UNIVERSITI PUTRA MALAYSIA

ELUCIDATION OF HOST CELL RESPONSE TO THE IMMUNOGEN MYCOLIC ACID EXTRACT OF Corynebacterium pseudotuberculosis IN GOATS

MOHAMMED NAJI AHMED ODHAH

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By

MOHAMMED NAJI AHMED ODHAH

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

March 2018

DEDICATION

To the spirit my parents: I will do all that I can do for your satisfaction in your graves, thank you of unconditional support with my life, I am honored to have you as my parents, thank you for giving me a chance to prove and improve myself through all my walk of life.

To my beloved wife, whose unconditional encouragement and support made it possible for me to commence PhD. I wish to express my heartfelt love to my children (Haya, Tasneem, Basel, Naji and Kareem) for coping with the undue paternal deprivation during the journey of my study. Most of all I pledge allegiance to the Lord Almighty for the strength and encouragement He has given me.

To my brothers and sisters: Hoping that with this research I have proven to you that there is no mountain higher as long as God is on our side. Hoping that, you will walk again and be able to fulfill your dreams.

To my teachers, instructors and mentors: my sincere thanks to make it reality, and utmost respect to all my teachers past, present and future, and to all teachers everywhere.

To my friends, I also dedicate this dissertation and give special thanks to my many friends who have supported me throughout this process.

I would like to conclude by again expressing my deepest gratitude and love to all.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in Fulfillment of the requirement for the degree of Doctor of Philosophy

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March 2018

Chairman : Associate Professor Faez Firdaus Jesse Abdullah, PhD
Faculty : Veterinary Medicine

Corynebacterium pseudotuberculosis is the causative agent of caseous lymphadenitis (CLA), a chronic disease of sheep and goats, characterized by the formation of suppurative abscesses in superficial and visceral lymph nodes and in the internal organs of small ruminants. The occurrence of CLA has been documented in the United States, Canada, Australia, New Zealand, South Africa, Brazil and Malaysia with the small ruminants being predominant. The prevalence of CLA among small ruminants in Malaysia is currently estimated at 30% and thus is a noteworthy disease in Malaysia. However, the paucity of information in the literature relating to the extraction of mycolic acids (MAs) from *C. pseudotuberculosis* and its host cell response and the need to investigate the mechanism by which *C. pseudotuberculosis* and its immunogen MAs adversely affects goats is an attempt to undertake this study. This study was also designed to test the hypothesis that acute phase protein, antibodies, mainly IgM and IgG, estrogen and progesterone hormones, cytokine, especially, IL-1β and IL-6 can be used as a diagnostic aid for CLA.

Twelve clinically healthy crossbred female Boer goats aged between 16-20 months, weighing 25-35 kg were used in this study. The experimental animals were non-pregnant, non-lactating and had no history of vaccination against CLA. The goats were divided into three groups (A, B and C) consisting of 4 animals each. The control group A was administered with 2 ml of sterile phosphate buffered saline (PBS) intradermally, whereas group B was inoculated with 2 ml of mycolic acid (1 gm/ml) intradermally and group C was inoculation with 2 ml of 1×10^9 CFU of *C. pseudotuberculosis* intradermally. Animals were monitored for the entire period (3 months) of the experiment for signs of the disease and blood samples were collected intermittently. The blood sample was collected in heparinized, EDTA plain tubes for

haematological, acute phase protein (APP), IgM and IgG antibodies, sex hormones (estrogen and progesterone) and cytokine (IL-1β and IL-6) analysis. At the end of the study, post-mortem examination of gross lesions was conducted mainly on lung, heart, liver, kidneys, spleen, ovaries, fallopian tubes, uterus, cervix, vagina as well as external and internal lymph nodes were examined to morphologic diagnosis tissues samples also collected for histopathology for analysis of cellular changes.

The inoculated goats in both *C. pseudotuberculosis* and MAs groups showed significant increase ($p<0.05$) in body temperature, heart rate, respiratory rate and sharp decrease in rumen motility was observed. Moreover, body condition score was significantly decreased ($p<0.05$) and enlargement with rupture of injection sites in both treated groups. Superficial lymph nodes showed abscess formation in *C. pseudotuberculosis* inoculated group only. Varying levels of effect on hematological profile in both treatment compared to the control groups was revealed. The *C. pseudotuberculosis* inoculated goats showed significant decrease ($p<0.05$) in red blood cell count and significant increase ($p<0.05$) in packed cell volume. On the other hand, significant decreases ($p<0.05$) in the haemoglobin and mean corpuscular hemoglobin concentration in both *C. pseudotuberculosis* and MAs groups. There was also a notable increase in the levels of white blood cells, neutrophils and lymphocytes in both *C. pseudotuberculosis* and MAs groups. Meanwhile, haptoglobin was increased from weeks 1-3 and reduced to within the normal range at week 4 in *C. pseudotuberculosis* group while the MAs group showed significant increase ($p<0.05$) in the these only in weeks 1 and 2. Similar treats were observed in serum amyloid A except that the increase observed in the *C. pseudotuberculosis* group was only in weeks 1 to 4. In addition, a significant increase ($p<0.05$) in IgM in *C. pseudotuberculosis* group was observed from weeks 2 to 5, while MAs group showed significant increase ($p<0.05$) from weeks 1 to 3. The level of the IgG was response in *C. pseudotuberculosis* group was significantly ($p<0.05$) higher throughout the study period for both groups. The concentration of IgG was steadily increased in the *C. pseudotuberculosis* and MAs treated groups peaking at week 9 with 32.82±8.56 ng/ml in *C. pseudotuberculosis* group and 28.41±1.27 ng/ml in MAs group. In addition estrogen hormone showed significant increase ($p<0.05$) in both treated groups from week 1 to 5 in *C. pseudotuberculosis* group and weeks 1 to 3 in MAs group. On the other hand progesterone hormone showed significant increase ($p<0.05$) from weeks 1 to 6 and 1 to 3 in *C. pseudotuberculosis* and MAs groups respectively. Furthermore, the cytokine (IL-1β) and was increased significantly ($p<0.05$) in weeks 2, 3, 5, 6, 9 and 10 for the *C. pseudotuberculosis* group, and week 5 to 10 in MAs group. In a similar vein, IL-6 showed significant increased ($p<0.05$) in week 5, 6, 7 and 8 for the *C. pseudotuberculosis* group, while MAs group showed significant increased ($p<0.05$) in week 2, 3, 4, 5, 6 and 8 compared to the untreated control group.

Post mortem examination of vital and reproductive organs and also internal and external lymph nodes showed mild to severe pathology in the *C. pseudotuberculosis* group, while the MAs group showed mild to moderate lesions. On the other hand, high rate of gross pathological changes were recorded in both groups in the vital organs and lymph nodes. There were, no significant gross pathological changes were observed in

the reproductive organs in both groups. In vital organs such as lung, heart, liver, kidneys, spleen, the main gross pathological lesions observed were congestion, haemorrhage, fatty atrophy and abscessation in *C. pseudotuberculosis* group. Moreover, the lymph nodes, revealed high percentage of abscess formation in different sizes in all goats in group C. While MAs group did not show any abscess in the visceral organs or the lymph nodes and reproductive organs despite enlargement of the lymph nodes.

The histopathological changes observed were significant in *C. pseudotuberculosis* inoculated group and the pathologies include congestion, oedema, and infiltration of inflammatory cells, degeneration and necrosis in the vital, reproductive organs and lymph nodes. The MAs inoculated group showed significant congestion, oedema, degeneration and necrosis.

Detection of the bacteria using conventional PCR revealed 100% detection of the bacteria in the *C. pseudotuberculosis* inoculated group.

Conclusively, this study was able to demonstrate varying clinical manifestations from both *C. pseudotuberculosis* and MAs inoculated groups. Classical signs of CLA were observed in the *C. pseudotuberculosis* group specifically abscess formation in superficial lymph nodes, while MAs group showed no abscessation. On the other hand, *C. pseudotuberculosis* and MAs showed significant changes in all heamatological parameters, acute phase protein, IgM and IgG antibodies, estrogen and progesterone concentrations. Significant changes were also observed in the cytokines (IL-1β and IL-6) Different response pattern in the group compared to *C. pseudotuberculosis* for the haematological parameters, acute phase protein, IgM and IgG antibodies, reproductive hormones as well as cytokines indicate different mechanisms. The gross and cellular changes were typical of CLA lesions in *C. pseudotuberculosis* inoculated group whilst MAs inoculated group showed less gross changes however, the cellular changes were severe, indicating the effect of MAs on tissues.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

MENGENAL PASTI TINDAK BALAS SEL BADAN KAMBING TERHADAP *Corynebacterium pseudotuberculosis* DAN EKSTRAK IMMUNOGEN ASID MYCOLIC

Oleh

MOHAMMED NAJI AHMED ODHAH

Mac 2018

Pengerusi : Profesor Madya Faez Firdaus Jesse Abdullah, PhD
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Corynebacterium pseudotuberculosis adalah merupakan agen penyakit "caseous lymphadenitis" ataupun CLA, penyakit kronik kepada kambing dan biri-biri yang boleh menyebabkan bisul yang bernanah pada nodus limfa luaran dan dalaman haiwan ruminan kecil tersebut. Penyakit CLA ini telah dilaporkan berlaku di Amerika Syarikat, Kanada, Australia, New Zealand, Afrika Selatan, Brazil dan Malaysia, terutamanya terhadap haiwan ruminan kecil. Dianggarkan bahawa kelaziman penyakit CLA di Malaysia adalah sebanyak 30%, menjadikan CLA satu penyakit yang perlu diberi perhatian di Malaysia. Tujuan kajian ini adalah untuk mengisi kekurangan maklumat mengenai pengekstrakkan asid mycolic daripada *C. pseudotuberculosis*, tindak balas sel perumah dan mekanisma *C. pseudotuberculosis* dan imunogen asid mycolic boleh menjejaskan kambing yang terlibat dalam kajian ini. Kajian ini juga direka untuk menguji hipotesis sama ada protein fasa akut, antibodi seperti IgM dan IgG, hormon progesteron dan estrogen dan sitokin seperti IL-1β dan IL-6 boleh digunakan untuk tujuan diagnostik terhadap penyakit CLA.

Sebanyak 12 ekor kambing betina Boer kacukan yang sihat secara klinikal berumur antara 16-20 bulan, berat badan antara 25-35 kg telah digunakan untuk kajian ini. Semua haiwan untuk eksperimen ini adalah tidak bunting, tidak menyusu dan tiada sejarah vaksinasi terhadap penyakit CLA. Kambing-kambing tersebut telah dibahagikan kepada tiga kumpulan (A, B dan C) dengan 4 ekor kambing di dalam setiap kumpulan. Kumpulan kawalan, iaitu kumpulan A telah diinokulasi dengan 2 ml saline buffer fosfat steril (PBS) melalui intradermal, manakala kumpulan B telah diinokulasi dengan 2 ml asid mycolic melalui intradermal dan kumpulan C telah diinokulasi dengan 2 ml 1×10^9 CFU *C. pseudotuberculosis* juga melalui intradermal. Semua haiwan telah dipantau sepanjang tempoh eksperimen (3 bulan) untuk tanda-

tanda klinikal penyakit dan sampel darah telah diambil secara berselang-seli. Sampel darah telah dikumpul di dalam tiub yang mengandungi heparin, EDTA dan juga tiub kosong untuk analisis hematologi, protein fasa akut (APP), antibodi IgM dan IgG, hormon pembiakan (estrogen dan progestron) dan sitokin (IL-1β dan IL-6). Pada penghujung kajian, pemeriksaan bedah siasat secara kasar telah dijalankan pada paru-paru, jantung, hati, buah pinggang, limpa, ovari, tiub fallopian, uterus, serviks, faraj serta nodus limfa dalaman dan luaran dan kesemua tisu dikumpul untuk pemeriksaan histopatologi dan perubahan sel.

Kambing-kambing dalam kumpulan yang diinokulasi dengan *C. pseudotuberculosis* dan asid mycolic menunjukkan peningkatan ketara ($p<0.05$) terhadap suhu badan, kadar degupan jantung dan kadar pernafasan manakala penurunan ketara dalam pergerakan rumen. Skor keadaan badan turut menunjukkan penurunan ketara ($p<0.05$), disamping pembesaran dan kerosakan tisu di kawasan suntikan di dalam kedua-dua kumpulan rawatan. Hanya kumpulan yang diinokulasi dengan *C. pseudotuberculosis* menunjukkan pembentukkan abses pada nodus limfa luaran. Hasil kajian ini turut menunjukkan pelbagai kesan yang berbeza pada profil hematologi pada kedua-dua kumpulan rawatan berbanding dengan kumpulan kawalan. Kumpulan kambing yang diinokulasi dengan *C. pseudotuberculosis* menunjukkan penurunan ketara ($p<0.05$) dalam kiraan sel darah merah dan peningkatan ketara ($p<0.05$) dalam jumlah sel berpadat. Manakala penurunan ketara ($p<0.05$) telah diperhatikan ke atas sel hemoglobin dan purata kepekatan hemoglobin korpuskular dalam kedua-dua kumpulan yang diinokulasi dengan *C. pseudotuberculosis* dan asid mycolic. Peningkatan ketara turut diperhatikan dalam tahap sel darah putih, neutrofil dan limfosit dalam kedua-dua kumpulan *C. pseudotuberculosis* dan asid mycolic. Sementara itu, protein fasa akut (haptoglobin) meningkat daripada minggu 1 hingga minggu 3 sebelum turun kepada paras normal pada minggu ke-4 untuk kumpulan *C. pseudotuberculosis* manakala kumpulan asid mycolic menunjukkan peningkatan ketara ($p<0.05$) hanya pada minggu 1 dan minggu 2, perubahan yang sama diperhatikan dalam tahap serum amyloid A, kecuali peningkatan dalam serum amyloid A diperhatikan dalam kumpulan *C. pseudotuberculosis* pada minggu 1 hingga minggu 4. Peningkatan ketara ($p<0.05$) turut diperhatikan dalam tahap IgM dalam kumpulan *C. pseudotuberculosis* daripada minggu 2 hingga minggu 5, manakala kumpulan asid mycolic menunjukkan peningkatan ketara ($p<0.05$) daripada minggu 1 hingga minggu 3. Tahap tindak balas IgG dalam kumpulan *C. pseudotuberculosis* adalah lebih tinggi secara ketara ($p<0.05$) untuk kedua-dua kumpulan sepanjang tempoh kajian. Tahap Ig G meningkat secara berterusan dalam kedua-dua kumpulan *C. pseudotuberculosis* dan asid mycolic dan memuncak pada minggu 9 dengan 32.82±8.56 ng/ml) dalam kumpulan *C. pseudotuberculosis* dan 28.41±1.27 ng/ml dalam kumpulan asid mycolic. Pada masa yang sama, hormon estrogen menunjukkan peningkatan ketara ($p<0.05$) dalam kedua-dua kumpulan rawatan daripada minggu 1 hingga minggu 5 dalam kumpulan *C. pseudotuberculosis* dan daripada minggu 1 hingga minggu 3 dalam kumpulan asid mycolic. Manakala hormon progesteron menunjukkan peningkatan ketara ($p<0.05$) daripada minggu 1 hingga minggu 6 untuk kumpulan *C. pseudotuberculosis* dan minggu 1 hingga minggu 3 untuk kumpulan asid mycolic. Tambahan pula, tahap sitokin (IL-1β) meningkat secara ketara ($p<0.05$) pada minggu 2, 3, 5, 6, 9 dan 10 untuk kumpulan *C. pseudotuberculosis* dan pada minggu 5 hingga

minggu 10 untuk kumpulan asid mycolic. Pada masa yang sama, IL-6 menunjukkan peningkatan ketara ($p<0.05$) pada minggu 5, 6, 7 dan 8 untuk kumpulan *C. pseudotuberculosis*, manakala kumpulan asid mycolic menunjukkan peningkatan ketara ($p<0.05$) pad minggu 2, 3, 4, 5, 6 dan 8 berbanding dengan kumpulan kawalan.

Pemeriksaan bedah siasat menunjukkan patologi yang ringan hingga teruk dalam organ penting dan organ pembiakan serta kedua-dua nodus limfa dalaman dan luaran di dalam kumpulan *C. pseudotuberculosis* manakala kumpulan asid mycolic menunjukkan patologi yang ringan hingga sederhana. Sebaliknya, kadar tinggi untuk perubahan patologi kasar telah direkodkan di dalam organ-organ yang penting dan nodus limfa kedua-dua kumpulan rawatan. Pada masa yang sama, tiada perubahan patologi ketara telah diperhatikan dalam pemeriksaan kasar di dalam organ pembiakan kedua-dua kumpulan. Organ penting seperti paru-paru, jantung, hati, buah pinggang dan limpa menunjukkan perubahan ketara dalam pemeriksaan patologi kasar seperti konjesi, pendarahan, atrofi berlemak dan pembentukkan abses di dalam kumpulan *C. pseudotuberculosis*. Tambahan pula, nodus limfa menunjukkan peratusan yang tinggi untuk pembentukkan abses dalam saiz yang berbeza untuk semua kambing dalam kumpulan C. Kumpulan asid mycoloic pula tidak menunjukkan pembentukkan abses di dalam organ-organ penting, organ pembiakan serta nodus limfa walaupun pembesaran nodus limfa telah diperhatikan.

Perubahan histopatologi yang ketara telah diperhatikan di dalam kumpulan yang diinokulasi dengan *C. pseudotuberculosis* dalam bentuk konjesi, edema, penyusupan sel keradangan, degenerasi dan nekrosis di dalam organ-organ penting, organ pembiakan dan nodus limfa. Kumpulan yang diinokulasi dengan asid mycolic pula menunjukkan konjesi, edema, degenerasi dan nekrosis yang ketara.

Pengesanan bakteria menggunakan PCR konvensional telah mengesan 100% bakteria tersebut di dalam kumpulan yang telah diinokulasi dengan *C. pseudotuberculosis*, manakala tiada bakteria yang dikesan di dalam kumpulan yang diinokulasi dengan asid mycolic seperti yang dijangka.

Secara keseluruhan, kajian ini dapat menunjukkan manifestasi tanda klinikal yang berbeza-beza di dalam kedua-dua kumpulan *C. pseudotuberculosis* dan asid mycolic. Tanda-tanda klasik penyakit CLA telah diperhatikan di dalam kumpulan *C. pseudotuberculosis* terutamanya dalam pembentukkan abses di dalam nodus limfa luaran manakala kumpulan asid mycolic pula tidak menunjukkan pembentukkan abses. Pada masa yang sama, kedua-dua kumpulan *C. pseudotuberculosis* dan asid mycolic menunjukkan perubahan ketara dalam semua parameter hematologi, protein fasa akut, antibodi-antibodi IgM dan IgG serta kepekatan estrogen dan progesteron. Perubahan ketara turut diperhatikan di dalam profil sitokin (IL-1β dan IL-6) manakala kumpulan asid mycolic menunjukkan corak tindak balas yang berbeza termasuk di dalam parameter hematologi, protein fasa akut, antibodi-antibodi IgM dan IgG, hormon pembiakan serta profil sitokin, menunjukkan mekanisme tindakan yang

berbeza. Perubahan kasar dan selular yang diperhatikan adalah tipikal bagi penyakit CLA di dalam kumpulan yang diinokulasi dengan *C. pseudotuberculosis* sementara kumpulan yang telah diinokulasi dengan asid mycolic pula menunjukkan perubahan kasar yang lebih sederhana manakala perubahan selular yang diperhatikan adalah lebih teruk, menunjukkan kesan asid mycolic pada tisu organ.

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I certify that a Thesis Examination Committee has met on 6 March 2018 to conduct the final examination of Mohammed Naji Ahmed Odhah on his thesis entitled "Elucidation of Host Cell Response to the Immunogen Mycolic Acid Extract of *Corynebacterium pseudotuberculosis* in Goats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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I hereby confirm that:

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) were adhered to.

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µg	Microgram
AGID	Agar gel immunodiffusion
APP	Acute phase proteins
CBC	Complete Blood Count
CFU	Colony forming unit
CLA	Caseous lymphadenitis
DVS	Department of Veterinary Service
E2	Estrogen Hormone
ELISA	Enzyme Linked Immunosorbent Assay
H&E	Hematoxylin and Eosin
Hb	Hemoglobin
Hp	Haptoglobin
I.V	Intravenous
IACUC	Institutional Animal Care and Use Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1β	Interleukin 1β
IL-6	Interleukin 6
IM	Intradermally
MAs	Mycolic Acid
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	Milligram
ml	Milliliter
ng	Nanogram
^{o}C	Degree celsius
OD	Optical Density
OIE	Office of International Epizootic
P4	Progesterone Hormone
PBS	Phosphate Buffered Saline
PCR	Polymerase Chain Reaction

PCV	Packed Cell Volume
PLD	Phospholipase D
RBC	Red Blood Cell
SAA	Serum Amyloid A
TPU	Taman Pertanian Universiti
UPM	Universiti Putra Malaysia
VLSU	Veterinary Laboratories Service Unit
WBC	White Blood

CHAPTER 1

INTRODUCTION

1.1 Background

Corynebacterium pseudotuberculosis (*C. pseudotuberculosis*) is the etiological agent that causes caseous lymphadenitis (CLA), a well-known disease of sheep and goats. The CLA is described by formation of one or many abscesses in lymph nodes (Paton, 2010).

The *C. pseudotuberculosis* is an intracellular, gram positive, facultative anaerobe, small curved rod. It is non-spore forming bacterium that is responsible for caseous lymphadenitis (CLA), a chronic contagious disease of sheep and goats worldwide (Dorella *et al.*, 2006a; Fontaine & Baird, 2008; Jesse *et al.*, 2011). Ruptured abscesses are the main source of *C. pseudotuberculosis* contaminating the environment. Animal exposure to the bacteria can be either by direct physical contact with the infected animal or indirectly via contaminated fomite (Stoops *et al.*, 1984; Collet *et al.*, 1994; Jesse *et al.*, 2008a).

Corynebacterineae is a suborder of pathogenic bacteria species that have cell membrane covered with waxy substances known as mycolic acids (MAs) such as *Corynebacterium diphtheria* and *Corynebacterium pseudotuberculosis*. Mycolic acids are the main and specific constituents of the Bacteria cell envelope. It is a long chain of fatty acids with a complex, structural design that ensures the impermeability of these bacteria cell membrane (Damien *et al.*, 2004; Jesse *et al.*, 2013a). Mycolic acids, a 2-alkyl, 3-hydroxy long-chain fatty acids, are part of the cell envelope of *Mycobacterium tubercular* (Daffé & Draper, 1997). MAsare found extractable using organic solvents or terminal esterification of the penta-arabinofuranosyl units of arabinogalactan (McNeil *et al.*, 1991).

Corynebacterium strains have been reported to be viable in the absence of MAs (Portevin *et al.*, 2004; Portevin *et al.*, 2005). It has been proven that the outer membrane was no longer observed in other mutant strains devoid of MAs (Zuber *et al.*, 2008). However there is still lack of information on the mechanism of action and host cell responses towards MAs (Carne, 1939; Onon, 1979). Therefore, this study was conducted to fill in the gap of the research of MAs in *C. pseudotuberculosis*.

It was clinically observed in *C. pseudotuberculosis* that a typical of CLA disease appearance is seen with a short incubation period of about two weeks. But the phospholipase D (PLD) inoculation showed little or no clinical signs which did not lead to any form of abscesses formation. PLD plays an important role in CLA development but it has a weaker triggering ability (Mahmood *et al.*, 2015).

The effects of *C. pseudotuberculosis* and PLD on the reproductive performances of non-pregnant does is very paramount. PLD and *C. pseudotuberculosis* causes infertility by its pathologic effects on the reproductive organs, coupled with the imbalances observed in hormonal levels which decreases and hence impede reproductive efficiency (Khuder *et al.*, 2012; Othman *et al.*, 2016). The changes in hormonal activities involves a sharp rise in the oestrogen and progesterone levels which is the main reason why it sequels to infertility as it impairs ovulation and subsequent implantation (Othman *et al*., 2016). A lot of attempt were made to study the effects of *C. pseudotuberculosis,* PLD and MAs on the reproductive performances in doe, but information at hand only gives insights on how *C. pseudotuberculosis* and PLD affects reproduction. Therefore, there is a paucity of information on the effects of mycolic acid on the reproductive performances in does.

The Acute-phase proteins (APPs) are synthetic proteins from the liver which either rise or decreases in plasma concentration during infections (Ceciliani *et al.*, 2002; Murata *et al.*, 2004). The APPs are basically summoned during tissue injury, trauma, infections and inflammatory conditions (Cray *et al.*, 2009; Abdullah *et al.*, 2013b). Haptoglubin and serum amyloid A are basic positive APPs of interest in this infection, whereby Zaid *et al*., (2016) reported that haptoglobin (Hp) increases in PLD and *C. pseudotuberculosis* infections which is an indication that *C. pseudotuberculosis* and PLD affects the titre of concentration of APPs in these infections. The researchers further indicated that the level of SAA is less elevated as compared to Hp, therefore, SAA is suggested to be less influenced by *C. pseudotuberculosis* and PLD. As stated above, a lot of attempts were made to study the effects of PLD, *C. pseudotuberculosis* and Mycolic acid on the concentrations of APPs in doe, but information at hand just as obtained for the reproductive functions only gives insights on how *C. pseudotuberculosis* and PLD affects serum Hp and SAA. Currently, there is no information available on the effects of mycolic acid on the concentrations of APPs in does.

The immunity to *C. pseudotuberculosis* has been described to be complex involving both cellular and humoral responses (Ellis *et al.*, 1991) with the cellular phase response, of mainly Th1 type, having more response than the humoral response in sheep and goats (Pepin *et al.*, 1997; Lan *et al.*, 1999). Cytokines involved in CLA infections are mainly associated with interleukin-1β and interleukin-6, and tumor necrosis factor-α (TNF-α) (Pepin *et al*., 1997; Jesse *et al.*, 2016).

In *C. pseudotuberculosis*, there is a significant stimulatory changes in the levels of cytokines mainly IL 1 β and IL 6. The cytokine IL 1 β concentration rises in *C. pseudotuberculosis* indicating that it infection actually occurs. Also, IL 6 was reported to have increased in its concentration in an in vivo study thereby indicating a chronic form of the infection. This information of the effects of this infection on cytokine concentration is only in relation to *C. pseudotuberculosis.* Hence, there is, inadequate or rather lack of viable information on the effects of PLD and mycolic acid on cytokine in CLA.

In *C. pseudotuberculosis,* abscess was formed in kidneys, liver, spleen tongue, eyes, diaphragm, heart, mammary glands, testes, joints and other nervous tissues (de Sá Guimarães *et al.,* 2011). In ewes, neonatal infection, still-birth and in a worst case scenario abortion are a common occurrence in this infection (Alonso *et al.,* 1992). In PLD, congestion, oedema, thrombosis, necrosis are seen as a result of the generalized toxemia. Also, degenerative changes, neutrophilic infiltration, macrophagic inclusions and necrosis are seen in the ovaries and uterus (Khuder et al., 2012). The histologic trend indicates that the foremost inflammatory alterations in lymph nodes of sheep and goats contain numerous neutrophilic and eosinophilic transmigration and micro-abscesses, the myeloperoxidase in the primary granules of the granulated leukocytes gives the pyogenic greenish pus colouration (Valli, 1993). Abscesses augment and coalesce constantly during inflammatory responses related to innate immune phase (Pepin *et al.,* 1994a).

The histopathological effects of MAs in this infection had not been widely studied and understood. However, a singular study in North Korea in 2014 indicated that MAs has immunogenic effects on a mice model (Kim *et al.,* 2014), which supressed broncho alveolar inflammation and pulmonary eosinophilic inflammation. An anti-CD25mAb treatment with MAs in this mouse model depleted $CD4^{+}CD25^{+}Foxp3^{+}$ T cells in the spleen (Kim *et al*., 2014). However, on the other hand, there is no record showing any evidence of MAs effect on histopathological findings as well as clinical signs in this disease condition. Therefore there is a gap of information on clinical signs as it relates to MAs.

Problem statement

Caseous lymphadenitis (CLA) is currently considered untreatable disease because of its encapsulated nature. It also has insidious effects on productivity of the small ruminant. Additionally, little is known about the host cell response of mycolic acid extract from *Corynebacterium pseudotuberculosis* and its role in pathogenicity and disease pathogenesis.

Hypothesis

- *Corynebacterium pseudotuberculosis* Mycolic acid's has immunogenic properties and a key role in host cell response that eventually contributes to the pathogenicity of *Corynebacterium pseudotuberculosis*.
- The host cell response induced by Mycolic acid has direct and/or indirect effects on female goat fertility.
- Reproductive hormones concentration altered with Mycolic acid immunogenic properties.
- Pathological changes has to appear as lesion in key reproductive, vital organs and lymph nodes.

Thus, the objectives of this study are:

1. To determine changes in clinical response and complete blood count (CBC) in goats after inoculation of *C. pseudotuberculosis* and its immunogen mycolic acid extract.
2. To estimate the acute phase proteins responses and the hormones concentration estrogen and progesterone between infection by *C. pseudotuberculosis* and Mycolic acid extract as immunogen.
3. To estimate the concentrations of antibodies (IgM, IgG) and pro-inflammatory cytokines between the infection by *C. pseudotuberculosis* and its immunogen Mycolic acid extract.
4. To identify *C. pseudotuberculosis* using PCR and histopathological changes of vital organs, reproductive organs, and lymph nodes between the infected goats with *C. pseudotuberculosis* and its immunogen Mycolic acid extract.

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