THE EFFICACY OF *GARCINIA MANGOSTANA* L. (MANGOSTEEN) PERICARP AS AN ADJUNCTIVE TO SECOND-GENERATION ANTIPSYCHOTICS FOR THE TREATMENT OF SCHIZOPHRENIA:

A DOUBLE BLIND, RANDOMISED, PLACEBO-CONTROLLED TRIAL

A thesis submitted as part of the requirement of a degree of

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By

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I declare that this thesis is my own, original work carried out under the supervision of Professor Kim Usher of the School of Nursing, Midwifery and Nutrition at James Cook University. No part of this work has been submitted in any form for another degree or diploma at any other university or institution of tertiary education. Any work that is not my own has been acknowledged in the text by appropriate references.

Dedication

To those persons in the 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.

The work on anxiety, depression and suicidal ideations I wish to dedicate to my home town, the people of Christchurch, New Zealand, in the aftermath of the earthquakes that continue to literally shake the city and the apparent apathy of the insurance industry which continue to affect the psyche of its inhabitants.

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.

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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.

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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

Chapter 1: Introduction

'Let thy food be thy medicine and thy medicine be thy food'

Hippocrates of Kos (460–359 BC)

1.0. Context of this research

The need for an additional tolerable and effective treatment option for schizophrenia is driven by unmet needs among those who experience the condition. The history of treatments for schizophrenia has been marked by a limited range of treatment options, which continue to be of suboptimal utility from the consumer perspective. Until the advent of antipsychotic drugs for schizophrenia in the 1950s, there were no treatment options that demonstrated efficacy for the symptoms of schizophrenia. The development of antipsychotic drugs led to the dopamine hypothesis, which attributes the symptoms of schizophrenia to overactive dopaminergic neurotransmitters (Seeman 1987). Currently, antipsychotic drugs remain the preferred treatment option for schizophrenia; however, many people achieve suboptimal therapeutic effect (Hogarty & Ulrich 1998).

This thesis aims to address this gap by assessing the potential of mangosteen pericarp to improve outcomes, comparative to the placebo, in a cohort of people with schizophrenia. The clinical trial tests mangosteen pericarp as an adjunctive treatment to second-generation antipsychotics for the management of chronic schizophrenia. Assessments of efficacy of the intervention are provided in the thesis. The study utilises a double blind, randomised, placebo-controlled trial design. Described within this chapter is the context of the problem under investigation (1.0), the justification for undertaking this work (1.1), the significance of the research being undertaken (1.2) and the rationale for the study design (1.3). The thesis structure and outline (1.4) are presented prior to a chapter summary (1.5).

1.1. Justification for the research

Nutraceuticals represent a potential therapeutic avenue to attempt to close the gap in recovery for those with schizophrenia. To date, any link between mental illnesses, such as schizophrenia and vitamin supplementation, has remained on the fringes of mainstream psychiatry. In other diverse fields, such as osteoporosis, the potential of nutraceuticals, including flavonoids (often targeting oxidative imbalances), are being explored (Welch & Hardcastle 2014). A recent focus

of work in schizophrenia has been defects in glutathione metabolism. Glutathione is the most ubiquitous antioxidant in the body and therefore has a primary role in the defense against oxidative stress. The presence of oxidative stress and impaired redox defenses, such as reduced glutathione levels and impaired antioxidant enzymes (glutathione S-transferase) in schizophrenia, have been recognised (Berk et al. 2008b). The existence of oxidative stress and deficient antioxidant enzymes are thought to be influenced by nutraceuticals (Roberts et al. 2006).

1.1.1. Schizophrenia

For the purpose of this study, schizophrenia was defined using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Schizophrenia is a widely defined chronic pattern of symptom domains, which include positive (sensory hallucinations, delusions, behavioural disturbance, disorganised thinking and speech) and negative symptoms (social withdrawal, blunted affect, lack of motivation, impaired judgement and inability to experience pleasure). The DSM-IV criterion for schizophrenia requires two or more positive or negative symptoms to have been present for the majority of a one-month period to support a diagnosis of schizophrenia (American Psychiatric Association 2000). Schizophrenia is widely reported to affect 1% of the world's population over the course of an individual's lifetime (Camargo et al. 2007). McGrath et al. (2008) report the median incidence of new cases of schizophrenia within the Queensland population as 0.02%.

The disorder onset is characterised by a prodromal period that manifests most commonly during early adulthood (Larson, Walker & Compton 2010). The prodromal period involves non-specific symptoms of social withdrawal and alterations in cognitive and behavioural functioning from previous levels of individual functionality (Larson, Walker & Compton 2010). Following a non-specific prodromal period, symptoms progress to manifest as a first episode of psychosis. The first episode of psychosis affects cognition, behaviour and emotions (Kring & Moran 2008). Schizophrenia is characterised in the chronic stages by periods of acute exacerbation, followed by episodes of remission.

1.1.2. Burden of schizophrenia in society

Mental illnesses, like cardiovascular diseases, are increasingly being managed in the home environment (Davidson et al. 2001). Unemployment, poverty, social isolation and stigma underscore the lived experience of chronic schizophrenia (Savilla, Kettler & Galletly 2008). A reduced life expectancy (by an average of 18.7 years) and an increased risk of completed suicide

are associated with schizophrenia (Laursen 2011). According to Rössler et al. (2005), the burden of schizophrenia represents 1.10% of disability-adjusted life years and 2.80% of years lived with disability. Research also indicates an established association of other disorders with schizophrenia. For example, major depression, anxiety disorders and substance abuse (Larson, Walker & Compton 2010) are often associated with schizophrenia. The presence of these other disorders adds to the burden of care shared by families (Chan 2011). The burden placed on families in caring for a family member with schizophrenia is well documented (Gutiérrez-Maldonado, Caqueo-Urízar & Kavanagh 2005; Caqueo-Urízar & Gutiérrez-Malsonado 2006). Restrictions placed on social and leisure activities, financial burden, employment difficulties, emotional impact on families and behavioural issues arising from the symptoms themselves have been described (Kuipers 1993). Various studies since that time have assessed how families cope with the burden (Cole & Reiss 2013). Carer health and quality of life is a prominent issue in the recent literature (Zahid & Ohaeri 2013; Boyer et al. 2012). There is a paucity of interventions becoming available for families to access, as caring for someone with a mental illness has been linked to high relapse rates (Sunanda, Ramesh & Eilean 2013). For instance, psycho-education (Sunanda, Ramesh & Eilean 2013), personalised nursing care plans for the home (Roldán-Merino et al. 2012) and psychosocial intervention for emotional expression in families are advocated (Pharoah et al. 2010; Gómez-Beneyto 2010). However, because of the burden under which many families are placed, many persons with schizophrenia are divorced from their family supports. Many are homeless.

1.1.3. Current treatments and side effects

While there is a multitude of current treatments employed for schizophrenia, both pharmaceutical and psychological, the current literature review will focus on second-generation (atypical) antipsychotics and nutraceuticals. To clarify, this project tests our intervention as an adjunctive to second-generation antipsychotic drugs.

1.1.3.1. Atypical/second-generation antipsychotics

Currently, the predominant treatments for schizophrenia are the pharmaceutical class of atypical (or second-generation) antipsychotic drugs (Table 1). Many second-generation antipsychotic drugs have been approved by regulatory authorities for the treatment of schizophrenia. The release of second-generation antipsychotic drugs occurred in global markets during the early 1990s. These drugs were developed as a response to the extrapyramidal side effect profiles of the first-generation antipsychotic drugs (Tandon & Fleischhacker 2005).

Table 1: Compiled list of second-generation antipsychotic drugs available in Australia at the time of the clinical trial

Generic name	Example of a trade name
Amisulpride	Solian
Aripiprazole	Abilify
Clozapine	Clozaril
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal
Ziprasidone	Zeldox

(Kumar & Sachdev 2009)

Compared to the typical agents, the second-generation antipsychotic drugs exhibit greater affinity for neurotransmitters other than dopamine, such as serotonin. Although antipsychotic agents remain the preferred treatment option for schizophrenia, a suboptimal therapeutic effect is achieved for many people. A previous systematic review and subsequent meta-analysis was conducted of randomised controlled trials (RCT) with placebo-designed trials to test the efficacy of second-generation antipsychotic drugs (Leucht et al. 2008). Leucht et al. (2008) found a moderate effect with a pooled responder efficacy of 18% and specific changes in negative symptoms (pooled effect size = 0.39), positive symptom domains (pooled effect size = 0.48) and depression (pooled effect size = 0.26). In other words, while the second-generation antipsychotic drugs have efficacy in schizophrenia, their effectiveness is limited.

1.1.3.2. Side effects

A secondary consideration of this thesis is that of unwanted effects from the use of second-generation antipsychotic drugs (Table 2). There appears to be strong evidence of an association between second-generation antipsychotic drugs and the development of metabolic syndrome, weight gain (Muench & Hamer 2010) or tardive dyskinesia (Correll & Schenk 2008). Metabolic syndrome represents a cluster of risk factors associated with cardiovascular disease such as diabetes, dyslipidemia and hypertension (Shirzadi & Ghaemi 2006). De Hert et al. (2006) confirm the higher incidence of metabolic syndrome in persons with schizophrenia over time; however, they note that metabolic syndrome is also present in drug-naïve persons. The factors associated with weight gain in schizophrenia are not well understood (Panariello, De Luca & De Bartolomeis 2010) and they may result from a number of complex interactions. Specific work in relation to weight gain and metabolic syndrome is outside the scope of this thesis. However,

participant weight was measured to determine broad associations between weight and other unwanted effects and response to treatment.

In a review, the incidence of tardive dyskinesia associated with chronic use of second-generation antipsychotic drugs is reported by Correll and Schenk (2008) to be 2.98% across 12 trials. Abnormal Involuntary Movement Scale (AIMS) scores for tardive dyskinesia are significantly reduced by treatment with the nutraceutical ginkgo biloba (Zhang et al. 2011), which has antioxidant properties in common with mangosteen pericarp. The efficacy of mangosteen pericarp for tardive dyskinesia has not been tested to date. Thus, as a secondary aim of the study, the efficacy of mangosteen pericarp on tardive dyskinesia will be tested.

Unwanted effects from the use of second-generation antipsychotic drugs are subjectively assessed using scales such as the Liverpool University Neuroleptic Side Effects Rating Scale (LUNSERS) (Taylor 2012). This tool tests several clusters of side effects including psychic side effects; extrapyramidal, hormonal, anticholinergic side effects; and autonomic, allergic reactions. Interestingly, extrapyramidal side effects (measured by LUNSERS) are considered to be due to the blockade of dopamine receptors, but have also been linked to metabolic syndrome (Shirzadi & Ghaemi 2006).

The impact of drug-related unwanted effects (for example, tardive dyskinesia) may have a profound effect on the lives of persons with schizophrenia. The assessment and treatment of unwanted effects is thought to be capable of improving the quality of life for persons with schizophrenia (Nicolaou 2012). In the long term, the influence of unwanted effects and insight is considered relevant to functionality in people with schizophrenia (Meehan & Lloyd 2012). One consequence of poor tolerability is adherence, although illness acceptance, stigma and other psychosocial factors play equally critical roles. Meehan and Lloyd (2012) note that many persons in the community are non-adherent with their prescribed second-generation antipsychotic drugs. Sacchetti et al. (2013) describe a paucity of educational interventions and other non-pharmaceutical techniques aimed at regaining adherence. A reduction in unwanted effects is likely to have a positive influence on adherence behaviour. This view is supported by Chiang et al. (2011), who found that negative attitudes were consistent with experiences of hormonal, psychic and general side effects. In contrast, Fischel et al. (2013) documented a mismatch between negative attitudes and personal experience when taking second-generation antipsychotic drugs.

Table 2: Some unwanted effects associated with second-generation antipsychotic drugs

Drugs commonly associated with unwanted effects	Unwanted effect associated with second-generation antipsychotic drugs	Psychopathological link
Olanzapine, clozapine (de Hert et al. 2006)	Weight gain	Not well understood (Panariello et al. 2010)
Clozapine, olanzapine (de Hert et al. 2006)	Metabolic syndrome	Sedentary lifestyle, poor diet and smoking status (Peet 2006)
Antipsychotic drugs (Correll & Schenk 2008)	Tardive dyskinesia	Maladaptive synaptic plasticity (Teo, Edwards & Bhatia 2012)

1.1.4. Nutraceuticals

'Nutraceutical' is a term used to describe agents that are considered health supplements, vitamins or minerals. There has been increasing interest in these compounds as target biological pathways. A recent report suggests that nutraceutical prescriptions account for around 24.1% of all prescriptions involving schizophrenia (Balhara, Yadav & Kataria 2012), despite minimal quality supportive data. Nutraceuticals may be a promising tool in closing the shortfall in recovery and reducing unwanted effects associated with second-generation antipsychotic drugs, although evidence is limited.

A tool used to test broadly the unwanted effects of second-generation antipsychotics is the LUNSERS. Preliminary evidence indicates an influence of polyphenol antioxidants in reducing some unwanted effects of second-generation antipsychotic drugs (Dietrich-Muszalska et al. 2012). Mangosteen pericarp possesses polyphenol antioxidant properties; however, its potential has not been tested to date. As a secondary consideration, the study will test the efficacy of mangosteen pericarp against residual side effects of second-generation antipsychotic drugs.

The role of nutraceuticals, such as ginkgo biloba and omega-3 fatty acid, has not been established in relation to tobacco smoking, illicit substances or alcohol use in schizophrenia. *N*-acetyl cysteine has been investigated as a treatment option for the modulation of glutamate neurotransmission in addictions such as tobacco smoking and marijuana use (Dean, Giorlando & Berk 2011). *N*-acetyl cysteine has been studied for use in schizophrenia since 2007 (Lavoie et

al. 2007). However, adjunctive treatments for schizophrenia such as *N*-acetyl cysteine (Berk et al. 2008a) and glycine (Heresco-Levy et al. 1996) are slow to be accepted by mainstream psychiatry.

1.1.5. Mangosteen pericarp

The current study tests mangosteen pericarp as an add-on to standard second-generation antipsychotic drugs. The Species Pantarum (Linnaeus, 1753) botanical description is *Garcinia mangostana*; genus *clusiaceae*; common name mangosteen (Chin & Kinghorn 2008) (Figure 1).

Figure 1: *Garcinia mangostana L.* tree bearing unripened fruit
Image available at: www.bijlmakers.com/fruit/mangosteen.html

The fruit extract tested for this study is the pericarp of the mangosteen. This is defined strictly as the dark red layer between the rind and flesh, although many manufacturers incorporate the rind into their products (Figure 2).

Figure 2: Mangosteen pericarp surrounding the white flesh of the fruit segments
Image available at: www.engineeredilifestyles.org/mangosteen.html

1.1.5.1. Usefulness of mangosteen pericarp

Reports by Chin and Kinghorn (2008) and Kaomongkolgit, Chaisomboon and Pavasant (2011) suggest that mangosteen has been used as a traditional medicine in Asia for afflictions such as urinary tract infections, diarrhoea, dysentery, inflammation and ulcers, as well as for wound management practices. Although mangosteen fruit and extracts have a traditional use for a number of afflictions, well-designed efficacy studies are lacking. Their potential is supported by pre-clinical work, which suggests a neuronal protective role for alpha-mangostin against iodoacetate-induced cell death in NG 108-15 cell models, at a concentration range of 50–100ug/ml (Weecharangsan et al. 2006).

1.1.5.2. Active components of mangosteen pericarp

Over 85 secondary metabolites have been isolated from the pericarp of mangosteen (Chin & Kinghorn 2008). Secondary metabolites belong to a narrow set of organic compounds that are involved in plant defense. An absence of secondary metabolites is thought to influence long-term survival. Secondary metabolites concentrated in the pericarp include anthocyanins and xanthenes. The anthocyanins isolated in mangosteen pericarp thus far are predominantly procyanidins, prodelphinidins and small quantities of stereoisomers (Fu et al. 2007). Of the stereoisomers, the epicatechins have been the most evaluated. The xanthene alpha mangostin is reported to be an active constituent of mangosteen (Figure 3) (Akao, Nakagawa & Nozawa 2008). Studies by Wang et al. (2012) and Zarena and Sankar (2009) indicate that the xanthenes

in mangosteen pericarp all possess polyphenol derivatives that act as antioxidants. The xanthenes have a characteristic structure consisting of a tricyclic aromatic ring system (Bumrungpert et al. 2009b).

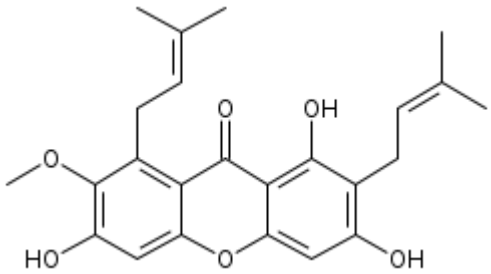

Figure 3: Structure of alpha mangostin
Image available publically at www.chemfaces.com

1.2. The significance of the research

Presently, mainstream treatment options provide a low chance for complete recovery for persons with schizophrenia. Results from a meta-analysis indicate that the figures for persons making a full recovery from schizophrenia are around 20%, with 40% social recovery (Warner 2010). The further development of measures that promote a full recovery from acute episodes of schizophrenia will be an advantage for the future management of chronic schizophrenia.

One consequence of suboptimal recovery from episodes of schizophrenia is that some symptom domains remain poorly treated by existing treatment options. Studies by Tandon, Nasrallah and Keshavan (2010) and Do et al. (2009) suggest that for many people, residual negative symptoms, cognitive impairments (memory, attention and language), poor social functioning and perceptual instability persist. As a result, many persons diagnosed with schizophrenia continue to be afflicted by symptoms regardless of availing themselves of the most up-to-date treatments. This finding occurs regardless of the current treatment provided. Therefore, this thesis aims to explore this problem of the deficits in therapeutic treatment.

1.2.1. Significance for nursing

For a large proportion of persons with schizophrenia, there remain many unmet needs. The literature uses the term 'deficit syndrome' to describe a continuum of impairment in symptoms and social and occupational domains (Strauss et al. 2010). Smith, Weston and Lieberman (2009) report, that 75% of people with schizophrenia experience an ongoing disability and relapse. In Australia, many persons diagnosed with schizophrenia are in receipt of the disability pension, placing a degree of burden on society. Results from a benchmark study indicate that there is a high incidence (77.1%) of depression, anxiety and suicidal ideation coexisting with schizophrenia (Rohde, Lewinsohn & Seeley 1991). More recent risk assessments support this view and suggest a 5% risk of completed suicide in persons with schizophrenia across an individual's lifetime (Hor & Taylor 2010). Impairments in social functioning may lead to social isolation (Hooley & Candela 1999), and habits such as tobacco smoking, illicit substance use and heavy alcohol use are associated with schizophrenia (Gregg, Barrowclough & Haddock 2007). A meta-analysis of tobacco smoking habits in schizophrenia shows a high degree of association compared to the general population across 20 nations (De Leon & Diaz 2005). A seminal paper indicates that addiction behaviours are associated with glutamate transmission (Kalivas 2009).

For those living with chronic schizophrenia, Barker and Buchanan-Barker (2004) describe a tidal model for recovery that aims to empower persons with a mental illness. This model is utilised by mental health nurses, along with education and strategies, to help persons with mental illness to cope with unmet needs (Chien, Kam & Lee 2001). McCann and Baker (2003) suggest that community mental health nurses and general practitioners are responsible for the continuity of mental health care in the community setting. However, Newell and Gournay (2008) argue that a new conceptual framework is needed for use in nurse education as well as to inform mental health nursing practice into the future.

While the tidal model and other proposed nursing models are largely based on a recovery approach, there appears to be some debate as to what constitutes recovery. Kelly and Gamble (2005) review the concept of recovery and argue that it can be viewed as either persistent core symptoms with some degree of functionality or alternatively as the absence of hospital admissions and cessation of symptoms. The current persistence of core symptom domains and reduced functionality is the likely outcome. However, work attempting to achieve reductions in the frequency of hospital admissions and reductions in core symptoms should not be diminished; nurses have an important role in working with persons to achieve this goal where possible. An effective and tolerable treatment option that promotes recovery from schizophrenia

would be advantageous for nurses to explore. Nurses have a dual obligation to adequately assess treatment efficacy and provide evidence-based information on which to base best practices.

1.2.2. Significance for mental health services

The Australian government has outlined a roadmap for the delivery of community-based mental health services. Harris et al. (2012) target housing and inpatient facilities in their roadmap for mental health funding in Australia until 2017. This road map is however, rather linear. A likely reason is that despite a large expenditure over an extended period, pharmaceutical companies have failed to develop novel treatments. Differentiation between individual antipsychotic drugs has focused on a reduction of side effect profiles, with less attention on these drugs' effectiveness (Fischel et al. 2013). Despite this emphasis, unwanted effects from the second-generation antipsychotic drugs persist.

1.3. Rationale for the study design

The choice of a placebo-controlled, randomised trial design for this study is based on internationally recognised standards for efficacy studies. The cohort under investigation comprises persons with schizophrenia with stable chronic symptoms.

Research in schizophrenia involves a vulnerable population. As such, the consideration of ethical principles in which to base the study design is of paramount importance. There are well-established and internationally recognised guiding principles for the researcher to address in designing such a study. Consequent to the convention at Helsinki (January 2005), guiding principles in the design of studies involving the mentally unwell were established (EUR/04/5047810/6) and endorsed by the World Health Organisation. The National Health and Medical Research Council (NHMRC) and Good Clinical Practice Guidelines, based on the Helsinki declaration endorsed in Australia, were followed in this study.

These guiding principles underpin the design and conduct of the clinical trial outlined within this dissertation. The ethical principles of nursing steer the direction of the study design, such as beneficence (promoting good), justice (promoting fairness), autonomy (respecting people's rights) and non-maleficence (doing no harm). Secondary principles of confidentiality, veracity (truthfulness and honesty) and fidelity (devotion to obligations, accuracy in reporting detail) were incorporated into the study design. For example, the study aimed to provide hope and beneficence for the participants.

The promotion of mental well-being as a tool for recovery places emphasis on goals and strengths (Slade 2010). The focus is thus on the formation of collaborative partnerships with persons living with schizophrenia and their families, to aim for improved health outcomes. The study has been designed in a manner that enables the empowerment of individuals by fostering an environment of collaboration and partnership formation.

There were additional special considerations for the cohort under study. Social isolation is a common factor within the cohort; thus, the use of advocates and general physicians as a point of contact acted as a buffer for introductions between the cohort and the researcher. The interview assessment tools were standardised and provide an operational measure of both symptom domains and unwanted effects from chronic use of second-generation antipsychotic drugs. There are valid and reliable measures for the assessment of outcomes.

Statistical analysis for this study will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines for clinical trials involving psychiatry. The Cronbach's alpha coefficient will provide validation of internal consistency for the individual outcome measures.

1.4. Thesis structure and outline

As a clinical trial, the thesis will conform to the James Cook University guidelines. Consequently, this thesis will consist of five chapters. The introduction (Chapter 1) has provided the context of the research. Justification for the research was outlined by defining schizophrenia, describing the burden it places on society and outlining current treatments options and their side effects. Mangosteen pericarp was introduced and its usefulness discussed in the context of its active components. The significance of the research was described in terms of unmet needs, nursing practice and mental health services. A rationale was given for the study design, which is based on the ability to determine a causal relationship among the variables. This design is in line with internationally recognised principles for the conduct of clinical trials in vulnerable cohorts. The thesis structure and outline are also presented.

Chapter 2 will provide an overview of the available literature. An overview of mechanistic disturbances leading to schizophrenia will be presented in terms of commonalities with the likely activity of mangosteen pericarp. Likely neurodevelopmental, environmental, genetic and autoimmune-based contributing factors will be presented, and the strength of all these data will be assessed. Neuronal health will be presented in terms of mitochondrial function, antioxidant enzymes, oxidative and nitrosative stress and lipid peroxidation. The known effect on residual symptom domains and, secondarily, the unwanted effects attributed to second-generation

antipsychotic drugs will be compared to established outcome measures. A rationale for testing mangosteen pericarp is provided, as is an overview of the neurobiological nexus between schizophrenia and mangosteen pericarp. Alternative therapies utilising nutraceuticals are discussed, and actions attributed to mangosteen pericarp will be discussed in relation to antioxidants and secondary metabolites. The safety of mangosteen pericarp will be presented prior to outlining the aims and hypotheses of the research, the chapter summary and the clinical trial methodology in Chapter 3.

Chapter 3 will outline the study design and methods, and address issues of recruitment and ethics, following CONSORT guidelines for the reporting of clinical trials. The results will be presented in Chapter 4. Reporting will follow CONSORT guidelines. Statistical analysis will follow established guidelines for clinical trials in psychiatry (Gueorguieva & Krystal 2004). The final chapter (Chapter 5) will provide a discussion, interpretation of the results, recommendations and future direction for research and practice. Following this, the thesis will be summarised.

1.5. Summary

For many persons, recovery from episodes of schizophrenia is incomplete. Existing treatments may not alleviate all of the symptoms of schizophrenia. In view of this, this chapter has explored the need for more tolerable and effective treatment options for schizophrenia and provided an overview of the current treatment options.

The approach for the thesis has been justified based on a gap in testing the efficacious effects of nutraceutical agents. A randomised, controlled trial with placebo design will be used to test the efficacy of mangosteen pericarp in schizophrenia, with the results reported within the five chapters of this dissertation. The study design has been rationalised in relation to the declaration at Helsinki, as mentally ill persons represent a vulnerable cohort for such research.

Chapter 2: Review of the Literature

'In the struggle for survival, the fittest win out at the expense of their rivals because they succeed in adapting themselves best to their environment'

Charles Darwin (1859)

2.0. Introduction

This chapter will review the known literature regarding both schizophrenia and mangosteen pericarp. It will begin with schizophrenia and previous studies tested with a similar approach, before culminating in the potential of mangosteen pericarp for the treatment of schizophrenia. Firstly, the methodology used in the literature review will be outlined (2.1). The neurobiology common to mangosteen pericarp and schizophrenia will then be introduced (2.2). It is widely understood that there are several factors underpinning the neurobiology of schizophrenia (2.3). Mitochondria (2.4) and oxidative stress (2.5) will be examined. Together, these factors are likely to have implications for neuronal health (2.6) and affect residual symptom domains (2.7). Alternative therapies (2.8) tested using RCT or open-label study designs will be reported, and the rationale for testing mangosteen pericarp will be provided (2.9). Secondary metabolites and antioxidant activity provide a background for the neurobiology nexus attributed to mangosteen pericarp and schizophrenia (2.10). The postulated safety of mangosteen pericarp will also be considered (2.11). This thesis aims to test adjunctively the efficacy of mangosteen pericarp as a novel treatment for schizophrenia (2.12). The research hypothesis will be clearly stated (2.13) and the chapter summarised (2.14).

This chapter will discuss the linkages between the established neurobiology in schizophrenia and the measurable outcomes that will be assessed in the clinical trial. This approach should enable understanding of the neurobiology implicated in schizophrenia as it relates to the documented activity associated with the pericarp of mangosteen fruit, that could support the rationale of the clinical trial.

2.1. Literature review methodology

A narrative review of the literature was undertaken to synthesise information pertaining to mangosteen pericarp and schizophrenia, as there have been no similar studies to date. Topics covered within the review are as follows: an overview of schizophrenia, nutraceuticals with

antioxidant properties, nutraceutical constituents common to mangosteen pericarp and mangosteen pericarp itself. Findings were summarised as a description of how mangosteen pericarp might be useful in schizophrenia. Electronic data sources including Google scholar, PubMed, Medline, lista, psych Info, Ovid, Scopus and the Cochrane database for systemic reviews were searched. The initial search commenced in 2005 and was subsequently extended to 2014. Papers included in the search had relevance for a general contextual background in schizophrenia, or direct relevance to neurobiology likely to be influenced by mangosteen pericarp activity or to outcomes measured in the clinical trial. Further papers outside this timeframe were included where necessary to provide an in-depth background of relationships between molecular disturbances. Other papers were excluded based on their examination of limited components of molecular pathways and factors such as repetition of printed material.

2.2. Molecular biology common to mangosteen pericarp and schizophrenia

Mangosteen pericarp shares commonalities that may be germane to schizophrenia pathology. It is clear that oxidative stress and antioxidant enzyme balance disturbance to pathways involving neurotransmitters (such as serotonin and dopamine) and cellular mitochondrial function (which provides the energy for all biochemical reactions) are of key importance. Some of these biological factors may be influenced by mangosteen pericarp, the focus of this thesis. It may be prudent to provide an introduction and overview of the interactions between these aspects of molecular biology.

Oxidative stress represents an imbalance between the level of reactive oxygen and nitrogen species and the body's ability to detoxify reactive intermediates or to repair the damage from oxidative stress. Oxidative stress is widely characterised by a disturbed redox state in which toxic effects are created by free radicals that alter proteins, lipids and deoxyribose nucleic acid (DNA) to manifest as cellular and metabolic injury (Zarena & Sankar 2009). Mitochondria have a role in the cellular response to oxidative stress. Mitochondria are structures present in eukaryotic cells and are surrounded by a membrane (Henze & Martin 2003).

Altered levels of both reduced and oxidised glutathione are thought to be indicative of the presence of oxidative stress. Glutathione is a major factor discussed within this review. It is a tri-peptide with multiple functions in cellular behaviour. The induction of the metabolising enzyme glutathione S-transferase acts simultaneously with glutathione in a cofactor arrangement (Pettersson & Mannervik 2001). Glutathione S-transferases are a family of isoenzymes that catalyse the conjugation of reduced glutathione to xenobiotic substrates to detoxify such substrates.

2.2.1. Strength of the available data

Oxidative stress and mitochondrial dysfunction have distinct roles in schizophrenia. A systemic review used multidimensional data to support the involvement of oxidative stress in psychiatric disorders such as schizophrenia (Ng et al. 2008; Bošković et al. 2011). A partial reason for this finding was dysregulation of antioxidant enzymes, which could increase oxidative stress. There appears to be strong evidence that implicates specific antioxidant enzymes in the pathophysiology of schizophrenia, such as glutathione and the glutathione S-transferase family. Genome studies support a statistically significant involvement of glutathione S-transferase family members (Mu class [GST M1] and theta class [GST T1]) and glutamate cysteine ligase in the pathogenesis of schizophrenia (Rodriguez-Santiago et al. 2009; Raffa et al. 2012). Post-mortem studies reveal significantly reduced levels of GSTM1 in the prefrontal cortex of persons diagnosed with schizophrenia and major depression (Gawryluk et al. 2011b). This finding is supported by glutathione S-transferases being involved in dopamine metabolism (Weingarten & Zhou 2001), an established dysfunction in schizophrenia (Davis et al. 1991). Impaired glutathione S-transferase functioning is also associated with progression of schizophrenia for an Iranian population (Kashani et al. 2011). Credible post-mortem evidence in schizophrenia implicates glutathione. Raffa et al. (2011) report reduced levels of glutathione in 27% of the cerebral spinal fluid of untreated persons, and 41% in the caudate post-mortem. Similarly, several studies confirm that glutathione is reduced by 27% in cerebral spinal fluid and 52% in the medial prefrontal cortex post-mortem (Do et al. 2000; Gawryluk et al. 2011a).

Mitochondrial alterations to purine and tryptophan metabolites are implicated in schizophrenia (Yao et al. 2013) and are linked to clinical symptom domains. These findings are detected in persons as early as the first episode of psychosis. For example, Yao et al. (2012) used high-pressure liquid chromatography to reveal altered purine metabolites influencing sensing and motor processing. Condray et al. (2011) linked neurotoxic and inhibitory compounds (derived from tryptophan metabolism) to a prediction of clinical severity and cognitive functioning.

2.3. Neurobiology of schizophrenia

The neurobiology of schizophrenia consists of a complex array of factors whose interplay is not well understood. There is substantial evidence revealing that neurodevelopment, genetic, environmental and autoimmune factors are likely contributors to the development of schizophrenia. It is unknown how these factors interplay in schizophrenia.

2.3.1. Neurodevelopment

Factors that occur during the gestational period or early childhood are widely thought to predispose a person to the development of schizophrenia. The factors prevalent in the current literature are prenatal stress, maternal infection, season of birth, maternal starvation and vitamin D (Walker, Curtis & Murray 2002; Khandaker et al. 2013).

It is unknown how these factors interplay to increase a person's vulnerability to schizophrenia. However, it is clear that by the first episode of psychosis, antioxidant defenses are inadequate (Mahadik & Mukherjee 1996; Yao et al. 1998). Antioxidant defense is a complex mechanism, recycling vitamin C, vitamin E and glutathione to neutralise reactive species (Reddy & Reddy 2011). A study by Matsuzawa and Hashimoto (2011) utilised magnetic resonance imaging to examine the antioxidant defense system in the brains of persons with schizophrenia. The researchers found that glutathione levels inversely correlated to negative symptoms of schizophrenia (Matsuzawa & Hashimoto 2011). Deficit antioxidant defenses are likely to leave neurons and other cellular structures vulnerable to damage from oxidative and nitrosative stress and micro-vessel toxins (Kamath et al. 2006). Devi and Chinnaswamy (2008) suggest the brain is particularly vulnerable to oxidative stress because the brain has a limited capacity to detoxify reactive oxygen species. Other contributing factors are that the brain has a high metabolic rate and contains polyunsaturated lipids for lipid peroxidation (Reiter 1995).

2.3.2. Environmental

Post-mortem evidence reveals reduced levels of glutathione and impaired antioxidant enzyme activity in persons experiencing their first episode of psychosis in schizophrenia (Raffa et al. 2011). Both glutathione and glutathione S-transferases have defined roles in defense against oxidative stress induced by environmental factors (Blokhina, Virolainen & Fagerstedt 2003). Depleted glutathione and glutathione S-transferase levels are likely to disable repair mechanisms pertaining to oxidative damage, prolong the toxic effect of free radical intermediaries and damage ribonucleic acid (RNA) and mitochondria.

The purported role of glutathione S-transferase in the body is detoxification. Reduced glutathione S-transferase levels affect the body's ability to detoxify both electrophilic substances and free radicals. Several studies have contributed to our collective understanding of free radical toxins. For example, the oxidation of catecholamine yields harmful agents such as o-Quinone formed from dopamine in schizophrenia (Gawryluk et al. 2011a), as well as dopachrome, noradrenochrome and adrenochrome (Harada, Tachikawa & Kawanishi 2001).

Gawryluk et al. (2011a) consider that o-Quinone is usually addressed by redox cycling and glutathione conjugation. The presence of low glutathione and glutathione S-transferase levels suggests the slow excretion of harmful toxins such as o-Quinone from the body.

In the absence of adequate antioxidant defenses, a backup metabolic response involving an oxidative shield in eukaryotes is thought to be activated (Naviaux 2012). The researcher suggests that cellular threats are sensed and that the memory of the event is then stored in mitochondria to enable further sensitivity (Naviaux 2013). This response is evidenced in schizophrenia by post-mortem studies. There is evidence of a perineuronal net that protects fast-spiking interneurons (Cabungcal et al. 2013). The researchers report that this shielding mechanism ordinarily protects neurons from the effects of oxidative stress and redox dysregulation (Cabungcal et al. 2013). However, it is vulnerable to oxidative stress, with excess oxidative stress likely to result in the failure of the oxidative shield (Naviaux 2012; Cabungcal et al. 2013). When an oxidative shield is persistently required, mitochondria are thought to alter cellular metabolism to shield the cell from further injury (Naviaux 2013). Schizophrenia is thought to be characterised by defects in multiple metabolic pathways involving mitochondria (Yao et al. 2013).

2.3.3. Genetic

An altered redox state would fail to maintain an appropriate cellular environment for mitochondrial and nuclear DNA repair to occur. Glutathione is known to participate in cell signalling and metabolic processes involving protein synthesis and DNA repair across all species of plants and animals (García-Giménez et al. 2012). Aberrant response signalling to DNA damage is implicated in schizophrenia (Catts et al. 2012). The cell ordinarily responds to DNA damage by increasing the expression of genes associated with DNA repair. Gene-association studies provide a clue as to which genes are involved in DNA repair (Chowdari, Bamne & Nimgaonkar 2011). There is evidence in schizophrenia of an antioxidant gene pattern including glutathione-related genes, glutathione synthesis genes, nitric oxide genes and mitochondrial genes (Chowdari, Bamne & Nimgaonkar 2011). This finding supports epigenetic factors in schizophrenia that alter gene expression (Roth et al. 2009) while preserving the underlying DNA sequences (Han et al. 2011). For example, oxidative stress is known to damage DNA directly or indirectly, for which glutathione S-transferase is a protective enzyme (Hayes, Flanagan & Jowsey 2005). Therefore, reduced glutathione S-transferase levels may result in the inadequate protection of DNA and proteins from oxidative stress-induced damage—which, together with RNA, are critical to sustaining life.

RNA molecules have a distinct role in coding for gene expression and in communicating cellular signals for protein synthesis. RNA is considered more sensitive to oxidative damage than is DNA (Li et al. 2007), with oxidative damage thought to influence RNA by producing metabolic changes to the cell that can induce apoptosis (Bellacosa & Moss 2003). Repair mechanisms are likely to be hampered by chronic inhibition of the neuronal survival/death (protein kinase B (Akt)) signalling pathway (Zheng et al. 2012; Mitchell 2013). Post-mortem studies of hippocampal tissues in schizophrenia confirm the presence of oxidative damage to RNA (Che et al. 2010).

2.3.4. Autoimmune process

In his seminal paper, Solomon (1987) postulates the involvement of an overstimulated immune system in schizophrenia. Recently, a plausible mechanism in relation to depression has been disclosed. Progressive autoimmune responses against auto-epitopes are associated with depression (Maes et al. 2012) and there appears to be strong evidence that damage from oxidative and nitrosative stress may stimulate auto-epitopes into provoking an immune response (Anderson, Maes & Berk 2012). Similarly, damage from oxidative and nitrosative stress is implicated in schizophrenia (Bošković et al. 2011).

With respect to schizophrenia, low levels of glutathione are likely to influence the progress of immune and inflammatory processes (Ballatori et al. 2009). In the presence of reduced glutathione levels, glutathione S-transferase is thought to overstimulate the immune system and catalyse changes in expression (Fonnum & Lock 2004). Results from a benchmark study by Ballatori et al. (2009) found a likely reason to be that during viral activity, glutathione activates cell signalling and host immune system response.

2.4. Mitochondria

Metabolic pathways are considered immature in newborns and children, to influence their neurodevelopment (Wood & Gibson 2009). Moreover, there is abundant evidence to support the occurrence of metabolic changes by mitochondria in schizophrenia to influence some neurotransmitter receptors. For example, an association between purine metabolites (for mitochondrial response to oxidative stress) and monoamine neurotransmitters has been established with regard to the first episode of psychosis (Yao et al. 2013). Transcriptional metabolites integrate signals from various pathways to regulate metabolism (Desvergne, Michalik & Wahli 2006). In schizophrenia, protein studies demonstrate that up to half of proteins are altered and up to 90% of perturbed transcriptional metabolites involve

mitochondrial and oxidative stress responses (Prabakaran et al. 2004). Naviaux (2013) suggests that the total load of environmental triggers becomes integrated by metabolism to regulate both the magnitude and form of metabolic response. This finding is concordant with fluctuations in clinical presentation and the characteristic pattern of remission followed by acute exacerbation of symptoms in schizophrenia.

Established measures of clinical outcomes are available to determine the severity of schizophrenia. Kay, Flszbein and Opfer (1987) developed the Positive and Negative Syndrome Scale (PANSS), which has become a widely accepted measure and which will be used in this study as the primary indicator. The mitochondrial density of activated lymphocytes was found to correlate to the PANSS measures for severity of psychosis and to abnormalities of energy metabolism (Uranova et al. 2007). Associations between purine metabolites and clinical symptoms have established the clinical relevance of altered metabolites to schizophrenia pathology (Yao et al. 2012).

2.5. Oxidative stress

The continued accumulation of excess free radical toxins over an extended period may contribute to a chronic neuronal injury (described by Fonnum & Lock 2004) linked to clinical symptom domains in schizophrenia. Fonnum and Lock (2004) disclose a mechanism of neuronal injury that involves a combination of depleted glutathione (increasing cellular susceptibility to oxidative stress), an excitotoxic mechanism (increasing oxidative stress, elevating calcium and impairing mitochondrial function) and the inhibition of enzymes for DNA repair. Further, some reactive oxygen species are known to act as second messengers in redox signalling to disrupt cellular signalling mechanisms.

Wang et al. (2009) analysed an oxidative stress marker (4-hydroxynonenal), finding a 47% increase within the anterior cingulated cortex in schizophrenia post-mortem. There appears to be strong evidence that negative symptoms measured by PANSS and other parameters, such as age of onset and type of schizophrenia, are associated with oxidative stress (Pazvantoglu et al. 2009). Findings thus far suggest that an overlap of oxidative and nitrosative stress may explain the association between schizophrenia and depression (Anderson & Maes 2012).

2.5.1. Nitrosative stress in schizophrenia

Post-mortem data reveal that nitric oxide metabolites are present with significantly increased levels of nitric oxide (up to 241 +/- 146 per mol/mg dry weight) in schizophrenia (Yao, Leonard & Reddy 2004). The presence of disturbed nitric oxide metabolites in schizophrenia and increased nitric oxide production are considered indicative of damage involved in the storage, uptake and release of neurotransmitters such as glutamate, acetylcholine, dopamine, gamma-aminobutyric acid (GABA), glycine, taurine, neuropeptides and noradrenaline (Bernstein, Bogerts & Keilhoff 2005).

2.5.2. Lipid peroxidation in schizophrenia

Reactive oxygen species and antioxidant enzymatic activity are coupled to the degradation of lipid membranes, known as lipid peroxidation (Singh et al. 2012). Zhang et al. (2006) propose a link between reduced PANSS scores and reduced oxidative stress and lipid peroxidation in persons with schizophrenia who smoke tobacco. In contrast, Charalabopoulos et al. (2005), testing plasma samples of smokers, found increased antioxidant capacity but a reduced ability of lymphocytes to resist neurotoxin-induced DNA damage.

Malondialdehyde is a product of oxidative lipid peroxidation, which also damages proteins and DNA in schizophrenia (Kuloglu et al. 2002). High levels of malondialdehyde in chronic schizophrenia not only indicate the presence of lipid peroxidation but also correlate with symptom domains. In one benchmark study, malondialdehyde levels were 163% higher in people with positive symptoms, 137% higher in those with negative symptoms and 132% higher in those with cognitive symptom domains (Devi & Chinnaswamy 2008). Medina-Hernandez et al. (2007) support this finding, as PANSS scores demonstrate higher levels of delusions and emotional withdrawal in persons with treatment-resistant schizophrenia. Lower scores for flow of conversation and lack of spontaneity in persons with schizophrenia are also reported across PANSS (Medina-Hernandez et al. 2007). The data indicate that malondialdehyde levels are positively correlated in tardive dyskinesia to AIMS scores, and inversely correlated to the PANSS measures (Zhang et al. 2006).

2.5.3. Reduced levels of glutathione in schizophrenia

In his benchmark paper, Smythies (1999) contends that synaptic plasticity is modulated by reduction-oxidation (redox) balance at the synaptic level. Redox balance requires adequate levels of glutathione to be present in both the reduced and oxidised forms. Yao, Leonard and Reddy (2006) report consistent findings in the caudate region on post-mortem, with decreased levels of the reduced glutathione form compared to the ratio of oxidised glutathione. Ballesteros et al. (2013) confirm the presence of a two- to five -fold elevation in oxidised glutathione levels in schizophrenia, in which condition a reduction in glutathione levels is associated with defects in the glutathione synthesis enzyme, glutamate cysteine ligase (Lavoie et al. 2007). Lavoie et al. (2007) argue that N-methyl-D-aspartate receptors are redox sensitive and that depleted glutathione is thought to diminish N-methyl-D-aspartate function to inhibit the long-term potentiation of signal transmission (associated with neuroplasticity, learning, memory and auditory sensing processes). Chronic glutathione depletion is suggestive of changes in glucose metabolism and glycogen utilisation in the astrocytes of rodent models (Lavoie et al. 2011). Altered glucose metabolism and glycogen utilisation are associated in the literature with diabetes (Cline et al. 2002).

In terms of relevance to the study, the Montgomery Asberg Depression Rating Scale (MADRS) is a measure of depression. Clinical Global Impression (CGI), is a measure of clinical response to treatment and the severity of schizophrenia (Guy 1976). Glutathione levels are found to be reduced in plasma and blood samples during depression, as measured by MADRS (Samuelsson et al. 2012), and inversely correlated to CGI scores (Raffa et al. 2009).

2.5.4. Reduced levels of glutathione S-transferase in schizophrenia

A link has been established between glutathione S-transferase and several measures of clinical relevance. Emerging evidence links GSTT1 to cardiac changes (QTc-interval prolongation) and smoking status in schizophrenia (Bahaoddini, Farrashbandi & Saadat 2009). With respect to schizophrenia, Miljevic et al. (1996) confirm that glutathione S-transferase levels are slightly decreased in blood and negatively correlated to paranoia as measured by PANSS in people with schizophrenia. Glutathione S-transferase activity corresponds to a significant reduction in negative symptoms (erythrocyte, G6PD) and positive symptom domains (ceruloplasmin ferroxidase levels) in schizophrenia (Devi & Chinnaswamy 2008).

2.6. Implications for neuronal health

As already mentioned, there is evidence of oxidative stress-induced damage and mitochondrial-induced changes in metabolites in schizophrenia of clinical relevance. It is clear that dysfunctional neurotransmission and altered neuroplasticity (Tsai et al. 1995; Arnold, Talbot & Hahn 2005), inadequate neuronal protection and architectural changes, such as abnormal glial cells (astrocytes, microglial and oligodendrocytes) (Bernstein, Steiner & Bogerts 2009) and neuronal atrophy, are of key importance in schizophrenia.

For instance, Loureiro et al. (2010) provide evidence of remodelling in cortical astrocytes in schizophrenia. Astrocytes are star-shaped glial components of the brain. They have a role in the protection of neurons, which they achieve by maintaining the brain's defenses. There appears to be strong evidence of the role of astrocytes to maintain blood brain integrity, ionic balance and the synaptic metabolism of glutamate and monoamines (Bernstein, Steiner & Bogerts 2009).

Astrocytes communicate with neuronal synapses and modulate synaptic plasticity, influencing neurotransmission. Yao et al. (2013) make the linkage between altered purine and tryptophan metabolites and alterations to neurotransmission (such as glutamate and dopamine) in schizophrenia. Zheng et al. (2012) list the neurotransmitters implicated in schizophrenia as dopamine, glutamate, GABA, serotonin and acetylcholine.

Modification of the supply of the antioxidant enzyme glutathione to astrocytes (Shih et al. 2006) and the activation of glutamate receptors (Gu et al. 2008) are noted in the literature pertaining to schizophrenia. Current evidence indicates that neurons do not produce glutathione, but are instead reliant on astrocytes for neuronal protection (Bahia, Rattray & Williams 2008). Reduced glutathione levels are likely to facilitate a cascade of excitotoxic signalling that may result in cell death (apoptosis). There appears to be strong correlation between astrocyte depletion of glutathione and an increased risk of neuronal apoptosis *in vitro* (Bahia, Rattray & Williams 2008). This finding is significant, as changes in dendritic apoptosis in schizophrenia are associated with autoimmunity (Chen et al. 2006). Alterations in the rate of apoptosis are likely to affect neuronal architecture in schizophrenia. Dendritic cells are tightly regulated by apoptosis, as they function as antigen-presenting cells (meaning that they present foreign antigens to the T-cell) in the immune system (Wu & Liu 2007). Alterations to the architecture of the brain's prefrontal cortex and hippocampus are established features in schizophrenia. Dendrites are known to have a decreased spine density in both the prefrontal cortex and cortical regions (Glantz & Lewis 2000).

In schizophrenia, neuronal damage is likely to influence those synapses involved in memory storage that connect neurons for the exchange of electrical and chemical impulses (Mayford, Siegelbaum & Kandel 2012). Synaptic plasticity is the ability of a neuronal connection or synapse to alter its strength in response to neurotransmission (Hughes 1958). Neuroplasticity is thus a central concept in schizophrenia that in part involves the manner in which RNA is expressed to be altered (Frost et al. 2004). As explained in Section 2.3.3 above, the role of RNA is to carry genetic information and to specify the amino acid sequences for gene expression. Interestingly, the export of RNA is capable of being regulated by the neuronal survival/death (Akt) signalling pathway (Quaresma, Sievert & Nickerson 2013). This activity is thought to enable alterations in neural synapses and pathways in response to behavioural, injurious or environmental processes (Pascual-Leone & Taylor 2011). Results from a benchmark study indicate that chronic inhibition of aspects of the Akt pathway may reduce dendritic size (Zheng et al. 2011). This finding suggests a defect in mitochondrial metabolism across species (Schieke et al. 2006). We know this because the mammalian target of rapamycin (mTOR) is chronically inhibited by the neuronal survival/death pathway and is known to control mitochondrial metabolism (Betz et al. 2013). Zheng et al. (2011) propose that together this reduction in neuronal survival/death pathway activity may explain aspects of cognitive impairment, synaptic abnormalities, dysfunctional neurotransmitter signalling, altered protein synthesis and neuronal atrophy evident in schizophrenia.

2.7. Effect on symptom domains

Mitochondrial dysfunction, reduced antioxidant enzyme levels (glutathione and glutathione S-transferase) and oxidative stress are consistently associated with symptom domains in schizophrenia (Table 3).

Many of the studies that associate mitochondria and symptom domains in schizophrenia utilise laboratory techniques or are conducted on components of mitochondrial processes. For example, Tsai et al. (2013) report a correlation between PANSS positive and total scores and mitochondrial enzymes associated with cell death.

Zhang et al. (2013) implicate oxidative stress in deficits of attention and cognitive functioning, as they find significantly lower scores using the Repeatable Battery for the Assessment of Neuropsychological Status in people with schizophrenia compared to controls. This tool is often used to detect cognitive impairment in schizophrenia (Duff et al. 2010). In support, an oxidative stress index in schizophrenia shows that severity of negative symptom domains is significantly correlated to oxidative stress levels on outcome measures of both the PANSS and the Brief

Psychiatric Rating Scale (BPRS) (Pazvantoglu et al. 2009). The BPRS is a measure of psychosis, depression, anxiety and behaviour (Overall & Gorham 1988).

A significant correlation exists between severity of negative symptom domains and low glutathione levels in schizophrenia across several measures. These measures include the GAF, Scale for the Assessment of Negative Symptoms (SANS), BPRS, Drug-induced Extrapyramidal Symptoms Scale and the cognitive performance tests of Word Fluency Test, Stroop Test, Trail Making Test, Wisconsin Card Sorting Test and Digit Span Distractibility Test (Matsuzawa et al. 2008) (Table 3). Moreover, reduced glutathione S-transferase activity is noted in the bloods of persons with positive symptom domains, correlating with PANSS scores in schizophrenia (Miljevic et al. 1996).

Table 3: Selection of tests commonly used to assess schizophrenia

Assessment of Schizophrenia	Symptom domains
Clinical Global Impression Improvement (CGI-I) and Severity (CGI-S)	Response to treatment over time (CGI-I) and severity of symptoms (CGI-S)
Repeatable Battery for the Assessment of Neuropsychological Status Word Fluency Test, Stroop Test, Trial Making Test, Wisconsin Card Sorting Test, Digit Span Distractibility Test	Cognition
Brief Psychiatric Rating Scale (BPRS)	Psychosis, depression, anxiety and behaviour
Montgomery Asberg Depression Rating Scale (MADRS)	Depression and severity of schizophrenia
Positive and Negative Syndrome Scale (PANSS)	Positive, negative and general symptoms
Scale for the Assessment of Negative Symptoms (SANS)	Negative symptoms
Global Assessment of Functioning (GAF)	Social and occupational functioning

Assessment of Schizophrenia	Symptom domains
Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)	Unwanted effects
Abnormal Involuntary Movement Scale (AIMS)	Tardive dyskinesia
Drug-induced Extrapyramidal Symptoms Scale	Extrapyramidal unwanted effects

2.7.1. Impact on unwanted effects of second-generation antipsychotic drugs

As a secondary consideration of this thesis, unwanted effects attributed to second-generation antipsychotic drugs are examined. However, a focus is on measureable unwanted effects with an established measure of clinical outcome. The efficacy of mangosteen pericarp in ameliorating these unwanted effects will be tested in the clinical trial.

LUNSERS was specifically designed to evaluate antipsychotic side effects. No studies to date have linked glutathione, glutathione S-transferase, oxidative stress or mitochondrial dysfunction to LUNSERS outcomes.

Tardive dyskinesia is the term used to describe the involuntary and repetitive movements primarily associated with chronic use of second-generation antipsychotic drugs. The symptoms of tardive dyskinesia can be categorised depending on the part of the body involved. Common symptoms include lip smacking, grimacing, a protruded tongue, puckering, pursing of the lips and rapid eye blinking. The fingers, limbs, torso and respiration may also be affected. The AIMS scale provides an operational measure of severity of tardive dyskinesia. A link has been proposed in the literature between the development of tardive dyskinesia and an oxidative mechanism (Lohr, Kuczenski & Niculescu 2003). Several antioxidants have been investigated, with a conflicting degree of success (see Lohr, Kuczenski & Niculescu 2003 investigating vitamin E). Lieberman et al. (2008) for example, suggest that second-generation antipsychotic drugs influence the antioxidant system by improving superoxide dismutase activity for protection against apoptosis (cell death). The proposed effect is associated with tardive dyskinesia in schizophrenia (Lieberman et al. 2008).

2.8. Alternative therapies

An obvious therapeutic target is simply to improve glutathione metabolism for the restoration of antioxidant defenses. Insufficient levels of antioxidant enzymes or antioxidants are known to increase oxidative stress. Free radicals are atoms, ions and/or molecules with unpaired valence electrons, which render free radicals chemically reactive. Free radicals may commence a chain reaction leading to cellular damage. Antioxidants interrupt the process by themselves being oxidised. Findings in relation to this approach are presented as alternative therapies for schizophrenia.

Some nutraceuticals and many psychotropics such as lithium, valproate and antipsychotic drugs are thought to be capable of influencing glutathione metabolism. Considering that many antioxidants influence the glutathione pathway (and other relevant antioxidant defense pathways) (Reddy & Reddy 2011), they have been suggested in the literature as a possible approach for the treatment of schizophrenia. A list of nutraceuticals with antioxidant properties previously evaluated is provided in Table 4. However, the number of well-designed trials of nutraceuticals in schizophrenia is limited. Antioxidants have previously been evaluated adjunctively in schizophrenia cohorts for pathology and medication side effects (Reddy & Reddy 2011). Moreover, antioxidants have not been consistently effective. A meta-analysis highlights insufficient changes to PANSS, but improved AIMS scores (for tardive dyskinesia) across supplementary antioxidant studies to date (Bošković et al. 2011).

Table 4: RCT/open label studies reporting nutraceuticals tested in schizophrenia (2005–2014)

Study	Cohort	Nutra-ceutical	Major findings	Outcome measures	Class, active ingredient
Sivrioglu et al. 2007 (open label)	*N* = 17 Schizophrenia and haloperidol	Vitamin C (1000mg /day) Vitamin E (800 IU/day) Omega-3 fatty acid (1000mg /day)	Reduction positive, negative symptoms & side effects over 16 weeks	BPRS (reduced 40%) SANS (reduced 52.2%)	Ascorbic acid, tocopherols with omega-3 docosahexaenoic acid (DHA) & eicosapentase-noic acid (EPA)

Study	Cohort	Nutra-ceutical	Major findings	Outcome measures	Class, active ingredient
Bentsen et al. 2013 (multicentre double blind RCT with 2x2 factorial design)	*N* = 99 Schizophrenia and usual treatment	Vitamin C (1000mg/ day) Vitamin E (364 IU/day) Omega-3 fatty acid (2000 mg/day)	Significant reduction in people with low but not high baseline levels of poly-unsaturated fatty acids	PANSS total score (p = 0.02)	Ascorbic acid, tocophenols with omega-3 docosahexae-noic acid (DHA) & eicosapentase-noic acid (EPA)
Doruk, Uzun & Özsahin 2008 (RCT)	*N* = 42 Schizophrenia and clozapine	Ginkgo biloba extract (120 mg/day)	Improves negative symptoms in schizophrenia over 12-week period	BPRS (mean reduction 7.0)	Antioxidant containing ginkgo biloba extract
Zhang et al. 2011 (RCT)	*N* = 157 Schizophrenia and tardive dyskinesia	Ginkgo biloba extract (240 mg/day)	Improves tardive dyskinesia over 12 weeks	AIMS (signify-cant but not PANSS)	Antioxidant containing ginkgo biloba extract
Loftis, Wilhelm & Huckans 2012 (RCT)	*N* = 25 Schizo-affective, schizophrenia, bipolar disorder and usual medications	Green tea extract (1200mg/day)	Non-significant over 8 weeks	PANSS, CGI, Hamilton depression and anxiety rating scales (HAM-A, HAM-D)	Polyphenol with epigallocatechin-3-gallate

*BPRS: Brief Psychiatric Rating Scale (Overall & Gorham 1988); SANS: Scale for the Assessment of Negative Symptoms; AIMS: Abnormal Involuntary Movement Scale; PANSS: Positive and Negative Syndrome Scale; HAM-A and HAM-D refer to the Hamilton Anxiety and Depression Rating Scales, respectively.

Vitamin C is a hydrophilic free radical scavenger with limited ability to cross the blood brain barrier; whereas vitamin E, which is lipophilic, is shown to afford some benefit on glycine levels in schizophrenia (Reddy & Reddy 2011). A combination study using vitamins E, vitamin C and omega-3 fatty acids over a 16-week period revealed a reduction in positive and negative symptoms (Sivrioglu et al. 2007) and an influence over neuroplasticity (Mahadik et al. 2006). This is supported by the findings of Bentsen et al. (2013) over a similar 16-week period, where the researchers reported a significant reduction in PANSS total scores for persons with low baseline polyunsaturated fatty acids (Bentsen et al. 2013).

Epicatechins, polyphenols with antioxidant properties *in vitro* (Spencer et al. 2001), are present in mangosteen pericarp (Fu et al. 2007) (Figure 4).

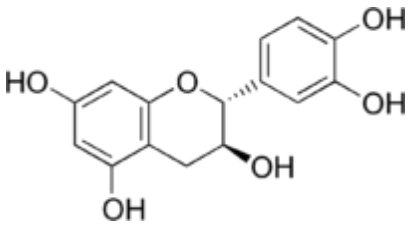

Figure 4: The chemical structure of epicatechin
Image available at: http://en.wikipedia.org/wiki/Catechin

Preliminary work supports the potential for epicatechins to influence second-generation antipsychotic drug efficacy and symptoms associated with schizophrenia. Lipid soluble antioxidants are found to be protective against lipid peroxidation (Sies 1997). The epicatechins in green tea are found to be more effective than quercetin (a flavonoid found in green tea, red apples, capers, dill, red onion and watercress to name a few) at reducing lipid peroxidation in human plasma (Dietrich-Muszalska et al. 2012). Due to their ability to cross the blood brain barrier, epicatechins have been evaluated, with findings thus far indicating that they are capable of reversing liver damage induced by reserpine (Al-Bloushi et al. 2009). The reductions in reactive oxygen and nitrogen species attributed to epicatechin in 50ug/ml green tea are proposed to protect against second-generation antipsychotic drug-induced side effects (Dietrich-Muszalska et al. 2012). With regard to schizophrenia symptoms in particular, Loftis, Wilhelm and Huckans (2013) tested green tea in a RCT with placebo over an eight-week period. The researchers report that green tea extract did not significantly reduce scores measured by PANSS, CGI, Hamilton depression and anxiety rating scales, albeit in a relatively small study (Loftis, Wilhelm & Huckans 2013).

Adaptogens have also been tested. Adaptogens are a group of plants reported to reduce cellular sensitivity to stressors. Wiegant et al. (2009) propose that a likely mechanism of action

involves, in part, activation of stress-response mediators such as nitric oxide, cortisol and stress-activated protein kinases. Some adaptogenic compounds show promise *in vitro* against schizophrenia symptom domains. For example, data indicate that white mulberry (*Morus Alba*) leaves reduce chronic foot shock-induced stress in rodent models of cognitive deficit and mental depression (Nade et al. 2009). Preliminary studies of adjunctive ginkgo biloba extract in schizophrenia suggest an improvement in negative symptom domains (Doruk, Uzun & Özsahin 2008) and tardive dyskinesia (Zhang et al. 2011) over 12-week periods (Table 4). Several responses to treatment with adaptogenic compounds are reported in relation to schizophrenia.

Studies of adaptogens, such as *schisandra chinensis* and *rhodiola rosea*, in schizophrenia are not randomised, and they use differential Russian diagnostic criteria for the 248 participants involved. The reported responses to adaptogen compounds vary but include reduction of psychoses and depression, reduction to antipsychotic side effects, reduced fatigue and improved mood and appetite (Panossian & Wikman 2010). Reductions to paranoid, catatonic and negative symptoms, addiction to alcohol and illicit substances and second-generation antipsychotic side effect profiles are reported to manifest as calm and sociable outlook, normalisation of reactions, improved mood and appetite and improved recovery times from acute psychotic episodes (Panossian & Wikman 2010). Reduced symptoms are documented across two studies involving persons with psychotic symptoms in paranoid and catatonic schizophrenia ($N = 50$) (Panossian & Wikman 2005). However, caution must be employed because, again, the Russian diagnostic criterion is applied to these findings and they are based on a small sample size with limited statistical analysis to support the findings.

2.9. Rationale for testing mangosteen pericarp

Anecdotal patient reports of the benefits of mangosteen extract triggered an interest in its potential.

2.10. Secondary metabolites

The pericarp of fruits and some leaves contains concentrated quantities of plant secondary metabolites. Whereas primary metabolites have a direct role in the reproduction, growth or development of the plant, secondary metabolites have a role in plant defense. Secondary metabolites, such as prenylated xanthene derivatives in mangosteen pericarp (Jung et al. 2006), have a distinct function for the protection of plants against environmental stressors (Yazaki 2006). The composition of mangosteen pericarp contains a unique astringent to defend against

insect, fungi, viral and bacterial infestation and predatory activity by animals. Plants naturally build resistance to environmental triggers by increasing glutathione S-transferase levels, which detoxify and regulate apoptosis (Dixon, Lapthorn & Edwards 2002).

Currently, the chemical properties of the thousands of secondary metabolites remain little understood, due in part to the complex nature of the interactions involved (Rhodes 1994). Secondary metabolites are known to possess pharmaceutical properties that are traditionally used as medicines. Such properties have been explored by pharmaceutical companies, with Ramachandra and Ravishankar (2002) estimating that 25% of all pharmaceuticals are derived from this source. The researchers provide us with some examples, including digoxin and morphine (Ramachandra & Ravishankar 2002).

Secondary metabolites such as those in the pericarp of mangosteen fruit confer protection against oxidative stress (Pérez-Rojas et al. 2009). The xanthene alpha mangostin is found to utilise an intrinsic pathway through mitochondria to increase the expression of mitochondrial RNA (Akao, Nakagawa & Nozawa 2008). Secondary metabolites from the mangosteen pericarp will be used to supplement humans, as a similar mitochondrial pathway may be germane to schizophrenia.

2.10.1. Antioxidant activity

Xanthones in the pericarp of mangosteen fruit may improve antioxidant enzyme levels (glutathione and glutathione S-transferase) (Chin & Kinghorn 2008). Scheepens, Tan and Paxton (2010) explain that polyphenols are highly bioactive compounds *in vitro* and in animal models, as they are characterised by multiple phenol structures. However, their bioavailability may be limited by their inability to cross the blood brain barrier. In schizophrenia, there is evidence to support the permeability of the blood brain barrier. Results from a benchmark study indicate that reduced levels of glutathione may compromise the blood brain barrier (Kamath et al. 2006). The researcher used Evans blue dye testing to reveal a 25% increase in the permeability of the brain cortex in rodent models (Kamath et al. 2006).

Xanthenes in mangosteen pericarp, such as alpha-mangostin, act as simple and complex phenolics (Akao, Nakagawa & Nozawa 2008) with antioxidant activity. These phenolics reduce oxidative and nitrative stress (Pérez-Rojas et al. 2009) by inducing phase II drug metabolising enzymes such as quinine reductase and glutathione S-transferase (Chin & Kinghorn 2008). Xanthone modulation of glutathione levels is affirmed by a reduced oxidative and nitrative stress during cisplatin-induced nephropathy (Pérez-Rojas et al. 2009).

Mangosteen pericarp might influence the antioxidant-signalling pathway that is thought to be chronically dysfunctional in schizophrenia (Yao & Keshavan 2011). Findings thus far suggest that antioxidant-signalling markers are altered within 24 hours of mangosteen pericarp administration (Akao, Nakagawa & Nozawa 2008), supporting increased uptake of mangosteen pericarp by the antioxidant-signalling pathway. Although untested in the brain, alpha mangostin is shown to attenuate reduced levels of superoxide dismutase, glutathione S-transferase and glutathione in rodent models for myocardial infarction (isoproternol) (Devi Sampath & Vijayaraghavan 2007). Specific mangosteen pericarp-induced improvements to glutathione and glutathione S-transferase levels are likely to facilitate the repair of mitochondrial transporters, damaged proteins, DNA and lipids as well as the detoxification of electrophiles.

2.10.2. Neurobiology nexus attributed to mangosteen pericarp and schizophrenia

This section will present evidence on the mangosteen pericarp activity that shares common neurobiology or pharmaceutical properties with schizophrenia.

Findings thus far indicate that a neuronal protective effect of mangosteen pericarp is present in a concentration range of 50–100ug/ml (NG 108-15 cell models) (Weecharangsan et al. 2006). Alpha mangostin has been found to have a positive effect when tested in a model of neuronal metabolic inhibition induced by oxidative stress (Reyes-Fermín et al. 2012). More specifically, alpha mangostin is reported to influence apoptosis by stimulating a cell-signalling pathway (involving MAPK/ERK, Akt, c-Myc/Max and p53) (Krajarng et al. 2011). This finding is germane to the development of this novel treatment for schizophrenia.

Mangosteen pericarp is reported to contain pharmaceutical properties that may be relevant to schizophrenia. For instance, the enzyme cyclooxygenase enzyme 2 (COX-2) is expressed in inflammation. Immune imbalance in schizophrenia and depression are thought to involve COX-2, prostaglandin activity and alterations to tryptophan and kynurenine metabolism (Muller & Schwarz 2008; Mueller 2010). COX-2 is critical for the production of prosteroids (precursors of hormones), giving it important implications for cardiac (Wu et al. 2006) and sexual functioning (Gheorghiu et al. 1996). A further role of COX-2 in schizophrenia may be its link to tyrosine. COX-2 activity is known to increase tyrosine hydroxylase activity, which contributes to the up-regulation of dopamine and its metabolites (Mizuno et al. 2007).

COX-2 inhibitors have been tested in schizophrenia and major depression for antipsychotic and antidepressant activity (Mueller 2010) with respect to cognition (Riedel, Schwarz & Engel

2005). Hawkey (1999) reports those COX-2 inhibitors were initially conceived in the search by pharmaceutical companies for a safer aspirin. Pro-inflammatory cytokines, associated with cognitive impairment in schizophrenia, are mediated by prostaglandins and COX-2 (Müller et al. 2006). Mangosteen pericarp has pharmaceutical action as a COX-2 inhibitor. Several groups have verified this finding *in vivo* across several cell lines (adipocyte, smooth muscle and RBL-2H3 for mast cells) (Bumrungpert et al. 2010; Bumrungpert et al. 2009a; Chen, Yang & Wang 2008; Nakatani et al. 2002). Chen, Yang and Wang (2008) confirm that alpha mangostin reduces prostaglandin E2 more potently than does serotonin or histamine 1. Alpha mangostin is also reported to be a competitive histamine 1 antagonist in smooth muscle cells (Chairungsrilerd et al. 1996).

Several studies suggest that many phenolic compounds are capable of interaction with neurotransmitters. For example, gamma-mangostin is a competitive serotonin 2a/2c antagonist in the rodent brain (Chairungsrilerd et al. 1998; Jang et al. 2012). Many serotonin antagonist actions are utilised in the design of antidepressant and antipsychotic drugs. The serotonin 2c receptors may influence dopamine in schizophrenia. There is evidence that serotonin 2c antagonism action may improve mesocorticolimbic dopamine functioning (Di Matteo et al. 2002). In support of this view, the efficacy of clozapine over other antipsychotic drugs is thought to be due to serotonin 2c antagonist activity (Wood et al. 2001). There is evidence to support a link between mangosteen pericarp serotonin 2c antagonist action and nitric oxide. In their benchmark study, Sukma et al. (2011) found that gamma-mangostin activity increases serotonin 2a/2c, muscarinic 4 and histamine messenger RNA expression. This occurrence is, in a manner, mediated by serotonin gene expression within neuroblastoma cell models (NG 108-15) (Sukma et al. 2011). Sukma et al. (2011) suggest that a likely mechanism is inhibition of nitric oxide production, pertinent to neurotransmission modelling.

In summary, secondary metabolites in mangosteen pericarp may protect against oxidative stress via an intrinsic pathway that involves mitochondria. To date, this approach to schizophrenia remains untested. Mangosteen pericarp may afford neuroprotection and influence some neurotransmitters to be of potential benefit for schizophrenia. Pharmaceutical evidence supports the potential for COX-2 inhibitors, histamine 1 antagonist and serotonin antagonist activities attributed to mangosteen pericarp for treatment of schizophrenia. To test these hypotheses, secondary metabolites in the pericarp of mangosteen fruit will be orally self-administered in a clinical trial.

2.11. Safety of mangosteen pericarp

Mangosteen pericarp is likely to be safe for humans. This finding is significant as safety has not been formally established, as until recently, the pericarp of mangosteen fruit was agricultural waste because of its bitter taste. Information from safety and toxicity studies will be of value to this thesis and will assist in establishing a recommended dose. Results from a benchmark study (Kosem et al. (2012) indicate that single doses of <500mg/kg of crude methanolic mangosteen pericarp extract do not produce acute toxicity in rodent models; the acute lethal dose (LD_{50}) in rodents is 1000mg/kg.

Mangosteen pericarp as a fruit extract is free of adverse notifications worldwide; however, there are a few human trials for efficacy and safety. Much of the reporting to date fails to follow the CONSORT guidelines, lacks adequate methodology or statistical analysis, utilises a small sample size and does not adequately isolate mangosteen as a single ingredient for testing. Preliminary studies of mangosteen pericarp have examined the potential benefits for a wide range of afflictions and disease processes, such as skin (Wang et al. 2012), mammary (Shibata et al. 2013) and pancreatic cancers (Xu et al. 2014); obesity (Udani et al. 2009); dental cares (Rassameemasmaung et al. 2008) and inflammation (Jang et al. 2012).

To date, three studies have involved the oral administration of compounds containing various concentrations of mangosteen pericarp (Kondo et al. 2009; Udani et al. 2009; Tang et al. 2009) (Table 5). However, reports of the mangosteen compound being delivered safely lack evidence of a useful adverse-event-reporting mechanism, as no clinical trials have been conducted. A case study links chronic use (greater than a year) of a blended juice containing mangosteen to lactic acidosis (Wong & Klemmer 2008). However, no cause–effect relationship is found because of the nature of case studies and because the mangosteen is not established as the single constituent used.

Table 5: Studies orally administering compounds of mangosteen pericarp in humans to date

Study	Cohort	Mangosteen pericarp extract	Major findings	Outcome measures
Tang et al. 2009 (RCT with placebo)	*N* = 59 Immune function and well-being	Product containing mangosteen, multivitamins and essential minerals was administered orally over a 30-day period	Improved IL-1 levels were significant, and self-appraisal of health status was positively reported despite lack of a formal tool	Peripheral T-helper cell frequency; Serum C-reactive protein levels; IL-1 Self-appraisal of health
Kondo et al. 2009 (RCT with 6-month washout period prior to induction)	*N* = 20 Absorption after acute administration in healthy cohort	Product containing mangosteen, aloe vera, green tea and multivitamins; measured one-hour post-oral administration	Findings of *in vivo* antioxidant effects with poor methodology disclosure in the abstract	Plasma
Udani et al. 2009 (RCT with placebo; 2-week washout period prior to induction) Clinical trial registration	*N* = 44 Inflammation, obesity, dose finding study	XanGo juice blend containing whole mangosteen and undisclosed quantities of ingredients; administered orally over an 8-week period	Significant alteration in C-reactive protein from baseline in group taking 18oz/day. No change in other markers. No side effects or ECG changes	High sensitivity C-reactive protein, inflammatory cytokines, lipid peroxidation. Safety assessed by ECG, self-reporting of side effects

*ECG refers to electrocardiogram

2.12. Research aims

This project aimed to address the proposed unmet needs by testing the efficacy of mangosteen pericarp fruit extract as an adjunctive to second-generation antipsychotic drugs for a potential novel treatment of schizophrenia.

The primary outcome measure was the total score on the PANSS total.

1. The primary aim was to determine whether mangosteen pericarp improves residual core symptom domains in schizophrenia as assessed by PANSS total scores.
2. Secondary efficacy measures included positive, negative and general symptoms, which were assessed using the PANSS subscales.
3. Co-morbid depressive symptoms and suicidal ideations were measured by MADRS.
4. Global psychopathology was measured using the Clinical Global Impression Scale for Severity (CGI-S).

Functioning and well-being were assessed using the GAF and the Self-Rated Life Satisfaction Scale (SRLS).

5. The GAF was also used to explore social functioning, and
6. self-reported quality of life was assessed using SRLS.
7. Habits (smoking, alcohol and use of illicit substances) were assessed pre- and post-intervention.

Adverse events and reductions in neuroleptic-associated side effects were explored

8. to determine whether measureable adverse effects from chronic use of second-generation antipsychotic drugs were affected by adjunctive use of mangosteen pericarp as measured by LUNSERS.
9. The presence of tardive dyskinesia and subsequent influence of mangosteen pericarp were assessed by AIMS.

2.13. Research hypothesis

In this study, the efficacy of 1000mg *Garcinia mangostana* L. (mangosteen) pericarp was compared to a placebo in individuals who were experiencing symptoms of schizophrenia and who were concurrently prescribed a second-generation antipsychotic drug.

It was hypothesised that mangosteen pericarp would:

1. improve therapeutic outcomes based on validated rating scales (PANSS, MADRS, CGI, SRLS, GAF) in relation to the symptoms of schizophrenia for the cohort over a 180-day period comparative to a placebo.
2. reduce the unwanted effects from second-generation antipsychotic drugs over a 180-day period compared to a placebo.

2.14. Summary

Deficits in core symptom expression and cognitive and social functionality in schizophrenia are linked in the literature to changes in mitochondrial metabolites and impaired redox defenses such as reduced glutathione levels and impaired antioxidant enzymes (glutathione S-transferases). This impairment is associated with central features of schizophrenia such as mitochondrial dysfunction, increased oxidative stress, dendritic spine density changes, upstream growth factor irregularities and downstream alterations to neurotransmission. These findings are replicated across multiple studies that have used well-defined outcome measures, such as the PANSS measure in a meta-analysis of anti-inflammatory benefits for schizophrenia (Sommer et al. 2012). Xanthones in the pericarp of mangosteen fruit may protect against oxidative stress and improve antioxidant enzyme levels (glutathione and glutathione S-transferase). This occurrence is thought to involve an intrinsic pathway through mitochondria. It is unknown what, if any, benefit this may have in schizophrenia. The research aims to test the efficacy of the pericarp fruit extract from the mangosteen in schizophrenia. The research hypothesis has been specified.

The efficacy of mangosteen pericarp in schizophrenia remains unknown, as it is currently untested. Mangosteen pericarp will be administered to persons exhibiting symptoms associated with schizophrenia and meeting inclusion criterion for the study. Mangosteen pericarp will be tested in a randomised, double blind and placebo-controlled trial using the methodology outlined in the following chapter. Outcomes of the study will be assessed in terms of well-described measures.

Chapter 3: Methodology and Study Design

'The scientific method actually correctly uses the most direct evidence as the most reliable, because that's the way you are least likely to get led astray into dead ends and to misunderstand your data'

Aubrey de Grey (1963–)

3.0. Introduction

The efficacy of mangosteen pericarp as a treatment for schizophrenia has not been tested to date. It is hypothesised that mangosteen pericarp will improve the therapeutic outcomes in schizophrenia in relation to symptom improvement and side effect profiles. Multiple established outcome measures will assess the efficacy, or otherwise, of mangosteen pericarp compared to a placebo and usual treatment, against symptom domains and adverse effects reported across several time points.

The parallel-group two-armed design for a randomised controlled trial was chosen to provide a sufficient level of scientific rigor to test the efficacy of the *Garcinia mangostana* L. extract (Figure 5).

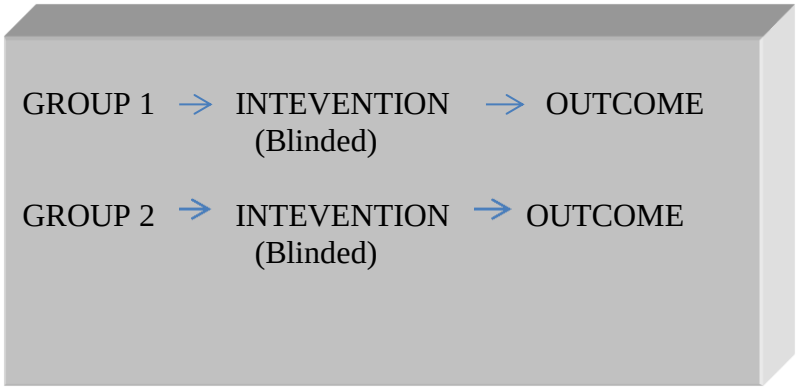

Figure 5: Parallel-group two-armed study design for an RCT

Clinical trials aim to generate data relating to the safety and efficacy of a potential product. Safety is established by the use of a formal reporting mechanism for the duration of the trial. Efficacy studies must be performed to support claims pertaining to the development of novel treatments. Efficacy studies aim to measure whether the intervention has a positive effect in a

controlled setting that provides high internal validity. To obtain a high level of internal validity, human efficacy studies require a high level of compliance. López-Torres et al. (2013) suggest that in studies of drugs for psychiatric illness, this requirement for high compliance is a barrier to the development of novel drug treatments.

An independent safety monitor, whose role it was to receive information of concern from the researcher, undertook the monitoring of safety. The safety monitor was required to ascertain whether any concerns raised were likely to be related to the products used in the intervention (including the placebo). An established pathway and process involving the Therapeutic Goods Administration and Human Research Ethics Committees is in place for reporting any serious adverse effects.

The remainder of this chapter describes the method and design for this study, including the participants (3.1), inclusion and exclusion criteria (3.2), withdrawal criteria (3.3), measurements (3.4), study procedure including the determination of the sample size (3.5) and the statistical methods (3.6). The final section is a chapter summary (3.7).

3.1. Participants

The study was undertaken over the period 21 November 2011 to 21 April 2013. Participants aged 18 years and over, who met the DSM-IV criteria for schizophrenia or schizoaffective disorder, were included. After informed written consent was obtained, potential participants were assessed for inclusion into the study. Proxy consent was not used due to ethical and practical limitations. Diagnosis of schizophrenia was confirmed at the first interview using the Mini International Neuropsychiatric Interview (MINI-plus) scale. This scale is widely accepted as the diagnostic tool used by psychiatry to assess the DSM-IV criteria for schizophrenia (Corves et al. 2013). Participants were recruited by investigators through advertisements displayed in prominent public places and by referral from treating physicians. Study feasibility was ensured by empowering consumer advocates with further advertising of the study, which occurred over an extended period.

Treating physicians were provided with initial information about the study and offered the opportunity to receive further information. Physicians were asked to voluntarily screen potential participants for their ability to consent, ability to meet the DSM-IV criteria and aggression risk. Aggression risk was assessed based on known current risks such as firearms at the property or recent escalation in violent behaviour. A high aggression risk represented a safety concern for the researcher aiming to conduct interviews and deliver intervention products to individuals.

Therefore, persons deemed to represent a high aggression risk for the researcher were excluded from participation. Confidentiality was maintained at all times throughout the process; this is of particular importance when working with a vulnerable cohort. Clustering occurred, as the physicians often advertised the study to all of their contacts meeting the criterion. While having participants volunteer for a study has been recognised as a potential bias, this was overcome in the study design by randomisation of the intervention.

3.2. Inclusion and exclusion criteria

Adult (aged 18 years and over) participants were randomised into the study if they met the inclusion criteria, including DSM-IV diagnosis for schizophrenia. Participants had to have concurrent symptoms of schizophrenia, as measured by a PANSS score of over 54, or at least two positive or negative symptom domains that were greater than two at baseline. Both males and females were studied. Sexually active participants of child-bearing age were asked to undergo a pregnancy test prior to inclusion due to ethical and legal considerations. Participants testing positive for pregnancy or planning pregnancy were excluded from the study. This approach was used to protect any unborn child from any unknown effect of mangosteen pericarp.

Persons were excluded from participation if they had a major co-morbid illness that potentially restricted their participation in the study. This was discussed with the participant prior to induction. Adherence with the requirements of informed consent and the treatment protocol was a requirement (Appendix A). An allergy to either mangosteen or rice flour was an exclusion criteria.

Persons who had been prescribed a second-generation antipsychotic drug were eligible for inclusion if they were stable on their treatment regimens for one month prior to induction, which provided a stable baseline to explore the efficacy of the trial agent. Changes to treatment regimens were acceptable as part of the trial protocol, as long as the basic second-generation antipsychotic agent remained the same. Non-compliance was managed by withdrawal from the study if the participant missed taking the intervention for seven consecutive days. As no interpreter was provided, potential participants had to have sufficient English to understand consent, the capacity to provide ongoing consent and the capability for compliance with study procedures.

In investigating the efficacy of mangosteen pericarp in schizophrenia, possible confounding factors include green tea and the combination including vitamin E, which studies have shown to

have efficacy (Sivrioglu et al. 2007). Therefore, regular intake of either green tea (less than 10 cups/day) or vitamin E supplementation (at least 1000mg/day) was a further exclusion criterion. Multivitamins were considered acceptable.

3.3. Withdrawal criteria

The withdrawal criteria included if participants ceased taking their allocated study intervention for seven consecutive days; withdrew consent or developed serious adverse effects associated with the study intervention; or ceased taking effective contraception or became pregnant. Limited alterations to a participant's medication regime were acceptable, providing treatment stability was maintained. Dose changes to existing medications (either increases or decreases in dose) were acceptable and these participants were allowed to continue in the trial. However, a change in a participant's primary antipsychotic required that they be withdrawn from the study. In cases in which another antipsychotic medication was prescribed secondary to the existing antipsychotic medication, this was allowed.

3.4. Measurements

The study validated clinical diagnosis using MINI-plus, a widely established benchmark (Sheehan et al. 1998). At the time that the study was conducted, DSM-IV was the current manual in use. Inter-rater reliability assessments were not required, as the same researcher conducted each interview. Data points were collected at baseline, 90 days, 150 days and at the final endpoint of 180 days to provide serial measures of outcomes (Figure 6). There were no changes to study outcome measures after the commencement of the study. Samples of the outcome measures were crosschecked by the study physician for quality assurance and accountability, in line with NHMRC guidelines. Participants received a follow-up phone call at one month post the conclusion of their participation in the study (data not collected). This call was to ascertain whether there were any residual concerns.

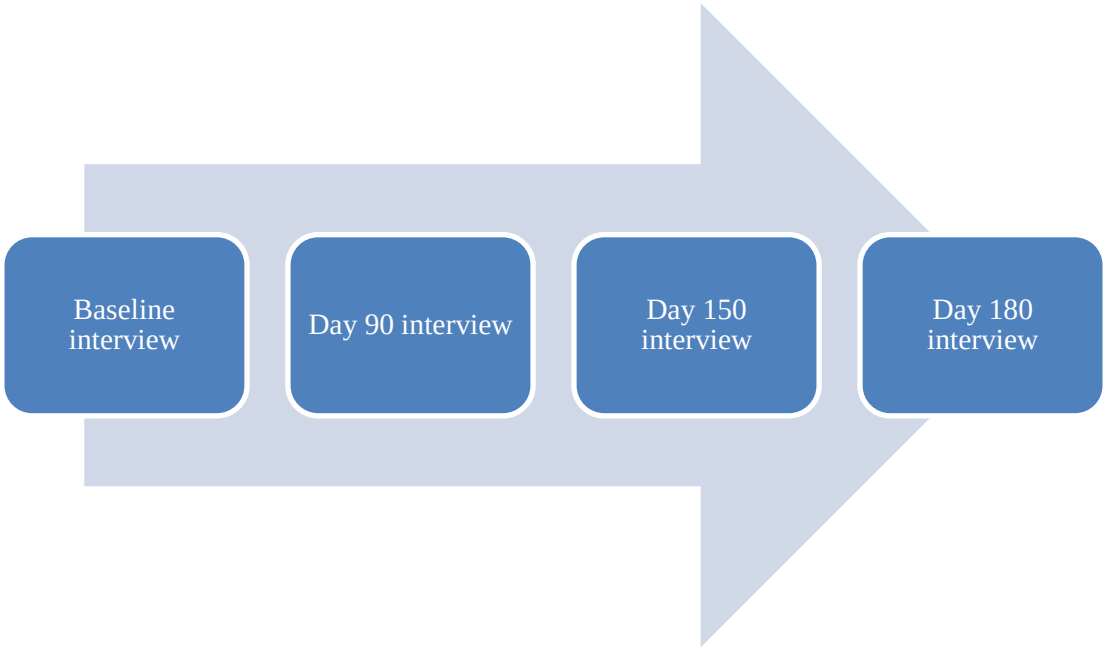

Figure 6: Visit schedule

Following consent and successful induction, participants were provided with a referral form for blood collection (C-reactive protein levels) and were directed to their nearest Sullivan-Nicolaides blood sampling laboratory. At the time of induction, participants were interviewed using the operationalised outcome measures, demographic assessment and use of habits, weighed and provided with a 90-day supply of intervention to establish a baseline. At 90 days, a second interview was conducted in which outcome measures were again assessed. Returned intervention bottles were accepted by the researcher for adherence monitoring and a further 90-day supply was delivered to the participant. At 150 days, a third interview was conducted in which the same outcome measures were assessed, pertaining to remission and response, functioning and well-being and unwanted effects. At 180 days, an endpoint interview was conducted that assessed outcome measures, the same participant demographics as at baseline, weight and habits. Returned intervention bottles were accepted by the researcher and a blood form for measuring C-reactive protein levels was provided by the researcher.

3.4.1. Participant demographics

The baseline interview collected demographic data related to sex, age, marital status, housing status, employment status and medical history, as well as whether any close family members had been diagnosed with schizophrenia. Details of history related to schizophrenia such as the onset of prodromal symptoms, duration of disease, frequency of hospital admissions and any precipitating factors were determined (Appendix B). In addition, participants were asked about their smoking, alcohol, medication and illicit substance use patterns and use of complementary

alternative medicine or dietary supplements. Participant weight was recorded and vital signs were monitored to support the safe monitoring of the interventions.

3.4.2. Outcome measures

Established valid, reliable outcome measures assessed the effect of the intervention on negative symptoms, cognitive domains and the level of social functioning in individuals who exhibit symptoms of schizophrenia. PANSS was first validated in 1987 by Kay, Flszbein and Opfer. According to Emsley et al. (2003), PANSS has good internal consistency, with a Cronbach's alpha coefficient of 0.88. The PANSS is an operationalised tool for assessing the severity of positive and negative symptoms of schizophrenia and general psychopathology. PANSS scores are derived from semi-structured interviews, although only the participant interview was tested in the current study. The rating scale for PANSS consists of seven positive items, seven negative items and 16 general psychopathology items. Each item is ranked from 1 to 7. Interviewers are required to be trained in the administration of PANSS for the purpose of standardised levels of reliability. The researcher conducting interviews in this study underwent such training, crosschecked by the study physician. Clinical trials involving schizophrenia have established PANSS, used as the primary measure for this study, as a widely recognised outcome measure (Kay, Flszbein & Opfer 1987).

The primary outcome measure, mean PANSS total, and secondary outcome measures were all assessed concurrently at specified interview times (Appendices C-E). These interviews occurred at baseline, 90 days, 150 days and 180 days approximately (Table 6). Secondary scales used included the MADRS (Appendix F), CGI (Appendix G), SRLS (Appendix H), LUNSERS (Appendices I-J), AIMS (Appendices K-L) and GAF.

MADRS is widely utilised to evaluate the severity of depression in the study of mood disorders, schizophrenia and other mental disorders. The MADRS scale consists of 10 questions for which a rating from 1 to 6 is applied. MADRS was designed in 1979 as an alternative to the Hamilton Rating Score of Depression for the assessment of antidepressant drug effects (Montgomery & Asberg 1979). According to Kim et al. (2005), MADRS has good internal consistency, with a Cronbach's alpha coefficient of 0.85.

The CGI is commonly used to measure the overall severity of illness and change across psychiatric disorders including schizophrenia. CGI has demonstrated validity and reliability at assessing cognitive deficits and functional ability (Ventura et al. 2008). CGI consists of two scales. The first ranks the severity of symptoms from 1 to 6, while the second ranks treatment

improvement from 0 to 7 (Guy 1976). The observational measure has both face-validly and reliably in assessing the diversity of schizophrenia symptom domains (Haro et al. 2003). According to Ventura et al. (2008), the CGI has good internal consistency, with a reported Cronbach's alpha coefficient of 0.69–0.96.

LUNSERS was developed as a specific measure for antipsychotic drug side effects (Day et al. 1995). It has been well validated and its reliability established in persons concurrently taking chlorpromazine compared with un-medicated persons (Day et al. 1995). LUNSERS consists of a 51-point checklist that correlates to a 16–40 value range across eight categories. One category contains red herrings that are then subtracted from the other scores to provide a LUNSERS total. According to Wolters et al. (2009), LUNSERS has good internal consistency, with a reported Cronbach's alpha coefficient of 0.85.

AIMS is a tool to measure tardive dyskinesia, an adverse response to chronic use of antipsychotic drugs, characterised by involuntary facial, mouth, trunk or limb movements, which are non-rhythmic and dance-like in appearance. AIMS has been proven reliable (Munetz & Benjamin 1988). A rating of 2 or higher on AIMS has been regarded as indicative of tardive dyskinesia. A 12-step set of instructions for application of the AIMS examination accompanies the 12-question score sheet, with rankings of severity across five columns. According to Schiffman et al. (2004), AIMS has good internal consistency, with a Cronbach's alpha coefficient of 0.83.

GAF scores are utilised by mental health nursing staff in the community setting to assess functioning in a social context in persons with schizophrenia. GAF subjectively rates psychological, social and occupational functioning (Gaite et al. 2005). It is represented numerically from 0 to 100. Vilaplana et al. (2007) report that GAF has good internal consistency, with a Cronbach's alpha coefficient of 0.85.

SRLS has been used in schizophrenia, major depression and anxiety disorders as a quality-of-life tool. SRLS consists of four questions, with accompanying rankings of 1, 2, 4 or 5. A ranking above 12 indicates dissatisfaction with life. According to Koivumaa-Honkanen et al. (2000), SRLS has good internal consistency, with a Cronbach's alpha coefficient of 0.74.

Table 6: Outcome measure guide

Scale	Domain	Subscale
Positive and Negative Syndrome Scale (PANSS)	Psychosis with regards to positive, negative and general symptoms of schizophrenia.	Positive and negative scales are measured across seven items on a scale of 1–7. The lowest score is 7 (normal) for each scale, and the highest possible score is 49. The general scale is measured across 16 items on a scale of 1–7. The lowest score is 30 (normal) and the highest possible score is 112. Total scores are measured across all 30 items on a scale of 1–7. The lowest score is 30 (normal) and the highest possible score is 210. Anxiety is a question ranked 1–7, with 1 as the lowest possible score and 7 as the highest.
Montgomery Asberg Depression Rating Scale (MADRS)	Depression and suicidal ideations	This consists of 10 items ranked 0–6. The lowest possible score is 0 and the highest is 60. Suicidal ideations are a question ranked as 0–6.
Global Assessment of Functioning (GAF)	Psychological, occupational and social functioning	This scale differs, as it has an upward trend to demonstrate improvements to functionality. The scores are divided into increments of tens and range from 1 to 100.

		For the purpose of data entry the first number in the range was entered so that 10–1 became 10, for instance. The lowest possible score is 100.
Clinical Global Impression (CGI)	Clinical functioning, severity and treatment improvement over time	CGI-S (severity) is ranked from 1 to 7 at each interview. CGI-I (improvement) is ranked from 1 to 7 at each post-baseline interview.
Self-Rated Life Satisfaction Score (SRLS)	Quality of life	Scores range from 1 to 5 across four questions. The lowest possible score is 4 and the highest is 20.
Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)	Unwanted effects from use of second-generation antipsychotic drugs	Scores differ across gender. Psychic (0–40); extrapyramidal (0–40); hormonal (male = 0–16 and female = 0–24); anticholinergic (0–20); miscellaneous (0–16); autonomic (0–20); allergic reactions (0–16); and then red herrings are subtracted. The total range of scores is 0–168 (males) and 0–176 (females).
Abnormal Involuntary Movement Scale (AIMS)	Tardive dyskinesia	Scores range from 1 to 5 across a 10-item list. The lowest possible score is 0 and the highest is 50.

3.5. Study procedure

Precautions to ensure adequate concealment of the allocation were taken. Presentation of the intervention occurred in opaque containers (labelled similarly for both arms of the clinical trial) within sealed bags. The researcher was blinded to the type of allocation. The allocation sequence was stored in a locked cabinet for the duration of the study. The cabinet key was kept in the possession of the clinical pharmacist who performed the randomisation.

Study assignment was by simple randomisation using a computer-generated table, performed by a clinical trial pharmacist. Random assignment of the groups ensured the initial groups were approximate to equal. Random allocation is able to cancel selection bias and control history and maturation, as changes will equally occur across both groups. No restrictions were placed on randomisation in the current study.

A clinical trial pharmacist conducted blinding and assigned the intervention to the blinding sequence. The researcher, who was blinded to the type of treatment, conducted assignment of treatments. This occurred sequentially and concurrently with study induction. Preliminary statistical analysis was conducted to determine the success or otherwise of the blinding. Successful randomisation was determined by comparing the groups at baseline, using independent-sample t-tests. The blinding code was revealed after analysis of the data, as there was no urgent medical contraindication. Therefore, the participants as well as the researcher conducting the interviews and statistical analyses were blinded to the treatment type.

Participants were asked to orally self-administer two capsules of 500mg once a day, to a total single daily dose of 1000mg for the period of 180 days. Mahadik et al. (2006) advocate 180 days as necessary for the reduction of oxidative stress in persons with schizophrenia; similar to the timeframe used for the *N*-acetyl cysteine studies. Therefore, mangosteen pericarp was tested for 180 days.

3.5.1. Ethical and legal consideration

Cohorts including mentally ill persons are a vulnerable population requiring particular ethical consideration. The Declaration of Helsinki guidelines establish 35 ethical principles for the conduct of human research (available at: http://www.wma.net/en/30publications/10policies/b3/). These were followed for the design of this clinical trial.

The study was conducted in accordance with Good Clinical Practice and National Health and Medical Research Council guidelines for clinical trials. Approval from the Cairns and Hinterland Human Ethics Research Committee (HREC/11/QCH/47-732) and James Cook University Human Ethics Research Committee (C9) were obtained. Although the interventions tested are foods under the surveillance of Queensland Health, a Therapeutic Goods Administration notification of intent to supply goods off label was accepted prior to induction of the first participant (Therapeutic Goods Administration trial number, 2011/0588 Protocol number V4 18.02.2011). As a consequence of this notification, an Australian clinical trial registration was lodged (ACTRN12611000910909). There were no changes to the methodology after randomisation occurred. Sullivan-Nicolaides were the pathology providers for the study. An ethical approval enabling blood collection by persons other than Sullivan-Nicolaides staff was obtained but was not utilised, as the changes did not improve the chance of compliance with blood sampling.

3.5.2. Registration number and protocol

The study was registered with the Australian and New Zealand Clinical trials registry on 25 August 2011, number: ACTRN12611000910909. The study protocol has been made available at https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id

3.5.3. Funding sources

James Cook University was the research sponsor, providing an Australian Postgraduate Award (APA) to Wendy Laupu with in kind support of computer access, printing and a locked cabinet for data. James Cook University was also involved in the administration of the study funding, clinical trial insurance and supervision of the PhD. The Graduate Research School of James Cook University provided $4500 funding. In addition, the School of Nursing, Midwifery and Nutrition provided $5000 and an additional $5000 PhD scholarship top up in funding per year. Mangosteen Dietary Supplements provided $10,000 funding (cash) and in kind support of VitalXan mangosteen powder, without a role in the study. The Far North Queensland Hospital Foundation provided $2500 funding to assist with data collection. The PhD student, Wendy Laupu, provided funding for the placebo, petrol and telephone costs in relation to the fieldwork ($7200).

3.5.4. Sample size

The requisite sample size was calculated for a pilot study. Based on the continuous measure of a simple random sample and on the hypotheses, a difference needed to be detected with the primary outcome measure, PANSS total score, to be considered of clinical relevance with adjunctive treatment. Statistical power is standardly set at 80% for an alpha level of 0.05 to provide a minimum level at which a statistical difference is detectable (Eng 2003).

Assuming a correlation of post-treatment scores with baseline measurements, for an effect of the dosage such that the experimental group (usual treatment and mangosteen pericarp) differs from the controls (usual treatment and placebo) by 9.56 standard deviations (Mallinckrodt et al. 2003), it was necessary to maintain power at above 80% with 36 participants in each group. In this way, the experiment would be capable of detecting a moderate difference between groups of both clinical and scientific interest. Ethical clearance was obtained to induct 50 persons per group into the study, allowing for a modest rate of attrition. The study stopped when it was clear there were sufficient participants remaining in the study to achieve at least one baseline and post-baseline set of data for 36 participants per group. No interim analyses were performed. Statistical analyses were performed on a cleaned database.

3.5.5. Presentation of the intervention

The raw mangosteen pericarp powder (VitalXan) was donated for the purpose of the study by Mr Tim McGrath of Mangosteen Dietary Supplements, Adelaide, Australia. The dried mangosteen pericarp powder and rice flour placebo (purchased from Piccones IGA store, Edmonton) were capsulated by Good Price Discount Pharmacy, Cairns, Australia. Generic 500mg green gelatin capsules were used to present the powder, matched for colour, weight and appearance, and labelled similarly to ensure concealment and blinding. A Therapeutic Goods Administration notification of intent to supply mangosteen pericarp (ACTRN12611000910909) and the placebo for the purpose of this study was accepted prior to the induction of any study participants. At the conclusion of the study, all remaining supplies of mangosteen pericarp and placebo were disposed of by the pharmacist in accordance with Good Clinical Practice Guidelines.

Mangosteen pericarp extract (or placebo) was an adjunct to usual therapy. The study did not alter participants' current treatment regimes, so participants' care was managed in the usual manner.

3.5.6. Mangosteen pericarp

Mangosteen fruit is reported by Chaovanalikit et al. (2012) to comprise 17% outer pericarp (rind), 48% inner pericarp and a phenolic content of 3,404mg gallic acid equivalent in 100g. Recently, spray drying has been shown to be the preferred method of preservation over vacuum drying (Chaovanalikit et al. 2012). In general, spray drying is shown to provide stability to the fruit for storage purposes (Carrillo-Navas et al. 2011). The dried mangosteen pericarp powder preparation used in this study was obtained by spray drying (according to Mangosteen Dietary Supplements, Adelaide, who donated the raw material). The spray drying method involves passing liquid steam over the fruit, which separates the solute into a solid and the solvent into a vapour. This hot air drying method has been widely recognised as standard. The advantage of this method is the quick drying process. Powder slurry is formed using a single step process to maximise profit and simplicity. Supporting the effectiveness of this hot air drying or low-pressure superheated steam drying method was an assay of xanthene from the pericarp at 75 degrees centigrade (Suvarnakuta, Chaweerungrat & Devahastin 2011). Stability is a concern for fruit pericarp. The recommendation of the importer was for the storage of the mangosteen pericarp at less than 30 degrees centigrade. The available literature suggests that humidity causes faster degradation of the spray dried powder (Yoshii et al. 2001). The general consensus warrants the storage of dried powders in a cool, dry place. The study was conducted in a tropical region, so participants were asked to keep their intervention containers similarly in a cool, dry place. The containers were maintained in appropriate air conditioning (for pharmaceuticals) within the clinical research unit and provided to participants at divided times concurrent with interviews.

3.5.7. Placebo

Rice flour was used as the placebo, as it has not been associated with allergies. Rice flour has been identified as an inert substance, has not been known to cross the gut barrier and was therefore considered unlikely to influence therapeutic outcomes. Rice flour is widely used in preparations of dietary supplements. The rice flour used in the study was purchased at Piccones IGA supermarket, Cairns and supplied by McKenzies, Victoria.

3.5.8. Setting

The study took place in a naturalistic setting that supported assessment of the intervention (Zwarenstein et al. 2008). The focus of this study was those persons with chronic schizophrenia. Participants included persons in receipt of the disability pension, homeless populations, persons

affected by illicit drugs and alcohol, and interstate visitors (due to this cohort's high degree of mobility). The integrated mental health services operating within the region assisted with management of this population of persons diagnosed with schizophrenia.

3.5.9. Study locations for data collection

The study site was located at the Cairns Campus of James Cook University. However, data collection occurred in both clinical and community settings, dependent on the requirements of the participant. In instances in which safety concern for the researcher might have arisen or where terrain in the rainy season was a limiting factor, an alternative arrangement was chosen, while maintaining participant confidentiality.

3.5.10. Data management

Careful recording and correlation occurred to reduce errors, and data was statistically tested for population sample parameters. The information was stored as de-identified data. There was double entry of data to minimise error. Each interview was coded (by interview and participant number) and correlated in separate manila folders. Manila folders were transported from the interview in a locked suitcase to the study site. These manila folders were held in a locked cabinet within the study site for the duration of the clinical trial. The data have been archived according to James Cook University policy, and further information pertaining to the clinical trial has been stored according to NHMRC requirements.

3.6. Statistical methods

Statistical analysis of results was designed to enable rigorous evaluation of a clinical trial. All randomised participants who had at least one post-baseline assessment were included in the analysis. Statistical analysis was conducted using SPSS-20 by the researcher, who was blind to the treatment assignment. All analyses were conducted by the intention-to-treat principle and in accordance with the International Conference on Harmonization E9 statistical principles (International Conference on Harmonization 1997, reported by Senn 2008).

Baseline demographics and parameters were described using descriptive statistics, such as mean and standard deviation. Comparisons between the intervention and placebo groups were made using appropriate parametric tests where data were normally distributed (independent-sample t-test) and non-parametric tests for categorical or non-normally distributed data (chi square test for independence).

Differences between the two groups' baseline demographic and schizophrenia characteristics were assessed to determine the success of randomisation. Inferential statistics, such as chi square test for independence and independent-sample t-tests were used in the analysis.

The primary and secondary outcome measures were modelled using mixed model repeated measures (MMRM). Repeated measures allow for fixed, categorical effects of group, visit number and group-in-visit interaction. The fixed factors used in the current study were group and time. MMRM includes specific variable data at each time point and allows for both between subject and independent factors (O'Brien & Kaiser 1985). MMRM is a favoured approach for analysis of data from clinical trials in psychiatry because it allows for missing data, as long as it is missing at random, and can cope with uneven spacing of the repeated measures (Lindstrom & Bates 1988). Planned comparisons using repeated methods were conducted to examine group differences in mean change on the outcome measures from baseline to endpoint across the four data points. All tests of treatment effects were conducted using a two-sided alpha level 0.05. Toepilitz covariance was used. For statistically significant findings where $p < 0.005$, *post-hoc* and simple main effects were applied to the MMRM model. Non-normally distributed measures such as AIMS were transformed where necessary. Explanatory and supplementary analyses were assessed by MMRM where applicable or described using inferential techniques if the sample was very small.

A reduction in any of the outcome measures was deemed of clinical relevance for the purpose of this study. A 0.05 level for alpha is considered a standard approach to support statistical significance, as it is thought to minimise type I errors in the null hypothesis (Mudge et al. 2012). Incorporated into the analysis of results, the null hypothesis will be rejected unless otherwise stated.

3.7. Summary

In sum, this study aimed to answer the efficacy of mangosteen pericarp as an adjunctive treatment in schizophrenia. As an efficacy study using a double blind, randomised, placebo-controlled trial design, potential has been established for an outcome of statistical significance. The following chapter presents the results of the study.

Chapter 4: Results

'I want to see a better life for all people, and equivalence should not be measured by tainted evidence in support of conviction; but by our characters that we address with clean fruit that bears justice'

Merle Rutledge, Jr. (2012)

4.0. Introduction

This study provided an opportunity to test a tolerable, practical and adjunctive dietary supplement that has a strong pre-clinical basis for treatment in schizophrenia. The results obtained during the course of this study are presented as a series of statistical analyses stemming from analysis of primary and secondary outcome measures obtained from participant interview at baseline, 90 days, 150 days and 180 days. Recruitment of participants for the study occurred over an 11-month period, from 21 November 2011 to 21 October 2012.

The results are reported in line with CONSORT guidelines. The results will be described in terms of an overview of the study (4.1), the demographics of the study (4.2), the baseline differences between groups (4.3), withdrawal and completion data (4.4), the primary efficacy measure (4.5), the secondary outcome measures (4.6), participants' functioning and well-being (4.7), side effects of second generation antipsychotic drugs (4.8), an analysis of participants' habits (4.9) and the explanatory and supplementary measures (4.10). This final section is a chapter summary (4.11).

4.1. Overview of the study

A total of 181 persons were approached for potential inclusion in the study (Figure 7). Some persons were lost to follow up during the initial screening process (11.88%, n = 12) or did not consent to participate in the study (47.52%, n = 48). Reasons for exclusion included failure to meet DSM-IV criterion for schizophrenia or schizoaffective disorder (5.94%, n = 6), insufficient positive symptoms (2.97%, n = 3), lack of capacity to provide informed consent (1.98%, n = 2), not stable on their current treatment regimen for at least one month (7.92%, n = 8), being outside the required age range (2.97%, n = 3), residing outside the zone (2.97%, n = 3), the presence of a co-morbid disease process that may have restricted their capability to complete the study (5.00%, n = 4) or representing a safety concern for the researcher (2.97%, n = 3). No one

was excluded because of green tea or vitamin E intake. There were no established allergies to the study interventions. Various reasons for an unwillingness to comply with aspects of the study protocol were presented by participants. One person cited salicylates; one person, rice flour; one person was unable to take capsules; one reported irritable bowel syndrome; and one person was unable to take fruit of any kind. In addition, some were non-compliant with aspects of the screening process or indicated an unwillingness to comply with treatment protocols (4.95%, $n = 5$).

Of the 48 persons who did not consent for the study, there was a clear pattern to rationale. A common theme was the presence of co-dependant relationships with close others ($n = 19$). Examples of this were perceptions that medical personal would increase medication doses (n = 4) and/or family members not wanting the dependant to improve ($n = 15$). Stigma was associated with a morbid fear of confidentiality breaches, despite reassurances from the researcher ($n = 5$). Many people denied they had schizophrenia ($n = 9$), despite being on a community involuntary treatment order under the care of a psychiatrist. Persons commonly claimed that they had a sensitivity to chemicals, which they perceived would be unlikely to be reported by the researcher ($n = 12$). This finding occurred in conjunction with paranoid ideation.

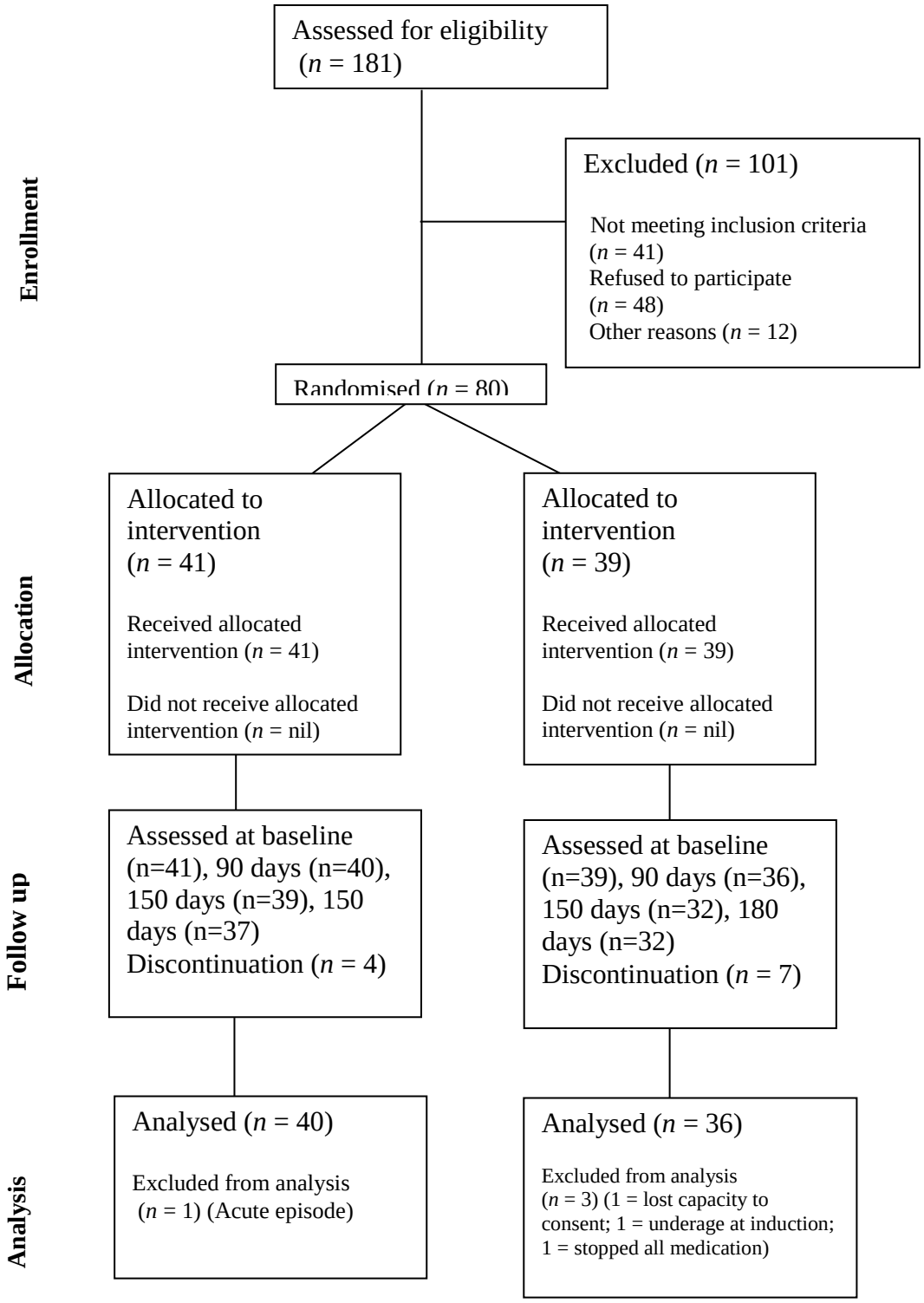

Figure 7: Participant flow analysis of the primary outcome measure

Modified from CONSORT 2010, available publically at:

http://www.consort-statement.org/

4.2. Demographics of the study sample

The sample comprised 80 participants. Participants resided in both rural (*n* = 33) and urban dwellings (*n* = 47), including three homeless persons and three persons living in communes (Table 10). The population was surprisingly mobile, often travelling long distances to see physicians of their choosing. Reviews by multiple practitioners, including mental health practitioners, general practitioners, alternative medicine practitioners, traditional healers and/or environmental doctors were very common (*n* = 70/80). The sample included many persons who lived in social and physical isolation. Several participants provided a rationale for moving to Queensland. This movement was based on how unwell they felt at any given time. Their rationale was that the Queensland Health Services were considered better than those in New South Wales (*n* = 7). The main reason provided for isolative habitation was to avoid neurotoxins (*n* = 63). A subgroup of participants in the study were Vietnam veterans (*n* = 5). These, and many other persons exhibiting paranoid thoughts, cited annual council spraying with roundup or 2,4-Dichlorophenoxyacetic acid, or 2, 4, 5 Trichlorophenoxyacetic acid (also referred to as Agent Orange) as exacerbating their symptoms and causing them distress (*n* = 63). Involvement in awareness campaigns focusing on issues such as environmental issues, anti-fluoridation and anti-establishment was common.

The mean age of the cohort was 49 years (*SD* = 12.61). The majority of the cohort was females who lived alone in housed accommodation and were infertile. The number of females of child-bearing age who were sexually active was low (33.30%, *n* = 14, *N* = 42). Pregnancy testing was conducted for these 14 women and no pregnancies were identified. Other female participants uniformly reported having undergone an early menopause. The majority of participants lived on a disability pension (70%, *n* = 56), although 30% had some employment. The range in weight at baseline was 41–149 kg.

Only 37.50% (n=30) of participants had a close family member(s) diagnosed with schizophrenia or schizoaffective disorder. Study participants reported stress as a major precipitating factor for acute episodes (81.30%, *n* = 65). The mean age at onset of the disorder was 26.27 years (*SD* = 12.16), with mean 22.13 years' duration of the disorder (*SD* = 12.24). The number of mental health admissions ranged from no previous admissions to 40 admissions. For ease of reporting, the number of admissions was categorised into none, one, two to nine or greater than 10 across a participant's lifetime. The majority of study participants reported at least two hospital admissions for their mental health over their lifetime. The habits of participants (tobacco smoking, alcohol use and illicit drug use) were assessed. Figures indicating use (yes/no) are reported, with the rationale that quantity and frequency appeared to be unreliably reported in the

cohort. One quarter of the cohort in the chronic stages of schizophrenia smoked tobacco and less than half used alcohol. Over a quarter of participants admitted to illicit drug use.

Most persons took a dietary supplement and over a quarter used a complementary alternative form of medicine. All participants were prescribed a second-generation antipsychotic drug; however, a staggering 70% (n = 56) of participants reported that they were non-adherent with their prescribed antipsychotic drugs. Non-adherence refers to not having taken their prescribed second-generation antipsychotic drug at any time in the past 4 weeks. Seven participants reported that persons 'did better' if they weaned off their antipsychotic drugs rather than remaining compliant for long periods.

4.3. Baseline differences between groups

Treatment bottles were randomised. The 80 persons who provided informed consent were allocated to treatment and placebo groups in sequence by a researcher who was blinded to the randomisation process. Forty-one participants were randomised to the placebo group and 39 were randomised to the mangosteen pericarp group.

The baseline differences between the treatment and placebo groups were assessed to enable the drawing of a conclusion regarding the success (or otherwise) of randomisation. Statistical analyses were conducted by original assigned groups, for which 80 persons were analysed in each of the characteristics described (Table 7).

At baseline, the two groups did not differ significantly with respect to age; t (78, N = 80) = -1.96, p = 0.05 or gender; χ^2 (1, N = 80) = 0.47, p = 0.50. There were no treatment group differences between those living alone or otherwise; χ^2 (1, N = 80) = 0.43, p = 0.51 or between those residing in a house or otherwise; χ^2 (1, N = 80) = 0.40, p = 0.53. Individuals in the pericarp group were significantly more likely to receive a disability pension; χ^2 (1, N = 80) = 5.26, p = 0.02.

Weight, which may point to a sedentary lifestyle or adverse effects of medications, was not significantly different between the treatment groups; t (78, N = 80) = 0.66, p = 0.51. The other factor associated with lifestyle in the target population was their habits. Rates of alcohol use; χ^2 (1, N = *80*) = 1.54, p = 0.46; tobacco use χ^2 (1, N = *80*) = 2.02, p = 0.16 and tetrahydrocannabinol (THC) use; χ^2 (1, N = *80*) = 2.71, p = 0.10 did not differ among treatment groups at baseline.

Rates of family history for schizophrenia did not differ between the treatment groups; χ^2 (1, *N = 80*) = 2.43, *p* = 0.12. Stress was a prominent precipitating factor, although it was not significantly different between treatment groups; χ^2 (2, *N* = 80) = 0.08, *p* = 0.96. Both the age of onset for the disorder; *t* (78, *N = 80*) = 0.13, *p* = 0.90 and the duration of the disorder; *t* (78, *N = 80*) = - 1.48, *p* = 0.14 were not significantly different between the groups. Hospital admission rates were also not significantly different between the groups at baseline; χ^2 (3, *N = 80)* = 2.09, *p* = 0.55.

Current treatments were assessed between groups at baseline. The use of complementary medicines did not differ significantly between treatment groups; χ^2 (1, *N = 80*) = 2.69, *p* = 0.10. The use of dietary supplements was non-significant between groups; χ^2 (1, *N = 80*) = 0.23, *p* = 0.63. Rates of medication compliance were comparably low in the two groups; χ^2 (1, *N = 80*) = 0.69, *p* = 0.41.

Table 7: Characteristics of interest, and statistical analysis of each group at baseline (*n* = 80)

Characteristic		**Placebo group**	**Pericarp group**	**Test statistic**	**Value**	**df**	***P* value**
Basic demographic							
Age	*M(SD)*	46.49(11.57)	51.92(13.19)	*t-test*	-1.96	78	0.05
Gender				χ^2	0.47	1	0.50
Female	*%(n)*	48.80(20)	56.40(22)				
Male	*%(n)*	51.20(21)	43.60(17)				
Females of child-bearing age & sexually active %Yes	*%(n)*	40.0(8)	27.3(6)	χ^2	0.76	1	0.38
Relationship status				χ^2	0.43	1	0.51
Married/de facto	*%(n)*	41.5 (17)	48.7 (19)				
Housing %Yes	*%(n)*	97.60(40)	94.90(37)	χ^2	0.40	1	0.53
Area				χ^2	1.75	1	0.19
Rural	*%(n)*	34.1(14)	48.70(19)				
Urban	*%(n)*	65.90(27)	51.30(20)				
Employment				χ^2	5.26	1	0.02#
Employed	*%(n)*	41.50(17)	17.90(7)				
Disability	*%(n)*	58.50(24)	82.10(32)				

pension/Other							
Weight	*M(SD)*	76.38(17.90)	73.52(20.96)	*t-test*	0.66	78	0.51
Family history %Yes	*%(n)*	29.30(12)	46.20(18)	χ^2	2.43	1	0.12
Illness features							
Precipitating factors				χ^2	0.08	2	0.96
Stress	*%(n)*	80.50(33)	82.10(32)				
Drugs & alcohol	*%(n)*	7.30(3)	7.70(3)				
Other	*%(n)*	12.20(5)	10.30(4)				
Age at onset	*M(SD)*	26.10(41)	26.46(39)	*t-test*	-0.13	78	0.90
Duration of illness	*M(SD)*	20.17(10.80)	24.18(13.43)	*t-test*	-1.48	78	0.14
Frequency of MH hospital admissions				χ^2	2.09	3	0.55
None	*%(n)*	24.40(10)	28.20(11)				
One	*%(n)*	31.70(13)	17.90(7)				
2–9	*%(n)*	26.80(11)	30.80(12)				
10 or more	*%(n)*	17.10(7)	23.10(9)				
Habits							
Alcohol use				χ^2	1.54	2	0.46
No	*%(n)*	58.50(24)	46.20(18)				
Little	*%(n)*	22.00(9)	33.30(13)				
Mod–severe	*%(n)*	19.50(8)	20.50(8)				
Tobacco use %Yes	*%(n)*	31.70(13)	17.90(7)	χ^2	2.02	1	0.16
Illicit drug use %Yes	*%(n)*	34.10(14)	17.90(7)	χ^2	2.71	1	0.10
Treatments							
Complimentary medicine %Yes	*%(n)*	19.50(8)	35.90(14)	χ^2	2.69	1	0.10
Dietary supplements %Yes	*%(n)*	53.70(22)	59.00(23)	χ^2	0.23	1	0.63
SGA drug compliance %No	*%(n)*	65.70(27)	74.40(29)	χ^2	0.69	1	0.41

Note: Percentage figures are expressed (%); n is the frequency of participants; MH is mental health; SGA is second-generation antipsychotic drugs; M is mean; SD is standard deviation; df is degrees of freedom; t-test is independent-samples t-test; χ^2 is independent chi square; # significant as $p < 0.05$.

There were no overall differences between the groups in the number of cases diagnosed with schizophrenia versus schizoaffective disorder; χ^2 (1, N = 80) = 2.00, p = 0.16. There was no significant difference between persons with paranoid, catatonic, residual, undifferentiated and disorganised schizophrenia at baseline within the placebo and pericarp groups.

There were no significant differences between treatment groups at baseline for PANSS total scores; t (78, N = 80) = -0.66, p = 0.51 (Table 8). Scores for other symptom measures (PANSS positive, negative and general and MADRS) did not differ between treatment groups at baseline. Similarly, scores for functioning and well-being did not differ between treatment groups at baseline. Based on these findings, differences between the groups on clinical and functional measures at baseline were found to be negligible, with randomisation consequently being considered as having been successful.

Table 8: Overall and between-group descriptive analysis (*M*[*SD*]) for baseline clinical and functioning measures (N = 80)

Clinical measure	**Overall cohort**	**Placebo group**	**Pericarp group**	**t-test value**	**df**	***P* value**
PANSS						
Positive	16.60 (6.19)	17.44 (7.08)	15.72 (5.03)	1.25	72.32	0.21
Negative	23.81 (7.50)	22.61 (8.44)	25.08 (6.24)	-1.49	73.63	0.14
General	38.50 (9.93)	37.63 (10.48)	39.41 (9.37)	-0.80	78	0.43
Total	78.91 (17.03)	77.68 (19.06)	80.21 (14.74)	-0.66	78	0.51
MADRS	18.68 (8.75)	17.54 (9.09)	19.87 (8.34)	-1.20	78	0.24
CGI-S	3.46 (1.06)	3.46 (1.08)	3.46 (1.05)	0.01	78	0.99
GAF	51.75 (13.10)	51.98 (14.11)	51.51 (12.13)	0.16	78	0.88
SRLS	11.36 (3.68)	11.32 (4.18)	11.41 (3.13)	-0.11	73.96	0.91

Note: M is mean; SD is standard deviation; df is degrees of freedom, adjusted to account for violation to the assumption of homogeneity of variance; t-test is independent-samples t-test.

4.4. Withdrawal and completion data

Of the 80 recruited to the study, four persons did not meet criteria for inclusion in the analysis, as they withdrew from the study prior to 90 days. In the placebo group, one person decided to withdraw secondary to an acute episode of schizophrenia. Of those in the mangosteen pericarp group, three were withdrawn by the researcher. One person was withdrawn when it was disclosed that he was not yet 18 years of age and had lied about his age at the time of induction.

Another person lost their capacity to consent due to incarceration in the legal system. The third person was withdrawn because her general practitioner discontinued all of her medications on learning that she was a participant in the study.

There was a 5.0% (n = 4) dropout rate at 90 days, which increased to 11.30% (n = 9) by 150 days and 15% (n = 12) by 180 days. There were no significant differences between treatment groups with respect to completion of interviews at 90 days; χ^2 (1, N = 80) =1.16, p = 0.28, 150 days; χ^2 (1, N = 80) = 3.42, p = 0.06 and 180 days; χ^2 (1, N = 80) = 0.52, p=0.47 (Table 9).

Table 9: Completion rates at 90, 150 and 180 days (n = 80)

Interview		**Total cohort**	**Placebo group**	**Pericarp group**	**Test**	**Value**	**df**	***P* value**
Baseline	*% (n)*	100.0 (80)	100.0 (41)	100.0 (39)				
90 days	*% (n)*	95.0 (76)	97.6 (40)	92.3 (36)	χ^2	1.16	1	0.28
150 days	*% (n)*	88.8 (71)	95.1(39)	82.1 (32)	χ^2	3.42	1	0.06
180 days	*% (n)*	85.0 (68)	87.8 (36)	82.1 (32)	χ^2	0.52	1	0.47

Note: χ^2 is chi square test for independence; df is degrees of freedom; % is percentage figures; n is the number of participants.

Those who completed all assessments (completers = 68) were compared to those who did not complete at least one post-baseline interview (non-completers = 12) (Table 10).

Table 10: Comparison of completers and non-completers over the 180 days of the trial

Characteristic		**Group**			**Value**	**df**	***P***
		Non-completer (*n* = 12)	**Completer (*n* = 68)**				**value**
Basic demographic							
Age	*M(SD)*	43.33 (12.22)	50.16 (12.48)	*t-test*	-1.75	78	0.08
Gender				χ^2	0.66	1	0.42
Female	*%(n)*	41.7 (5)	54.4 (37)				
Male	*%(n)*	58.3 (7)	45.6 (31)				
Relationship status				χ^2	4.58	1	0.03
Married/de facto	*%(n)*	16.7 (2)	50.0 (34)				
Housing %Yes	*%(n)*	100.0 (12)	95.6 (65)	χ^2	0.55	1	0.46
Area				χ^2	1.54	1	0.22
Rural	*%(n)*	25.0 (3)	44.1 (30)				
Urban	*%(n)*	75.0 (9)	55.9 (38)				
Employment							
Employed	*%(n)*	8.3 (1)	33.8 (23)	χ^2	3.16	1	0.08
Disability pension/other	*%(n)*	91.7 (11)	66.2 (45)				
Weight	*%(n)*	84.7 (23.8)	73.3 (18.2)	*t-test*	1.91	78	0.06
Family history %Yes	*%(n)*	41.7 (5)	36.8 (25)	χ^2	0.11	1	0.75
Illness features							
Precipitating factors				χ^2	7.42	2	0.02
Stress	*%(n)*	75.0 (9)	82.4 (56)				
Drugs & alcohol	*%(n)*	25.0 (3)	4.4 (3)				
Other	*%(n)*	0.0 (0)	13.2 (9)				
Age at onset	*M(SD)*	26.9 (11.7)	26.2 (12.3)	*t-test*	0.20	78	0.84
Duration of illness	*M(SD)*	16.3 (9.7)	23.2 (12.4)	*t-test*	-1.80	78	0.08
Frequency of MH hospital admissions				χ^2	2.56	3	0.46
None	*%(n)*	41.7 (5)	23.5 (16)				
One	*%(n)*	16.7 (2)	26.5 (18)				
2–9	*%(n)*	16.7 (2)	30.9 (21)				
10 or more	*%(n)*	25.0 (3)	19.1 (13)				

Characteristic		Group			Value	df	*P* value
		Non-completer (*n* = 12)	Completer (*n* = 68)				
Habits							
Alcohol use				χ^2	0.20	2	0.90
No	*%(n)*	58.3 (7)	51.5 (35)				
Little	*%(n)*	25.0 (3)	27.9 (19)				
Mod–severe	*%(n)*	16.7 (2)	20.6 (14)				
Tobacco use %Yes	*%(n)*	41.7 (5)	22.1 (15)	χ^2	2.09	1	0.15
Illicit drug use %Yes	*%(n)*	41.7 (5)	23.5 (16)	χ^2	1.73	1	0.19
Treatments							
Complimentary medicine %Yes	*%(n)*	25.0 (3)	27.9 (19)	χ^2	0.04	1	0.83
Dietary supplements %Yes	*%(n)*	58.3 (7)	55.9 (38)	χ^2	0.03	1	0.88
SGA drug compliance %No	*%(n)*	41.7 (5)	75.0 (51)	χ^2	5.40	1	0.20

Note: M is mean values; SD is the standard deviation; t-test is independent-samples t-test; χ^2 is chi square for independence; % is percentage figures; SGA is second-generation antipsychotic drugs; n is the frequency of participants.

Non-completers were significantly less likely to be married; χ^2 (1, N =80) = 4.58, p = 0.03, more likely to have alcohol and drugs as a precipitating factor; χ^2 (2, N =80) = 7.42, p = 0.02 and more compliant with second-generation antipsychotic medications; χ^2 (1, N =80) = 4.58, p = 0.03 than study completers; χ^2 (1, N = 80) = 5.40, p = 0.02.

4.5. Primary efficacy measure, PANSS total

The estimated means and standard errors from the MMRM analysis for the PANSS total are displayed in Figure 8. For the PANSS total score, the omnibus interaction between treatment group and assessment occasion was significant, F (3, 114.35) = 10.86, p < 0.01, indicating that the two groups were performing differently over time. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ} = 42.52, SE = 3.86) as compared to the placebo group (M_{Δ} = 12.72, SE = 3.66), t (64.74) = -5.60, p < 0.01. Effect size was calculated based on difference scores from baseline to 180 days. Group differences based on the difference scores indicated a large effect

size for the PANSS total score (1.41) (Cohen 1992). Similarly, the rate of change was greater in the pericarp group between baseline and 150 days (pericarp M_{Δ}= 34.75, *SE* = 3.55; placebo M_{Δ} = 16.38, *SE* = 3.30; *t* (129.27) = 3.79, $p < 0.01$). Further, the rate of change was greater in the pericarp group between baseline and 90 days (pericarp M_{Δ} = 32.47, *SE* = 3.04; placebo M_{Δ} = 17.122, *SE* = 2.90; *t* (185.56) – 3.66, $p < 0.01$).

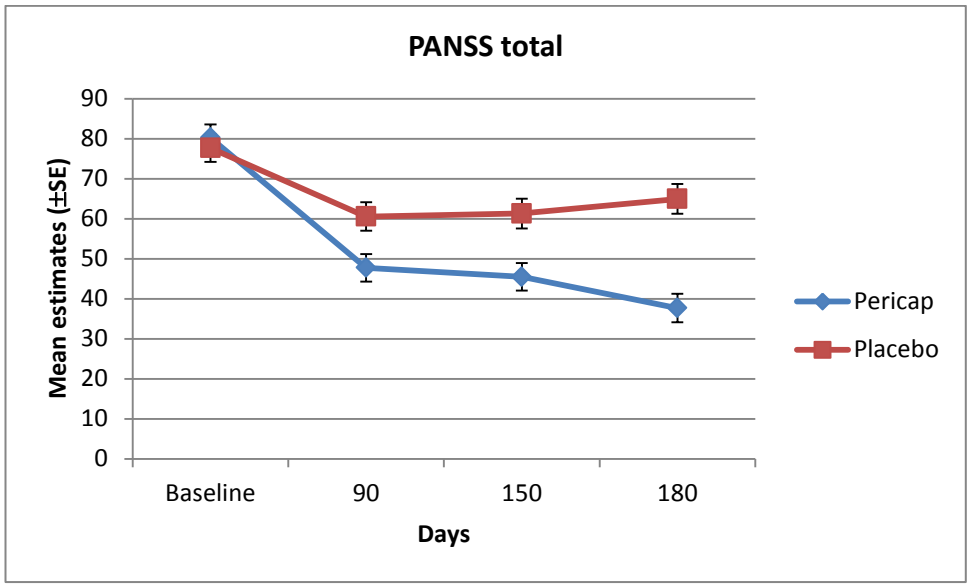

Figure 8: Mean estimate and standard errors for PANSS total in each group, across interviews and over time

4.5.1. Adherence

For efficacy, a high level of adherence is desirable. Persons who were non-adherent to their study treatment for seven consecutive days were withdrawn from the study. As a marker for adherence, this is reliable, as some persons refused to return the empty containers because the size and shape of the container was useful to them for storage of seeds or paint. The placebo group took 98% of the prescribed intervention for 95% of the time. The mangosteen pericarp group took 98% of the prescribed intervention for 94% of the time.

4.6. Secondary outcome measures

In the following section, MADRS measures the response to depression and suicidal ideations; while PANSS's positive, negative and general symptom categories represent the core symptoms of schizophrenia and schizoaffective disorder.

4.6.1. PANSS positive

The estimated means and standard errors from the MMRM analysis for the PANSS positive scale are displayed in Figure 9. For the PANSS positive score, the omnibus interaction between treatment group and assessment occasion was significant, F (3, 126.08) = 2.97, p = 0.03, indicating that the two groups were performing differently over time. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ}= 7.01, SE = 1.11) as compared to the placebo group (M_{Δ}= 2.61, SE = 1.05), t (83.62) = -2.88, p < 0.01.

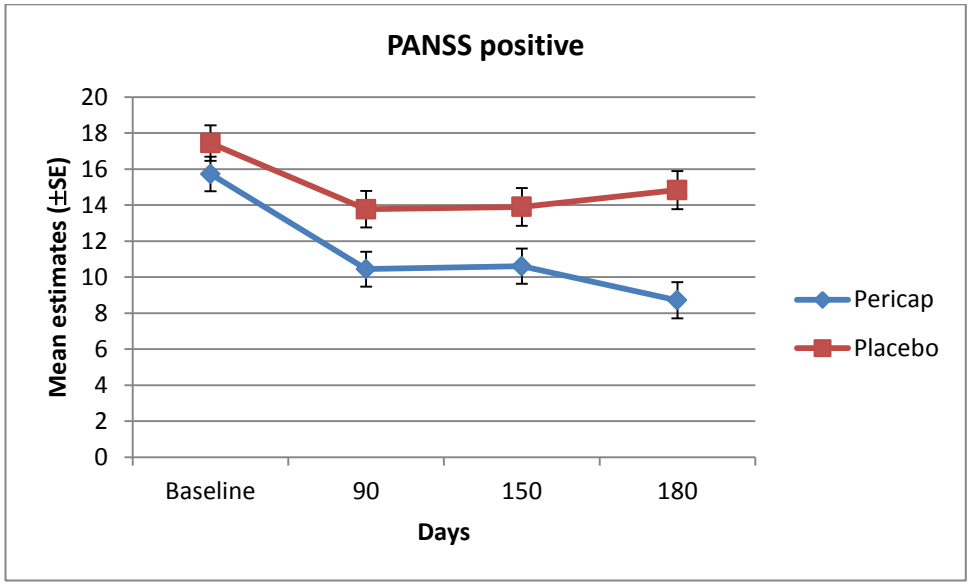

Figure 9: Mean estimate and standard error scores for PANSS positive in each group, across interviews and over time

4.6.2. PANSS negative

The estimated means and standard errors from the MMRM analysis for the PANSS negative score are displayed in Figure 10. For the PANSS negative score, the omnibus interaction between treatment group and assessment occasion was significant, F (3, 119.77) = 10.77, p < 0.01, indicating that the two groups were performing differently over time. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ}= 15.48, SE = 1.56) as compared to the placebo group (M_{Δ} = 3.96, SE = 1.49), t (71.40) = -5.34, p < 0.01. Similarly, the rate of change was greater in the pericarp group between baseline and 150 days (pericarp M_{Δ}= 13.21, SE = 1.46; placebo M_{Δ}= 3.75, SE = 1.36; t (137.14) = -4.75, p < 0.01). Further, the rate of change was

greater in the pericarp group between baseline and 90 days (pericarp M_{Δ} = 11.69, *SE* = 1.24; placebo M_{Δ}= 5.49, *SE* = 1.19; *t* (188.68) = -3.60, *p* < 0.01).

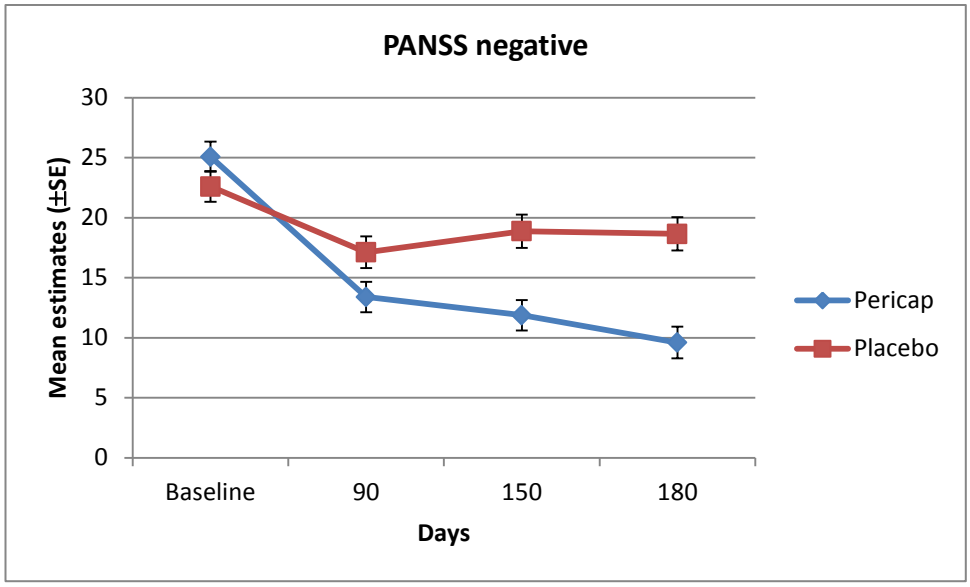

Figure 10: Mean estimate and standard error scores for PANSS negative in each group, across interviews and over time

4.6.3. PANSS general

The estimated means and standard errors from the MMRM analysis for the PANSS general scale are displayed in Figure 11. For the PANSS general score, the omnibus interaction between treatment group and assessment occasion was significant, *F* (3, 129.27) = 9.24, *p* < 0.01, indicating that the two groups were performing differently over time. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ}= 20.10, *SE* = 1.95) as compared to the placebo group (M_{Δ}= 6.23, *SE* = 1.85), *t* (79.35) = -5.17, *p* <.01. Similarly, the rate of change was greater in the pericarp group between baseline and 150 days (pericarp M_{Δ} = 15.54, *SE* = 1.66; placebo M_{Δ} = 9.14, *SE* = 1.70; *t* (132.91) = -2.94, *p* < 0.01). Further, the rate of change was greater in the pericarp group between baseline and 90 days (pericarp M_{Δ} = 16.50, *SE* = 1.84; placebo M_{Δ}= 7.93, *SE* = 1.58; *t* (171.52) = -3.33, *p* < 0.01).

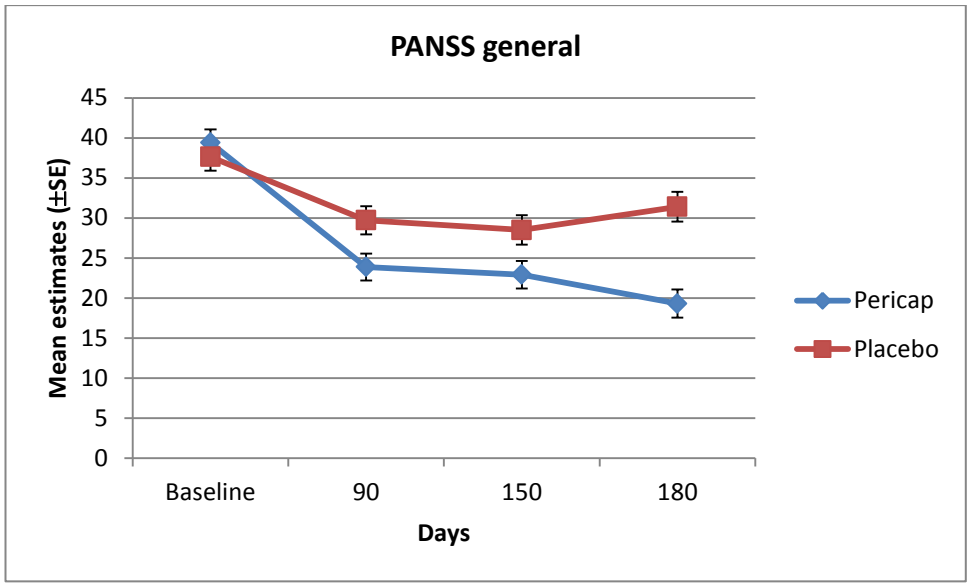

Figure 11: Mean estimate and standard error scores for PANSS general in each group, across interviews and over time

4.6.4. MADRS

The estimated means and standard errors from the MMRM analysis for MADRS are displayed in Figure 12. For the MADRS score, the omnibus interaction between treatment group and assessment occasion was significant, F (3, 108.85) = 7.59, p < 0.01, indicating that the two groups were performing differently over time. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ}= 16.70, SE = 1.59) as compared to the placebo group (M_{Δ}= 6.49, SE = 1.52), t (75.74) = -4.64, p < 0.01. Similarly, the rate of change was greater in the pericarp group between baseline and 150 days (pericarp M_{Δ}= 12.88, SE = 1.47; placebo M_{Δ}= 7.70, SE = 1.37; t (130.74) = -2.59, p = 0.01). Further, the rate of change was greater in the pericarp group between baseline and 90 days (pericarp M_{Δ} = 10.82, SE = 1.18; placebo M_{Δ}= 6.58, SE = 1.13; t (192.49) = -2.60, p = 0.01).

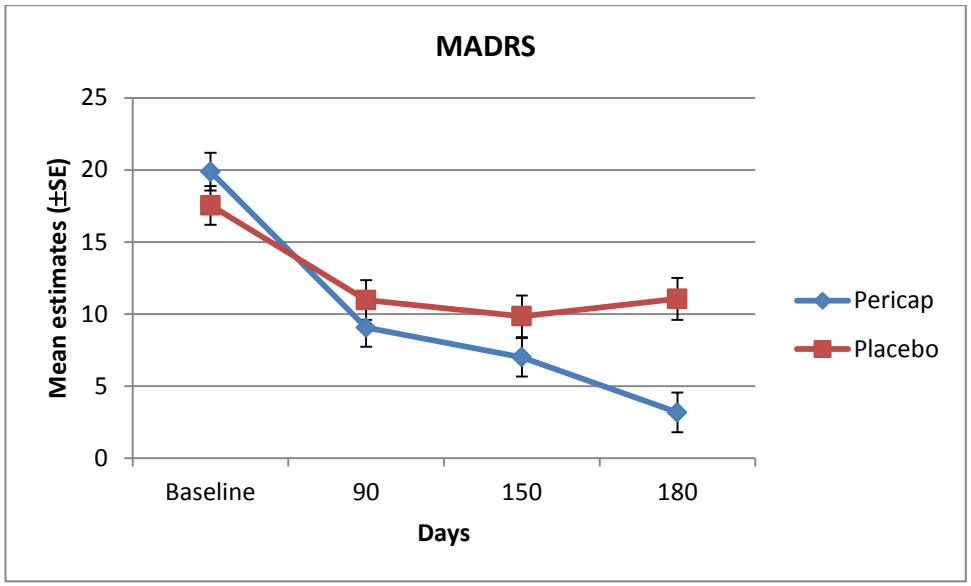

Figure 12: Mean estimate and standard errors for Montgomery-Asberg Depression Rating Scale in each group, across interviews and over time

4.6.5. CGI-S

CGI-S is an outcome measure designed to demonstrate global changes in the severity of psychopathology. The estimated means and standard errors from the MMRM analysis for CGI-S are displayed in Figure 13. For the CGI-S score, the omnibus interaction between treatment group and assessment occasion was non-significant, F (3, 155.40) = 2.50, p = 0.06, although the two groups were performing differently over time. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ}= 1.47, SE = 0.21) as compared to the placebo group (M_{Δ}= 0.74, SE = 0.20), t (92.53) = -2.58, p = 0.01. Similarly, the rate of change was greater in the pericarp group between baseline and 150 days (pericarp M_{Δ} = 1.08, SE = 0.17; placebo M_{Δ} = 0.57, SE = 0.16; t (138.83) = -2.20, p = 0.03).

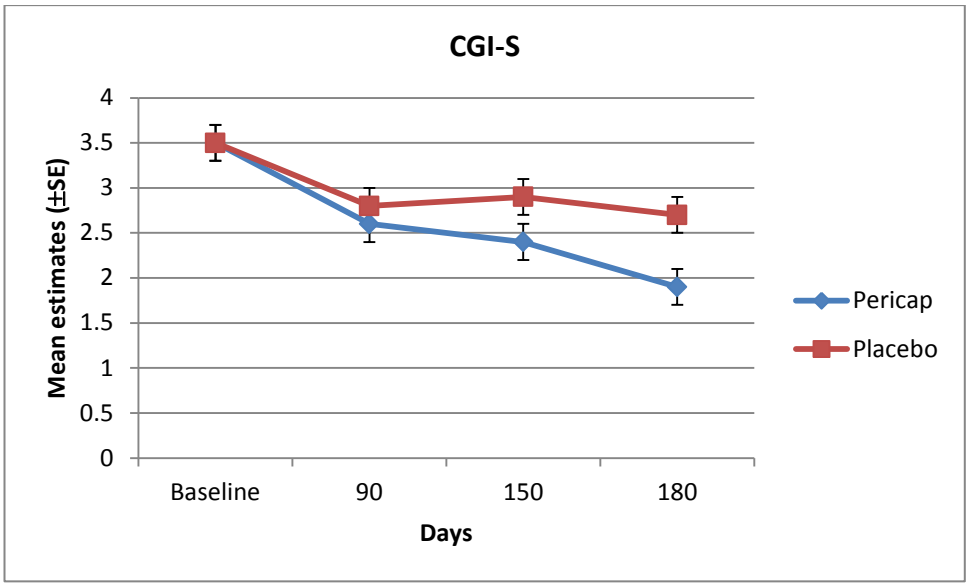

Figure 13: Mean estimate and standard error scores for CGI-S in each group, across interviews and over time

4.7. Functioning and well-being

Three outcome measures have been assessed for functioning and well-being. These are the GAF, the CGI-I and SRLS.

4.7.1. GAF

The estimated means and standard errors from the MMRM analysis for GAF are displayed in Figure 14. For the GAF score, the omnibus interaction between treatment group and assessment occasion was not significant, F (3, 129.83) = 1.70, p = 0.17. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ} = 18.97, SE = 2.87) as compared to the placebo group (M_{Δ} = 10.08, SE = 2.73), t (71.68) = -2.25, p = 0.03).

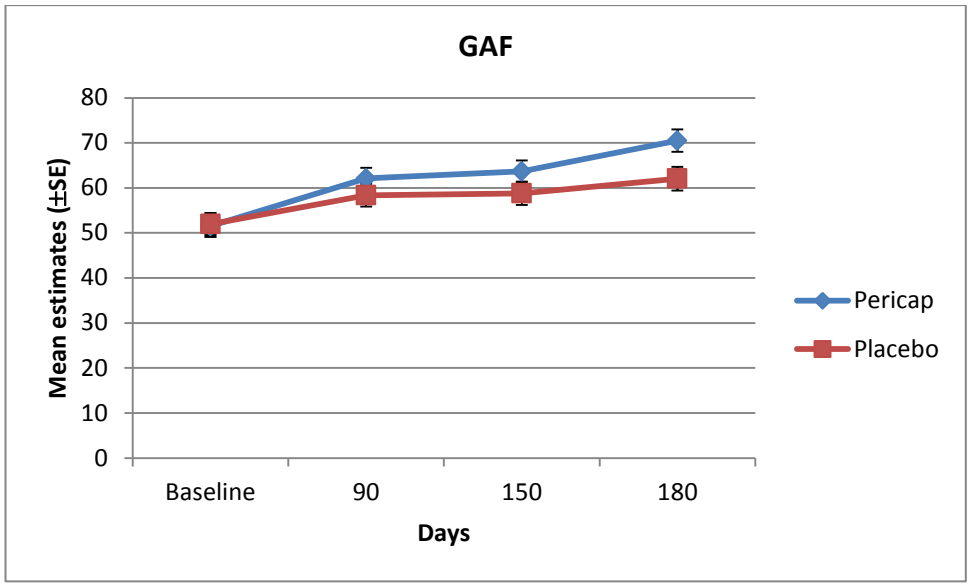

Figure 14: Mean estimate and standard error scores for GAF in each group, across interviews and over time

4.7.2. CGI-I

CGI-I is an outcome scale designed to measure the global effect of treatment over time (Figure 15). Independent-sample t-testing was conducted at 90, 150 and 180 days to enable assessment of alterations in the severity of symptoms. There was a significant improvement in symptom severity for participants at each time point relative to baseline. Symptom severity at 90 days was significantly higher in the placebo group (M = 2.98, SD = 1.14) versus the pericarp group (M = 2.33, SD = 1.10), t (72.58) = 2.23, p = 0.03. The mean CGI-I for 150 days was significantly greater in the placebo group (M = 3.15, SD = 1.55) than the pericarp group (M = 2.31, SD = 1.40), t (69) = 2.38, p = 0.02. At 180 days, the placebo group (M = 3.17, SD = 1.40) also had significantly higher symptom severity than the pericarp group (M = 1.84, SD = 0.85), t (66) = 4.63, $p < 0.01$.

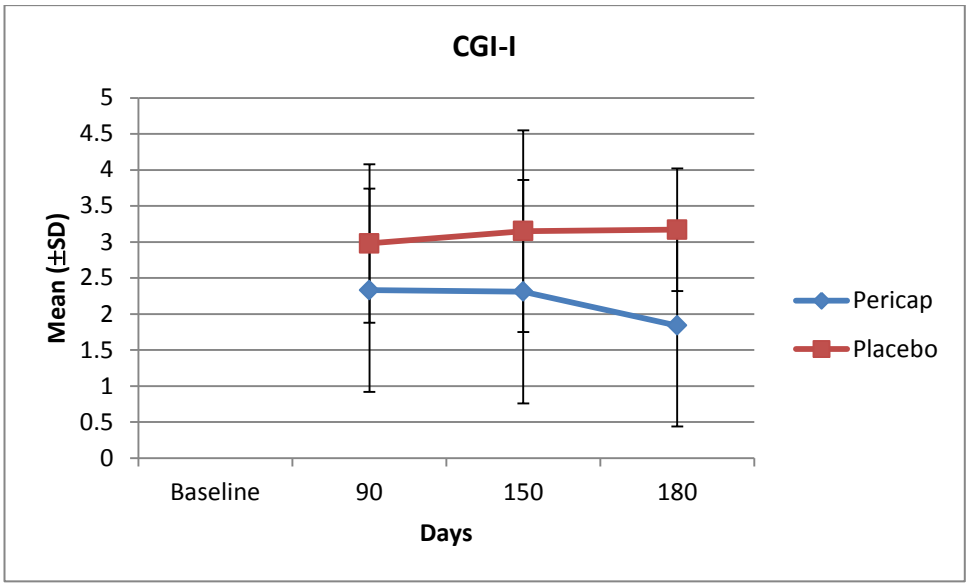

Figure 15: Mean and standard deviation scores for CGI-I in each group, across interviews and over time

4.7.3. SRLS

The estimated means and standard errors from the MMRM analysis for SRLS are displayed in Figure 16. For the SRLS score, the omnibus interaction between treatment group and assessment occasion was significant, F (3, 141.86) = 2.66, p = 0.05. However, examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ}= 3.23, SE = 0.63) as compared to the placebo group (M_{Δ}= 0.87, SE = 0.60), t (84.85) = -2.73, p < 0.01.

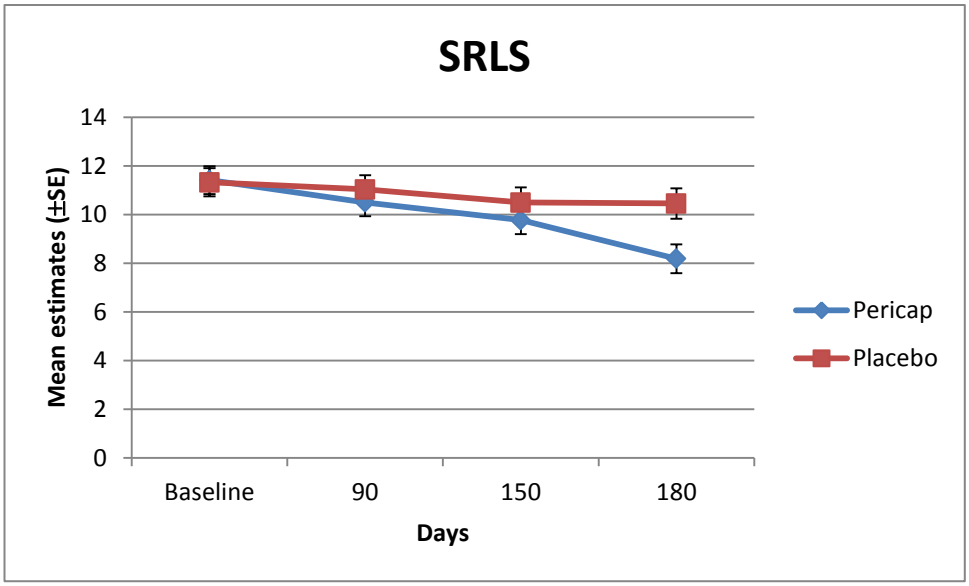

Figure 16: Mean estimate and standard error scores for SRLS in each group, across interviews and over time

4.8. Side effects of second-generation antipsychotic drugs

Valid and reliable scales are available for the assessment of side effects from the use of second-generation antipsychotic drugs. These include LUNSERS, and AIMS for tardive dyskinesia.

4.8.1. LUNSERS

The estimated means and standard errors from the MMRM analysis for LUNSERS are displayed in Figure 17. For the LUNSERS score, the omnibus interaction between treatment group and assessment occasion was significant, F (3, 106.24) = 11.34, $p < 0.01$, indicating that the two groups were performing differently over time. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ}= 30.44, SE = 3.62) as compared to the placebo group (M_{Δ}= 8.05, SE = 3.44), t (98.49) = -4.49, $p < 0.01$. Similarly, the rate of change was greater in the pericarp group between baseline and 150 days (pericarp M_{Δ} = 27.29, SE = 3.20; placebo M_{Δ}= 6.74, SE = 2.99; t (132.45) = -4.70, $p < 0.01$). Further, the rate of change was greater in the pericarp group between baseline and 90 days (pericarp M_{Δ} = 27.35, SE = 2.45; placebo M_{Δ}= 9.05, SE = 2.34; t (196.87) = -5.40, $p < 0.01$).

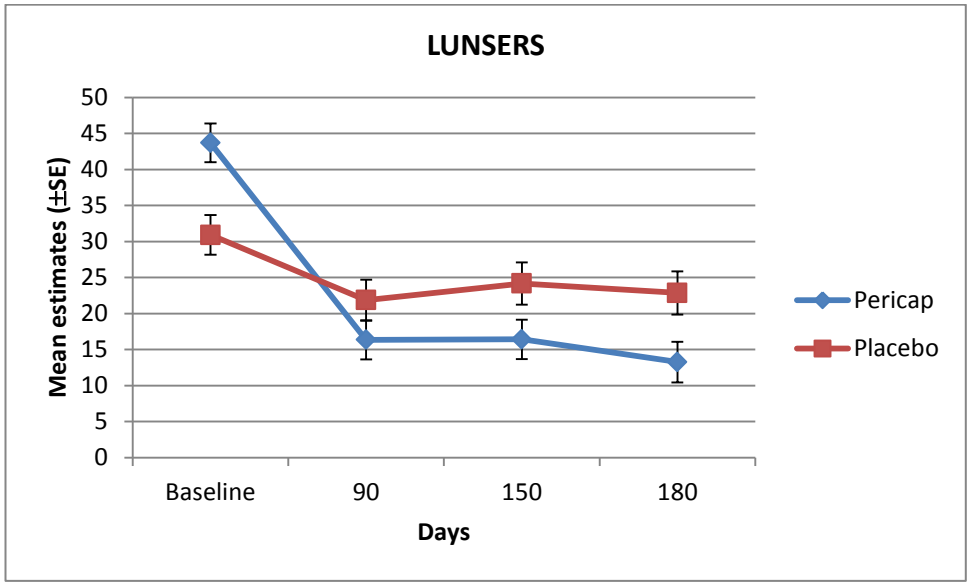

Figure 17: Mean estimate and standard errors for LUNSERS in each group, across interviews and over time

4.8.2. AIMS

Our aim was to test whether abnormal scores were present and then to assess the effect of these abnormal scores in the placebo and pericarp groups. Overall, AIMS was not derived from a normally distributed population. The estimated means and standard errors from the MMRM analysis for AIMS are displayed in Figure 18. For the AIMS score, the omnibus interaction between treatment group and assessment occasion was non-significant, F (3, 156.61) = 1.28, p = 0.28, indicating that the two groups were performing similarly over time. Examination of planned comparisons indicated that the rate of change between baseline and 90 days; t (141.99) = -1.91, p = 0.06, 150 days; t (127.44) = -0.66, p = 0.51 and 180 days; t (116.63) = -1.42, p = 0.16 was not significantly different between the two groups.

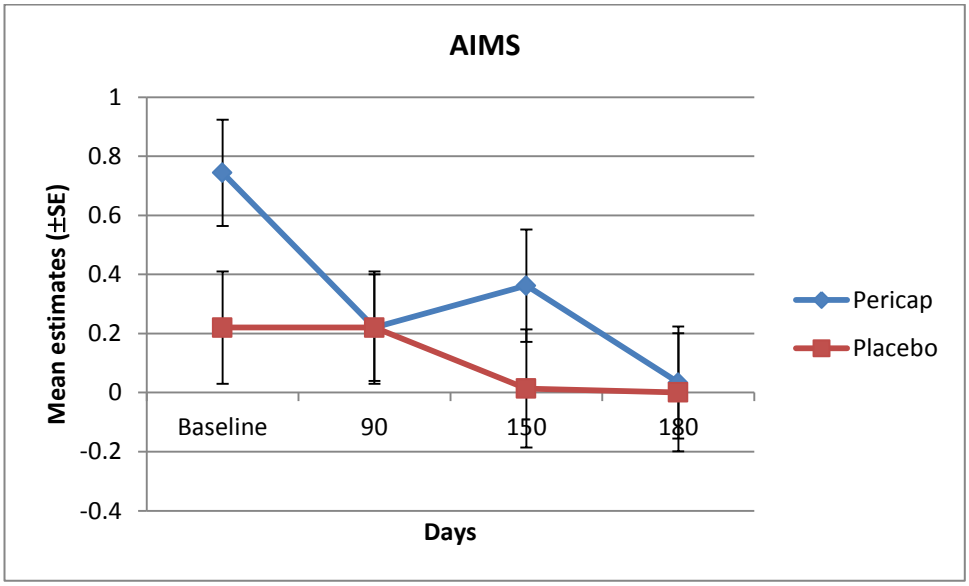

Figure 18: Mean estimate and standard error scores for AIMS in each group, across interviews and over time

4.9. Analysis of habits

At 180 days, there were no significant differences between groups with respect to alcohol use; placebo 35.00% (n = 14), pericarp 5.60% (n = 10), χ^2 (1) = 0.82, p = 0.37, or tobacco use; placebo 30.00% (n =12) v. pericarp 12.80% (n = 5), χ^2 (1) = 3.45, p = 0.06. The results for THC use were unreliable, as measures for comparing the concentrations and amount of THC cannot be fully quantified.

4.10. Explanatory and supplementary measures

4.10.1. Effect sizes

To support the analysis of efficacy, effect sizes were benchmarked by Cohen's *d* (Table 11) for those analyses with statistically significant differences between groups.

Table 11: Effect sizes for outcome measures (difference between baseline and 180 days)

Outcome measure	Cohen's *d*	Effect size
PANSS total	1.41	Large
PANSS positive	0.71	Medium
PANSS negative	1.28	Large
PANSS general	1.26	Large
MADRS	1.19	Large
CGI-S	0.69	Medium
CGI-I	1.15	Large
GAF	0.59	Medium
SRLS	0.60	Medium
LUNSERS	1.09	Large
Anxiety	0.87	Large
Suicidal ideations	0.48	Small

Note: Cohen's d effect sizes: 0.2 is small; 0.5 is medium; 0.8 is large.

4.10.2. Safety data

Over the conduct of the study, only one adverse report was submitted to the ethics committee. No events of a serious nature were experienced that warranted reporting to the Therapeutic Goods Administration. This report was of an adverse headache, secondary to cervical stenosis (Table 12). This report proved to be behavioural in nature, as the participant involved, subsequently requested assistance from the researcher for his weekly shopping. An unintended effect was thoughts of self-harm without action reported by one participant, on a background of previous such thoughts. Based on this data, the study is considered to have been delivered safely.

Table 12: Safety data for the clinical trial (N = 80)

Adverse event	Treatment group	Outcome
Headache	Mangosteen pericarp group	Led to treatment
Thoughts of self-harm	Placebo group	Led to treatment

Note: No calculations were performed

4.10.3. Response

Leucht et al. (2009) recommended that PANSS total score be rescaled from 1–7 to a ratio scale of 0 to 6. Changing the properties of the scale allows for calculation of percentage reduction in symptoms. In Leucht et al.'s (2009) paper, there is an error in how the percentage reduction is calculated. Leucht et al. (2009) presented a formula as $\frac{(PANSS_{baseline}-PANSS_{endpoint})\times 100}{(PANSS_{endpoint}-30)}$; however, the denominator should comprise $PANSS_{baseline}$ and not $PANSS_{endpoint}$. With this revised formula, percentage reduction is accurately calculated between baseline and 180 days for PANSS total scores (Table 13).

The two groups differed significantly with respect to percentage reduction in symptoms from baseline to 180 days; χ^2 (4) = 22.52, $p < 0.01$. *Post-hoc* comparisons of proportions (using Bonferroni correction) indicated that the placebo group was significantly more likely to get worse from baseline to 180 days ($p < 0.05$), whereas the pericarp group was significantly more likely to have a 75–100% reduction of symptoms between baseline to 180 days ($p < 0.05$).

Table 13: Response as represented by percentage reduction in symptoms from baseline to 180 days as measured by PANSS total scores

Percentage reduction	Placebo	Pericarp
0%	33.30(12)	0.00(0)
1–24%	11.10(4)	6.30(2)
25–49%	22.20(8)	6.30(2)
50–74%	2.80(1)	6.30(2)
75–100%	30.60(11)	81.30(26)

Note: Placebo and pericarp group %(n) participants.

4.10.4. Suicidal ideations

Suicidal ideations are an item from the MADRS (Figure 19). The estimated means and standard errors from the MMRM analysis for suicidal ideations are displayed in Figure 19. For the suicidal ideations score, the omnibus interaction between treatment group and assessment occasion was non-significant, F (3, 170.63) = 2.13, p = 0.10. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ}= 1.09, SE = 0.17) than the placebo group (M_{Δ} = 0.56, SE = 0.16); t (100.87) = -2.30, p = 0.02.

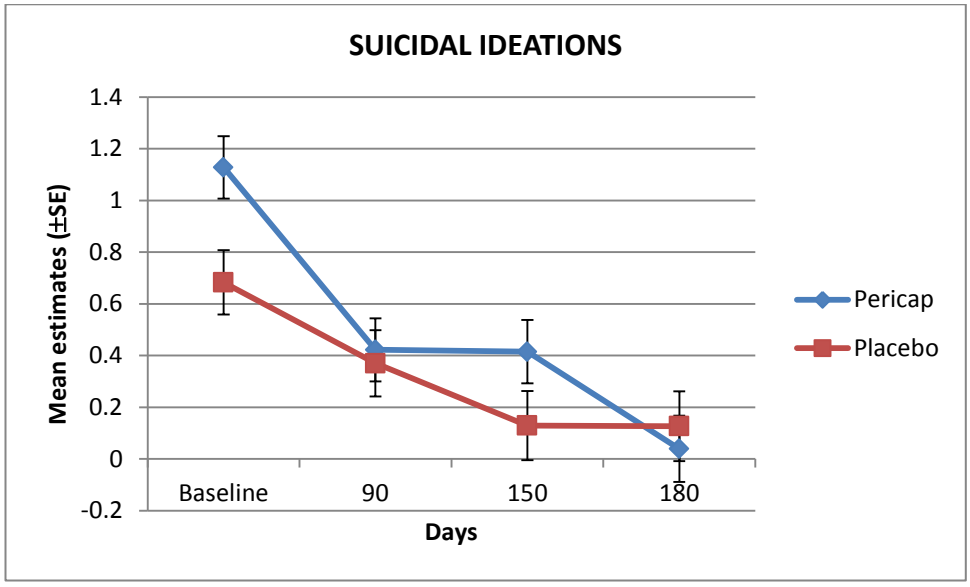

Figure 19: Mean estimate and standard error scores (item 10) from the MADRS for suicidal ideations in each group, across interviews and over time

4.10.5. Anxiety

The anxiety item from the PANSS was used to determine the severity of anxiety symptoms over the duration of the trial (Figure 20). From the MMRM, the omnibus interaction was significant, F (3,139.84) = 4.12, p <0.01. The rate of change between baseline and 180 days was significantly greater in the pericarp compared to the placebo group; t (96.74) = 3.23, p < 0.01. Significant differences in rate of change were also observed between baseline and 90 days; t (169.68) = 2.28, p = 0.02 and baseline and 150 days; t (138.26) = 2.82, p < 0.01.

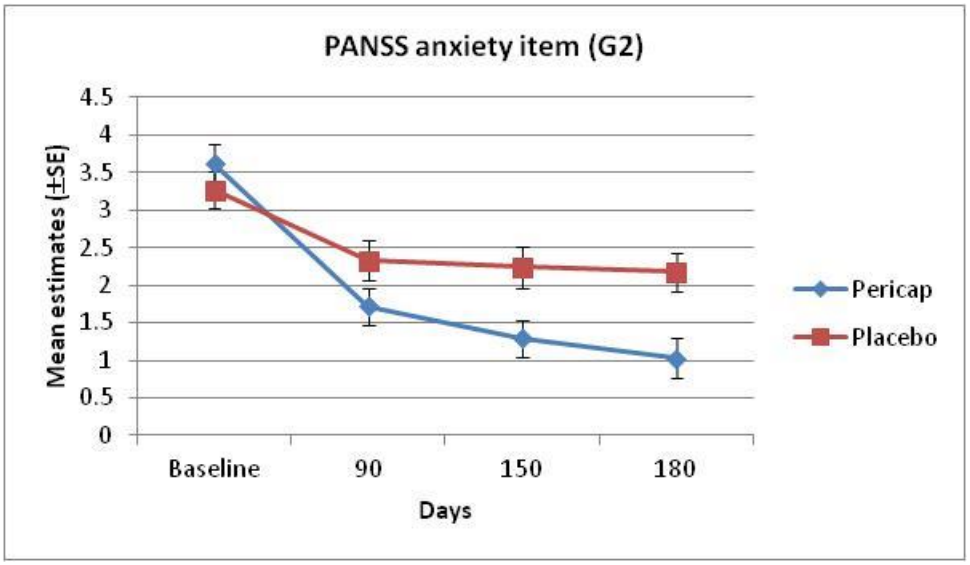

Figure 20: Mean estimate and standard error scores for anxiety (item G2) from the PANSS in each group, across interviews and over time

4.10.6. Weight

At 180 days, the mean weight for the placebo group was 77.31 (*SD* = 17.25) and for the pericarp group the mean was 71.79 (*SD* = 18.17). The placebo group had a weight increase of 0.93kgs (*SD* = 5.12), while the pericarp group had a reduction of mean weight of 1.72kgs (*SD* = 7.50). There was no statistically significant difference in the change of weights from baseline to 180 days; t (78) = -1.86, p = 0.07.

4.10.7. C-reactive protein

Missing data in relation to C-reactive protein levels means that the result is not quantifiable.
Only 37.50% (n = 30) of persons undertook blood sampling for C-reactive protein levels at baseline, declining to 21.25% (n = 17) by 180 days. Reasons disclosed by participants for non-adherence with blood sampling were largely related to paranoia, including fear of needles (4.00%, n = 2), fear of leaving their property (6.00%, n = 3) and fear of exposure to neurotoxins at the blood laboratory (48.00%, n = 24). The information pertaining to our test suggests that an acceptable range of C-reactive protein levels is under 3mg/L (supplied by Sullivan-Nicolaides laboratories). Of the persons who did undertake blood sampling, elevated C-reactive protein was not a uniform finding, being only present in 20.00% (n = 6) at baseline and 11.76% (n = 2) of persons at 180 days. Of the latter group, one of those persons reported an acute viral infection at 180 days.

4.10.8. Adherence with taking prescribed second-generation antipsychotic drugs

Adherence is a widely acknowledged challenge facing mental health services in relation to chronic use of second-generation antipsychotic drugs. Participants were asked whether they took their prescribed medication at baseline; if so, they were asked how often they took it and how much of the time in the last month they had missed doses. Adherence and non-adherence figures for study participants with regards to their prescribed second-generation antipsychotic drugs are derived from data reported by participants.

It is of interest to investigate the PANSS total at 180 days of those who were non-adherent with second-generation antipsychotic drugs at baseline as an indirect indication of the effect of monotherapy with mangosteen. The estimated means and standard errors from the MMRM analysis for PANSS total for the non-adherent group (n = 54) are displayed in Figure 21. For the PANSS total score for the non-adherent group, the omnibus interaction between treatment group and assessment occasion was significant, F (3, 71.18) = 8.81, p < 0.01, indicating that the two groups were performing differently over time. Examination of planned comparisons indicated that the rate of change between baseline and 180 days was significantly greater in the pericarp group (M_{Δ} = 44.23, SE = 4.65) as compared to the placebo group (M_{Δ} = 11.75, SE = 4.65), t (38.00) = -4.94, p < 0.01. Similarly, the rate of change was greater in the pericarp group between baseline and 150 days (pericarp M_{Δ}= 36.47, SE = 4.30; placebo M_{Δ}= 15.94, SE = 4.25; t (87.87) = -3.39, p < 0.01). Further, the rate of change was greater in the pericarp group between baseline and 90 days (pericarp M_{Δ}= 33.43, SE = 3.50; placebo M_{Δ} = 15.93, SE = 3.52); t (142.02) = -3.53, p < 0.01). These results mirror the treatment group differences observed for the PANSS total for the entire cohort.

Figures for each of the secondary outcome measures (PANSS, MADRS, CGI-S, GAF, SRLS, LUNSERS and AIMS) and the supplementary measures (anxiety and suicidal ideations) for the non-adherent groups are presented in the following pages.

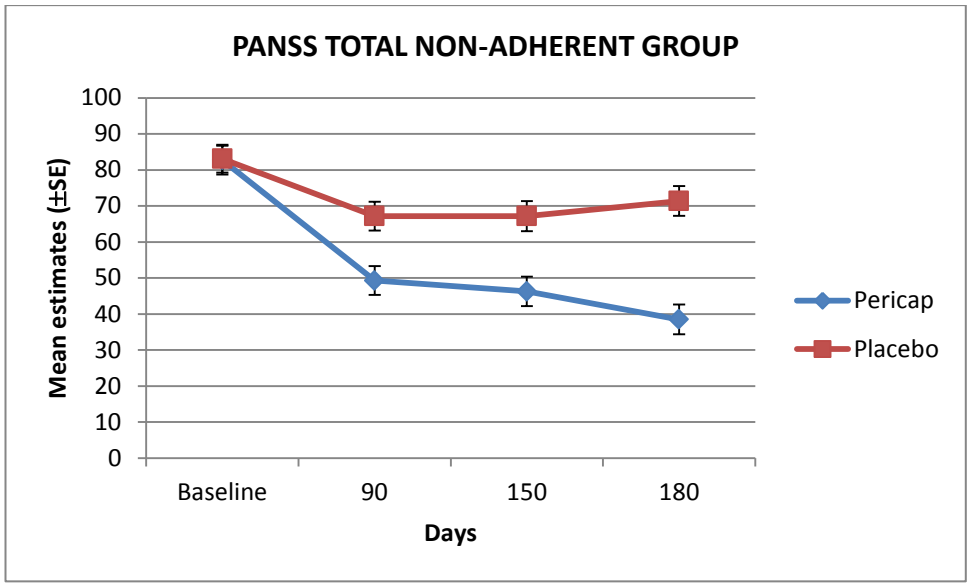

Figure 21: Mean estimate and standard error scores for PANSS total in SGA drug non-adherent participants in each group, across interviews and over time

Measures for the PANSS positive (Figure 22), PANSS negative (Figure 23) and PANSS general scales (Figure 24) favour the mangosteen pericarp group compared to the placebo group.

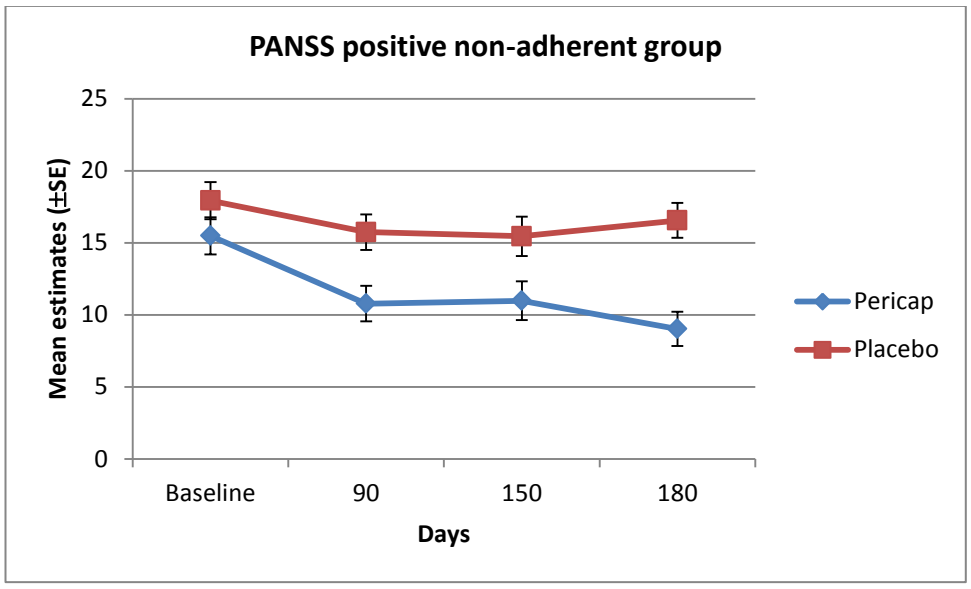

Figure 22: Mean estimate and standard error scores for PANSS positive in SGA drug non-adherent participants in each group, across interviews and over time

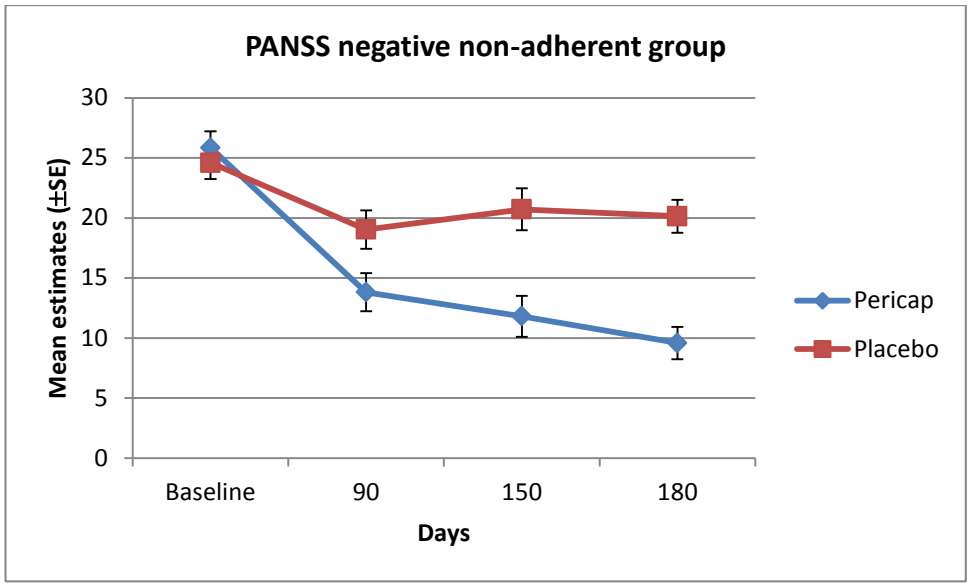

Figure 23: Mean estimate and standard error scores for PANSS negative in SGA drug non-adherent participants in each group, across interviews and over time

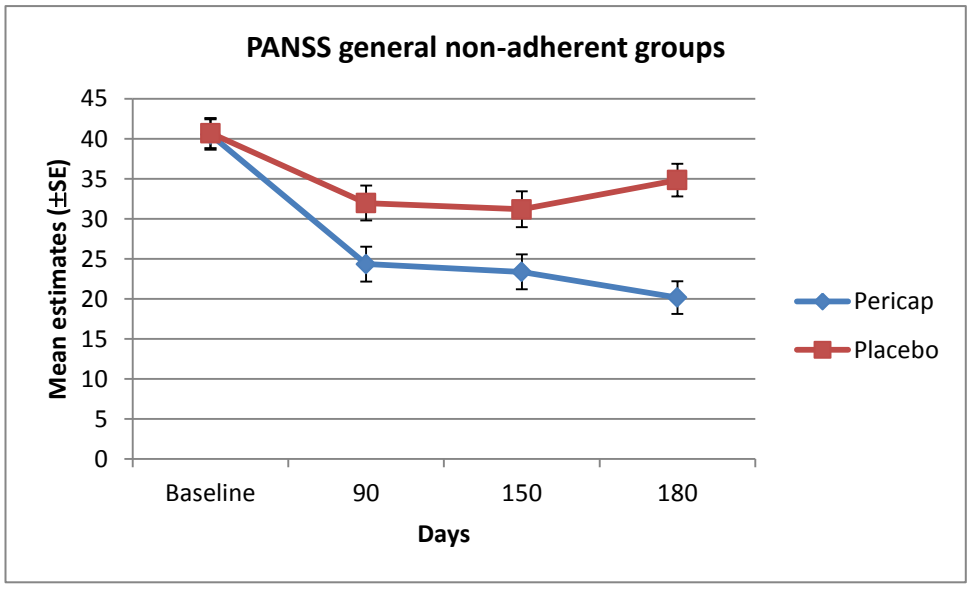

Figure 24: Mean estimate and standard error scores for PANSS general in SGA drug non-adherent participants in each group, across interviews and over time

MADRS scores across groups are similar over time compared to significant differences for the overall cohort (Figure 25).

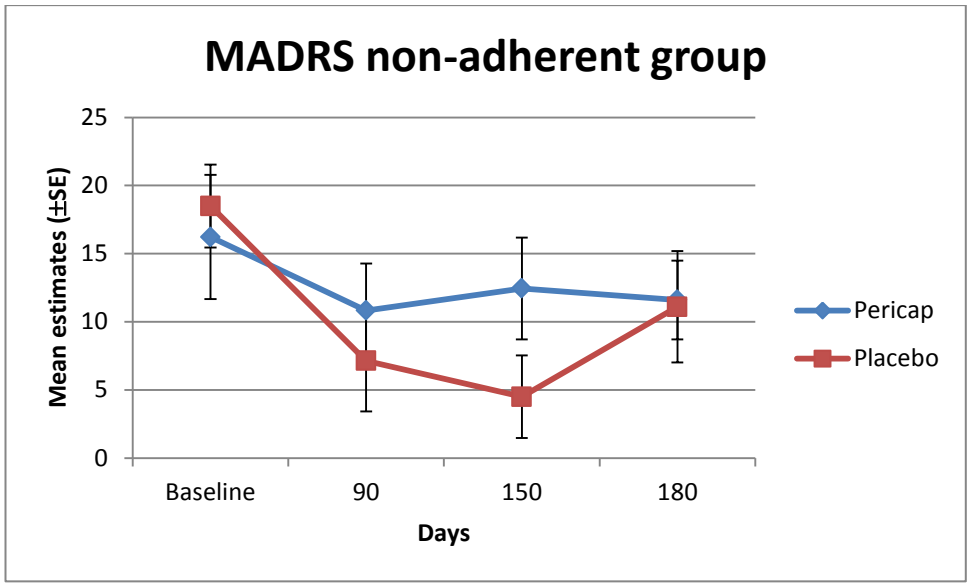

Figure 25: Mean estimate and standard error scores for MADRS in SGA drug non-adherent participants in each group, across interviews and over time

Measures of functioning (CGI-S, Figure 26; GAF, Figure 27; SRLS, Figure 28) favour the mangosteen pericarp group compared to the placebo group.

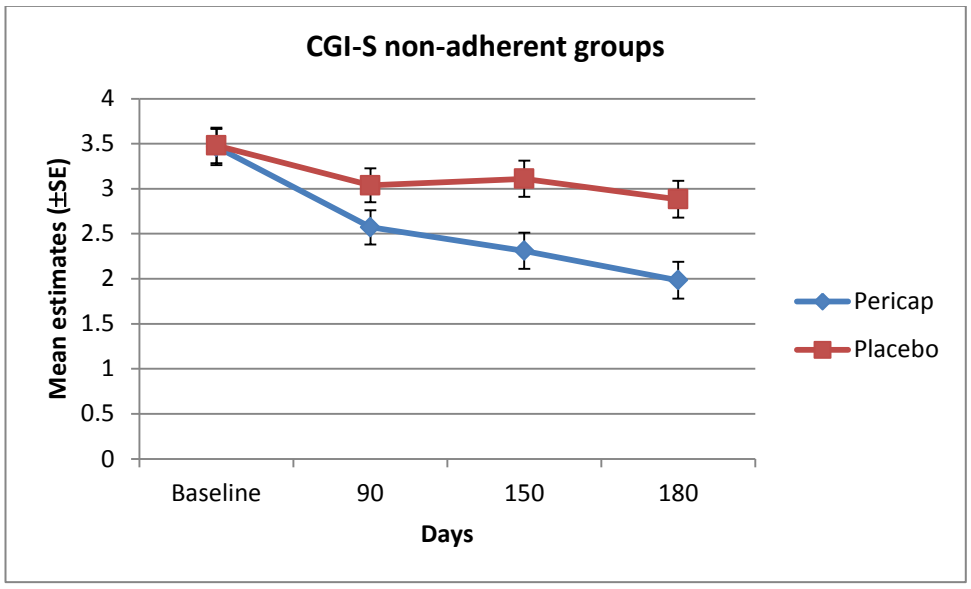

Figure 26: Mean estimate and standard error scores for CGI-S in SGA drug non-adherent participants in each group, across interviews and over time

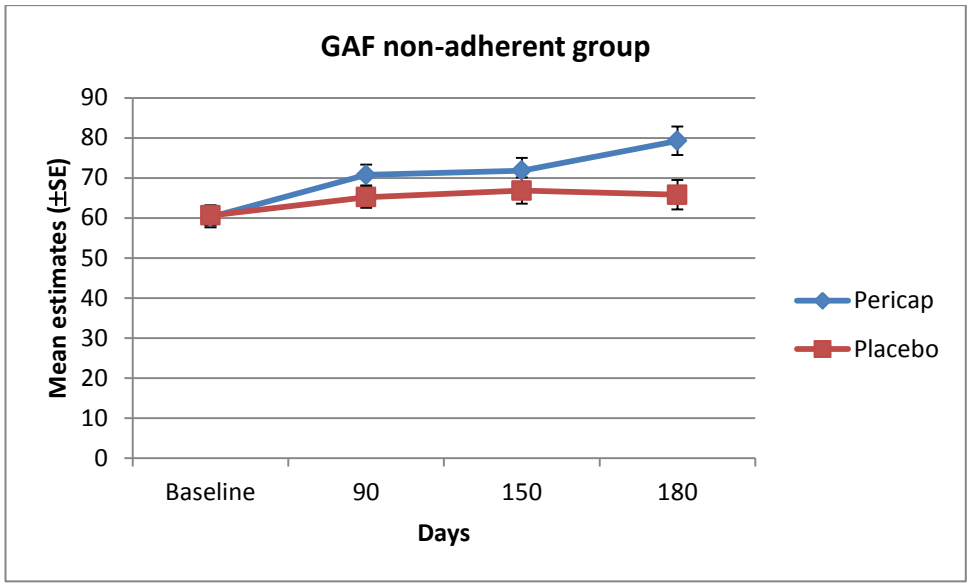

Figure 27: Mean estimate and standard error scores for GAF in SGA drug non-adherent participants in each group, across interviews and over time

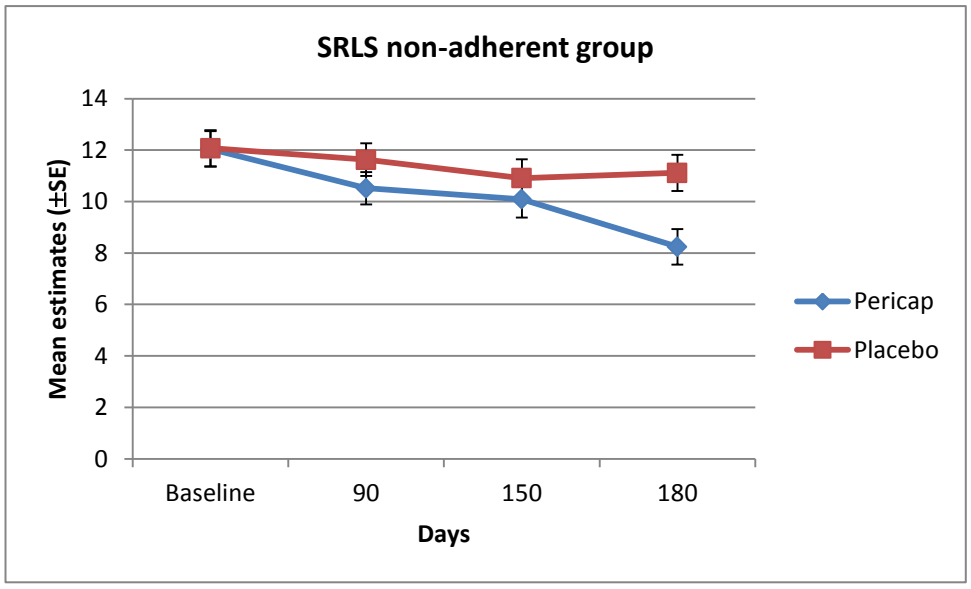

Figure 28: Mean estimate and standard error scores for SRLS in SGA drug non-adherent participants in each group, across interviews and over time

Measures used to assess side effects related to the use of second-generation antipsychotic drugs favour the mangosteen pericarp group compared to the placebo group. However, both groups demonstrate similar responses to tardive dyskinesia.

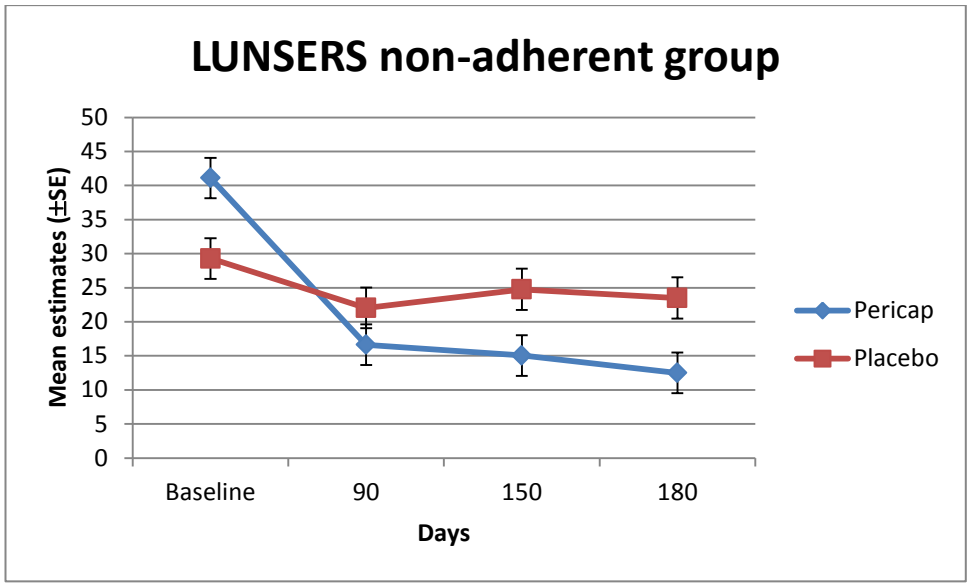

Figure 29: Mean estimate and standard error scores for LUNSERS in SGA drug non-adherent participants in each group, across interviews and over time

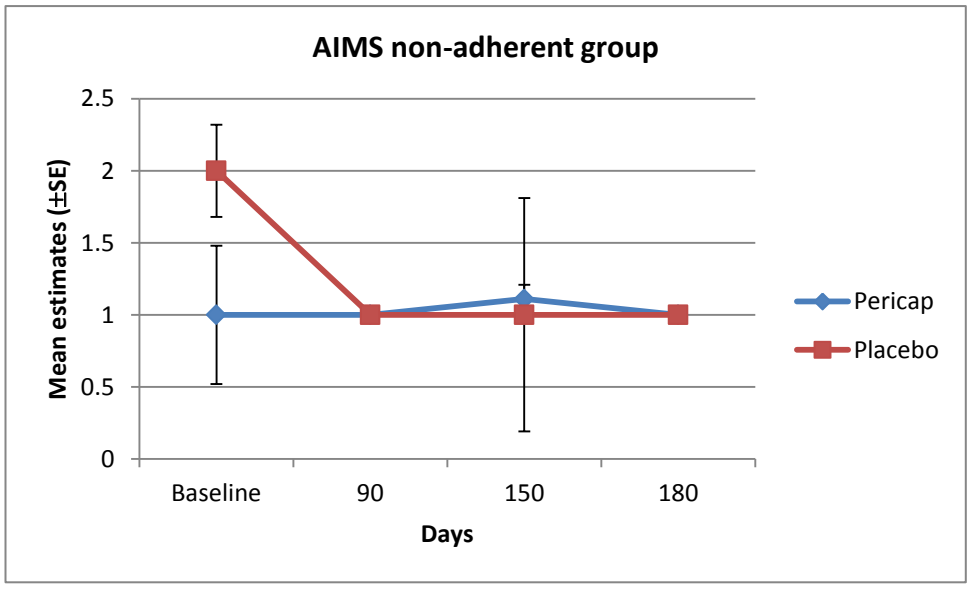

Figure 30: Mean estimate and standard error scores for AIMS in SGA drug non-adherent participants in each group across interviews and over time

4.11. Summary

Characteristics of the overall sample were described at baseline using descriptive statistics. The process of recruitment and participant flow were described. Characteristics of the total cohort were compared to those who dropped out of the study, revealing this to have occurred at random. Completer's analysis found that there was no bias between those who completed and did not complete the study.

The study tested mangosteen pericarp for efficacy, benchmarked by successful randomisation, a high level of intervention adherence and statistically significant findings with regards to PANSS total score as the primary indicator. There were no major differences between the placebo and pericarp group at baseline across either diagnoses or measures of clinical functioning; so randomisation was successful. The primary outcome measure of PANSS (total) was found to be significantly different between groups at 180 days. The mangosteen pericarp group showed efficacy beyond that of the placebo group, with a large effect size. The response to treatment, benchmarked by PANSS total scores, was very large for the pericarp group comparative to the placebo group.

Persons who were non-adherent with taking their prescribed second-generation antipsychotic drugs were assessed across the placebo and pericarp groups to examine the effect of monotherapy with mangosteen pericarp. These findings were significantly different in the treatment groups across scores for PANSS total, which mirrored our findings across PANSS total scores for the entire cohort. Other measures across non-adherent groups mirrored the findings of the total group, such as on PANSS positive, PANSS negative, PANSS general, LUNSERS, GAF, SRLS and CGI-S scores. The scores for the MADRS and AIMS outcome measures were similar at endpoint across the placebo and pericarp non-adherent groups.

Secondary dimensional measures of outcome were assessed. Mangosteen pericarp actions were found to have significantly affected residual core symptom domains in schizophrenia across all PANSS scores, MADRS scores and CGI-S. Functioning and well-being (GAF, SRLS, CGI-I) were different between groups at 180 days.

Unwanted side effects of second-generation antipsychotic drug use measured by LUNSERS were found to be significantly different at 180 days. However, tardive dyskinesia (measured by AIMS scores) was not different between groups at 180 days. There were no differences between placebo and pericarp groups with regards to habits such as alcohol and tobacco use. Suicidal ideations and anxiety scores were significantly different between groups at 180 days. Weight was not different between the groups at 180 days. Findings in relation to C-reactive protein levels were unreliable.

The overall pattern in results support the efficacy of the mangosteen pericarp group with a large effect size comparative to the placebo group in the sample investigated. The study interventions were delivered safely.

Chapter 5: Discussion

'If we mean to thrive and do good, break open the gaols and let out the prisoners'

2 Henry VI, 4.3.15 William Shakespeare (1591)

5.0. Introduction

Our research hypothesis explores the efficacy of 1000mg *Garcinia mangostana* L. (mangosteen) pericarp as compared to a placebo in individuals experiencing symptoms of schizophrenia and concurrently prescribed a second-generation antipsychotic drug. It was hypothesised that mangosteen pericarp would improve therapeutic outcomes in relation to schizophrenia symptoms in the cohort. The study was designed to provide preliminary results of efficacy of mangosteen pericarp in a cohort of people with schizophrenia. A secondary consideration was a change in the side effects associated with second-generation antipsychotic drugs.

The key findings are as follows:

1. We determined that mangosteen pericarp improved residual core symptom domains in schizophrenia. Core symptom domains measured by PANSS were consistently and significantly improved ($p < 0.01$) by the use of mangosteen pericarp, both as an adjunctive to second-generation antipsychotic drugs and in the non-adherent group ($p < 0.01$).
2. We determined that co-morbid depressive symptoms and suicidal ideations were impacted by mangosteen pericarp treatment, measured by MADRS. The MADRS scores were significantly reduced ($p = 0.01$) in favour of the mangosteen pericarp group. Suicidal ideations were also significantly reduced ($p = 0.02$).
3. We determined that mangosteen pericarp altered the severity of psychopathology and improved functioning by measuring CGI-S. CGI-S scores were significantly improved ($p = 0.03$).
4. We determined that mangosteen pericarp influenced social and psychological functioning. This was assessed by the GAF and found to be significantly improved ($p = 0.03$).
5. We determined that mangosteen pericarp improved treatment. CGI-I ($p < 0.01$) was significant.
6. The self-reported quality of life obtained from adjunctive treatment with mangosteen pericarp was assessed by SRLS and was significant ($p < 0.01$) between groups.

7. Habits such as smoking, alcohol and use of illicit substances were assessed by usage pre- and post-intervention. Changes to alcohol and tobacco patterns of use were non-significant. Data indicating the use of illicit substances were unable to be sufficiently quantified and are not reported.
8. The measureable adverse effects from chronic use of second-generation antipsychotic drugs were measured by the LUNSERS. Our findings were significant ($p < 0.01$).
9. Tardive dyskinesia was present in the cohort sample and assessed by scores for AIMS. However, our findings were not significant ($p = 0.16$) and were possibly a consequence of good clinical management.

This study was delivered safely and was found on closer examination to have been both valid and reliable. Our results support mangosteen pericarp as a novel treatment for schizophrenia. Evidence for this assumption was our primary indicator; PANSS total (in the non-adherent group) was significantly different ($p < 0.01$) at 180 days between groups. These findings have been established in the context of an adjunctive treatment to second-generation antipsychotic drugs and/or other nutraceutical preparations that the participant was taking at the time of the intervention, as we did not alter the management practices of participants' clinicians in any way. Thus, our findings should be viewed as having occurred beyond that of any other treatment the person may have used except for green tea and vitamin E, which were exclusion factors. No participant reported taking in either green tea or vitamin E.

The key finding of this study was efficacy of 1000mg/day encapsulated mangosteen pericarp powder for the reduction of symptoms associated with schizophrenia. This study is the first to demonstrate the efficacy of mangosteen pericarp as an adjunct to second-generation antipsychotic drugs for the treatment of schizophrenia.

This chapter will provide a synthesis of the study findings (5.0), including an interpretation of the results (5.1), a discussion (5.2), an outline of the limitations (5.3) and clinical implications (5.4), recommendations (5.5) and a summary of the thesis (5.6).

5.1. Interpretation

Summerfelt and Meltzer (1998) propose that both efficacy and effectiveness are requirements for the evaluation of interventions in psychiatry. Efficacy was evidenced in our study by a high level of compliance with the intervention and significant ($p < 0.01$) results for the primary indicator at 180 days that favoured the mangosteen pericarp group.

Core symptoms and functionality have long been considered central domains of the illness (Foussias & Remington 2010). In particular, negative symptoms were significantly affected. There have been several novel attempts to reduce the negative symptoms associated with schizophrenia; for example, by the administration of glycine (Buchanan 2013) and the prescription of antidepressant drugs (Singh et al. 2010). However, translation into clinical practice has thus far been slow. Othman et al. (2013) suggest that negative symptoms are related to quality of life and a deficit syndrome. Our results indicate that measures of social, psychological and cognitive functionality and quality of life improved significantly between treatment groups. Overall mechanisms such as improved glutathione, glutathione S-transferase levels, RNA and mitochondrial repair and reductions in oxidative stress need to be explored by further work to determine whether they correlate to improvement in clinical outcome.

Unwanted effects of second-generation antipsychotic drugs were significantly reduced across LUNSERS measures. The majority of literature on this topic refers to management of side effects utilising clinical manipulation of pharmacological regimens (Morrison et al. 2000). This technique is also employed to manage tardive dyskinesia. Successful clinical management, non-adherence to antipsychotics or fluctuations over time are possible reasons for our findings in relation to tardive dyskinesia, as both groups demonstrated improvement. Soares and McGrath (1999) propose that treatment for tardive dyskinesia has often been hampered by small sample sizes; however, some effective treatments are available based on single study results.

The lived experience of schizophrenia is associated in the literature with habits such as a sedentary lifestyle, poor diet, high alcohol consumption, high THC (cannabis) use, tobacco smoking and stress (Bobes et al. 2010). In contrast, the majority of our study cohort did not drink alcohol and did not use tobacco products. A likely reason is the nature of the cohort under investigation. Smoking, the use of illicit substances and alcohol intake have been long been associated clinically with self-medication during the acute exacerbation of symptoms related to schizophrenia (Chambers, Krystal & Self 2001). Hayes and Pulford (1995) noted that barbiturates transcriptionally activate glutathione S-transferase to support the occurrence of self-medication in the acute phase of the illness. This is an area that may warrant further detailed investigation in future studies.

5.1.1. Explanatory and supplementary

Exploratory and supplementary analysis was conducted. The study interventions were delivered safely. Effect sizes pertaining to outcome measures of clinical relevance were small to large. Response scores were calculated based on a ratio scale, following corrections to Leucht et al.

(2009). Worsening of symptoms in the placebo group may be attributable to the involvement of phase II metabolism in the pathology of schizophrenia, whereas reduction of symptoms in the placebo group is likely to be attributable to current treatments including second-generation antipsychotic drugs and vitamins, or complementary treatments. However, the overall response to treatment in the mangosteen pericarp group can only be attributed to the mangosteen pericarp, thus providing preliminary evidence for a novel treatment in schizophrenia. Having said this, there may be some bias due to participant expectations for a positive outcome. This response to treatment would benefit from verification in a larger cohort.

Suicidal ideation was significantly impacted by mangosteen pericarp ($p = 0.02$). Plausible explanations for both groups having improved are that suicide may be a proxy for overall illness severity, the study may have provided hope or this improvement may have been linked to change in depressive or other symptom clusters. Hope has been recognised as a therapeutic tool for suicidal ideations (Drake et al. 1984). Besides suicidal ideations, anxiety is often associated with schizophrenia. Anxiety was also reduced in the mangosteen pericarp group comparative to the placebo group. Our finding appears to reinforce earlier work that implicates oxidative stress in the genesis of anxiety (Bouayed et al. 2009).

In their review, Faulkner, Cohn and Remington (2010) disclose a modest weight reduction from pharmacological treatments comparative to a larger effect with cognitive-behavioural options. The effect of mangosteen pericarp on weight did not differ significantly between groups, despite numerically greater loss in the mangosteen pericarp group, which was arguably a type II error. This finding is in contrast to a study by Stern et al. (2013) that tested a herbal preparation containing mangosteen pericarp. While the study had a positive outcome, the mangosteen pericarp was not the only ingredient; within the context of our findings, it is plausible that the findings of Stern et al. (2013) were not solely attributable to the mangosteen pericarp.

C-reactive protein levels are a biomarker for inflammation. Missing data meant the result was not quantifiable. To date, an established biomarker in schizophrenia has not been established. Elevated C-reactive protein levels were not uniformly present at baseline in those in the cohort who undertook blood sampling. Therefore, an examination of C-reactive protein was unlikely to provide substantial information regarding the biochemical pathways involved in schizophrenia that may be affected by mangosteen pericarp. Much more pre-clinical work using rodent modelling is required to establish the activity of mangosteen pericarp.

Repetition of the outcome measures with regard to the non-adherent subgroup in both the pericarp and placebo groups produced a mirrored effect comparative to the total cohort. An

exception to this were the scores for MADRS and AIMS. A plausible explanation for this finding is potentiation of the drug effects by mangosteen pericarp to indicate support for the adjunctive treatment of depression. However, this assumption requires further investigation beyond that of a single study. Findings from monotherapy associated with tardive dyskinesia (AIMS) are not easily interpreted and may reflect a small sample size.

5.2. Discussion

The problem this study aimed to address was the unmet treatment needs of people diagnosed with schizophrenia and the gap in their symptomatic cognitive, social and psychological domains. To address this gap, we tested encapsulated mangosteen pericarp at a dose of 1000mg/day for a period of 180 days. The rigorous study design, validity and reliability of results all supported an answer to the problem this thesis aimed to address. The results showed that mangosteen pericarp improved core symptom domains, measures of functionality and well-being in the cohort tested. Together with the calculated response to treatment, this work supports the potential value of supplementation with mangosteen pericarp for persons with symptoms of schizophrenia. Mangosteen pericarp may be useful for schizophrenia; however, much pre-clinical work is required to ascertain its mechanism of action.

Second-generation antipsychotic side effects measured using the LUNSERS were reduced. Of interest, the high levels of LUNSERS scores comparative to the high level of non-adherence with prescribed second-generation antipsychotic drugs in the cohort suggests that non-adherence was partial in many individuals, or that LUNSERS scores represented non-specific phenomenon of the LUNSERS.

There was a distinctive pattern to results, formed across multiple outcome measures. This may denote the induction of neuronal protection; however, structural and functional scanning or neuropsychological testing is required for confirmation. Emerging evidence from studies involving mangosteen xanthene support this view (Reyes-Fermín et al. 2012; Shan et al. 2011). The concept of neuronal protection has received a reasonable amount of interest in the literature pertaining to schizophrenia. Berger, Wood and Mcgorry (2003) provide evidence of neuronal structural changes that they argue may be counteracted by neuronal protective strategies. This concept is extended by Lieberman, Malaspina and Jarskog (2006), who propose a role for neuronal protection with regard to preventing progression and improving functionality in schizophrenia. These assumptions have not been proven. Ehrenreich et al. (2006) tested human erythropoietin without improvement in psychopathology or social functioning; however, Miskowiak et al. (2013) had a positive result in relation to depression. In contrast, our data

indicate improved clinical functionality and well-being in the intervention group. A plausible explanation for this finding is the integration of neuronal and antioxidant signalling.

Having said this, 180 days may be an insufficient length of time to achieve optimal functioning using a natural product. Although no data were collected, participant follow up revealed continual fluctuations in clinical presentation from those measures achieved at 180 days. In the future, we recommend that persons take the mangosteen pericarp for longer than 180 days, although further work is urgently required to ascertain an optimal length of time.

A review of the literature conducted to examine treatments for schizophrenia, divided into categories of either second-generation antipsychotic drugs or nutraceuticals, demonstrated the current lack of efficacy studies used to establish causal relationships for nutraceuticals. To date, the focus of most add-on studies has been efficacy. The suboptimal treatment of schizophrenia has been well documented in connection to the efficacy of antipsychotic drugs, and indeed formed the primary concern that this thesis aimed to address. In terms of neuronal protection for schizophrenia, studies thus far have examined stem cells (Ono et al. 2010) or recumbent erythropoietin (Ehrenreich et al. 2010). A causal relationship was established between the reduction of core symptom domains in schizophrenia and the mangosteen pericarp group. Field observations pointed to a reduction in the frequency and severity of core symptoms; however, the long-term influence of mangosteen pericarp in the cohort has not been established. For some people, schizophrenia involves an autoimmune process. Nevertheless, mangosteen pericarp is emerging as a treatment for schizophrenia.

5.3. Strengths and limitations

The main feature of this clinical trial is that the response rates appear too good to be true.
There are several limitations to this clinical trial. The response rates appear to be too good to be true and may represent some bias (despite successful randomisation and double blinding) from participant expectations for a positive outcome. Statistical analysis involved standardised modelling for psychiatry that is similarly applied to studies seeking to assess the efficacy of pharmaceuticals. It is possible that this statistical model, although applied correctly, carries some bias. The high level of compliance was undoubtedly influenced by the role of mangosteen pericarp in reinforcing delusional thinking and a recruitment helper who requested that participants remain on the study until 90 days. The trial involved a single site. The effectiveness of mangosteen pericarp has therefore not been tested among a highly compliant cohort and could benefit from replication in a multisite study. Also, this study represented the first time that mangosteen pericarp has been tested in this cohort, so it is likely to produce high effect sizes.

There is no guarantee that participants took their allocated intervention, even if they did return their allocated containers. However, the response rates do not support that this hypothesis. Sources of bias, imprecision and multiplicity of analyses represented potential limitations on the study. The following section will explain how potential limitations were managed.

5.3.1. Sources of potential bias

Effects of attrition across the groups were assessed by conduction of a completer's analysis. Reasons for non-enrolment into the study were explored. Non-consent, which included co-dependant relationships with close others, was the major factor preventing enrolment. The accuracy of data was crosschecked by the study physician across 10% of interviews. This was crosschecked against the data collected by the researcher in the field, and any discrepancy was arbitrated. Situational containments (contributors to measurement errors) have been known to arise when the person is aware that they are being interviewed. The study was conducted in a manner that facilitated participant comfort by having interviews conducted at a place of the participant's choosing, by engaging with the participant in partnership formation so that they had a vested interest in the research and by the relaxed, informal manner in which the interviews were conducted. Factors causing interference in interviews over time were dealt with by randomisation. The placebo and pericarp groups were truly blind. One researcher conducted all interviews to manage the risk of inconsistent interview administration. All items used to measure the outcomes were standardised and operationalised.

Response rates to enrolment in the study were assessed and presented as recruitment and participant flow. The rate of participant enrolment was 44.00%, evidenced by the sample description at baseline. The overall characteristics of the sample population were described at baseline and conform to the characteristics of the known target population. However, gender differences (47.40% male; 52.60% female) were slightly less than the distribution known for schizophrenia. There were negligible baseline differences between the groups. Selection of study participants occurred over an 11-month period, and was associated with modest attrition figures. Social desirability was probably not a concern for the study, as the study interviews were conducted in isolation and the outcome measures used in the interviews were operationalised. However, given the dynamic nature of the Internet and the selection process, it would be difficult to conclude definitively that this was so.

5.3.2. Imprecision

The researcher was trained in the administration of the PANSS primary outcome measure to minimise mistakes in reliability. In addition, data were entered twice prior to analysis and cleaned of any recording discrepancies prior to being locked.

5.3.2.1. Multiplicity of analyses

Both internal and external validity were ascertained to support the viability of the study results. The researcher attempted to minimise testing and regression artefacts by the use of outcome measures with established reliable Cronbach's alpha scores. The study was capable of supporting statistical conclusions and providing results that were both valid and reliable. Our sample size was calculated for a pilot study. Given the large effect size of our primary indicator (PANSS total = 1.41), 12 participants per group were required to support our power analysis. Our sample size was thus adequately powered.

5.3.2.2. Threats to internal validity

Management of tardive dyskinesia by physicians may have been confounding, as the two groups behaved non-significantly over time (p = 0.16). Researcher observations suggest that certain events during the course of the experiment were likely to provide stress to participants such as, the belief that the end of the world would occur on the 21th December, 2012. The study protocol was blinded so the researcher was unaware of the group selection prior to the completion of the study and the data analysis. The outcome measures used were operationalised, valid and reliable to account for any changes that occurred. Testing plots of mean estimates across outcome measures indicated a steep change at 90 days comparative to baseline scores across multiple outcome measures. However, this pattern is likely to be a consequence of treatment effect. The scores for 150 days and 180 days suggest that this threat was minimised over time. Outlying scores were not removed during the statistical analysis. Descriptive analysis and the presence of a consistent pattern of graph results across multiple outcome measures supported this decision. Methods employed by the researcher to reduce potential threats such as testing and regression artefacts have been outlined, and suggest that accumulative events were minimal. Systemic threats were controlled by the use of operationalised outcome measures.

5.3.2.3. Generalisability and external validity

The characteristics of the study sample were described at baseline. A key aspect of the study setting was that it was conducted from a university campus. A determinant of the study results was that the actual interview sites involved a variety of geographical locations in both urban and

rural settings. Health services within the region investigated included an inpatient facility and broader community facilities. Resources required in the naturalistic setting are unlikely to differ between study settings; for example, transport and access to the outcome measure templates (available on the internet). The results are capable of impacting the target population via multimedia and word of mouth. In sum, the choice of setting for the study was not too narrow and so is likely to support the generalisability of the results from the study.

The external validity of the study was determined by examining the population, setting, treatments, outcome measures and times. The sample at baseline indicates that randomisation was successful across treatment groups, which were drawn from an experimentally accessible population. Evidence that the study sample was drawn at random from the target population comes from the similarities in demographic characteristics to that target population. An exception was the finding that gender was not evenly distributed in the cohort, comparative to widely accepted incidence and prevalence figures that suggest that gender is evenly distributed in the target population (Ochoa et al. 2012). The study represented inhabitants of both urban and rural ecological settings to support ecological validity. With the use of a variety of ecological settings, it is plausible that the results may differ from a cohort with different antipsychotic drug treatment patterns. There was no significant difference between treatment groups living in rural and urban settings. The results of outcome measures supported temporal validity, as the data were analysed over a period of 180 days from baseline.

Variation in treatments was evidenced by testing the study intervention as an adjunctive to second-generation antipsychotic drugs. Second-generation antipsychotic drugs prescribed among the cohort were risperidone, clozapine, olanzapine, quetiapine and aripiprazole. Outcomes were obtained across different but related variables, as outcome measures demonstrated a similar pattern across multiple measures. The assessment of external validity for the study indicated that study participants were drawn from an experimentally accessible population. Our findings were externally valid across all indices.

5.4. Clinical implications of the findings

Given the consistent pattern in reporting across multiple outcome measures, these data support modulation of multiple symptom domains of schizophrenia, afforded by 1000mg/day encapsulated mangosteen pericarp over a 180-day period. Our findings in relation to core symptom domains, functionality and well-being may be related to improved glutathione and glutathione S-transferase levels, which are *in vitro* effects of mangosteen; however, this is speculative. This finding suggests that neuronal protection and the induction of mitochondrial

repair mechanisms might have occurred, although this would have to be tested for in future pre-clinical studies.

These results have provided evidence of clinical efficacy for mangosteen pericarp in schizophrenia. Evidence for this finding came from analysis of the primary outcome measure. Reductions in unwanted effects from second-generation antipsychotic drugs were found. The significance of these findings will only be established with the passage of time, as they warrant further investigation beyond that which can be answered in a single study.

5.4.1. Families and carers

Mangosteen pericarp is potentially meaningful in terms of the reduction of burden and improved quality of life among the cohort and caregivers. In their seminal paper, Provencher and Mueser (1997) link positive and negative symptoms to increased burden on families. Our findings indicate that core symptoms and measures for functionality and well-being were significantly improved, with a large effect size, by treatment with mangosteen pericarp. In relation to the chronicity of schizophrenia, cognitive functioning is thought to influence adaption and skills training for persons with this disorder (Bowen et al. 1994). Various groups have identified relationships between functionality and the lived experience of schizophrenia. Relationships between aspects of functionality and symptoms in schizophrenia have been established as clinically meaningful (Pandina et al. 2013). These aspects of the disorder have been linked to quality of life for persons living with schizophrenia (Karadayı, Emiroğlu & Üçok 2011). Nevertheless, the burden of families has been well documented. Foldemo et al. (2005) are concerned with quality of life aspects of caring for persons diagnosed with schizophrenia. The assumption could be made that a reduction in carer burden would indirectly lead to improvements in carer quality of life. However, further work is required to test this assumption.

5.4.2. Mental health services

The availability of effective treatments is meaningful to persons with schizophrenia. There have been no major breakthroughs in the treatment of schizophrenia since the inception of chlorpromazine in the 1950s. More recently, pharmaceutical companies have failed to discover adequate novel treatment options or to greatly reduce unwanted effects from use of second-generation antipsychotic drugs. The result has been a limited quantity of novel treatment options available for clinical use that are well tolerated. This study provides a novel treatment option for schizophrenia that demonstrates clinical efficacy. The high level of adherence suggests that the intervention was well tolerated. The study intervention was delivered safely. This dissertation

thus provides preliminary evidence to inform and guide future directions of mental health service delivery for those persons in the chronic stages of schizophrenia.

5.5. Recommendations

This study has contributed to the collective understanding of schizophrenia and provided some interesting outcomes to direct future work in the field, including that involving other brain disorders and mangosteen pericarp in relation to the prevention of mental health disorders.

5.5.1. Research

As this was a pilot study, a similar study with a much larger sample is needed to confirm our results and facilitate the incorporation of mangosteen pericarp into clinical practice. Pre-clinical studies using rodent modelling are imperative to provide evidence of mechanisms of action in relation to mangosteen pericarp. The glutathione system needs to be explored for potential biomarkers in schizophrenia. The potential of mangosteen pericarp for the treatment of other neuropsychiatric disorders needs to be assessed.

5.5.2. Education

Information about the nexus between schizophrenia and mangosteen pericarp should be made available to practitioners and educators for consideration.

5.6. Thesis summary

Our study hypothesis was that mangosteen pericarp would improve measures of therapeutic outcome in relation to the symptoms of schizophrenia for the cohort by 180 days comparative to placebo. This hypothesis is supported by significant findings across the primary outcome measure and multiple secondary outcome measures, supporting the efficacy of 1000mg/day of encapsulated mangosteen pericarp compared to the placebo group in the cohort tested. It was further hypothesised that mangosteen pericarp would reduce the unwanted effects from second-generation antipsychotic drugs over a 180-day period compared to the placebo. Our data indicate significant improvement in side effects scored by LUNSERS. Changes to tardive dyskinesia were differentially expressed.

This dissertation aimed to address the unmet needs of persons with schizophrenia in relation to residual core symptom domains and functionality. The neurobiology common to schizophrenia and mangosteen pericarp was explored. A review of the literature highlighted an impairment of antioxidant defenses that increased susceptibility to oxidative stress and a persistently evoked oxidative shield, for which mitochondria alter metabolites. Alterations to neurotransmission, multiple metabolites and neuronal damage are thought to be characteristic of schizophrenia. The available literature also reveals that neuronal and antioxidant signalling is chronically inhibited in schizophrenia and linked to architectural changes within the brain. Previous attempts to address the concern have tested for the modulation of glutathione metabolism. The current approach aimed to protect against oxidative stress via a mitochondrial pathway. Secondary metabolites from the pericarp of mangosteen fruit were supplemented in people with schizophrenia. Mangosteen pericarp was chosen because it was anecdotally supported, contains astringent properties and unique prenylated xanthene. A clinical trial was conducted.

Our aims were met with regard to a reduction of core symptom domains and improvements on measures of functionality and well-being, as these were supported by our data. These findings were present in the total cohort analysed and were mirrored across monotherapy in the groups, with the exception of measures for mood and tardive dyskinesia. This statement is evidenced by data that establishes efficacy supported by a very large effect size, the significance of the primary indicator and the attainment of a high level of adherence for the intervention. Safe delivery of the intervention was demonstrated.

The findings of this study are capable of a reduction of core symptoms and increased quality of life and improved functionality in the cohort. In addition, mangosteen pericarp is likely to be a well-tolerated and clinically efficient treatment option which is capable of helping to meet the needs of persons with schizophrenia. Therefore, mangosteen pericarp does have a positive effect in schizophrenia.

Final Word:

'Schizophrenia may no longer be viewed as a syndrome devoid of all hope.'

Wendy Laupu (2014)

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Appendices

These appendices consist of interview sheets used in data gathering for the clinical trial. These forms are unformatted for this thesis and may include small errors (American spelling) as they were presented to the Human ethics committees. The forms are operational and standardised forms that are internationally accepted for the assessment of persons diagnosed with schizophrenia. GAF interview forms remain the property of the Washington Mental Health Research Institute and are available:

Desk Reference to the Diagnostic Criteria from DSM-IV-TR pp 44–48. (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington DC: American Psychiatric Association, 2000.

Appendix A - *Consent form*

Appendix B – *Demographic information sheet*

Appendix C – *PANSS Interview and note-taking*

Appendix D – *PANSS*

Appendix E – *PANSS Rating*

Appendix F – *Montgomery-Asberg Depression Rating Scale*

Appendix G – *Clinical Global Impression (Severity and Improvement)*

Appendix H – *Self-Rated Life satisfaction Scale*

Appendix I – *LUNSERS Score sheet*

Appendix J – *LUNSERS*

Appendix K – *AIMS Examination Procedure*

Appendix L - *AIMS*

Participant Information and Consent Form

Study Title: The efficacy of *Garcinia mangostana* L. (mangosteen) pericarp as an adjunct with second generation antipsychotics for the treatment of schizophrenia: a double-blind, randomized, placebo controlled trial

Funding Body: James Cook University, VitalXan

Investigators: Principal Investigator: Professor Kim Usher.
Associate Researcher (s): Wendy Laupu (PhD candidate), Professor Michael Berk, Dr Olivia Dean

Site: Geographical area within 100 kilometre radius of Cairns, Grafton Street post office, excluding the Coral Sea in Far North Queensland, Australia.

The results of this research will be used by the researcher Wendy Laupu to obtain a Docurate of Philosophy degree, in nursing with the James Cook University. This research has been initiated by the investigator, Wendy Laupu, a registered nurse at Cairns Base Hospital and a PhD student of the James Cook University, who has an ongoing clinical and research interest in schizophrenia.
The research project is funded by a donation from the VitalXan company and James Cook University.
This research is being co-ordinated by James Cook University with associated researchers from Barwon Health Service, Geelong and Orygen Research Centre of Melbourne University.

Introduction

You are invited to take part in this research project. THIS STUDY INVOLVES THE RESEARCH OF THE EFFECT OF MANGOSTEEN FRUIT RIND ON THE CORE SYMPTOMS OF SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHICH YOU EXPERIENCE AND SECONDARILY, THE SIDE EFFECTS OF YOUR ATYPICAL ANTIPSYCHOTIC MEDICATION.

This medication is:
amisulpride (solian), aripiprazole (abilify), asenapine (saphris), blonanserin (lonasen), clotiapine (entumine), clozapine (clozaril), illoperidone (fanapt), mosapramine (cremin), olazapine (zyprexa), paliperidone (invega), perospirone (lulbu), quepin (specifer), quetiapine (seroquel), remoxipride (roxiam), risperidone (risperdol), sertindole (serdolect), sulpiride (sulpirid or eglonyl), ziprasidone (geodon or zeldox), zotepine (nipolept).

You are invited to participate in this research project because your treating psychiatrist has previously given you a diagnosis of schizophrenia or schizoaffective disorder.

This participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this Participant Information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part you might want to talk bout it to a relative, friend or healthcare worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you will be telling us that you understand what you have read and that you give your consent to participate in the research project and the research processes that are described. You will be given a copy of this Participant Information and Consent Form to keep as a record.

Background

Scientific research has shown second generation antipsychotic medications do not always provide adequate therapy for every person with schizophrenia. This study proposes to assist your current antipsychotic treatment by adding a dietary supplement (or a placebo) to your treatment regime. The treatment is an extract from the mangosteen fruit and is called mangosteen pericarp. Mangosteen pericarp is produced from the outer rind of the mangosteen fruit and may be useful in crossing the blood brain barrier. Other antioxidants do not actively enter the brain when taken in oral form.

Participation in this study will involve taking either two placebo or mangosteen pericarp capsules once a day for 180 days. 180 days has been shown in a previous study to be the length of time required for you to have the balance between pro and antioxidants, restored in your body.

Oxidative stress is believed to be one factor that impacts on the symptoms you experience. When the levels of antioxidants in the brain are decreased or the levels of oxidants (free radicals) are increased the balance is shifted and may lead to cellular damage. This is known as oxidative stress. The main antioxidant in your body, glutathione has been found to be decreased in several studies involving people with schizophrenia. Additionally, lifestyle factors including smoking, cannabis and other illicit substances, alcohol, stress, a high fat diet and lack of exercise can increase the levels of oxidative stress, and inflammation within your cells. We believe mangosteen pericarp may help to reduce oxidative stress and sub-clinical inflammation.

We have found scientific evidence which leads us to think that schizophrenia may the result of nerve impulses being initiated by a different pathway to other people, which is also activated by long term use of the medications. We hope that mangosteen pericarp

may reduce the activation of the wrong pathway and activate the ordinary pathway to provide neuroprotection. However, we do not know exactly what effect this may have on your schizophrenia.

Purpose

The purpose of this project is to find out whether mangosteen pericarp is able to have an effect on the symptoms of schizophrenia that remain despite your use of antipsychotic medication, and that this is safely delivered. A second purpose is to note if the mangosteen pericarp has any effect on the side effect profile of the antipsychotic medication that you have been prescribed by your treating doctor. We expect to find that as mangosteen pericarp decreases the reported symptoms of participants, when compared to the placebo and that the side effect profile will decrease from baseline. We are interested to study these matters because we believe that a tolerable and practical treatment option is what you as consumers, request. We expect that approximately one hundred people will participate in this project.

Procedures

Participation in this project will involve 4 separate interviews at the same time as you consent, after 3 months, 5 months, and at the end of the trial. These interviews are anticipated to take 2 hours, then 1 hour respectively. You are welcome to have breaks as you need during this process.

Blood tests will be requested before and after the trial. These bloods will be stored at -80 C degrees for collective analysis at the end of the trial.These blood tests will include markers of protein carbonylation such as, ELISA assay; plasma protein levels including, C-reactive protein. C-reactive protein has been associated with severe schizophrenia, metabolic processes, and side effects of medication.

At monthly intervals, either the mangosteen pericarp or placebo treatment that has been assigned to you, will be delivered by Wendy Laupu and an opportunity to discuss any questions or concerns will be provided.

The randomization procedure will use computer generated tables to assign a study treatment to you. This will be either the placebo or mangosteen pericarp treatment. The pharmacist will be the only person to know which study treatment you are taking, until the time of statistical analysis, at the end of the study. A study number will be assigned to you by the pharmacist. When you consent to join the study, you will be allocated the next number in the sequence provided by the pharmacist.

Follow-up after the treatment intervention will include contact from Wendy Laupu, approximately one month after completion to answer any questions and provide support.

You will not be paid for your participation in this research, however upon induction and completion a $25 gift voucher of appreciation will be given to you. An Aboriginal and Torres Strait Islander mental health support worker is available.

Consent to provide blood samples

The collection of blood forms a mandatory component of the project. The blood collected will be used for research related purposes alone. The blood samples will not be identifiable, as only the study code and your date of birth will be used to identify the samples. Thus, confidentiality will be maintained as the laboratory will not know your name and address and you will be identified at the laboratory by your study code and date of birth. The only commercial use of your blood samples will be as published material in a peer-reviewed journal article, which will be available for marketing purposes. The blood samples will be discarded by the laboratory, in line with standard practice and at the conclusion of laboratory analysis.
You will be asked to provide additional consent for the collection of your blood during the research project. These blood tests will be free of charge.

Risks and Discomforts

Possible Risks

While we foresee minimal risk in taking part in this study, this is an experimental treatment and some risks cannot be foreseen.

It is possible that you will experience discomfort during the course of blood tests. Having blood taken may cause some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which blood is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated. To minimise the occurrence of discomfort when having a blood test, we ask that you drink at least two glasses of water prior to the test, as you would when you have other blood tests. We plan to minimise any discomfort by directing you to a local blood laboratory for the testing which will be conducted by trained technicians who take blood on a regular basis.

The effects of mangosteen pericarp on the unborn child and on the newborn are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will re required to undergo a pregnancy test prior to commencing the research project. If you are male you should not father a child during the course of the study. Both male and female participants are strongly advised to use effective contraception during the course of the research for a period until the completion of the study. You should advise your treating doctor immediately if you become pregnant or father a child. Your doctor will withdraw you from the study and advise on further medical attention should this be necessary.

If you become upset or distressed as a result of your participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by persons who are not members of the research team. In addition, you may prefer to suspend or end your participation in the research if distress occurs.

There may be additional risks that the researchers do not expect or do not know about. Tell a member of the research team immediately about any new or unusual symptoms that you get.

Significant New Findings

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss whether this new information affects you.

Possible Benefits

We cannot guarantee or promise that you will receive any benefits from this research.

However, possible benefits may include that the mangosteen pericarp adjunctive treatment will improve your symptoms of schizophrenia or schizoaffective disorder and hence your clinical outcome. The reduction of side effects form a longterm goal of this project as a natural, tolerable and practical treatment option for persons diagnosed with schizophrenia or schizoaffective disorder.

Other treatments during this research project

It is important to tell your doctor and the research staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the research staff about any changes to these during your participation in the research. Changes in your treatment will not necessarily mean that you must discontinue your participation in this research project.

Alternative treatments

Your medical assessment and treatment will in no way be altered by your decision whether or not to take part, or by your answers to the questions. No additional tests, investigations or treatment will be involved other than those already described. The questions will be asked by a Registered nurse and confidentiality will be maintained by the use of a number, allocated to you for all trial documentation.
The questionnaires ask about your age, sex, marital, employment, housing status and about the disease, if any family members also have schizophrenia and to provide medical background of disease, length of time and nature of the illness. The questions are of a nature very similar to those you might routinely be asked by your treating psychiatrist or nurses caring for you in hospital because of your schizophrenia or schizoaffective disorder. Additionally the nature of prescribed and complementary medication, dietary supplements that you are taking, any side effects will be asked.
You do not have to participate in this research study to receive treatment for your condition. Other medications and treatments are available. You should discuss these alternative treatments with your treating doctor.

Voluntary Participation and Withdrawal

Participation in any research project is voluntary. if you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment or your relationship with those treating you or your relationship with Queensland Health or James Cook University.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw.

This notice will allow that person or the research supervisor to inform you of there are any health risks or special requirements linked to withdrawing.

If you decide to leave the project, the researchers would like to keep the information gathered about you and your blood samples that have been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them before you join the research.

Your study clinician may end your participation in this research program for any reason that they feel is appropriate. These may include but are nor limited to an adverse event, injury, a medical condition which may place you at risk of further complications if you continue to participate, failure to take the dietary supplement as instructed, or termination of the study by the investigators or for other administrative reasons.

Privacy, Confidentiality and Disclosure of Information

Data will be collected on data sheets which will be sent directly to the principle investigator. Data sheets will be stored in a secure locked cabinet. You are being asked for specific use of your data, for this project only.

In accordance with the Information Privacy Act (2009) you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

Confidentiality and Access to Your Records

Records of your participation in this study will be held confidential so far as permitted by law. This will include de-identification of all documents relating to the trial by assigning you a random number that will identify you in terms of a data set and not an individual. However, your research investigators, regulatory agencies, James Cook University Human Ethics committee and the Cairns Base Hospital Research and Ethics Committee, will be able to inspect and have access to confidential data that identifies you by name. Any analysis, interpretation and publication of information collected during this trial pursuant with the Information Privacy Act (2009). Records relating to the results of the study will be kept for 15 years, and you may access that information if required.

Results of this Project

We plan to notify participants of the outcome of this research in general, by speaking at consumer group meetings or being available to provide direct feedback upon request. We anticipate that the findings of this research will be made available to consumer groups as a leaflet, free of charge and this research will be published in peer-reviewed journals to facilitate professional understanding of our findings. Wendy Laupu's thesis will be available on-line as part of the Australian Digital Thesis program. The findings, of the study, once published will be available to the Vitalxan company, for the purpose of marketing as they have generously provided support to enable this project to occur. No identifiable information of participants will be provided to the Vitalxan company.

Injury During Trial

In the event that you suffer an injury as a result of participating in this trial, hospital care and treatment will be provided at no extra cost if you elect to be treated as a public patient at the public health service. If you would like to continue with this dietary supplement at the end of the trial it is available for purchase over the internet, however to the best of our knowledge, 180 days is a treatment.

Questions

The outline of the research study has been described to you in this consent form. For additional information and answers to questions regarding this research study or if you experience any medical problems, please contact:

Professor Kim Usher

- **Phone - 40421391**
- **Email: kim.usher@jcu.edu.au**

Wendy Laupu

- **Phone - 0413 632 907**
- **Email: wendy.laupu@jcu.edu.au**

If you seek emergency care, or if hospitalisation is required, please alert the treating doctor that you are enrolled in a research project conducted by Professor Kim Usher. You will be provided with a wallet card to help you to do so.

This project will be carried out according to the National Statement of Ethical Conduct in Research Involving Humans (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of Cairns Base Hospital and the Human Research Ethics Committee of James Cook University. If you have any complaints about any aspect of the project, the way it is being conducted or any questions abour your rights as a research participant, then you may contact:

The chairperson of the Human Research Ethics Committee, Cairns Base Hospital; phone: 4226 8011

OR

The chairperson of the Human Research Ethics Committee, James Cook University; phone: 4781 6108

You will need to tell either of these chairpersons the name of one of the researchers given in this section above.

CONSENT FORM

Study Title: The efficacy of *Garcinia mangostana* L. (mangosteen) pericarp as an adjunct with second generation antipsychotics for the treatment of schizophrenia: a double-blind, randomized, placebo controlled trial.

I have read, or have had read to me this document and I understand the purposes, procedures and risks of this research project (Version 13 dated 18 February, 2011) as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I understand that I will be given a signed copy of this document to keep.

I understand that the researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

I understand that I am required to provide a blood sample for this project.

I consent to allow the investigators of this research to keep any information and blood samples in the event that I withdraw from this study.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date (participant to date)

_____ _____
Signature of Witness Date (witness to date)

_____ _____
Signature of investigator Date (investigator to date)

Participant ID: _____

Template For Clinical Non-Drug/Device Research Projects available from Queensland Health.

DEMOGRAPHICS
MANGOSTEEN-SCHIZOPHRENIA TRIAL

PARTICIPANT NUMBER _____

- AGE _____
- SEX _____
- MARTIAL STATUS _____
- HOUSING _____
- EMPLOYMENT _____
- MEDICAL HISTORY _____

_____

_____

- CLOSE FAMILY WITH SCZ/SCZAFFECTIVE Y N
- ONSET OF PRODROMAL SYMPTOMS _____
- DURATION OF DISEASE _____
- FREQUENCY OF HOSPITAL ADMISSIONS _____

_____

_____

- PRECIPATATING FACTORS _____

_____

- SMOKER Y N
- ALCOHOL _____
- MEDICATIONS _____

_____

_____

- ILLICT SUBSTANCE USE Y N
- COMPLEMENTARY ALTERNATIVE MEDICINE _____

_____

_____

- DIETARY SUPPLEMENTS _____

_____

_____

WEIGHT _____

VITAL SIGNS: Temp ..... BP ...../..... Resp..... Pulse.....

Mangosteen pericarp-SCHIZOPHRENIA TRIAL

PANSS Interview Sheets

	Participant ID#

PANSS INTERVIEW RESULTS

Note-taking sheets (1)

1.Awareness of Dx – fully – slight – unaware
2.Awareness of severity of illness – fully – slight – unaware
3.Awareness of benefit of medication – fully – slight – unaware
4.Plans for next few days to next few weeks – yes – no
Details:
5.Plans for next month or later in the year – yes – no
Details:
6.Strange experiences – yes – no
Details:
7.Strange noises – yes – no
Details:
8.Communication from radio, TV, God, newspaper etc. – yes – no
Details:
9.Voices – yes – no
9 (a) How many?
9 (b) Male or female or both?
9 (c) Loud or soft?
9 (d) Clear or vague?
9 (e) Good or bad?
9 (f) Fear?
9 (g) Content? Orders/directives?
Version 27 dated 18.02.2011 Page 1 of 4

Mangosteen pericarp -SCHIZOPHRENIA TRIAL	
PANSS Interview Sheets	
Participant ID#	
PANSS INTERVIEW RESULTS	
Note-taking sheets (2)	
10. Visions – yes – no	
Together with voices? What? How clear?	
Details:	
11. Smells – yes – no	
Details:	
12. Sensations – yes – no	
Details:	
13. Where do the voices &/or visions and/or smells and/or sensations come from?	
Details:	
14. Do you think you are being controlled or possessed?	
Details:	
15. Thoughts when on own?	
Details:	
16. Philosophy and/or beliefs?	
Details:	
Version 27 dated 18.02.2011 Page 2 of 4	

PANSS INTERVIEW RESULTS

Note-taking sheets (3)

Participant ID#	

17. Relations with family and friends and others?

(Alone or with others; Trust or distrust; Fear; Speak behind back; Spying; Plotting)

Details:

18. Grandiosity?

(Special talents/abilities/powers/ESP/mission; Morals; relation to God; Fame/Wealth/TV/Newspaper/Stage/Radio)

Details:

19. Guilt?

(Worthiness; bad person; past guilt; punishment; suicide)

Details:

20. Depression?

(Mood/Happy/Sad/High/Low/Weepy/Appetite/Sleep/Work)

Details:

21. Anxiety?

(Worries/Nerves/Tension/Panic/Tremor/Shakes/Sweats)

Details:

22. Orientation?

Details:

23. Similarities & Proverbs?

Details:

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

Participant ID# _____

CARD NUMBER

POSITIVE SCALE (P)

P1 Delusions
Beliefs which are unfounded, unrealistic, and idiosyncratic. Basis for rating: thought content expressed in the interview and its influence on social relations and behaviour.

P2 Conceptual disorganization
Disorganized process of thinking characterized by disruption of goal-directed sequencing, eg. Circumstantial, tangential, loose associations, thought block. Basis for rating: cognitive-verbal processes observed during the course of interview.

P3 Hallucinatory behaviour
Verbal report or behaviour indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory or somatic realms. Basis for rating: verbal report and physical manifestations during the course of interview as well as reports of behaviour by primary care workers or family.

P4 Excitement
Hyperactivity as reflected in accelerated motor behaviour, heightened responsivity to stimuli, hypervigilance, or excessive mood lability. Basis for rating: behavioural manifestations during the course of interview as well as reports of behaviour by primary care workers or family.

P5 Grandiosity
Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame power, and moral righteousness. Basis for rating: thought content expressed in the interview and its influence on behaviour.

P6 Suspiciousness/persecution
Unrealistic and exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean one harm. Basis for rating: thought content expressed in the interview and its influence on behaviour.

P7 Hostility
Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behaviour, verbal abuse, and assaultive. Basis for rating: interpersonal behaviour observed during the interview and reports by primary care workers or family.

NEGATIVE SCALE (N)

N1 Blunted affect
Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings, and communication gestures. Basis for rating: observation of physical manifestations of affective tone and emotional responsiveness during the course of the interview.

N2 Emotional withdrawal
Lack of interest in, involvement with, and affective commitment to life's events. Basis for rating: reports of functioning from primary care workers or family and observation of interpersonal behaviour during the course of the interview.
N3 Poor rapport
Lack of interpersonal empathy, openness in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. Basis for rating: interpersonal behaviour during the course of interview.
N4 Passive/apathetic social withdrawal
Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition. This leads to reduced interpersonal involvements and neglect of daily activites.
N5 Difficulty in abstract thinking
Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problem-solving tasks. Basis for rating: responses to questions on simularities and proverb interpretation, and use of concrete vs abstract mode during the course of interview.
N6 Lack of spontaneity and flow of conversation
Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactional process. Basis for rating: cognitive-verbal processes observed during the course of interview.
N7 Stereotyped thinking
Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. Basis for rating: cognitive-verbal processes during the course of interview.

GENERAL PSYCHOPATHOLOGY SCALE (G)

G1 Somatic concern
Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease. Basis for rating: thought content expressed in the interview.
G2 Anxiety
Subjective experience of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. Basis for rating: verbal report of guilt feelings during the course of interview and the influence of attitudes and thoughts.
G3 Guilt feelings
Sense of remorse or self-blame for real or imagined misdeeds in the past. Basis for rating: verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.
G4 Tension
Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, or profuse sweating and restlessness. Basis for rating: verbal report attesting to anxiety and thereupon, the severity of physical manifestations of tension observed during the interview.

G5 Mannerisms and posturing
Unnatural movements or posture as characterized by an awkward, stilted, disorganized or bizarre appearance. Basis for rating: observation of physical manifestations during the course of interview as well as reports from primary care workers or family.
G6 Depression
Feelings of sadness, discouragement, helplessness and pessimism. Basis for rating: verbal report of depressed mood during the course of interview and its observed influence on attitude and behaviour.
G7 Motor retardation
Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. Basis for rating: manifestations during the course of interview as well as reports by primary care worker or family.
G8 Uncooperativeness
Active refusal to comply with the will of significant others, including the interviewer, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. Basis for rating: interpersonal behaviour observed during the course of interview as well as reports by primary care workers of family.
G9 Unusual thought content
Thinking characterized by strange, fantastic, or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical and patently absurd. Basis for rating: thought content expressed during the course of interview.
G10 Disorientation
Lack of awareness of one's relationship to the milieu, including persons, place, and time which may be due to confusion or withdrawal. Basis for rating: responses to interview questions and orientation.
G11 Poor attention
Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli. Basis for rating: manifestations during the course of interview.
G12 Lack of judgement and insight
Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognize past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalization or treatment, decisions characterized by por anticipation of consequences, and unrealistic short-term and long-range planning. Basis for rating: thought content expressed during the interview.
G13 Disturbance of volition
Disturbance in the wilful initiation, sustenance, and control of one's thoughts, behaviour, movements, and speech. Basis for rating: behaviour during the course of interview and reported by primary care worker or family.
G14 Poor impulse control
Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary, or misdirected discharge of tension and emotions without concern about consequences. Basis for rating: behaviour during the course of interview and reported by primary care workers or family.

G15 Preoccupation
Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behaviour. Basis for rating: interpersonal behaviour observed during the course of interview.
G16 Active social avoidance
Diminished social involvement associated with unwarranted fear, hostility, or distrust. Basis for rating: reports of social functioning by primary care worker or family.

Mangosteen Pericarp-Schizophrenia Trial

PANSS RATING SCALE

PATIENT ID#				*DATE*	

Instructions: Circle the appropriate rating score for each item for each dimension following the specified clinical interview.

Refer to the Rating Manual for item definitions, description of anchoring points, and scoring procedure.

1=Absent 2=Minimal 3=Mild 4=Moderate 5=Moderate Severe 6=Severe 7=Extreme

	POSITIVE SUBSCALE							
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual Disorganization	1	2	3	4	5	6	7
P3	Hallucinatory Behavior	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/Persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
	NEGATIVE SUBSCALE							
N1	Blunted Affect	1	2	3	4	5	6	7
N2	Emotional Withdrawal	1	2	3	4	5	6	7
N3	Poor Rapport	1	2	3	4	5	6	7
N4	Passive/Apathetic Social Withdrawal	1	2	3	4	5	6	7
N5	Difficulty in Abstract Thinking	1	2	3	4	5	6	7
N6	Lack of Spontaneity and Flow of Conversation	1	2	3	4	5	6	7
N7	Stereotyped Thinking	1	2	3	4	5	6	7
	GENERAL PSYCHOPATHOLOGY							
G1	Somatic Concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt Feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerism and Posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor Retardation	1	2	3	4	5	6	7
G8	Uncooperative	1	2	3	4	5	6	7
G9	Unusual Thought Content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor Attention	1	2	3	4	5	6	7
G12	Lack of Judgement and Insight	1	2	3	4	5	6	7
G13	Disturbance of Volition	1	2	3	4	5	6	7
G14	Poor Impulse Control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7

G16 Active Social Avoidance	1	2	3	4	5	6	7

	TOTAL	PERCENTILE	RANGE
Positive Scale Score			
Negative Scale Score			
Composite Score (Pos. - Neg. Scores)			
General Psychopathology Score			
Number of Positive Symptoms Rated > 3			
Number of Negative Symptoms Rated > 3			
SYNDROMAL CLASSIFICATION:			

Participant ID# _____ Date _____

MONTGOMERY-ASBERG DEPRESSION SCALE (MADRS)

Instructions: The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The investigator must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). It is important to remember that it is only rare on the items in the scale. If definite answers cannot be elicited from the participants, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice. This scale may be used for any time interval between ratings, but this must be recorded.

1. *Apparent sadness*

Representing despondency, gloom and despair reflected in speech, facial expression and posture. Rate; on depth and inability to brighten up.

0 = No sadness
1
2 = Looks dispirited but does brighten up without difficulty
3
4 = Appears sad and unhappy most of the time
5
6 = Looks miserable all the time, extremely despondent.

2. *Reported sadness*

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 = Occasional sadness in keeping with the circumstances
1
2 = Sad or low but brightens up without difficulty
3
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances
5
6 = Continuous or unvarying sadness, misery or despondency

3. *Inner tension*

Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 = Placid. Only reflecting inner tension.
1
2 = Occasional feelings of edginess and ill-defined discomfort
3
4 = Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances
5
6 = Continuous or unvarying sadness, misery or despondency.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the participant's own normal pattern when well.

0 = Sleeps as usual

1

2 = Slight difficulty dropping off to sleep or slightly reduced light or fitful sleep

3

4 = Sleep reduced or broken by at least two hours.

5

6 = Less than two or three hours sleep

5. Reduced appetite

Representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 = Normal or increased appetite

1

2 = Slightly reduced appetite

3

4 = No appetite. Food is tasteless.

5

6 = Needs persuasion to eat.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of intensity produced.

0 = No difficulties in concentrating

1

2 = Occasional difficulties in collecting one's thoughts.

3

4 = Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.

5

6 = Unable to read or hold a conversation without great initative.

7. Lassitude

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 = Hardly no difficulty in getting started. No sluggishness.

1

2 = Difficulties in starting activities

3

4 = Difficulties in starting simple routine activities which are carried out with effort.

5

6 = Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 = Normal interest in the surroundings and in other people.

1

2 = Reduced ability to enjoy usual interest.

3

4 = Loss of interest in surroundings. Loss of feelings for friends and acquaintances.

5

6 = The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thought of guilt. Inferiority, self-reproach, sinfulness, remorse and ruin.

0 = No pessimistic thoughts.

1

2 = Fluctuating ideas of failure, self-reproach or self-depreciation.

3

4 = Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.

5

6 = Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not be in themselves influence the rating.

0 = Enjoys life or takes it as it comes.

1

2 = Weary of life. Only fleeting suicidal thoughts.

3

4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.

5

6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Total score: _____

Mangosteen pericarp-SCHIZOPHRENIA TRIAL						
Clinical Global Impressions						
CGI-Severity						
Patient ID#					***Date***	
Considering your total clinical experience, how MENTALLY ILL is the patient at THIS time? ***Check only ONE item***						
	1	***Normal and not ill at all***				
	2	***Borderline mentally ill***				
	3	***Mildly mentally ill***				
	4	***Moderately mentally ill***				
	5	***Markedly mentally ill***				
	6	***Severely mentally ill***				
Notes:						
Rating:						

Mangosteen pericarp-SCHIZOPHRENIA TRIAL					
Clinical Global Impressions					
CGI-Improvement					
Patient ID#		***Date***			
Compared to the patient's condition at baseline, how much has the severity of the patient's illness changed over time? Check only ONE item					
	0	***Not assessed***			
	1	***Very much improved***			
	2	***Much improved***			
	3	***Minimally improved***			
	4	***No change***			
	5	***Minimally worse***			
	6	***Much worse***			
	7	***Very much worse***			
Notes: ***NOT APPLICABLE FOR FIRST INTERVIEW***					

SELF-RATED LIFE SATISFACTION SCALE

Do you feel your life at present is:

Very interesting (1)	**Fairly interesting (2)**	**Fairly boring (4)**	**Very boring (5)**
Very happy (1)	**Fairly happy (2)**	**Fairly sad (4)**	**Very sad (5)**
Very easy (1)	**Fairly easy (2)**	**Fairly hard (4)**	**Very hard (5)**
Do you feel at the present moment that you are:	**Very lonely (5)**	**Fairly lonely (4)**	**Not lonely at all (1)**

The response 'cannot say' should be marked as a 3. If a response is missing 3 times then the scoring must be discarded due to missing data.
The range of possible scores is 4-20. Satisfied = 4-11; Dissatisfied = 12-20.
So, as the score increases, life satisfaction decreases.

Total score _____ **Life satisfaction rating _____**

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LUNSERS SCORE SHEET

Antipsychotic side effects	Extrapyramidal side effects
2 Difficulty staying awake during the day 4 Increased dreaming 9 Difficulty concentrating 14 Tension 18 Tiredness 21 Difficulty remembering things 23 Lack of emotions 26 Depression 31 Sleeping too much 41 Difficulty getting to sleep Possible range 0-40 Score _____	19 Muscle stiffness 29 Slowing of movements 34 Muscle spasms 37 Over wet or drooling mouth 40 Restlessness 43 Shakiness 48 Parts of the body moving of their own accord, eg. Foor moving up and down Possible range 0-40 Score _____
Hormonal side effects	**Anticholinergic side effects**
7 Swollen or tender chest 13 Period problems (f) 17 Increased sex drive 24 Difficulty in achieving climax 46 Reduced sex drive 50 Periods less frequent (f) Possible range 0-24 Female 0-16 Male Score _____	6 Dry mouth 10 Constipation 32 Difficulty passing water 38 Blurred vision 51 Passing a lot of water Possible range 0-20 Score _____
Miscellaneous side effects	**Other autonomic side effects**
5 Headaches 22 Losing weight 39 Putting on weight 44 Pins and needles Possible range 0-16 Score _____	15 Dizziness 16 Feeling sick 20 Palpitations 27 Increased sweating 35 Diarrhoea Possible range 0-20 Score _____
Red herrings	**Allergic reactions**
3 Runny nose 8 Chill blains 11 Hair loss 12 Urine darker than usual 25 Weak fingernails 28 Mouth ulcers 30 Greasy skin 33 Flushing of face 42 Neck muscles aching 45 Painful joints Possible range of 0-40 Score _____	1 Rash 35 Sensitivity to the skin 47 New or unusual skin marks 49 Itchy skin Possible range of 0-16 Score_____
Possible range of scores	**Total Score _____**
Rate the columns 0-4 Not = 0; Little = 1; Mod = 2; Lot = 3; Very = 4	Version 20 dated 28.01.2011 Page 1 of 1

LUNSERS

Version 21 dated 18.02.2011 Page 1 of 2

Participant ID Assessment date
Male
Female
Please indicate how much you have experienced each of the following symptoms in the last month by ticking the appropriate boxes.

		Not	Little	Mod	Lot	Very
1	Rash					
2	Difficulty staying awake in the daytime					
3	Runny nose					
4	Increased dreaming					
5	Headaches					
6	Dry mouth					
7	Swollen or tender chest					
8	Chill blains					
9	Difficulty concentrating					
10	Constipation					
11	Hair loss					
12	Urine darker than usual					
13	Period problems					
14	Tension					
15	Dizziness					
16	Feeling sick					
17	Increased sex drive					
18	Tiredness					
19	Muscle stiffness					
20	Palpitations					
21	Difficulty remembering things					
22	Losing weight					
23	Lack of emotions					
24	Difficulty achieving climax					
25	Weak fingernails					
26	Depression					
27	Increased sweating					
28	Mouth ulcers					
29	Slowing of movements					
30	Greasy skin					
31	Sleeping too much					
32	Difficulty passing water					
33	Flushing of face					
34	Muscle spasms					
35	Sensitivity to sun					
36	Diarrhoea					
37	Over-wet or drooling mouth					
38	Blurred vision					

39	Putting on weight					
40	Restlessness					
41	Difficulty getting to sleep					
42	Neck muscles aching					
43	Shakiness					
44	Pins and needles					
45	Painful joints					
46	Reduced sex drive					
47	New or unusual skin marks					
48	Parts of the body moving of their own accord, eg. Foot moving up or down					
49	Itchy skin					
50	Periods less frequent					
51	Passing a lot of water					

AIMS EXAMINATION PROCEDURE

The chair to be used in this examination should be a hard, firm one without arms.

1. Ask the participant whether there is anything in his/her mouth, and if there is remove it.
2. Ask participant about the current condition of his/her teeth. Ask participant if he/she wears dentures. Do teeth or dentures bother the participant now?
3. Ask participant whether he/she notices any movements in mouth, face, hands, or feet. If yes, ask to describe and to what extent they currently bother participant or interfere with his/her activities.
4. Have participant sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (look at entire body movements in this position).
5. Ask participant to sit with hands hanging unsupported (observe hands and other body areas).
6. Ask participant to open mouth (observe tongue at rest and repeat).
7. Ask participant to protrude tongue (observe for abnormalities of movement).
8. Ask participant to tap thumb with each finger, as rapidly as possible for 10-15 seconds: separately with right hand, then with left hand).
9. Flex and extend participant's left and right arms, one at a time (note any rigidity).
10. Ask participant to stand up (observe body areas in profile).
11. Ask participant to extend both arms outstretched in front with palms down (observe trunk, legs, and mouth).
12. Have participant walk a few paces, turn, and walk back to chair (observe hands, gait, and repeat).

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Participant ID# _____
Current medication & dose

Complete the examination procedure before entering these ratings

	None	Minimal	Mild	Moderate	Severe
Facial & oral movements					
1. Muscles of facial expression					
2. Lips & peri oral area					
3. Jaw					
4. Tongue					
Extremity movements					
5. Arms					
6. Legs					
Trunk movements					
7. Neck, shoulders, hips					
Overall severity					
8. Severity of abnormal movements					
9. Incapacitation					
10. Participant stated awareness of abnormal movements					
Dental status					
11. Current problems with teeth/dentures					
12. Usually wear dentures or not?					