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Dedication

To those persons in Cairns Hospital Integrated mental Health Service low-dependence unit, who continue to fill themselves by plastering butter on white bread and drinking copious cola beverages, thanks for the inspiration.

I would like to dedicate this book to the children, for whom, I believe that finding natural treatments for mental illness is of paramount importance into their future.

Acknowledgements

'I suffered from Shizzophreenier. It seemed to spell my doom, as if I had emerged from a chrysalis, the natural human state, into another kind of creature, and even if there were parts of me that were familiar to human beings, my gradual deterioration would lead me further and further away, and in the end not even my family would know me.'

Janet Frame (1924–2004)

I sincerely thank all the persons who put their faith in me, those who participated and those who recruited for me. I am but a vessel for your information. I wish to thank all the physicians, mental health nurses and general good fairies who gave their time and assistance to supporting my goal and aspirations. I wish to acknowledge the lady suffering from cancer who so graciously shared her mangosteen secret, which she claimed improved her energy levels.

I especially wish to acknowledge the assistance of my supervisors Professors Kim Usher and Michael Berk, Dr Olivia Dean and Associate Professor Susan Cotton. Thanks also to Dr Tessa Cookson (mental health physician for the study), Dr Elizabeth Emmanuel (for assessing the safety of the study for its duration), Sue Richmond (for monitoring the clinical trial) and Megan Marriot (the clinical trial pharmacist). Thanks to Professor Lois Salamonsen, Jenny Hercus, Stella Green, Dr Jenny Sando, Dr Duncan Adams and Associate Professor Mary Hercus-Rowe, whose kindness made this research possible. Thank you to Professor Joseph Brimacombe for facilitating my research path and the late Mervyn Thompson for mentoring my writing skills. I most of all wish to thank my husband Gelly Laupu and sons, Max and Gordon, who endured the PhD process, at times going without because of it.

Statement on the Contribution by Others

Fees: Nil

Stipend Support: Australian Postgraduate Award, plus \$5000 per annum top up from the School of Nursing, Midwifery and Nutrition.

Supervision: Kim Usher, Michael Berk, Olivia Dean and Susan Cotton.

Other collaborations: Dr Elizabeth Emmanuel (safety monitor), Sue Richmond (clinical trial monitor), Meagan Marriot (clinical trial pharmacist) and Alemka Russell from Queensland Health. Also consumer advocates, participant physicians and study participants.

Statistical support: Associate Professor Susan Cotton. Initial assistance was received from Emeritus Professor Rhondda Jones, Angela Reid and Associate Professor Petra Buettner.

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Use of infrastructure external to organisational unit within JCU: Initial statistical support, Postgraduate Centre computer, printing facilities and desk.

Specific Contributions to the Clinical Trial

Approvals

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research, 2007. The proposed research study received human research ethics approval from the James Cook University Human Research Ethics Committee (approval number C9). Direction for approvals was provided to Wendy Laupu by Dr Olivia Dean and Sue Richmond. Professor Michael Berk and Dr Olivia Dean assisted Wendy Laupu with the preparation of the National Ethics Application Form application. Suzie Grinter lent Wendy Laupu the use of her computer at a time when Wendy's work space was under renovation. The ethics submissions were prepared by Wendy Laupu, edited by Professor Kim Usher and signed off by Associate Professor Lee Stewart. The Therapeutic Goods Administration submission was managed by Wendy Laupu. The subsequent Australian and New Zealand clinical trial registration was conducted by Wendy Laupu with guidance from Dr Olivia Dean.

Education

Direction for learning how to apply the outcome measures was provided by Professor Michael Berk and Dr Olivia Dean. Education for the use of the Positive and Negative Syndrome Scale was provided to Wendy Laupu by Alemka Russell (psychologist) at Queensland Health. A consent form template was provided by Stella Green (Queensland Health). Initial guidance was received from Professor Kim Usher. Thesis preparation was guided by Professor Michael Berk, Dr Olivia Dean and Associate Professor Susan Cotton (statistics) who specialise in similar clinical trials. Professor Lois Salamonsen provided mentoring assistance (thesis layout for efficacy

studies). Professors Kim Usher and Michael Berk, Associate Professor Susan Cotton and Dr Olivia Dean assisted with edits of the thesis.

Recruitment

Recruitment was managed by Wendy Laupu with the aid of many hands. Initially posters advertised the study and treating physicians were alerted to the study by letter. This occurred across 25 towns in the targeted region. Organisations and individuals who advertised initially for the study were public and private health centres, pharmacies, Lifeline, Centre-link, health food stores, churches, non-government organisations, the Honorable Curtis-Pitt, homeless outreach groups, psychologists, supermarkets, libraries, the Returned Services League and Queensland Health staff (outside working hours). Anyone who was willing was recruited for word of mouth advertising. A special mention and word of thanks must go to Pamela Valenti, Jeff Guest, Mike Scrase and Cliff Timmins for all of their hard work. Treating physicians were asked to screen potential participants.

Study

Supervision for the PhD candidate Wendy Laupu and administration for the study was conducted by Professor Kim Usher. This included financial administration, oversight of all aspects of the study and necessary contractual arrangements. Project funding was obtained by Wendy Laupu and contractual arrangements were made and managed by Professor Kim Usher, Associate Professor David Lindsay and James Cook University's legal representative, Jasper Taylor. Clinical trial insurance was obtained by Wendy Laupu through James Cook University. Wendy Laupu managed the conduct of the study, which involved liaison with the compounding pharmacy (Georgina Twomey), Sullivan-Nicolaides clinical trial coordinator (Courtney Butler) and clinical trial pharmacist (Meagan Marriot). Blinding, randomisation, dispensing, labelling for the clinical trial and recording were conducted by Meagan Marriot.

Safety monitoring was undertaken by Dr Elizabeth Emmanuel, and the internal monitor was Dr Tessa Cookson. Dr Cookson acted as the study physician to monitor any concerns and for medical administration such as prescriptions, laboratory forms and crosschecking of Wendy Laupu's field work. The 305 interviews were conducted by Wendy Laupu. Start-up meetings were initiated by Professor Michael Berk and Dr Olivia Dean. Closedown meetings were undertaken by Wendy Laupu. Dr Tessa Cookson signed off on matters pertaining to the medical administration of the trial (blood forms, prescribing of the intervention and crosschecking of the fieldwork). Professor Kim Usher and Dr Tanya Park signed off on matters pertaining to clinical trial supervision and original data. Dr Elizabeth Emmanuel signed off with regards to the safe delivery of the intervention. Meagan Marriot signed off on the clinical trial logs (compliance, blinding, randomisation, dispensing and labelling).

Statistical analyses

Associate Professor Petra Buettner checked the power analysis calculation. Professor Michael Berk directed Wendy Laupu to utilise mixed model repeated measures (MMRM) for the modelling of statistical analysis under the guidance of Associate Professor Sue Cotton. Emeritus Professor Rhondda Jones provided information for Wendy Laupu to set up the MMRM analysis. Planning and the checking of the *post hoc* and other statistical analyses were provided by Associate Professor Susan Cotton. Susan Jaccups provided some statistical direction; however, it differed from acceptable analysis of clinical trials in psychiatry. The statistical analysis itself was conducted by Wendy Laupu using the SPSS20 program.

Abstract

Background: Current treatments for schizophrenia, while effective, often lead to partial functional recovery for affected individuals. The neurobiology of schizophrenia consists of a complex array of factors whose interplay is not well understood. As a consequence, schizophrenia remains sub-optimally treated by existing therapeutic options. With a paucity of available novel therapies for schizophrenia and a lack of biologically driven targets being explored by pharmaceutical companies, there is a need for investigator-initiated trials examining novel pathways for the reduction of core symptoms and improved functionality. A review of the literature identifies the presence of mitochondrial dysfunction, oxidative stress and impaired redox defenses such as reduced glutathione levels and impaired antioxidant enzymes (glutathione S-transferase) in the primary disorder. Secondary metabolites in mangosteen pericarp are hypothesised to protect against oxidative stress by evoking an intrinsic pathway including mitochondria. It is unclear whether mangosteen pericarp may affect the severity of negative and positive symptoms and cognitive and social functioning in schizophrenia. These symptom domains are known to persist despite wide use of existing treatment options. The current study aims to assess whether adjunctive treatment with mangosteen pericarp influences these residual symptom domains in individuals with schizophrenia.

Methods: A randomised, placebo-controlled adjunctive trial was conducted. Structured interviews using the Mini International Neuropsychiatric Interview (MINI-plus) were conducted to establish the diagnosis of schizophrenia or schizoaffective disorder. The efficacy of the intervention on symptom domains was assessed using established outcome measures, consisting of structured interviews at baseline, 90 days, 150 days and 180 days. The primary outcome measure was the Positive and Negative Syndrome Scale (PANSS) total score, with secondary measures including the PANSS subscales (positive, negative and general), the

Montgomery Asberg Depression Rating Scale (MADRS), the Clinical Global Impression Improvement (CGI-I) and Severity scales (CGI-S), the Abnormal Involuntary Movement Scale (AIMS), the Self-Rated Life Satisfaction Scale (SRLS), the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) and the Global Assessment of Functioning (GAF). It was hypothesised that adjunctive mangosteen pericarp would reduce symptoms of schizophrenia indexed by PANSS total scores compared to placebo. The study followed Good Clinical Practice and National Health and Medical Research Council guidelines for clinical trials. Participants were randomly allocated to either 1000mg/day of encapsulated *Garcinia mangostana* L. (mangosteen) pericarp powder or a matching placebo for a period of 180 days, in addition to treatment as usual.

Results: The primary and secondary measures were assessed at each interview. The placebo and experimental group had statistically significant differences between groups on the primary and secondary outcomes at the 180-day endpoint. The efficacy of mangosteen pericarp was supported by a high level of compliance and significant difference of the primary indicator, PANSS total ($p < 0.01$), with a large effect size (1.41) between groups at endpoint.

Secondary measures demonstrated significant between-group differences across all measures of dimensional outcome: PANSS positive ($p < 0.01$), PANSS negative ($p < 0.01$), PANSS general ($p < 0.01$), MADRS ($p = 0.01$) and CGI-S ($p = 0.03$). Functioning and well-being measures were significantly different between groups for SRLS ($p < 0.01$) and GAF ($p = 0.03$). The effect of treatment over time was different between groups, as measured by CGI-I ($p < 0.01$). Side-effect rating across LUNSERS scores indicated significant between-group differences ($p < 0.01$), with greater reduction in the mangosteen pericarp group. There were non-significant differences between groups of tardive dyskinesia ($p = 0.16$) measured by AIMS scores. Tobacco and alcohol use did not differ between groups at 180 days. Mangosteen pericarp was well tolerated.

Conclusions: Our data supports a causal relationship between mangosteen pericarp and a reduction of symptom domains associated with schizophrenia. Our results support the efficacy of 1000mg/day encapsulated mangosteen pericarp compared to the placebo for the treatment of schizophrenia and schizoaffective disorder.

Australian and New Zealand Clinical Trial Registration number:
ACTRN12611000910909.

Table of Contents

Dedication	i
Acknowledgements	ii
Statement on the Contribution by Othersi	iii
Specific Contributions to the Clinical Trial.....	v
Abstract	viii
Table of Contents	xii
List of Tables	xv
List of Figures	xvii
Abbreviations	xix
Chapter 1: Introduction	1
1.0 Context of this research	1
1.1 Justification for the research	2
1.1.1. Schizophrenia	2
1.1.2. Burden of schizophrenia in society	3
1.1.3. Current treatments and side effects	4
<i>1.1.3.1. Atypical/second-generation antipsychotics</i>	5
<i>1.1.3.2. Side effects</i>	6
1.1.4. Nutraceuticals	8
1.1.5. Mangosteen pericarp	9
<i>1.1.5.1 Usefulness of mangosteen pericarp</i>	11
<i>1.1.5.2. Active components of mangosteen pericarp</i>	11
1.2. The significance of the research	12
1.2.1. Significance for nursing	13
1.2.2. Significance for mental health services.....	15
1.3. Rationale for the study design.....	15
1.4. Thesis structure and outline	17
1.5. Summary	18
Chapter 2: Review of the Literature	20
2.0. Introduction	20
2.1. Literature review methodology.....	21
2.2. Molecular biology common to mangosteen pericarp and schizophrenia	22
2.2.1. Strength of the available data	23
2.3. Neurobiology of schizophrenia.....	24
2.3.1. Neurodevelopment	24
2.3.2. Environmental	25
2.3.3. <i>Genetic</i>	27
2.3.4. Autoimmune process	28
2.4. Mitochondria.....	29

2.5. Oxidative stress	30
2.5.1. Nitrosative stress in schizophrenia	31
2.5.2. Lipid peroxidation in schizophrenia.....	31
2.5.3. Reduced levels of glutathione in schizophrenia	32
2.5.4. Reduced levels of glutathione S-transferase in schizophrenia...	33
2.6. Implications for neuronal health	33
2.7. Effect on symptom domains	36
2.7.1. Impact on unwanted effects of second-generation antipsychotic drugs	38
2.8. Alternative therapies	39
2.9. Rationale for testing mangosteen pericarp.....	44
2.10. Secondary metabolites	44
2.10.1. Antioxidant activity	45
2.10.2. Neurobiology nexus attributed to mangosteen pericarp and schizophrenia.....	47
2.11. Safety of mangosteen pericarp.....	49
2.12. Research aims	52
2.13. Research hypothesis.....	53
2.14. Summary	53
Chapter 3: Methodology and Study Design.....	55
3.0. Introduction	55
3.1. Participants	56
3.2. Inclusion and exclusion criteria	58
3.3. Withdrawal criteria	59
3.4. Measurements	60
3.4.1. Participant demographics	62
3.4.2. Outcome measures.....	62
3.5. Study procedure	68
3.5.1. Ethical and legal consideration.....	69
3.5.2. Registration number and protocol	70
3.5.3. Funding sources.....	70
3.5.4. Sample size	71
3.5.5. Presentation of the intervention.....	71
3.5.6. Mangosteen pericarp	72
3.5.7. Placebo.....	73
3.5.8. Setting.....	74
3.5.9. Study locations for data collection	74
3.5.10. Data management	74
3.6. Statistical methods	75
3.7. Summary	77
Chapter 4: Results	78
4.0. Introduction	78
4.1. Overview of the study	79
4.2. Demographics of the study sample	82

4.3. Baseline differences between groups.....	84
4.4. Withdrawal and completion data	88
4.5. Primary efficacy measure, PANSS total.....	92
4.5.1. Adherence.....	94
4.6. Secondary outcome measures	94
4.6.1. PANSS positive.....	94
4.6.2. PANSS negative.....	95
4.6.3. PANSS general.....	96
4.6.4. MADRS.....	97
4.6.5. CGI-S.....	98
4.7. Functioning and well-being	99
4.7.1. GAF	99
4.7.2. CGI-I.....	100
4.7.3. SRLS.....	101
4.8. Side effects of second-generation antipsychotic drugs.....	102
4.8.1. LUNBERS	102
4.8.2. AIMS	103
4.9. Analysis of habits.....	104
4.10. Explanatory and supplementary measures.....	105
4.10.1. Effect sizes.....	105
4.10.2. Safety data	105
4.10.3. Response.....	106
4.10.4. Suicidal ideations.....	107
4.10.5. Anxiety	108
4.10.6. Weight	109
4.10.7. C-reactive protein.....	109
4.10.8. Adherence with taking prescribed second-generation antipsychotic drugs	110
4.11. Summary	116
Chapter 5: Discussion	119
5.0. Introduction.....	119
5.1. Interpretation.....	121
5.1.1. Explanatory and supplementary	123
5.2. Discussion	125
5.3. Strengths and limitations.....	128
5.3.1. Sources of potential bias.....	129
5.3.2. Imprecision	130
5.3.2.1. <i>Multiplicity of analyses</i>	130
5.3.2.2. <i>Threats to internal validity</i>	131
5.3.2.3. <i>Generalizability and external validity</i>	131
5.4. Clinical implications of the findings.....	133
5.4.1. Families and carers	134
5.4.2. Mental Health services	135
5.5. Recommendations.....	135

5.5.1. Research.....	135
5.5.2. Education	136
5.6. Thesis summary	136
Bibliography.....	139
Appendices	163
Appendix A—Consent form(participant information & consent form) Error! Bookmark not defined.	
Appendix B—Demographic information sheet Error! Bookmark not defined.	
Appendix C—PANSS Interview Sheets.. Error! Bookmark not defined.	
Appendix D—PANSS	Error! Bookmark not defined.
Appendix E—PANSS Rating Scale	Error! Bookmark not defined.
Appendix F—MONTGOMERY-ASBERG DEPRESSION SCALE (MADRS)	186
Appendix G—Clinical Global Impressions Error! Bookmark not defined.	
Appendix H—Self-Rated Life Satisfaction Scale	164
Appendix I—LUNSERS Score Sheet..... Error! Bookmark not defined.	
Appendix J—LUNSERS	Error! Bookmark not defined.
Appendix K—AIMS Examination Procedure Error! Bookmark not defined.	
Appendix L—Abnormal Involuntary Movement Scale (AIMS) Error! Bookmark not defined.	

List of Tables

Table 1: Compiled list of second-generation antipsychotic drugs available in Australia at the time of the clinical trial.....	5
Table 2: Some unwanted effects associated with second-generation antipsychotic drugs	8
Table 3: Selection of tests commonly used to assess schizophrenia.....	37
Table 4: RCT/open label studies reporting nutraceuticals tested in schizophrenia (2005-2014).....	40
Table 5: Studies orally administering compounds of mangosteen pericarp in humans to date.....	51
Table 6: Outcome measure guide	66
Table 7: Characteristics of interest, and statistical analysis of each group at baseline (n = 80).....	86
Table 8: Overall and between-group descriptive analysis ($M[SD]$) for baseline clinical and functioning measures (n = 80).....	88
Table 9: Completion rates at 90, 150 and 180 days (n = 80)	89
Table 10: Comparison of completers and non-completers over the 180 days of the trial.....	91
Table 11: Effect sizes for outcome measures (difference between baseline and 180 days)	105
Table 12: Safety data for the clinical trial (n = 80)	106
Table 13: Response as represented by percentage reduction in symptoms from baseline to 180 days as measured by PANSS total scores.....	107

List of Figures

Figure 1: <i>Garcinia mangostana L.</i> tree bearing unripened fruit	10
Figure 2: Mangosteen pericarp surrounding the white flesh of the fruit segments	11
Figure 3: Structure of alpha mangostin	12
Figure 4: The chemical structure of epicatechin	42
Figure 5: Parallel-group two-armed study design for an RCT	55
Figure 6: Visit schedule.....	61
Figure 7: Participant flow analysis of the primary outcome measure	81
Figure 8: Mean estimate and standard error scores for PANSS total in each group, across interviews and over time.....	93
Figure 9: Mean estimate and standard error scores for PANSS positive in each group, across interviews and over time.....	95
Figure 10: Mean estimate and standard error scores for PANSS negative in each group, across interviews and over time	96
Figure 11: Mean estimate and standard error scores for PANSS general in each group, across interviews and over time	97
Figure 12: Mean estimate and standard error scores for Montgomery-Asberg Depression Rating Scale in each group, across interviews and over time	98
Figure 13: Mean estimate and standard error scores for CGI-S in each group, across interviews and over time	99
Figure 14: Mean estimate and standard error scores for GAF in each group, across interviews and over time	100
Figure 15: Mean and standard deviation scores for CGI-I in each group, across interviews and over time	101
Figure 16: Mean estimate and standard error scores for SRLS in each group, across interviews and over time	102

Figure 17: Mean estimate and standard error scores for LUNBERS in each group, across interviews and over time	103
Figure 18: Mean estimate and standard error scores for AIMS in each group, across interviews and over time	104
Figure 19: Mean estimate and standard error scores(item 10) from the MADRS for suicidal ideations in each group, across interviews and over time	108
Figure 20: Mean estimate and standard error scores for anxiety (item G2) from the PANSS in each group, across interviews and over time.....	109
Figure 21: Mean estimate and standard error scores for PANSS total in SGA drug non-adherent participants in each group, across interviews and over time	112
Figure 22: Mean estimate and standard error scores for PANSS positive in SGA drug non-adherent participants in each group, across interviews and over time	112
Figure 23: Mean estimate and standard error scores for PANSS negative in SGA drug non-adherent participants in each group, across interviews and over time	113
Figure 24: Mean estimate and standard error scores for PANSS general in SGA drug non-adherent participants in each group, across interviews and over time	113
Figure 25: Mean estimate and standard error scores for MADRS in SGA drug non-adherent participants in each group, across interviews and over time	113
Figure 26: Mean estimate and standard error scores for CGI-S in SGA drug non-adherent participants in each group, across interviews and over time	114
Figure 27: Mean estimate and standard error scores for GAF in SGA drug non-adherent participants in each group, across interviews and over time	114
Figure 28: Mean estimate and standard error scores for SRLS in SGA drug non-adherent participants in each group, across interviews and over time	115

Figure 29: Mean estimate and standard error scores for LUNSERS in SGA drug non-adherent participants in each group, across interviews and over time 115

Figure 30: Mean estimate and standard error scores for AIMS in SGA drug non-adherent participants in each group, across interviews and over time 116

Abbreviations

AIMS	Abnormal Involuntary Movement Scale
Akt	Protein kinase B
APA	Australian Postgraduate Award
BPRS	Brief Psychiatric Rating Scale
X ²	Chi square
CGI	Clinical Global Impression
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase enzyme 2
df	Degrees of freedom
DHA	Docosahexaenoic acid
DNA	Deoxyribose nucleic acid
DSM-IV	Diagnostic and statistical manual of mental disorders
ECG	Electrocardiogram
EPA	Eicosapentanoic acid
GABA	Gamma-aminobutyric acid
GAF	Global Assessment of Functioning
GSTM1	Glutathione S-transferase Mu class
GSTT1	Glutathione S-transferase Theta class
HAM A	Hamilton Anxiety Rating Scale
HAM D	Hamilton Depression Rating Scale
LD ₅₀	The amount of toxin capable of killing 50% of the population
LUNSERS	Liverpool University Neuroleptic Side Effect Rating Scale
MADRS	Montgomery Asberg Depression Rating Scale
M	Mean
M _Δ	Mean difference
MH	Mental health
MINI	Mini International Neuropsychiatric Interview-plus

MMRM	Mixed model repeated measures
mTOR	Mammalian Target Of Rapamycin
NHMRC	National Health and Medical Research Council
PANSS	Positive and Negative Syndrome Scale
%	Percentage
RCT	Randomised controlled trials
Redox	Reduction-oxidation Reaction
RNA	Ribonucleic acid
SANS	Scale of Assessment of Negative Symptoms
SD	Standard deviation
SGA	Second-generation antipsychotic drug
SRLS	Self-Rated Life Satisfaction Scale
t-test	Independent samples t-test
THC	tetrahydrocannabinol