



UNIVERSITI PUTRA MALAYSIA

***DEVELOPMENT OF A DNA BIOSENSOR BASED ON MAGNETIC
NANOPARTICLES FOR THE DETECTION OF *Ganoderma boninense****

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**DEVELOPMENT OF A DNA BIOSENSOR BASED ON
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Ganoderma boninense

By

Roozbeh Hushiarian

**Thesis Submitted to the School of Graduate Studies, Universiti Putra
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Philosophy
January 2015**



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

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**Chair: Professor Nor Azah Yusof, PhD.
Faculty: Science**

The unique electrochemical and optical properties of nanoparticles combined with the relative ease with which their shape and size can be controlled is currently showing promise in the development of new biosensors. In particular, magnetic nanoparticles are of great interest in DNA sensors for their ability to both separate biological macromolecules as well as to optimize DNA hybridization.

The intent of this research was to address the gap in knowledge about the fundamentals of the molecular interactions between DNA and nanoparticles, especially magnetic nanoparticles.

The pathogen selected was the basidiomycete *Ganoderma boninense*, the main cause of basal stem rot disease which continues its devastating effect on oil palm trees in South East Asia. A designed DNA sequence and its complementary strains – a sequence of 18s rRNA gene of *Ganoderma boninense* - was taken as the template.

The work in this thesis was built on understood mechanisms from previous studies with the goal of further optimizing a DNA biosensor. One major part of the research involved the design and construction of an optical magnetic nanoparticle-based biosensor using quantum dots as markers. This clearly demonstrated that DNA can bind to the surface of iron oxide nanoparticles and that they can act as effective biomolecule carriers. The detection limit of the designed optical nanosensor was calculated as 2.19×10^{-9} M. The sensitivity of the system was increased by 20% using a two step hybridization method. A new innovative software package was used to better understand the mechanism of detection.

The other major section introduced an electrochemical method for sensing and conclusively showed that it could bring a representative sequence of an analyte to the

biorecognition surface. The electrochemical sensor based on magnetic nanoparticles showed a sensitivity of 1.1×10^{-16} M and then this method was further extended to successfully increase the selectivity of this system by the novel use of DNA ligase. The indirect detection of the target DNA using DNA ligase was successfully performed with a detection limit of 5.37×10^{-14} M. This creative ligation-based mechanism was ultimately employed to detect the extracted genomic DNA of the pathogen.

The methods and results in this study enhance the understanding of molecular interactions between DNA and nanoparticles and contribute to the body of work attempting to address the outstanding issue of improving the selectivity and sensitivity of DNA biosensors.



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

TAJUK TESIS

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Ciri-ciri unik elektrokimia dan optic bagi partikel nano yang digabungkan dengan kemudahan untuk mengawal bentuk dan saiz mereka menjadikan mereka bahan terkini untuk pengembangan pengesanan biologi. Secara khususnya, partikel nano magnet mempunyai kepentingan besar dalam sensor DNA berdasarkan keupayaan mereka memisahkan makromolekul biologi serta mengoptimumkan penghibridan DNA.

Tujuan kajian ini adalah untuk mengatasi jurang pengetahuan dalam asas-asas interaksi antara molekul DNA dan partikel nano terutamanya partikel nano magnet.

Patogen yang dipilih adalah basidiomycete *Ganoderma boninense*, punca utama penyakit reput akar stem yang terus member kesan buruk ke atas pokok-pokok kelapa sawit dan pengeluaran minyak sawit di Malaysia, Indonesia dan Papua New Guinea. Jujukan DNA yang direka dan strain pelengkapannya - urutan 18s rRNA gen *G. boninense* – telah diambil sebagai templat.

Kerja-kerja di dalam tesis ini telah dibina di atas mekanisme difahami daripada kajian sebelum ini dengan matlamat mengoptimumkan lagi biosensor DNA. Satu bahagian utama penyelidikan yang melibatkan reka bentuk dan pembinaan berdasarkan nanopartikel magnet biosensor optic menggunakan titik kuantum sebagai penanda. Ini jelas menunjukkan bahawa DNA boleh terikat kepada permukaan nanopartikel besi oksida dan mereka boleh bertindak sebagai pembawa biomolekul berkesan. Had pengesanan nanosensor optic yang direka adalah 2.19×10^{-9} M. Kepekaan system itu meningkat sebanyak 20% dengan menggunakan kaedah penghibridan dua langkah. Satu pakej perisian baru yang inovatif telah digunakan untuk lebih memahami mekanisme pengesanan.

Bahagian utama yang lain memperkenalkan satu kaedah elektrokimia untuk pengesanan dan ia telah menunjukkan secara konklusif bahawa ia boleh membawa urutan wakil analit ke permukaan biopengesanan itu. Sensor elektrokimia berdasarkan nanopartikel

magnet menunjukkan sensitiviti 1.1×10^{-16} M dan kemudian kaedah ini telah diperluaskan lagi untuk berjaya meningkatkan selektiviti system ini dengan penggunaan ligase DNA. Pengesanan tidak langsung DNA sasaran menggunakan DNA ligase telah berjaya dilakukan dengan had pengesanan 5.37×10^{-14} M. Mekanisme berasaskan ligation akhirnya digunakan untuk mengesan DNA genomik yang diekstrak daripada patogen.

Adalah dipercayai bahawa kaedah dan keputusan dalam kajian ini meningkatkan pemahaman interaksi antara molekul DNA dan NPs dan ia kemudiannya menyumbang kepada badan kerja dalam menangani isu tertunggak meningkatkan pemilihan dan kepekaan pengesanan biologi DNA.



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I certify that a Thesis Examination Committee has met on 14 January 2015 to conduct the final examination of Roozbeh Hushiarian on his thesis entitled "Development of a DNA biosensor based on magnetic nanoparticles for the detection of *Ganoderma boninense*" 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 Ph.D. degree.

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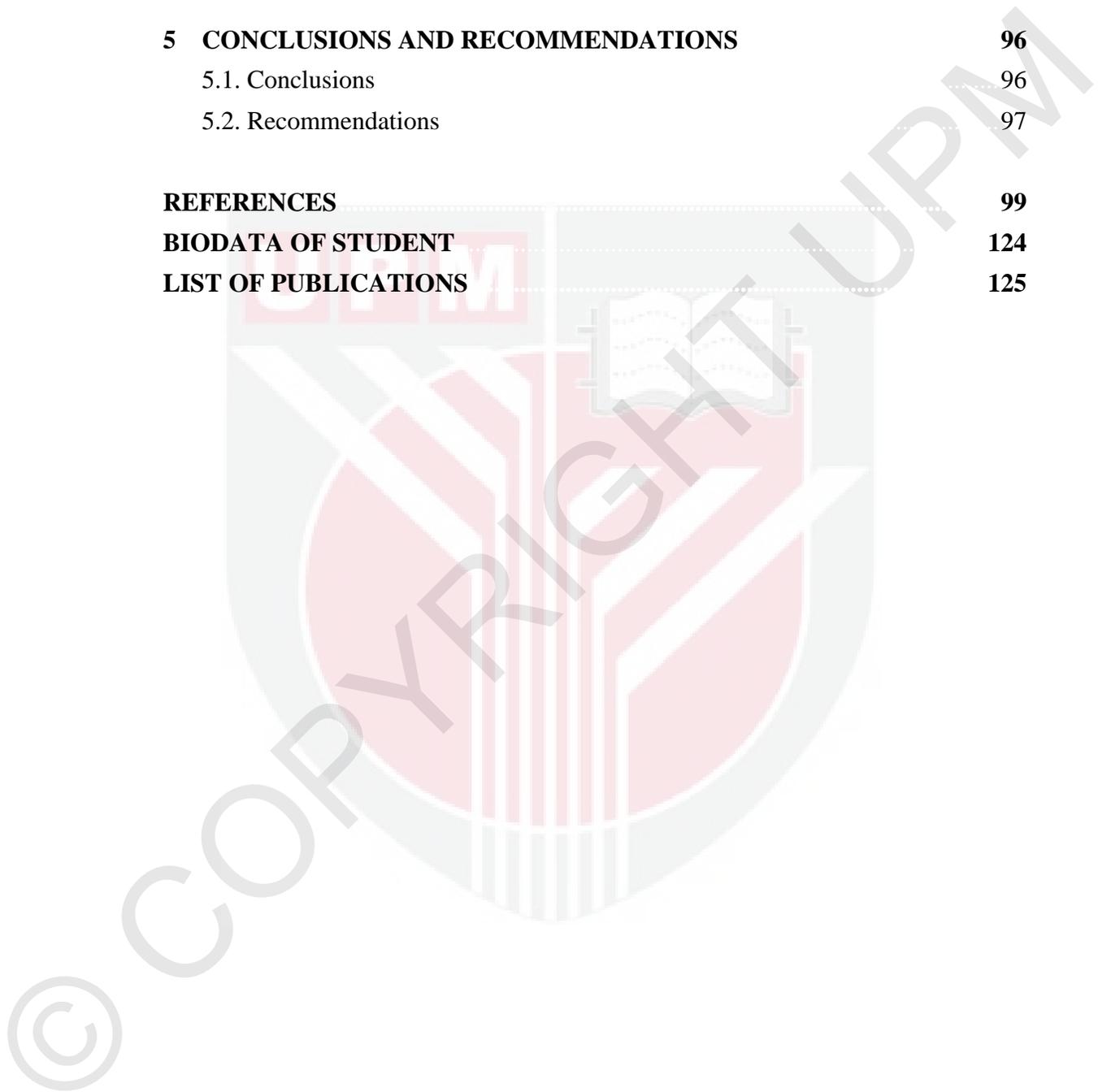
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LIST OF ABBREVIATIONS

AFLP	Amplified fragment length polymorphism
AFM	Atomic force microscopy
AuE	Gold electrode
AuNP	Gold nano particle
BPPG	basal plane pyrolytic graphite
BSR	basal stem rot
CLIO	Cross-linked iron oxide
CNT	Carbon nanotube
CV	Cyclic voltammetry
D	Diffusion coefficient
DGGE	Denaturing Gradient Gel Electrophoresis
DMSO	Dimethyl sulfonate
DNA	Deoxyribonucleic acid
DPA	3, 3'-dithiopropionic acid
dppz	dipyrido [3, 2-a: 2', 3' -c] phenzine
DPV	Differential pulse voltammetry
dsDNA	Double stranded deoxyribonucleic acid
E	Potential
EDC	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EDTA	Ethylenediamine tetraacetic acid
EDX	Energy-dispersive X-ray
E_f	End potential
E_i	Start potential
EIS	Electrochemical impedance spectroscopy

E_{pa}	Anodic peak potential
E_{pc}	Cathodic peak potential
ES	Electrochemical sensor
ΔE_p	Peak separation
ELISA	Enzyme-Linked Immunosorbent Assay
F	Faraday constant
FESEM	Field Emission Scanning Electron Microscope
FISH	Fluorescent <i>in situ</i> Hybridization
FRET	Fluorescence resonance energy transfer
FWHM	Full width at half maximum
<i>G. boninense</i>	<i>Ganoderma boninense</i>
GCE	Glassy carbon electrode
GMO	Genetically modified organism
GPES	General purpose electrochemical system
HPLC	High-performance liquid chromatography
i	Current
i_p	Peak current
i_a	Anodic current
i_c	Cathodic current
i_d	Diffusion current
i_{pa}	Anodic peak current
i_{pc}	Cathodic peak current
IAC	Internal amplification controls
ISE	Ion-selective electron
ISFET	Ion-selective field effect transistor
ITS	Internal transcript sequence

JCPDS	Joint Committee on Powder Data Standards
LOD	Limit of detection
MIP	Molecularly imprinted polymer
MNP	Magnetic nanoparticle
MOSFET	Metal-oxide semiconductor field effect transistor
MPA	3-mercaptopropionic acid
MRI	magnetic resonance imaging
MW	Molecular weight
NHSS	N-hydroxysulfo succinimide
NMR	Nuclear magnetic resonance
NP	Nanoparticle
PCR	Polymerase chain reaction
PDA	Potato dextrose agar
PDB	Potato dextrose broth
PDC	Poly-2, 6-pyridinedicarboxylic acid
PEDOT	Poly(3,4-ethylenedioxy thiophen)
PEG	Polyethylene glycol
Phen	1,10-Phenanthroline
PNA	Peptide nucleic acid
PSS	Poly(styrene sulfonic acid)
QCM	Quartz crystal microscopy
QD	Quantum dot
qtpy	2, 2',- 4, 4'' . 4', 4''' -quaterpyridyl
RAMS	Random Amplification Microsatellite
RAPD	Random Amplification of Polymorphic DNA
rDNA	Ribosomal DNA

RFLP	Restriction Fragment Length Polymorphism
RNA	Ribonucleic acid
rRNA	Ribosomal RNA
SAM	Self assemble monolayer
SDS	Sodium dodecyl sulfate
SEM	Scanning Electron Microscopy
SERS	surface enhanced raman spectroscopy
SPE	Screen-printed electrode
SPM	scanning probe microscopy
SPR	surface plasmon resonance
SSCE	Silver-silver chloride electrode
ssDNA	Single stranded deoxyribonucleic acid
ssPNA	Single stranded peptide nucleic acid
SWV	Square wave voltammetry
TE	Tris-HCl-ethylenediamine tetraacetic acid
TEM	Transmission Electron Microscope
T _{hyb}	Hybridization temperature
T _m	Melting temperature
TGGE	Temperature Gradient Gel Electrophoresis
TOPO	Trioctylphosphine oxide
UPM	Universiti Putra Malaysia
USR	upper stem rot
UV	Ultra violet
v	Scan rate
XPS	X-ray photoelectron spectrometry
XRD	X-ray diffraction

CHAPTER I

INTRODUCTION

The backdrop for this work is the South East Asian nation of Malaysia. Malaysia is one of the world's top exporters of palm oil, which is also a major generator of foreign exchange for the country and called by some its 'economic backbone' (Shariff 2014). There are currently 5.23 million hectares of land covered by palm oil trees (May 2013).

1.1. Context and problem statement

Like other farmers in all parts of the world, oil palm planters are faced with a range of problems caused by pests, diseases and weeds which can negatively impact the normal healthy growth of their plants and thus reduce crop yield. However, in Malaysia one disease stands out as having the most devastating effect. That is the basal stem rot disease (BSR) caused by the bracket fungus *Ganoderma boninense* (Ariffin et al. 2000; Singh 1990; Turner 1981) in oil palm plants.

At first, the disease was reported only in older age palms but it is now known to infect all stages of oil palm plants. Although symptoms of the disease do not appear until it is in its late stage and its progression is slow it can destroy thousands of hectares of oil palm plantations causing serious economic losses to the industry and country. Until today, there is high demand for sustainable detection and control of this disease (Naher et al. 2013).

As plantation owners and researchers have not been able to effectively control this insidious disease, predominantly through lack of an appropriate detection method, a contribution to understanding this pathogen would seem to be a worthwhile problem to be addressed by our study.

1.2. Biosensors and nanotechnology

Whilst the pathogen to be used in the study is indisputably worthy enough of attention and provides an appropriate context and problem statement, it is the technical aspect of the research and the methods used which make it far more broadly applicable and contribute equally significantly to scientific knowledge.

Firstly, the use of biosensors is at an exciting and dynamic stage in their development as they advance towards becoming invaluable tools in the fields of medicine, agriculture and biotechnology. To continue their phenomenal growth, researchers working with biosensors are having to cross disciplines, particularly now into the field of nanotechnology. Nanomaterials can demonstrably improve the sensitivity and performance of biosensors through new signal transduction technologies. The development of new tools and processes to fabricate, measure and image nanoscale objects have led to the development of sensors that interact with extremely small

molecules for analysis. These advances are particularly relevant to the work in this study in the area of DNA biosensing, where the demands are for low concentration detection and high specificity (Sagadevan and Periasamy 2014).

1.2.1. Magnetic Nanoparticles as tools

A popular nanomaterial, MNPs can be manipulated using a magnetic field. They have been the frequent focus of recent research because of their potential use in catalysis including nanomaterial-based catalysts (Lu et al. 2004), biomedicine, magnetic resonance imaging (MRI) (Mornet et al. 2006), magnetic particle imaging (Gleich and Weizenecker 2005), data storage (Hyeon 2003), environmental remediation, nanofluids (Philip et al. 2008), optical filters (Philip et al. 2003), and defect sensors (Mahendran and Philip 2012).

In the DNA biosensors in this work, we used ferromagnetic (iron) nanoparticles as multi-purpose tools for separation of the biological macromolecules and to optimize DNA hybridization as well as separation.

1.2.2. Method of oligonucleotide detection

The two key systems selected to decode and study the genetic makeup of *G. boninense* are DNA optical and electrochemical biosensors both of which are receiving much attention from medical and scientific researchers with their enormous promise for cheap and quick diagnosis.

Generically, biosensors are devices comprising two main parts: a bioreceptor which is the biological component and a transducer which converts the recognition into a measurable signal.

There are many types of biosensors currently in use, including resonant, optical and thermal but it is the electrochemical biosensor which is most frequently used to detect hybridized DNA and DNA-binding drugs (Syam et al. 2012), with optical biosensors being used almost as frequently.

DNA is a nucleic acid which composes all known forms of life along with the other three major macromolecules. Most DNA molecules are double-stranded helices, consisting of two long biopolymers made of simpler units called nucleotides. Because one strand of DNA specifically binds a second strand of DNA, this allows us to use short DNA strands called oligonucleotides (oligos) as our tools.

1.2.3. Structure and stability of DNA

DNA is stabilized by hydrogen bonding in the interior of the double helix. In a DNA sequence there will be thousands of these H-bonds which make DNA very stable.

The DNA double helix is also stabilized primarily by base-stacking interactions among aromatic nucleobases.

As DNA plays such a key role in the transfer of genetic information, over the past fifty years there has been considerable research undertaken around methodologies which enable determination of specific DNA sequences via hybridization. Nucleic acid hybridization with sensitive optical, electrochemical and gravimetric transducers has resulted in the development of DNA sensors and DNA chips (Syam et al. 2012) and showing outstanding promise in medical and other scientific fields like the pathogen detection in this work.

1.3. The approach

Although this research was opted to base on recent methods which had been used with success by other researchers in the field, the approach which was taken was novel - the ways in which the methods were applied and the tools used being unique and new.

While the context for application of the biosensors was *G. boninense*, the systems and processes designed successfully and implemented for its detection are not limited to this pathogen but contribute broadly to the field of DNA nanosensors.

1.3.1. General objectives

To develop and optimize the application of magnetic nanoparticles in a DNA biosensor for detecting *Ganoderma boninense*.

1.3.2. Specific objectives

1. To design the DNA sequences related to *G. boninense* such that they can have the potential to be used as biorecognition sites in biosensors for the detection of the pathogen
2. To design and construct an optical magnetic nanoparticle-based DNA biosensor using quantum dots as markers
3. To optimize the sensitivity of the designed optical DNA nanosensor
4. To couple the separation mechanism with an electrochemical sensing method
5. To study the sensitivity of the designed electrochemical system and increase the selectivity of the designed electrochemical DNA nanosensor
6. To employ the electrochemical sensing system on the crude DNA samples

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