

300 A NEW ANTIMICROBIAL EPICATECHIN DIMER FROM THE STEM-BARK OF COMMIPHORA PEDUNCULATA

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Background: Infectious disease is the commonest cause of death world-wide; this is attributable to poverty and increasing incidences of multiple drug resistance; necessitating the development of new effective and safer antimicrobial agents. *Commiphora pedunculata* Stem bark has been used in traditional medicine for the treatment of infected wounds. This study was aimed at isolating and elucidating the structure of some of the constituent(s) responsible for the previously reported antimicrobial activity.

Methods: Extensive chromatographic separation of the ethylacetate fraction using silics gel and Sephadex LH-20 led to isolation of new Epicatechin (5→5) epicatechin. The structure of this compound was elucidated using 1 & 2D NMR spectroscopy. The antimicrobial activity of the compound was investigated using agar diffusion and broth dilution techniques and the organisms tested are clinical isolates obtained from the Department of Medical Microbiology, Ahmadu Bello University Teaching Hospital, Zaria- Nigeria and include *VRE, Salmonella enteritidis, Providencia rettgeri, Shigella dysenteriae, Proteus mirabilis, Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa, Klebsiella pneumonia, MRSA, Bacillus subtilis, Bacillus cereus, Corynebacterium ulcerans, Escherichia coli, Candida albicans, Candida tropicalis and Candida stellatoidea.*

Results: The compound was found to have activity against all the organisms tested (Zone of inhibition 22–34 mm) with the exception of MRSA, *Streptococcus pyogenes, Salmonella enteritidis, Proteus mirabilis, Providencia rettgeri and Candida tropicalis.*

Conclusion: The compound demonstrated good antimicrobial activity against the susceptible organisms which further validates the ethno-medicinal use of the plant.

301 A NOVEL DOPAMINE REUPTAKE INHIBITOR, NS18313 INDUCES SPONTANEOUS ERECTIONS IN RATS

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Erectile dysfunction is frequent and new approaches are required to optimize the success rate of the treatment of the disease. The present study investigated whether a newly developed amine transport inhibitor, NS18313, affects erectile function in rats. Amine uptake was evaluated *in vivo*, erectile responses were measured in anaesthetized rats, and isometric tension was measured in corpus cavernosum strips. NS18313 inhibited dopamine uptake, while there was less effect on 5-hydroxytryptamine and noradrenaline uptake. Measured as intracavernosal pressure in anaesthetized rats, NS18313 dose-dependent increased the number and the duration of spontaneous erections. These increases and/or duration were inhibited after cutting the proximal cavernosal nerve or pretreatment with the dopamine D2 receptor antagonist, clozapine. Pretreatment with the phosphodiesterase type 5 inhibitor, sildenafil, enhanced the duration and magnitude of increase in intracavernosal pressure induced by NS18313. In isolated cavernosal strips, NS18313 induced concentration-dependent relaxations which were inhibited in the presence of an inhibitor of nitric oxide synthase inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), and enhanced by sildenafil. NS18313 did not change relaxations or contractions induced by electrical field stimulation in corpus cavernosum strips. The present findings suggest that NS18313 stimulates erectile function mainly by a central mechanism involving dopamine reuptake inhibition. The perspective is that this novel drug targetable mechanism can be used to initiate erection or to support the effect of drugs with a peripheral mechanism of action on erectile function.

302 A NOVEL DUAL PPAR α/γ AGONIST YR4-42 IMPROVES GLUCOSE METABOLISM WITH UNIQUE LIPID- REGULATING PROPERTIES IN THE ABSENCE OF WEIGHT GAIN

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Background: The peroxisome proliferator-activated receptors (PPARs) are intimately linked with the metabolism of glucose and lipid. PPAR γ activation improves insulin resistance while PPAR α activation promotes lipid metabolism, as such, they are both potential therapeutic targets for Type 2 diabetes mellitus (T2DM). However, some PPAR agonists are reported with side effects, including body weight gain, edema, and tissue failure. This study investigated the effects of a novel dual PPAR α/γ agonist, YR4-42, on glucose and lipid metabolic disorders in diabetic mice.

Method: The *in vitro* activation of PPAR α/γ by YR4-42 was characterized by a cell-based PPAR α/γ -Gal4 chimera-receptor-induced luciferase reporter assay, and further confirmed by PPAR γ mediated pre-adipocyte differentiation and PPAR α/γ target gene expression. *In vivo* effect of YR4-42 was examined in spontaneous diabetic KKAY mice. Total body weight, systemic glucose/insulin tolerance and plasma biochemical parameters were measured, lipid profiles in muscle, liver were analyzed, and the influence of YR4-42 on metabolic genes or proteins in target tissues was examined.

Results: YR4-42 activated both PPAR α and PPAR γ (with EC₅₀ values of 1.18 and 0.23 μ M respectively). Additionally, YR4-42 promoted 3T3-L1 pre-adipocyte differentiation accompanied with up-regulated expression of adipose specific genes. And in L02 liver cells, YR4-42 induced the transcriptional activation of PPAR α and its target genes. In KKAY mice, YR4-42 ameliorated insulin resistance and hyperlipidemia (reducing the levels of plasma glucose, insulin, triglycerides, free fatty acids and cholesterol.) without body weight gain after 30 days of treatment. Furthermore, YR4-42 improved hepatic steatosis by decreasing the accumulation of triglycerides and cholesterol as well as the level of transaminase in the liver. The influence of YR4-42 on gene expression profile may include suppressing gluconeogenesis, enhancing fatty acid oxidation, accelerating reverse cholesterol transport and increasing cholesterol efflux from bile secretion process.

Conclusions: By simultaneous activation of PPAR α and PPAR γ , YR4-42 exhibited beneficial effects on hyperglycemia and dyslipidemia without the reported PPAR γ -side effects. The present data suggest that YR4-42 would be a potential lead compound against T2DM and related metabolic disorders.

303 A NOVEL LQT5 TRANSGENIC RABBIT MODEL FOR THE ASSESSMENT OF PROARRHYTHMIC SIDE EFFECTS OF DEVELOPMENTAL COMPOUNDS

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The reliable prediction of the proarrhythmic risk associated with novel compounds under development is essential, however, it remains unsatisfactory. In spite of some existing *in vivo* animal proarrhythmia models, new models with better predictive value for proarrhythmic risk assessment are needed. In this study, we carried out the primary characterization of a novel transgenic LQT5 syndrome rabbit proarrhythmia model, based on the overexpression of human *KCNE1*, carrying a missense mutation identified in a Chinese LQT syndrome family. The proarrhythmic susceptibility of LQT5 transgenic rabbits was evaluated by administration of the I_{Kr} blocker dofetilide (20 μ g/kg). In anesthetized transgenic (TG; n=26) and wild type rabbits (WT; n=27), the ECG was continuously registered before, during and following the infusion of dofetilide, and arrhythmia development was also monitored. Conventional ECG parameters characterizing repolarization duration, the QT and frequency corrected QT intervals (QT_c), were not different in the two groups at baseline (QT: 146.9 \pm 3.18 in WT vs.

145.7 ± 2.87 ms in TG; QT_c: 156.8 ± 2.63 in WT vs. 155.6 ± 2.12 ms in TG, all $P > 0.05$). Following the administration of dofetilide, QT and QT_c intervals were significantly prolonged in both groups to a similar extent (QT_c: 169.4 ± 3.37 in WT and 167.8 ± 3.17 ms in TG). However, the short-term variability of the QT interval, a novel ECG parameter suggested for the better estimation of repolarization temporal instability and proarrhythmic risk, was higher in KCNE1 transgenic rabbits compared to wild type at baseline (4.8 ± 0.26 in TG vs. 2.8 ± 0.15 ms in WT, $P < 0.05$). Following the administration of dofetilide, the incidence of the typically drug induced Torsades des Pointes arrhythmia was significantly higher in transgenic rabbits compared to wild type (77% in TG vs. 51.8% in WT, $P < 0.05$). In summary, our results strongly suggest KCNE1 transgenic rabbits have higher susceptibility to drug induced arrhythmias and may represent a useful model for testing the proarrhythmic potential of new drugs under development.

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ACTIVITY OF SECURINEGA VIROSA IN BEHAVIOURAL MODELS OF PARKINSON'S DISEASES

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Background: Parkinson's disease (PD) is a complex multifactorial disease and the second most common neurodegenerative disorder of the central nervous system after Alzheimer's disease (AD). Current initial therapies are associated with loss of effectiveness over time and untoward effects. *Securinega virosa* is a commonly used medicinal plant in African Traditional Medicine for the management of mental illnesses. In this study the activity of the methanol root bark extract of *Securinega virosa* in behavioural models of Parkinson's disease was evaluated.

Methods: Methanol root bark extract of *Securinega virosa* (50 and 100 mg/kg, p.o) was administered 1 h prior to the administration of reserpine (1 mg/kg) and haloperidol (1 mg/kg). Cataleptic score was obtained in each mouse 1 h after haloperidol and 4 h after reserpine administration by gently placing the fore paws of each animal on a 4 cm high block at 1 h interval over a period of 4 h. The effect of the extract on motor coordination was also investigated using beam walking assay test in mice. The time to complete the task as well as the number of foot slips was determined in each mouse 1 h after administration of the extract.

Results: The extract at the higher dose of 100 mg/kg significantly ($P < 0.05$) decreased the mean cataleptic score induced by haloperidol by a factor of about 3 at the end of 120 min. This was comparable to that of the standard agent, benzhexol (0.5 mg/kg) used. Against reserpine, the extract (100 mg/kg) significantly ($P < 0.05$) reduced the mean cataleptic score at the end of 180 min. Benzhexol significantly decreased the scores at both 180 and 240 min when compared with control. Conversely, the extract at all the doses tested did not significantly alter the time taken to complete the walking task as well as the number of the foot slips in the beam walking assay study.

Conclusion: These findings suggest that the methanol root bark extract of *Securinega virosa* possess activity in behavioural model of Parkinson disease and a potential candidate for further evaluation.

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ACUTE AND SUB CHRONIC (28-DAY) ORAL TOXICITY OF PSEUDOCEDRELA KOTSCHYI METHANOL EXTRACT IN SPRAGUE-DAWLEY RATS

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Abstract: *Pseudocedrela kotschy* has been extensively used in traditional medicine for the treatment of rheumatism, malaria, dysentery and epilepsy.

Purpose: The purpose of the research is to determine the safety profile of the methanolic extract of *Pseudocedrela kotschy* stem bark through acute and sub chronic toxicity in female and male rats.

Methodology: In the acute oral toxicity trial single dose of 2000 mg/kg was administered to five nulliparous female rats. In the sub chronic study 48 rats (24 males and 24 females) were grouped into 4 groups of 12 animals (six males, six females) and treated with *P. kotschy* extract at a dose of 40, 200 and 1000 mg/kg respectively.

Result: The acute toxicity study showed no signs of toxicity such as general behaviour changes and mortality. Assessment for signs of chronic toxicity indicated no abnormalities in the test groups as compared to the controls. Haematological and biochemical values in treated groups were normal in comparison with the control group. Insignificant changes in body weight, internal organ weight and general behaviour were considered to be incidental.

Conclusion: Therefore, the stem bark methanol extract of *P. kotschy* given orally to female and male rats did not induce acute and chronic toxicity in the rats at the doses administered.

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ACUTE AND SUB-CHRONIC TOXICITY STUDIES OF METHANOL ROOT EXTRACT OF SECURIDACA LONGEPEDUNCULATA IN MICE

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Background: *Securidaca longepedunculata* (SL) is a popular medicinal plant believed to have over 100 medicinal uses, some for long-term management of chronic illnesses such as sleeping sickness, tuberculosis and mental diseases. Despite this widespread use, not much has been reported about its toxicity and hence this study investigated acute and sub-chronic toxicity of its methanol root extract in mice, after appropriate institutional ethical approval.

Methods: Roots of SL were extracted with methanol; and LD₅₀ was determined in acute toxicity testing. In the sub-chronic study, 96 male albino mice were divided into four groups of 24 each, with three of the groups receiving 20%, 10% and 5% of the extract's LD₅₀ (equivalent to 0.56, 0.28, 0.14 mg/kg respectively), while the control group received normal saline. All drugs were administered i.p. daily for 28 days. Six mice from each group were sacrificed on days 14, 28 and 56 only (as they did not survive to the proposed 90 days) and parameters to assess effects on blood, liver and kidney were determined.

Results: The LD₅₀ was found to be 2.83 mg/kg which was regarded as quite toxic. Data for day 28 showed that the extract significantly ($P < 0.05$) decreased RBC ($\times 10^6/\mu\text{L}$) to 6.02 ± 0.19 (0.56 mg/kg) and 6.74 ± 0.43 (0.28 mg/kg) when compared to the control 10.68 ± 0.34. PCV (%) was similarly reduced to 41.80 ± 5.84 and 42.00 ± 4.72 compared to control of 48.60 ± 3.93. Hb and WBC were however not affected. The extract significantly ($P < 0.05$) and dose-dependently increased ALT and AST while ALP was decreased. The corresponding pair values in U/L for control and highest extract dose for the three liver enzymes were 26.00/41.83, 17.83/29.50 and 59.67/43.83 respectively (SEM omitted). Total albumin (G/L) also decreased significantly ($P < 0.05$) and dose-dependently from 41.50 to 31.67, while urea (mM) increased from 2.23 to 4.08 and total protein (G/L) was unaffected (SEM omitted). Changes in these parameters on days 14 and 56 were similar indicating toxicity to blood, liver and kidney with the day 56 data being the most profound.

Conclusion: SL may induce anaemia, and damage the liver and kidney; and hence should be used with caution for management of chronic illnesses.

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ADVANCE OF PROGESTERONE RECEPTOR ANTAGONISTS IN CHINA

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Progesterone (P) exerts a range of important biological effects by interacting with progesterone receptor (PR), which distributes in many crucial organs, including reproductive, bone, cardiovascular and nervous