



Research Paper

Uncaria rhynchophylla (Gouteng) ameliorates neuronal damage induced in a ketamine mouse model

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ABSTRACT

In the quest to alleviate symptoms of ketamine addiction and akin neuronal degenerations, alkaloids of *Uncaria rhynchophylla* (Gouteng) were found to have curative effect. This study investigated whether or not Gouteng can ameliorate ketamine induced neuronal damage. Different groups of mice were administered treatments with ketamine, Gouteng, ketamine, followed by Gouteng (G+K) and saline. Behavioral test was carried out to unravel Gouteng's effect singly or after interaction with ketamine on memory. Histopathology was done to determine cell death and biochemical assays to compare the levels of neurotransmitters among different treatment groups. Performance of the G+K group in consolidated memory test was far better than the ketamine group, followed, as second, by Gouteng group. In histopathology, cell death was observed in prefrontal cortices and hippocampi of the ketamine group; with predominate loss of pyramidal cells in the prefrontal cortices, while no apparent loss of cells was observed in G+K group and Gouteng group, pointing to a neuroprotective ability of Gouteng. For neurotransmitters, ketamine group had higher level of serotonin than G+K group and Gouteng group. For GABA, G+K group had the highest level. Ketamine was documented to tag onto GABAA receptors that probably affected the depressive phase of ketamine addiction. Gouteng itself could be used as a hypnotic and thus the high GABA level warranted the effect. Dopamine level, on the other hand, was highest in ketamine group and interaction with Gouteng lowered it. On the whole, Gouteng appeared to protect a portion of memory and enhance survival of neurons in ketamine treated animals.

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INTRODUCTION

Ketamine is a well-known dissociative anaesthetic since the 1960s (Domino et al., 1965). It acts on the GABAA receptor to produce anaesthesia (Tan et al., 2011) and reacts with NMDA receptors during its action (Yew, 2015). Ketamine does not induce significant respiratory depression (Saraswat, 2015) nor cardiac depression (Johnstone, 1976). This property allowed ketamine of controlled dosage to become an excellent anaesthetic. However, the dissociative psychotropic effects combined with availability also caused it to become a popular substance of abuse. Ketamine abuse as a recreational addictive agent had increased from 1978 onwards (Mion, 2017) with its increased role as a “dance

drug” and its sought-after effects (Jansen, 2000). In the cases where ketamine is abused, many detrimental effects have been reported. In the brains of animal models such as mouse and monkey, ketamine addiction led to brain function deficits and general neuronal death (Sun et al., 2011, 2014; Mak et al., 2010), and particularly in the hippocampus and frontal cortex (Yew, 2015). Memory loss was therefore a feature of the addiction (Morgan et al., 2009; Morgan and Curran, 2006; Enomoto and Floresco, 2009) and long-term addiction led to formation of beta-amyloid and mutated tau protein in the users’ brains (Yew, 2015; Yeung et al., 2010). In addition, locomotion deficits

were found in the monkey (Sun et al., 2014). In human, ketamine affected not only neurons but white fibres as well (Wang et al., 2013). Atrophy as well as lesions was observed in the prefrontal cortex, occipital cortex, basal forebrain and cerebellum in humans (Wang et al., 2013). In the quest to alleviate the sufferings of ketamine addicts and those with akin neuronal degenerations such as Alzheimer's, it was suggested that a herb *Uncaria rhynchophylla* may be effective in treating heroin (Mischoulon and Rosenbaum, 2008), met-amphetamine and ketamine addictions (Zhu et al., 2017), as well as ameliorating neurodegenerative pathology such as Alzheimer's (Shin et al., 2018; Fujiwara et al., 2006). *U. rhynchophylla*, commonly known as *Gouteng*, is a traditional Chinese medicine that has been long known for treating head ailments, e.g. epilepsy, anxiety, hypertension and psychotic episodes (Zhang et al., 2018; Liu et al., 2012; Hsu et al., 2013; Li et al., 2018). The plant of *Gouteng* contains 38 chemical constituents including 26 alkaloids, 6 flavonoids, 2 triterpenoids, 2 chlorogenic acids and two unidentified compounds. The chemicals extracted from the hook on the stem are agonistic to 5-HT_{1A} and 5-HT_{2C} receptors while the chemicals from the leaves are agonistic to MT₂ (melatonin) receptors (Zhang et al., 2017).

However, up to now, there are no animal studies on how ketamine and *Gouteng* can interact and how *Gouteng* may exert the curative effect; hence the aim of the present study.

MATERIALS AND METHODS

Experimental animals, groups and treatments

This study was approved by the Research Ethics Review Panel for Animal Experiments of the Hong Kong College of Technology. The 12-week old ICR (Institute of Cancer Research) mice used in the study were provided by Laboratory Animal Services Centre of the Chinese University of Hong Kong. Mice were kept in a room at 22±1°C with 12:12 h light /dark cycles and water and food pellets were available *ad libitum*. Forty eight mice were randomly divided into four groups and received different treatments daily for three months. They were the *Gouteng* treated group, ketamine treated group, *Gouteng* plus ketamine cotreated group, and the saline control group. For the *Gouteng* treated group (group G), 0.41 g/kg *Gouteng* concentrated granule (in solution and equivalent to 2.05 g/kg *Gouteng* herb) was administered to the mice by intragastric gavage (IG) and normal saline was administered to the mice by intraperitoneal injection (IP). For the ketamine treated group (group K), normal saline was administered to the mice via IG and 30 mg/kg ketamine was introduced to mice via IP. For the *Gouteng* and ketamine co-treated group (group G+K), 0.41 g/kg *Gouteng* concentrated granule (in solution) was administered to the mice via IG and 30 mg/kg was introduced to the mice via IP. For control group (group C),

normal saline was introduced to the mice via IG and IP. The dose of ketamine used in this study (30 mg kg⁻¹) is a sub-anaesthetic dose for mice and is regarded as a recreational dose for mice in literature (Sun et al., 2011; Enomoto and Floresco, 2009). At the end of the three-month treatment, all groups were assessed in behavioral tests and then sacrificed for harvesting of brain tissue samples. Three whole brain samples of each group were fixed in 10% phosphate buffered formalin for further histological study and five whole brain samples of each group were snap frozen for biochemical assays.

Behavioral studies

Consolidated memory test

Consolidated memory test was used to assess the memory of the mice. Four objects of different shapes were placed at the corners of a square box of 50 cm × 50 cm. The location of the objects changed in every training day. One of the objects was selected to be the target object of our experiment. Mice were trained for 5 consecutive days and food was deprived to maintain 85-90% free-feeding body weight. There was only one 10-min trial in each training day. In each trial, a mouse was placed at the center of the box and was allowed to navigate the box. When the mouse stayed in an area (target object area) less than 5 cm away from the target object for 1 s on the first day, 5 s on the second and third days and 10 s on the fourth and fifth days, a small piece of standard chow was provided to the mouse near the target object as a reward. The mouse was allowed to enjoy the food and then the mouse was relocated to the center of the box for another round of navigation. This 'navigation and reward' tasks were repeated for 10 min in each trial. On the sixth day, the mouse was placed at the center of the box and allowed to navigate in the box for 5 min. No food reward was provided to the mouse even when it stayed in the target object area. The time that the mouse stayed in the target object area was recorded. A longer time staying in the target object area reflected a better consolidated memory of feeding at that area.

Histological studies

After sacrifice of the mice, brains were excised and fixed in 10% phosphate buffered formalin, dehydrated in alcohol, cleared in xylene, embedded in paraffin, and sectioned into 5 µm sections. The sections were deparaffinized, rehydrated for further staining.

Hematoxylin and eosin (H&E) stain

In H&E stain, the rehydrated sections were stained in Mayer's hematoxylin solution for 5 min, differentiated in acid alcohol, blued in running tap water and stained in

eosin solution for 2 min. The sections were then dehydrated in alcohol, cleared in xylene and mounted in dibutylphthalate polystyrene xylene (DPX). Morphology and structures of different parts of the brain were observed under bright-field microscope.

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)

TUNEL was performed using ApopTag® Peroxidase In-Situ Apoptosis Detection Kit (EMD Millipore, US) according to the manufacturer's instruction manual. Morphometry of the TUNEL positive cells for apoptosis were conducted through midsagittal and paramidsagittal (1 mm from median) sections of the whole brain. From these sections, the regions of the prefrontal, hippocampi and cerebella were identified. From the prefrontal region, under 400X magnification, 1500 μm^2 of each optical field was employed for the counting of TUNEL positive cells. After counting of one optical field, a 1000 μm^2 area was spared when moving to the next optical field. The counting of field followed the contour of the prefrontal cortex. This is to make sure fields are enlisted accordingly without bias and with no personal selection from the evaluators. These animals were used and a total of 24 fields ($n=7$ in each of the three groups) were counted for each ketamine, *Gouteng*, *Gouteng* plus ketamine and saline control group. For the hippocampi, the CA1 to CA3 region was used for counting, with optical fields of 750 μm^2 at 400X. The enlisted fields were again taken with a space of 750 μm^2 in between. In view of the small size of the hippocampi, regional fields were enlisted along a straight line from lateral to medial. Likewise, $n=9$ fields in each of the 3 animals of ketamine, *Gouteng* plus ketamine, *Gouteng* alone and saline alone groups. For the cerebellum, the 400X optical fields enlisted followed the contour of the cerebellar cortex from anterior to posterior with a space of 1000 μm^2 in between previous and subsequent counting fields. Each counting field was of 1500 μm^2 size. Again $n=28$ fields for each animal and $n=3$ for each group with ketamine, *Gouteng*, *Gouteng* plus ketamine and saline group. Positive control of the TUNEL stain was obtained from the degenerating retina of a megalophthalmic Black Moor goldfish (Ying et al., 2009).

Biochemical assays

Enzyme-linked immunosorbent assay (ELISA) of gamma-aminobutyric acid (GABA), dopamine and serotonin

The GABA, dopamine and serotonin content in brain were quantified by GABA ELISA™ (LDN, Germany), Dopamine Research ELISA™ (LDN, Germany) and Serotonin Research ELISA™ (LDN, Germany), respectively. All the procedures were done according to the manufacturer's instruction

manual. The snap frozen tissues were homogenized in cold phosphate buffered saline (PBS) by sonication. Clear homogenate was obtained by centrifugation at 12000g, 4°C for 15 min. Sodium metabisulfate and stabilizer provided by the kit were added to the homogenate for dopamine ELISA and serotonin ELISA, respectively. The ELISA plates were incubated with homogenate, antiserum, enzyme conjugate and substrate sequentially. The absorbance at 450 nm wavelength of the substrate was then measured by microplate reader.

Glutamate assay

The glutamate content in brain was quantified by Glutamate Assay kit (Abcam, UK). All the procedures were done according to the manufacturer's instruction manual. Diluted brain tissue homogenate was incubated with enzyme reagent mix provided with the kit at 37°C for 30 min. The absorbance at 450nm of the reaction mixture was then measured by microplate reader.

RESULTS

Histological studies

Histology and TUNEL in situ identification of apoptotic cells

The relative morphometric results are shown in Figures 1 to 5. Some apoptotic cells were apparent in the prefrontal cortex in the ketamine treated group (Figure 1a). Ketamine and *Gouteng* treated group had a significant decrease in number of apoptotic cells (Figure 1b). In comparison between groups, the ketamine treated groups had a higher TUNEL counts. In the ketamine plus *Gouteng* group, a significant decrease of TUNEL counts was observed when compared with the ketamine group (Figure 6e). For the hippocampi, both *Gouteng* plus ketamine and ketamine alone groups showed few apoptotic cells in the pyramidal layer (Figure 2a and b). While in the polymorphic layer, there were significantly more apoptotic cells in the ketamine treated mice than the *Gouteng* plus ketamine treated mice (Figure 2c and d). A comparison of TUNEL-positive cell count of the 5 groups is shown in Figure 6. Similarly, apoptotic cells did not appear in any significant amount in the purkinje and granular layer of the cerebellum but were only evident in the molecular layer (Figure 3a). Ketamine treated mice had higher TUNEL counts and were significantly different from that of the *Gouteng* plus ketamine treated mice that had lower number of TUNEL positive cells, especially in the molecular layer (Figures 3a and b, and 6a). Comparison of the choroid plexus also showed that there were more TUNEL positive cells in the epithelium of the ketamine alone group than the

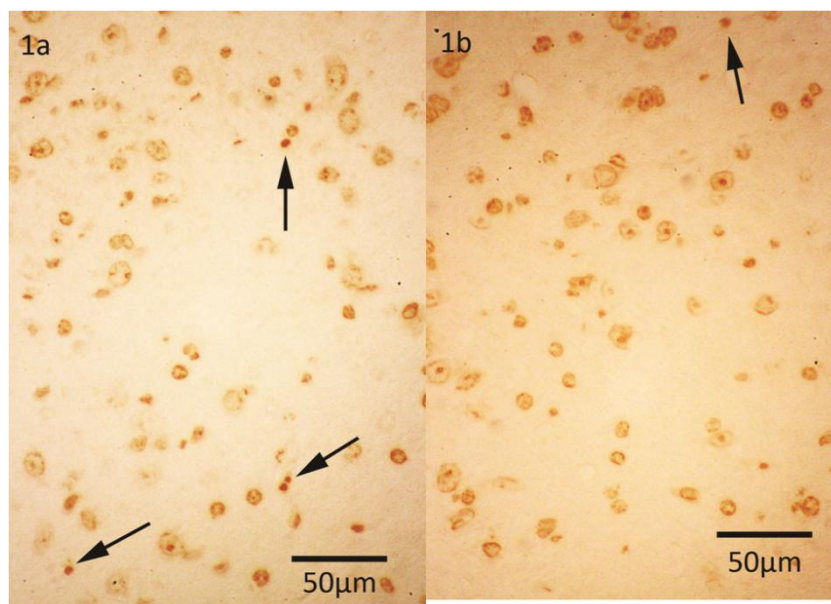


Figure 1: a). Prefrontal cortex of ketamine treated alone mice. Arrows indicate apoptotic cells (nuclei) (400x); b). Prefrontal cortex of mice treated with both *Gouteng* and ketamine. Arrow indicates apoptotic cell. Note sample in 1b has less apoptotic cells than that in 1a.

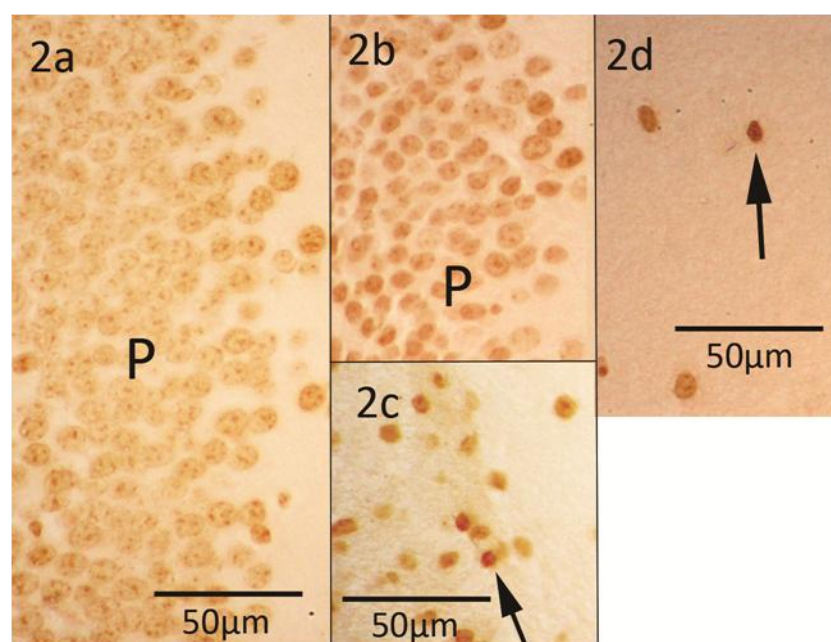


Figure 2: a). Hippocampus of *Gouteng* plus ketamine treated animal. Note no significant apoptotic cells are observed in pyramidal layer (P) (400x); b). Hippocampus of ketamine treated mice showing few apoptotic cells in pyramidal layer (P) (400x); c). Hippocampus of ketamine treated mice showing apoptotic cells (arrow) in polymorphic layer (400x); d). Hippocampus of *Gouteng* plus ketamine treated mice showing less apoptotic cell (arrow) in polymorphic layer than that of ketamine treated mice. (400x).

Gouteng plus ketamine group (Figure 4a and b) as well as the *Gouteng* or control group. The TUNEL positive cells on

cuboidal epithelial cells of the choroid plexus in the 4th ventricle of 3 animals in each group and 4 counted areas

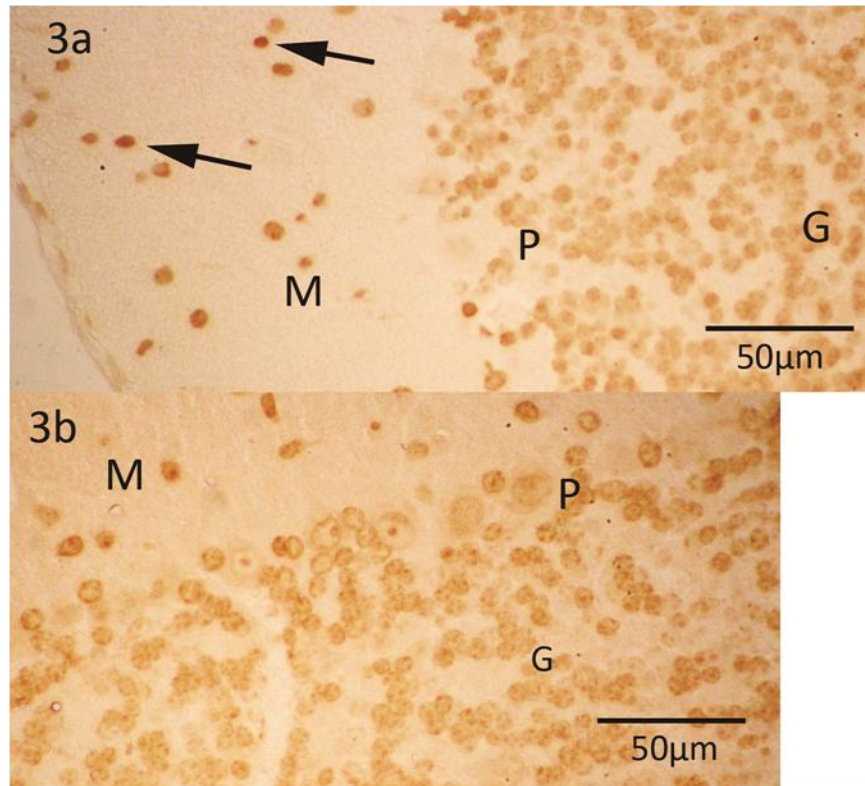


Figure 3: a). Cerebellum of the ketamine treated mice. Note apoptotic cells in molecular layer (M) but no significant appearance of apoptotic cells in purkinje (P) and granular cell layer (G) (400x); **b).** Cerebellum of *Gouteng* plus ketamine treated mice showing less apoptotic cells in molecular (M) layer than the group in Figure 3a, and no apoptotic cell in purkinje (P) and granular (G) layer (400x).

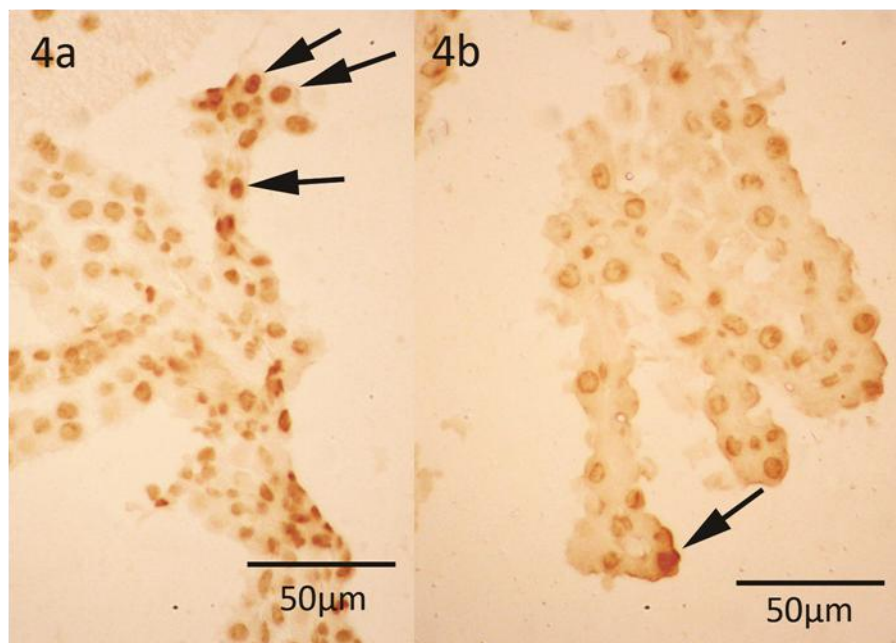


Figure 4: a). Choroid plexus of the ketamine treated mice showing apoptotic cells (arrows) (400x); **b).** Choroid plexus of *Gouteng* plus ketamine treated mice showing less apoptotic cells (arrows) (400x).

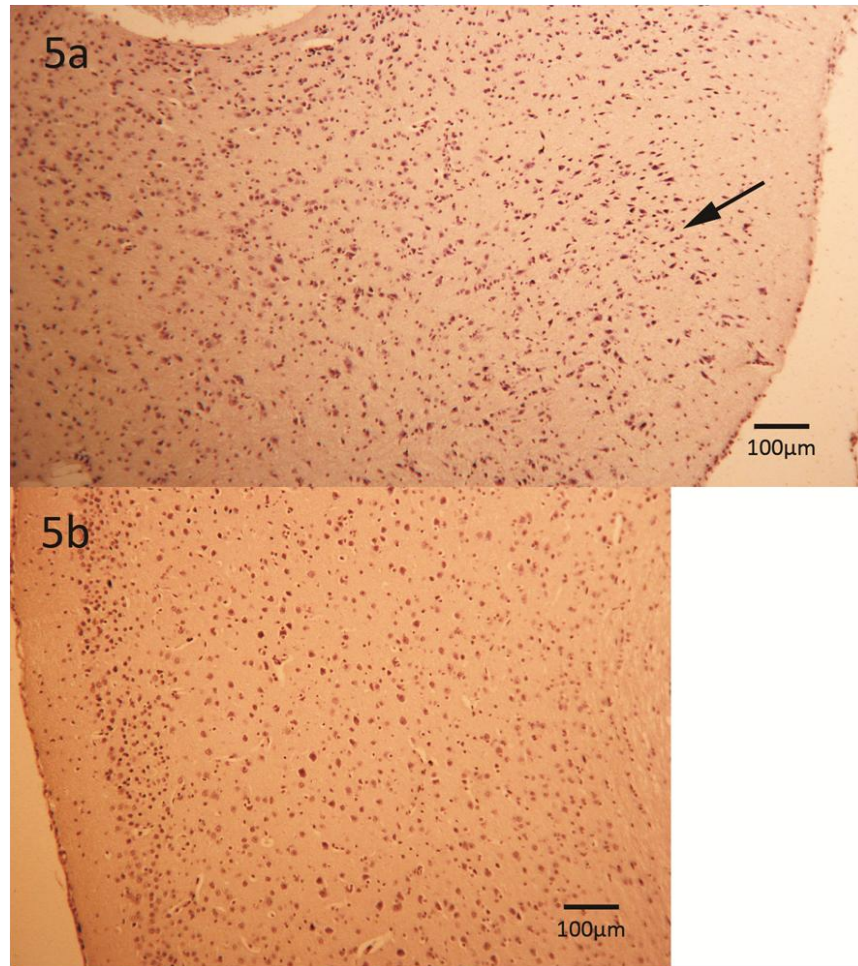


Figure 5: a). Prefrontal cortex of ketamine treated mice showing disorientation of cortical layer (100x); **b).** Prefrontal cortex of *Gouteng* plus ketamine treated mice with clear cortical layering (100x).

per 30 total cells in each animal were counted. Data are shown as follow: ketamine alone group is 4.7 ± 1 . *Gouteng* plus ketamine group is 2.1 ± 0.85 . *Gouteng* alone group is 0.4 ± 0.18 and the saline group is 0.3 ± 0.17 . Difference between ketamine versus *Gouteng* plus ketamine is significant ($p < 0.05$) and so is ketamine versus *Gouteng* alone or saline ($p < 0.05$).

Histologically, the hippocampi and cerebellum were unremarkable in all groups but the prefrontal cortex of the ketamine group had focal disrupted layering of the cortex (Figure 5a), which was not present in the *Gouteng* plus ketamine, *Gouteng* and control saline groups (Figure 5b).

Behavioral studies

Consolidated memory test

In consolidated memory test, the mouse identified a target

figure with awards of food afterwards in training. In final assessment, no food was provided and the mouse waited at the vicinity of the figure for food. The *Gouteng* alone and *Gouteng* plus ketamine cotreated groups had longer waiting time than ketamine treated group or saline control group. In other words, the mice remembered the figure and waited at the vicinity of the figure for a much longer time for food, reflecting a better consolidated memory of the rewards in the past (Figure 7).

Neurotransmitters level

Quantitative results of selected neurochemicals of different groups are shown in Figure 8. Serotonin was the highest in ketamine treated mice brain while *Gouteng* and ketamine interaction lowered it (Figure 8a). GABA was high in *Gouteng* treated but highest in the *Gouteng* plus ketamine group (Figure 8b). Dopamine ELISA showed that the

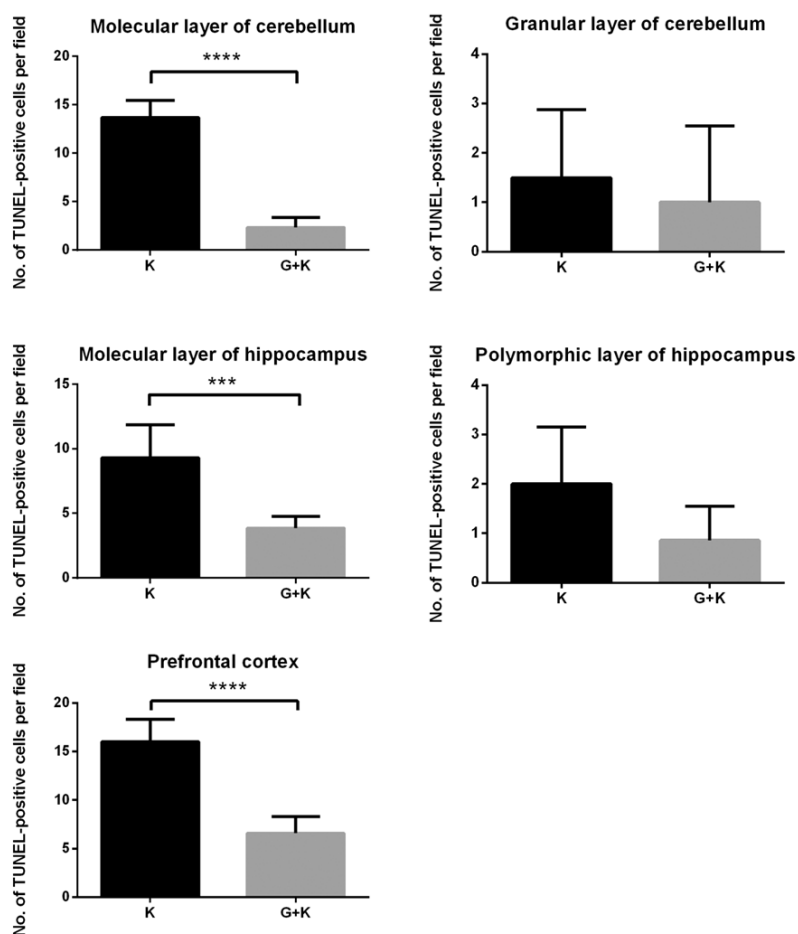


Figure 6: Number of TUNEL positive cell per field in different regions of brain in different groups of mice.
 * means $P \leq 0.05$, ** means $P \leq 0.01$, *** means $P \leq 0.001$ and **** means $P \leq 0.0001$.

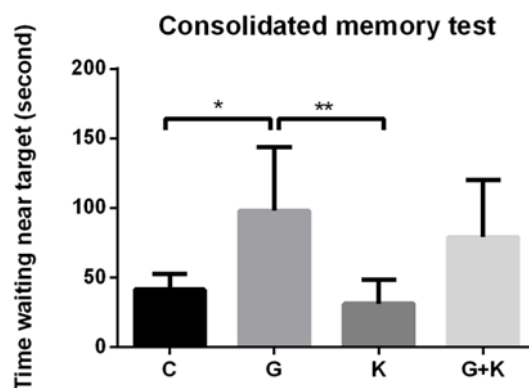


Figure 7: Time waiting near target in different groups of mice in consolidated memory test.
 * means $P \leq 0.05$ and ** means $P \leq 0.01$.

ketamine treated group had the highest level of dopamine in the brain, almost 50% more than the control. *Gouteng*

treatment on the mice alone did not raise the dopamine level of the brain however, and *Gouteng* treatment lowered

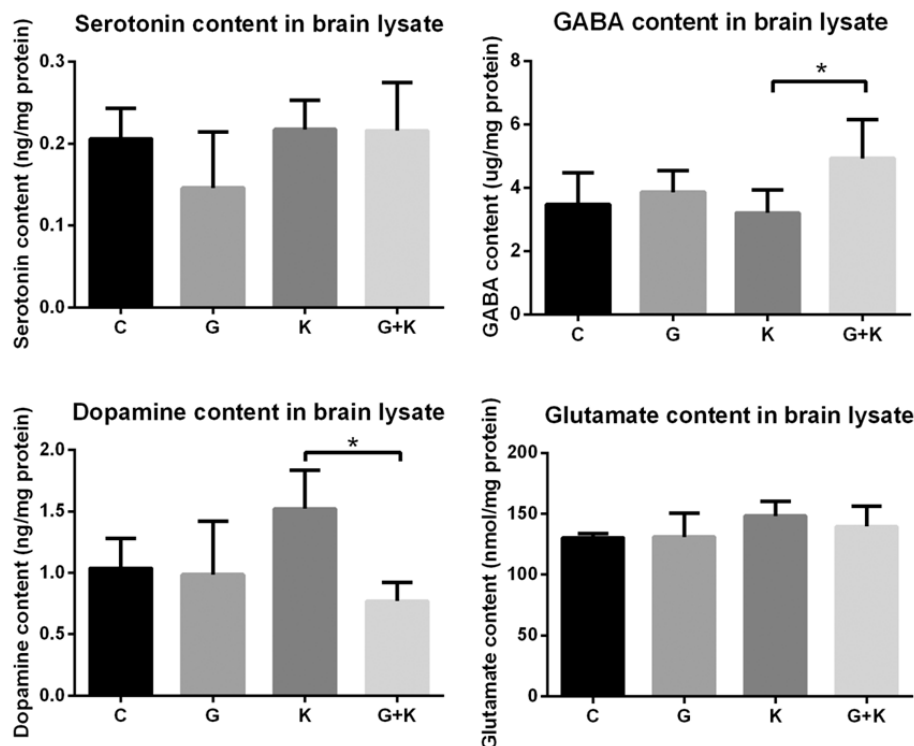


Figure 8: Neurotransmitter content in brain lysate of different groups of mice.
* means $P \leq 0.05$.

the raise of dopamine by ketamine in the brain (Figure 8c). Glutamate level had no significant difference among all groups (Figure 8d).

DISCUSSION

Our results indicated that after ketamine was administered along with *Gouteng*, cell death was insignificant in the prefrontal cortex, polymorphic layer of hippocampus, and molecular layer of cerebellum, while for those ketamine injected alone mice, those areas had a lot of cell death. In fact, both amyloid and mutated tau proteins were reported to be located in the brains of mice and monkeys treated with ketamine (Sun et al., 2014; Yeung et al., 2010). Cellular protection was one of the features of extracts from *Gouteng*, either through protection from oxidation (Li et al., 2018) or inhibition of excessive Ca^{2+} influx (Shimada et al., 1999). Other alternative mechanisms of cellular protection included: upregulation of myocyte transcript factor, regulation of bcl/bak pathway and potentiation of PI3 kinase/ AKT pathway via downregulation of GSK3-beta (Hu et al., 2018). Our studies pointed out that *U. rhynchophylla* has an effect of protection of cell death, and protection of consolidated memory which is a long term memory involving transfer between both hippocampus and prefrontal cortex (Cahill and McGaugh, 1996). The presence of TUNEL cell death in the choroid plexus showed the toxic

effect of ketamine upon the CSF production and *Gouteng* plus ketamine appeared to be able to lessen the toxicity on choroid plexus.

This study showed that apoptosis was highest in quantity in the central nervous system (CNS) of the ketamine treated mice as compared with *Gouteng* treated, *Gouteng* and ketamine cotreated and the control group. The presence of cell death in the CNS after ketamine treatment has been documented already (Yew, 2015). What was new here was that the prefrontal cortex had much more apoptotic cells than hippocampus and cerebellum after ketamine insult in the mice. Further, different layers of the same region might not be equally vulnerable. For example, cells in the strata oriens and reticularis were the most vulnerable parts in the hippocampus. The most important thing was that when *Gouteng* treatment was given together with ketamine, the damage on the CNS as revealed by TUNEL and memory tests appeared to be less apparent. This seemed to indicate that there was indeed a protective role of *Gouteng* on ketamine damage of the CNS. *Gouteng*, when used alone on the mice in this study (with a dosage equivalent to 10 g/60kg body weight in human), had no apparent detrimental effect on the brain when compared with the control group. At present, there is a lack of treatment for ketamine induced CNS damage as well as other neurodegenerations such as Alzheimer's disease; neuroprotective agents such as *Gouteng* might perhaps be useful as a supplement for this purpose.

Our results also pointed out that the consolidated memory of recognition with award (feeding) in *Gouteng* and ketamine cotreated mice was improved. Memory improvement can be triggered by: 1, inhibition of NMDA receptors by *Gouteng* (Chen et al., 2016; Yang et al., 2018). 2, anti-acetylcholinesterase activity initiated by Geissoschizine methyl ether N-oxide or catechin, components of *Gouteng* (Jiang et al., 2015).

These mechanisms could also increase muscle activity and memory (Chen et al., 2016; Jiang et al., 2015). The ability of this herb to suppress beta-amyloid further supports its protective role in Alzheimer degeneration (Chen et al., 2016). Our neurochemical analysis on serotonin production showed ketamine treated mice actually produced more serotonin than the other groups, though serotonin was also produced by *Gouteng* treated mice. Additional antidepressive effect of *Gouteng* may come from the norepinephrine and serotonin triggered by isorhynchophylline in *Gouteng* (Xian et al., 2017). Another suggestion was that catechin of *Gouteng* acted on melatonin receptor which could have antidepressive action as well (Geng et al., 2019).

The neurochemical analysis of this study further demonstrated that: 1, Both *Gouteng* and ketamine treated mice had brains with serotonin, GABA, glutamate and dopamine. 2, Serotonin, glutamate and dopamine level were on average higher in the ketamine treated group than other groups whilst GABA level was higher on average in the brains of *Gouteng* plus ketamine treated group.

Serotonin was long known to have an excitatory effect on mood, but too much serotonin could lead to social phobia, agitation, anxiety, tremor and rise in temperature (Ener et al., 2003). The action of serotonin was usually associated with 5-HT_{1A} and 5-HT_{2A} receptors for the mental domains. In this study, it was shown that ketamine alone and *Gouteng* plus ketamine induced more serotonin production than the other groups studied. *Gouteng* plus ketamine did not cause significant decrease on the serotonin level elevated by ketamine alone group. That may imply that *Gouteng* preserved the excitatory effect on mood. On the other hand, *Gouteng* plus ketamine induced higher GABA level than ketamine treated brains alone. Since ketamine was recorded to tie to GABA_A receptors (Tan et al., 2011), the hypnotic effects of GABA would likely be also present in *Gouteng*. Furthermore, Ketamine also led to slightly more (but different than control) production of glutamate in the brain while interaction between ketamine and *Gouteng* decrease the level only slightly. Glutamate was known to be an excitotoxic transmitter and once bound to NMDA receptors would induce calcium influx and cellular calcium overload, leading to neuronal cell death (Platt, 2007). As our TUNEL studies showed that *Gouteng* could exert neuroprotective property quite well on the ketamine treated brain, yet the *Gouteng*-ketamine interaction here showed only minimum downregulation of glutamate, the neuroprotective effect on cell death probably were not

through just downregulation of glutamates but rather via the pathways mentioned previously in this paper. Dopamine increased in the ketamine treated brain has been well documented (Tan et al., 2012). Dopaminergic fibers of the brain came from the tegmentum of the midbrain (Tan et al., 2012). It is interesting to note that *Gouteng* did not elevate dopamine levels in the CNS and actually could, when added to ketamine treatment, down regulate and control the rise of dopamine by ketamine treatment alone. This would mean that the excitatory phase of ketamine toxicity could be regulated by *Gouteng*.

Conclusions

In summary, as *Gouteng* interacting with ketamine could produce neuroprotective effects and ameliorate the damage on neurons and the addition of *Gouteng* produce little toxicity on the brain, this herb has the potential to serve as adjunct treatment for the wellbeing of addicts on ketamine. Because the neurodegenerative modes of ketamine was similar to other degenerations in apoptosis, mutated tau protein and amyloid production (Yew, 2015; Yeung et al., 2010), the herb *Gouteng* may have greater application.

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