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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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Project funding: The project sponsor was James Cook University, who contributed funding via the Graduate Research School and the School of Nursing, Midwifery and Nutrition. External funding was received from Mangosteen Dietary Supplements and the Far North Queensland Hospital Foundation.

Use of infrastructure external to JCU: External supervisors at Deakin University, Barwon Health and Orygen Research Centre, Queensland Health Clinical Research Unit at Cairns Hospital, Good Price Pharmacy at 318 Mulgrave Road, Cairns (compounding), Suliivan Nicolaides Laboratories, private vehicle, mobile telephone, treating physicians.

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.

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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	Cyclooxgenase 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	Eicosapentasenoic 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