RESEARCH ARTICLE Am. J. PharmTech Res. 2017; 7(4) ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

**Journal home page:** http://www.ajptr.com/

# Evaluation of Anti Inflammatory and Analgesic Activity of Rhizome of *Swertia Petiolata*

**G.N.Bader[1*], P.A.Mir[1], S.Ali[2]**

*1.Department of pharmaceutical Sciences, University of Kashmir, Hazratbal Srinagar*

*2.Department of Biochemistry, Hamdard University, Hamdard Nagar, New Delhi*

## ABSTRACT

Aqueous and hydro-alcoholic extracts of rhizome of *Swertia petiolata* were evaluated for their anti-inflammatory activity against carrageenan induced rat hind paw oedema. Hydro-alcoholic extract decreased the inflammation by 66.66%, 68.10% and 77.7% at 1, 2 and 3 hours post treatment, while as the aqueous extract decreased the inflammation by 68%, 68% and 70.30% respectively. Aceclofenac (used as a standard anti-inflammatory allopathic control) could alleviate the inflammation to 62%, 64.05% and 66.66% under the identical experimental conditions. The extracts also exhibited good analgesic activity when tested by Tail Flick, Tail Clip and Hot plate Methods. The analgesic activity was evidenced by an increase in the reaction time by 8 and 7.5 seconds, 1 hour post treatment of hydro-alcoholic and aqueous extracts, respectively as determined by tail flick method. The analgesic activity was also confirmed by tail clip and hot plate methods. In the tail clip method the increase in reaction time was by 8 and 8.1 seconds. Whereas by hot plate method it was 7.7 and 7.5 seconds. Aceclofenac under the similar conditions increased the reaction time by 9.5, 9.5 and 9.2 seconds respectively by the above methods.

**Keywords:** *Swertia petiolata*, antiinflammatory activity, analgesic activity.

*Corresponding Author Email: gbader2007@gmail.com

Received 14 March 2017, Accepted 15 April 2017

Please cite this article as: Bader GN *et al.*, Evaluation of Anti Inflammatory and Analgesic Activity of Rhizome of Swertia Petiolata. American Journal of PharmTech Research 2017.

## INTRODUCTION

Inflammation is a complicated biological phenomenon, which in short can be defined as reaction of tissues to injury in higher animals. The pathophysiological study of the disease shows complex vascular, lymphatic and local tissue reactions at the site of injury. Essentially, it is a normal and necessary defense and repair response of the body. The basic symptomatic features of inflammation are swelling, heat, pain, redness and subsequent reduction in structural and functional organization (Abbas and Lichtman 2009). The basic difference between acute and chronic inflammation lies in the duration of inflammatory process. Acute inflammation lasts for a week or two, where as chronic inflammation lasts for months, sometimes years or whole life and is associated with increased activity of cellular components. Inflammation is characterized by three phases, which are interrelated and merged one into another. These are:

Transudative phase

It is the first phase of inflammatory response, also known as degenerative stage. In this phase cellular degradation occurs in the traumatized area. The vessels are destroyed and haemorrhage ensues which leads to localized compression and necrosis. The epithelial cells and some of the fibroblasts as well as their cytoplasm become vacuolated and their nuclei undergo pyknosis and karyorrhesis. Various highly active substances are liberated at the site of injury, which include histamine, serotonin, kinins, leucotoxin exudin (Coutaux *et al*., 2005), prostaglandins (Emanuela and Garret 2011) thromboxane $A_2$ (Funk and FitzGerald), prostacyclin (Moncada *et al*., 1991), besides some other mediators of inflammation. These substances also called as chemical mediators cause dilatation of blood vessels and increase their permeability leading to erythema and oedema at the site of injury. Various proteolytic enzymes are released in high concentration at the site of injury and act as mediator genase for production of polypeptides as bradykinin and kallidin (Fumimasa *et al*., 2013). There are number of evidences to suggest that not only endogenous proteases participate in the development of inflammatory reactions but also exogenous enzymes can act as inflammatogenic stimulus (Geetha and Hudson 2009).

In the inflammatory process prostaglandins are released at concentration, that indicates their potential role in the inflammatory reaction (Terence and Peter 2009). These induce most of the signs of inflammation, erythema, pain, vasodilatation and oedema. The fatty acid hydroperoxides have been shown to cause erythema and pain (Huang *et al*., 2006). Platelet aggregation is believed to play an important role in the initiation of micro-thrombi and vascular inflammation (Kunal 2015). Platelets are the storage pools of adenine dinucleotide (ADP), serotonin (5-HT), histamine, prostaglandins, calcium ions and α-granules .These permeability factors are released due to aggregation and damage of platelets induced by ADP, adrenaline and thrombi.

**Exudative phase**

The passive phenomenon of haemorrhage and necrosis are followed by active tissue and cellular reactions such as vascular dilation and diapedesis giving rise to leucocyte migration. There is increase in capillary number engorging with blood or haemostasis. This alteration is responsible for heat and redness observed in inflamed areas. Active congestion develops at the edge of the wound followed by extravasation of serous fluid from the lumen of the dilated vessels in the extravascular spaces, which soon accompanies the vasodilatation giving rise to local oedema (Ratnasooriya *et al*., 2005). A number of lytic enzymes including lysosomal enzymes and hydrolases are released into the inflammatory exudates either from injured local cells or during phagocytic activity of migrating cells (Rita *et al*., 2011). These enzymes such as acid phosphatase, β-glucuronidase, hyaluronidase and phospholipases cause further damage of the injured tissue by lysing them and the fluids originating from the necrotic process mixed with the serous material that extruded from the vessels, yield characteristic material called pus.

**Proliferative phase**

The repair or Proliferative phase is the last phase of inflammatory reaction. It includes proliferation of capillaries and young fibroblasts. The epithelium of young fibroblasts start elaborating collagen fibres. The cellular proliferation penetrates the exudates producing a highly vascularized reddish mass termed "granulation tissue", which develops to fill the wedge of wound. A number of enzymes such as cathapsin, lipases and nucleases catalyze the degradation and cleaning of inflammatory debris.

**Plants as a source of medicine**

Natural resources such as plants have always been considered as a reliable and diverse source of molecules to be used as medicines. Use of botanicals in medicines, dietary supplements, and functional food is common worldwide. According to W.H.O. estimation, around 80% of the world's population depends on alternative system of medicines for their primary health care. The plants are the major constituents of various alternative systems of medicines used worldwide since ancient times. Recent times have seen a steep rise in the herbal medicine. This increase is a reflection of the fact that the therapies developed along the principles of western medicine are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing and poor countries. However, the acceptability of the herbal medicine is usually low due to a lack of information on the scientific validation of the claim. Further, many species have not been fully characterized and there is an emerging need for the same.

Kashmir region of Himalaya is a rich source of diversified herbs and shrubs of medicinal importance. Among various species of plants of medicinal importance, the family *Gentianaceae* holds a distinct place, as various genera of this family are medicinally important and have been used over years in various parts of the world to treat different ailments. There are around 1000 species of this family. Among the plants often used in traditional medicine, *Swertia* species are quite important and have been used as crude drugs in Indian Pharmacopoeia. These species contain many phytoconstituents which are used to protect against various diseases. There are about 250 species of *Swertia,* distributed worldwide, out of which near about 32 species occur in India with 15 species in north west Himalaya. About 9 species of *Swertia* have been reported from Jammu and Kashmir. These grow in grasslands, slopes or alpine bugyal. A perusal of data reveals that the genus *Swertia* is heteromorphous as the species occupy habitat ranging from mesophytic, more or less xeric to temperate conditions from low to high (alpine) altitude (490—6250mts). In westen Himalayas these species are found in Sonamarg, Batote, Banks of Chenab, Gulmrg, Baderwah, Gilgit, Lidder valley, Sindh valley, Drass, Banihal, Aharbal, Zanskar and Banamarg.

*Swertia petiolata* is a perennial, erect, rhizomatous, simple or branched, glabrous herb. The rhizomes are covered with old petiole bases, and the stem terete and hollow. Radical and lower1-2 pairs of cauline leaves have long petiole, elliptic-oblong, spathulate, petiole dilated, connate near base, 5-nerved, upper cauline leaves usually opposite in 3's, narrowly lanceolate, sessile, amplexicaule, 3-nerved. Inflorescence lax, few to many flowered, panicle solitary axillary or axillary and terminal, cluster of 3-5 flowered peduncle terete, bracts foliaceous, sessile, narrowly elliptic lanceolate. Flowers pentamerous, variously coloured, pedicels unequal, calyx lobes lanceolate or linear lanceolate, glabrous 1-3 nerved, margins denticulate, corolla lobes 5, oblong, glands 2, orbicular or ovoid, with ciliate fimbrial at base, anthers bluish, capsule oblong- ellipsoid, many seeded coloured reddish brown.

*S. petiolata* is widely distributed in India, Pakistan, Tibet, East Afghanistan and China. In India, it is found in Jammu & Kashmir, Himachal pardesh, and U.P hills. It is widely distributed in the area of Jammu & Kashmir from Zanskar, Gilgit, Rinchagma, Kaspucha, Sangam, Rucham pass, Burzil pass, Pirpanchal, Kishanganga valley, Jehlum valley, Harmukh slope, Khuihama forest, Sarbal pass, Gulmarg, Deosai plains, Amaranth way, Apharwat, Sheshnag, Mahaguna pass, Khillanmarg, Banamarg etc. The flowers and fruits come in late July to September.

## MATERIALS AND METHOD

**Identification and collection**

For the present study, *S. petiolata* was collected from Banamarg and Gulmarg (2950-3300 mt) areas of vale of Kashmir in the month of October.

**Experimental model**

Inbred pathogen free adult male wistar rats (180-200gm body weight), in an environmentally controlled room with a 12 h light-dark cycle at constant room temperature (24 ± $2^0$C) and relative humidity (60 ± 15 %), were used throughout the study. Animals were acclimatized for one week before starting the experiment. A maximum of six rats were kept in polypropylene cages. Animals had free access to pellet diet (Hindustan lever Ltd, Bombay, India) and water ad libitum. Guidelines issued by the CPCSEA for the care and use of laboratory animals were followed.

**Experimental Design**

**Preparation of extracts**

Shade dried rhizomes of *S. petiolata* were crushed in a mixer grinder. The crushed material was subjected to extraction in soxhlet apparatus at 60-70°C for 6 hours continuously in hydro-methanol (20:80). The extracted material was evaporated to dryness under reduced pressure at 40-50°C. The crude extract was dried and suspended in distilled water and used in further studies. Percent yield of the extract was calculated as 20.3 %, Similarly, the powdered material was cold extracted with water for 24 hours with occasional stirring. The extract was filtered and dried and the percent yield calculated as 15.5%.

**Evaluation of the anti-inflammatory activity**

Animals were divided into five groups: Group I (Normal Control) received normal saline, Group II rats (Inflammation model) were injected carrageenan, while Group III and IV, (Experimental rats) were injected carrageenan and given *Swertia petiolata* extracts (aqueous and hydro-alcoholic extracts respectively). Group V rats were injected carrageenan and treated with Aceclofenac (5 mg/kg body weight) as a standard allopathic antiinflammatory drug. The doses of the extracts administered to rats were 1gm/kg body weight for aqueous extracts and 200 mg/ kg for hydro-alcoholic extracts. The measurement of hind paw volume was carried out1, 2 and 3 hours post carrageenan injection using plethysmograph.

Oedema was induced in the left hind paw of rat by injecting 0.1 ml of 1% carrageenan solution, prepared by suspending 0.1g carrageenan in 10 ml normal saline solution. Respective test drugs and the allopathic control (aceclofenac) were given orally an hour prior to carrageenan injection at a dose level of 200 mg/kg body weight for hydro alcoholic extract and 1gm/kg body weight for aqueous extract. Aceclofenac was used at a dose level of 5 mg/kg body weight. Oedema was measured 1,2 and 3 hours post carrageenan injection using a plethysmometer. Percent inhibition was calculated as follows:

% inhibition =Vc-Vt/ Vc X 100

Where Vc is the volume of oedema following carrageenan injection, and Vt is the volume of oedema in extract/drug treated group. Volume of oedema was derived by taking the difference in the volume of left hind paw receiving carrageenan injection, minus the volume of the right hind paw, which was not given carrageenan injection.

**Analgesic Activity**

Male rats (Wistar strain) were divided into 4 groups. In addition to the control rats (group I), experimental rats from Group II and III received, respectively, the aqueous and the hydro-alcoholic extracts of *S. petiolata* whereas Group IV received Aceclofenac (5 mg/kg body weight). Analgesic activity of each extract was determined using standard pharmacological methods (tail flick method, hot plate method, and tail clip method).

**Experimental design and analgesic activity**

Analgesic activity of the extracts was determined by the following methods in male wistar rats.

a) Tail flick method

b) Hot plate method

c) Tail clip method

**Tail flick method *(Swapnil et al., 2012)***

The animals were divided into 4t groups, each group containing six animals. Group-I received normal saline and acted as control, group-II & III received aqueous and hydro-alcoholic extracts of *S.petiolata*, whereas group-IV received aceclofenac (5mg/kg body weight). Two hours post administration of the extracts and standard drug, the animals were held in a position with the tail protending out on the coil of analgesiometer. A current of 5 volts was applied and the time taken by the animals to withdraw (flick) the tail was taken as the reaction time.

**Hot plate method (Amanda *et al.*, 2011)**

The animals 2 hours post treatment were placed on a hot plate, maintained at 55°c. The reaction time (the time between placing the animals on the hot plate and licking of the fore or hind paws by the animals) was noted. The mean increase in the reaction time in treated groups was compared with that recorded in control animals to determine the analgesic activity.

**Tail clip method (Agbaje *et al.*, 2008)**

An artery clip with thin rubber sleeves was applied to the base of rat-tail to produce a painful stimulus. Control animals make a continuous effort to dislodge the clip by biting it. Analgesia makes the animals indifferent to the pain produced by clip presser.

Two-hour post treatment, the artery clip was applied to the base of tail, and the reaction time was noted. The mean increase in the reaction time in treated group was compared with that recorded in control animals to determine analgesic activity.

## RESULTS AND DISCUSSION

Results presented in the table-1 and 2 provide clear evidence suggesting the anti-inflammatory and analgesic role of *Swertia* petiolata collected from Banamarg and Gulmarg areas of vale of Kasmhir. Significant alleviation of pain and inflammation was demonstrated by the the extracts (Tables 1 & 2) which was comparable to aceclofenac, the standard anti-inflammatory and analgesic drug. The findings are in accordance with the earlier studies on other *Swertia* species, particularly *Swertia chirata*, which is widely used in India to treat fever, inflammatory diseases and malaria (Wungsem *et al*., 2013; Abhishek *et al*., 2011; Sampath *et al*., 2010) .

**Table 1: Showing anti-inflammatory activity of *S. petiolata* extracts against carrageenan induced hind paw oedema in Wistar rats.**

| Group | Percent reduction in paw volume | | |
|---|---|---|---|
| | 1 hr post treatment | 2 hr post treatment | 3 hr post treatment |
| S.T (H/A) | 70.00 ± 0.07 | 72.10 ± 0.09 | 74.07 ± 0.011 |
| S.T (Aq) | 56.00 ± 0.04 | 59.00 ± 0.06 | 66.66 ± 0.08 |
| Aceclofenac | 62.00 ± 0.10 | 64.05 ± 0.09 | 66.66 ± 0.07 |

S.P (H/A): *S. petiolata* hydro-alcoholic extract; S.P (Aq): *S. petiolata* aquous extract. The results are expressed as Mean ± S.E of six animals.

**Table 2: Analgesic activity exhibited by delayed reaction time (in Seconds) following the oral doses of *Swertia petiolata* extracts**

| Extracts | Increase in the reaction time (in seconds) | | |
|---|---|---|---|
| | Tail flick method | Tail clip method | Hot plate method |
| S.P (H/A) | 8.0 ± 0.003 | 8.0 ± 0.005 | 7.7 ± 0.008 |
| S.P (Aq) | 7.5 ± 0.004 | 8.1 ± 0.008 | 7.6 ± 0.009 |
| Aceclofenac | 9.5 ± 0.009 | 9.5 ± 0.007 | 9.2 ± 0.010 |

S.P (H/A): *S. petiolata* hydro alcoholic extract; S.P (Aq): *S. petiolata* aquous extract. The results are expressed as Mean ± S.E of six animals

Inhibition of carrageenan-induced inflammation is one of the most suitable test procedures to screen antiinflammatory agents. Oedema formation in paw is the result of a synergism between various inflammatory mediators that increase vascular permeability and/or mediators that increase blood flow (Mahesh *et al*., 2009). The development of carrageenan-induced oedema is bi-phasic: the first phase is attributed to the release of histamine, 5-hydroxytryptamine and kinins, and the second phase is related to the release of prostaglandins (Sur *et al*., 2003; Shiv *et al*., 2004; Sudipta *et al*., 2011). Both steroids and non-steroidal anti-inflammatory drugs (like aspirin and indomethacin) inhibit biosynthesis of prostaglandins. Steroids inhibit conversion of membrane phospholipids to arachidonic acid and thus block formation of leukotriene, prostacyclin, PGE2 and related prostaglandins whereas non-steroidal antiinflammatory drugs irreversibly inactivate cyclo-oxygenase. Moreover, so far very few antiinflammatory agents have been shown to have direct antaqqistic action against exogenous prostaglandins. Also oxygen derived free radicals and oxidants have been shown to play an important role in various forms of inflammation (Souza *et al*., 2009; Salvatore *et al*., 2001).

In order to identify the compounds responsible for the biological activities observed, many compounds as Xanthones, mangiferin, α-mangostin, isomangostin, α-mangostin triacetate, besides some other compounds, as ursolic acid have been separated from the extracts of *S. chirata*, and reported to be antiinflammatory (Chauhan & Prabhu 2013; Banerjee *et al*., 2000). Several reports are there which suggest a strong role of ursolic acid in antiinflammatory action. It not only inhibits human leucocyte elastase, but also 5-lipoxigenase and cycloxygenase activity (Danielea *et al*., 2005; Bharat *et al*., 2006). The mechanisms of antiinflammatory activity of ursolic acid have been attributed to inhibition of histamine release from mast cells (Tourandokht *et al*., 2005; Jéssica *et al*., 2015; Patricia *et al*., 2010) and to inhibition of complement activity (Micelia *et al*., 2005). Moreover, ursolic acid has exhibited strong inhibitory activity on the production of nitric oxide in macrophages (Ryu *et al*., 2000). Polyphenols were demonstrated as possessing in vivo antiinflammatory properties too (Moreira *et al*., 2000; Ueda *et al*., 2002). Moreover, the irridoids and seco-irridoids could also contribute to antiinflammatory effect (De Mirando *et al*., 2000; Diaz *et al*., 2000). Flavonoids also have been known to possess antiinflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral and anticarcinogenetic activities. Phytochemical studies on *swertia petiolata* have shown presence of alkaloids, flavonoids and sterols etc (Bader et al, 2017) with known antiinflammatory activity. The extracts also increased the pain threshold by all methods tested. To conclude it can be assumed that the antiinflammatory and analgesic activity of *S.Petiolata* is either due to one of these compounds or all of them may be acting synergistically at different levels of inflammation. This also gathers support from the fact that hydro-alcoholic extract of the herb showed more antiinflammatory activity than aqueous extract, which may be due to the presence of more antiinflammatory phytoconstituents in hydro-alcoholic extracts than in aqueous extracts.

## CONCLUSION

Herbs are an integral part of nature and contain various natural substances that can promote health. Both forms (aquous and hydro-alcohlic) of the extract have shown significant antiinflammatory activity with carrageenan induced paw oedema model in rats. The hydro-alcoholic extract is found to possess greater antiinflammatory activity than aqueous extract, which may be due to presence of more antiinflammatory principles in the hydro-alcoholic extract. In our study, the analgesic activity of the specie highlighted the importance of the extracts in traditional preparations.

## REFERENCES

1. A.S. Moreira, V. Spitzer, E.E. Schapoval, E.P. SchenkelAntiinflammatory activity of extracts and fractions from the leaves of Gochnatia polymorpha Phytotherapy Research, 2000; 14; 638-640.
2. Abhishek Mathur, Satish K. Verma, Santosh K. Singh, Deepika Mathur, GBKS Prasad, V.K. Dua. Pharmacology Investigation of anti-inflammatory properties of Swertia chirayta and Gloriosa superb. Recent Research in Science and Technology 2011, 3(3): 40-43
3. Agbaje Esther Oluwatoyin, Adeneye Adejuwon Adewale, and Adeleke Tijani Isaac. Anti-Nociceptive and Anti-Inflammatory Effects of a Nigerian Polyherbal Tonic Tea (PHT) Extract in Rodents. Afr J Tradit Complement Altern Med. 2008; 5(3): 247–256.
4. Amanda Gunn, Erin N. Bobeck, Ceri Weber, and Michael M. Morgan. The Influence of Non-Nociceptive Factors on Hot Plate Latency in Rats. J Pain. 2011; 12(2): 222–227.
5. Banerjee Shivaji, Tapas Kumar Sur, Suvra Mandal, Prabhash, Chandra Das, Sridhar Sikdar. Assessment of the anti-inflammatory effects of Swertia chirata in Acute and chronic experimental models in male albino rats. Indian Journal of Pharmacology 2000; 32: 21-24
6. Bharat B Aggarwal, Haruyo Ichikawa, Prachi Garodia, Priya Weerasinghe, Gautam Sethi, Indra D Bhatt, Manoj K Pandey, Shishir Shishodia & Muraleedharan G Nair. From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer. Expert Opin. Ther. Targets, 2006; **10**(1):87-118

7. Chauhan R. S. & Prabhu Dutt. Swertia ciliata - A New Source of Mangiferin, Amaroswerin and Amarogentin**. J** Biologically Active Products from Nature**,** 2013**;** 3 **(2);** 161-165.
8. Danielea C., Dahamnab S., Firuzia O., Sekfalib N., Sasoa L., Mazzantia G. Atractylis gummifera L. poisoning: an ethnopharmacological review. J Ethnopharmacology (2005) 175–181
9. De Miranda AL, Silva JR, Rezende CM, Neves JS, Parrini SC, Pinheiro MLB, Cordeiro MC, Tamgborini E, Pinto AC. Anti-inflammatory and analgesic activities of the latex containing triterpenes from Himatanthus sucuuba.Planta Med. 2000; 66: 284-286.
10. Díaz AM, Abad MJ, Fernández L, Recuero C, Villaescusa L, Silván AM, Bermejo P. In vitro anti-inflammatory activity of iridoids and triterpenoid compounds isolated from Phillyrea latifolia L. Biol Pharm Bull. 2000; 23(11):1307-13.
11. Bader, G. N., Mir, P. A., Naqash, A., Ali, T., Wadoo, R. and Ali, S. "Phytochemical screening and evaluation of Hepatoprotective potentialof Swertia petiolata against Thioacetamide induced Hepatotoxicity in rats" , International Journal of Current Research, 2017, 9(06):52737-52747.
12. Huang M.-T., G. Ghai, and C.-T. Ho. Inflammatory Process and Molecular Targets for Antiinflammatory Nutraceuticals. Comprehensive Reviews in Food Science and Food Safety, 2006; 3(4).
13. Jéssica A. Jesus, João Henrique G. Lago, Márcia D. Laurenti, Eduardo S. Yamamoto and Luiz Felipe D. Passero. Antimicrobial Activity of Oleanolic and Ursolic Acids: An Update. Evidence-Based Complementary and Alternative Medicine, 2015, 14 pages.
14. Mahesh S. Paschapur, M. B. Patil, Ravi Kumar and Sachin R. Patil. Evaluation of anti-inflammatory activity of ethanolic extract of Borassus flabellifer L. male flowers (inflorescences) in experimental animals. J Medicinal Plants Res., 2009; 3(2), 049-054.
15. Micelia N., M.F. Tavianoa, D. Giuffridab, A. Trovatoa, O. Tzakouc, E.M. Galatia. Anti-inflammatory activity of extract and fractions from Nepeta sibthorpiiBentham. Journal of Ethnopharmacology, 2005; 261–266
16. Patricia F. Esteves, Ricardo M. Kuster, Nancy dos S. Barbi & Fabio de S. Menezes. Chemical Composition and Cytotoxic Activity of Lepechinia speciosa (St. Hill) Epling. Lat. Am. J. Pharm., 2010, 29 (1): 38-44.
17. Rita Rotondo, Maria Bertolotto, Gaia Barisione, Simonetta Astigiano, Susanna Mandruzzato, Luciano Ottonello, Franco Dallegri, Vincenzo Bronte, Silvano Ferrini, and

Ottavia Barbieri. Exocytosis of azurophil and arginase1-containing granules by activated polymorphonuclear neutrophils is required to inhibit T lymphocyte proliferation. J Leukocyte Biology; 2011; 89, 721-727.

18. Ryu Y, Oak MH, Yoon SK, Cho DI, Yoo GS, Kim TS, Kim KM. Antiallergic and anti-inflammatory triterpenes from the herb of Prunela vulgaris. Planta Med. 2000; 66:358–360.
19. Salvatore Cuzzocrea, Dennis P. Riley, Achille P. Caputi, and Daniela Salvemini. Antioxidant Therapy: A New Pharmacological Approach in Shock, Inflammation, and Ischemia/Reperfusion Injury. Pharmacol Rev., 2001; 53:135–159.
20. Sampath Kumar K. P., Debjit Bhowmik, Chiranjib, Biswajit and Margret Chandira. Swertia chirata: A traditional herb and its medicinal uses. J. Chem. Pharm. Res., 2010, 2(1): 262-266
21. Shiv Kumar, M. S. Ganachari, Banappa, V. S. Nagoor. Anti-inflammatory activity of Ziziphus jujuba Lam leaves extract in rats. J natural remedies, 2004; 4/2; 183 – 185
22. Souza Filho M.V.P., R.T. Loiola, E.L. Rocha, A.F.L. Simão, A.S. Gomes, M.H.L.P. Souza and R.A. Ribeiro. Hind limb ischemic preconditioning induces an anti-inflammatory response by remote organs in rats. Braz J Med Biol Res, 2009, 42(10) 921-929
23. Sudipta Das, Pallab K Haldar, Goutam Pramanik, Siva P Panda, and Samit Bera. Evaluation of Analgesic and Anti-Inflammatory Activity of Diospyros Cordifolia Extract. Afr J Tradit Complement Altern Med. 2011; 8(1): 11–14.
24. Sur Tapas Kumar, Biswas Tuhin Kanti, Ali Liaquat, Mukherjee Biswapati. Anti-inflammatory and anti-platelet aggregation activity of human placental extract. Acta Pharmacol Sin., 2003; 24 (2): 187-192
25. Swapnil R. Jaiswal and Smita D. Sontakke. Experimental evaluation of analgesic and anti-inflammatory activity of simvastatin and atorvastatin. Indian J Pharmacol. 2012; 44(4): 475–479.
26. Tourandokht Baluchnejadmojarada, Mehrdad Roghani, Farshad Roghani-Dehkordi. Antinociceptive effect of Teucrium polium leaf extract in the diabetic rat formalin test. J Ethnopharmacology, (2005); 207–210
27. Ueda H, Yamazaki C, Yamazaki M. Luteolin as an anti-inflammatory and anti-allergic constituent of Perilla frutescens. Biol Pharm Bull. 2002; 25:1197–1202. [PubMed]
28. Wungsem Rungsung, Sreya Dutta, Debajyoti Das, Jayram Hazra. A brief review on the Botanical Aspects and Therapeutic Potentials of Important Indian Medicinal Plants. International J Herbal Medicine 2013; 1 (3): 38-45

29. Ratnasooriya W.D., S.A. Deraniyagala, G. Galhena, S.S.P. Liyanage, S.D.N.K. Bathige & J.R.A.C. Jayakody. Anti-inflammatory Activity of the Aqueous Leaf Extract of Ixora coccinea. J Pharmaceutical Biology; 2005; 43(2); 147-152
30. Geetha Srikrishna and Hudson H Freeze. Endogenous Damage-Associated Molecular Pattern Molecules at the Crossroads of Inflammation and Cancer. Neoplasia. 2009 Jul; 11(7): 615–628.
31. Kunal Mahajan. Microparticles in Atherosclerosis: Biomarkers of Disease. J Clin Exp Cardiolog 2015, 6:1
32. Terence Peters and Peter J Henry. Protease-activated receptors and prostaglandins in inflammatory lung disease**.** Br J Pharmacol. 2009 Oct; 158(4): 1017–1033.
33. Fumimasa Amaya, Yuta Izumi, Megumi Matsuda, and Mika Sasaki. Tissue Injury and Related Mediators of Pain Exacerbation. Curr Neuropharmacol. 2013 Dec; 11(6): 592–597.
34. Coutaux A, Adam F, Willer JC, Le Bars D. Hyperalgesia and allodynia: peripheral mechanisms. Joint Bone Spine. 2005;72(5):359–371.
35. Emanuela Ricciotti, and Garret A. FitzGerald**.** Prostaglandins and Inflammation. Arterioscler Thromb Vasc Biol. 2011 May; 31(5): 986–1000.
36. Funk CD, FitzGerald GA. COX-2 inhibitors and cardiovascular risk. J Cardiovasc Pharmacol.2007; 50:470–479.
37. Abbas A.B.; Lichtman A.H. "Ch.2 Innate Immunity". In Saunders (Elsevier).Basic Immunology. Functions and disorders of the immune system (3rd ed.). (2009). ISBN 978-1-4160-4688-2.
38. Monkada, S., Flower, R. J., Vane, J. R. (1991) “The pharmacological basis of therapeutics” (Eds) Goodmann, J. R., Gillman, A. Macmillan publishing company, New York, 11th Edition.