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Interpreting outcomes from the supplementation of mangosteen rind powder capsules in schizophrenia and schizoaffective disorders

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ABSTRACT

The incorporation of a polymer into the spray drying process may have enhanced the bioavailability of the mangosteen rind powder. To clarify the relationship between mangosteen rind powder and schizophrenia or schizoaffective disorder the thesis describing the pilot study was revisited and interpreted. The health of the cell is compromised early in schizophrenia and affective disorder, evidenced by impaired antioxidant defences and oxidative stress. A neurobiological feature of schizophrenia is apoptosis (cell death). Higher levels of glutathione S-transferases are likely to promote cell viability instead of apoptosis and act as a biomarker for schizophrenia. Mangosteen rind powder is likely to improve the level of glutathione S-transferases; however an assay would potentially confirm this assumption. The pilot study confirms that mangosteen rind powder capsules show a positive signal of efficacy and effectiveness in schizophrenia and affective disorder for people without a co-morbid medical condition. The treatment was delivered safely and well tolerated amongst the cohort over a period of 180 days. These findings support the supplementation of mangosteen rind powder capsules at the dose of 1000mg/day for the augmented treatment of schizophrenia and affective disorders. The findings will also be discussed in terms of disability burden and the mental health system.

Keywords: neuropsychiatry, neuroprotection, cytoprotection, biomarker, pericarp

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INTRODUCTION

Garcinia mangostana L. is the botanical name given to a tropical tree, whose purplish ripe fruit is commonly known as mangosteen. The large molecular size and water solubility of the mangosteen fruit rind (or pericarp) molecule suggests that like many polyphenols, it too has low bioavailability. For the purpose of testing in a randomised controlled trial, the mangosteen rind powder was encapsulated. The mangosteen rind powder is manufactured from the fruit rind by a process of spray drying. The incorporation of a polymer into the spray drying process enables covalent bonding to form a gel in the presence of low heat[1]. Polymers are utilised by the food industry to preserve the active ingredient of the fruit. This activity seems to improve the otherwise low bioavailability of the product[2]. Given this recent information, it may be appropriate to revisit my thesis in an endeavour to better understand the relationship between mangosteen rind powder and schizophrenia or affective disorder. The thesis is entitled, 'the efficacy of *garcinia mangostana* L. (mangosteen) pericarp as an adjunctive to second-generation antipsychotics for the treatment of schizophrenia: A double blind, randomized, placebo-controlled trial'[3,6].

As an investigative paper the methodology employed was to examine portions of the thesis[3,6] at a time. Each section of the thesis was paraphrased and analyzed to draw out the meaning, then it was compared with current literature. Literature was accessed on Google scholar and google where appropriate to do so.

RESULTS AND DISCUSSION

Psychiatry seeks to label and categories mental illnesses. Publications by the American Psychiatric Association are the widely accepted standard used to describe and predict patterns of mood, emotions, behaviour, thoughts attributed to a particular diagnostic category. The study Utilized DSM-IV criteria which has since been superseded by DSM-V. A diagnosis of schizophrenia is based around the pervasive presence of positive, negative and general psychopathology, whereas affective disorders also incorporate the influence of mood and anxiety. These symptoms distort reality in relation to sensory perception, thinking, speech, emotions, behaviour, mood, judgment or an inability to experience pleasure. Following a non-specific prodromal phase, the acute onset of their first episode of psychosis marks the start of a lifetime of acute exacerbation followed by periods of remission of these symptoms. A sub-optimal quality of life for the individual and their loved ones accompanies this diagnosis. Lifestyle factors such as, poor diet, heavy use of alcohol and illicit substances have a negative impact on the course of mental illness. Schizophrenia and schizoaffective disorder are often refractory in nature. Despite availing themselves of the latest antipsychotic medication, many people continue to experience negative symptoms, perceptual disturbance

and sub-optimal cognitive and social functionality[3-6]. Given the conceptual framework of diagnoses and lack of widely accepted biomarkers; clinical trials rely on structured interviews that assess changes in individual presentation of symptoms, functionality and quality of life across time.

Chapter two

The testing of nutraceutical agents in mental illnesses has consistently lacked well designed trials. Previous objections to findings in relation to adaptogens are dissipating as further studies are consistently supporting their biological activity. Adaptogens are thought to protect against stress-induced responses[7]. The potential of adaptogens to influence physical and emotional-stress induced responses has recently been evaluated in elite athletes; finding significantly enhanced tolerance to stress[8].

The activity of mangosteen fruit extract may modulate stress-responses by inhibition of p38 MAPK signalling[9,10]. Glutathione S-transferases are known to modulate stress responses by reducing apoptotic signals involving p38 MAPK[11]. The traditional activity attributed to glutathione S-transferases was fully described in the thesis[3,6]. Glutathione S-transferases are also known to modulate signal transduction pathways beyond apoptosis, to also influence cell proliferation and differentiation[12].

As a polyphenol, mangosteen rind powder also has this further influence over cellular signalling and metabolic response[13] germane to the neuropathology of schizophrenia, affective disorder and cancer pathologies. *In vitro* studies confirm the potential activity of xanthene for cognitive functioning[14]. *In vivo* and *in vitro* studies are establishing that xanthene modulate signal transduction pathways to influence proliferation[15]. Xanthenes in mangosteen fruit extract are thought to act as a protective agent for cells[16]. Specific xanthones, α-mangostin, gartanin, 8 deoxygartanin and 3-isomangostin contribute to this protective activity[17]. This process may be mediated by a reduction in oxidative stress and apoptosis[18]; evidenced by a neuroprotective benefit attributed to α-mangostin in neuroblastoma cell lines[19]. The thesis assumes the similar pattern of findings across multiple outcome measures is indicative of neuroprotection[3,6]. Neuroprotection is an emerging concept common to both the psychiatric and mangosteen literature. Protection of neurons following injury and to prevent degeneration may potentially influence a broad array of neuropsychiatric disorders. This concept has relevance to the neurobiology of schizophrenia and affective disorders. While the concept of neuroprotection is receiving a reasonable amount of interest in the psychiatric literature, the neuroprotective role of antipsychotic drugs remains controversial. The neuroprotective hypothesis suggests that changes to the brain's grey matter in schizophrenia and affective disorder, may be offset by antipsychotic agents[20].

This rationale is given for the prophylactic prescribing of antipsychotic drugs which is not supported by imaging studies and clinical trials in schizophrenia and psychosis[21].

Impaired antioxidant defences in schizophrenia and affective disorders contribute to oxidative stress. However oxidative stress markers are considered to be inconsistent in schizophrenia[22]. Indicators of oxidative stress did not show any correlation between oxidative stress markers and symptom domains in chronic schizophrenia[23]. In the thesis, 180 days was the length of time that the study ran[3,6]. This choice in the study design was based on the assumption that oxidative stress would be reduced by 180 days in persons with chronic schizophrenia[24]. It was assumed that 180 days would indicate the process of cellular viability was underway and that the cell was reverting to a more healthy state.

In the context of traditionally recognized cellular activities; oxidative stress, perturbed redox regulation and antioxidant defences shed light on the state of cellular health. Instead of oxidative stress markers, antioxidant enzymes demonstrate significant correlation to symptom domains (PANSS scores) in schizophrenia[25]. Glutathione S-transferases are antioxidant isoenzymes that also participate in antioxidant defence. Increased glutathione S-transferase levels are thought to aid the restoration of neuronal viability[26]. This view is supported as glutathione S-transferases are a clinical marker of cell viability for organ transplantation[27]. A glutathione S-transferase assay would confirm the usefulness of glutathione S-transferases as a biomarker in schizophrenia.

Chapter three

There were several choices made during the design of the study, which warrant further investigation in the context of study findings. The cohort was chronically mentally ill people, living in real world conditions, which allow the study to evaluate both efficacy and effectiveness in the population. The clinical trial excluded people with a major co-morbid disease process[3,6]. Diabetes mellitus is a co-morbidity often associated with schizophrenia and affective disorder. As this was a pilot study, mangosteen rind powder has not been tested in this subgroup of people with co-morbidities. The sample size was adequate for a pilot study[3,6]. The choice of mixed model and repeated methods not only allows for missing data[3,6] but also controls type I errors. The participant and researcher were both blinded to the intervention that the participant was self-administering[3,6]. The intervention was presented in green gelatin capsules that had a rather bitter taste if broken. The high adherence figures therefore suggest that the fruit treatment was well tolerated and that blinding was not broken.

Chapter four

Participant demographics favoured people on the disability pension and confirmed the chronicity of the disorder in the participant population under investigation. Heavy illicit drug,

alcohol and tobacco use were representative in our demographics. Characteristics of our participant population included the use of multiple practitioners and willingness of the population to travel in order to access these practitioners. Subgroups of participants reported multiple chemical sensitivities and having undergone early menopause. Multiple chemical sensitivities are associated with perceptual disturbance following an 18% reduction in protein required for the olfactory neurons to function[28] and linked to paranoid thoughts. In this study treatment regimens were not altered and were managed by the participant's usual physician. Many people reported concurrent use of a raft of dietary and complementary medicines in addition to second generation antipsychotic drugs. Having been prescribed these drugs, many also reported non-compliance with the prescribed regimens. This finding is a well-recognised concern in the public mental health system, within the region where the study was conducted. Baseline readings of symptom domains, functionality and habits were not significantly different between the interventional groups to support the success of randomisation.

Standard rating scales during structured interviews were used to measure participant changes over time. F values greater than 1 support the findings were not due to chance. Assessment of treatment effects used a two-sided alpha level of 0.05. The intervention group values for P were rounded to suit the thesis format. Symptom domains were indicative of cognitive and social functionality (table 1).

Table 1: Between group analysis of symptom domains and global outcome measures

SCALE	*P* VALUE
PANSS total	<0.001*
PANSS positive	0.034*
PANSS negative	<0.001*
PANSS general	<0.001*
Anxiety (G2) on PANSS subscale	<0.001*
MADRS	<0.001*
GAF	0.17
SRLS	0.05
CGI-S	0.06
CGI-I	<0.001*

*Statistically significant with alpha 0.05

Symptom domains were assessed using the Positive And Negative Syndrome Scale (PANSS) and Montgomery-Asberg Depression Rating Scale (MADRS) as a participant self-reported measure of mood. Without the benefit of rounding the group scores for PANSS positive become, F (3, 126.08) = 2.97, p = 0.034 at the omnibus interaction. The planned comparisons, t (83.62) = -2.88, p =0.005. Similarly, PANSS negative scores are more significant as the omnibus interaction is, F (3, 119.77) = 10.77, $p < 0.001$ and the planned comparisons are, t (71.40) = -5.34, $p < 0.001$. For general psychopathology the omnibus interaction for the PANSS general score is, F (3, 129.27) = 9.24, $p < 0.001$ and planned

comparisons also favour the mangosteen rind powder group, t (79.35) = -5.17, $p < 0.001$. Anxiety is a subscale of PANSS (G2). The omnibus interaction was significant, F (3, 139.84) = 4.12, $p < 0.001$. The rate of change between baseline and 180 days was also significant, t (96.74) = 3.23, $p < 0.001$. For mood, the omnibus interaction is, F (3, 108.85) = 7.59, $p < 0.001$ and the planned comparisons are, t (75.74) = -4.64, $p < 0.001$. At baseline, 50% of participants in the study admitted to suicidal ideations. The study is likely to have provided participants in both groups with hope, which is a well-recognised therapeutic tool used by clinicians[29,3,6]. The similar pattern to findings was reported across multiple scales that were assessed by both the researcher and participant. This supports a significant reduction in the symptoms of schizophrenia and schizoaffective disorder, in the mangosteen rind powder group compared to the placebo group. However, the severity of symptoms did not markedly differ between the interventional groups (CGI-S p=0.06) although this occurred at a significantly greater rate within the mangosteen rind powder group.

The cohort is known to be refractory to treatment, so it is difficult to improve global functioning at a clinically significant level. Overall measures of social function and quality of life were not significantly different between groups at 180 days, although there were significant changes within the groups. Social functionality assessment was based on global assessment of functioning (GAF) scores, in which only the rate of change in the planned comparisons was significant between groups, t (71.68) = -2.25, p = 0.028). Participant quality of life was reported by participants using self-rated life satisfaction scoring (SRLS). Quality of life scores were not significantly different for the omnibus interaction between treatment groups, F (3, 141.86) = 2.66, p = 0.05, but were improved within the groups at the examination of planned comparisons for 180 days, t (84.85) = -2.73, $p < 0.008$.

Efficacy, effectiveness, safety and tolerability

The efficacy of mangosteen rind powder capsules was measured by a statistically significant change in PANSS total scores over the 180 day study period and effect sizes that used Cohens d. The actual p value favouring the mangosteen rind powder group at 180 days is $p<0.001$ which enables us to reject the hypothesis and accept the large effect size more readily.

The effectiveness of supplemental mangosteen rind powder treatment was evident by significant changes favouring the mangosteen rind powder group, across all symptom domains for schizophrenia and schizoaffective disorder by 180 days. Participants responded well to treatment with the mangosteen rind powder group (81.3%) comparative to the placebo group (30.6%)[3,6]. This was also supported by clinically significant improvements to treatment over time, t (66) = 4.63, $p < 0.001$. The study interventions were delivered safely. The fruit

extract was well tolerated by participants with high adherence data (94-95% adherence over 98% of the study time)[3,6]. There were no side effects reported from either the mangosteen rind powder or the rice flour placebo.

SUMMARY

The supplementation of mangosteen rind powder capsules is therefore supported as a treatment for schizophrenia and schizoaffective disorder. The response rates and effect sizes for the mangosteen rind powder are superior to old treatments (any treatment regimen the participant was on). Findings from this pilot study demonstrate a positive signal of efficacy and effectiveness under real world conditions. Caution should be taken in implementing this finding in people with co-morbid diabetes or other conditions where the study has not tested the intervention. The cohort under study is notoriously refractory to treatment. The main strength of this study is that a rigorous methodology was applied to a food to support regulatory requirements for the supplement to come into general use as a nutraceutical/ over the counter agent. Statistical analysis controlled for a type I error and our findings suggest that a type II error did not exist. The weakness of this data remains the lack of biomarkers to support neuropathology. Interpretation of these findings has also proved difficult without the benefit of molecular analysis of the mangosteen rind powder. This was outside the scope of the thesis and requires a special column to cater for the large molecular size of the mangosteen rind powder molecule. These factors are being addressed by a larger multisite study currently underway in Australia.

In the context of previous studies, the mangosteen rind powder study provided methodological rigour and validity comparative to similar studies involving nutraceutical agents. The use of antioxidants in schizophrenia has provided limited evidence of replication[30]. Polyphenols are thought to show promise in relation to established neurobiology such as, synaptic plasticity[31] for psychiatric disorders. The primary argument for testing polyphenols is their purported mechanism of activity[32]. Yet bioactive polyphenols have shown weak positive signals; confounded by poor methodological rigour.

In terms of the burden of illness, the mangosteen rind powder reduced symptom domains in a chronically unwell cohort to improve participant cognitive functioning, but had limited influence over social functionality, symptom severity and quality of life. Remission was unable to be assessed as the basis for this assessment is over a six month period and would require a longitudinal study. The burden of disability is unlikely to be influenced by mangosteen rind powder capsules alone. The underlying aetiology of schizophrenia needs to be addressed. Low protein, seafood and seaweed dietary intakes are linked to selenium and iron deficiency at the first episode of psychosis in the cohort[33].

Australian and New Zealand Clinical Trial Registration number: ACTRN12611000910909.

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DEDICATION

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