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Article

Exploration of Solanum xanthocarpum Schrad. & Wendl. against Mycobacterium avium Subspecies paratuberculosis and Assessment of Its Immunomodulatory and Anti-Inflammatory Potential

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Abstract: Mycobacterium avium subspecies paratuberculosis (MAP), being a dairy-borne pathogen, resistant of pasteurization and other sterilization techniques, is a major cause for development of inflammatory bowel disorders such as Johne's disease (JD) in dairy animals and Crohn's Disease (CD) in humans, for which no therapy is available to date. In the absence of effective therapy or a vaccine, management of CD has been accomplished by removal of the affected intestines. However, usually, even after removal of 2/3 of the intestine, CD reoccurs. Hence, there exists a need to develop an alternative therapy for such infection. The potential of herbals remains unexplored against MAP and related infections. Therefore, the conducted study is a novel initiative for the evaluation of anti-mycobacterial activity of bioactive extracts of Solanum xanthocarpum Schrad. & Wendl. against MAP infection. The said plant was authenticated according to the Ayurvedic Pharmacopoeia of India. Qualitative and quantitative evaluation of the extracts were done using chromatographic and spectroscopic techniques. Preliminary in vitro pharmacological assessments revealed the immunomodulatory and anti-inflammatory potential of the extracts. REMA assay was conducted to determine their anti-MAP activity along with determination of the best active extract. The hydro-alcoholic extract showed the best inhibition of MAP, providing a potential ray of hope against this emerging major pathogen of animals, and associated with Crohn's disease and other autoimmune disorders in human beings.

Keywords: Solanum xanthocarpum Schrad. & Wendl.; Johne's disease (JD); Crohn's disease (CD); Mycobacterium avium subspecies paratuberculosis (MAP); immunomodulatory; anti-inflammatory

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1. Introduction

In India, Mycobacterium avium subspecies paratuberculosis (MAP) infection is endemic in domestic livestock [1]. The infection has been reported in ruminants, wild life [2,3] and human beings. Live bacilli have been recovered from milk in domestic livestock [4,5], human breast milk [6], and other milk products [5,7]. These bacilli are excreted through milk and are not inactivated during pasteurization [8], resulting in human infection. Infection has also been associated with a large number of autoimmune disorders in the human population [9]. Infection of domestic livestock with MAP also leads to huge losses in productivity [1]. Infected animals are characterized by a decline in body condition, weight loss (which might or might not be accompanied with diarrhea), loss in productivity (milk and meat) and reduced fertility. They also become susceptible to other infections due to the growth of bacilli within macrophages in the germinal centres of lymph nodes.





Article

Ursolic Acid and Solasodine as Potent Anti-Mycobacterial Agents for Combating *Paratuberculosis*: An Anti-Inflammatory and In Silico Analysis

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Abstract: Mycobacterium avium subspecies paratuberculosis (MAP) infection in domestic livestock causes persistent diarrhea, weight loss, and death and is also a potential cause of Crohn's disease (CD) in humans; notably, treatments against MAP are insufficient, costly, and can cause adverse reactions. Hence, plant-derived bioactive constituents have been taken into consideration in this regard. Herein, we present the results of two bioactive constituents (Solasodine and Ursolic acid) that were evaluated for their safety and efficacy against MAP protein (Dephospho-Coenzyme A kinase (DPCK) by utilizing in vitro assays and different tools of in silico biology. The ADME/t-test, the drug-likeness property test, pharmacophore modelling, and PASS prediction have proven that both the constituents have better binding capacities than the available antibiotic drugs used to target protein inhibition pathways. Through our observations, it can be inferred that these two phytochemicals can be adequately used to treat paratuberculosis, thereby combating inflammatory bowel disorders (IBD) of an autoimmune nature.

Keywords: Crohn's disease; Dephospho-Coenzyme A kinase (DPCK) protein; in silico; *Mycobacterium avium* subspecies *paratuberculosis* (MAP); REMA assay; solasodine; ursolic acid

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Citation: Navabharath, M.; Srivastava, V.; Gupta, S.; Singh, S.V.; Ahmad, S. Ursolic Acid and Solasodine as Potent Anti-Mycobacterial Agents for Combating *Paratuberculosis*: An Anti-Inflammatory and In Silico Analysis. *Molecules* 2023, 28, 274. https://doi.org/10.3390/ molecules28010274

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1. Introduction

Mycobacterium avium subspecies paratuberculosis is the causative agent of Johne's disease (JD), a chronic infectious disease of ruminants that is widespread throughout the world and causes significant production losses and human infection (Zoonotic) (MAP). In ruminants, the disease causes debilitation or cachexia. Due to its zoonotic potential, it has received significant attention. IBD, Crohn's disease, ulcerative colitis, Type 1 diabetes, thyroiditis, and rheumatoid arthritis are examples of autoimmune diseases and co-morbidities that increase susceptibility to MAP infection [1-11]. When MAP infects susceptible people, it often kills MAP bacilli in the gut, thereby causing inflammatory reactions and possibly harmful inflammatory reactions in other organs. In some cases, chronic diseases have been suspected to be associated with the etiology of Mycobacterium avium subspecies paratuberculosis (MAP) in domestic livestock. This pathogen is endemic across the globe. It is estimated that around 72.0% of US dairy cattle flocks are infected with Johne's disease. In the last 28 years, there has been an increasing trend in the bio-load of domestic livestock [12], which is found to be highest (16.0-54.7%) in sheep, followed by buffaloes (28.3-48.0%), cows (6.0-39.3%), and goats (9.4-20%) [13]. Global and Indian researchers have revealed extremely high levels of live MAP bio-loads in raw and liquid milk as well as milk products. Using six tests (Microscopy, IS900 PCR, I_FAT, d_ELISA,