



Sarcoptes Scabiei Mite Protein As A Cause Of Oxidative Stress On Parasite-Infested Skin

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ABSTRACT

S. scabiei infestation triggers many reactions including allergic reactions, inflammation, innate immune reactions, and activation of immune components in the skin accompanied by oxidative stress stages. This article aims to examine the genetic characterization of *S. scabiei* and gain a better understanding of host-parasite interactions with particular emphasis on skin oxidative stress parameters such as oxidant/antioxidant balance, stress parameters, and immune responses. This article is compiled as a systematic review by examining a number of relevant publications. Based on this search, it was found that to determine the effect of *S. scabiei* infestation on the oxidant/antioxidant balance in serum, oxidative stress markers such as total antioxidant activity (T-AOC), total nitric oxide concentration (TNO), lipid peroxide levels, and malonyldialdehyde (MDA) were used, as well as antioxidant enzyme levels; superoxide dismutase (SOD), glutathione-S-transferase (GSH) and catalase. Oxidative stress has been shown to be involved in the pathogenesis of several parasitic infectious diseases including scabies. Host cell metabolism produces ROS and RNS. At low to moderate levels, they are involved in several physiological functions including cell signaling and immune function. Conversely, at high levels, they cause damage to molecules including lipids, proteins, lipoproteins, and nucleic acids starting from a chain reaction of free radical formation leading to a condition known as oxidative stress. This article recommends a meta-analysis study to obtain more in-depth review results for further research..

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INTRODUCTION

The mite *Sarcoptes scabiei* var. *Hominis* causes the human skin infestation commonly known as scabies. Scabies is identified as a neglected tropical infectious disease, occurring worldwide among all ages, races, genders and socioeconomic strata. It is estimated that about 1-10% of the global population is infested with scabies and infestation rates as high as 50-80% in certain populations. More than 15 different varieties

have been identified which are morphologically similar but have marked physiological and genetic variations in different hosts.(Shumaila et al., 2018)

S. scabiei modulates host immunity, inflammation, and complement reactions to occur on the host skin. *S. scabiei* infestation triggers multiple reactions including allergic reactions, inflammation, innate immune reactions, and activation of immune components in the skin. The salivary fluid of burrowing mites contains different bioactive compounds with the potential to affect host physiological functions.

A study was conducted to determine the oxidant/antioxidant balance in serum after *S. scabiei* infestation, Oxidative stress markers such as total nitric oxide (NO) levels, total serum antioxidant activity, malonyldialdehyde (MDA) concentrations, and antioxidant enzyme levels (superoxide dismutase (SOD), glutathione-S-transferase (GSH), and catalase) were determined and compared with controls. NO levels were evaluated using a commercial kit. The principle of the test is the reduction of NO₃, which is then converted into a blue azo compound. Absorbance was recorded at 630 nm. Antioxidant activity in serum was estimated using a colorimetric kit. Lipid peroxidation levels were measured by malonyldialdehyde (MDA) measurement. MDA levels in serum were measured using a commercial colorimetric-based test kit. Serum catalase, superoxide dismutase, and glutathione-S-transferase levels were measured using ELISA-based methodology using catalase test kits, superoxide dismutase test kits, and glutathione test kits according to the protocol. (De et al., 2020)

METHOD

This article was compiled using a systematic review method by reviewing several relevant scientific publications. Literature searches were conducted through several databases such as Google Scholar and PubMed, using keywords that are in accordance with the topic of study. The selected articles met the inclusion criteria in the form of topic suitability, publication within a certain time frame, and being available in full-text form. Data from the selected articles were analyzed descriptively to present a comprehensive synthesis of findings.

RESULT

Step 1. Microscopic Examination Before Oxidative Stress Testing

Clinical examination in mammals shows that severe pruritus is associated with hyperkeratosis and crusting of the skin. The animal's skin appears thickened and wrinkled, which is typical of crusted scabies/Norwegian scabies.. Based on clinical symptoms, skin scrapings from infested animals were examined under a microscope for the presence of mites. Microscopic examination confirmed the presence of eggs, eggs with six-legged larvae, and the nymph stage of *S. scabiei* (Figure 1). The nymph stage has short legs. The third and fourth pairs of legs never protrude outside the body. Morphologically, the mites cannot be distinguished from other Sarcoptes. (De et al., 2020)

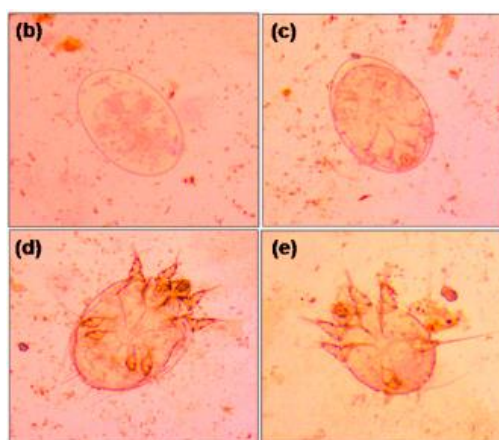


Figure 1. *Sarcptes scabiei* infestation. (b) mite eggs, (c) eggs containing larvae, (d) mite nymphs, (e) mite larval stage (400x magnification) (De et al., 2020)

Scabies is considered a disease of the poor in underdeveloped and developing countries and is a neglected tropical disease. Its wide host range makes its presence necessary for differential identification for epidemiological studies and for designing eradication strategies. Infestation of *S. scabiei* in multiple hosts including humans, pets, livestock, laboratory animals, and wild animals worldwide leads to the spread and dissemination of the pathogen. Bidirectional interactions between humans, animals, pathogens, and the environment may be the reason behind multi-host adaptation (Alexander et al., 2018)

Step 2. Molecular Identification Before Characterization of Oxidative Stress Markers

For molecular confirmation, one mitochondrial gene (COX1) and one nuclear gene (VSSC) were amplified using *Sarcptes*-specific primers and amplicons of both genes were detected in infested pigs whereas no amplicons were observed in control pigs. The specificity of PCR was verified using pig flea (*Haematopinus suis*) DNA as a negative control for both genes. For differential diagnosis and molecular characterization, COX1 and VSSC sequences were obtained with a length of 686 bp and 498 bp, respectively. For phylogenetic analysis, a study took representative sequences of *S. scabiei* COX1 and VSSC from different hosts distributed in different geographical areas. The phylogenetic tree based on VSSC sequences showed three distinct host-specific clusters, one for human isolates (Cluster A) and two for animal isolates (Figure 2c). Within animal isolates, pig and erinaceus isolates formed one cluster (Cluster B) while oryctolagus, golden jackal, vulpes, and canis isolates formed another cluster (Cluster C). Andaman pig isolates were included in Cluster B along with Israeli, Australian pig isolates, and Israeli erinaceus isolates. The VSSC-based phylogenetic tree is presented in Figure 2d and three distinct clusters are depicted (De et al., 2020)

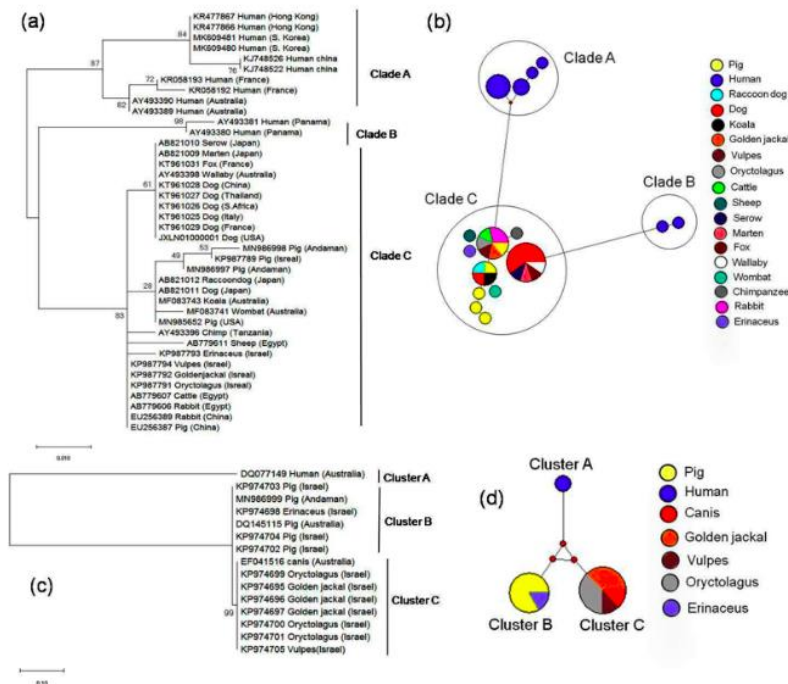


Figure 2. Evolutionary relationships of different *S. scabiei* isolates. (a) COX1-based phylogenetic tree, (b) COX1-based network profile, (c) VSSC-based phylogenetic tree, (d) VSSC-based network profile (De et al., 2020)

Since morphological and serological tests are not much of a basis for multi-host adaptation and success in identifying the degree of variation, molecular markers have been used as an alternative. The mitochondrial cytochrome C oxidase subunit I gene (COX1) is an established alternative differential diagnostic tool. The universal marker mitochondrial cytochrome C oxidase subunit I for species identification due to its high variability is being widely used for DNA coding of medically important parasites. Erster et al. used the nuclear marker VSSC for genetic characterization of *S. scabiei* from multiple hosts in Israel. In this study, we used COX1 and VSSC markers for molecular characterization of *S. scabiei* isolated from pig hosts. The COX1-based phylogenetic tree (Figure 2a) showed that isolates in the animal clade (Clade C) were phylogenetically closer to Clade B (human isolates from Panama) than to Clade A (human isolates from Hong Kong, South Korea, China, France, and Australia). In general, human *S. scabiei* isolates are heterogeneous, and the closeness of Clade B and Clade C may be due to low gene flow between mites of these groups (Pentinsaari et al., 2016)

Stage 3. Determination of Oxidative Stress-Inducing Mite Proteins

To determine the effect of *S. scabiei* infestation on the oxidant/antioxidant balance in serum, oxidative stress markers such as total antioxidant activity (T-AOC), total nitric oxide (TNO) concentration, lipid peroxide levels, and malonyldialdehyde (MDA), as well as antioxidant enzyme levels; superoxide dismutase (SOD), glutathione-S-transferase (GSH) and catalase were determined and compared with control animals. The infested group showed significantly higher serum total nitric oxide (TNO) concentrations compared to the control group. Total antioxidant activity (T-AOC) in the infested group was significantly lower than the control group. Catalase activity, SOD, and GSH



concentrations in infested animals decreased significantly compared to control animals. On the other hand, MDA concentrations in the infested group were found to be significantly higher than the same value in the control group (De et al., 2020)

To investigate whether *S. scabiei* infestation causes stress to the host animals, the levels of stress biomarkers such as serum cortisol concentration and serum levels of four heat shock proteins (HSP20, HSP40, HSP70, and HSP90) in control and infested animals were analyzed by a study. The serum cortisol concentration in the infested group was found to be significantly higher than that of the control group. HSP20, HSP70, and HSP90 were upregulated in infested animals compared to control animals. On the other hand, no significant changes were detected in the levels of HSP40 between control and infested animals (Alexander et al., 2018)

Serum concentrations of three apoptosis markers (Caspase 3, 7, and 8) in infested and control animals were recorded by the researchers. Upregulation of all three apoptosis markers was detected in the infested group compared to the control group. The effect of *S. scabiei* infestation on immunoglobulin concentrations and cytokine levels was evaluated. Significantly higher serum concentrations of IgA, IgG, and IgM were detected in the infested group compared to the control group. Upregulation of pro-inflammatory cytokines (IL-2, IL-6, IL-12, IL-1 β , and IFN- γ) and anti-inflammatory cytokine IL-4 were detected in the infested group compared to the control group. On the other hand, no significant difference in IL-8 concentrations between the two groups was detected. [5] Increased ALT, AST, ALP, LDH, CK, and decreased albumin and glucose levels in infested animals indicate organ damage, especially impaired liver function. Oxidative stress has been associated with cell necrosis and apoptosis through activation of several cell signaling pathways such as JNK, mitogen-activated protein kinase (MAPK) leading to cell and organ damage. It is a well-known fact that oxidative stress causes liver damage because the liver is the main target organ of ROS. In addition, free radicals, especially ROS catalyze the oxidation of LDL to produce oxidized LDL which also promotes cellular apoptosis in various organs

In this study, crustose scabies caused oxidative stress in pigs which may have adverse effects on organs including the liver. Organ damage due to oxidative stress may explain the increased levels of AST, ALT, and alkaline phosphatase. Alterations in biochemical parameters were also reported in goats and dogs affected by scabies. Since the liver is the main organ for albumin synthesis and glucose formation through gluconeogenesis and glycogenolysis, impaired liver function may be due to the low levels of glucose and albumin in infested animals. In addition, high ROS have been reported to interfere with insulin signaling leading to increased insulin secretion; which may be another reason for the low glucose concentration in infested animals. Conversely, the upregulation of globulin production in infested animals may be due to the production of antibodies against *S. scabiei* antigens. (Beigh et al., 2016)

Increased levels of pro-inflammatory cytokines after infestation may be the cause of dyslipidemia. Increased serum levels of pro-inflammatory cytokines such as IL-2, IL-6, IL-12, IL-1 β , and IFN- γ in infested animals were detected in this study. Pro-inflammatory cytokines such as IL-6, IFN- γ inhibit the activity of lipoprotein lipase (LPL) which inhibits the clearance of VLDL and LDL cholesterol leading to increased concentrations

in the blood. In addition, crusted scabies induces oxidative stress in animals, and under oxidative stress conditions, ROS induces activation of atherogenic genes through NF-kappa B which may further explain atherogenic dyslipidemia in infested animals. In addition, alopecia due to infestation disrupts the skin-environment interface which in turn inhibits thermoregulation as excessive heat loss to the environment occurs through the skin. This creates a negative energy balance in the host. Mobilization of fat from fat stores to meet the energy deficit may lead to an imbalance in the lipid profile. An imbalance in fatty acid composition in adipose tissue with up-regulated omega-6 acids and down-regulated omega-3 acids in wombat hosts infested with *S. scabiei* has been reported.

The results of the study showed that crusted scabies can change the lipid profile into atherogenic dyslipidemia with high susceptibility to cardiovascular disorders in animals (Martin et al., 2018)

A study determined serum cortisol concentrations which are considered as stress biomarkers. The study found a significant increase in serum cortisol concentrations in infested animals compared to control animals indicating that infestation triggers a stress response. The hypothalamic-pituitary-adrenal (HPA) axis, an important stress hormone regulator, is thought to be involved in the production of cortisol hormone. Under stress conditions, activation of the HPA axis followed by increased plasma cortisol levels is an adaptive response of the host. HSPs are constitutively produced under normal physiological conditions whereas any stress including environmental stress, viral infection, glucose deprivation, toxic exposure, and oxidative stress induces overexpression of HSPs or cellular stress proteins.

HSPs are classic examples of proteins involved in a number of physiological functions. In addition to acting as chaperones and protein folding, the involvement of HSPs in immune functions such as antigen processing and presentation, innate receptor expression and stimulation of innate immunity has been well documented by numerous studies. In addition, HSPs, especially HSP70 and 27 play a critical role in stress-induced DNA repair by modulating DNA repair enzymes, thereby maintaining genome integrity. Stress regulates intracellular HSP production and release into the circulation via a non-classical secretory pathway. In the study, crustose scabies induced cellular and oxidative stress which in turn may stimulate excessive HSP expression. Thus, activation of the heat shock response regulated by HSPs is a mechanism of adaptation under stress (Pockley & Henderson, 2018)

Oxidative stress shifts the intracellular environment towards an oxidative state which in turn disrupts the native conformation of proteins and proteins lose their folded structure. HSPs act as sensors of cellular redox changes in both prokaryotes and eukaryotes; thus signaling for activation of the heat shock stress response. HSP70 and HSP90 act as major sensors of protein misfolding. In addition, HSP27 has been reported to act as an antioxidant by preventing glutathione oxidation under oxidative stress. HSP70 and HSP90 act as anti-apoptotic proteins; they exert their role by binding to apoptosis protease activity factor 1 (Apaf-1) which blocks the downstream cascade of the apoptotic pathway. In the study, animals infected under oxidative stress conditions may have induced cellular apoptosis. This is supported by the upregulation of serum levels of apoptosis markers in infected animals. Upregulation of HSPs in infected animals may be an adaptive mechanism to prevent cellular apoptosis (Bolhassani & Agi, 2019)

Oxidative stress has been reported to be involved in the pathogenesis of several diseases including parasitic infections. Cellular metabolism produces reactive oxygen species



(ROS) and reactive nitrogen species (RNS). At low to moderate levels, they are involved in several physiological functions including cell signaling and immune function. Conversely, at high levels, they cause damage to molecules including lipids, proteins, lipoproteins, and nucleic acids starting a chain reaction of free radical formation leading to a condition known as oxidative stress. Therefore, tight regulation of ROS and RNS production and the balance between beneficial and detrimental effects are essential for cellular homeostasis. Under oxidative stress, the antioxidant defense system elicits several antioxidant enzymes to combat free radicals and maintain homeostasis (Phaniendra et al., 2015)

Superoxide dismutase (SOD), catalase, and glutathione peroxidase act as first-line antioxidant defenses against disease, suppressing or preventing the formation of reactive species in cells. SOD catalyzes the conversion of O_2 to H_2O_2 which is further reduced to H_2O and O_2 by catalase or glutathione peroxidase. In a study, it was observed that crustose scabies caused an increase in total serum NO production in pigs. Although the study did not measure ROS, induction of oxidative stress in infested animals was seen from the decrease in total antioxidant capacity, catalase activity, SOD, and GSH concentrations and an increase in MDA concentrations compared to control animals. The downregulation of T-AOC and antioxidant enzymes suggests that they have been consumed excessively to overcome oxidative stress.

S. scabiei infestation is associated with modulation of various parameters of the host immune response; humoral, adaptive, and inflammatory immune responses. IgA, IgG, and IgM are the major immunoglobulins associated with humoral immunity. IgM is produced in the early stages of the antibody response to foreign antigens. IgG, as the most abundant antibody in blood and extracellular fluids, is involved in the systemic immune response. IgA is generally associated with mucosal immunity and is mainly found in secretions. In this study, an upregulation of total IgA, IgG, and IgM was observed in infested pigs compared to the control group. The increased immunoglobulin levels in infested animals indicate that the mites have elicited an antibody-mediated immune response to mite antigens although it is not possible to know whether the antibody response is specific to *S. scabiei* or not. The upregulation of total IgG may be due to secondary bacterial infection which is common in scabies infestation. Increased IgG in rabbits, dogs infested with *S. scabiei*, and humans has been reported. Elevated circulating IgA levels have been reported in human crusted scabies (Luo et al., 2013)

A study assessed the systemic inflammatory response of animals by determining serum levels of pro-inflammatory cytokines including IL-1 β , IL-2, IL-6, IL-12, and IFN- γ and anti-inflammatory cytokine IL-4. Cytokines play an important role in host immune and inflammatory responses as well as in maintaining tissue integrity. The study noted a dysregulation of cytokine balance that may be due to modulation of immunity by antigens released by *S. scabiei*. Th1 and Th2 are the two major subpopulations of T helper cells and parasitic infections are associated with Th1 or Th2 polarized immune responses. IL-2, TNF- β , and IFN- γ are specific cytokines of Th1 cells while Th2 cells release IL-4, IL-5, IL-10, and IL-13 as typical cytokines. Naive T helper cells (Th0) can be differentiated into Th1 or Th2 based on different activation pathways; Cytokines such as IFN- γ and IL-

12 activate Th0 cells to Th1, conversely, IL-10 and IL-4 are important stimulatory cytokines for Th2 cell polarization. The delicate balance between various cytokines is essential for homeostasis of mammalian species and an imbalance can pose a threat to health (Hu et al., 2013)

In this study, *S. scabiei* infestation was associated with upregulation of IL-2, IFN- γ , IL-1 β , and IL-4 indicating both Th1 and Th2 responses. The most likely cause of the mixed Th1/Th2 response may be a dysregulation of the cytokine balance due to modulation of immunity by *S. scabiei*-released antigens or changes in cytokine levels after chronic infection. Th1 immune responses are generally associated with protection in most infectious diseases while Th2 immune responses elicit high levels of antibody production and cell-mediated inflammation. In addition, allergic inflammatory diseases are dominated by Th2 immune responses. The induction of mixed Th1/Th2 immune responses in this study suggests that the immune response to scabies is complex and analysis of local immune responses is needed to better understand this disease. Th2 responses have been described as the dominant immune response in crusted scabies and other allergic inflammatory disorders. Bioactive compounds in arthropod saliva trigger different immune responses against their hosts. Low molecular weight saliva components cannot act as antigens but can bind to skin proteins as haptens and stimulate Th1 responses. Some salivary antigens can cause basophil hypersensitivity (Th1 response) by binding to epidermal Langerhans cells. Salivary antigens can also trigger Th2 responses associated with IgE production and type I hypersensitivity. (Cicchese et al., 2018)

Stage 4. Histopathology of Skin Affected by Oxidative Stress Due to Scabies

Parakeratotic hyperkeratosis is characterized by thickening of the stratum corneum and the presence of a core. Mites along with their exoskeletons and remains are detected in the stratum corneum tunnel of the epidermis and appear as gaps in the upper epidermis. The epidermis shows acanthosis and spongiosis associated with dense eosinophilic dermal infiltration. Perivascular or diffuse superficial lymphocyte and histiocyte infiltration, accompanied by neutrophils and eosinophils are perivascular or diffuse lymphocyte and histiocyte infiltration, accompanied by neutrophils and are clearly visible in the dermis. There is psoriasiform hyperplasia characterized by projection of the epidermis into the dermis for interdigitation with dermal papillae (De et al., 2020) Excessive squama production indicates crust formation (Figure 3).

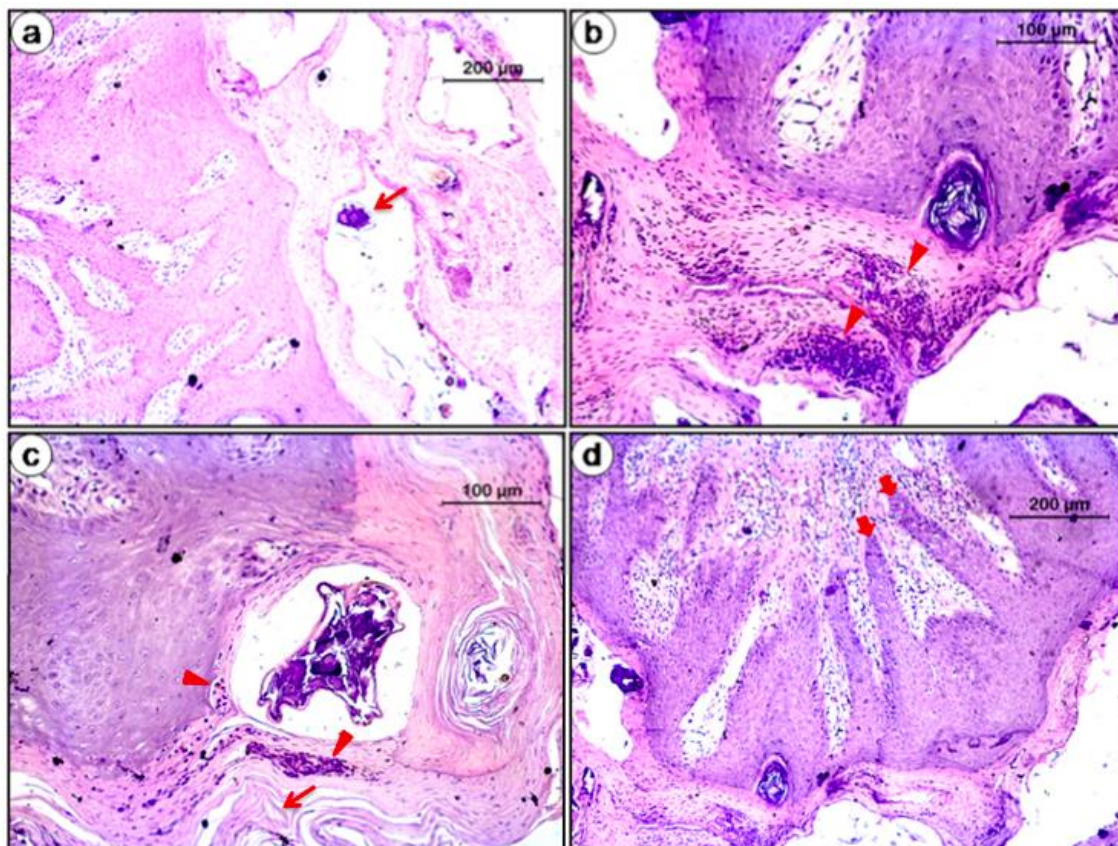


Figure 3. Histopathological picture of skin infested with scabies. (a) Mites with their axoskeletons in the stratum corneum of the epidermis, (b,c) parakeratotic hyperkeratosis characterized by thickening of the stratum corneum and excessive scale production (De et al., 2020)

The histopathological findings in Kumar et al's study are similar to the classic narrative of sarcoptic scabies in mammalian species. Antigenic materials including excretions and secretions of the mites trigger a hypersensitivity reaction in the skin which may be the reason behind the eosinophilia observed in infested animals. This observation is consistent with other studies in vulpes, raccoon dogs, wombats and Iberian ibex (Espinosa et al., 2017)

CONCLUSION

Oxidative stress has been shown to be involved in the pathogenesis of several parasitic infectious diseases including scabies. Cellular metabolism produces ROS and RNS. At low to moderate levels, they are involved in several physiological functions including cell signaling and immune function. Conversely, at high levels, they cause damage to molecules including lipids, proteins, lipoproteins, and nucleic acids starting a chain reaction of free radical formation leading to a condition known as oxidative stress. Therefore, in the production of ROS and RNS and the balance between beneficial and detrimental effects is crucial for cellular homeostasis. Under oxidative stress, the

antioxidant defense system elicits several antioxidant enzymes to combat free radicals and maintain host homeostasis.

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