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Searsia chirindensis reverses the potentiating effect of prenatal stress on the development of febrile seizures and decreased plasma interleukin-1β levels

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ABSTRACT

It is estimated that more than 80% of patients with epilepsy live in developing countries with 50–60% of them being children. This high prevalence is perpetuated by low socio-economic challenges, poor health care facilities and lack of drug affordability. *Searsia chirindensis* formerly known as *rhus* chirindensis and commonly known as 'Red Current' is a popular traditional medicinal plant, which has been used to treat a number of illnesses such as heart complaints and neurological disorders. The aim of this study is to investigate the effects of *S. chirindensis* on the development of febrile seizure in a prenatally stressed rat. Febrile seizures were induced by administering lipopolysaccharide to 14-day-old rat pups followed by kainic acid. A subset of the rats was treated with *Searsia* after induction of febrile seizures. Interleukin-1β (IL-1β) levels were measured in plasma. Lipid peroxidation was determined in liver tissue. Our data shows that treatment with *Searsia* reduced interleukin-1β levels in plasma of the febrile seizure rats and prevented lipid oxidation in the liver. Prenatal stress is dampened by the beneficial effects of *Searsia* on seizure development in rat pups. These results highlight the potentiating effects of *Searsia* in the reversal of febrile seizures and prenatal stress effects.

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1. Introduction

Despite the common occurrence of febrile seizures worldwide, the aetiology and management remains problematic (Di Filippo et al., 2008). Febrile seizures may be a consequence of middle ear infection (otitis media) often accompanied by flu, gastro enteritis, respiratory infections and other immune activation infections (Gulec and Noyan, 2001; Dube et al., 2009; Hoeijmakers et al., 2015). Interleukin-1β (IL-1β) has been suggested to be one of the major cytokines mediating the sudden abnormal neuronal firing that occurs during a febrile seizure (Vezzani and Baram, 2007; Riazi et al., 2010; Koziol et al., 2014). Studies have also shown that chronic stress that leads to prolonged high levels of glucocorticoids, may eventually result in immune incompetence, abnormal inflammatory responses, impaired cognition and a hormonal imbalance (Burton and Waddell, 1999; Corcoran et al., 2003; McEwen, 2003; de Kloet, 2009). These consequences, especially during the prenatal period, have been shown to exaggerate febrile seizure severity in the offspring (Qulu et al., 2012).

Treatment of febrile seizures includes the use of drugs such as diazepam, phenobarbital and valproate (Farwell et al., 1990; Knudsen, 1996; Lahat et al., 2000; Camfield and Camfield, 2014). Diazepam is absorbed slowly in the intestine as a result it is given rectally or intravenously (Lahat et al., 2000; Camfield and Camfield, 2014). The side effects of diazepam include rear brain stem depression that may lead to bradypnoea and respiratory arrest (Lahat et al., 2000; Ohlraun et al., 2013). Phenobarbital, which is commonly used in Africa, has been shown to decrease cognitive performance (Farwell et al., 1990; Knudsen, 1996). Valproate, although very effective, is also not commonly prescribed due to the high mortality rate associated with its use (Knudsen, 1996; Koziol et al., 2014).

Apart from the adverse effects associated with the use of these drugs, the World Health Organisation (2005) reported that socio-economic problems in Africa leave patients in rural areas faced with the twin challenges of affordability and availability of these drugs. This scenario has resulted in many rural African communities resorting to the use of medicinal plants as the first line treatment for a variety of illnesses (Diamond, 2000). Recently it has been estimated that 70–80% of the world's population rely on traditional herbal medicine to meet their primary health care needs

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(Uprety et al., 2010, 2012). This increased use resulted in many scientific studies being conducted to systematically elucidate the molecular mechanisms by which these medicinal plants render their beneficial effects (Uprety et al., 2011, 2012).

Searsia chirindensis also known as 'Red Current', is commonly found in the eastern parts of Southern Africa (Venter and Venter, 2005). The bark of *Searsia* is used to treat different illnesses such as heart complaints, neurological disorders and rheumatism (Ojewole, 2008). The phytochemistry of *Searsia* shows the presence of triterpenoids which have been shown to possess anti-inflammatory properties, antioxidants such as flavonoids and tannin – known to scavenge reactive oxygen species, and steroids – which also have anti-inflammatory properties (Greaves, 1976; Volker Dehmlow et al., 1998; Kohen and Nyska, 2002). The objective of this study was to evaluate whether *Searsia* can dampen the effect of prenatal stress on the development of febrile seizures, and if it does so, by attenuating the immune response associated with febrile seizures. In addition lipid peroxidation of the liver was measured so as to determine whether *Searsia* may be toxic to other organs.

2. Methods and materials

2.1. Animals

Thirty-six Sprague-Dawley pups were used in the study. The mating pairs were obtained from the Biomedical Resource Centre of the University of KwaZulu-Natal, where they were housed under standard laboratory conditions of 22 °C room temperature, 70% humidity, and a 12 h light/dark cycle (lights on at 06 h 00). Food and water were freely available. All experimental procedures were approved by the Animal Ethics Research Committee of the University of KwaZulu-Natal (Ethical number 075/10) and were in accordance with the animal ethics guidelines of the National Institutes of Health, USA.

2.2. Mating

Ten female and five male rats were mated. Vaginal smears were taken daily for four days to examine the female oestrus cycle (Freeman, 1994; Qulu et al., 2012). A male rat was placed in the cage with the female rat when the female rat was in pro-oestrus. Vaginal smears were taken the following morning. The presence of sperm in the smear indicated successful mating and was regarded as gestational day 0 (GND 0). Following a successful mating the male rat was removed from the cage.

2.3. Prenatal stress protocol

On gestational day 14 (GND14) the pregnant rats were divided into two groups, namely, a non-stressed and a stressed group. The non-stressed rats were left undisturbed in their home cages. The stressed rats were taken to a different room and placed in rodent restrainers for 45 min, 3 times a day at 3 h intervals, starting at 09 h 00 (Patin et al., 2004; Wilson et al., 2013). The rats were returned to the housing room at the end of each stress period. Six animals were subjected to restraint stress between GND 14–20.

2.4. Postnatal handling

Following birth, both male and female offspring were used. We did not separate male and female rats as hormonal variations in pre-weaning females were irrelevant (Ramirez and Sawyer, 1965). The pups remained with the dams until postnatal day (PND) 14.

Table 1
Scoring of the seizure intensity (Heida et al., 2004; Ojewole, 2008).

Stage	Response
0	No response
1	Ear and facial twitching
2	Loss of postural control
3	Myoclonic jerks and rearing
4	Clonic convulsions – animal falling on its side
5	Repeated severe tonic – clonic convulsions

2.4.1. Induction of seizures

On PND 14, the dams were removed and placed in separate cages. The pups were taken to the experimental room 1 h before intraperitoneal (i.p.) injection of lipopolysaccharide (LPS, 200 μg/kg i.p.; *Escherichia coli* serotype, KOMA Biotech, USA) in order to acclimatise to the new environment. To induce the febrile seizures, the LPS injection was followed 2.5 h later by an injection of kainic acid (1.75 mg/kg, i.p., KOMA Biotech, USA) (Heida et al., 2004). All the drugs were dissolved in saline, control rats received an equivalent volume of saline.

2.5. Preparation of Searsia stem-bark aqueous extract

Fresh pieces of *Searsia* stem-bark were identified by a Taxonomist/Curator from the Botany Department of the University of KwaZulu-Natal as stem-bark of *Searsia* (Baker F.) (family: Anacardiaceae) with original voucher number 4594000, asersion no. 1228/ward herbarium. A kilogram of the air-dried *Searsia* was pounded and milled into a powder using a blender. The powder was extracted twice with methanol at room temperature for a period of 48 h. The blended methanol extract was filtered and concentrated at low pressure on a rotary evaporator at 60 ± 1 °C. The resulting methanol extract was freeze-dried yielding a yellowish-red brown powdery crude *Searsia* stem-bark extract. The extract was weighed and subsequently dissolved in saline for use at the required concentration. Control rats received equivalent saline injections (i.p.).

Searsia stem-bark extract was freshly prepared and administered intraperitoneally (1000 mg/kg) after the injection of kainic acid but prior to the onset of seizure activity. Visible convulsion took between 15 and 45 min to appear following kainic acid injection.

2.6. Assessment of convulsions

The convulsive behaviour of each rat was monitored and recorded using a Space security system camera for a period of 1.5 h following kainic acid and saline injections. Signs of neurological malfunction such as hind-limb tonic seizures or convulsive behaviour were recorded as per Ojewole (2008). Seizure duration was analysed by assessing the amount of time the animals displayed behavioural convulsions. The severities of the behavioural convulsions were scored as described in Table 1.

2.7. Plasma and tissue collection

On PND 15 non-stressed and prenatally stressed rats treated with saline or LPS and kainic acid, with or without *Searsia*, were decapitated and trunk blood was collected into ethylenediaminetetraacetic acid (EDTA) plastic tubes and spun at 10,000 rpm for 10 min. The plasma obtained was stored in Eppendorf tubes at −80 °C. The livers of the animals were also harvested into sterile plastic containers and stored in a −80 °C biofreezer.

2.7.1. Plasma analysis

IL-1β concentration in rat plasma was measured using a commercially available ELISA kit (BioLegend, USA). A pre-coated 96-well plate was used to conduct the assay. In order to optimise

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