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Study on Efficacy of Resveratrol in Treatment of Cryptosporidiosis in Experimentally Infected Mice

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ABSTRACT

Background: *Cryptosporidium* is a zoonotic protozoan parasite causing cryptosporidiosis in humans and animals. It is a major diarrheal contributor in developing nations and the second leading cause of death in children under five. While Nitazoxanide is the standard treatment, its efficacy is modest in children and immunosuppressed individuals. Consequently, resveratrol is being investigated as a potential natural antiparasitic agent.

Objectives: This experimental animal study represents a new trial to assess the anti-parasitic effect of resveratrol as a treatment for cryptosporidiosis in immunosuppressed mice, either on its own or in conjunction with nitazoxanide.

Materials and methods: Fifty laboratory-bred male albino mice were orally infected with 3000 *Cryptosporidium* oocysts. These animals were then divided into two main groups. **Group A** served as the control, comprising a negative control subgroup (uninfected, untreated) and a positive control subgroup (infected, untreated). **Group B** consisted of infected mice that received treatment with either nitazoxanide, resveratrol, or a combination of both. Evaluation was conducted using parasitological and histopathological parameters.

Results: All treated groups showed a significant reduction in the shedding of *Cryptosporidium* oocysts. The greatest reduction occurred in the group treated with a combination of nitazoxanide and resveratrol, followed by the group treated with resveratrol alone. The group treated with nitazoxanide showed the least reduction. Remarkable improvement of the histopathological findings was observed especially after receiving combined nitazoxanide & resveratrol followed by resveratrol treated group and then the nitazoxanide treated mice.

Conclusion: Resveratrol can serve as an effective treatment for *Cryptosporidium* spp. infection, whether used on its own or in conjunction with nitazoxanide.

Keywords: Resveratrol, Nitazoxanide, *Cryptosporidium.*

INTRODUCTION

Cryptosporidium is a ubiquitous protozoan parasite, a member of the phylum Apicomplexa, which is characterized by obligate intracellular parasitism and the presence of an apical complex facilitating host cell invasion. This parasite is responsible for significant global burden of diarrheal disease, demonstrating a particular and severe impact on immunocompromised individuals, in whom infections tend to be more prolonged, severe, and potentially life-threatening [(1)].

The ramifications of cryptosporidiosis are especially profound within developing countries, where its prevalence and severity are often exacerbated by poor socioeconomic conditions, inadequate sanitation, and compromised public health infrastructures. Children, notably, represent the most vulnerable demographic within these regions. In this population, cryptosporidiosis-induced persistent diarrhea can inflict severe and prolonged adverse effects on their crucial nutritional status [(2)], significantly impair their growth trajectory, and impede their overall physical and cognitive development, leading to chronic malabsorption and stunting [(3)].

Furthermore, *Cryptosporidium* has been definitively identified as a predominant causative agent of both waterborne and foodborne disease outbreaks on a global scale. A recent comprehensive epidemiological analysis indicated a global infection prevalence approximating 7.6%, underscoring its pervasive presence and capacity to induce acute intestinal illness [(4)].

Cryptosporidiosis is unequivocally regarded as the most dangerous opportunistic infection for patients with acquired immunodeficiency syndrome (AIDS), owing to their profoundly compromised cellular immunity, and similarly poses a grave threat among malnourished children, who possess weakened immune defenses. Transmission of cryptosporidiosis occurs almost exclusively via the fecal-oral route, specifically through the ingestion of a relatively low infectious dose of viable oocysts shed in the feces of infected humans or animals. While acute watery diarrhea remains the most ubiquitous and hallmark symptom observed in both immunocompetent and immunosuppressed persons, the clinical spectrum of cryptosporidiosis can also encompass a range of other debilitating symptoms. These may include abdominal cramps, uncomfortable bloating,

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unintentional and significant weight loss, and profound fatigue [5].

Nitazoxanide (NTZ) presently constitutes the singular pharmaceutical agent that has received specific approval from the Food and Drug Administration (FDA) for the treatment of cryptosporidiosis. While NTZ has demonstrated a clear efficacy in accelerating clinical recovery and reducing oocyst shedding in immunocompetent individuals, its therapeutic effectiveness is notably modest and often insufficient in young children and, particularly, in severely immunosuppressed patients [6]. This necessitates the urgent development of novel therapeutic strategies that not only possess potent anti-parasitic action but also simultaneously aim to bolster or restore the patient's underlying immune status, facilitating more effective parasite eradication and preventing recurrence [7].

In parallel, **Resveratrol (RSV)**, a natural non-flavonoid polyphenol abundantly present in various common fruits such as grapes (especially red grape skins), berries, and peanuts, has garnered considerable and expanding scientific interest within the biomedical community. As a phytoalexin, RSV plays a role in plant defense mechanisms, and recent comprehensive investigations have consistently reported that RSV exerts a remarkably diverse array of beneficial biochemical and physiological effects highly pertinent to human health, including cardioprotective, neuroprotective, and anti-carcinogenic properties [8]. Oral administration of RSV has been mechanistically shown to significantly mitigate intestinal inflammation, primarily by acting as a potent antioxidant, exhibiting robust anti-inflammatory properties. Moreover, RSV actively contributes to the prevention of detrimental bacterial translocation across the gut barrier by strengthening and maintaining its structural and functional integrity [9].

Beyond its established effects on inflammation and gut barrier function, Resveratrol has also demonstrably exerted direct anti-protozoal activities against a range of parasitic species, including *Leishmania* spp., showing promise in leishmaniasis treatment [10], and *Giardia lamblia*, a common intestinal flagellate [11]. Furthermore, its broad therapeutic potential extends to compelling anti-helminthic effects, proving effective against various parasitic worms such as *Schistosoma mansoni*, [12], *Trichinella spiralis* [13], and the larval stages of both *Echinococcus granulosus* and *Echinococcus multilocularis* [14]. These diverse antiparasitic actions further broaden the potential applications of RSV in global health.

MATERIAL AND METHODS

The present analytical experimental animal study was conducted during the period from September 2022 to April 2023 at Theodor Bilharz Research Institute (TBRI) in Giza, Egypt.

Experimental Animals

Fifty laboratory-bred male Swiss albino mice (CD1 strain), aged 3-4 weeks and weighing 20-25g each, were utilized in this research. The animals were procured from the *Schistosoma* Biological Supply Program (SBSP) at TBRI. Prior to the study, mice were confirmed to be free of parasitic infections via microscopic examination of their stool for three consecutive days. Throughout the study, animals were maintained in individual laboratory cages under specific pathogen-free conditions, with a controlled lighting cycle and a constant temperature of 24°C. They had access to standard laboratory water and a diet comprising 24% protein, 4% fat, and approximately 4-5% fiber. Animals were housed in the biological unit of TBRI, shielded from direct sunlight.

Immunosuppression

Immunosuppression was induced through the administration of synthetic corticosteroids, specifically **dexamethasone** (Dexazone, Kahira Pharmaceuticals and Chemical Industries Company, Egypt). Mice received 0.25 µg/g/day of dexamethasone orally via esophageal gavage. The administration of this regimen commenced on a daily basis two weeks preceding oral inoculation with *Cryptosporidium* oocysts and continued throughout the entire experimental period to maintain an immunosuppressed state [15].

Infection Protocol

Oocysts of *Cryptosporidium* were sourced from TBRI in Giza, Egypt. Fecal samples were obtained from diarrheic cages. The inoculum was calibrated to achieve an oral infection of mice with 3000 *Cryptosporidium* oocysts per animal, administered via esophageal gavage [16]. Following inoculation, individual fecal pellets were collected from the mice and subjected to parasitological examination using the modified Zeihl-Neelsen stain to detect *Cryptosporidium* spp. oocysts, thereby confirming successful infection.

Mice were subsequently allocated into two primary groups, each further divided into subgroups of 10 mice:

- **Group A: Control Group**
  - GA1: Immunosuppressed, non-infected, non-treated (Negative control).
  - GA2: Immunosuppressed, infected with 3 x 10^3 oocysts/mouse, non-treated (Positive control).
- **Group B: Infected and Treated Group**
  - Mice in this group were infected with 3 x 10^3 oocysts/mouse and subdivided into:
    - GB1: Immunosuppressed, infected and treated with **Nitazoxanide (NTZ)**.
    - GB2: Immunosuppressed, infected and treated with **Resveratrol (RSV)**.

- GB3: Immunosuppressed, infected and treated with a **combined NTZ & RSV** regimen.

Treatment Regimens

Nitazoxanide (NTZ) (Medizen Pharmaceutical Industries for Utopia Pharmaceuticals) was administered orally as a suspension at a dose of 100 mg/kg/day for ten consecutive days.

Resveratrol (RSV) (C14H12O3; molecular weight 228.25 g/mol; purity > 98%), procured from Sigma-Aldrich (St. Louis, MO, USA), was administered orally as a freshly prepared suspension in 0.5% carboxymethyl cellulose in distilled water. The dose was 100 mg/kg daily for 10 days [(17)].

Mice designated for combined therapy received both NTZ at 100 mg/kg/day and RSV at 100 mg/kg/day for duration of 10 days.

Drug Efficacy Assessment

Parasitological Examination

Following drug administration, fecal pellets were collected from infected mice on days 7, 15, and 21 post-infection (p.i.). These samples underwent parasitological examination using Kinyoun's Acid-Fast stain (cold method) to enumerate *Cryptosporidium* oocysts within 50 µl aliquots [(18)]. The parasitic burden was subsequently expressed as the number of parasites per gram of feces [(16)]. The percentage reduction in the number of the shedded oocysts was calculated according to the following equation:

$$\frac{\text{(Mean number of the oocysts in the infected control group-mean number of oocysts in the treated group)}}{\text{(Mean number of the oocysts in the infected control group)}}$$

Histopathological examination:

Sections of the small intestine were meticulously excised and processed for **histopathological examination** to ascertain structural alterations in the affected tissues. Tissues were fixed in 10% formalin and subsequently embedded in paraffin. Histopathological sections, 4 µm in thickness, were stained with hematoxylin & eosin at the pathology laboratory of TBRI. Microscopic evaluation was conducted to identify pathological changes and quantify cure rates post-drug intervention.

Ethical consideration

The Research Ethics Committee of the Faculty of Medicine at Al-Azhar University in Egypt provided full ethical oversight and approval for this research, ensuring compliance with institutional guidelines for responsible research conduct. Moreover, all experimental animals used in this lab study were managed in accordance with the rigorous ethical and technical guidelines established by the Theodor Bilharz Research Institute (TBRI) in Giza, Egypt, particularly regarding animal rights for scientific purposes. All experimental animals were handled according to protocols that strictly adhered to internationally recognized guidelines, including those established by the National Institutes of Health (NIH, 1996) and its later amendments regarding the ethical treatment and comprehensive care of laboratory animals. This commitment guaranteed that all animal procedures were conducted humanely and with the highest regard for animal welfare during the study according to Helsinki declaration.

Statistical Analysis

The collected data underwent a comprehensive process of revision, coding, and tabulation before systematic entry into a personal computer for subsequent analysis. Data were presented and analyzed judiciously according to the specific characteristics of each parameter obtained. Descriptive statistics involved the calculation of mean ± standard deviation (SD) for all parametric numerical data, providing measures of central tendency and dispersion. For analytical statistics, a One-way Analysis of Variance (ANOVA) test was employed to ascertain statistically significant differences between the means of more than two study groups, while the Paired t-test was utilized to assess statistical significance between the means of two related groups. Furthermore, the percent reduction in oocyst counts, relative to infected non-treated oocysts, was quantitatively determined using the formula: (Infected non-treated−Infected treated/Infected non-treated) ×100. Across all analyses, a P-value of less than 0.001 ($P < 0.001$) was predetermined as the threshold for considering the difference between experimental groups to be highly statistically significant.

RESULTS

Parasitological study: It was noted that NTZ led to a significant reduction in the shedding of oocysts in the stool to 157.3 ± 27.9, 145.8 ± 9.9 and 131.7± 21.2 which represented about 46.3%, 49.4 and 52% reduction of oocysts, at 13th, 15th and 21st day post infection in relation to infected untreated controls (table 1).

This observation was upheld significantly for RSV treatment with reduced mean number of oocysts to 132.0±16.3, 118.3±10.9 and 98.1±14.2, reaching about 55%, 59% and 64.2%) at 13th, 15th and 21st day post infection respectively relative to infected untreated controls (table 2). The highest oocyst reduction was in mice treated with combined NTZ & RSV that was 99.5±7.4, 91.7±13.9 and 73.6±11.7 reaching about 66%, 68.2% and 73.2% respectively at 13th, 15th and 21st day post infection (table 3).

Table (1): The mean count of *C. parvum* oocysts/gm feces and percentage of reduction at 7th, 13th, 15th and 21st days post infection in NTZ treated group (G B1)

Group / Day	Control (G A2) (Mean±SD)x10^3	(NTZ) (G B1) (Mean±SD)x10^3	% Reduction	P-value
7th (p.i).	298.9±68.1	298.9±68.1		
13th (p.i).	293.1±67.1	157.3±27.9	46.3%	<0.001**
15th (p.i).	288.3±51.0	145.8±9.9	49.4%	<0.001**
21st (p.i).	274.2±41.2	131.7±21.2	52.0%	<0.001**

**p-value <0.001 is highly significant.

Table (2): The mean count of *C. parvum* oocysts/gm feces and percentage of reduction at 7th, 13th, 15th and 21st days post infection in **RSV** treated group **(G B2).**

Group / Day	Control (G A2) (Mean±SD) x10^3	RSV (G B2) (Mean±SD) x10^3	% Reduction	P-value
7th (p.i)	298.9±68.1	298.7±67.7		
13th (p.i)	293.1±67.1	132.0±16.3	55.0%	<0.001**
15th (p.i)	288.3±51.0	118.3±10.9	59.0%	<0.001**
21st (p.i)	274.2±41.2	98.1±14.2	64.2%	<0.001**

**p-value <0.001 is highly significant.

Table (3): The mean count of *C. parvum* oocysts/gm feces and percentage of reduction at 7th, 13th, 15th and 21st days post infection in combined **NTZ &RSV** treated group **(G B3).**

Group / Day	Control (G A2) (Mean±SD) x10^3	NTZ&RSV (G B3) (Mean±SD) x10^3	% Reduction	P-value
7th (p.i)	298.9±68.1	298.7±67.7		
13th (p.i)	293.1±67.1	99.5±7.4	66.0%	<0.001**
15th (p.i)	288.3±51.0	91.7±13.9	68.2%	<0.001**
21st (p.i)	274.2±41.2	73.6±11.7	73.2%	<0.001**

**p-value <0.001 is highly significant

Histopathological Findings

Compared to the, uninfected control group (Fig. 1), the intestinal sections stained with H&E from the *Cryptosporidium*-infected control group (Fig. 2) exhibited clear pathological changes consistent with cryptosporidiosis. These included distorted villous architecture, characterized by a reduction of villous height to crypt length ratio. Additionally, there was focal villous epithelial necrosis with ulceration and a noticeable depletion of goblet cells. The villous core also showed expansion due to inflammatory cellular infiltrate.

Treatment with Nitazoxanide (NTZ) alone demonstrated only minimal improvement in histopathological alterations (Fig. 3). The sections still presented moderate to severe villous atrophy, ulcerated tips, and continued inflammatory cell infiltration in the lamina propria.

Conversely, treating the infected group with Resveratrol (RSV) resulted in mild improvement (Fig. 4). These sections largely maintained their mucosal architecture, showed a moderate number of goblet cells, and had only a mild mixed inflammatory cellular infiltrate.

Most notably, intestinal sections from the infected group treated with combined NTZ and RSV (Fig. 5) displayed remarkable improvement in the histopathological changes induced by cryptosporidiosis. This was evident through a preserved villous configuration with only a mild mixed inflammatory cellular infiltrate.

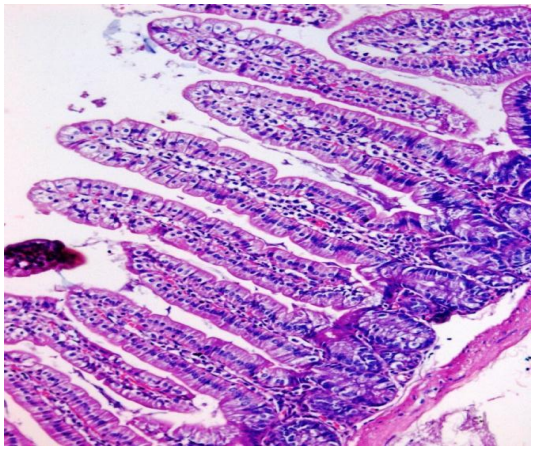

Figure 1: Sections of small intestine from **G A1** (negative control) showed nearly normal villous architectures with average length and width of villi. Goblet cells were moderate in number with a healthy well-defined brush border (H&E stain x 200).

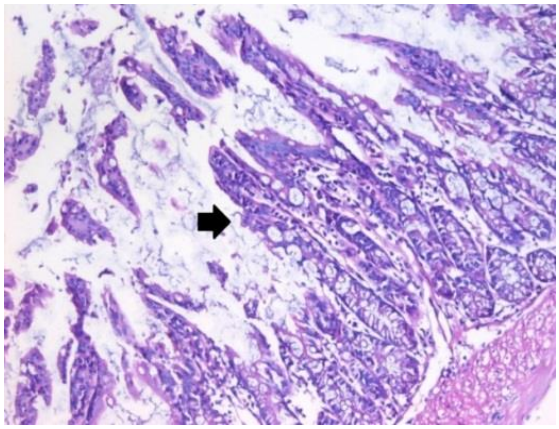

Figure 2: Sections of small intestine from **G A2** (positive control) showed distorted villous pattern and marked inflammatory changes (black arrow) (H& E A, X200).

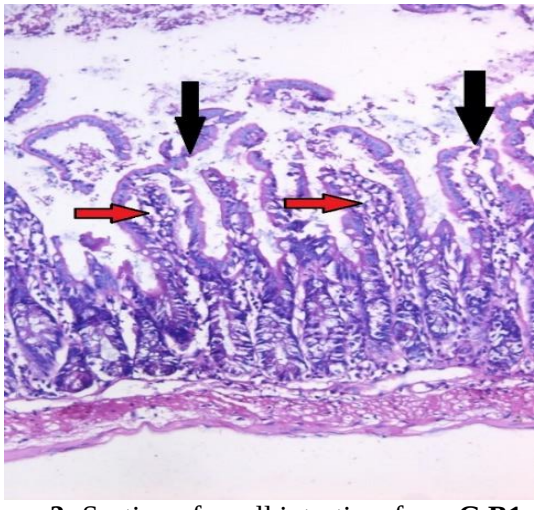

Figure 3: Section of small intestine from **G B1 (**treated with NTZ) showed distorted villous pattern with shortening and ulceration of tips (black arrows) and moderate inflammatory changes (red arrows) (H & E, X200).

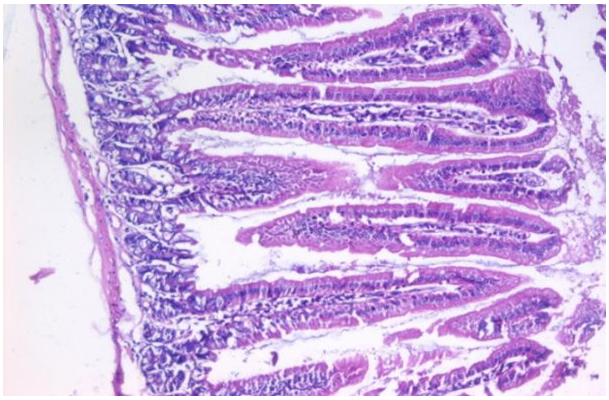

Figure 4: Section of small intestine from **G B2 (**treated with RSV) showed mostly preserved mucosal architecture and mild inflammatory changes (H& E, X200).

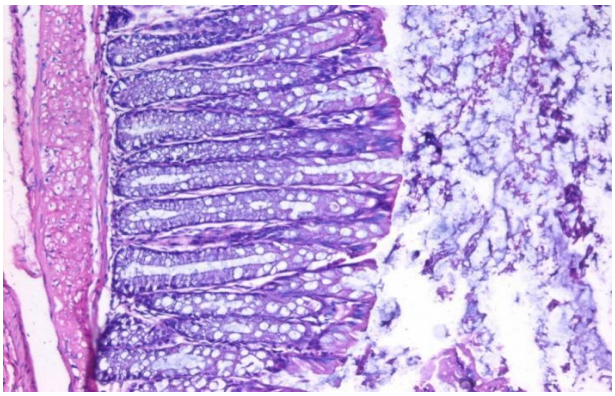

Figure 5: Sections of small intestine from **G B3** (treated with combined NTZ& RSV) showed preserved villous pattern and mild inflammatory changes (H& E, X200).

DISCUSSION

At present, there are no available vaccines against *C. parvum* and therapeutic agents that target the parasite have limited efficacy. So, developing new, safe and effective antiparasitic compounds targeting the parasite would limit the global morbidity and mortality rates. This is particularly true for children residing in developing countries, where the pervasive issues of poor sanitation and frequent waterborne outbreaks significantly contribute to the high incidence and severity of the disease [(19)].

Nitazoxanide (NTZ) is currently the sole FDA-approved drug for cryptosporidiosis. Numerous studies have investigated NTZ monotherapy or its combination with other agents for treating *Cryptosporidium* infection [(20)]. In the current study, NTZ treatment in infected mice resulted in a highly significant reduction in oocyst shedding (52.0%) by day 21 post-infection ($p < 0.001$). These results are in alignment with previous research by **Oshiba *et al.* [(21)] and Abdelmaksoud *et al.***

[22], who reported comparable oocyst reduction rates (50%, and 53.5%) in immunocompromised mice treated with NTZ.

Regarding Resveratrol (RSV), this experimental animal study is the first to report its *in vivo* effect on *Cryptosporidium* infection. Resveratrol treatment in immunosuppressed mice led to a highly significant reduction in oocyst shedding (64.2%) by day 21 post-infection ($p < 0.001$).

Notably, the combination of NTZ and RSV demonstrated a synergistic effect against infection in mice, resulting in a significantly greater reduction in oocyst shedding ($p < 0.001$). Mice receiving combined NTZ and RSV therapy exhibited a 73.2% reduction in oocyst shedding by day 21 post-infection ($p < 0.001$). This represents the highest reduction observed, surpassing NTZ alone (52.0%) and RSV alone (68.70%) on the same day. These results align with studies reporting synergistic effects of NTZ combined with other drugs in *Cryptosporidium* treatment. For instance, **Taha *et al.*** [23] found that combining Atorvastatin with NTZ yielded a 72.8% reduction in oocyst shedding, higher than NTZ alone (52.3%) or Atorvastatin alone (55.2%) in immunocompromised infected mice.

Interestingly, RSV as a monotherapy in the current study achieved a higher percentage of oocyst reduction than NTZ alone. The most substantial reduction was observed with the combined NTZ & RSV treatment. This supports the established anti-parasitic properties of RSV, consistent with findings for other protozoa. For example, **Pais-Morales *et al.*** [17] showed RSV inhibited *E. histolytica* trophozoite virulence *in vitro* and *in vivo* by halting cell development and inducing oxidative stress. **El-Sayed *et al.*** [24] demonstrated a potent inhibitory effect of RSV against *Babesia bovis in vitro*, suggesting its potential as a standalone or combination therapy with traditional antibabesial drugs like azithromycin to mitigate side effects. Also, **Mousavi *et al.*** [25] reported valuable inhibitory effect of RSV against *Leishmania* in both *in vitro* and *in vivo* assays, with no cytotoxicity to the cell line used. It's noteworthy that RSV can modulate cellular immunity and possesses numerous biological activities, including antimicrobial, antioxidant, anti-inflammatory, cardioprotective, neuroprotective, and anticancer properties [8,26]. Furthermore, RSV inhibits the growth of certain pathogenic bacteria and fungi and is recognized as a therapeutic compound for various infectious diseases, extensively utilized in preclinical studies [27].

Cryptosporidium-infected, non-treated mice exhibited profound histopathological alterations in the intestinal mucosa. These changes included dislodging of the brush border, asymmetrical loss of epithelial cells, villous shortening, atrophy, broadening, a decreased villous height to crypt length ratio, goblet cell depletion, and infiltration of the lamina propria with inflammatory cells, primarily lymphocytes and eosinophils, in response to infection. These findings concur with **Henin** [28]**.**

Nitazoxanide treatment resulted in only mild improvements in intestinal structure, characterized by persistent epithelial shedding of intestinal villi and noticeable subepithelial edema. Moderate inflammatory cell infiltrations were observed in the mucosa and submucosa, consistent with reports by **Abdelmaksoud *et al.*** [22] **and Ghareeb *et al.*** [29].

In contrast, histopathological examination of RSV-treated mice revealed partial improvement in cryptosporidiosis-induced changes. Evidence of the enhancement involved a partial recovery of the intestinal mucosa, preserved villous patterns, and regeneration of goblet cells. Mild non-specific inflammatory cell infiltrations were noted in the lamina propria and villous core, with a moderate reduction in the villous height to crypt length ratio.

Mice treated with the combination of NTZ & RSV demonstrated marked improvement in histopathological changes. This included complete healing of the intestinal mucosa, preserved villous patterns with a normal small intestinal crypt-to-villous ratio, regeneration of goblet cells, and a mild lymphocytic inflammatory reaction in the villi and lamina propria. This improvement can be attributed to the reduced oocyst burden and/or the known anti-inflammatory activities of the compounds, leading to decreased cytokine production. Overall, this study successfully demonstrated the restoration of normal villous structures and a reduction in oocyst shedding in the feces of experimental animals following RSV treatment (100 mg/kg). Furthermore, the study revealed that RSV has superior efficacy compared to NTZ, the current drug of choice for cryptosporidiosis.

CONCLUSION

Given the persistent global burden and limitations of current cryptosporidiosis treatments, there is an urgent focus on novel alternatives. Resveratrol (RSV), as a monotherapy, demonstrated remarkable improvements in parasitological and histopathological parameters, indicating its potential as a drug candidate. Crucially, the strategic combination of Nitazoxanide (NTZ) and RSV exhibited a pronounced synergistic antiparasitic effect. This combination led to significantly enhanced reductions in oocyst shedding and substantial improvement in intestinal damage, surpassing the effects of NTZ alone. This study provides robust evidence for the anti-*Cryptosporidium* efficacy of RSV, highlighting its promise in combined

therapeutic regimens for effective cryptosporidiosis control.

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