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Drug Information of Auranofin and Its Effectiveness in Covid-19

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ABSTRACT
Gold metallo-drug, Auranofin is a gold containing triethyl phosphine, mostly it is advised to administer orally, to avoid Auranofin toxicity proper rational drug dose administration should be done, Auranofin has multi target mechanism and indication over Rheumatoid Arthritis, psoriatic Arthritis and HIV, it also has anti-bacterial, anti-parasitic, anti-inflammatory, anti-retroviral(anti-viral) activity and anti-cancer activity.As SARS-COV-2 has recently emerged as a new public health threat. Herein, we suggest that the FDA-approved Auranofin, inhibits SARS-COV-2 replication in human cells at low micro molar concentration.It might be a useful drug to limit SARS-CoV-2 infection and to treat the associated pneumonia according to the rational accurate dosing.
KEY WORDS: SARS CoV-2, Covid-19, Auranofin, Anti-viral, Gold Metallo-drug, Multi-purpose indication.

I. INTRODUCTION:

Metal based agents form variegate and attractive class of drugs with a number of therapeutic applications[1]. In medicine, Gold complexes have a long lasting history and have been used as disease modifying anti-rheumatic drugs (DMADs) for the treatment of rheumatoid arthritis.[2] Auranofin (AF) a gold-containing triethyl phosphine [3],is a drug approved by the FDA in 1985 for the treatmentof rheumatoid arthritis mainly acting through a modulation ofthe immune response. AF shows an acceptable toxicity profileand is safe for human use. The exact mechanism of action ofAF, most likely a multitarget one, is still debated [1]Intensive research on other possible therapeutic applications of the lead compound Auranofin and other gold species has focused on anti-infective and anti-cancer agents. The application of gold complexes as antiviral drugs has not been studied very intensively, although some promising results suggest a possible future use as human immunodeficiency virus (HIV) therapeutics.[2]Gold compounds history- gold is the oldest drug capable of arresting progression of RA. Because of high severe toxicity (hypertension, dermatitis, stomatitis, kidney/liver/bone marrow damage) it has gone out of use. Auranofin the orally active gold compound is found to be less toxic.[4]

II. DRUG INFORMATION OF AURANOFIN

Auranofin is available in oral form as capsules containing 3 mg AF. AF is (2,3,4,6-tetra-O-acetyl-1-thio-ß-D-glucopyranosato-S-) (triethyl–phosphine) gold. AF contains 29% gold.[5] Each RIDAURA capsule, with opaque brown cap and opaque tan body, contains AF , 3 mg, and is imprinted with the product name RIDAURA. Inactive ingredients consist of benzyl alcohol, cellulose, cetylpyridinium chloride, D&C Red No. 33, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate,

povidone, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide and trace amounts of other inactive ingredients. [5] Ridaura (auranofin) is a gold preparation, The mechanism by which AF exerts its therapeutic effect has not been established.[6] Like other gold-containing drugs, it also has the potential for gold toxicity.[5] In patients with adult rheumatoid arthritis or psoriatic arthritis, Ridaura may modify disease activity as manifested by synovitis and associated symptoms, and reflected by laboratory parameters such as elevated ESR. There is no substantial evidence, however, that gold-containing compounds induce remission of rheumatoid arthritis. Clinically the usual time of onset of therapeutic response to AF is 3 to 4 months. Continuing therapy beyond this time depends upon patient responsiveness, which includes improvement in parameters such as joint swelling, tenderness, pain, morning stiffness and grip strength. Continuing therapy beyond 6 months is unwarranted in patients showing insufficient improvement in the above parameters, and AF should be discontinued because of potential serious adverse reactions.[6]

III. PHARMACOKINETICS

Auranofin is rapidly metabolized and intact AF has never been detected in the blood. Studies of the pharmacokinetics of AF have involved measurement of gold concentrations. Approximately 25% of the gold in auranofin is absorbed. The mean terminal plasma half-life of AF gold at steady state was 26 days (range 21 to 31 days; n=5). The mean terminal body half-life was 80 days (range 42 to 128; n=5). Approximately 60% of the absorbed gold (15% of the administered dose) from a single dose of AF is excreted in urine; the remainder is excreted in the feces. In clinical studies, steady state blood-gold concentrations are achieved in about three months. In patients on 6 mg AF/day, mean steady state blood-gold concentrations were 0.68 ±0.45 mcg/mL. In blood, approximately 40% of AF gold is associated with red cells, and 60%associated with serum proteins. In contrast, 99% of injectable gold is associated with serum proteins. Mean blood-gold concentrations are proportional to dose; however, no correlation between blood-gold concentrations and safety or efficacy has been established.[5]

IV. INDICATIONS AND CLINICAL USE

Auranofin is indicated in the management of adults with active (classical or definite) rheumatoid arthritis who have not responded to adequate trials of conventional anti-inflammatory therapy. It might also be of benefit in patients with psoriatic arthritis.[6]AF should be added to a comprehensive baseline program, including non-drug therapies. Unlike anti-inflammatory drugs, AF does not produce an immediate response. Therapeutic effects may be seen after three to four months of treatment, although improvement has not been seen in some patients before six months. When cartilage and bone damage has already occurred, gold cannot reverse structural damage to joints caused by previous disease. The greatest potential benefit occurs in patients with active synovitis, particularly in its early stage.In controlled clinical trials comparing AFwith injectable gold, AF was associated with fewer dropouts due to adverse reactions, while injectable gold was associated with fewer dropouts for inadequate or poor therapeutic effect. Physicians should consider these findings when deciding on the use of AF in patients who are candidates for chrysotherapy.[6]AF prompted a lot of interest during the last years for its versatility and for the chance to be repurposed for differenttherapeutic indications such as an antibacterial, anticancer, or antiparasitic agent.[7]Significant activity against HIV was reported as well; AF entered accordingly clinical trials as an antiretroviral agent.[8]

V. CONTRAINDICATIONS

AF is contraindicated in patients with a history of any of the following gold-induced disorders: anaphylactic reactions, necrotizing enterocolitis, pulmonary fibrosis, exfoliative dermatitis, bone marrow aplasia or other severe hematologic disorders.[5]AF has been shown to be embryotoxic in rats at dose levels of 5 mg/kg/day or higher and both embryotoxic and teratogenic in rabbits at doses of 0.5 mg/kg/day or higher. Therefore, AF should not be given to pregnant women. Furthermore, women of childbearing potential should be made aware of the necessity to avoid pregnancy during treatment and for at least six months after because of the slow excretion of gold and its persistence in the body tissues after discontinuation of treatment.[6]Gold is excreted in rodent milk following the administration of AF. It is not known whether AF is excreted in human milk; however, injectable gold appears in the milk of nursing mothers following administration. Therefore, it is recommended that AFnot be given during nursing.[6]AF administration to rats and mice, gold is excreted in milk. Following theadministration of injectable gold, gold appears in the milk of nursing women; human data on AF are not available.[5]

VI. WARNINGS AND PRECAUTIONS

Auranofin contains gold and, like other gold-containing drugs, can cause gold toxicity. Danger signs of possible gold toxicity include the following: fall in hemoglobin, leukopenia below 4000 WBC/mm3, granulocytes below 1500/mm3, decrease in platelets below 150,000/mm3, proteinuria, hematuria, pruritus, rash,

stomatitis or persistent diarrhea. Therefore, it is recommended that white blood cells with differential, platelet count, haemoglobin, urinary protein and renal and liver function be measured prior to AF therapy to establish a baseline and to identify pre-existing conditions.[6]In a 24-month study in rats, animals treated with AF at 0.4, 1.0 or 2.5 mg/kg/day orally (3, 8 or 21 times the human dose) or gold sodium thiomalate at 2 or 6 mg/kg injected twice weekly (4 or 12 times the human dose) were compared to untreated control animals. There was a significant increase in instances of renal tubular cell karyomegaly and cytomegaly and renal adenoma in the animals treated with 1.0 or 2.5 mg/kg/day of AF and 2 or 6 mg/kg twice weekly of gold sodium thiomalate. Malignant renal epithelial tumors were seen in the 2.5 mg/kg/day AF and in the 6 mg/kg twice weekly gold sodium thiomalate-treated animals. In a 12-month study, rats treated with AF at 23 mg/kg/day (192 times the human dose) developed adenomas of the renal tubular epithelium, whereas those treated with 3.6 mg/kg/day (30 times the human dose) did not.[6] Teratogenic Effects— Pregnancy Category C. Use of AFby pregnant women is not recommended. Furthermore, women of childbearing potential should be warned of the potential risks of AF therapy during pregnancy. Pregnant rabbits given a AF at doses of 0.5, 3 or 6 mg/kg/day (4.2 to 50 times the human dose) had impaired food intake, decreased maternal weights, decreased fetal weights and an increase above controls in the incidence of resorptions, abortions and congenital abnormalities, mainly abdominaldefects such as gastroschisis and umbilical hernia. Pregnant rats given AF at a dose of 5 mg/kg/day (42 times the human dose) had an increase above controls in the incidence of resorptions and a decrease in litter size and weight linked to maternal toxicity. No such effects were found in rats given 2.5 mg/kg/day (21 times the human dose). Pregnant mice given AF at a dose of 5 mg/kg/day (42 times the human dose) had no teratogenic effects. There are no adequate and well-controlled AF studies in pregnant women.[5]

VII. ADVERSE REACTIONS

The adverse reactions listed below are based on observations on 4784 rheumatoid arthritis patients treated with AF of whom 2729 were treated for more than 1 year and 573 for more than 3 years. The overall incidence of adverse reactions was 62%, of whom 18.6% discontinued therapy. The most common adverse reactions were diarrhea (47%), rash (24%) pruritus (17%), abdominal pain (14%) and stomatitis (13%). More serious adverse reactions were anemia (1.6%), leukopenia (1.9%), thrombocytopenia (0.9%) and proteinuria (5.0%). The highest incidence was during the first 6 months of treatment. However, reactions can occur at any time throughout the course of therapy.Clinical trials were conducted assessing AF in the treatment of 438 psoriatic arthritis patients. The nature and incidence of adverse reactions were similar to those observed in rheumatoid arthritis patients.[6]

VIII. SYMPTOMS AND TREATMENT OF OVERDOSAGE

In case of acute overdosage, immediate induction of emesis or gastric lavage and appropriate supportive therapy are recommended. AF overdosage experience is limited. A 50-year-old female, previously on 6 mg AF daily, took 27 mg (9 capsules) daily for 10 days and developed an encephalopathy and peripheral neuropathy. AF was discontinued and she eventually recovered. There has been no experience with treating AF overdosage with modalities such as chelating agents; however, they have been used with injectable gold and may be considered when treating AF overdosage.[5]

IX. PHARMACODYNAMICS AND DOSAGE AND ADMINISTRATION

In animal studies auranofin had no significant effect on hemodynamic and electrocardiographic parameters, pulmonary function, central nervous system activity, gastric mucosa or the endocrine system. AF showed a slight antidiuretic effect in rats (2 - 40 mg auranofin/kg p.o.) but not in dogs (0.6 - 1.2 mg auranofin/kg p.o.). AF (up to 15 mg gold/kg p.o.) failed to induce liver enzyme activity in rats.[6] The usual adult starting dosage is 6 mg per day. This dose may be given: twice a day: one 3 mg capsule with breakfast and one with the evening meal oronce a day: two 3 mg capsules with breakfast
ortwo 3 mg capsules with the evening meal[6]

X. ROLE OF AURANOFIN IN COVID-19:

The outbreak of the COVID-19 pandemic in early 2020 poses dramatic problems to the health systems as no vaccine or truly effective drugs are yet available. The international scientific community is struggling to find new substances capable of contrasting the SARS-CoV-2 virus. A straightforward strategy to disclose compounds readily available to clinicians is drug repurposing, i.e. the use of drugs that were previously approved by the FDA for a different therapeutic indication. A few promising compounds against SARS-CoV-2 were identified through drug repurposing, e.g. remdesivir, chloroquine and hydroxychloroquine, tocilizumab, etc., but their therapeutic efficacy in COVID-19 patients is still debated. On the other hand, extensive screenings are conducted on thousands of novel molecules using combinatorial libraries or in silico docking experiments to discover new effective antiviral agents. Despite the intense research efforts, no metal compound is currently

being tested against the SARS-CoV-2 virus.[9]The current pandemic outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an unprecedented global health crisis with to date more than 7 million infected individuals.[10][11] While the world struggles with the control of the fast outspread of this coronavirus and it's enormous impact on healthcare, economy and society, efforts to develop vaccines and therapeutics have been undertaken worldwide at a rate, which moderndrug discovery has not witnessed ever. The lack of an effective antiviral drug for the treatment of the Coronavirus disease-2019 (COVID-19) has triggered major drug repurposing efforts, however, to this date no approved therapeutic has proven to have sufficient efficacy in the many ongoing clinical trials. The urgent development of new innovative drug candidates against SARS-CoV-2 is the most important mission that medicinal chemists are currently facing.Regarding drug activity evaluation, several molecular pathways have been in the focus of the search for a possible COVID-19 treatment based on strategies that had already been considered for the SARS-CoV and Middle East respiratory syndrome MERS-CoV outbreaks.[12] Amongst others these include the entry of the coronavirus into the host cell (e.g. the interaction of TMPRSS2[13] or ACE2 with spike proteins of the coronavirus [14]), the viral replication process in the host cell (e.g. the proteases 3CLpro [15] and PLpro [12][16][17]), transcription, the nucleocapsid protein, or exocytosis of the new virion.[12][16][18]Gold-based compounds have shown promising activity against a wide range of clinical conditions and microorganism infections. Auranofin, a gold-containing triethyl phosphine, is an FDA-approved drug for the treatment of rheumatoid arthritis since 1985[1]. It has been investigated for potential therapeutic application in a number of other diseases including cancer, neurodegenerative disorders, HIV/AIDS, parasitic infections and bacterial infections [1][19]. Auranofin was approved by FDA for phase II clinical trials for cancer therapy [20,21,22]. Oral auranofin was effective in rodent models of various parasitic infections (23,24]. A preclinical study showed that auranofin significantly reduces HIV load in combination with antiretroviral therapy [25]. A clinical trial is ongoing to develop auranofin as a drug candidate to reduce the latent viral reservoir in patients with HIV infection utilizing the role of auranofin in redoxsensitive cell death pathways [26,27]. The mechanism of action of auranofin involves the inhibition of redox enzymes such as thioredoxin reductase, induction of endoplasmic reticulum (ER) stress and subsequent activation of the unfolded protein response (UPR) [19],[28],[29],[30]. Inhibition of these redox enzymes leads to cellular oxidative stress and intrinsic apoptosis [31],[32] In addition, auranofin is an anti-inflammatory drug that reduces cytokines production and stimulate cell-mediatedimmunity [33]. It has been reported that auranofin interfereswith the Interleukin 6 (IL-6) signaling by inhibiting phosphorylationof JAK1 and STAT3 [34], [35] The dual inhibition of inflammatory pathways and thiol redox enzymes by auranofin makes it an attractive candidate for cancer therapy and treating microbial infections. Coronaviruses are a family of enveloped viruses with positive sense, single-stranded RNA genomes[36]. SARSCoV- 2, the causative agent of COVID-19, is closely related to severe acute respiratory syndrome coronavirus (SARS-CoV-1) [36],[37]. It is known that ER stress and UPR activation contribute significantly to the viral replication and pathogenesis during a coronavirus infection [38]. Infection with SARS-COV-1 increases the expression of the ER protein folding chaperons GRP78, GRP94 and other ER stress related genes to maintain protein folding [39]. Cells overexpressing the SARS-COV spike protein and other viral proteins exhibit high levels of UPR activation [40][41]Thus, inhibition of redox enzymes such as thioredoxin reductase and induction of ER stress by auranofin could significantly affect SARS-COV-2 protein synthesis.[42] In addition, SARS-COV-2 infection causes acute inflammation and neutrophilia that leads to a cytokine storm with over expression of IL-6, TNF-alpha, monocyte chemoattractant protein (MCP-1) and reactiveoxygen species (ROS)[37] . The severe COVID-19 illness represents a devastating inflammatory lung disorder due to cytokines storm that is associated with multiple organ dysfunction leading to high mortality [37],[43] Taken together, these studies suggest that auranofin could mitigate SARS-COV-2 infection and associated lung damage due to its anti-viral, anti-inflammatory and anti-ROS properties.Hussin A. Rothan et al, investigated the anti-viral activity of auranofin against SARSCoV- 2 and its effect on virus-induced inflammation in human cells. We infected Huh7 cells with SARS-CoV-2 (USA-WA1/2020) at a multiplicity of infection (MOI) of 1 for 2 h, followed by the addition of 4 μM of auranofin. DMSO (0.1%) was used as control (the solvent was used to prepare drug stock). We used Huh7 cells in this study as these cells are highly permissive for SARS-COV-2 replication. Cell culture supernatants and cell lysates were collected at 24 and 48 h after infection. Virus RNA copies were measured by RT-PCR using two separate primers specific for the viral N1 region and N2 region [42], [44] . As depicted in Fig. 1, treatment of cells with auranofin resulted in a 70% reduction in the viral RNA in the supernatants compared to the DMSO at 24 h after infection. At 48 h, there was an 85% reduction in the viral RNA in the supernatants compared to the DMSO. Similarly, the levels of intracellular viral RNA decreased by 85% at 24 h and 95% at 48 h in auranofin-treated cells compared to the DMSO-treated cells. Both set of primers showed nearly identical results. We next assayed virus titers in cell culture supernatants by plaque assay. Treatment with auranofin significantly reduced SARS-COV-2 infectivity titers in cell culture supernatants at 48 h after infection.To determine the effective concentration of auranofin that inhibits 50% of viral replication (EC50), we treated SARS-COV-2 infected Huh7 cells with serial dilutions of auranofin. Supernatants and cell lysates were collected at 48 h after infection and viral RNA was quantified by RT-PCR.

The data were plotted in graphs using non-linear regression model (GraphPad software). At 48 h, there was a dose-dependent reduction in viral RNA levels in the auranofin-treated cells. (Fig. 1) represents the EC50 values of auranofin treatment against SARS-CoV-2 infected Huh7 cells. Auranofin inhibited virus replication in the infected cells at EC50 of approximately 1.4 μM. It is important to note that in this study, we used 20 to 100-times more virus dose (MOI of 1) to infect the cells compared to the recently published reports on anti-viral activities of chloroquine, hydroxychloroquine and remdesvir againstSARS-COV-2 in vitro.[45.]Auranofin inhibits replication of SARS-COV-2 in human cells. Huh7 cells were infected with SARS-COV-2 at a multiplicity of infection (MOI) of 1 for 2 h and treated with 4 μM of auranofin or with 0.1% DMSO. Cell pellets and culture supernatants were collected at 24 and 48 h after infection and viral RNA levels were measured by RT-PCR using primers and probe targeting the SARS-COV-2 N1 region and the SARS-COV-2 N2 region. The cellularRNA extracted from infected cells was quantified, normalized and viral RNA levels per ug of total cellular RNA were calculated. The resultswere identical for both set of primers showing dramatic reduction in viral RNA at both 24 and 48 h. SARS-COV-2 infectivity titers were measured in cell culture supernatants at 48 h after infection by plaque assay. Data represent the mean ± SEM, representing two independent experiments conducted in duplicate, t-testp < 0.001.[36][46]To assess the effect of auranofin on inflammatory response during SARS-COV-2 infection, we measured the levels of key cytokines in auranofin and DMSO-treated cells at 24 and 48 h after infection [47]. SARS-COV-2 infection induces a strong up-regulation of IL-6, IL-1β, TNFα and NF-kB in Huh7 cells. Treatment with auranofin dramatically reduced the expression of SARS-COV-2-induced cytokines in Huh7 cells. SARS-COV-2 infection resulted in a 200-fold increase in the mRNA expression of IL-6 at 48 h after infection compared to corresponding mock-infected cells. In contrast, there was only a 2-fold increase in expression of IL-6 in auranofin-treated cells.TNF-α levels increased by 90-fold in the DMSO-treated cells at 48 h after infection, but this increase was absent in the auranofin-treated cells. Similarly, no increase in the expression of IL-1β and NF-kB was observed in the auranofin-treated cells. Taken together these results demonstrate that auranofin inhibits replication of SARS-COV-2 in human cells at low micro molar concentration. We also demonstrate that auranofin treatment resulted in significant reduction in the expression of cytokines induced by virus infection. These data indicate that auranofin could be a useful drug to limit SARS-CoV-2 infection and associated lung injury. Further animal studies are warranted to evaluate the safety and efficacy of auranofin for the management of SARS-COV-2 associated disease.

XI. SARS-COV-2 INFECTION AND DRUG TREATMENT

In this study, we used a novel SARS-COV-2 (USA-WA1/2020) isolated from an oropharyngeal swab from a patient in Washington, USA (BEI NR-52281). Virus strain was amplified once in Vero E6 cells and had titers of 5 × 106 plaque-forming units (PFU)/mL. Huh7 cells (human liver cell line) were grown in DMEM (Gibco) supplemented with 5% heat-inactivated fetal bovine serum. Cells were infected with SARS-COV-2 or PBS (Mock) at a multiplicity of infection (MOI) of 1 for 2 h [47, 48, 49, 50]Cell were washed twice with PBS and media containingdifferent concentrations of auranofin (0.1–10 μM, Sigma) or DMSO (0.1%, Sigma) was added to cells. Supernatants and cell lysates were harvested at 24 and 48 h after infection. The cytotoxicity of auranofin in Huh7 cells was measured using trypan blue method as described previously[51]. Briefly, Huh7 cells were treated with different concentrations of auranofin (0.1–10 μM) for 48 h and percentage cell numbers were quantified using trypan blue.

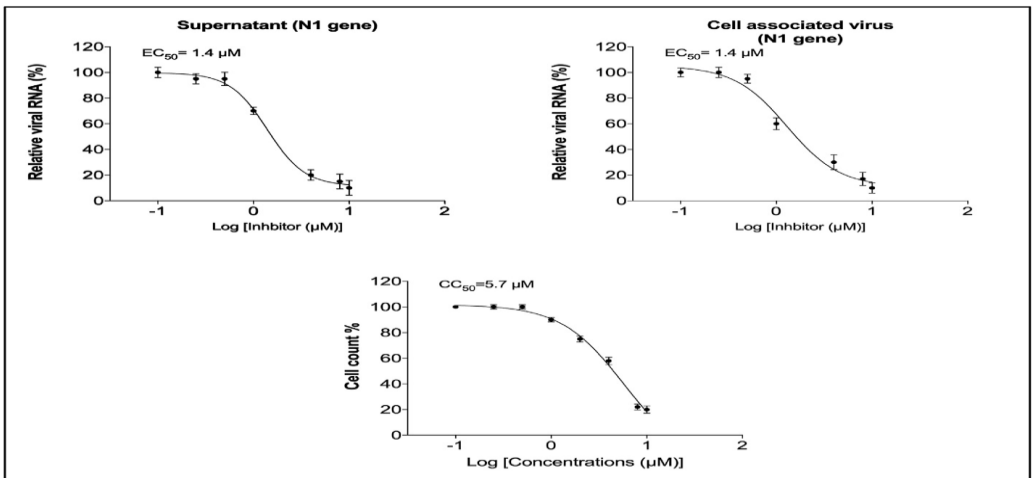

Fig.1. Dose-dependent reduction in SARS-COV-2 RNA in the auranofin-treated cells: The SARSCOV- 2 infected Huh7 cells were treated with serial dilutions of auranofin (0.1–10 μM). Viral RNA in the cell pellets and culture supernatants were quantified by RT-PCR using primers and probe targeting the SARS-COV-2 N1.

The data were plotted in graphs using non-linear regression model (GraphPad software).Auranofin inhibited virus replication in the infected cells at EC50 of approximately 1.4 μM. The cytotoxic concentration of 50% was approximately 5.7 μM. Data represent two independent experiments conducted in duplicate.[36][52]

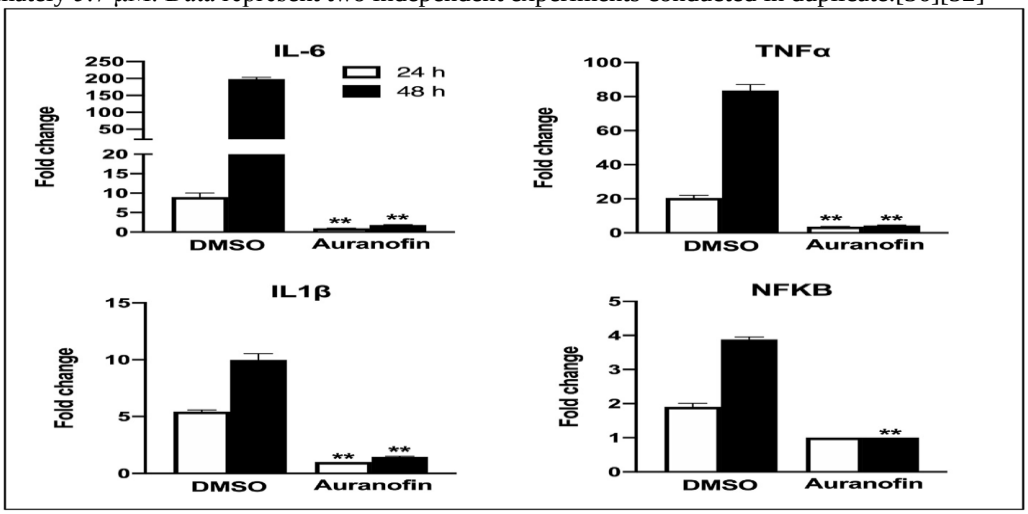

Fig. 2. Auranofin treatment dramatically reduced the expression of SARS-COV-2-induced cytokines in human cells: mRNA levels of IL-6, IL-1β, TNFα and NF-kB were determined using qRT-PCR at 24 and 48 h after infection. The fold change in infected cells compared to corresponding controls was calculated after normalizing to the GAPDH gene. Data represent the mean ± SEM, representing two independent experiments conducted in duplicate. [36][46]

XII. DISCUSSION

Hussin et al reported that the FDA-approved drug, auranofin, inhibits SARS-COV-2 replication in human cells at low micro molar concentration. Treatment of cells with auranofin resulted in a 95% reduction in the viral RNA at 48 h after infection. Auranofin treatment dramatically reduced the expression of SARS-COV-2-induced cytokines in human cells. These data indicate thatauranofin could be a useful drug to limit SARS-CoV-2 infection and associated lung injury due to its antiviral, anti-inflammatory and anti-reactive oxygen species (ROS) properties.Maria Gil-Moles et al, according to their evaluation the lead compound Auranofin and gold metallic acts as inhibitors of 2 relevant drug targets of SARS-CoV-2, the gold metallo drugs were effective inhibitors of theinteraction of the SARS-CoV-2 spike protein with the ACE 2 host receptor and interferes with the viral entry process.Tiziano Marzo et al, during their review process they reported at a low micro molar concentration Auranofin strongly inhibits SARS-COV-2 replication in human cells with a spectacular 95% reduction in the viral RNA. In addition, AF was found to dramatically reduce the expression of SARS-COV-2-induced cytokines in human cells, in line with the previous observations.[52]The above results of in review excellently supports our review proposal and suggests the multi-purpose and multi target mechanism of Auranofin in RA, Psoriasis, anti-cancer and anti-inflammation. It might be a useful drug to limit SARS-CoV-2 infection and treat the associated pneumonia. We believe and suggest that an extensive in vivo and in vitro investigational study panels should be set up for Auranofin and other drugs or agents which are showing anti-covid action, for betterment of best combat fight against covid 19 and relief of patient quality of life.

XIII. CONCLUSION

Our review proposesthe multi-purpose indication and multi target mechanism of the metallo-drug Auranofin in RA, Psoriasis, anti-cancer, anti-inflammationanti-bacterial, anti-parasitic and anti-retroviral activity. It might be a useful drug to limit Covid 19 SARS-CoV-2 infection and treat the associated pneumonia according to the rational accurate dosing.

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