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Quercetin supports acaricidal activity of ivermectin against naturally acquired sarcoptic mange in pigs

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ABSTRACT

Sarcoptic mange triggers continuous oxidative onslaughts, resulting in severe oxidative stress in pigs and, to date, no antioxidant has been evaluated for the treatment of naturally infested pigs. This randomized clinical trial aimed to assess the ameliorative potential of the antioxidant quercetin (QR) when integrated with ivermectin (IVM) in the treatment of sarcoptic mange in pigs. The control group (T_0, n=10) consisted of healthy subjects. The first treatment group (T_1, n=10) consisted of infested pigs receiving the standard treatment (subcutaneous IVM only) while the second treatment group (T_2, n=10) consisted of infested pigs receiving integrated treatment (subcutaneous IVM plus oral QR). On day 0, the circulating malondialdehyde (MDA) was significantly higher and superoxide dismutase (SOD), reduced glutathione (GSH), catalase (CAT), total antioxidant capacity (TAC) and antioxidative minerals (zinc, copper, iron) were lower in all infested pigs compared to the healthy subjects. On day 14 post-treatment, maximum recovery was observed in the MDA, SOD, GSH, CAT, TAC, zinc, copper and iron in group T_2 and the results returned to normal earlier in group T_2 than in T_1. Likewise, more significant improvements in parasitological cure rate, scratching index and skin score were recorded after treatment in group T_2 than group T_1. These results suggest the greater effectiveness of IVM plus QR than IVM alone against sarcoptic mange, and quercetin may be recommended as an ancillary therapy with IVM to negate severe oxidative stress, improve post-therapy convalescence and produce a speedy recovery in pigs.

Key words: integrated treatment; oxidative stress; pigs; quercetin; sarcoptic mange

Introduction

Sarcoptic mange is a common and easily transmissible dermatological condition of mammals (RAMBOZZI et al., 2007). In pigs, it is mainly caused by the burrowing mite, *Sarcoptes scabiei* var *suis* (SMETS and VERCRUYSSE, 2000; DE VEGA et al., 1998). It causes a vesico-pustular inflammation of the skin, characterised by scabby lesions, pruritus, head shaking, erythema, papular dermatitis, alopecia and hyperkeratotic crusts in the ears (SUBRAMANEYAAN et al.,

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2012). In addition, sarcoptic mange can stimulate oxidative stress and thus damage to lipids, proteins, DNA, etc. (DIMRI et al., 2014). Oxidative stress has already been demonstrated in sarcoptic mange in buffalo (DIMRI et al., 2008), dogs (BEHERA et al., 2011) and camels (SALEH et al., 2011). Scanty literature is available on the application of antioxidants along with the standard scabicidal drug IVM (ivermectin) to combat oxidative stress in pigs caused by *S. scabiei* mites. Ivermectin is a widely used anti-parasitic drug against endoparasites and ectoparasites in domestic animals (SUAREZ et al., 2013). It acts as an agonist of γ-aminobutyric acid (GABA) receptors and glutamate-gated chloride-channels (BLOOM, 1996), it interferes with the gastrointestinal function of parasites, leading to starvation (RENUKAPRASAD et al., 1989) and generates free radicals resulting in a cytotoxic effect on the parasite (GURGOZE et al., 2003; ZAHNER et al., 1997).

Free radicals play an important role in host defense against invading mites, however, their excessive production leads to lipid peroxidation (LPO) of cellular membranes, tissue damage and metabolic dysfunction (SINGH and DIMRI, 2013). Although several endogenous antioxidants, such as superoxide dismutase (SOD), glutathione (GSH) and catalase (CAT), are present in the body, uncontrolled generation of oxidants overpowers them and exogenous antioxidant supplementation may be required (CAMKERTEN et al., 2009). One such exogenous antioxidant is quercetin (3, 5, 7, 3', 4'-pentahydroxyflavone) which is a typical flavonoid antioxidant (HOLLMAN and ARTS, 2000) and it exerts its strong antioxidant effect by direct scavenging of reactive oxygen or nitrogen species (ROS/RNS), suppression of enzyme activity associated with ROS production, and chelation of metal ions from redox reaction (MIRA et al., 2002; MIDDLETON et al., 2000; ZHU et al., 2000).

This study aimed to assess integrated treatment strategy and combine the oral antioxidant quercetin with standard ivermectin therapy to inhibit free-radicals and thus, support the scabicidal effect of ivermectin in infested pigs. Here, we report for the first time the use of adjunct quercetin therapy in pigs to counter the oxidative stress co-occurring during sarcoptic mange.

Materials and methods

Study design. The study was carried out on a population of young domestic pigs (1-3 years) of both sexes raised in the Doon valley of Uttarakhand state, Northern India (latitudes 29°58' N and 31°2' N and longitudes 77°34' E and 78°18' E). All the pigs were raised under similarly organized farming systems. Thirty crossbred pigs were included in the present study. After thorough clinico-parasitological examination, the pigs were divided into three groups. Clinically healthy pigs served as healthy controls and received no treatment (T_0, n=10). Pigs suspected as having scabies with evident clinical signs, such as intense pruritus, small red papules, crust formation, ear shaking and alopecia, were selected. The confirmatory diagnosis was performed by microscopic examination of skin scrapings from the margins of active lesions and identification of *S. scabiei* var *suis* mites based on their characteristic morphological features. A minimum of 10 fields were examined and the pigs with at least 3 mites per field were regarded as scabies positive. Twenty pigs positive on microscopic examination that exhibited at least three clinical signs were recruited for the present study and divided into two treatment groups. The first group of infested pigs (T_1=Scabies+/IVM+, n=10) received two subcutaneous IVM injections (1% w/v) (Hitek™, Virbac Animal Health India Pvt. Ltd.) (0.3 mg/kg) at a one week interval. The second infested group (T_2=Scabies+/IVM+/QR+, n=10) received integrated treatment in the form of IVM (in the same manner as in T_1), plus QR (Quercetin™, MRM) (25 mg/kg bid per os) (HSIU et al., 2002) daily for 1 week. All the procedures were conducted in compliance with the universal ethical standards and had approval from the Institutional Animal Ethics Committee, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India (approved under SEED/SARTHI/HP/19/2012). The blood collection from the auricular vein and all clinico-parasitological examinations were done on days 0, 7 and 14. Serum was harvested and stored at -20 °C until further processing.

Clinico-parasitological examination.

a) Parasitological cure rate. This is the proportion of pigs negative for *S. scabiei* var *suis* on the basis of microscopic examination of the deep skin scrapings obtained after the first treatment. A minimum of 10 fields were examined.

b) Scratching index (SI). The infested pigs were observed shortly before each treatment in groups for 15 minutes, and SI was calculated as the number of scratching episodes divided by the number of pigs observed. SI above 0.4 was considered positive for sarcoptic mange (SMETS et al., 1999).

c) Skin score. The skin lesions were scored weekly for clinical severity on a 0-8 scale (0=normal, 1=mild papular rash, 2-4=papular rash, exudate, red skin, > 4=crusts, 8=severe crusts, ear lesions) (RAMPTON et al., 2013).

Oxidant-antioxidant profiling. 10% RBC hemolysate was prepared by the method of QASIM and MAHMOOD (2015) and used to measure circulating malondialdehyde (MDA) concentration and the activities of antioxidant enzymes. Lipid peroxidation (LPO) was determined by the method of PLACER et al. (1966) and expressed as nmoles of MDA per ml. Superoxide dismutase (SOD) activity was measured by the method of MARKLUND and MARKLUND (1974) and MASAYASU and HIROSHI (1979). SOD was expressed as U/mg Hb. Catalase (CAT) activity was measured by the method of COHEN et al. (1970) and expressed as U/mg Hb. Reduced glutathione (GSH) was estimated by the method of PRINS and LOOS (1969) and expressed as mmol/L. Total antioxidant capacity (TAC) was measured by the method of MILLER and RICE-EVANS (1997) using a test kit (Sigma-Aldrich Co.™, USA) and expressed as mmol/L. The serum concentration of antioxidant minerals, such as iron (Fe), zinc (Zn) and copper (Cu), was measured using commercial test kits (Coral Clinical Systems™, India). The concentration of each mineral was expressed in µg/ml.

Statistical analysis. Data were subjected to analysis of variance for a randomized clinical trial. The analysis was done using the SPSS program for Windows, version 17 (SPSS, Chicago, IL, USA).

Results

The effect of the integrated treatment on clinico-parasitological indices. On day 0, clinical signs were observed such as intense pruritus, erythematous skin, patchy alopecia, hyperkeratosis and crust. In the treatment groups, skin lesions began to heal gradually and became normal by day 14. However, early (3-5 days) and maximum recovery was seen in group T_2, i.e. the integrated treatment group. The skin scrapings of infested pigs were examined three times on days 0, 7 and 14. On day 0, microscopic examination of infested pigs showed the presence of *S. scabiei* var *suis* mites. The parasitological cure rate for groups T_1 and T_2 on day 7 was 50% and 60%, while on day 14, it increased to 80% and 100%, respectively. On days 7 and 14, there was a more profound reduction in pruritus and skin lesions in group T_2 (the integrated treatment group) compared to T_1 (Fig. 1). On day 0, the SI of the infested pigs (T_1 & T_2) ranged from 0.7 to 2.2, while it was ≤ 0.3 in healthy subjects (T_0). On days 7 and 14, there was a marked reduction in pruritus and faster improvement in SI was noticed in group T_2 compared to T_1 (Fig. 2).

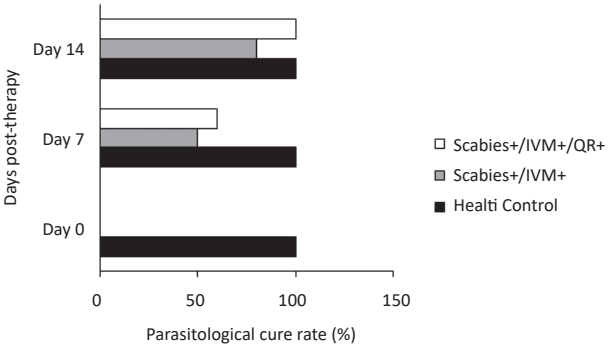


Fig. 1. The effect of different treatments on the parasitological cure rate of pigs

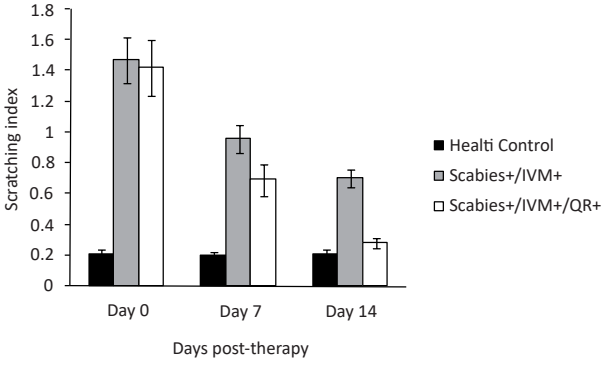


Fig. 2. The effect of different treatments on the scratching index of pigs

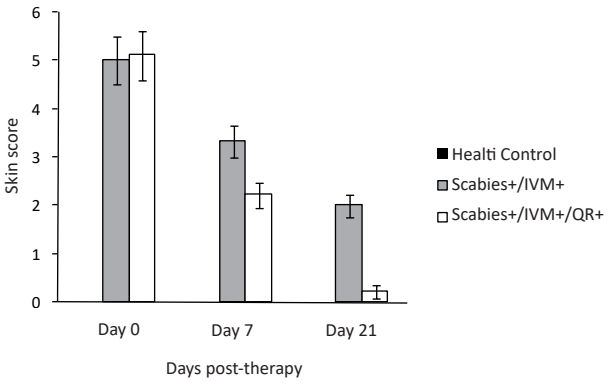


Fig. 3. The effect of different treatments on skin score of pigs

Before treatment on day 0, the skin scores of infested pigs (T_1 & T_2) were found to lie in the range of 3-8, while they remained 0 in healthy pigs. On day 7, there was considerable healing and a non-significant (P>0.05) reduction of skin scores in group T_2 compared to T_1. However, on day 14, the skin scores of IVM/QR-treated pigs reached baseline values, while they remained elevated in T_1 treated with IVM alone (Fig. 3).

The effect of the integrated treatment on circulating MDA levels. On day 0, blood MDA levels (LPO marker) of all the infested pigs in groups T_1 & T_2 were significantly (P<0.05) increased in comparison with the healthy controls (T_0). On day 7, no appreciable improvement was recorded in MDA values in T_1, however, there was a significant (P<0.05) reduction in MDA in T_2. On day 14, baseline values were reached in T_2 while MDA levels were still significantly elevated and far from normal in T_1 (Table 1). This clearly indicates faster recovery and the better efficacy of IVM/QR integrated therapy in pigs with sarcoptic mange.

Table 1. The effect of different treatments on oxidative stress biomarkers in pigs

Group	Day 0	Day 7	Day 14	Mean	SE*		Day 0	Day 7	Day 14	Mean	SE*
LPO (nmol MDA/ml)							SOD (U/mg Hb)				
T_0	4.02^{aA}	4.01^{aA}	4.01^{aA}	4.01	0.05		2.02^{aB}	2.03^{aC}	2.02^{aB}	2.02	0.04
T_1	7.95^{cB}	6.99^{bC}	5.89^{aB}	6.94	0.05		0.50^{aA}	0.94^{bA}	1.27^{cA}	0.90	0.02
T_2	7.97^{cB}	6.28^{bB}	4.08^{aA}	6.11	0.06		0.49^{aA}	1.07^{bB}	2.01^{cB}	1.19	0.03
Mean	6.65	5.76	4.66				1.00	1.35	1.77		
SE*	0.06	0.05	0.05				0.03	0.02	0.03		
GSH (mmol/L)							CAT (U/assay)				
T_0	5.08^{aB}	5.07^{aC}	5.09^{aB}	5.08	0.03		5.16^{aB}	5.16^{aC}	5.17^{aB}	5.16	0.02
T_1	2.48^{aA}	3.86^{bA}	4.59^{cA}	3.64	0.03		2.57^{aA}	3.32^{bA}	4.29^{cA}	3.39	0.02
T_2	2.48^{aA}	4.40^{bB}	5.02^{cB}	3.97	0.04		2.58^{aA}	4.19^{bB}	5.15^{cB}	3.97	0.01
Mean	3.35	4.44	4.90				3.44	4.22	4.87		
SE*	0.03	0.03	0.03				0.02	0.02	0.02		

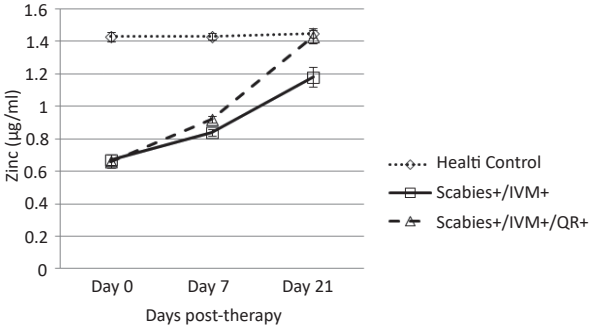
Table 1. The effect of different treatments on oxidative stress biomarkers in pigs (continued)

Group	Day 0	Day 7	Day 14	Mean	SE*		Day 0	Day 7	Day 14	Mean	SE*
TAC (mmol/L)											
T_0	1.01^{aB}	0.97^{aB}	0.98^{aB}	0.99	0.02						
T_1	0.39^{aA}	0.63^{bA}	0.81^{cA}	0.61	0.02						
T_2	0.38^{aA}	0.74^{bB}	0.99^{cB}	0.70	0.04						
Mean	0.59	0.78	0.93								
SE*	0.01	0.03	0.03								

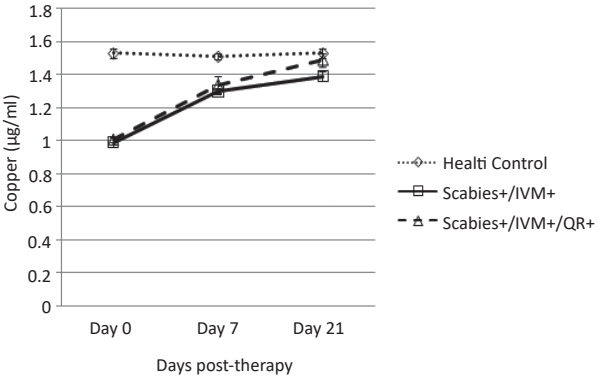
*Pooled standard error.
^{a,b,c}Values in row bearing different superscripts differ (P<0.05).
^{A,B,C}Values in column bearing different superscripts differ (P<0.05).
T_0, Healthy Control; T_1, Scabies+/IVM+; T_2, Scabies+/IVM+/QR+.

The effect of the integrated treatment on SOD, CAT, GSH and TAC. The activities of antioxidant enzymes such as SOD, GSH and CAT, along with TAC in infested and healthy pigs are summarized in Table 1. In comparison with the control group, all infested pigs (T_1 & T_2) had significantly (P<0.05) decreased values of SOD, GSH, CAT and TAC at the beginning of treatment. However, on comparative evaluation of T_1 and T_2, it was observed that the mean values of SOD, GSH, CAT and TAC significantly increased and a more rapid return towards normalcy was recorded on days 7 and 14 in the IVM/QR-treated pigs (T_2) compared with the IVM-treated pigs (T_1).

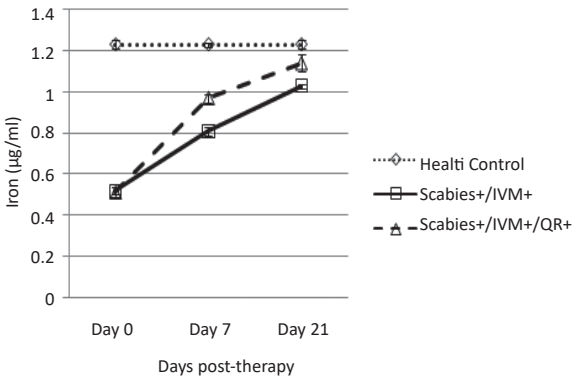
The effect of the integrated treatment on Zn, Cu and Fe. Before treatment (day 0), all the infested pigs (T_1 & T_2) showed a significant (p<0.05) reduction in Zn, Cu and Fe, in comparison with healthy subjects. The comparison of serum concentrations of Zn, Cu and Fe at the end of days 7 and 14 of treatment between groups T_1 and T_2 proved the IVM/QR treatment to be more effective than IVM treatment in infested pigs (Fig. 4). By day 14, the altered values returned more towards normalcy in IVM/QR-treated pigs and were comparable to the healthy group T_0.



(a)



(b)



(c)

Fig. 4. The effect of different treatments on serum (a) zinc, (b) copper and (c) iron status of pigs

Discussion

Consistent with published literature, we found an oxidant/antioxidant imbalance in all the pigs suffering from mange (BHAT et al., 2017; LAMBETH and NEISH, 2014; CAMKERTEN et al., 2009). Pigs are more prone to oxidative stress due to high body fat content (an excellent substrate for LPO). Oxidative stress is an imbalance between ROS and antioxidants, and it serves to restrict the further proliferation of mites. However, an overload of oxidative radicals leads to harmful effects on the skin (TROUBA et al., 2002). The free-radicals induce alterations in cell membranes which leads to excessive LPO (oxidant) and cellular death (KANNAN and JAIN, 2000). A higher degree of LPO reduction was seen in the pigs that received the integrated treatment (IVM+/QR+) and this could be attributed to the effective free-radical neutralizing effects of QR (MIRA et al., 2002; MIDDLETON et al., 2000; ZHU et al., 2000).

Before treatment, the endogenous antioxidants, such as SOD, GSH, CAT and TAC, were significantly reduced in infested pigs due to their overuse in neutralizing free radicals, and similar findings were described in scabies in dogs (BEHERA et al., 2011) and camels (SALEH et al., 2011). The delayed recovery in infested pigs after treatment with IVM alone may be associated with excess generation and accumulation of free radicals to counter the mites, resulting in severe oxidative stress and the loss of cellular function (BEHERA et al., 2011). Thus, antioxidant such as QR, if supplemented with IVM, might inhibit free radicals, increase oxidative stress tolerance, and help to bring about speedy recovery in pigs.

In the present study, all infested pigs had decreased serum Zn and Cu, which might have occurred due to their increased consumption for synthesis of essential antioxidant enzymes (Cu-Zn-SOD and ceruloplasmin) during sarcoptic mange (AL-QUDAH et al., 2010). The decrease in serum Fe might have occurred due to its sequestration in compartments to make it unavailable for the Fenton reaction, and the subsequent generation of free radicals was inhibited in the pigs (BEIGH et al., 2013).

Maximum and faster clinical recovery was noted in pigs supplemented with oral QR since it is necessary for the proficient scavenging of oxidative radicals produced in excess by the body to check the growth and proliferation of mites in pigs (MATSUDA et al., 2003). Our findings are suggestive of the therapeutic usefulness and higher combinatorial efficacy of IVM plus QR than IVM alone against *S. scabiei* var *suis* infestation in pigs. Hence, oral QR may be recommended as an adjunct therapy with IVM for reducing oxidative stress and improving post-therapy convalescence during sarcoptic mange in pigs.

Conclusions

The clinical infestation with *S. scabiei* var *suis* mites induces a state of oxidant-antioxidant imbalance in pigs. The oxidant (LPO/MDA) levels were higher while levels of antioxidants and associated trace minerals were lower in pigs suffering from sarcoptic mange compared with normal subjects. This indicates that pigs infested with sarcoptic mange were under increased oxidative stress and required exogenous antioxidant supplementation besides IVM. The pigs that received IVM+QR therapy exhibited maximum recovery. Taken together, these data support the notion that integrated treatment (IVM with QR) results in direct therapeutic targeting of reactive oxygen species by the antioxidant QR and thus leads to a speedy recovery in pigs.

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SAŽETAK

Sarkoptoza u svinja pokreće poremećaje koji rezultiraju teškim oksidacijskim stresom za koji još uvijek nije otkriven antioksidans kojim bi se prirodno infestirane svinje tretirale. Cilj je ovog randomiziranog kliničkog istraživanja bio procijeniti antioksidacijski potencijal kvercetina (QR) u kombinaciji s ivermektinom (IVM) u liječenju sarkoptoze u svinja. U kontrolnoj su skupini (T_0, n=10) bile zdrave jedinke. U prvoj su pokusnoj skupini (T_1, n = 10) infestirane svinje dobile standardnu terapiju (samo IVM primijenjen supkutano), dok su infestirane svinje u drugoj pokusnoj skupini (T_2, n = 10) primile integriranu terapiju (supkutano IVM i oralno QR). Nulti dan cirkulacijski je malondialdehid (MDA) bio znakovito veći, dok su superoksidna dismutaza (SOD), reducirani glutation (GSH), katalaza (CAT), ukupan anitoksidacijski kapacitet (TAC) i antioksidacijski minerali (cink, bakar i željezo) bili smanjeni u infestiranih svinja u usporedbi sa zdravim jedinkama. Četrnaesti dan poslije liječenja uočen je maksimalan oporavak u pogledu pokazatelja MDA, SOD, GSH, CAT, TAC, cinka, bakra i željeza u skupini T_2 te njihov raniji povratak na uobičajene vrijednosti u skupini T2 u odnosu na skupinu T1. Osim toga, u skupini T2 u odnosu na skupinu T1 zapaženo je znakovito poboljšanje u stopi izliječenosti parazitoze, indeksu grebenja i bodovanju promjena na koži. Ovi rezultati upućuju na veću učinkovitost IVM-a u kombinaciji s QR-om nego IVM-a upotrijebljenog kao samostalna terapija sarkoptoze u svinja. Zaključuje se da bi kvercetin mogao biti dodatna terapija uz IVM kako bi se poništili teški učinci oksidacijskog stresa, poboljšala poslijeterapijska rekonvalescencija i ubrzao oporavak svinja.

Ključne riječi: integrirana terapija; oksidacijski stres; svinje; kvercetin; sarkoptoza