beckman's second-biggest seller behind Tagamet.

The patents had expired on Dyazide in 1980, but complications arose with the introductions of generics, because the formulation of Dyazide resulted in variable batches that made it impossible for generic manufacturers to show that their versions were bioequivalent.

Bolar Pharmaceutical was in the running to be the first to bring a generic, but its application was delayed by these concerns about whether its formulation provided the same amount of each drug; these were complicated by accusations that Bolar had fraudulently substituted Dyazide for its own version to conduct studies that were submitted to the FDA.] Shortly after Bolar's generic was approved, further concerns were raised with regard to Bolar's applications to market generics more generally; these findings among others raised widespread concern among doctors and the public over whether generics were really the same as branded drugs. Bolar ended up recalling its generic form of Dyazide and withdrawing the product in 1990.In 1991 the US Justice Department on behalf of the FDA filed 20 criminal charges against Bolar for its fraud, and early the next year Bolar pled guilty and agreed to pay a $10M fine. Public concern over the safety of generic drugs was further exacerbated by a Congressional investigation into bribery at the FDA by generics companies that found pervasive corruption; the investigation had been spurred by the generics company Mylan, which had hired private investigators based on its beliefs that competitors were getting unfair advantages in getting their generics approved.

Mylan itself developed a version of a Triamterene/hydrochlorothiazide combination drug after the Dyazide patent expired, and used a different, more stable formulation as well as different dosages of each active ingredient (50 mg hydrochlorothiazide and 75 mg Triamterene, compared with Dyazide's 25 mg hydrochlorothiazide and 50 mg Triamterene) so it had to get approval as a new drug, as opposed to a generic; their product was called Maxzide and was approved in 1984.The higher dose allowed once per day dosing, which Mylan and its marketing partner, Lederle, believed would help it compete against Dyazide, which had $210M in sales in 1983.

Mylan's patents on the drug were declared invalid in court, and its marketing exclusivity expired in 1987, prompting a rush of generic competition and litigation by two of them, American Therapeutics Inc.

and Vitarine Pharmaceuticals, with the FDA.Vitarine, along with Par Pharmaceutical, were two of the companies that Mylan had targeted in its investigation into corruption and it turned out that Par and Vitarine had each used Mylan's Maxzide to obtain its bioequivalence data, leading both companies to withdraw its generic competitor to Mylan's product. Generics eventually entered the market.

DISCOVERY AND DEVELOPMENT:

- Triamterene was first synthesized and developed in the late 1950s by Merck & Co., Inc., a pharmaceutical company.
- The development of Triamterene was part of a broader effort to create effective diuretics to treat conditions characterized by fluid retention.

INVESTIGATION:

INVESTIGATION OF TRIAMTERENE AS AN INHIBITOR OF THE TGR5 RECEPTOR: IDENTIFIED IN CELLS AND ANIMALS:

G-protein-coupled bile acid receptor 1 (GPBAR1), also known as Takeda G-protein- coupled receptor 5 (TGR5), GPR131, or M-BAR, is a member of the membrane-boundG-protein-coupled receptor family. TGR5 is expressed throughout the body; it is expressed at high levels in the placenta and spleen but is expressed at lower levels in other tissues, such as the heart, liver, lung, stomach, kidney, gallbladder, intestine, brown adipose tissue, and endocrine glands. The wide distribution of TGR5 indicates that bile acids may have many unknown functions throughout the body.

Regarding signaling, TGR5 activation may induce cyclic adenosine monophosphate (cAMP) to activate protein kinase A, which can induce the transduction of down streams signaling. Therefore, TGR5 is known to regulate the lipid and glucose metabolism, energy homeostasis, and inflammation. TGR5 activation has also been reported to induce glucagon-like peptide-1 (GLP-1) secretion from cultured cells, including mouse enteroendocrine stanniocalcin-1 cells and human intestinal NCI-H716 cells.5 GLP-1 may reduce glucagon secretion and increase insulin secretion to decrease hyperglycemia through a glucose-dependent mechanism. Therefore, TGR5 agonists improve metabolic disorders in obese and insulin-resistant mice. Moreover, in addition to its role as a gastrointestinal and metabolic regulator, TGR5 also has important roles in the immune system. Therefore, many studies have focused on the applications of TGR5 agonists.

However, thepleiotropic effects of TGR5 activation may result in some adverse reactions, such as pruritus and inappropriate gallbladder filling. Moreover, TGR5 activation may promote cholangiocyte proliferation to increase the risk of cholangiocarcinoma. Recently, TGR5 was shown to be expressed in human gastric cancer, although this finding was controversial compared to data from a previous report. Therefore, questions remain regarding the essential role of TGR5 inhibition in clinical applications. However, TGR5 antagonists have not been developed, with the exception of DFN406, recently described antagonist.

Triamterene (6-phenyl-2, 4, 7-pteridinotriamine) is a widely used, mild diuretic that reduces potassium ion secretion to decrease the reabsorption of chloride ions in distal tubular cells. Blockade of Na+ channels with Triamterene May hyperpolarize the luminal membrane to reduce the K+,H+, Ca+ and Mg2+ excretion rates. Therefore, Triamterene is applied as a K+-sparing diuretic in the clinic. In addition, Triamterene is known to block the epithelial sodium channel on the luminal side of the collecting tubule in kidney. However, Triamterene has been shown to have other effects in addition to its K+-sparing effect as a treatment hypertension. Triamterene has also been described to be an inhibitor of vascular endothelial growth factor binding. Recently, a TGR5 agonist was found to relax the urinary bladder by inhibiting the opening of the Na+/Ca2+ exchanger (NCX). Therefore, we aimed to understand the effect of Triamterene on TGR5.

In the current study, we propose that Triamterene inhibits TGR5. CHO-K1 cells transfected with the TGR5 gene were used to investigate the effect of Triamterene on glucose uptake. The effects of Triamterene on calcium influx and signals induced by TGR5 activation were also examined inNCI-H716 cells. Furthermore, the effects of Triamterene on the blood glucose and GLP-1 levels were further characterized in streptozotocin (STZ)-induced diabetic rats administered with the TGR5 agonist.

MATERIALS AND METHODS:

Animals

Male Sprague–Dawley (SD) rats weighing 240–270 g were obtained from the National Laboratory Animal Center (Taipei, Taiwan) and maintained at the animal center of Chi Mei Medical Center. The animal experiments were approved by the Institutional Animal Ethics Committee (No 103120201) of Chi Mei Medical Center. Animal studies Were performed under anesthesia with sodium pentobarbital (35 mg/kg, ip) to minimize the animals suffering. All experiments conformed to the Guide for the Care and

Use Of Laboratory Animals and the guidelines of the Animal Welfare Act.

Induction of diabetes in rats:
A single intravenous (i.v.) injection of 65 mg/kg STZ (Sigma–Aldrich) was administered to rats to induce type 1-like diabetes. Animals were considered diabetic once their plasma glucose level reached $320 mg/dl in addition to presenting diabetic features. Studies were then started 2 weeks after the successful induction of diabetes.

Determination of blood glucose and GLP-1 levels in diabetic rats:
Diabetic rats were orally administered 5 mg/kg/day sita-gliptin (an inhibitor of DPP-4) or a vehicle for 14 days before treatment with the test substance. Blood samples Were obtained from the femoral vein of rats. The plasma glucose concentration was then measured using a glucose kit and an automatic analyzer (Quick-Lab, Ames; Miles, Inc., Elkhart, IN, USA). The plasma GLP-1 level was estimated using an enzyme-linked immunosorbent assay (ELISA).

Cell culture:
The human NCI-H716 cells and CHO-K1 cells were purchased from the Culture Collection and Research Center (BCRC) of the Food Industry Institute (Hsin-Chiu, Taiwan). Human NCI-H716 cells (BCRC No CCL-251) were cultured in RPMI 1640 medium containing 10% (v/v) fetal bovine serum (FBS) and 2 mM l-glutamine in the presence of 5% CO2. CHO-K1 cells (BCRC No CCL-61) were cultured in F-12K growth medium containing 10% FBS and The cells were subculture.

Transfection of TGR5 in CHO-K1 cells:
The CHO-K1 cells were transfected with the human GPBAR1 gene that had been cloned into an expression vector (pCMV6-Entry; OriGene, Rockville, MD, USA).

One day later, successful transfection was confirmed using Western blotting methods. The bands for TGR5 (32 kDa) denoted TGR5 expression, and β-actin (43 kDa) was used as an internal reference. Next, the TGR5–CHO-K1 cells were treated with the indicated concentrations of agonists, LCA or betulinic acid. The effectiveness of triamterene was also investigated using a 30 min pretreatment.

Determination of the calcium level:
We applied the fluorescent probe Fura-2 to examine the changes in intracellular calcium concentrations ([Ca2+] i). Briefly, NCI-H716 cells were incubated with 5 μ mol/LFura-2 before the treatment with the indicated concentrations of agonist. Moreover, in some experiments, the cells were incubated with triamterene for 30 min prior to the agonist treatment using the method shown in the Glucose uptake section. [Ca2+] i was then determined using the methods.

Results for above methods:

Effect of triamterene on TGR5 activation in TGR5–CHO-K1 cells:
We used Western blots to confirm that the TGR5 protein was expressed in CHO-K1 cells (Figure 1A). The TGR5 protein expressed in TGR5–CHO-K1 cells was functional. The direct effect of triamterene on the TGR5 was then investigated. After incubation with the agonists LCA (Figure 1B) or betulinic acid (Figure 1C), the 2-NBDG concentration was significantly increased in TGR5–CHO-K1 cells. Moreover, the increased intracellular 2-NBDG concentration was markedly reduced by triamterene in a dose-dependent manner. However, a 30 min pretreatment with KB-R7943 at a dose sufficient to block the NCX24 did not modify
The increase in the 2-NBDG levels induced by the agonists LCA or betulinic acid.

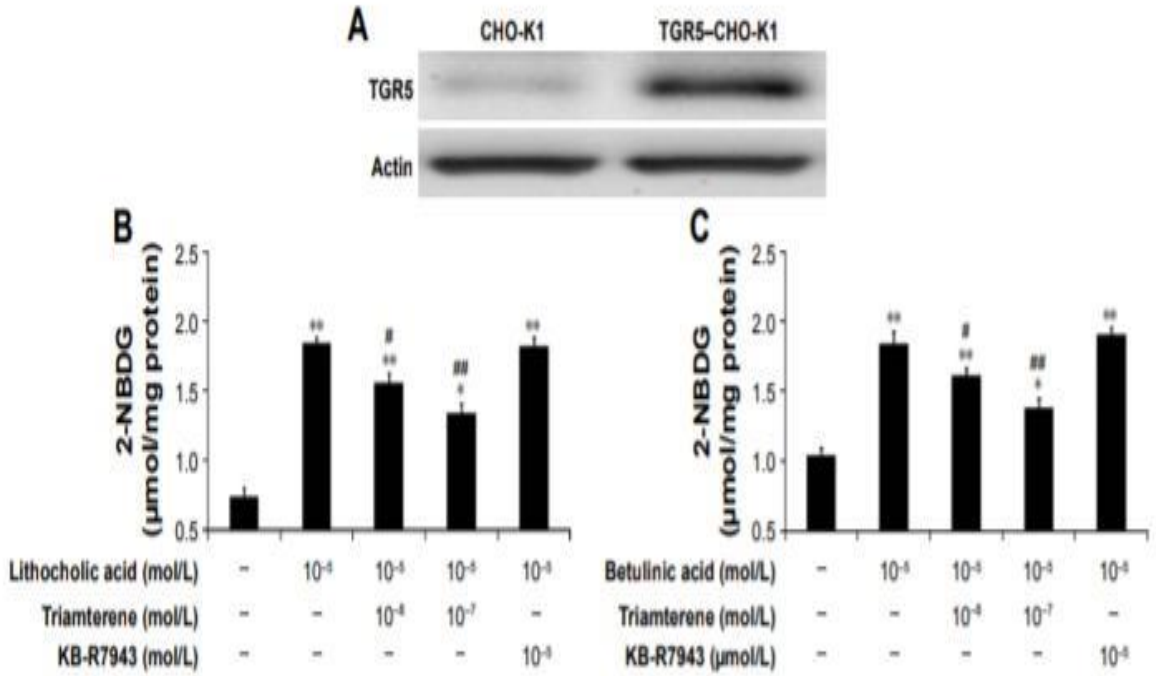


Fig1: Inhibitory effect of triamterene on glucose uptake induced by TGR5 agonist in TGR5 transfected cell.

Effects of triamterene on calcium influx induced by TGR5 activation in cultured NCI-H716 cells:

In general, the cultured NCI-H716 intestinal cell line has been widely used to study GLP-1 secretion. A TGR5 agonist-induced increase in GLP-1 secretion from NCI-H716 cells via calcium influx has been previously reported. NCI-H716 cells exhibited a dose-dependent increase in the calcium concentrations following treatment with the TGR5 agonists LCA and betulinic acid. Treatment with triamterene competitively inhibited the action of LCA in NCI-H716 cells (Figure 2A). Triamterene induced a similar competitive inhibition of the betulinic acid-induced changes in calcium concentrations in
NCI-H716 cells. (Figure 2B).

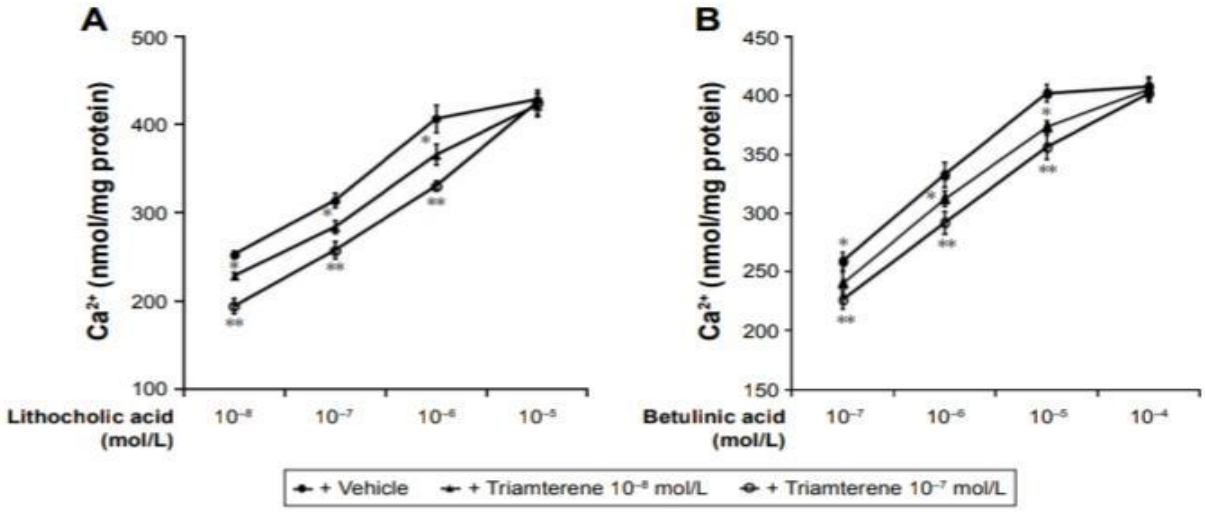


Fig 2: Inhibitory effect of triamterene on TGR5 agonist induced ca+ influx in NCI-H716cell

Effect of triamterene on plasma GLP-1 levels in diabetic rats:

Diabetic rats were orally administered 5 mg/kg/day sita-gliptin (an inhibitor of DPP-4) or a vehicle for 2 weeks before treatment with the testing substance. In STZ-induced diabetic rats, TGR5 agonists further increased the plasma GLP-1 levels induced by sita-gliptin at a dose sufficient to block DPP-4, as shown in Figure 4A and B. Triamterene dose-dependently attenuated the TGR5 agonist-induced increase in the GLP-1 levels (Figure 4A and B). Furthermore, TGR5 activation markedly attenuated the hyperglycemia in diabetic rats, and this action was also potentiated by the DPP-4 inhibitor sita-gliptin (Figure 5A and B). Therefore, the effects of TGR5 agonist's onGLP-1 secretion to decrease hyperglycemia in type 1-like diabetic rats seem to be markedly regulated by DPP-4, the GLP-1-inactivating enzyme. In addition, triamterene produced a dose-dependent reversion of these effects induced by TGR5 agonists. However, triamterene (50 mg/kg) alone did not modify the plasma glucose or GLP-1 levels in diabetic rats. Moreover, the plasma insulin levels in type 1-like diabetic rats (0.57±0.11 ng/L; n=8) were not modified (P.0.05) by LCA (0.56±0.08 ng/L; n=8) or betulinic acid (0.55±0.12 ng/L; n=8). Triamterene (50 mg/kg) alone did not modify the plasma insulin levels (0.58±0.08 ng/L; n=8) in these diabetic rats. Therefore, the TGR5 agonists do not appear to induce changes in insulin levels in type 1-like diabetic rats. Fig4: Effect of triamterene on plasma GLP-1 induced by TGR5 agonist in type-1like diabetes rat Fig4: Effect of triamterene on plasma GLP-1 induced by TGR5 agonist in type-1like diabetes rat.

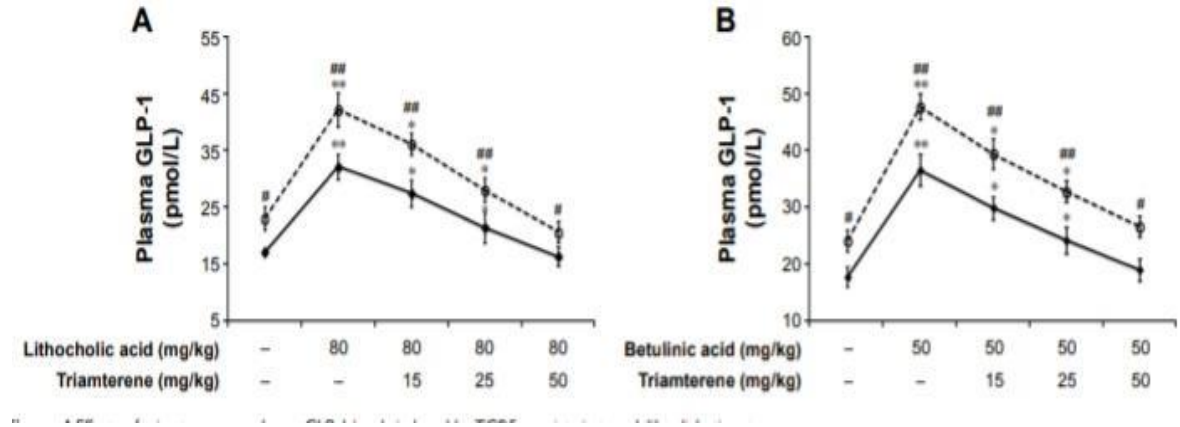


Fig4: Effect of triamterene on plasma GLP-1 induced by TGR5 agonist in type-1like diabetes rat

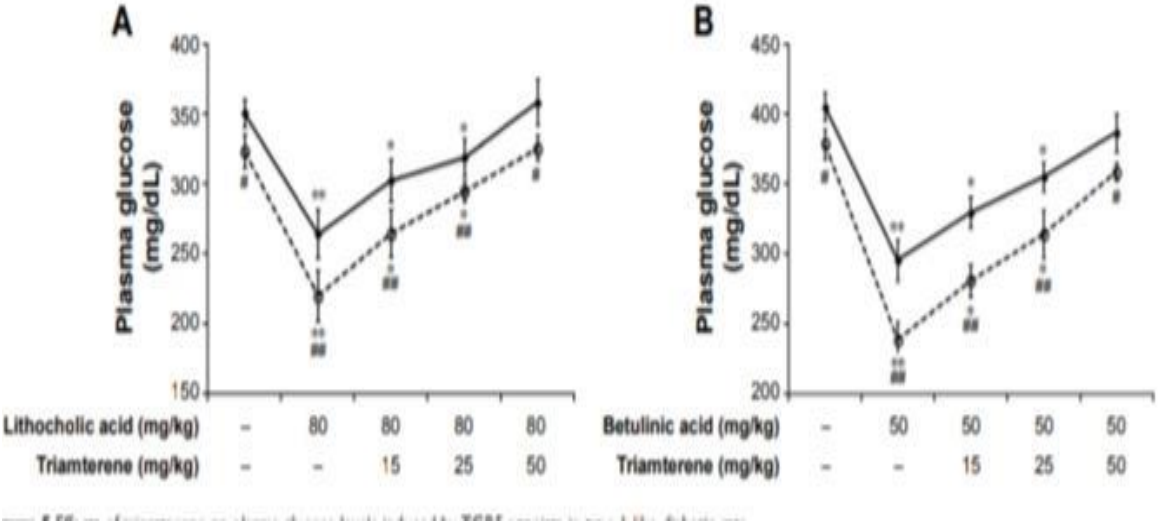


Fig5: Effect of triamterene on plasma glucose level induced by TGR5 agonist in type-1 like diabetes rat

NEW APPROACHES IN DRUG DISCOVERY:
INTRODUCTION:

Germ line mutations in DNA mismatch repair (MMR) genes, including MLH1, MSHβ, MSH6 and PMSβ can lead to Lynch Syndrome, an autosomal condition also known as hereditary non polyposis colorectal cancer (HNPCC)(1). Patients with this condition have an 80% lifetime risk of developing colorectal cancer and a 60% lifetime risk of developing endometrial cancer. In addition, patients are also at an increased risk of developing other cancers such as small bowel, pancreatic, prostate, urinary tract, liver, kidney, and bile duct cancer. Defects in the MMR system can also occur as a result of somatic mutations or epigenetic silencing. Significantly, it is thought that 15% of all colorectal cancers and γ0% of all endometrial cancers have loss of a functional MMR pathway (2, 3). Furthermore, mutations in the MMR gene, MSH6 have been identified inβ6-41% of temozolomide-resistant glioblastoma (GBM) patients and mediate temozolomide resistance (4-6). More recently, a number of studies have shown that a reduction in MMR protein levels, in particular MSHβ and MSH6, occurs upon GBM recurrence and that transcript levels of MMR genes are prognostic for patient survival after temozolomide treatment (6-8). Synthetic lethality with loss of DNA repair proteins has previously been successfully exploited (9-13). To date, a number of studies have identified synthetic lethal interactions with specific MMR gene mutations or specific tumor types (9, 10, 14, 15). In this study, we carried out drug-repositioning compound screens in a panel of MMR-deficient cellular models from a range of different tumor types, to identify drugs that sensitize with MMR loss in general. We identified the potassium-sparing diuretic drug, Triamterene as a novel therapeutic agent in MMR-deficient tumor cells. Our data suggest that the selectivity of Triamterene is based on its anti-folate activity and is dependent on expression of the folate synthesis enzyme, thymidylate synthase. Taken together, ourdata reveals that Triamterene is a promising novel therapeutic strategy for the treatment of MMR-deficient disease in a range of different tumor types.

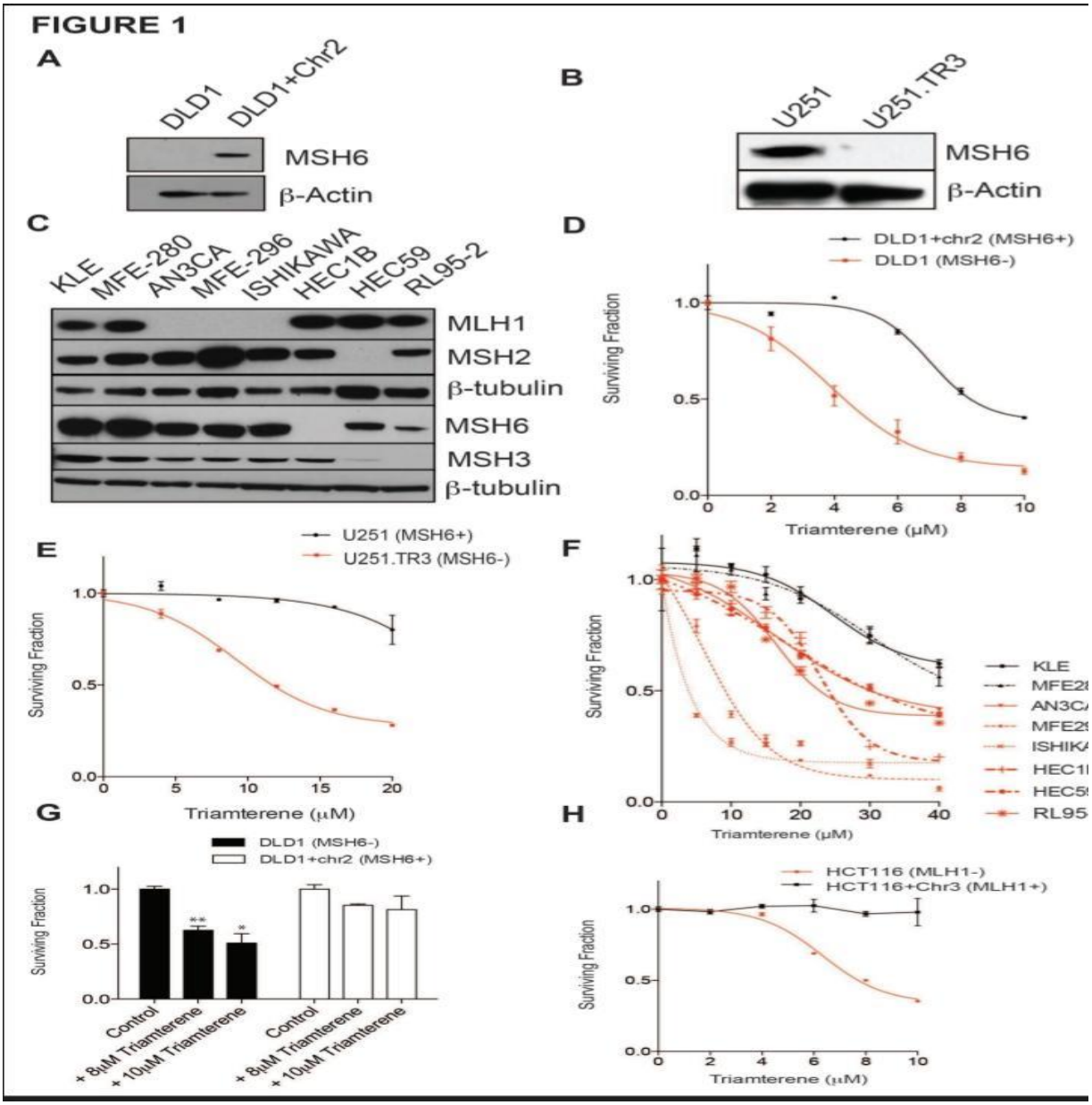
MATERIALS AND METHODS:
CELL LINES:

The Uβ51.TRγ GBM cell lines were a kind gift from Dr. David Louis (Massachusetts General Hospital, MA, USA). In the original paper (5), the nomenclature for these cell lines was A17β.TRγ. In a subsequent correction to the paper, this nomenclature was updated to Uβ51.TRγ (MSH6-) (16). We have STR profiled these cell lines and confirm they originate from Uβ51 cells. The Uβ51 (MMR+), MFE-β80 (MMR+), MFE-β96 (MLH1-), KLE (MMR+), ANγCA (MLH1-), HEC1B (MSH6-), RL95-β (MSHβ-, MSH6-, MSHγ-) and ISHIKAWA (MLH1-) cell lines were purchased from ATCC. The colorectal DLD1 (MSH6-) and DLD1+Chrβ (MMR+) cell lines and endometrial HEC59 (MSHβ-) cell lines were a kind gift from Dr. Thomas Kunkel (National Institute of Environmental Health Sciences). The human colon cancer cell line HCT116 (MLH1-) and HCT116+Chrγ (MMR+) were a kind gift from Dr. Alan Clark (NIEHS). DLD1 and DLD1+Chrβ cells were grown in RPMI (Sigma-Aldrich), 10% FBS and 1% penicillin-streptomycin at γ7 °C with 5% COβ. All other cell lines were grown in DMEM (Sigma-Aldrich), 10% FBS and 1% penicillin-streptomycin at γ7 °C with 5% COβ. DLD1+Chrβ and HCT116+Chrγ cells were maintained under selective pressure of 400 µg/ml geneticin (G418 sulfate, Roche). Uβ51.TRγ cells were maintained in 100 µM TMZ (Santa Cruz). All cell lines were authenticated on the basis of STR-profile, viability, morphologic inspection, and were routinely mycoplasma tested.

MMR deficiency increases the toxicity of triamterene in a range of tumor-derived
Cell lines

To identify compounds that can sensitize MMR-deficient cells, we screened a large Panel of cell lines with a range of different MMR gene mutations from a number of tumors Types. These included the MSH6-deficient colorectal cancer cell line DLD1 and its Isogenic MSH6-proficient DLD1+Chrβ cell line (Figure 1A), the previously characterized Temozolomide-resistant MSH6-deficient Uβ51.TRγ GBM cell line and the isogenic MSH6-proficient Uβ51 cell line (Figure 1B; (5, 16)) and a panel of endometrial cancer cell lines; KLE (MMR-proficient), MFE-β80 (MMR-proficient), MFE-β96 (MLH1-deficient), ISHIKAWA (MLH1-deficient) and HEC1B (MSH6-deficient; Figure 1C) Based on the concept of drug repositioning, of identifying previously approved compounds for new clinical indications, cells were screened in the presence of either vehicle (DMSO) or a compound library comprising 1018 FDA-approved drugs. This approach aimed to identify compounds with previous unknown potential for repurposing as MMR-selective drugs. Analysis of our screens revealed that the potassium-sparing diuretic compound, Triamterene was a promising candidate for a new MMR-selective drug. Validation experiments revealed that, although the sensitization was variable depending on the MMR-defect, however when compared to the MMR-proficient cells, treatment with Triamterene induced toxicity over a range of concentrations specifically in

MMR-deficient cells (Figure 1D-F). Triamterene also caused sensitivity in MMR-deficient cells, in comparison to MMR-proficient cells, in a clonogenic survival assay (Figure 1G). To further investigate this selectivity for MMR deficiency, we measured cell viability of the MLH1-deficient colorectal cancer cell line HCT116 and its isogenic matched-paired MLH1-proficient cell line, HCT116+Chrγ when treated with Triamterene (Figure 1H). Significantly, Triamterene also induced selectivity in the MLH1-deficient HCT116 cells, but not in MLH1-proficient cells. Significantly, we observed selectivity in all MM deficient cell lines tested, regardless of MMR mutation or tumor type, while no significant effect was observed in MMR-proficient cells. This suggests that Triamterene is selective with loss of MMR pathway function and may provide a novel therapeutic strategy in a wide range of cancers.



CPCSEA GUIDELINES FOR THE CARE AND USE OF LABORATORY ANIMALS:

GOAL

The goal of these Guidelines is to promote the humane care of animals used in biomedical and behavioral research and testing with the basic objective of providing specifications that will enhance animal well-being, quality in the pursuit of advancement of biological knowledge that is relevant to humans and animals.

VETERINARY CARE

Adequate veterinary care must be provided and is the responsibility of a veterinarian or a person who has training or experience in laboratory animal sciences and medicine. Daily observation of animals can be accomplished by someone other than a veterinarian; however, mechanism of direct and frequent communication should be adopted so that timely and accurate information on problems in animal health, behavior, and well-being is conveyed to the attending veterinarian. The veterinarian can also contribute to the establishment of appropriate policies and procedures for ancillary aspects of veterinary care, such as reviewing protocols and proposals, animal husbandry and animal welfare; monitoring occupational health hazards containment, and zoonosis control programs and supervising animal nutrition and sanitation. Institutional requirements will determine the need for full-time or part-time or consultative veterinary services.

QUARANTINE, STABILIZATION AND SEPARATION

Quarantine is the separation of newly received animals from those already in the facility until the health and possibly the microbial status of the newly received animals have been determined. An effective quarantine minimizes the chance for introduction of pathogens into an established colony. A minimum duration of quarantine for small lab animals is one week and large animals is 6 weeks (cat, dog and monkey) Effective quarantine procedures should be used for non-human primates to help limit exposure of humans zoonotic infections. Regardless of the duration of quarantine, newly received animals should be given a period for physiologic, psychological and nutritional stabilization before their use. The length of time stabilization will depend on the type and duration of animal transportation, the species involved and the intended use of the animals. Physical separation of animals by species is recommended to prevent interspecies disease physiological and behavioral changes due to interspecies conflict. Such separation is usually accomplished by housing different species in separate rooms; however, cubicles, laminar-flow units, cages that have filtered air or separate ventilation, and isolators shall be suitable alternatives. In some instances, it shall be acceptable to house different species in the same room, for example, if two species have a similar pathogen status and are behaviorally compatible.

SURVEILLANCE, DIAGNOSIS, TREATMENT AND CONTROL OF DISEASE

All animals should be observed for signs of illness, injury, or abnormal behavior by animal house staff. As a rule, this should occur daily, but more-frequent observations might be warranted, such as during postoperative recovery or when animals are ill or have a physical deficit. It is imperative that appropriate methods be in place for disease surveillance and diagnosis (Annexure 1 and 2).Unexpected deaths and signs of illness, distress, or other deviations from normal health condition in animals should be reported promptly to ensure appropriate and timely delivery of veterinary medical care. Animals that show signs of a contagious disease should be isolated from healthy animals in the colony. If an entire room of animals is known or believed to be exposed to an infectious agent (e.g., Mycobacterium Tuberculosis in non-human primates), the group should be kept intact and isolated during the process of diagnosis, treatment, and control. Diagnostic clinical laboratory may be made available.

ANIMAL EXPERIMENTATION INVOLVING HAZARDOUS AGENTS

Institutions should have policies governing experimentation with hazardous agents. Institutional Biosafety Committee whose members are knowledgeable about hazardous agents are in place in most of the higher level education, research institutes and in many pharmaceutical industries for safety issues. This committee shall also examine the proposal on animal experiments involving hazardous agents in addition to its existing functions (Annexure– 8).Since the use of animals in such studies requires special consideration, the procedures and the facilities to be used must be reviewed by both the Institutional Biosafety Committee and Institutional Animal Ethics Committee (IAEC).

DURATIONS OF EXPERIMENTS

No animal should be used for experimentation for more than 3 years unless adequate justification is provided.

PHYSICAL RESTRAINT

Brief physical restraint of animals for examination, collection of samples, and a variety of other clinical and experimental manipulations can be accomplished

manually or with devices be suitable in size and design for the animal being held and operated properly to minimize stress and avoid injury to the animal. Prolonged restraint of any animal, including the chairing of non-human primates, should be avoided unless essential to research objectives. Less restrictive systems, such as the tether system or the pole and collar system, should be used when compatible with research objectives. The following are important guidelines for the use of restraint equipments: Restraint devices cannot be used simply as a convenience in handling or managing animals. The period of restraint should be the minimum required to accomplish the research objectives. Animals to be placed in restraint devices should be given training to adapt to the equipment. Provision should be made for observation of the animal at appropriate intervals. Veterinary care should be provided if lesions or illness associated with restraint are observed. The presence of lesions, illness, or severe behavioral change should be dealt with by the temporary or permanent removal of the animal from restraint.

PHYSICAL FACILITIES

(a:) Building materials should be selected to facilitate efficient and hygienic operation of animal facilities. Durable, moisture-proof, fire-resistant, seamless materials are most desirable for interior surfaces including vermin and pest resistance.

(b) Corridor(s): should be wide enough to facilitate the movement of personnel as well as equipments and should be kept clean.

(c) Utilities: such as water lines, drain pipes and electrical connections should preferably be accessible through service panels or shafts in corridors outside the animal rooms.

(d) Animal room: doors should be rust, vermin and dust proof. They should fit properly within their frames and provided with an observation window. Door closures may also
be provided. Rodent barriers can be provided in the doors of the small animal facilities.

(e) Exterior windows: Windows are not recommended for small animal facilities. However, where power failures are frequent and backup power is not available, they may be necessary to provide alternate sources of light and ventilation. In primate rooms, windows can be provided.

(f) Floors: Floors should be smooth, moisture proof, nonabsorbent, skid-proof, resistant to wear, acid, solvents, adverse effects of detergents and disinfectants. They should be capable of supporting racks, equipment, and stored items without becoming gouged, cracked, or pitted, with minimum number of joints. A continuous moisture-proof membrane might be needed. If sills are installed at the entrance to a room, they should be designed to allow for convenient passage of equipment.

(g) Drains: Floor drains are not essential in all rooms used exclusively for housing rodents. Floor in such rooms can be maintained satisfactorily by wet vacuuming or mopping with appropriate disinfectants or cleaning compounds. Where floor drains are used, the floors should be sloped and drain taps kept filled with water or corrosion free mesh. To prevent high humidity, drainage must be adequate to allow rapid removal of water and drying of surfaces.

(h) Walls and ceilings: Walls should be free of cracks, unsealed utility penetrations, or imperfect junctions with doors, ceilings, floors and corners. Surface materials should be capable of withstanding scrubbing with detergents and disinfectants and the impact of water under high pressure.

PRE-CLINICAL STUDY:

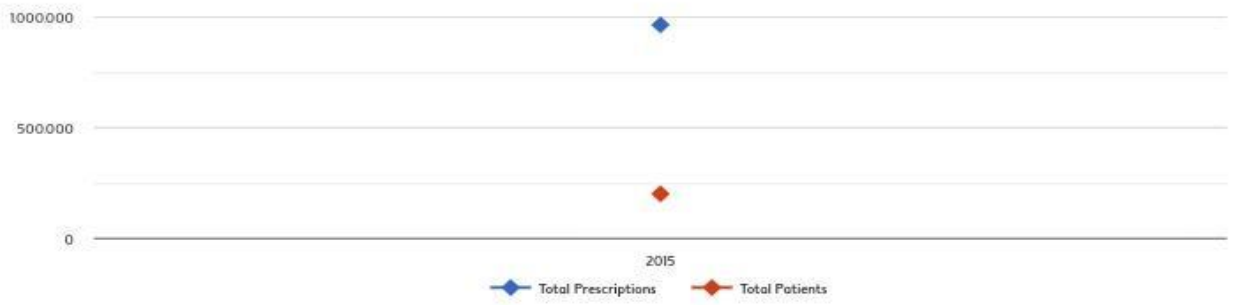
Intact and adrenalectomized rats were subjected to a five-day treatment with triamterene in a daily dose of 1.5 mg/100 g body weight. Triamterene was also administered to a group of intact, salt-loaded, rats. The activity of Na-K-ATP-ase in the kidney plasma membranes of intact and adrenalectomized rats treated with triamterene was decreased by 22.4% (p less than 0.05) and 37.2% (p less than 0.05), respectively. The activity of Na-K-ATP-ase in the renal plasma membranes of intact, salt-loaded, rats underwent greater decrease--63% (p less than 0.05). If the decreased activity of Na-K-ATP-ase in the kidney plasma membranes of rats treated with triamterene manifested the diuretic action of triamterene, results obtained in adrenalectomized rats would suggest that triamterene acts directly on the kidney, not via the adrenal glands.

BIOSTATISTICS DATA:

Triamterene Summary for 2020:

Top drug rank	#0 (0)
Estimated number of prescriptions in the United States (2020)	0
Estimated number of patients in the United States (2020)	0
Average total drug cost (USD)	
Per prescription	$0.00
Per day of therapy	$0.00/day
Average out-of-pocket cost (USD)	
Per prescription	$0.00
Per day of therapy	$0.00/day

Total Prescriptions and Patients Per Year (2013 - 2020):



FDA approval information:

Established Pharmacologic Class (EPC):	Potassium-sparing Diuretic
Initial FDA approval date:	Prior to January 1, 1982
First FDA applicant:	Rx
First dosage form:	Capsule (oral)

REFERENCES:

1. Chakravarty R, Samanta K, Mandal P, Karmakar S. Mechanism of action of diuretic and anti-diuretic drugs. In How Synthetic Drugs Work 2023 Jan 1 (pp. 369-390). Academic Press.
2. Li Y, Cheng KC, Niu CS, Lo SH, Cheng JT, Niu HS. Investigation of triamterene as an inhibitor of the TGR5 receptor: Identification in cells and animals. Drug design, development and therapy. 2017 Apr 5:1127-34.
3. Guillotin D, Austin P, Begum R, Freitas MO, Merve A, Brend T, Short S, Marino S, Martin SA. Drug-repositioning screens identify Triamterene as a selective drug for the treatment of DNA Mismatch Repair deficient cells. Clinical Cancer Research. 2017 Jun 1; 23(11):2880-90.
4. Fiori J, Ballardini R, Andrisano V, Cavrini V. Photostability studies on the furosemide–triamterene drug association. IL farmaco. 2003 Sep 1; 58(9):867-73.
5. Sica DA, Gehr TW. Triamterene and the kidney. Nephron. 1989 Dec 9; 51(4):454-61.
6. Gilfrich HJ, Kremer G, Möhrke W, Mutschler E, Völger KD. Pharmacokinetics of triamterene after iv administration to man: determination of bioavailability. European journal of clinical pharmacology. 1983 Aug; 25:237-41.
7. Gines JM, Arias MJ, Holgado MA, Arevalo MF, Rabasco AM. Dissolution rate study of fresh and aging triamterene-urea solid dispersions. Drug development and industrial pharmacy. 1994 Jan 1; 20(17):2729-40.
8. Hip UT. L ong-term use of the photosensitizing antihypertensive drugs, hydro-chlorothiazide, combined hydrochlorothiazide-triamterene, and nifed. ARCH INTERN MED. 2012 Sep 10; 172(16).
9. Darken M, McBurney EI. Subcutaneous lupus erythematosus-like drug eruption due to combination diuretic hydrochlorothiazide and triamterene. Journal of the American Academy of Dermatology. 1988 Jan 1; 18(1 Pt 1):38-42.
10. Vargas F, Fuentes A, Sequera J, Méndez H, Fraile G, Velásquez M, Medina R. In Vitro Approach to investigating the phototoxicity of the diuretic drug triamterene. Toxicology in vitro. 1998 Dec 1; 12(6):661-7.