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Anti-inflammatory effect of *Guiera senegalensis* roots in Wistar albino rats

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ABSTRACT

Acute and chronic anti-inflammatory effects of *Gueira senegalensis* roots methanolic extract (GSRM) was evaluated against carrageenan induced paw oedema in Wistar albino rats. Methanolic extract of *G. senegalensis* roots was prepared and the phytochemical analysis was performed. Phytochemical screening of GSRM, revealed the presence of saponins, tannins, flavonoids, sterols and triterpens. In acute study, the extract of *G. senegalensis* roots was investigated at a dose of 100, 200 and 400 mg/kg. Diclofenac sodium (10 mg/kg) was used as standard anti-inflammatory drug. The paw size of rats was measured at 0 hours (before carrageenan injection), 1, 2, 3 and 4 hour after carrageenan injection. In the chronic model; GSRM was dosed after insertion of cotton pellets till the 7th day, then the pellets were removed surgically, dried and weighed. Histopathological examination of subcutaneous tissues was also performed.

In acute inflammatory model, the paw oedema induced by carrageenan was significantly inhibited by oral administration of GSRM compared with untreated and diclofenac groups. The inhibition of oedema by the 400 mg/kg GSRM dose (66.61%) was better than that caused by 200 mg/kg dose (39.7%) and the100 mg/kg dose (35.47%), but less than the inhibition caused by diclofenac sodium (75.56%). In the cotton pellet granuloma method, the formation of granulomatous tissues was significantly decreased in rats that received GSRM. Maximum inhibition was produced by diclofenac sodium (41.71%) compared with dose of 400 mg/kg (17.42%) and 200 mg/kg (21.27%) of GSRM. Sections of subcutaneous tissue showed infiltration of inflammatory cells which indicated the reaction of extract in the

body compared with untreated control group.
This study concluded that the extract of *G. senegalensis* roots is effective in the treatment of acute and chronic inflammation. Further studies are recommended to isolate, identify and characterize the active ingredient(s) responsible of the anti-inflammatory effects of methanolic extract of *G. senegalensis* roots.

Introduction:

Inflammation is a defensive reaction of the body against infections and injuries. Oedema formation, leukocyte infiltration and granuloma formation represent typical features of inflammation (Sokeng et al. 2013).

In rural areas many plants are traditionally used effectively as remedy to treat many diseases including inflammatory conditions (Atawodi 2005; Namsa et al. 2009), Nowadays, medicinal plants are presenting tremendous promise for preventive intervention in the pathogenesis of many diseases, as well as in their treatment (Atawodi 2005), especially diseases such as cancer (Surh and Ferguson 2003; Tsao, Kim, and Hong 2004; Mehta and Pezzuto 2002), ulcer (Borrelli and Izzo 2000; Repetto and Llesuy 2002), diabetes (Sabu and Kuttan 2002) and others (Lampe 2003; Youdim and Joseph 2001; Perry et al. 1998; Miller 1998; Mahmood et al. 2017). The relationship between the antioxidant compounds in plants and their effectiveness in the treatment of these diseases has been described (Manach et al. 2004; Sabu and Kuttan 2002; Yang et al. 2001; Repetto and Llesuy 2002).

Plants comprise a huge number of phytoconstituents that synergistically act on different target elements of the complex cellular pathway (Kumar et al. 2013). Medicinal plants have been source of wide variety of biologically active compounds for many centuries and used extensively as crude material or as pure compounds for treating various disease conditions (Arif et al. 2009). The use of herbal medicines is becoming popular due to toxicity and side-effects of allopathic medicines. There are over 1.5 million traditional practitioners use medicinal plants for preventive, promotional and curative applications (Upadhayay et al. 2012; Vikrant and Arya 2011; Tiwari 2008).

Various inflammatory conditions have been treated successfully by medicinal plants. The inflammatory reactions comprise different enzyme activation, mediator release, fluid extravasations, cell migration, tissue breakdown and repair (Iwueke, Nwodo, and Okoli 2006). A great number of inflammatory mediators including kinins, platelet-activating factor (PAF), prostaglandins, leukotrienes, amines, purines, cytokines, chemokines and adhesion molecules, has been found to act on specific targets, leading to local release of other mediators from leukocytes and further attraction of leukocytes, such as neutrophils, to the site of inflammation (Bellik et al. 2012). The discharge of these mediators leads to stimulation of recruited inflammatory cells which elicit the initiation and maintenance of an inflammatory response, causing a change from the acute phase to the chronic phase of inflammation (Hamsa and Kuttan 2011). The reaction of these mediators that act to inhibit amplified inflammatory responses could be a promising therapeutic targets for anti-inflammatory agents including medicinal plants. Prostaglandins a pro-inflammatory mediator is one of such therapeutic targets that some of the potent anti-inflammatory agents of clinical relevance such as non-steroidal anti-inflammatory plants (NSAIDs) own their activity (Iwueke, Nwodo, and Okoli 2006).

Guiera senegalensis belongs to family Combretaceae, and locally known as Gebaish. It's a small shrub found mainly in West Africa. It's well known in the Sahel, where it grows gregariously, and forming abundant single-species colonies on fallow clay or sandy soils (Somboro et al. 2011). In Africa, it is used in traditional medicine to treat a variety of diseases, particularly malaria, fungal diseases, snake bite and intestinal disorders (Fiot et al. 2004; Ancolio et al. 2002; Silva and Gomes 2003; Abubakar et al. 2000). It is stated that the extract of *G. senegalensis* roots reduced the frequency of diarrhoea produced by caster oil (Shettima et al. 2012). The strong antioxidant effect of this plant suggests that it may exert valuable therapeutic effect in oxidative-stress related diseases; the antioxidant activity of the plant related to its phytoconstiuents including alkaloids (Ancolio et al. 2002; Ene-OjoAtawodi and Onaolapo 2010; Manach et al. 2004). *G. senegalensis* is useful as an ethnoveterinary product to increase milk production in cows and to treat fowlpox infection in chickens (Dénou et al. 2016). The plant is also reported to be hepatoprotective, antibacterial and anti-inflammatory (Oshobu and Geidam 2014; Faso 2011). The aim of this study was to evaluate anti-inflammatory activity of *Guiera senegalensis* roots methanolic extract in carrageenan induced paw oedema as acute model and on cotton pellet granuloma as chronic model in rats.

Fig.1. *G. senegalensis*-tree including roots

Source: http://www.west African plants.senckenberg.de/images/pictures/guiera-senegalensis-tm2011-05-2

Material and methods:

Plant material and extraction:

Guiera senegalensis roots were collected from Natural habitat in North kordofan. The roots were identified by expert botanists in Medicinal and Aromatic Plants, Traditional Medicine and Research Institute, National Center for Research, Khartoum, Sudan. The plant material was dried under shed. The extraction was performed by soxhlet apparatus using methanol as chemical extractor (Harborne 1984).

Experimental animals:

Wistar albino rats weighing 100-150g of both sexes were obtained from Medicinal and Aromatic Plants, Traditional Medicine and Research Institute, National Center of Research, Khartoum, Sudan. The animals were reserved in plastic cages in the Animal House, College of Veterinary

Medicine, Sudan University of Science and Technology. They were maintained under standard environmental condition and provided with standard rat diet containing several nutrients and free access of water. Rats were acclimatized before experimentation for at least 7 days to laboratory condition.

Carrageenan –induced paw oedema in rats (acute anti-inflammatory model)

Twenty five rats were randomly divided into 5 equal groups: Group 1: rats received distilled water only (1ml/100g) and served as control; Group 2: animals were given the standard anti-inflammatory drug diclofenac sodium (10mg/kg). Group 3,4 and 5 received GSRM at doses 100mg/kg, 200 mg/kg and 400 mg/kg orally, respectively. One hour after the administration of the treatments, carrageenan (0.1 ml, 1% w/v in saline) was injected into the sub planter tissue of the right hind paw of each rat to induce oedema. The paw size was measured using a digital vernier caliper at 0 hour (before carrageenan injection), 1, 2, 3 and 4 hour after carrageenan injection (Ramprasath, Shanthi, and Sachdanandam 2004). The percentage of inhibition of oedema was obtained using following formula:

$$\text{Percentage inhibition} = \frac{(Vt - Vo\ control - Vt - Vo\ \text{treated})}{Vt - Vo\ control} \times 100$$

Where Vo = Paw volume of test/control group at 0 hr

Vt= Paw volume of test/control group at that particular time interval

Cotton Pellets induced granuloma (chronic anti-inflammatory model):

Twenty eight rats of either sex (100-150g) were randomly divided into 4 groups of 7 rats each. The animals were anaesthetized with ketamine anaesthesia (50mg/kg), before subcutaneous implantation of sterile cotton pellets (20mg) in lumber region to induce chronic inflammation. Group 1: control, rats received distilled water only (10ml/kg). Group 2: rats were administered orally with the standard drug diclofenac sodium at dose of 10mg/kg. Group 3: rats were treated orally with *GSRM* at a dose of 100 mg/kg. Group 4: rats were administrated orally GSRM at a dose 200 mg/kg. Group 5 rats were given *G.senegalensis* roots methanolic extract at a dose 400mg/kg orally. The plant extract and standard drug were administered orally for 6 consecutive days from the day of cotton pellet implantation. On the 7th day animals were sacrificed by an over dose of ketamine anaesthesia. The cotton pellets were removed surgically, dried at 60˚C for 24 hours until constant weights were obtained and weighed. The increment in dry weight of the pellets over 20 mg was taken as an index of granuloma formation (Ramprasath, Shanthi, and Sachdanandam 2004).

$$\text{Percent inhibition} = = \frac{(Wt - Wo)\ control - (Wt - Wo)\ \text{treated}}{(Wt - Wo)\ control} \times 100$$

Where, Wo = Weight of the cotton pellets in control animal.

Wt = Weight of the cotton pellets in drug treated animals.

Histopathological methods:

The piths covered with granuloma tissue was dissected out, and immediately fixed in 10% formalin. These were processed in paraffin and sections 4-6 µm were prepared and stained with hematoxylin and eosin stains.

Statistical analysis:

Data was expressed as the mean ± SEM. Differences between experimental groups were compared by one way analysis of variance (ANOVA).The results were considered statistically significant at $P<0.05$ (Gomez, Gomez, and Gomez 1984).

Results:

Phytochemical screening

Chemical constituents of *G. senegalensis* roots methanolic extract contained high amount of saponins, tannins and triterpens. Moderate amount of flavonoids and traces of serols. The plant material was devoid of cumarins, alkaloids, anthraquinones and cyanogenic glycosides.

3.2 Carrageenan induced acute inflammation.

In the acute inflammation model, the standard drug diclofenac sodium (10mg/kg) showed significant ($p>0.05$) inhibition of paw oedema at 1st, 2nd, 3rd and 4th hours of induction (33.73%, 41.61%, 56.87% and 75.56% respectively). Rats given 400mg/kg of GSRM showed significant ($p>0.05$) gradual inhibition of paw oedema from 1st to 4th hours; the inhibition rates were 22.03%, 28.14% 66.61% and 42.99%, respectively when compared to control rats. Rats that received 200mg/kg of GSRM showed significant ($p>0.05$) inhibition in paw oedema (22.79%) at 1st hours and the inhibition increased gradually at 2nd (28.87%), 3rd (35.13%) and 4th (35.13%) hours. Rats administered 100mg/kg of GSRM also showed significant ($p>0.05$) inhibition of paw oedema at 1st, 2nd, 3rd and4th hours when compared with control rats. The dose 200 mg/kg GSRM dose gave comaratevely better results at 1st and 2nd hours but the 400 mg/kg was more effective in reducing paw oedema at the 3rd and 4th hours. The standard drug diclofenac sodium produces the highest inhibition especially at 4th hours (75.56%) see Table 1.

Table (1) Anti–inflammatory activity and inhibition percentage (%) of *G. senegalensis* roots methanolic extract on carrageenan induced paw oedema in rats

Groups	Dose	1 Hr	2 Hr	3 Hr	4 Hr
Control	I ml /rat	2.06 ± 0.43^{a}	2.09 ± 0.06^{a}	2.05 ± 0.04^{a}	1.98 ± 0.63^{a}
Diclofenac sodium	10mg/kg	1.35 ± 0.13^{d} (33.73%)	1.12 ± 0.09^{c} (41.61%)	0.88 ± 0.13^{d} (56.87%)	0.47 ± 0.13^{d} (75.56%)
GSRM 100	100mg/kg	1.60 ± 0.13^{c} (21.80%)	1.59 ± 0.15^{b} (23.32%)	1.33 ± 0.16^{b} (35.07%)	1.15 ± 0.15^{b} (35.47%)
GSRM 200	200mg/kg	1.68 ± 0.08^{b} (22.79%)	1.63 ± 0.16^{b} (28.87%)	1.49 ± 0.17^{b} (35.13%)	1.20 ± 0.17^{b} (39.07%)
GSRM 400	400mg/kg	1.60 ± 0.73^{c} (22.03%)	1.50 ± 0.05^{b} (28.14%)	1.16 ± 0.05^{c} (42.99%)	0.65 ± 0.10^{c} (66.61%)

Keys; GSRM 100; G.*senegalensis* roots methanolic extract 100 mg/kg, GSRM 200; *G.senegalensis* roots methanolic extract 200 mg/kg; GSRM 400; G.*senegalensis* roots methanolic extract 400 mg/kg .Values are expressed as mean ±SEM, means within the same column with different superscripts are significantly different at $p>0.05$ ($n=5$)

3.3 Cotton pellets granuloma.

Oral administration of GSRM at a dose of 200 and 400 mg/kg for 7 days had significantly ($P<0.05$) reduced the granuloma formation induced by cotton pellets compared to untreated control rats. Rats that received diclofenac sodium showed the maximum inhibition rate (41.71%) of granuloma formation. There was no significant difference ($p>0.05$) between rats administered 200mg/kg of GSRM and the standard drug diclofenac sodium (10mg/kg). However, both 200 and400 mg/kg doses of GSRM showed lower in inhibition rate of granuloma formation ($p>0.05$), comparable to diclofenac sodium (table 2)

Table (2) Inhibition rate of *G. senegalensis* roots methanolic extract on cotton pellet induced granuloma in rats

Groups	Dose	Dry weight	Inhibition rate %
Control	1 ml b.w	31.3 ± 3.63^{a}	-
Diclofenac sodium	10mg/kg	17.2 ± 0.49^{c}	41.71
GSRM 200	200mg/kg	21.5 ± 1.34^{cb}	21.27
GSRM 400	400mg/kg	24.4 ± 1.04^{b}	17.42

Keys; GSRM 100; G.*senegalensis* roots methanolic extract 100 mg/kg, GSRM 200; G.*senegalensis* roots methanolic extract 200 mg/kg; GSRM 400; G.*senegalensis* roots methanolic extract 400 mg/kg .Values are expressed as mean ±SEM, means within the same column with different superscripts are significantly different at p>0.05 (n=5)

3.4 The effect of oral treatment of GSRM on development of granulomatous inflammation in subcutaneous tissue.

In control rats, there was diffuse intensity fibroplasia with infiltration of monocytes and lymphocytes and capillary proliferation. Some sections showed loose young fibrous tissue with few neutrophils infiltration (Fig.2).

Rats administered diclofenac sodium as a standard drug showed loose fibrous tissue, excessive capillary proliferation and neutrophils and mononuclear cell infiltration; neutrophils were predominant (Fig.3).

In rats given 200mg/kg of GSRM fibrovascular tissues proliferation with fibrin deposition and intense neutrophils infiltration were seen. Some sections showed immature fibrous tissue with or without mononuclear cells infiltration (Fig.4).

In rats treated with 400mg/kg of GSRM sections showed loose connective tissues and young fibroblast with infiltrations of neutrophils and mononuclear cells. Some sections showed bundle of fibrin (Fig.5).

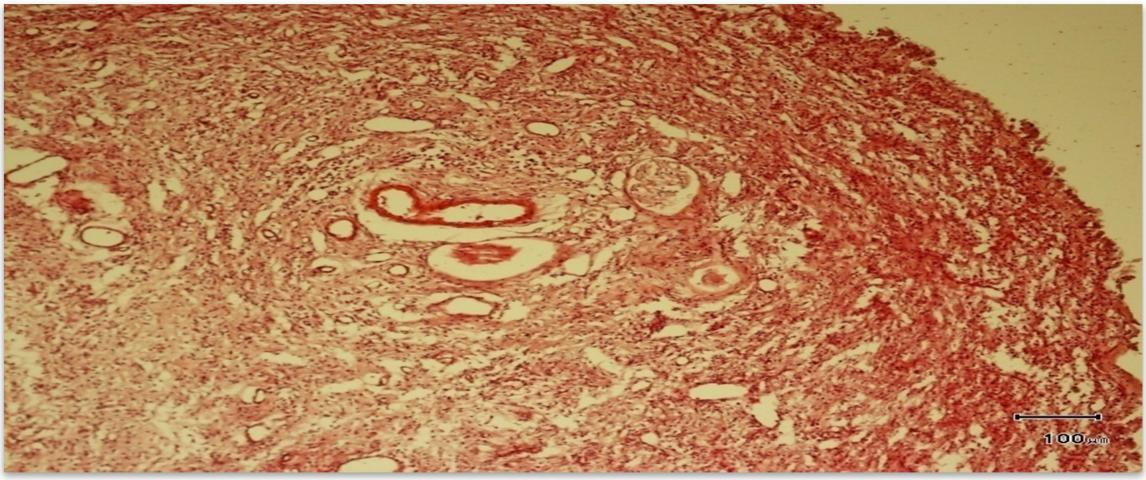
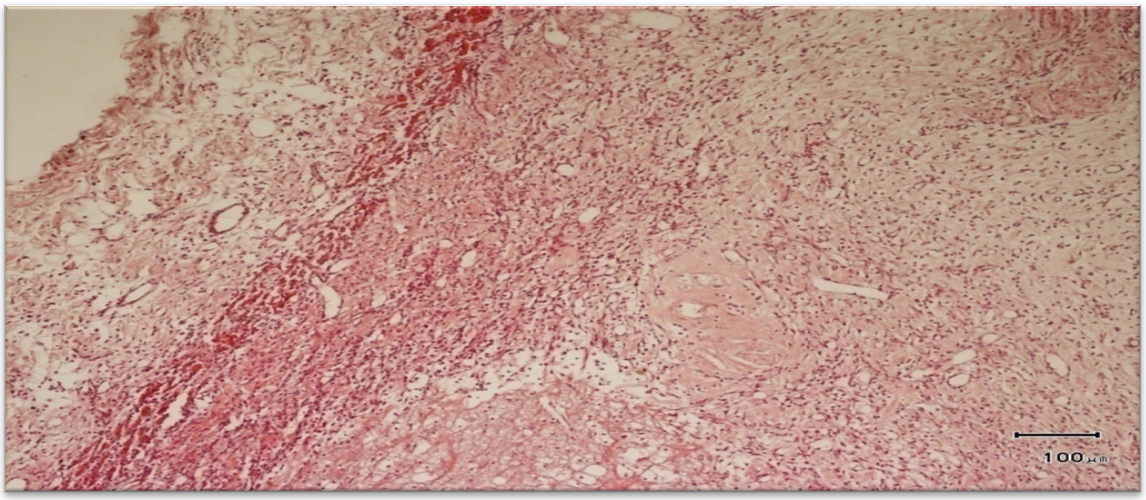


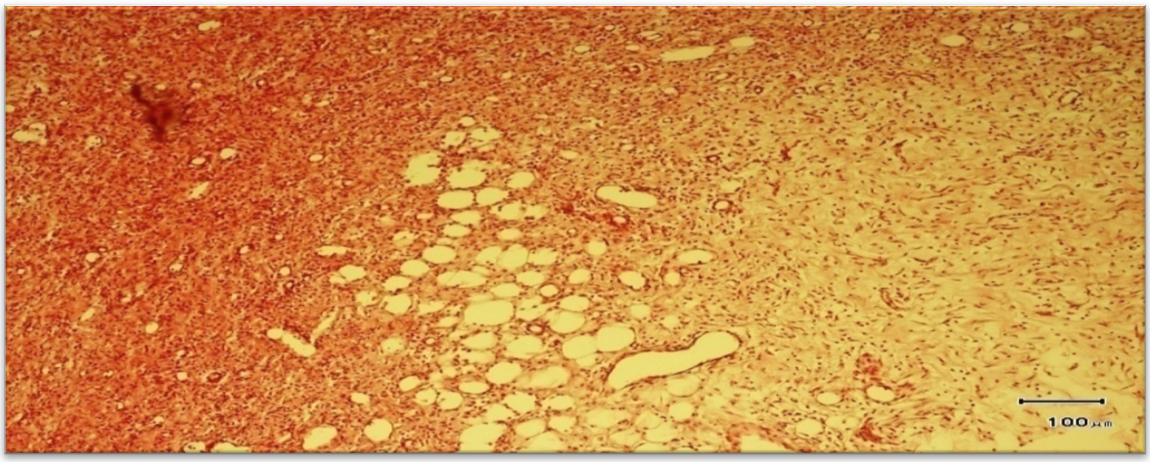
Fig.2 control rat: Subcutaneous tissue showing diffuse fibrosis with monocytes and lymphocytes infiltration. H&E stain X40.

Fig.3. Rat treated with diclofenac sodium 10mg/kg: Subcutaneous tissue showing loose connective tissue with



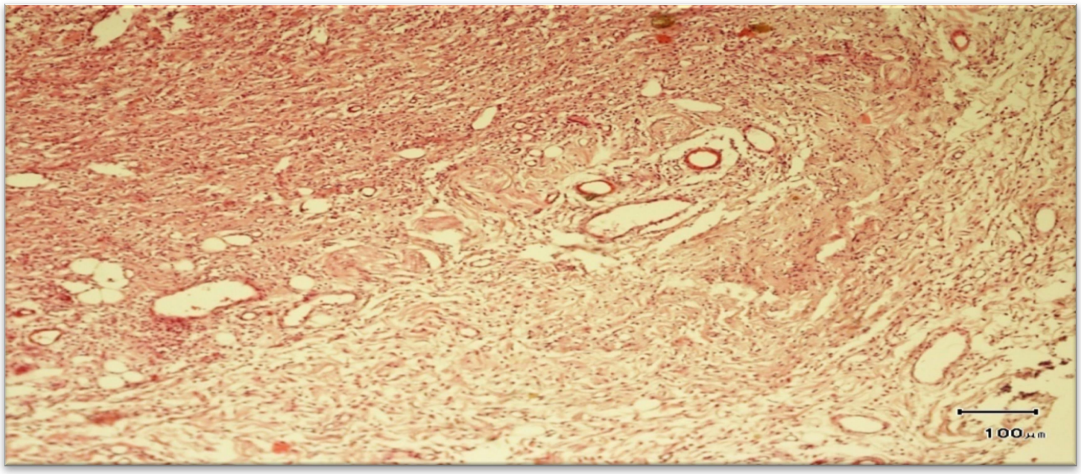
neutrophils infiltration and deposition of fibrin. H&E stain X40**.**

Fig.4. Rat treated with 200mg/kg GSRM: subcutaneous tissue showing growing vascular tissue, fibroplasia and infiltration of



lymphocytes. H&E stain X40.

Fig.5. Rat treated with 400mg/kg GSRM: subcutaneous tissue showing loose connective tissue with dense infiltration of neutrophils, presence of fibroblasts and some bundle of fibrin (H&E stain) Lower magnification.



Discussion:

G. senegalensis, a multipurpose tree, is used extensively by rural people in traditional medicine to treat various illnesses including inflammation (Fiot et al. 2004). This study was conducted to evaluate the anti-inflammatory effect of *G. senegalensis* roots methanolic extract in acute and chronic models in Wister albino rats.

The injection of carrageenan into rats produced a localized acute inflammatory response characterized grossly by an increase of paw size and pain as a result of increased vascular permeability, and microscopically by cell infiltrations and exudation. This is in agreement with the result of (Venkataranganna et al. 2000).

Administration of GSRM at a dose of 100, 200 or 400 mg/kg orally produced a significant inhibition in the rats paw oedema in both phases of inflammation. The medium (200mg/kg) and high (400 mg/kg) doses of *GSRM* were found to be more effective in reducing paw oedema (39.07 and 66.61% respectively) at 4thhour post carrageenan injection compared with control rats. While the low dose (100 mg/kg) was less effective (35.47%). This result disagrees with (Jigam et al. 2011), who found no anti-inflammatory activity in a dose of 300 mg/kg and 600 mg/kg of *G. senegalensis* leaves ethyle acetate and methanolic extract compared with a standard acetyl salicylic acid at dose 20 mg/kg .

This present study indicates that oral treatment with different doses of GSRM significantly reduced the paw oedema in rats but not effective as the standard drug, diclofenac sodium.

The ability of GSRM to reduce the carrageenan induced paw oedema may be attributed to its content of chemical components having anti-inflammatory properties. This could be supported by the result of the treatment of chronic granulomatous inflammation induced by cotton pellets.

Furthermore, the methanolic extracts of *G. senegalensis* roots were also evaluated in the treatment of chronic inflammation using cotton pellet induced granuloma.

In chronic inflammation model, the transudative, exudative and proliferative components of chronic inflammation have been extensively evaluated by the model of cotton pellet granuloma. In this study, control group showed a remarkable formation of granulation tissue which was indicated by increase in dry cotton pellet weight after removal from the incision.

Animals treated with medium dose 200mg/kg and high dose 400mg/kg showed a significant decrease in granulation tissue compared with control group whereas rats treated with diclofenac sodium 10mg/kg showed highly significant decrease in granulomatus reaction compared to control and treated rats. This may be due to the ability of extract in reducing the number of fibroblasts and synthesis of collagen and mucopolysaccharide, which are natural proliferative agents of granulation tissue formation (Babu, Pandikumar, and Ignacimuthu 2009).

Phytochemical screening of *G. senegalensis* revealed the presence of saponins, tannins, flavonoids, serols and triterpens. The plant material was devoid of cumarins, alkaloids, anthraquinones and cyanogenic glycosides. (Somboro et al. 2011), isolated terpenoids, saponins, alkaloids, mucilages, flavonoids, tannins, and cardiotonic from the roots. Histopathological examination of the granuloma tissues showed significant fibrovascular proliferation, fibrin deposition and intense neutrophils infiltration in test groups compared with control rats, which indicate the positive anti-inflammatory action of *G. senegalensis* methanoilc extract.

From the above results it is clear that the methanol extract of *G. senegalensis* has an anti-inflammatory activity, which lend to the use of this plant in inflammatory conditions as proposed in folklore medicines.

It is concluded that the methanolic extract of *Guirea senegalensis* roots displays a significant effect in acute and chronic anti-inflammatory models compared with standard drug declofenac sodium especially in acute inflammation. The anti-inflammatory effect of *G. senegalensis* is supported by histopathological changes in granulomatous reactions in the chronic inflammatory model. The anti-inflammatory activity of *G. senegalensis* roots methanolic extract may be attributed to the inhibition of prostaglandin, synthesis as a result of inhibition of cyclooxygenese.

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