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Niclosamide: over an antithelminitcs drug

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ABSTRACT: Niclosamide is an oral anthelmintic drug used to treat parasitic infections in millions of people worldwide. However recent studies have indicated that niclosamide may have broad clinical applications for the treatment of diseases other than those caused by parasites. These diseases and symptoms may include cancer, bacterial and viral infection, metabolic diseases such as Type II diabetes, NASH and NAFLD, artery constriction, endometriosis, neuropathic pain, rheumatoid arthritis, sclerodermatous graft-versus-host disease, and systemic sclerosis. Among the underlying mechanisms associated with the drug actions of niclosamide are uncoupling of oxidative phosphorylation, and modulation of Wnt/β-catenin, mTORC1, STAT3, NF-κB and Notch signaling pathways. Here we provide a brief overview of the biological activities of niclosamide, its potential clinical applications, and its challenges for use as a new therapy for systemic diseases.

Keywords- Niclosamide, Parasitic Infection, Endometriosis, Sclerodermatous, Arthritis.

I. INTRODUCTION

Niclosamide is an FDA approved anthelmintic drug. It is highly effective drugs against cestodes infecting man-taenia saginata.solium phyllobothrium and hymenolepis nana, as well as pinworm (enterobius) to treat the tapeworm infection in humans and others animal the drugs appears to act by inhibiting oxidative phosphorylation in the mitochondria and interfering with anaerobic generation of ATP by the tapeworm[1,2,3]. Injured by niclosamide, recently, this drugs is demonstrated beneficial effect against obesity-related type 2 diabetes through the same mechanism in the mitochondria of the mouse liver Niclosamide was discovered in the. Bayer chemotherapy research laboratories in 1953 [4,5]. It was originally developed as a molluscicide to kill snails, an intermediate host of schistosomiasis, and was marketed as Bayluscide in 19591. In 1960, scientists at Bayer found it to be effective against human tapeworm (cestoda)Niclosamide (trade name Niclocide), a teniacide in the antihelminthic family which is especially effective against cestodes, has been approved for use in humans for nearly 50 yearsNiclosamide inhibits oxidative phosphorylation and stimulates adenosine triphosphatase activity in the mitochondria of cestodes (e.g. tapeworm), killing the scolex and proximal segments of the tapeworm both in vitro and in vivo. Niclosamide is well tolerated in humans [6,7,8]. The treatment of Taenia Saginata (beef tapeworm), Diphyllobothriumlatum (fish tapeworm) and Dipylidium Caninum (dog tapeworm) in adult is 2 g as a single oral dose.Further treatment of Hymenolepisnana (dwarf tapeworm), the same oral dose is used for 7 days**.** It is available mainly as two types of dosage forms, tablets and suspensions. Suspensions are mainly used for animals, especially cattle and sheep[9,10]. The biggest problem with the formulation of niclosamide suspensions is that the anhydrous crystal form has an affinity for water and as such, onhydration**,**. Recently, several groups have independently discovered that niclosamide is active against cancer cells, though its precise mechanism of antitumor action is not fully understood. Accumulating evidence suggests that niclosamide targets multiple signalling pathways such as nuclear factor kappa B (NFκB), Wnt/β -catenin, and Notch, most of which are closely

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involved with cancer stem cell proliferation[11,12].Colorectal cancer is the second leading cause of cancer-related deaths in the United States Current chemotherapy regimens do not target one of the most important underlying pathological mechanisms: the Wnt signaling pathway Severe Acute Respiratory Syndrome (SARS) is a respiratory illness caused by the infection of Severe Acute Respiratory Syndrome coronavirus (SARS-Cove)(1-2)[13,14]. The major symptoms of SARS are hyperpyrexia, chilling, cough and dyspnea Vascular endothelial cells play an important role in the regulation of vascular tone, vascular permeability, angiogenesis and vascular inflammatory response Angiogenesis is the process of forming new blood vessels from an existing vascular bed and is a fundamental component of normal developmental processes such as reproduction, pregnancy and wound healing, but it is also involved in pathologic processes such as inflammation, tumour growth and metastasi[15,16] .Niclosamide has shown antiproliferative activity in a broad spectrum of cancer cells including hematologic cancer cells (e.g., acute myeloid leukemia, AML) and solid tumor cells (e.g., colon cancer, breast cancer, and prostate cancer[17,18].

CHEMISTRY OF NICLOSAMIDE

Niclosamide [2', 5-dichloro-4'-nitrosalicylic is a parasiticide drug widely used in Mexico to treat human and animal helminthiasis.Structurally, niclosamide belongs to a large group of lipophilic, weakly-acidic molecule1 It is practically insoluble in water soluble in 150 of ethanol 1 in 400 of chloroform ,and in 350 of either ,sparingly soluble in acetone[19,20].

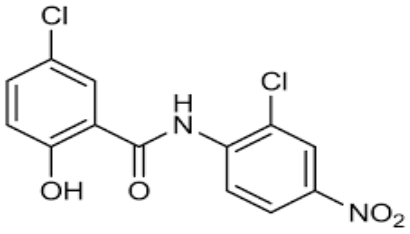

Fig-1Niclosamide

Niclosamide is a salicylanilide with anticestodal activity that was discovered in 1958. Ii was the drug-of-choice before the discovery of praziquantel. As part of our drug discovery program, we decided to examine at the potential of this drug commercially available salicylic acids and anilines were coupled in hot xylenes in the presence of PCl3 to furnish niclosamide analogues R1–R4 substituents are defined in Fig. 2, 3, and 4 [21,22,].

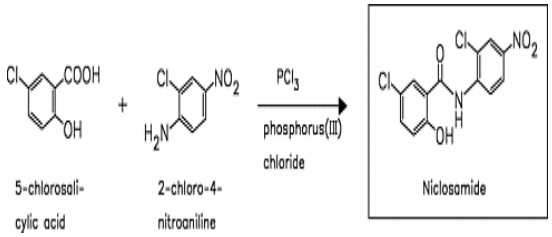

Fig- 234

PHARMACOLOGICAL ACTION OF NICLOSAMIDE

ANTHELMINTIC ACTIVITY

Niclosamide is the second drugs of choice for D.latum, T.saginata, and H.nana it is poorly absorbed from the GIT tract .it inhibits the oxidative phosphorylation on the mitochondria of the parasite and rapidly kills adult worms. It binds to β-Tubulin and inhibits microtubule polymerization .It also blocks glucose transport into the parasite that reason intestinal parasites are immobilized or die slowly[23,24,25].

PHARMACOLOGY- NIclosamide has many pharmacological and biochemical actions.

Multiple pathway inhibitor for anti-cancer efficacy Niclosamide on multiple intracellular signaling pathway the signaling molecules in these pathway are either over expressed, constitutively active or mutated in many cancer cells and thus render niclosamide as a potential anticancer agent the effect of niclosamide on these pathways are described below the Wnt/β-catenin signaling pathway regulates cancer progression including tumor initiation, tumor growth, cell senescence, cell death. The rapid development of new anticancer drugs that are safe and effective is a common goal shared by basic scientists, clinicians and patients[26,27,28]. The

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current review discusses one such agent, namely niclosamide, which has been used in the clinic for the treatment of intestinal parasite infections [29,30]. Recent studies repeatedly identified niclosamide as a potential anticancer agent by various high-throughput screening campaigns. Niclosamide not only inhibits the Wnt/b-catenin, mTORC1, STAT3, NF-jB and Notch signaling pathways, but also targets mitochondria in cancer cells to induce cell cycle arrest[31,32],growth inhibition and apoptosis. A number of studies have established the anticancer activities of niclosamide in both in vitro and in vivo models .Activation of either the serine/threonine protein kinase Akt (also known as protein kinase B or PKB) or the extracellular signal-regulated kinase (ERK) pathway, or inhibition of the adenosine monophosphate activated protein kinase (AMPK) pathway, leads to activate mTORC1 signaling[33,34]. As downstream effectors of Akt, mTORC1 has been described as the most essential effectors in driving cell proliferation and susceptibility to oncogenic transformation. This leads to the targeting of mTORC1 as a therapeutic strategy in many types of cancer [35,36].

Treat the ovarian cancer Niclosamide FDA approved salicylamide used for the Niclosamide is the potent Wnt/β Catenin inhibitor target the Wnt/β Catenin pathway lead to cellular-proliferation and increase the call death these finding warrant further research of this drugs and other niclosamide analogs as a treatment option for ovarian cancer. Patients as citestum or spheres were thawed and incubated overnight at 37 °C in X-vivo media Tumorspheres were dissociated in 500 µL of Accutase (Innovative Cell Technologies, San Diego, CA) to achieve 80% single cell suspension. To measure cells with high aldehyde dehydrogenase (ALDH) activity, the aldefluor assay (StemCell Technologies, Durham, NC) was performed according to the manufacturer's protocol. After staining, cells were washed with Hanks' Balanced Salt solution (HBSS) (Sigma-Aldrich) and resuspended in a 200 µL ALDEFLUOR buffer and then stained for CD133 for 30 minutes on ice. All samples were analyzed on an LSRII flow cytometer (BD Biosciences)[37,38].

Treat the breast cancer is a leading cause of death in women 10. Development of new therapies will be necessary to reduce mortality. Lu et al. reported that niclosamide inhibits Wnt/β-catenin signaling by promoting Wnt co receptor LRP6 degradation in breast cancer cells 11. Subsequently this group reported that niclosamide acts synergistically with a monoclonal antibody that specifically activates TRAIL death receptor 5 to inhibit tumor growth of basal-like breast cancers Fonseca et al. reported that Niclosamide inhibits mTORC1 signaling inMCF-7 breast cancer cells[39,40]. Mechanistic studies indicated Niclosamide lowered the cytoplasmic pH and may indirectly lead to inhibition of mTORC1 signaling. Niclosamide also was found to prevent the conversion of non-breast cancer stem cells into cancer stem cells. This mechanism is associated with inhibition of the IL6- JAK1-STAT3 signal transduction pathway. Identified niclosamide as a potent STAT3 inhibitor, suppressing STAT3 transcriptional activity, using a cell-based STAT3-dependent dual luciferase reporter assay[41,42]. used a high-throughput drug screen using breast cancer spheroid growth and found out that niclosamide inhibited the formation of breast cancer spheroids and induced apoptosis in breast cancer spheroids in vitro and tumor growth in vivo 16. Karakas et al. reported that niclosamide enhanced the antitumor activity of palladium(II) saccharinate complex of terpyridine, leading to enhanced cytotoxic activity in breast cancer stem cells[43,44] . Triple-negative breast cancer is defined by the lack of expression of estrogen receptor and progesterone receptor, and lack of HER2 amplification, accounts for about 15% breast cancers and lacks effective therapies reported that niclosamide inhibits ionizing radiation-induced Wnt/β-catenin signaling in triple negative breast cancer cells in vitro and in vivo niclosamide alone or in combination with cisplatin represses the growth of xenografts of cisplatin-resistant triple-negative breast cancer cells. reported that niclosamide reversed the epithelial-to-mesenchymal transition phenotype, inhibited Akt, ERK, and Src signaling pathways, and inhibited the proliferation of both cisplatin-sensitive (CS) and cisplatin resistant (CR) triple-negative breast cancer 231 cells in vitro. Niclosamide alone or in combination with cisplatin also could repress the

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growth of xenografts in mice bearing either 231-CS or 231-CR cells[45,46].

Inhibiting the inflammatory and angiogenic activation-Niclosamide is known to have anti-cancer and anti-inflammatory activities Niclosamide also suppresses VEGF-induced angiogenesis in vivo. Niclosamide attenuated IKK-mediated activation of NF-jB pathway in TNFa-induced endothelial cells. It is a based on mechanisms in the treatment of various diseases, including rheumatoid arthritis and cancer .Niclosamide reduces the adhesion of human monocyte cells to HUVECs. Niclosamide also reduced protein expression of VCAM-1 and ICAM1 in HUVECs. Niclosamide significantly inhibited HUVEC proliferation, migration and cord-like structure formation. Niclosamide also suppresses VEGF-induced angiogenesis in vivo. Niclosamide attenuated IKK-mediated activation of NF-Jb pathway in TNFa-induced endothelial cells. Niclosamide also suppresses VEGF-induced endothelial VEGFR2 activation and downstream P-AKT, P-mTOR and P-p70S6K[47,48].

Niclosamide use in psoriasis like skin inflammation-Psoriasis is a debilitating chronic skin disease characterized by inflamed, sharply demarcated, erythematous plaques with epidermal hyperproliferation, hyperkeratosis, parakeratosis, dermal capillaries dilation, and infiltration inflammatory cells. Terminal deoxy-nucleotidyl transferase- mediated dUTP nick- end labeling (TUNEL) assay was used to measure the apoptotic cell death quantitatively. To perform the assay, cells were cultured in co focal chamber slides (Eppendorf, Germany) and treated withNCL followed by EGF stimulation after 2 hr, and incubated for 24 hr, and then cells were fixed with 4% paraformaldehyde. After washing with PBS, the cells were treated with proteinase K (20 μg/ml in PBS) for 15 min at 37°C and processed using a FragEL™ DNAFragmentation Detection Kit, Fluorescent- Tat Enzyme (MerckMillipore) according to the manufacturer's instructions. The cells were then counter- stained with DAPI. The images were captured by Leica TCS SP8 Laser Scanning Spectral Confocal Microscope, Germany at ×400 magnification[49,50].|

Prostate cancer-Nearly 30,000 American men die as a result of their prostate cancer each year Since the1940s, the treatment of advanced prostate cancer has focused almost exclusively on inhibiting the androgen receptor (AR)-signaling program Indeed, over the past decade it has been discovered that even in men with castration-resistant prostate cancer (CRPC) Niclosamide, an FDA-approved anti-helminthic drug, has activity in preclinical models of castration-resistant prostate cancer (CRPC). Potential mechanisms of action include degrading constitutively active androgen receptor splice variants (AR-Vs) or inhibiting other drug-resistance pathways (e.g.Wnt-signaling)Several mechanisms of resistance to next-generation AR-directed therapies have been described, including: i) activation of canonical AR-signaling through AR amplification, AR overexpression and/or maintenance of intratum oral androgens; ii) AR-signaling activation via feedback pathways (e.g. AKT/mTOR/Pi3K, NF-κB, Wnt/β-catenin); and iii) activation of the AR program via mutations (e.g. AR ligand binding domain mutation) or AR substitutions (e.g. AR splice variants; Glucocorticoid Receptor-signaling Of these mechanisms, the emergence of alternatively spliced AR variants (AR-Vs), which maintain constitutive activity in spite of lacking the AR ligand-binding domain, has received substantial attention. Inhibiting AR-V activity has been shown to be an effective strategy in preclinical models and the emergence of AR-V7, the most prevalent AR-V, has been associated with a lack of response to abiraterone and enzalutamide While the emergence of AR-Vs provides an elegant biologic rationale for why drugs that interfere with the AR-ligand interaction may not be effective, it remains unclear whether AR-V expression is a driver of disease progression or merely reflection that a larger resistance program has been activated Concentrations from 81.8 to 327 ng/mL[51,52,53].

On inflammation and migration of fibroblast-like synoviocytes from patients with rheumatoid arthritis-Rheumatoid arthritis (RA) is a common chronic inflammatory disease that may cause synovial inflammation, hyperplasia of the synovial tissues, and joint damage Fibroblast-like synoviocytes (FLS) are key players in the path physiological process of RA RA-FLSs regulate the

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secretion of inflammatory mediators, such as TNF-a,IL-6, and IL-1bThe importance of proinflammatory cytokines has been underscored by the success of biologics in treating disease by blocking the effects of cytokines such as TNF-a, IL-1b or IL. RA-FLSs share many similar Niclosamides and reduce the secretion of IL-1b, IL-6, IL-8, IL-17A and IFN-c from TNF-a-induced RA FLS in a dose-dependent manner[54,55].

Human osteosarcoma(OS) is the most common non-haematological malignant tumor of bone in children and adults, with its peak incidence in the teens. OS usually involves the metaphysic of long bones where high bone turnover occurs during longitudinal growth spurts usually involves the metaphysic of long bones where high bone turnover occurs during longitudinal growth spurts OS is characterized by a high propensity for lung metastasis with10%-20% having detectable metastases at diagnosis These pulmonary lesions are responsible for the high mortality associated with OS.[56,57].Only about 15-20% of patients have radiographically detectable pulmonary metastases, while approximately 80% of the patients either will developer already have radio graphically undetectable micro metastases[58,59].

Osteoclast formation and osteoblast differentiation-The bone destruction disease including osteoporosis and rheumatoid arthritis are caused by the imbalance between osteoblast genesis and osteoclast genesis. Inhibition of the NF-κBpathway was responsible for decreased osteoclast genesis. Recently many studies indicated that niclosamide, the FDA approved an antihelminthic drug, and Bone is a dynamic tissue consisting of various types of cells which are undergoing renewal and repair process termed "bone remodeling". The Osteoclasts and osteoblasts are major cells types' forbonere-modelling. The increase in number of osteoclast could contribute to extreme bone resorption and the decrease in differentiation of osteoblast to reduce new bone formation, disrupts the balance bone remodeling, and results in the loss of bone that are pathological hallmarks of osteoporosis,inflammatory joint disease and rheumatoid arthritis[60,61].

Inhibits oxaliplatin neurotoxicity while improving colorectal cancer Neuropathic pain is a limiting factor of platinum-based chemotherapies.We sought to investigate the Neuro-protectivepotentialofniclosamide in peripheral neuropathies induced by oxaliplatin.Normal neuron-like and cancer cells were treated in vitro with oxaliplatin associated or not with an inhibitor of STAT3 andNF-kB, niclosamide. CellPlatinum-based chemotherapies elicit their antitumor effects by compromising the integrity of DNA via the formation of adducts and impairing the functioning of mitochondrial processes these impairments ultimately lead to a burst of oxidative stress, which in turn promotes cell death processes. Oxaliplatin is able to induce functional abnormalities in dorsal root ganglia and axonal voltage-gated sodium channels as well as voltage-gated potassium channels .Oxaliplatin also induces a deregulation in calcium intracellular signaling as well as homeostasis Niclosamide prevents oxaliplatin-induced increased levels of IL6, TNFa and advanced oxidized protein products[62,63]

Niclosamide and neuropathic pain-Neuropathic pain is a pathological condition ejecting about 6–8% of the population worldwide where chronic pain emanates from damaged or diseased soma to-sensory nerves. There are few elective therapies. Reported that niclosamide is a low-nanomolar allosteric antagonist of Group I Metabio-tropic glutamate G protein coupled receptors (milers), with high selectivity for Group I over homologous Group III milers. Preclinical data demonstrated that in a mechanical hyperalgesia model of neuropathic pain in rats, pain-related behaviour is reversed by niclosamide treatment Wnt signalling underlies pathogenesis of neuropathic pain. Both Niclosamide and an inhibitor of Wnt release (IWR) were eff ective in two rodent pain models Calcium mobilization assays and cross-receptor selectively experiments are conducted to characterize the pharmacological activity of niclosamide. A focused series of niclosamide analogues is then prepared to elucidate key structural determinants that emerged from computational molecular mode-ling analysis on drug-receptor interactions[64,65].

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Inhibits dengue virus infectionDengue virus (DENV)-which is transmitted by the bite of mosquitoes of thee Aedesgenus, causes approximately 390 million infections annually belongs to the genus Fl virus of the family Flaviviridae with a single-stranded, positive sense RNA genome approximately 11 kb in length. The genome of DENV contains a single open reading frame encoding a poly-protein precursor, which is further cleaved into three structural proteins (capsid (C), remembrance (pr-M), and envelope (E) proteins) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5), which have roles in the pathogen-host interaction and pathogenesis . Patients with DENV infection are usually asymptomatic. However, 3 to 14 days after the infective mosquito bite, some patients exhibit extreme symptoms, including headache, vomiting, fever, rash, myalgia, and retro-orbital pain. Moreover, some patients further progress to life-threatening severe DENV infection, which is characterized by CNS impairment, multiple organ failure, plasma leakage and severe bleeding (dengue hemorrhagic fever and dengue shock syndrome). To date, there is no effective antiviral drug available for blocking infection[66,67].

Zia infection-Zika Virus (ZIKV) is a mosquito-transmitted flavivirus that has been the cause of recent public health concern mostly due to its causative link to microcephaly, a congenital birth defect in which babies are born with abnormally small heads and deficits in brain development. With recent epidemics in Central and South America, there is an urgent need to develop physiologically relevant ZIKV-infection models that can be used to study the pathophysiology of the disease and to identify new potential therapeutic agents. These in vitro studies have helped to elucidate some of the molecular mechanisms contributing to the pathogenesis of ZIKV infection. For example, it was recently shown that ZIKV-infected cranial neural crest cells (CNCCs) secrete multiple factors that may have a paracrine effect on surrounding tissues during development This is important because most cases of microcephaly involve not only brain deformities but also craniofacial abnormalities, suggesting that the detrimental effect of ZIKV is not restricted to cells of neural lineage[68].

Niclosamide Attenuates Colorectal Cancer Stemness-Colorectal cancer is a major health problem worldwide owing to its high prevalence and mortality rates although earlier diagnosis by advanced technology and new treatment regimens have considerably improved the survival of patients with colorectal cancer in the past decades, nearly 50% of patients withColorectal cancer still face recurrence at local or distant sites after conventional therapyNiclosamide suppresses CSC populations and them self- renewal activities in colorectal cancer cells; Disruption of the LEF1/DCLK1-B axis by niclosamide eradicates cancer stemness and elicits therapeutic effects on colorectal cancer initiation, progression, and resistance[69].

Human Renal Cell Cancer Cells- Renal cell carcinoma (RCC) is the most lethal of the urological cancers and accounts for about 3% of all malignancies in adults, with about 300, 000 new cases per year and about 120, 000 deaths per year worldwide. As it is most common in older men, active and passive cigarette smoking, obesity and hypertension are known risk factors although most patients do not have an identifiable risk factor; and the pathogenic mechanisms underlying the established risk factors remain unclear Niclosamide is further shown to synergize with Sorafenib in suppressing RCC cell proliferation and survival. In the xenograft tumor model, Niclosamide is shown to effectively inhibit tumor growth and suppress RCC cell proliferation[70].

Blockade in non-small cell lung cancer-Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality and has poor prognosis. In recent years, advances in the treatment of NSCLC have been substantial land promising with the effective application of immune therapies, including anti-programmed cell death 1ligand (PD-L1) and anti-programmed cell death 1 (PD-1) antibodies (nivolumab, atezolizumab and pembrolizumab), in selected populations of advanced NSCLC with high tumor mutation burden (TMB) or elevated pretreatment PD-L1 expression. Immune checkpoint blockades, particularly-targets of co-inhibitory pathways in T cells, niclosamide could decrease the expression of PD-L1 in both

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concentration and time-dependent manner in NSCLC cells, which was linked to the blockage of p-STAT3 binding to the promoter of PD-L1 [71].

Broad Spectrum Antiviral Agent Niclosamide-The recent outbreak of coronavirus disease 2019 (COVID-19) first detected in Wuhan, China, was caused by a 2019-nCoV) by the International Committee on Taxonomy of Viruses.Coronaviruses (CoVs) are enveloped and positive sense single-stranded RNA viruses belonging to the family Coronaviridae within the order Nidovirales. Many coronaviruses infect humans and other mammalian hosts. Coronavirus can be divided into four genera (alpha, beta, gamma, and delta), of which alpha and beta coronaviruses are known to infect humans. Niclosamide exerts its anticestodal effect by inhibiting oxidative phosphorylation and stimulating adenosine triphosphate activity in the mitochondria[72].

Nonalcoholic fatty liver disease- Nonalcoholic fatty liver disease is an early indication of the metabolic syndrome where lipids abnormally accumulate in the liver

About 15-30% of the world's population is affected by non-alcoholic fatty liver disease, a leading cause for Type 2 diabetes, non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma addition to effects on diabetic symptoms, also described the effect of niclosamide ethanolamine salt to reduce liver fat accumulation (steatosis) in mice fed a high fat diet plus niclosamide ethanolamine salt[73].

Niclosamide and tuberculosis-Itis the second-most common cause of death from infectious disease. In an effort of overcoming multidrug resistant to current therapies, tested antifungal and antihelminthic drugs by evaluating their ability to inhibit the growth of M.tuberculosis strain H37Ra.Niclosamide was found to have the inhibitory growth with minimum inhibitory concentration of 0.5–1 the authors also suggested its topic application to Treat surface-located tuberculosis, i.e. skin or intestinal tuberculosis infections. Subsequently, a number of research groups have reported the ability of niclosamide and related salicylanilide derivatives to inhibit the growth of M. tuberculosis and reported the effect of pH on growth inhibition[74].

Niclosamide and anthrax - Anthrax is a zoonotic disease caused by infection by Bacillus anthracis. Despite the development of an anthrax vaccine, the disease remains a public health threat using an established image-based assay that monitors the endocytosis and translocation of a beta-lactamase-fused anthrax lethal factor to identify small molecules that block anthrax toxin internalization. They found that niclosamide protected RAW264.7 macrophages and CHO cells exposed to anthrax lethal toxin, and also defended cells from Pseudomonas exotoxin and diphtheria toxin. Thus, one of the mechanisms of niclosamide action may involve endosome acidification[75].

Niclosamide and Pseudomonas Aeruginosa-Many bacteria use quorum sensing to coordinate certain behaviours such as biofilm formation, virulence, and antibiotic resistance. Screened a library of FDA-approved drugs for their ability to inhibit the quorum sensing response in the Gram-negative pathogen Pseudomonas aeruginosa. They identified niclosamide as an inhibitor of the P. aeruginosa quorum sensing response, and of production of acetyl homoserine lactone, a quorum sensing signaling molecule. Niclosamide affected the transcription of about 250 genes in P. aeruginosa, with a high degree of target specificity toward the quorum sensing-dependent genes[76].

Niclosamide and Type 2 diabetes mellitus-Type 2 diabetes mellitus affects more than 25 million Americans, and is the seventh leading cause of death in the U.S While making lifestyle changes can have an impact in managing diabetes and medications have effective outcomes, but some patients often become refractory to therapy. Niclosamide was reported to be an uncoupler of oxidative phosphorylation and is believed to disrupt the pH homeostasis of the parasite to kill worms. To seek new avenues for diabetes treatment, first demonstrated that a more water soluble form of niclosamide, niclosamide ethanolamine salt, uncouples mammalian mitochondria They added niclosamide ethanolamine salt to the food of mice fed a high fat diet in order to achieve drug exposure in vivo and overcome niclosamide low exposure in mice when dosed to intermittently They found that

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niclosamide ethanolamine salt treatment led to reductions in metabolic symptoms, with increased rate of energy expenditure, elevated oxygen consumption rate, and increased lipid oxidation. Niclosamide ethanolamine salt also had an effect on preventing elevation of fasting blood glucose and basal plasma insulin concentrations, while improving insulin sensitivity and reducing body weight gain in mice fed with a high fat diet[77].

II. CONCLUSIONS

Beyond its approved medical use for parasitic disease treatment, niclosamide has demonstrated preclinical activity in many disease models, ranging from cancer and metabolic diseases to multiple types of infections currently there are four clinical trials of niclosamide in colon cancer and prostate cancer in the Clinical Trials.gov clinical trials registry. Others will surely follow as the beneficial effects of niclosamide are appreciated in specific diseases. Improvement of the pharmacological and pharmacokinetic properties of niclosamide through re-formulation or pro-drug strategies is approaches to make more widespread use of this drug. The development of novel niclosamide derivatives that are biased toward targeting specific signaling pathways or biological functions in specific systemic diseases is a second approach to make use of the remarkable power of niclosamide.

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